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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

Is there a place for endoscopic management in post-cholecystectomy iatrogenic bile duct injuries?

Hong-Qiao Cai, Guo-Qiang Pan, Shou-Jing Luan, Jing Wang, Yan Jiao

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Abstract

In this editorial we comment on the article by Emara *et al* published in the recent issue of the *World Journal of Gastrointestinal Surgery*. Previously, surgery was the primary treatment for bile duct injuries (BDI). The treatment of BDI has advanced due to technological breakthroughs and minimally invasive procedures. Endoscopic and percutaneous treatments have largely supplanted surgery as the primary treatment for most instances in recent years. Patient management, including the specific technique, is typically impacted by local knowledge and the kind and severity of the injury. Endoscopic therapy is a highly successful treatment for postoperative benign bile duct stenosis and offers superior long-term outcomes compared to surgical correction. Based on the damage features of BDI, therapeutic options include endoscopic duodenal papillary sphincterotomy, endoscopic nasobiliary drainage, and endoscopic biliary stent implantation.

Key Words: Post-cholecystectomy; Iatrogenic; Bile duct injuries; Endoscopic management; Benign bile duct stenosis

Core Tip: Post-cholecystectomy iatrogenic bile duct injuries (BDI) are not uncommon and hence deserve more attention. The treatment of BDI has evolved with the improvements in technology and minimally invasive procedure. Endoscopic treatment looks promising and effective treatment options for iatrogenic BDI.

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INTRODUCTION

Post-cholecystectomy bile duct injury (BDI) is a serious complication caused by medical treatment that can lead to narrowing or leakage, significantly affecting quality of life and resulting in high healthcare expenses[1]. Laparoscopic cholecystectomy (LC) is the primary cause of injury in cases of BDI, responsible for around 80% of BDI cases[2]. Although the occurrence of LC-related BDI has decreased, the total number of cases remains significant due to the frequent performance of cholecystectomy[3]. Treating BDI promptly upon discovery is crucial to prevent complications such as biliary peritonitis, suppurative cholangitis, sepsis, secondary multiple organ dysfunction syndrome, and other catastrophic effects[4]. Previously, the primary therapy choices were surgical procedures. The treatment of BDI has advanced due to technological breakthroughs and minimally invasive procedures[5]. Endoscopic and percutaneous treatments have largely supplanted surgery as the primary treatment for most instances in recent years. For patients with BDI, the therapeutic strategies must be adapted not only to the type of injury, but also to the patient's clinical conditions, taking into consideration the availability of resources and level of expertise of the treating team. Patient management is typically impacted by local knowledge, as well as the nature and degree of the injury.

ENDOSCOPIC SURGERY

Endoscopic surgery is mostly utilized for managing BDI following biliary tract surgery and is the primary treatment for moderate BDI biliary leakage[6]. Research indicates that biliary leakage caused by BDI can be effectively addressed in 78% to 100% of patients with endoscopic or radiographic intervention[7,8]. Based on the injury characteristics of BDI, treatment can involve endoscopic procedures including endoscopic duodenal papillary sphincterotomy, endoscopic nasobiliary drainage (ENBD), and endoscopic biliary stent implantation[9].

ENDOSCOPIC THERAPY FOR POSTOPERATIVE BENIGN BILE DUCT STENOSIS

Endoscopic therapy is an excellent treatment for postoperative benign bile duct stenosis (BBS) and provides superior long-term outcomes compared to surgical correction[10]. To tailor the optimal treatment method for each patient, it is essential to individualize each specific situation. The effectiveness rate of endoscopic therapy ranges from 60% to 90% in extensive investigations[11,12]. A study conducted on the long-term follow-up of postoperative treatment for BBS demonstrated that endoscopic treatment was deemed safer, effective, less intrusive, and reproducible[13]. Therefore, endoscopic retrograde cholangiopancreatography + ENBD was suggested as the optimal treatment for BBS. Full coverage self-expanding metal stents are now the primary treatment for BBS, surpassing plastic stents because to their notable benefits of increased safety and success rates, uncomplicated technology, and reduced need for endoscopic procedures [14,15]. Roux-en-Y hepaticojejunostomy should be considered in patients with significant bile duct resection or ischemia, provided that the surgical route is not restricted.

NEW TECHNOLOGIES IN ENDOSCOPIC THERAPY

Full coverage self-expanding stents should be the primary therapy option for individuals with BBS[16]. Traditional endoscopic or percutaneous interventional therapy may not be effective in achieving biliary drainage in severe BBS. New technologies, like small-diameter through-the-scope magnets (2.4 mm), have been created to enhance the success and effectiveness of endoscopic therapy. These magnets are simple to position and offer both safety and efficacy. Treating entire blockage of biliary connections following a whole liver transplant is highly effective[17]. Magnetic compression anastomosis relies on the fibrosis and necrosis of the constricted tissue. Endoscopists and interventional radiologists position magnets at opposite ends of a narrow area using endoscopic technology to create a magnetic force for bile duct anastomosis. Magnetic compression anastomosis has been proven effective and safe in multiple case reports and series [18]. Endoscopic ultrasound guided biliary drainage is a new device that offers the benefits of endoscopy and percutaneous methods without the need for a catheter[19].

STENT SIZE AND SPHINCTEROTOMY

The significance of stent size and sphincterotomy in decreasing the pressure gradient across the sphincter of Oddi is still a topic of debate. A bigger stent theoretically enhances biliary drainage. In a single randomized experiment, 7-Fr and 10-Fr stents were compared for their effectiveness in resolving bile leaks. The results indicated a slight tendency towards better resolution with the bigger 10-Fr stents, however this difference was not statistically significant. Furthermore, unresolved cases with 7-Fr stents were addressed by inserting a bigger stent[20]. The data does not provide conclusive evidence, although the current study did show a non-significant decrease in time to resolution when using bigger stents. There is less agreement on the effectiveness of sphincterotomy combined with stent placement in treating these patients. Avoiding a sphincterotomy when feasible reduces the risk of bleeding or perforation[21]. Sphincterotomy is linked to a rise in complication rates ranging from 7.3% to 9.8% and a death rate of up to 1.3%[22]. Sphincterotomy is contraindicated in patients with coagulopathy. Mavrogiannis *et al*[23] showed that sphincterotomy did not provide any extra advantage in resolving leaks. However, they and other authors propose that there might be an increased occurrence of pancreatitis in the absence of sphincterotomy[24,25].

CLINICAL IMPLICATIONS

Prevention is the most effective approach to treating diseases, like BDI. Therefore, it is crucial to have a thorough understanding of the risk factors associated with BDI. Effective management of BDI necessitates the cooperation of multidisciplinary teams, leveraging the unique strengths of each department, and taking into account various factors such as common BDI classification, patients' liver function grade, comorbidities, multi-organ function, and infection control. This approach aims to develop a rational, comprehensive, and personalized treatment strategy to optimize patients' clinical outcomes[26].

CONCLUSION

Previously, the primary therapy options for BDI were surgical procedures. The treatment of BDI has advanced due to technological breakthroughs and minimally invasive procedures. Endoscopic and percutaneous treatments have largely supplanted surgery as the primary treatment for most instances in recent years. Patient management is typically impacted by local knowledge, as well as the nature and degree of the injury. Endoscopic therapy is an excellent treatment for postoperative benign BBS and provides superior long-term outcomes compared to surgical correction. BDI damage characteristics can be treated with endoscopic procedures such endoscopic duodenal papillary sphincterotomy, ENBD, and endoscopic biliary stent implantation.

FOOTNOTES

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Abstract

Pancreatic ductal adenocarcinoma (PDAC), which is notorious for its aggressiveness and poor prognosis, remains an area of great unmet medical need, with a 5-year survival rate of 10% - the lowest of all solid tumours. At diagnosis, only 20% of patients have resectable pancreatic cancer (RPC) or borderline RPC (BRPC) disease, while 80% of patients have unresectable tumours that are locally advanced pancreatic cancer (LAPC) or have distant metastases. Nearly 60% of patients who undergo upfront surgery for RPC are unable to receive adequate adjuvant chemotherapy (CHT) because of postoperative complications and early cancer recurrence. An important paradigm shift to achieve better outcomes has been the sequence of therapy, with neoadjuvant CHT preceding surgery. Three surgical stages have emerged for the preoperative assessment of nonmetastatic pancreatic cancers: RPC, BRPC, and LAPC. The main goal of neoadjuvant treatment (NAT) is to improve postoperative outcomes through enhanced selection of candidates for curative-intent surgery by identifying patients with aggressive or metastatic disease during initial CHT, reducing tumour volume before surgery to improve the rate of margin-negative resection (R0 resection, a microscopic margin-negative resection), reducing the rate of positive lymph node occurrence at surgery, providing early treatment of occult micrometastatic disease, and assessing tumour chemosensitivity and tolerance to treatment as potential surgical criteria. In this editorial, we summarize evidence concerning NAT of PDAC, providing insights into future practice and study design. Future research is needed to establish predictive biomarkers, measures of therapeutic response, and multidisciplinary stra tegies to improve patient-centered outcomes.

Key Words: Pancreatic adenocarcinoma; Neoadjuvant treatment; Chemotherapy; Upfront surgery; Radiotherapy; Response evaluation

Core Tip: Pancreatic ductal adenocarcinoma, which is notorious for its aggressiveness and poor prognosis, remains an area of great unmet medical need. The most important determinant of survival is surgical resection. Nearly 60% of patients who undergo upfront surgery for resectable tumours are unable to receive adequate adjuvant chemotherapy (CHT). An important paradigm shift to achieve better outcomes has been the sequence of therapy, with neoadjuvant CHT preceding surgery. Three surgical stages have emerged for the preoperative assessment of nonmetastatic pancreatic cancers: Resectable, borderline-resectable and unresectable locally advanced tumours. In the development of new neoadjuvant and induction strategies, the distinct molecular and biological characteristics of the various pancreatic cancer subgroups need to be integrated to optimize the selection and sequencing of both established and novel treatment modalities that may improve survival outcomes.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC), which is notorious for its aggressiveness and poor prognosis, remains an area of great unmet medical need, with a 5-year survival rate of 10% - the lowest of all solid tumours. Surgical resection is the most important predictor of survival (due to lower morbidity and death rates) along with postoperative adjuvant treatment. The sole potentially curative treatment is surgical resection; nevertheless, the 5- and 10-year overall survival (OS) rates for surgery by itself are quite low, at 10.4% and 7.7%, respectively. The actual rates are even lower, as these numbers represent the "best of the best" in clinical trial patients; real-world results are much worse[1].

Merely 20% of patients are diagnosed with resectable pancreatic cancer (RPC) or borderline RPC (BRPC) illness, whereas the remaining 80% have tumors that are unresectable, have distant metastases, or are locally advanced pancreatic cancer (LAPC)[2]. Single-agent adjuvant chemotherapy (CHT) increases the 5-year OS rate for upfront, locally resectable PDAC (about 20% of all patients) from 8% for surgery alone to 16%-21% with adjuvant therapy[3-6]. Gemcitabine plus capecitabine in unselected patients, including those older than 80 years, provided a median OS (mOS) of 28 months. Modified folinic acid, fluorouracil, irinotecan, and oxaliplatin (mFOLFIRINOX) in selected patients younger than 79 years of age increased 3-year OS to 63.4% and mOS to 54.4 months[7,8].

Nearly 60% of patients who undergo upfront surgery for RPC are unable to receive adequate adjuvant CHT due to postoperative complications and early cancer recurrence[9]. Just 7% of Medicare patients, for instance, were able to receive all prescribed adjuvant CHT, according to a recent study. Although it is not common to finish because of the previously described reasons, adjuvant CHT for pancreatic cancer patients who have received upfront surgical resection is associated with a greater chance of survival. Patients who undergo appropriate surgical resection for pancreatic cancer often experience cancer recurrence and are not cured, even with aggressive adjuvant management[10].

STAGING CRITERIA

Radiographically localized pancreatic adenocarcinoma is staged based on anatomical tumour-vessel interfaces into RPC, BRPC, and LAPC. Three fundamental ideas form the basis of these classifications: (1) Increasing vascular involvement may raise the risk of harboring radiographically occult metastatic disease; (2) Margin negative resection is more frequently linked to long-term survival; and (3) Margin positivity increases with increasing degree of vascular involvement[11]. The complexity and variability of classification based on these criteria is demonstrated by the fact that, even in high-volume institutions, approximately 30% of patients were misclassified anatomically in a prospective multicenter clinical trial[12]. Three subsets were developed by the MD Anderson Cancer Center Pancreatic Cancer Group (BR-A, BR-B, and BR-C) to evaluate patients with BR-PDAC and determine resectability using parameters other than anatomic criteria. The anatomic criteria for BR disease are met by BR-A disease, and it lacks any additional characteristics that would prevent surgical resection. The biological characteristics of extra-pancreatic disease, such as biopsy-proven lymph node metastases, elevated carbohydrate antigen 19-9 (CA 19-9) levels (1000 U/mL), and indeterminate liver lesions, are indicative of BR-B disease. Individuals diagnosed with BR-C illness form a conditional group that takes into account comorbidities such as advanced age (> 80 years) or an ECOG performance status of 2 or higher[13].

The systemic inflammatory response of cancer cells is involved in cancer progression and malignant transformation [14]. An elevated neutrophil-to-lymphocyte ratio is associated with poor OS and poor cancer-specific survival in patients with advanced-stage disease, and it is predictive of survival after resection of early-stage PDAC[15]. In PDAC patients receiving neoadjuvant treatment (NAT), the systemic inflammation response index (SIRI) can predict the survival of patients following resection and neoadjuvant chemotherapy (NACT), while the post-treatment systemic immune-inflammation index may be a useful prognostic marker[16]. Changes in the SIRI were associated with OS, but the preoperative SIRI was correlated with disease-free survival[17].

Treatment paradigms must be modified in light of advances in biomarkers, such as the discovery of circulating tumor DNA (ctDNA), based on staging criteria that take into consideration morphological restrictions, the biological predisposition for distant failure, and patient performance status[18]. Furthermore, circulating tumour cells can be isolated in the bloodstream of patients with early-stage pancreatic cancer, and their levels are correlated with the probability of survival[19].

SEQUENCE OF THERAPY

A significant paradigm change that has improved outcomes is the order in which therapies are administered, with NACT coming before surgery. Three surgical stages have emerged for the preoperative assessment of nonmetastatic pancreatic cancers: RPC, BRPC, and LAPC. Identifying patients with aggressive or metastatic disease during initial CHT, reducing tumour volume before surgery to improve the rate of margin-negative resection (R0 resection, a microscopic margin-negative resection), lowering the rate of positive lymph node occurrence at surgery, offering early treatment of occult micrometastatic disease, and evaluating tumour chemosensitivity and tolerance to treatment as potential surgical criteria are all part of the main objective of NAT, which aims to improve postoperative outcomes through an enhanced selection of candidates for curative-intent surgery. Selecting patients with a high chance of undergoing margin-negative resection based on response evaluation represents one of the most difficult scenarios with NAT[20]. The primary risk associated with neoadjuvant therapy is that about 30% of patients will develop metastatic disease while receiving treatment. Thus, a crucial unmet need is instruments to help physicians choose first-line CHT regimens that are more effective[21].

As such, it is critical to carefully weigh the various therapeutic options and customize them in light of clinically meaningful biomarkers. We can improve our capacity to choose patients who will most likely benefit from NACT by finding strong predictive markers. Additionally, the discovery of prognostic markers can help guide treatment choices and offer insightful information about the overall course of the disease.

CURRENT TREATMENT TRENDS IN NAT

Due to a lack of randomized phase III trials, NACT for RPC is not currently included in clinical guidelines. However, it may be an alternative to surgery first for patients with clearly resectable disease who only have suspicious imaging findings of metastasis, CA 19-9 levels suggestive of metastatic disease, or who require medical optimization before surgery. Some studies support the use of NAT for treating resectable tumours[22,23], and others have shown that NAT may be considered for patients with resectable tumours and high-risk features[24,25]. A retrospective study aimed at exploring patient subgroups with high-risk resectable PDAC for selecting candidates who may benefit from NAT reported that NAT is an effective treatment for patients with resectable PDAC, particularly when the tumour is in contact with the portal vein/superior mesenteric vein and has a CA 19-9 concentration ≥ 150 U/mL[26]. Propensity score matching analysis of retrospectively analyzed early-stage PDAC patients showed that in patients with early-stage resected pancreatic head adenocarcinoma, NAT followed by resection demonstrated a significant survival benefit when compared with upfront surgery, while the analysis, which represented an updated nationwide retrospective study, also supports multiagent NACT *vs* upfront surgery[27,28]. On the other hand, prospective randomized studies like NORPACT1 (neoadj mFOLFIRINOX 4 cycles and adj mFOLFIRINOX 8 cycles *vs* adj mFOLFIRINOX 12 cycles)[29], PANACHE01-PRODIGE48 (neoadj mFOLFIRINOX 4 cycles and adj chemo 8 cycles *vs* neoadj FOLFOX 4 cycles and adj chemo 8 cycles *vs* adj chemo 12 cycles)[30], and SWOG S1505 (neoadj mFOLFIRINOX 12 wk and adj mFOLFIRINOX 12 wk *vs* neoadj gem/nab-P 12 wk and adj gem/nab-P 12 wk) did not confirm the usefullness of NACT[31]. Additionally, there was no evidence supporting the use of NACT in the PREOPANC-2 study, which used mono-agent neoadjuvant chemoradiotherapy (NACRT)[32]. However, neoadjuvant therapy in these patients serves as a biological time-test and increases the delivery of multimodal therapy. Neoadjuvant therapy was not expected to be beneficial in patients with RPC, according to a meta-analysis of 111 cohort series neoadjuvant response rates and resection rates. However, roughly one-third of patients with nonresectable tumors could be anticipated to have a resectable tumor after neoadjuvant therapy, with a similar survival rate to those with primary resectable tumors[25]. Ongoing and future trials, such as Alliance A021806 (perioperative mFOLFIRINOX *vs* adjuvant mFOLFIRINOX)[33] and PREOPANC-3 (perioperative mFOLFIRINOX *vs* adjuvant FOLFIRINOX)[34], are intended to provide additional insight into the function of neoadjuvant therapy in patients with RPC.

A short course of neoadjuvant therapy, usually administered for two months before surgery, boosts the 12-month OS to roughly 77% in patients with borderline-resectable disease (with R0/R1 resection rates of 64%-85%), compared with 40% with upfront surgery (with a resection rate of 75%). An 18-month OS of 67% can result from a prolonged course of NACT, often lasting 4 months. Additionally, after 4-6 months of induction combination CHT with or without radiation therapy, 20% of patients with unresectable nonmetastatic PDAC may undergo resection, even in the absence of a

discernible radiological response, improving their OS[35]. An optimal NAT regimen has not been agreed upon due to a lack of data from randomized clinical trials[36]. The two most efficient CHT regimens for PDAC are FOLFIRINOX and gemcitabine-nab-paclitaxel (GNP). For patients with pancreatic adenocarcinomas that were both resectable and borderline resectable, neoadjuvant FOLFIRINOX *vs* neoadjuvant gemcitabine-based CRT did not show any OS benefit, according to the first study's phase III PREOPANC-2 trial data. Specifically, the mOS was 21.9% and 21.3% [hazard ratio (HR) = 0.87; 95% confidence interval (CI): 0.68-1.12; P = 0.28]. Between treatment arms, resection rates (77% *vs* 75%, respectively; P = 0.7) and serious adverse rates (49% *vs* 43%, respectively; P = 0.26) were likewise comparable[32]. The resection rate, R0 resection rate, and 2-year OS did not differ between the groups, according to the SWOG-1505 study, which assessed mFOLFIRINOX and GNP in the NAT setting of RPC. The toxicity profiles of the GNP and mFOLFIRINOX groups in this investigation did not significantly differ, which is noteworthy[31]. The NAPOLI 3 trial, which included liposomal irinotecan in the NALIRIFOX regimen, showed statistically significant and clinically meaningful improvements in OS and progression-free survival (PFS) compared with nab-paclitaxel and gemcitabine in patients with metastatic PDAC who had not previously received treatment in the metastatic setting. However, FOLFIRINOX is not superior in head-to-head comparisons[37]. According to the phase II nITRO trial, perioperative NALIRIFOX is safe and effective, and it should be further studied in randomized trials that contrast it with current CHT regimens for patients with BRPC and LAPC as well as standard surgery upfront followed by adjuvant therapy in patients with RPC[38].

Prospective randomized phase II and III trials exclusively enrolled patients with LAPC in the LAP-07 trial only, and other data supporting NAT in LAPC patients were derived from retrospective reports[39]. Apart from LAPC, which represents a true unresectable tumour, patients who suffer liver oligometastasis from PDAC may be candidates for surgery after NACT according to a meta-analysis based on small studies without randomized controlled trials and according to the opinions of one-third of the experts[40-42].

The role of radiation or chemoradiation during NAT for BRPC remains unclear. There is considerable debate on the best NAT regimen, and it is still uncertain whether is better for BRPC: NACT or NACRT[35]. CRT and maintenance CHT were examined in 449 patients in the LAP-07 study, who did not have progressing illness after CHT alone. After receiving either gemcitabine and erlotinib or gemcitabine alone for four months (the first randomization), 269 participants were randomly assigned to receive either CHT or CRT for an additional two months of treatment. Although CRT was linked to delayed locoregional development, the mOS in the CRT group did not improve[39]. When FOLFIRINOX was the primary induction therapy, the CONKO-007 trial yielded remarkably comparable outcomes. Without impacting OS or PFS, the addition of CRT raised the pathological complete response rate[43]. Some theoretical advantages of new radiotherapy techniques over conventional radiation include shorter treatment times, more focused treatment fields, higher biological effective doses, and the potential for better sparing of adjacent organs at risk. One such technique is stereotactic body radiotherapy, which targets primary tumors with minimal margins and high single doses in few fractions. The problem of delivering ablative doses while minimizing severe toxicity may potentially be solved by magnetic resonance-guided radiotherapy, or MRgRT[44].

RESPONSE EVALUATION

One of the greatest difficulties faced when dealing with NAT is identifying patients who are highly likely to undergo margin-negative resection based on response evaluation. It is widely recognized that conventional imaging has its limitations when it comes to restaging tumors[45]. PDAC is characterized by a significant presence of desmoplastic stroma, accounting for a substantial portion of the tumor volume, often estimated to be as high as 90%. This stroma is believed to primarily arise from cancer-associated fibroblasts[46]. The Response Evaluation Criteria in Solid Tumours have certain limitations when it comes to PDAC with a high presence of desmoplastic stroma. This is because commonly used imaging methods like computed tomography or magnetic resonance imaging cannot accurately distinguish between fibrosis caused by NACT and viable tumor tissue that remains. As a result, it becomes difficult to accurately determine the resectability of the tumor based solely on imaging studies conducted after neoadjuvant therapy. Numerous studies have also highlighted that the radiological appearance following neoadjuvant therapy does not necessarily reflect the patient's actual response to the treatment[47].

Numerous institutions have made efforts to assess the biochemical response using CA 19-9, a widely recognized tumor marker in PDAC. Nevertheless, there has been a lack of consistency in the evaluation criteria employed by different institutions[48]. Moreover, the evaluation of treatment outcomes becomes complex when there are disparities between radiological and biochemical responses[49]. Yun *et al*[50] categorized patients into three groups based on their response to NACT and prognosis: Biochemical responders (BR+), BR-/radiology-only responders (RR+), and nonresponders (BR-/RR-). The research revealed that the 3-year survival rate differed significantly among the BR+ group (71.0%), the BR-/RR+ group (53.6%), and the BR-/RR- group (33.1%) (P < 0.001). Furthermore, the response to NACT was highlighted as a crucial factor in predicting recurrence risk, with HR of 2.15 (95%CI: 1.19-3.88; P = 0.011) for BR-/RR+ patients and 3.82 (95%CI: 2.41-6.08; P < 0.001) for BR-/RR- patients when compared to BR+ patients. Irrespective of the response to NACT, patients who underwent adjuvant CHT exhibited a significantly improved 3-year OS rate in comparison to those who did not[50]. Newhook *et al*[51] proposed innovative classification systems A (progressively decreasing to normal), B (fluctuating bidirectionally towards normal), C (consistently within normal range), D (decreasing but not normalizing), and E (increasing without normalization) based on the dynamics of CA 19-9. The study findings indicated that categories A and B, where CA 19-9 levels eventually normalize post NACT, are linked to favorable prognoses, while types D and E, where CA 19-9 levels remain elevated post NACT, are associated with poorer outcomes. Hence, apart from CA 19-9,

investigations should be carried out to assess the efficacy of NACT by examining glucose metabolic activity or utilizing more sensitive biomarkers like ctDNA[52-54].

The efficacy of adjuvant CHT in patients who have undergone NACT remains a topic of debate. Drawing comparisons between the outcomes of adjuvant and neoadjuvant trials poses a challenge due to the fact that adjuvant trials typically involve only those patients with resected pancreatic cancer who are deemed suitable for adjuvant therapy without any signs of disease progression. On the other hand, neoadjuvant studies generally encompass all patients with RPC, as determined by diagnostic imaging, prior to the initiation of any treatment. Therefore, comparisons of the survival outcomes of patients in neoadjuvant and adjuvant trials are difficult if not impossible[55,56].

The development of cytotoxic treatments for various phases of pancreatic cancer has predominantly relied on empirical methods. A reductionist strategy aimed at creating therapies that target crucial genetic mutations has seen minimal achievements. Nevertheless, several elements of neoadjuvant therapy for PDAC, such as the most effective treatment plan, the incorporation of radiotherapy, and the identification of suitable candidates for neoadjuvant therapy, still require further clarification. Since other tumors with a much better prognosis have a greater number of average mutations, such as breast and colorectal cancers, and because the genetic spectra of colorectal, brain, and pancreatic tumors are similar, the average number of genetic alterations in PDAC tumors is insufficient to explain the abnormally poor prognosis and response to therapy[57,58].

There is accumulating research suggesting a relationship between pancreatic cancer subtype (classical *vs* basal-like) and treatment response[59]. Basal-like PDAC was resistant to FOLFIRINOX, paclitaxel, and tyrosine kinase inhibitors, whereas the classical transcriptional subtype was more susceptible to epidermal growth factor receptor suppression by erlotinib. These data significantly underscore the need for molecular subtyping in therapeutic decision-making in patients with PDAC[60].

CONCLUSION

The development of new neoadjuvant and induction strategies must take into account the distinct molecular and biological characteristics of the various pancreatic cancer subgroups, optimizing the selection and sequencing of both established and novel treatment modalities to improve survival rates. We can improve our capacity to choose patients who will benefit most from NACT by identifying strong prognostic markers. Moreover, prognostic markers can provide valuable insight into the overall disease course and illuminate treatment choices. Future studies are wanted to set up predictive biomarkers, measures of healing response, and multidisciplinary techniques to enhance patient-targeted outcomes.

FOOTNOTES

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EDITORIAL

Clinical diagnostic advances in intestinal anastomotic techniques: Hand suturing, stapling, and compression devices

Ah Young Lee, Joo Young Cho

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Abstract

The development of intestinal anastomosis techniques, including hand suturing, stapling, and compression anastomoses, has been a significant advancement in surgical practice. These methods aim to prevent leakage and minimize tissue fibrosis, which can lead to stricture formation. The healing process involves various phases: hemostasis and inflammation, proliferation, and remodeling. Mechanical staplers and sutures can cause inflammation and fibrosis due to the release of profibrotic chemokines. Compression anastomosis devices, including those made of nickel-titanium alloy, offer a minimally invasive option for various surgical challenges and have shown safety and efficacy. However, despite advancements, anastomotic techniques are evaluated based on leakage risk, with complications being a primary concern. Newer devices like Magnamosis use magnetic rings for compression anastomosis, demonstrating greater strength and patency compared to stapling. Magnetic technology is also being explored for other medical treatments. While there are promising results, particularly in animal models, the real-world application in humans is limited, and further research is needed to assess their safety and practicality.

Key Words: Anastomoses; Diagnostic advances, Anastomotic techniques; Technique; Intestine

Core Tip: The development of techniques for the creation of intestinal anastomoses, such as hand suturing, stapling, and compression anastomoses, represents a significant advancement in surgical practice. Compression anastomosis devices reduce inflammation compared to sutured anastomosis, and they yield leakage and stenosis rates similar to those of standard sutured and stapled colorectal anastomoses. Recent reports suggest that these devices facilitate the safe and efficient creation of intestinal anastomoses. For instance, compression anastomoses have exhibited a greater bursting strength and wider patency than stapled anastomoses, even after chemoradiotherapy. Nevertheless, the potential of compression anastomosis, including its safety and practicality, warrants further investigation.

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INTRODUCTION

The development of techniques for the creation of intestinal anastomoses, such as hand suturing, stapling, and compression anastomoses, represents a substantial advancement in surgical practice. An ideal anastomotic connection must have sufficient strength to prevent leakage during peak tissue weakness and minimize tissue fibrosis, which could lead to stricture formation. A key prerequisite for optimal anastomosis is stress-free alignment of the wound edges, ensuring an adequate blood supply[1].

In principle, anastomosis has several stages: Hemostasis and inflammation (days 0-3), proliferation (days 4-14), and remodeling and scar maturation (from day 15 onward). Colorectal anastomoses are typically created using mechanical staplers or one or more suture layers[2]. This process can trigger an inflammatory response characterized by a foreign body granulomatous reaction at the anastomosis site, potentially leading to stricture formation due to the ongoing release of profibrotic chemokines, *e.g.*, transforming growth factor-β and platelet-derived growth factor[3]. This issue has spurred numerous attempts to create "sutureless" bowel–bowel anastomoses[4].

The intestinal anastomotic healing process can be divided into the acute inflammatory, proliferative, and remodeling or maturation phases. As collagen is the most critical molecule in determining the strength of the intestinal wall, its metabolism is vital to our understanding of anastomotic healing[4].

Incorrectly performed anastomoses can lead to severe complications, such as peritonitis, sepsis, or death related to complications following gastrointestinal resection surgery[5]. Colorectal anastomotic leakage is a common postoperative complication, particularly after anterior resection of the rectum. The incidence of anastomotic leakage varies from 1% to 24%, with higher rates typically being observed in elective rectal anastomoses (12%-19%) than in colonic anastomoses (11%)[4]. Specifically, the leakage rates in ileocolic anastomoses are approximately 1%-4%, and those in colocolic anastomoses are 2%-3%. The risk of leakage is greater in complex surgeries than in simple surgeries, particularly in lower colorectal anastomoses, reaching 10%-14%[6].

A compression anastomosis device that can be used in a minimally invasive manner can address a wide range of surgical challenges, including malignant bowel obstruction, traumatic bowel injury, enterostomy closure, and congenital anomalies of the esophagus and intestines[7-9]. The concept of compression anastomosis, first introduced in 1826, has been explored and refined over time[10,11]. These devices, with recent developments based on nickel–titanium alloy rings that require no suture fixation, have been proven safe in elective and emergency settings[12]. As they leave no foreign bodies at the surgical site, they reduce inflammation compared with sutured anastomosis, and they yield similar leakage and stenosis rates to those of standard sutured and stapled colorectal anastomoses[13].

Despite advances in safety, anastomotic techniques are primarily evaluated on the basis of the risk of leakage. These techniques can be categorized according to their reproducibility, associated trauma, complexity, and usability. Flawless anastomotic healing is crucial for successful patient recovery. However, despite the use of various implants and methodologies, the risk of complications, such as anastomotic leakage (with rates of up to 10%) and stenosis, remains high. These complications are the leading causes of morbidity and mortality after visceral surgery.

Compression devices operate *via* a simultaneous process of pressure necrosis and repair at the anastomotic site. The entrapped bowel undergoes marked ischemia, tissue necrosis, and sloughing off of the inner, compressed tissue into the fecal stream while the outer bowel tissues heal. Recent reports have suggested that these devices facilitate the safe and efficient creation of intestinal anastomoses[14]. For instance, compression anastomoses have exhibited a greater bursting strength and wider patency than stapled anastomoses[15], even after chemoradiotherapy[16].

Magnamosis, comprising two self-assembling magnetic rings, represents a major advancement in endoscopically compatible systems for full-thickness compression anastomoses of the bowels. The device design includes convex-concave, radially symmetric halves that self-align magnetically and ring-shaped magnetic halves for immediate patency. The mating surfaces have a specially engineered radial topography to promote gradual remodeling and healing of compressed intestinal walls[17].

The use of enteric magnets for anastomosis was first described in animal models and then later in humans. Magnetic technology is increasingly used in the medical field for various treatments, including vascular anastomoses[18,19] and the treatment of gastrointestinal diseases.

In human trials, the use of flat magnetic rings for mucosa-to-mucosa anastomosis has been explored, with patency occurring after 7-12 d[20]. However, two cases of anastomotic leaks were reported during the follow-up of 21 patients [21]. Magnacystostomy has also been proposed as a minimally invasive technique for suprapubic cystostomy, particularly when typical methods are contraindicated. Magnetic treatment for short urethral strictures is effective in children[22].

In animal models, magnamoses (gastrojejunostomy and jejunojejunostomy) develop strengths comparable to or greater than those of hand-sewn or stapled anastomoses. The advantages of these devices include ease of insertion, coupling, and removal as well as their less invasive nature compared with other devices. However, the time required for anastomotic completion can vary among organs, and this technique may not be suitable for patients who require immediate decompression[23].

Although the system has been used to create side-to-side colorectal anastomoses, failures due to magnetic-ring detachment have been reported. Additionally, mild-to-moderate stenoses were observed in some cases, although these decreased in severity over time[24].

CONCLUSION

Despite their theoretical benefits, the utility of these compression devices in clinical settings remains limited. Real-time monitoring of the healing process is often not feasible, leading to a reliance on traditional or slightly more advanced methods. However, magnetic anastomosis is not just confined to clinical trials; it is already being employed in clinical practice, notably in cases of long gap esophageal atresia and cholangiojejunostomy[25]. We also expect its scope of use to expand to the treatment of fistulas in the pancreatobiliary area. Nevertheless, the potential of compression anastomosis in certain scenarios warrants further investigation regarding its safety and practicality.

FOOTNOTES

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EDITORIAL

Surgical treatment of inflammatory bowel disease: From the gastroenterologist's stand-point

John K Triantafillidis

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Abstract

Treatment of ulcerative colitis (UC) and Crohn's disease (CD) represents, in the majority of cases, a real challenge to the gastroenterologist's abilities and skills as well as a clinical test concerning his/her levels of medical knowledge and experience. During the last two decades, our pharmaceutical arsenal was significantly strengthened, especially after the introduction of the so-called biological agents, drugs which to a large extent not only improved the results of conservative treatment but also changed the natural history of the disease. However, colectomy is still necessary for some patients with severe UC although smaller compared to the past, precisely because of the improvements achieved in the available conservative treatment. Nevertheless, surgeries to treat colon dysplasia and cancer are increasing to some extent. At the same time, satisfactory improvements in surgical techniques, the pre-and post-operative care of patients, as well as the selection of the appropriate time for performing the surgery have been noticed. Regarding patients with CD, the improvement of conservative treatment did not significantly change the need for surgical treatment since two-thirds of patients need to undergo surgery at some point in the course of their disease. On the other hand, the outcome of the operation has improved through good preoperative care as well as the wide application of more conservative surgical techniques aimed at keeping as much of the bowel *in situ* as possible. This article discusses the indications for surgical management of UC patients from the gastroenterologist's point of view, the results of the emerging new techniques such as transanal surgery and robotics, as well as alternative operations to the classic ileo-anal-pouch anastomosis. The author also discusses the basic principles of surgical management of patients with CD based on the results of the relevant literature. The self-evident is emphasized, that is, to achieve an excellent therapeutic result in patients with severe inflammatory bowel disease in today's era; the close cooperation of gastroenterologists with surgeons, pathologists, imaging, and nutritionists is of paramount impor-

tance.

Key Words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Surgery; Treatment; Ileo-anal-pouch anastomosis; Indications; Techniques

Core Tip: The main indications for surgery in inflammatory bowel disease concern acute or chronic complications and/or failure of the conservative treatment. Emergency surgery in Crohn's disease (CD) is performed in cases of intestinal obstruction, presence of perineal or intra-abdominal abscesses, and toxic colitis, while in patients with ulcerative colitis (UC) emergency surgery concerns bowel perforation, toxic megacolon, and uncontrolled bleeding. Elective surgery in CD concerns cases of strictures or perianal disease, while in patients with UC elective surgery is applied mainly in cases of patients unresponsive to conservative treatment. To achieve an excellent therapeutic result, the cooperation of a gastroenterologist, surgeon, pathologist, imaging physician, and nutritionist is necessary.

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INTRODUCTION

Treatment of ulcerative colitis (UC) and Crohn's disease (CD) represents a real challenge to the gastroenterologist's abilities and skills as well as a good clinical test concerning his/her levels of medical knowledge and experience. During the last two decades, our pharmaceutical arsenal was significantly strengthened, especially after the introduction of the so-called biological agents, drugs which to a large extent not only improved the results of conservative treatment but also changed the natural history of the disease.

The long-term course and evolution of CD are characterized by relative resistance to treatment, frequent recurrences, and high rates of both initial surgery and reoperations. Surgery is the second part of the treatment available today after the first which corresponds to medical treatment. It is well-argued that a delay in referring a patient for surgery can result in significant postoperative complications and prolonged hospital stay. This means that clinical gastroenterologists should correctly calculate the severity of the disease, as well as the effectiveness of the applied medication to choose the appropriate time when the patient will be taken to the operating room so that the maximum possible benefit could be obtained. Probably in the future, there will be a satisfactory basis for an individualized schedule of surgical intervention based on data related to radiomics, metabolomics, and microbiomics which would become accessible in daily clinical practice.

Regarding UC patients, colectomy is still necessary in some proportion of patients although smaller compared to the past, probably due to the improvements achieved in the available conservative treatment. On the other hand, surgeries to treat colon dysplasia and cancer are increasing to some extent. At the same time, satisfactory improvements in surgical techniques, the pre-and post-operative care of patients, as well as the selection of the appropriate time for performing the surgery have been noticed.

Regarding CD patients, conservative treatment aims at the disappearance of the symptoms of the disease, the healing of the intestinal mucosa, the improvement of the quality of life, and the prevention of complications. Surgery represents the second "hand" of the comprehensive treatment of CD, although the decision to choose the most appropriate time to perform the surgery has been controversial for a long time[1]. However, despite the significant improvements achieved in the conservative treatment of CD, these did not significantly change the need for surgical treatment since two-thirds of patients need to undergo surgery at some point in the course of their disease. The outcome of the operation has improved through good preoperative care as well as the wide application of more conservative surgical techniques aimed at keeping as much of the bowel *in situ* as possible. It should be particularly emphasized that due to the advances in conservative treatment, there is a tendency among gastroenterologists to consider surgical treatment as a last resort and indeed this opinion is also widespread among patients. This has the disadvantage of delaying surgery which may therefore increase the rate and severity of postoperative complications and severe nutritional deficits. Although the decision for surgery instead of conservative treatment is the patient's "prerogative" this will be done under the guidance of the attending physician, except in cases of complications in which surgery is required anyway[2].

The surgical approach to CD should generally be minimally invasive because it is associated with earlier recovery, fewer complications, fewer adhesions and incisions, and preserved body image and fertility. Today, stricturoplasty has replaced segmental small bowel resection, laparoscopic procedures are performed with increasing frequency replacing open surgery, permanent ileostomy is eliminated through restorative procedures, and loss of continence is improved with anal fistula plug application. Single-incision laparoscopic surgery reduces postoperative pain and improves the aesthetic result of surgery. The diseased intestinal segment can be removed from the site of the surgical incision, through a created

stoma, or natural openings (*e.g.*, transvaginal), although the magnitude of the actual benefit of this method has not been adequately determined. In patients with severe perianal disease or rectal involvement, transperitoneal total proctectomy may be feasible with the benefit of avoiding repeat laparotomy. Through transsphincteric resection of the rectum, the risk of damage to the pelvic autonomic nerves is significantly reduced, while the risk of presacral abscess formation is reduced by leaving mesorectal tissue. Minimally invasive surgery and related techniques have become standard clinical practice in the surgical treatment of patients with CD. These developments achieve a reduction in hospital stay, a reduction in morbidity, and an improvement in aesthetic results[3].

This article discusses recent topics on surgical management of UC patients from the gastroenterologist's point of view, results of the emerging new techniques such as transanal surgery and robotics, as well as alternative operations to the classic ileo-anal-pouch anastomosis (IAPA). The article also refers to the basic principles of surgical management of patients with CD based on the results of the current literature. Finally, the self-evident is emphasized, that is, to achieve an optimal therapeutic outcome in patients with severe inflammatory bowel disease (IBD) in today's era. To achieve this close cooperation of gastroenterologists, surgeons, pathologists, radiologists, and nutritionists is of paramount importance.

SURGERY FOR CD

Surgery in CD patients is generally following certain rules, has specific indications, and is performed by experienced surgeons. The cooperation of a gastroenterologist, surgeon, and physicians of other specialties, cooperated by nutritionists-dietitians is required, as the risk of short bowel syndrome lurks behind every surgical manipulation. The gastroenterologist with experience in the diagnosis and treatment of patients with IBD, as well as with deep acquaintance with the current statements concerning IBD contributes significantly for patients to achieve a favorable outcome. Finally, extensive enterectomy is no longer necessary and it can be potentially dangerous. The prevailing trend is not to remove the entire diseased intestine, but only the part responsible for the symptoms that brought the patient to the operating room. Thus the risk of short bowel syndrome due to extensive resection is reduced.

While complicated CD benefits from surgical treatment, uncomplicated disease is a major point of dispute regarding conservative or surgical treatment options. The current treatment of the disease aims to stop the progression of the inflammatory process and to prevent the occurrence of irreversible fibrosis and other tissue damage through two treatment strategies, the step-up and the top-down approach. The gradual introduction of stronger pharmaceutical agents into the treatment of patients has the disadvantage that treatment may be delayed resulting in the creation of permanent damage to the affected part of the bowel. On the contrary, the top-down approach can constitute "over-treatment" as a result of which the patient receives biological agents that he does not need and is thus exposed to potential risks as a consequence of their unnecessary use.

Recently, it has been argued that early surgery could be an appropriate treatment option both in terms of clinical results and treatment costs[4]. In this phase, it is considered that the surgeon should be included in the decision-making process already from a very early stage of the disease. Several studies show that delaying surgery in anticipation of disease improvement with biological agents is responsible for suboptimal management, failure to achieve adequate disease control, and the need for extensive resections resulting in increased complications including malnutrition, abscesses, and fistulas. Data suggest that early surgery does not harm disease progression and may offer some advantages[2]. The main indications for surgery in patients with CD are shown in Table 1.

SURGERY FOR UPPER GASTROINTESTINAL CD

It should be pointed out at the outset that the data regarding the surgical treatment of CD located in the esophagus, stomach, or duodenum are quite few. The frequency of the involvement of the upper gastrointestinal tract fluctuates according to various studies from 17%-75%[5]. Esophageal involvement is around 2%. Surgery is rarely required for CD located in the esophagus. Usually, endoscopic dilation or segmental resection helps effectively. Gastric and/or duodenal involvement is also rarely seen (0.5%-4%). Currently, there is no consensus regarding the optimal surgical management of gastroduodenal CD. Surgical treatment can be applied in patients resistant to conservative management, taking into account the possibility of the existence of dysplasia or cancer in stenotic areas. Profound bleeding and obstruction of the gastric outlet are also important indications. This last case is treated with antrectomy with Roux-en-Y bypass or laparoscopic bypass surgery with gastrojejunostomy[6].

SURGERY FOR SMALL BOWEL CD

CD of the small intestine manifests clinically as inflammatory and/or fibrous stricture, penetrating disease, or a combination of both. In cases of intestinal stricture, it is necessary to determine whether the nature of the stricture is fibrous, inflammatory, or both. This is necessary because in the case of the inflammatory nature of the stenosis, the appropriate treatment with the pharmaceutical agents is expected to improve the inflammation and therefore the stenosis as well as the clinical picture. On the contrary, in the case of the fibrotic nature of the stenosis, conservative treatment is not expected to achieve significant clinical benefits. As mentioned elsewhere, early surgical resection has equally good

Table 1 Main indications for surgery in patients with Crohn's disease

Indications	Treatment
Bowel obstruction	Conservative: Elimination of inflammation. On failure: Surgical resection of narrowed segment or endoscopic balloon dilatation
Intraabdominal abscess	Percutaneous drainage - administration of antibiotics. Surgery: Failure to improve septic symptoms, abscess rupture, multiple abscesses, enterectomy
Presence of fistulae	Simple fistulae: Pharmaceutical agents, enteral nutrition, biologic agents. Complex enteric fistulae: Surgery, treatment of sepsis, nutritional support
Perianal disease	Fistulae: Multidisciplinary approach, antibiotics, biological agents, surgery, stems cells. Abscess: Surgical drainage, antibiotics
Perforation	Emergency surgery
Massive bleeding	Conservative, endoscopic, invasive hemostasis. On failure: Emergency surgery
Malignancy	Absolute indication for surgery
Failure of conservative treatment	Drug intolerance, failure of biological agents, antibiotics, enteral nutrition, and total parenteral nutrition

and longer-lasting results compared to the administration of biological agents. Furthermore, various surgical techniques such as wide mesenteric resection, lateral anastomosis, or Kono-S seem to offer significant help. Long-term administration of metronidazole or ornidazole also has good results at the cost of some side effects, in a significant proportion of patients. Finally, penetrating disease requires a multidisciplinary approach with special attention to the nutritional rehabilitation of patients, the restoration of deficits, and skin care[7].

Surgical treatment of strictures of the small intestine

Strictures in which the inflammatory component predominates are usually treated conservatively and/or surgically. As a rule, CD is diagnosed by clinical gastroenterologists and is therefore treated conservatively with surgery following if necessary. In the L1RIC study patients with terminal ileitis unresponsive to conservative treatment underwent either treatment with an anti-tumor necrosis factor (TNF)-α agent or laparoscopic ileocolonic resection. One year later, quality of life did not differ between the two groups, but costs were significantly lower in the group that underwent surgery[8]. Five years later, none of the operated patients required re-excision and only 25% required treatment with biological agents. In the group that received anti-TNF-α treatment, half of the patients required surgery while the rest received treatment with a biological agent[9]. The incidence rates of postoperative anastomotic leak after elective ileocecal or ileocolonic resection with ileocolonic anastomosis in CD range from 2% in patients with a stapled side-to-side anastomosis to 14% in patients with a handsewn end-to-end anastomosis[10]. In case of recurrence, the operation can be repeated.

If the nature of the stricture is predominantly fibrous and the inflammatory component, as visualized on magnetic resonance imaging (MRI), is minimal or absent, or there is prestenotic dilatation or a history of episodes of incomplete intestinal obstruction, the patient is not expected to be substantially helped by conservative treatment and surgery is inevitable. Depending on the extent and location of the stenosis, endoscopic dilation may be attempted beforehand, but the author's opinion is in favor of surgical intervention. In cases of (fibrous) strictures, either segmental enterectomy or stricturoplasty should be performed. In the absence of fistulizing disease, cancer, or inflammatory mass, stricturoplasty is an alternative for resection. Long-term results indicate similar recurrence rates of resection as compared to stricturoplasty. The most frequently performed technique is the Heineke-Mikulicz one, in which a longitudinal incision is made along the stricture, which is then converged transversely. In this way, the length of the intestine is kept unchanged. If required, multiple stricturoplasties can be performed. Short strictures could be repaired with conventional stricturoplasty such as Heineke Mikulicz (< 10 cm) or Finney (10-25 cm), while in cases of large or multiple stenotic areas, non-conventional operations such as isoperistaltic side-to-side (or Michelassi) stricturoplasty could be applied[11].

Terminal ileitis with fistula

The indication for surgery in patients with entero-enteric, entero-abdominal, or enterovesicular fistulas is certain when there are symptoms indicative of the presence of complications such as urinary tract infections or bowel obstruction. Enteroenteric fistulas are usually asymptomatic and are treated only when there is a stricture. A special subgroup is symptomatic patients with fistulizing disease that does not respond to conservative treatment. In these patients, due to the possibility of the co-existence of an inflammatory mass, the decision to operate should be made early. It is pointed out that resection surgery should be focused on the affected organ. The pre-operative performance of the two basic diagnostic tests, *i.e.*, colonoscopy and MRI enterography, is of paramount importance.

Intra-abdominal abscesses

Small abscesses are treated with antibiotics. Abscesses larger than 3 cm or multiple abscesses require percutaneous drainage combined with conservative treatment. Conservative treatment should precede since this allows the improvement of the general condition of the patient and is accompanied by fewer postoperative complications, fewer stoma, limitation of bowel resection, and higher rates of laparoscopic intervention[12]. The presence of a stricture and a

small portion of diseased bowel also require intervention with *in situ* drainage. The abscess is drained, enteral or parenteral nutrition and antibiotics are administered, and immunosuppressants are discontinued. After 2 wk, laparoscopic resection could be attempted.

Other surgical issues

An important clinical question is related to the preoperative factors that increase the length of postoperative hospital stay in patients who underwent surgery. In a very recently published study of a large number of patients (1710 with CD and 1291 with UC), it was found that clinically significant factors contributing to increased postoperative length of hospital stay were rectal surgery, creation of a new ileostomy, preoperative hospitalization, hypoalbuminemia and the presence of bleeding disorder. Of interest was the finding that chronic use of corticosteroids, immunosuppressants, and biological agents including orally administered small molecule drugs, was insignificant[13]. Another clinical question concerns the possible relationship between serum infliximab (IFX) levels and the presence of endoscopic recurrence in patients undergoing cecal and ileal resection for CD. In 21 patients who underwent ileocecal resection and were given IFX for 4 wk before or after surgery, serum IFX levels were determined concurrently with colonoscopy. Patients were divided into two groups according to the presence or absence of endoscopic recurrence. Of the 21 patients included in the study, 7 experienced endoscopic recurrence, and 14 did not. The results showed that patients with endoscopic recurrence had previously been treated with biological agents more often compared to the group of patients without endoscopic recurrence. No differences were observed concerning the median values of serum IFX levels between the two groups. This study suggests that low serum IFX levels are not associated with postoperative endoscopic recurrence[14].

Diarrhea is a common symptom in CD patients who have undergone segmental enterectomy, especially after removal of the terminal ileum and cecum. Since fecal calprotectin levels are within normal limits (meaning the absence of inflammation), the most likely mechanism responsible for the onset of diarrhea is bile salt malabsorption. In these cases, oral administration of cholestyramine is the appropriate therapeutic approach. Of course, other mechanisms are involved in the etiology of postoperative diarrhea, causing the clinical gastroenterologist to be called upon to deal with postoperatively[15].

SURGERY FOR LARGE BOWEL CD

In cases of CD involving the large bowel, resection of the affected part of the bowel is the method of choice. Surgical procedures include subtotal colectomy and segmental enterectomy. Of these, subtotal colectomy with end ileostomy and intraperitoneal rectal closure (Hartmann) can be performed in cases of colon involvement that does not respond to conservative treatment, and urgently in cases of toxic megacolon, perforation, or significant bleeding[16]. The time to perform the surgery is an important part of the therapeutic effort since sufficient and appropriate conservative treatment can save part of the large bowel, but also includes the risk of delaying the operation with significant consequences on the patient's situation and the occurrence of complications such as wound breakdown, the appearance of intra-abdominal abscesses, small bowel obstruction, ileostomy-related complications, and bleeding. However, a decrease in these complications (5%-10%) was noticed during the last years[17].

Surgical procedures in large bowel CD include subtotal colectomy and segmental enterectomy. Of these, ileocolonic resectomy with end ileostomy, and intraperitoneal rectal closure (Hartmann procedure) can be performed in cases of colon involvement that does not respond to conservative treatment, and urgently in cases of toxic megacolon, perforation, or significant bleeding[16]. The size of the resection depends on the extent of the disease and the presence of symptoms. In localized colon disease (single localization with involvement of less than one-third of the colon), the resection concerns only the affected part. Segmental resection has higher recurrence rates than proctocolectomy. Avoiding a permanent stoma outweighs the increased risk of recurrence. In cases of multi-segmental CD of the colon, two segmental resections are performed when the disease affects the proximal and distal segments of the colon and when two segments of the colon are significantly distant from each other. In these cases, a segmental resection with two anastomoses is performed. Subtotal colectomy with ileorectal anastomosis is performed when the disease affects the anion and the entire sigmoid. Alternatively, a separate segmental resection could be performed.

Ileocolonic resection is the most frequently performed type of surgery in CD patients with many types of techniques and anastomoses. Usually the recurrence of CD after ileocolonic anastomosis occurs without significant clinical symptoms, which means that the monitoring of patients mainly by checking the levels of calprotectin in the feces and with periodic colonoscopies should be done systematically. There are data to support that the application of this type of surgery can influence the occurrence or non-occurrence of postoperative recurrence[18].

Elective subtotal colectomy or segmental enterectomy is performed in treatment-resistant CD colonic involvement. Results in both procedures are similar although functional results may be superior to segmental enterectomy[19]. In cases of universal involvement of the colon operations include subtotal colectomy, or total colectomy with permanent ileostomy. An important issue regarding the surgical strategy and practice concerns the choice of performing proctocolectomy or simple proctectomy in patients with treatment-resistant Crohn's proctitis or proctocolitis. The operation is performed trans-sphincterically using the Transanal Minimally Invasive Surgery (TAMIS) technique in combination with laparoscopy[20]. The TAMIS technique achieves better access to the pelvic anatomy compared to the conventional abdominal approach. In CD located in the descending and/or sigmoid, a left hemicolectomy is applied. Sigmoid resection can be achieved using the top-down approach with laparotomy, laparoscopy, or *via* TAMIS. The TAMIS technique is also applied in cases of rectum deformed by scarring processes with a transanal approach or by combining a transabdominal laparoscopic or open technique, achieving preservation of the sphincter mechanisms of the anus.

In patients with severe refractory CD, proctectomy can be performed either through close rectal dissection leaving the mesorectum in situ, or through total mesorectal excision (TME)[21]. Stricturoplasty is not applied in the CD of the colon. The risk of the existence of a malignant neoplasm is quite high.

An important question that arises in the daily management of patients with ileocecal involvement of CD is whether early enterectomy should be performed, or drug therapy should be applied. There are some studies supporting the first version. Husnoo *et al*[22] in their most recently published systematic review and meta-analysis included a total of 8 studies, with 1867 patients. In the early intestinal resection group, they found a reduced need for drug therapy. The rate of bowel resection at 5 years was 7.8% in the early resection group and 25.4% in the drug-treated group. Even the early resection group (ileocecal resection of ileo-cecal-anion resection) showed longer survival without further surgery. These results suggest that early resection in selected patients with ileocolic CD represents a reliable alternative treatment[22]. Active CD of the small intestine with the simultaneous presence of an intra-abdominal abscess is treated with antibiotics and percutaneous or surgical drainage, as long as there are no obstructive symptoms, depending on the clinical case, followed by later resection.

The existing data support the assumption that ileocaecal resection is a reasonable treatment option in patients with limited CD who have failed conventional treatment. It should be pointed out that most studies comparing early surgery with the use of biological agents are retrospective and the criteria for selecting patients for one or the other treatment are unclear. Thus, patients who underwent early surgery had more severe symptoms and complications of the disease, making the comparison of the groups flawed. Furthermore, there is great heterogeneity in the definition of early surgery. Nevertheless, early surgery is considered safe and feasible and may be advantageous compared to surgery at a later stage.

The role of the mesentery

In recent years, the role of the mesentery in CD has been extensively discussed with controversial opinions. It has been argued that the mesentery may be involved in the pathogenesis of the disease since it contains an abundance of inflammatory cells, while others support the possibility that the changes seen in the mesentery are secondary. During either proctectomy or ileocolonic resection, the surgeon must decide whether or not to include the mesentery in the tissues to be removed through total mesorectal resection or close bowel resection. Supporters of the role of the mesentery believe that the fat around the diseased stenotic small intestine is colonized by microorganisms such as *Clostridium innocuum*, causing an inflammatory reaction with fat production and fibrosis[23]. On the other hand Coffey *et al*[24] claim that they observed significantly lower recurrence rates after ileocolonic resection and mesenterectomy (2.9%) compared to conventional, closed ileocolic resection (40%). However, these data should be accepted with caution since the groups compared had different follow-up and conservative treatment, much more since similar or even better results were observed with the Kono-S anastomosis, thus questioning the effect of this technique per se[25,26]. The so-called Kono-S anastomosis has gained significant surgical interest in the attempt to prevent the recurrence of CD. Also, the Kono-S technique (antimesenteric hand-sewn functional end-to-end anastomosis) seems to achieve very satisfactory results in reducing the recurrence rate of the anastomosis. Patient follow-up showed that anastomotic recurrence occurred in a small percentage of patients. This new approach is superior to stapled functional end-to-end anastomosis because the stumps are sewn together creating a stabilizing structure. The technique requires a careful mesenteric resection to obtain the best possible blood supply as well as preserve the innervation. The Kono-S technique prevents postoperative recurrences[27].

EMERGENCY SURGERY FOR CD

The surgical treatment of CD represents a challenge for the modern surgeon, who, to implement the most appropriate surgical intervention, must design an appropriate plan of action, after taking into account many clinical and laboratory parameters of the patient. Indications for surgical management of CD include poor response to conservative treatment and/or the occurrence of acute or chronic complications. Elective surgery is reserved for cases of obstructive phenomena that do not respond to conservative treatment. The main indications for emergency surgery are toxic megacolon, obstructive ileus, intestinal perforation, intra-abdominal abscess, and massive bleeding. These patients are usually immunosuppressed being treated with biological agents and/or immunosuppressants, possibly septic, with many nutritional deficits, that is, conditions that favor the occurrence of postoperative complications and a poor prognosis in terms of survival. Usually, however, the significant help provided during the surgical intervention with the administration of antibiotics, plasma whole blood, and fluid restoration, results in the successful completion of the operation. It should be emphasized that many of the patients require postoperative admission to an intensive care unit[28]. From the above, it becomes clear that for the complete and adequate treatment of the patient, the close cooperation of specialists consisting of gastroenterologist, surgeon, nutritionist, radiologist, and nurse specialized in the care and treatment of stoma is required. Individualized treatment is the basis of a successful therapeutic approach.

SURGERY FOR FIBROSTENOTIC CD

Regarding the fibrostenotic type of the disease, it appears that despite the introduction of biological agents into CD therapy, fibrostenotic bowel disease occurs in one-third of patients, thus increasing morbidity. Conservative treatment with biological agents and (short-term) corticosteroids is now considered the first-line treatment for inflammatory

strictures. However, conservative treatment does not significantly help in cases of strictures in which the fibrous element predominates. Many of these patients will eventually need surgery. Depending on the characteristics of the stenosis, endoscopic minimally invasive techniques such as endoscopic balloon dilation and endoscopic stricture plastic surgery performed in specialized centers are quite safe with little risk of complications. Surgery is indicated in patients considered unfit for endoscopic treatment[29].

Strictures of the digestive tract mainly concern the small intestine. In most cases, they concern the area of the ileocecal valve and less often other parts of the ileum or jejunum. Duodenal strictures due to CD are quite rare. The treatment of small bowel strictures includes stricteroplasty, surgical resection, and endoscopic dilatation. Plastic surgery of strictures with a conventional method should be done when the length of the stricture is less than 10 cm. In extensive disease with a large stenosis, non-conventional plastic methods should be applied due to the risk of losing a large part of the intestine.

Indications for plastic surgery of the strictures concern diffuse involvement of the small intestine with multiple strictures, stricture in patients who had undergone a previous large resection of the small intestine, rapid recurrence of the disease manifested as an obstruction, stricture in patients with short bowel syndrome, non-inflammatory fibrous bowel stenosis, and finally stenosis located in the duodenum. Contraindications to plastic surgery of strictures include free or hidden perforation, the existence of multiple strictures in a small part of the intestine, stricture near a part chosen for resection, stricture of the large bowel, and suspicion of the presence of cancer at the site of the stricture.

Endoscopic dilatation of strictures in patients with CD is the preferred technique for treating accessible, short-length strictures. It should only be performed with surgical coverage. It is an accepted technique for the treatment of mild or moderate stenotic disease. The results suggest a short- to medium-term benefit since it can delay surgery by up to 3 years on average. On the question of whether endoscopic dilatation or surgical excision of the narrowed part should be performed, the available data are not sufficient to provide a clear answer. A very recent retrospective study investigated the safety and efficacy of endoscopic balloon dilatation in patients with duodenal stenosis due to CD compared with surgery. Thirty patients underwent endoscopic dilatation and 18 underwent surgery. Patients in the operated group showed significant symptomatic improvement compared to patients in the endoscopic dilatation group as well as significantly longer recurrence-free survival at the cost of more postoperative adverse events (16.67% *vs* 0.74% respectively). Approximately 27% of patients who underwent endoscopic dilatation required surgery at a later stage. These results show that surgery in patients with duodenal stenosis due to CD offers longer recurrence-free survival. In contrast, endoscopic dilation is safe and effective with minimal side effects but is associated with frequent recurrences [30].

If the patient has previously undergone ileocolonic resection and a stricture has developed at the anastomosis, it is initially treated with endoscopic dilatation before resection. In the case of ileo-jejunal CD with recurrence in the ileocolonic area, stricturoplasty is a safe alternative to resection, with similar clinical results. When the disease is located in the duodenum, the only surgical intervention when deemed necessary is the bypass with gastroenteroanastomosis.

The presence of a clinical picture compatible with intestinal obstruction in a patient with CD is always worrying for both the gastroenterologist and the surgeon who will decide whether the patient will be taken to surgery or not. Regarding the etiology of incomplete small bowel obstruction, it seems that magnetic enterography and computed tomography offer significant help in the correct diagnosis by determining, among other things, the possible site of obstruction. Treatment with powerful anti-inflammatory drugs including biologic agents reduces the need for surgery in symptomatic CD of the small intestine in which the inflammatory component of the strictures predominates[31].

IAPA IN CD: IS IT FEASIBLE?

IAPA is classically applied only to patients suffering from UC. However, this surgical approach is also applied to a small proportion of carefully selected patients with CD to restore intestinal continuity in which there is no perianal disease, and the CD is located exclusively in the colon. In most cases, however, the presence of CD in the pouch is revealed either after a detailed examination of the colectomy surgical specimen, or during follow-up with the diagnosis established by endoscopy and biopsies taken on the occasion of pouchitis. Even in cases in which the preoperative diagnosis of the disease was indeed UC, 10% will present with inflammation of the pouch, the characteristics of which resemble CD. The diagnostic approach of patients with pouchitis resembling phenotypically CD should be based on the evaluation of risk factors predisposing to the appearance of the disease and the endoscopic picture of the pouch. Moreover, previous history, the histological picture, the location of the complications in the pouch, and the time of appearance of the complications will help in the correct diagnosis. However, the prognosis of CD diagnosed in a pouch performed in a patient with a previous diagnosis of UC is poor. In the future, this area should be systematically investigated both in terms of preventive and therapeutic strategies[32].

In the case of pouchitis due to CD, the underlying IBD is manifested either exclusively in the ileum, in the small intestine, or even as a perianal disease with characteristics similar to the classic disease (inflammatory, stenotic, fistulizing type). Treatment is usually conservative with biological agents. Because at least 60% of the pouches are not functioning properly, especially in cases of fistulizing disease or accompanying severe perianal disease, it is necessary to remove the pouch surgically. In uncomplicated patients, long-term outcomes are comparable to those of patients undergoing IAPA for UC[33].

In a recent review, Hassan *et al*[34] studied the functional postoperative outcomes as well as the type and impact of complications during long-term follow-up of patients with IBD. The data from 49 studies finally included in the study were analyzed. Regarding pouchitis, the median value of the incidence of chronic pouchitis and pouch failure was 17.1% and 6.9%, respectively. Multivariate analysis correlated the occurrence of pouchitis with preoperative corticosteroid use,

extensive UC, and the presence of extraintestinal manifestations. Regarding pouch failure they found in the multivariate analysis that it was significantly related to the preoperative diagnosis of CD, the development of perioperative pelvic septicemia, and the presence of anastomotic leak. The study also highlighted the long-term complications with the main representative being the multiple bowel movements per day. Despite all this, and given the high rate of long-term patient satisfaction, the gastroenterologist should recommend the operation after adequately informing the patient and his relatives regarding the long-term effects of the operation[34].

TREATMENT OF POUCHITIS

Very recently the relevant recommendations of the American Gastroenterological Association were published (2024). These guidelines suggest that, in patients with UC who have undergone IAPA and who present with intermittent symptoms of pouchitis, the use of antibiotics is recommended. Probiotics are also recommended for patients who respond to antibiotics but have frequent relapses. In patients who respond to antibiotics but relapse after discontinuation ("chronic antibiotic-dependent pouchitis"), chronic antibiotic use is recommended. Alternatively, immunosuppressants or immunomodulators (*e.g.*, biologic agents or oral small molecule drugs) can be used. In patients with recurrent pouchitis with inadequate response to antibiotics ("chronic antibiotic-dependent pouchitis"), the use of immunosuppressants, or biological agents, is recommended. Corticosteroids can be used as an alternative. The use of corticosteroids and immunosuppressants is recommended in the group of patients in whom IAPA was erroneously performed and who present a clinical and laboratory picture of pouchitis. In patients presenting with symptoms of cuffitis, the topical use of mesalazine and corticosteroids is recommended[35].

POSTOPERATIVE FOLLOW-UP AND TREATMENT OF CD PATIENTS

The Rutgeerts score was developed to predict disease progression based on postoperative endoscopic appearance and to guide medical therapy. However, this grading system groups ileal lesions and anastomotic lesions into the same category. The modified Rutgeerts score distinguishes lesions found in the anastomosis from those occurring in the neoterminal ileum. This system is expected to help in understanding the role of anastomotic lesions in the development of CD. Non-invasive diagnostic methods, such as small bowel ultrasound, are highly sensitive and specific in the hands of experienced specialists in detecting postoperative recurrences. Postoperative treatment with biological agents reduces the rate of endoscopic recurrence. However, preoperative treatment with anti-TNF-α agents may influence the postoperative response to these agents. New surgical techniques such as Kono-S (antimesenteric functional end-to-end anastomosis) may reduce postoperative recurrence rates[36].

The answer to the question of whether preoperative treatment with biological anti-TNF agents affects the rate of postoperative complications is not clear. In a systematic review and meta-analysis Cira *et al*[37] investigated the effect of treatment with anti-TNF-α agents applied during the previous 12 wk before surgery on the type and rate of postoperative complications occurring within 30 d postoperatively in patients with IBD. The authors chose the preoperative period of 12 wk since this is the period where the effect of the anti-TNF drugs is still present, although decreasing. This meta-analysis included 55 studies with a total of 22714 patients. Postoperative complications, readmission rate, and intra-abdominal septic complications were found to be significantly higher in patients who received preoperative anti-TNF-α agents. In addition, a significantly higher rate of intra-abdominal abscess development as well as hospital admissions was found in CD patients treated with anti-TNF-α agents. It was also found that concomitant use of immunosuppressants with anti-TNF-α agents was associated with a significantly lower mortality rate. It therefore appears that receiving anti-TNF-α agents within 12 wk preoperatively increases the short-term rate of postoperative complications in IBD and especially in CD patients[37].

It is known that after surgery for CD the disease recurs in a significant proportion six months after the surgery. Previous clinical studies including meta-analyses have demonstrated the good effectiveness of anti-TNF-α agents in the prevention of postoperative recurrences. In a recent review, Gisbert and Chaparro[38] describe data from 37 relevant studies with 1863 patients 29%, of which had proven endoscopic recurrence 6-12 months after surgery. They found that the combination of thiopurines with anti-TNF-α agents resulted in controversial results, but could potentially be tried in patients who had previously been treated with anti-TNF agents[38]. Also, a recent retrospective study noticed that among 1037 patients undergoing ileocolic resection for CD, 278 received postoperative biological agents as a maintenance treatment. It was found that early initiation of an anti-TNF-α agent within 4 wk after surgery, was associated with a reduced rate of postoperative recurrence[39]. IFX administered postoperatively does not differ in efficacy from adalimumab. There is no need to change the anti-TNF-α used preoperatively to another anti-TNF-α agent. The period of administration, although unspecified, should be long (months or years). If there is proven postoperative endoscopic and clinical recurrence, anti-TNF-α agents are the recommended choice. It therefore appears that postoperative use of biological agents reduces endoscopic and clinical disease recurrence. This is of particular importance in the group of patients at high risk for postoperative recurrence such as patients under 30 years of age, current smokers and patients who have previously undergone more than one operation mainly for perianal disease. With the data so far, it seems that the administration of anti-TNF-α agents for the prevention of postoperative relapse in CD patients should be preferred over the other biological agents. Vedolizumab seems to be quite effective in high-risk patients, while ustekinumab also appears to be effective but the data are relatively insufficient[38]. Further investigation is needed to explore the role of new biological agents in the postoperative management of CD patients. It should be noted that nitroimidazoles

(metronidazole and ornidazole) have been used successfully in the postoperative management of patients with CD, although the side effects of chronic administration of metronidazole and to a lesser extent ornidazole should be taken into account. Immunosuppressants of the thiopurine type also reduce the risk of clinical but not endoscopic recurrence.

MINIMALLY INVASIVE SURGERY IN PATIENTS WITH CD

In recent years, the application of minimally invasive surgery in the treatment of patients with CD has been an important step forward. The method presents significant advantages not only in terms of safety but also in other parameters such as reduced length of hospitalization, satisfactory aesthetic results, and the creation of fewer intra-abdominal adhesions which can create further clinical problems. Minimally invasive surgery is not only a modern but also a future challenge since it is an ideal method for patients with CD who, due to the nature of the disease, often present with thickened mesentery, fistulae, abscesses, and intra-abdominal masses. It seems that there are prospects for further defining the indications and results of its application as well as technical improvements and developments in the method itself[40].

Laparoscopic surgery should be preferred in case of ileocolic resection in CD when an experienced surgeon is available. In more difficult cases or when a second resection is required, there is no data in favor of the laparoscopic operation as the first choice. It is emphasized that the principles applied in the laparoscopic technique must be the same as in the open one. The minimally invasive surgical access is the element that differentiates and excels laparoscopy from open surgery. In cases of entero-intestinal fistulas, resection is performed only in the part of the intestine affected by the disease, while the intestine is sutured in one or two layers (the same applies to the intestine and the bladder). However, if both communicating parts are affected, *e.g.*, ileum/sigmoid then both are resected.

TREATMENT OF PERIANAL CD

Perianal disease, one of the most distressing complications of CD with a significant impact on quality of life, occurs in 25%-35% of CD cases increasing to approximately 40%, 20 years after initial diagnosis[41]. It can manifest as perianal fistula, fissures, skin tags, strictures, ulcerations, hemorrhoids, or malignancy. Fecal incontinence and pain are the most undesirable clinical features of the disease, which often force patients to seek hospital help. It is accompanied by significant morbidity and a significant reduction in the level of quality of life.

To successfully manage the patient with perianal fistula, a multidisciplinary team of specialists should be established (as repeatedly emphasized in various sections of this review) to achieve remission of the bowel lumen and fistula inflammation, as well as repair of the underlying dysfunction of the fistula[42]. Perianal fistula occurs in approximately 25% of patients with CD. MRI, colonoscopy, and examination under general anesthesia are necessary actions to categorize the patient with a fistula and choose the most appropriate therapeutic approach. The situation represents a diagnostic and therapeutic challenge for the team of specialists that deal with it since its various manifestations require a different therapeutic approach. Today, we indeed have a multitude of therapeutic options, namely conservative (antibiotics, immunosuppressants, biological agents, administration of stem cells), or surgical, all with specific indications depending on the peculiarities of each case. The existing conservative treatment options mainly include biological agents and immunosuppressants administered always under close clinical and laboratory monitoring. Surgical drainage of perineal abscesses before conservative treatment and seton placement are necessary actions. More permanent surgical access can be discussed, however, when the intense inflammatory phenomena subside. The use of stem cells is a promising approach in patients with CD perianal fistulae. Success rates of conservative and surgical treatment vary and failures are common[43]. The resistant nature of the disease indicates the need for a better classification as well as an understanding of its immunopathogenesis to rationalize therapeutic options in each case[44]. Successful management requires a delicate balance between the goal of eliminating the fistula and maintaining normal stool flow. Generally, surgical treatment must be conservative and based on the patient's cooperation, who should fully understand the purpose of the operation.

Various surgical approaches could be applied to treat symptomatic, simple, and low trans-sphincteric fistula, as well as those that cause severe symptoms. In general, extensive drainage and opening of fistulas as well as sphincterotomy are avoided. The main goal is the drainage of abscess cavities and the maintenance of open drainage channels by placing settons. The existence of intraabdominal fistulas is not a technical surgical problem. In addition to detaching the thick intestinal loop from the abdominal wall, the affected part of the bowel (small or large intestine and cecum) must be removed.

In the treatment of patients with complex perianal CD, surgical bypass of the passing stool stream from the rectum appears to help a certain proportion of patients, particularly in cases of treatment-resistant perianal disease. The data so far show that fecal bypass results in an early clinical response in the majority of patients although chances of restoring the fecal stream to the previous situation are very small (20%). About half of the patients in these cases need to undergo a proctectomy. The most important factor in treatment failure is rectal involvement by CD. Combining fecal diversion with biological agents does not improve diversion outcomes. Therefore, the bypass of the faecal stream finds its application as a treatment modality offering short clinical relief and avoiding immediate proctectomy. Despite initial disappointing results, the administration of biological agents alone or in combination (dual biological therapy) alongside fecal bypass should be evaluated in future studies[45].

In a recent multicenter retrospective study, the authors collected data from 197 patients with CD who had undergone rectal *in situ*-preserving fecal diversion surgery and for whom at least two years of follow-up data were available. At the end of the follow-up, 92 (46.7%) of the 197 patients, finally underwent a proctectomy, while 105 (53.3%) did not. Of these

105 patients, 50 (47.6%) underwent re-anastomosis while in the remaining 55 the rectal obstruction from the fecal stream still existed. Of these 55 patients, most still reported symptoms, while patients who underwent fecal flow restoration were symptomatic in approximately 50%. Of the total number of patients included in the study, three-quarters either underwent rectal removal or remained symptomatic. Finally, the percentage of patients in whom restoration of intestinal continuity was performed was 15%. Only 5% achieved re-anastomosis without disease recurrence[46].

Regarding the penetrating type of the disease, it is argued that appropriate surgical planning is expected to reduce the risk of penetrating disease caused by the disease itself or at the time of surgery, while it is expected to improve the disease in cases of already established penetrating disease. To achieve this goal, a careful preoperative evaluation of the patient should be performed, an improvement of the nutritional status should be achieved using enteral or parenteral nutrition, and any coexisting septic complication should be appropriately treated[47].

In conclusion, patients with fistulizing CD should be treated by a multidisciplinary team with the main participants being the gastroenterologist and the specialized digestive surgeon. Early recognition of fistulas is essential for the rapid implementation of therapeutic interventions. Endoscopic ultrasound helps to anatomically define the lesions and to perform drainage of coexisting septic collection. MRI of the perineum offers important diagnostic help not only in terms of the exact localization of lesions but also in monitoring the therapeutic results. Finally, the expected therapeutic effect should be discussed with the patient since complete healing or even improvement of the fistula disease is not always possible. Today, between chronic seton drainage, taking anti-TNF-α for one year, and surgical closure with a short course of anti-TNF-α in patients with high perianal Crohn's fistulas with a single internal opening anti-TNF-α or surgical closure of their high perianal fistula either administration of anti-TNF-α agents or surgical closure of the perianal fistula through various techniques is preferred[48].

COLORECTAL CANCER AND DYSPLASIA IN PATIENTS WITH IBD

It has long been known that patients with IBD and extensive bowel involvement are at increased risk of developing colorectal cancer (CRC) after several years from the onset of bowel disease. It appears that chronic intestinal inflammation is the main predisposing factor causing carcinogenesis through the creation of precancerous lesions (dysplasia) that ultimately progress to cancer. The molecular similarities with sporadic cancer are several (although not fully understood), including the gut microbiome and gut immune responses. The concept of cumulative inflammatory burden over time highlights the importance of ongoing monitoring for histological evidence of inflammation as a significant risk factor for CRC development in an IBD setting. Dysplasia is the most important precancerous condition for which early identification and removal can temporarily prevent surgical resection of the bowel[49]. We can predict and better manage CRC in IBD patients in the coming years since the widespread application of new anti-inflammatory drugs, better identification and removal of precancerous lesions, and better utilization of genetic, immunological, and environmental factors associated with carcinogenesis will become widely available[50].

Patients with IBD who have undergone colectomy and in whom the rectum remains *in situ* are at increased risk of developing cancer of the rectal stump. In a recent systematic review and meta-analysis of 23 studies of rectal stump cancer in operated IBD patients, Georganta *et al*[51] found that the overall incidence of rectal cancer was 1.3%, which is lower than reported. Further analysis showed that the incidence of carcinoma in patients with a nonfunctioning rectal stump and patients with an ileorectal anastomosis was 0.7% and 3.2%, respectively. Patients with a reported diagnosis of colorectal dysplasia, as well as patients with a positive history of colorectal carcinoma, had higher odds of developing rectal carcinoma. Since there are no clear guidelines regarding the screening of these patients, it is necessary to carry out relevant studies that will precisely determine the way and methods of performing the screening[51].

The risk of cancer in the rectal region as well as cancer of the distal rectum and anus in patients with perineal CD is increased. Patients should be treated (as has been emphasized elsewhere) multidisciplinary by a team of experts[52]. Examination under general anesthesia continues to be an important part of the diagnostic effort and subsequent therapeutic interventions. The role of intracanal ultrasound in experienced hands is quite significant in providing diagnostic information. Finally, the fact that perianal disease can develop after IAPA should not be overlooked.

As is known, the term interval cancer is defined as the cancer that develops in the colon of patients who underwent a screening colonoscopy in a short period after a negative initial colonoscopy. IBD patients are submitted to CRC screening programs because of the increased risk of developing dysplasia and CRC. Nevertheless, just as it happens in the case of the normal population, cases characterized as interval cancers can also appear during the surveillance of patients with IBD. Currently, there is insufficient information regarding the exact period of CRC diagnosis after a previous negative colonoscopy, and the factors favoring its appearance[53].

SPECIAL TOPICS IN THE SURGICAL TREATMENT OF CD

Appendectomy

The relationship between appendectomy and the clinical manifestation of UC is largely well-known. Existing data support that the performance of an appendectomy, especially if it was performed for acute appendicitis, exerts a protective effect against the appearance of UC. It is known that the appendix exerts an important immunological effect in both healthy individuals and those suffering from various diseases and that its removal entails important effects on the gut microbiome and immune responses. Recently, Zhang *et al*[54] published a systematic review and meta-analysis in

which the relationship of prior appendectomy and the onset and course of CD was evaluated. A total of 28 studies were included in their analysis. The authors found a positive association between prior appendectomy and risk of CD, and indeed the risk remained independent of the reason for which the appendectomy was performed (presence or absence of acute appendicitis). They also observed significant differences in the rates of histologic inflammation in the terminal ileum and colon of CD patients with prior appendectomy and CD patients who had not undergone prior appendectomy. These data suggest that the risk of developing CD, particularly of the terminal ileum, increases after appendectomy in contrast to what is observed in UC patients[54]. The same contrast between CD and UC patients is observed, as has also been known for a long time, about smoking habits. However, according to the author of this review, regarding the association of previous appendectomy and the occurrence of CD, it should be investigated if the surgery for acute appendicitis was performed erroneously and if the acute appendicitis was in fact due to *Yersinia enterocolitica* infection. In these cases, it is worth investigating the role of a possible *Yersinia enterocolitica* infection through the detection of YOP antibodies in the serum (western blot analysis)[55].

If terminal ileitis suggestive of CD is found at laparotomy for appendicitis, enterectomy should not be performed. A surgical finding of terminal ileitis or appendicitis should be considered as a non-specific finding. It is pointed out that the differential diagnosis from infectious enteritis (*e.g.*, *Yersinia species*) is impossible. Even if it is Crohn's ileitis, resection may not be indicated if the main character of the symptoms is inflammatory. Only when there are obstructive symptoms, or if the proximal bowel is distended and the inflamed bowel has a typical CD picture with mesenteric thickening is the surgeon justified in performing an enterectomy.

Haemorrhoidectomy

Regarding the performance or not of hemorrhoidectomy in patients with CD, the existing data are relatively insufficient. It is generally known that the standard practice of gastroenterologists is to avoid recommending hemorrhoidectomy in patients with CD because of the possibility of poor wound healing that may ultimately lead to proctectomy. A review of 4 studies analyzing data from 67 patients undergoing hemorrhoidectomy reported no cases of proctectomy or poor wound healing related to previous hemorrhoidectomy. Four (6%) cases of postoperative bleeding and 2 cases (3%) of postoperative perianal abscess were observed while 1 case developed anal stricture. These data suggest that hemorrhoidectomy can be performed in patients with CD provided that the disease is in endoscopic and clinical remission. In the future, prospective studies should prove whether the above conclusion is correct as well as what is the preferred type of surgical intervention[56].

Obesity

It is well established that IBD patients and especially CD patients, are obese, at least at the time of initial diagnosis of the disease. This phenomenon seems to exist also in the economically emerging countries of the world in which the incidence of IBD, as well as obesity, is on the rise. The role of obesity in IBD appears to be aggravating although the results are at least partially conflicting. Obesity is supported by most studies as negatively affecting the course of the disease, as well as the effectiveness of conservative and surgical treatment of patients while influencing medical and surgical treatments by promoting inflammatory reactions through pro-inflammatory cytokines produced by the adipose tissue. It is interesting to note that isolation of the mesentery from the surgical anastomosis *via* the KONO-S technique significantly reduces the rate of disease recurrence at the anastomotic site[57].

Some overweight IBD patients desire bariatric surgery to lose weight. The available scientific data regarding the effectiveness of bariatric surgery in patients with IBD is not clear. However, in a recent systematic review of 22 published relevant clinical trials, Mian and Khan[58] concluded that in patients with IBD, bariatric surgery is safe and effective as it results in significant weight loss at 6 and 12 months post-surgery, without significant side effects or effects on the underlying intestinal disease. However, when recommending bariatric surgery gastroenterologists should keep in mind that bariatric surgery itself may predispose to de novo IBD development[58].

Surgery for IBD in the elderly

There is a widespread impression among gastroenterologists that in elderly patients with exacerbation of underlying CD, surgery should be avoided, and if conservative treatment is preferred, immunosuppressants or biologic agents should be avoided for the fear of an increased incidence of side effects. Elderly patients indeed have much co-morbidity which may aggravate the underlying enteropathy. In addition, data for these patients are much less than for adult or pediatric patients because large studies usually exclude elderly patients. There is a misconception that elderly patients with CD are only treated with frequent and continuous steroid use, resulting in under-treatment. Surgery in the elderly should be performed safely as long as approved indications are met[59].

GENERAL RECOMMENDATIONS FOR THE SURGICAL TREATMENT OF CD PATIENTS

It is a fact that the introduction of biological agents into the therapeutic quiver has resulted in considering surgery in CD patients as a last resort. The result was the perpetuation of alternating therapeutic regimens with different biological agents and for long periods. However, the failure of these therapeutic regimes resulted in poor nutritional status, the appearance of complications, and greater clinical severity of the disease. An earlier prospective study showed that effective conservative treatment increases the rate of elective surgery, but at the cost of a significant increase in stricture and intestinal obstruction as indications for surgery as well as an increase in operations for acute conditions such as intestinal perforations and peritonitis[60], thus questioning what was previously published[61]. Today, it is considered

well-founded that early surgical resection in patients with limited disease unresponsive to conservative treatment is indicated since it is a feasible and safe option. Several guidelines now recommend it as an equal therapeutic alternative to medical treatment[62]. Preoperatively, patients should be in good nutritional status and, if possible, on reduced doses of corticosteroids. Patients with fistulas or abscesses are a particular therapeutic challenge whose surgical treatment includes extensive enterectomies, increasing the risk of complications, as well as the appearance of short bowel syndrome. Initial conservative treatment can limit the disease making surgery safer. If conservative treatment does not produce satisfactory results, surgery by an experienced surgeon is considered necessary and without time delays. The initiation of postoperative treatment with biological agents is recommended. The group of patients with strictures should be treated either endoscopically or surgically[63]. In these patients, insisting on the use of biological agents may delay surgery, but it cannot eliminate it as a possibility. Finally, in patients with short bowel syndrome, the application of conservative treatment methods such as the administration of home parenteral nutrition is indicated. Surgery should no longer be considered as a treatment of last resort for medically refractory or complicated CD but should be regarded as a satisfactory alternative in terms of efficacy, quality of life, and cost as first-line therapy or even as part of combination therapy with biologics agents, under certain conditions. Operated patients with CD should be checked periodically for the possibility of endoscopic recurrence, the early treatment of which is expected to have positive effects on the long-term outcome of the disease. However, it should be taken into account that there is no complete unanimity regarding the characterization of endoscopic lesions and their significance. The role of the continuously added new biologic agents in the prevention of postoperative complications is expected to be determined shortly. New surgical techniques, *e.g.*, the Kono-S technique, may improve postoperative recurrence rates.

SURGICAL TREATMENT OF UC

A better understanding of the natural history of UC, the possibilities and complications of drug therapy, and the creation of surgical modalities that preserve bowel continence with satisfactory quality of life have led to an expanded role for surgery in patient management since removal of the entire affected colon is the only treatment that achieves the definitive elimination of the disease, at the same time eliminating the possibility of developing of malignancy. The likelihood of colectomy in patients with UC depends on many factors. The severity of the disease, age, tolerance, and response to medication, as well as the degree of acceptance of surgical modalities by both patients and treating physicians, are important parameters that should be assessed before a patient with UC is guided to the operating room. In recent years there have been significant developments in surgical techniques (transvaginal surgery and robotics), indications for staged procedures, adoption of the multidisciplinary approach to the patient's problem, surgical alternatives to ileal pouch-anal anastomosis, and pharmaceutical treatment before and after surgery[64].

Regarding the rate of UC patients undergoing surgery, Dai *et al*[65] in a recent systematic review and meta-analysis of 31 studies including 294359 adult UC patients found that colectomy rates at 1, 5, and 10 years after diagnosis were 3%, 5%, and 10%, respectively. The pooled relative risk for colectomy after the introduction of biological agents into our pharmaceutical arsenal was 0.68 at 1 year and 0.71 at 5 years after diagnosis. It is therefore demonstrated that the overall colectomy rate in the last three decades has decreased to some extent and that the therapeutic use of biological agents has contributed to this decrease[65]. Biological factors, with the reduction of surgical intervention rates in patients with severe disease, have shifted surgical interventions in the direction of treating dysplastic lesions and colon cancer. Surgical treatment is still recommended in patients with severe extraintestinal manifestations such as pyoderma gangrenosum or in cases of hemolytic anemia resistant to cortisone and splenectomy.

The following conditions should also be evaluated before surgery: Patients undergoing colectomy who have been treated with at least 20 mg prednisolone daily for more than 6 wk, as well as patients treated with biological agents who do not respond to therapy, are initially treated with subtotal colectomy, due to the increased risk of surgical complications (five times the risk of infections and the pouch). Administration of azathioprine preoperatively does not increase the risk of postoperative complications. Colectomy performed immediately after cyclosporine administration does not have a greater risk of postoperative complications. Administration of anti-TNF agents may predispose to postoperative complications, especially in cases of emergency colectomy.

Scientific care of hospitalized patients with severe CD requires coordination among a multidisciplinary team[66]. If the patient does not improve, the digestive surgeon should be consulted. During hospitalization, there should be frequent communication between the gastroenterologist responsible for the patient and the surgeon who will take over the patient in case of surgery. This collaboration will make it possible to make joint decisions about the time of surgery, the regulation of the received conservative treatment, but also the planning of a coordinated postoperative course[67]. Table 2 shows the indications for surgery in UC patients.

EMERGENCY SURGERY FOR UC

UC may appear in a severe form either as an initial manifestation or during the progression of a disease that has already been diagnosed. Toxicity is clinically manifested by tachycardia, fever, pallor, lethargy, or collapse from dehydration or sepsis. Abdominal tenderness, hypotension, electrolyte disturbances, anemia, dehydration, confusion, and more than 8 bowel movements per 24 h are often present, which are often bloody. The clinical picture is not always complete, which may lead to an underestimation of the severity of the disease, especially in patients receiving immunosuppressives. So, the frequency of bowel movements is often reduced when a toxic megacolon develops, while the presence of decreased

Table 2 Main indications for surgery in ulcerative colitis

Indications	Treatment
Emergency situations	
Acute severe UC refractory to medical treatment	70% of patients will eventually need surgery
Uncontrollable sepsis	
Colonic perforation	Surgery – antibiotics
Toxic megacolon	Emergency operation
Severe bleeding	Emergency operation. Colectomy should not be delayed
Elective indications	
Dysplasia	Endoscopic surveillance with targeted biopsies for early detection. In cases of dysplasia endoscopic resection and continued surveillance. Surgery for unresectable dysplasia, and multi-focal low-grade dysplasia
Cancer	Surgical treatment
Medically refractory disease	Surgical treatment (preferably IAPA)

UC: Ulcerative colitis; IAPA: Ileo-anal-pouch anastomosis.

bowel sounds or abdominal tenderness often indicates severe disease even if the patient is relatively well. Worsening diarrhea or bleeding even when there is no acute abdomen is of equal value. Severe anemia, severe electrolytic disorders, dehydration, and impaired renal and/or liver function are parameters that reflect the severity of the disease. The therapeutic effect of treatment should be constantly clinically and laboratory evaluated. If the patient does not respond sufficiently or shows any serious complications, he is urgently taken to the operating room.

Today the mortality rate of severe UC attacks does not exceed 2%. This impressive change is due to the establishment of clear criteria for discontinuing the conservative treatment of severe disease in favor of early surgery, to the shift in surgical tactics from emergency proctocolectomy to subtotal colectomy with terminal ileostomy and preservation of the rectum, usually in the form of a mucous fistula at the level of sigmoid, as well as in preoperative treatment with cyclosporine and anti-TNF-α factors (IFX)[68].

Subtotal colectomy

The subtotal colectomy with end ileostomy and preservation of the rectum excised as a rectosigmoid mucosal fistula represents a good choice in emergency UC surgery for many surgeons. This type of operation is less traumatic because it removes the cause of the toxicity and allows the gradual discontinuation of medications, without requiring the creation of an anastomosis or manipulations in the inflamed pelvis, while leaving open all surgical possibilities later on. Moreover, it can be performed even by surgeons who have no special experience in UC surgery. Total colectomy with convergence of the Hartmann stump in the acute phase is indicated when there is a perforation in the rectosigmoid or when there is a very intense inflammation that prevents this part of the intestine from reaching the level of the abdominal wall and being excised[69]. In the acute phase, total proctocolectomy with permanent ileostomy usually has no place. It is an operation with significant morbidity and should be avoided.

Total proctocolectomy with permanent ileostomy

This kind of operation eliminates the disease as well as the need for medication, and the patient quickly returns to his work and activities. It can be performed one or two times if the first operation is performed urgently. The ileostomy is constructed at the level of the terminal ileum and is created in the right lower quadrant of the abdominal wall. The resection of the lower third of the rectum is performed in the trans-sphincteric space, thus allowing the integrity of the pelvic floor to be preserved, ensuring faster healing of the perineal wound. The operation can be applied to patients in poor general condition or very advanced age, with sphincter insufficiency, or those who cannot cope with the increased care required in the case of moderate ileostomy or ileoanal anastomosis. It is also the final solution when other interventions have failed[70]. In patients with malignancy of the middle or lower third of the rectum, it is (at least for some surgeons) the operation of choice.

This kind of operation is not without complications *e.g.*, bleeding, effusion, and delayed healing, especially when performed urgently. The main disadvantages of the method are the permanent ileostomy with medical (high flow, strictures) and social implications, the possibility of injury to the pelvic nerves, and the possible complications from the perineal trauma. An ileostomy is a cause of significant morbidity in 15% of cases, for which surgery is usually required *e.g.*, obstruction, or peristomal hernia. Other choices are local skin irritation (40%), water and electrolyte disturbances, and an increased incidence of nephrolithiasis and gallstones. Ultimately, however, patients gradually adapt and more than 90% achieve an almost normal life and declare themselves satisfied with the result.

Subtotal colectomy with ileorectal anastomosis

The operation was developed in an attempt to avoid ileostomy. The possibility of injuring the pelvic nerves is small and the patient avoids both permanent ileostomy and perineal trauma. Its functional results are acceptable, 4 or 5 bowel movements per day on average with periodic use of antidiarrheal drugs and a high degree of patient satisfaction (55%-89%). The best functional results seem to be achieved in patients with a relatively short duration of the disease. Overall, however, it appears that in experienced centers ileorectal anastomosis has no advantage in perioperative morbidity, continence, or long-term functional outcomes.

The procedure should not be performed at one time in emergency UC surgery, because of the increased chance of rupture of the anastomosis. The increased risk of developing neoplasia in the remaining rectum (6%-15%), is a serious disadvantage of the procedure since it requires lifelong endoscopic monitoring of the patients. Furthermore, technically, the ileorectal anastomosis assumes that the rectum has been relatively spared from the disease without showing significant fibrosis or reduction of its contractility and size, factors that further limit the indications for the intervention, which ultimately can only be applied to 20% of patients. A significant percentage (30%) of patients with an ileorectal anastomosis will experience significant problems from the rectum, eventually leading to resection and permanent ileostomy or IAPA. In this sense, subtotal colectomy with ileorectal anastomosis can be considered as an "intermediate operation" that postpones the definitive solution to the future, more specifically in young male patients who wish not to expose themselves to impairment of their sexual function, due to injury of the nerve plexuses during the preparation of the rectum. The complication rate after surgery is high due to the underlying chronic inflammation, the effect of corticosteroids and immunosuppressants as well as the inherent complexity of the surgical procedures. Postoperative complications are divided into early and late. Specific complications are associated with extensive surgical procedures such as proctocolectomy, or with complex reconstructive procedures such as ileoanal pouch and continent ileostomy[71].

IAPA

The disadvantages of proctocolectomy with permanent ileostomy, as well as functional problems and the possibility of developing rectal cancer after ileorectal anastomosis, led to the search for new surgical techniques. This operation corresponds to total colectomy and ileoanal anastomosis with the insertion of an artificial ileum made from the terminal ileum. The method has gained wide acceptance and application in recent years and is today the surgery of choice for UC patients, because it provides the patient with near-normal functionality in terms of defecation and continence, ensuring complete eradication of the disease[72].

Although it is a relatively complex surgery, the mortality rate is relatively low (less than 1%). On the contrary, the morbidity is significant (13%-58%). The nosological background and the use of corticosteroids are blamed for some of the complications, the great majority of which are directly related to the surgical technique. Nevertheless, the rate of complications is decreasing with experience. Contraindications to the intervention are disorders of the sphincter mechanism, the existence of known CD, the patient's mental instability, and his non-compliance with the postoperative treatment. Technical problems may be caused by the patient's body type and previous intra-abdominal operations. The presence of neoplasia should alter the operative strategy. If the malignancy is located in the lower third of the rectum, performing an ileoanal anastomosis is contraindicated, while in tumors of the upper rectum and colon, resection should be performed according to the rules of surgical oncology.

For the successful outcome of IAPA, it is essential that the pouch reaches the dentate line without tension and having adequate vascular supply. The surgical techniques that have occasionally been used are reported in a recent systematic review in which the authors analyzed the relevant data of 1181 patients included in 19 clinical studies. A total of six different surgical techniques aimed at mesenteric lengthening were described, such as pouch folding, construction of different types of pouches, stepladder incisions, skeletonization of vessels, division, and ligation of mesenteric vessels, and using an interposition vein graft. The disadvantage of these studies is the absence of randomization or prospective character[73].

Satisfactory results regarding continence during the day and solid stools are reported in the literature. Over 60% of patients report that the bowel movement is perfect, without pain and the patient can delay the bowel movement for at least 20-30 min. The results are not ideal in terms of nocturnal continence and it is not uncommon to experience minor leaks or even incontinence at bedtime. Bowel frequency and nocturnal continence improve during the first year after surgery. Patients average about 6 semi-formed bowel movements per day. Bowels are more frequent in elderly patients (patients over 50 have 8 ± 4 bowel movements per day, while patients under 50 have 6 ± 3 bowel movements per day). There is no difference in the number of bowel movements between men and women. Usually, patients do not need to empty the bladder during sleep, although one or two nocturnal bowel movements are acceptable. Complete incontinence rarely occurs.

Pouch complications could occur with the increased frequency following the application of minimally invasive techniques including laparoscopic and robotic surgery[74]. Recently, reoperation surgery in patients who have previously undergone IAPA has been developed to a satisfactory extent and is expected to improve the quality of life of patients without the need for a permanent stoma. In patients who develop pouchitis, fistulae, or obstruction, they may have CD which predisposes them to pouch failure. In these patients, re-operative access to the ileum can restore these complications by avoiding the removal of the pouch and the creation of a permanent or temporary stoma.

Of the reported postoperative complications, intestinal obstruction is the most common. It occurs in 10%-22% and requires surgical reoperation in a large percentage. Also common is the occurrence of pelvic sepsis (5%-6%), with or without leakage from the anastomosis, as well as the occurrence of intra-abdominal effusion (6%). It is especially important to exhaust all the types of conservative treatment before deciding to re-operate to deal with septic complications: 92% of those treated conservatively will manage to maintain the pouch. Stenosis of the ileoanal anastomosis (4%-

16%) is usually successfully treated and the pouch is preserved in more than 80% of patients presenting with this complication. Inflammation in the pouch (pouchitis) may develop. Conservative treatment in acute and chronic cases is relatively effective although quite complicated. Nevertheless, a small percentage of patients will need to undergo a permanent ileostomy due to non-response to conservative treatment[75].

The appearance of IAPA-related fistulae is one of the most important complications with serious morbidity (repeated surgeries) and significant effects on the preservation of the pouch. A recent systematic review and meta-analysis of 34 studies with 770 patients with IAPA-related fistulae found that the complication incidence ranged from 1.5%-12%. CD was the cause of pouch-vaginal fistula in one-fourth of the cases. Depending on the type of intervention, the overall fistula recurrence rate was 49.4% and was related to repeat IAPA, transvaginal repair, and transanal ileal pouch advancement flap. The overall failure rate was 19% and was related to pouch excision, persistence of diverting stoma, and persistent fistula. In conclusion, the study showed that pouch-vaginal fistulas are more frequent compared to other types of fistulae, often occurring in underlying CD. The risk of recurrence after surgical treatment is 50%. Repeated IAPA is the recommended surgical approach with a 50% recurrence rate[76].

From the technical point of view, it is known that to create the IAPA it is necessary to preserve a small part of the anal canal and the lower part of the rectum, parts which include the anal transition zone corresponding to a more circular part of the dentate line. This part together with the rectal cuff can present endoscopic and clinical pictures compatible with active UC as well as dysplastic precancerous lesions since their mucosa corresponds to colonic mucosa. Because of this, patients are required to be subject to systematic surveillance before and after surgery. The duration of surveillance depends on the presence or absence of dysplasia. In patients without precancerous lesions, monitoring can be done at sparse intervals. The treatment of patients with dysplasia in the anal transition zone is difficult and includes mucosectomy, pouch removal, or a redo pelvic pouch[77]. Restorative proctocolectomy with IAPA is also the surgical procedure of choice in patients with familial adenomatous polyposis[78].

In summary, IAPA significantly improves the quality of life of patients with IBD or familial polyposis. Preoperatively, patients should undergo a thorough evaluation that includes a review of all previous clinical and laboratory (colonoscopy, imaging, and histology) data, bowel cleansing, and the application of prophylactic therapy against deep vein thrombosis. The type of surgery (open, laparoscopic, or robotic) depends on the patient's condition, recent treatment, the urgency or non-urgency of the operation, and the degree of specialization of the surgeon. The most commonly preferred type of pouch is the J-shaped one. Good preoperative evaluation and good postoperative care of patients in centers experienced in performing the procedure are expected to reduce postoperative complications[79].

MINIMALLY INVASIVE SURGERY IN UC

The past three decades have seen significant advances in the use of minimally invasive techniques in UC patients. The safety, efficacy, and feasibility of performing laparoscopic and robotic approaches *e.g.*, subtotal colectomy, total proctocolectomy, and IAPA have been demonstrated through the publication of the results of several relevant studies. Compared to open procedures, minimally invasive techniques show equivalent or better short-term postoperative results as well as similar or improved bowel and sexual function, and fertility. It is emphasized that while minimally invasive techniques are safe and feasible in selected patients with UC, surgeons must adhere to the principles of proctectomy and pouch creation, and not hesitate to convert the operation to open if necessary[80]. These operations include the following categories: (1) Conventional; (2) Laparoscopic surgery; (3) Hand-assisted laparoscopic surgery; (4) Single incision laparoscopic surgery; and (5) Robotic surgery[40]. Minimally invasive techniques could also be applied in other conditions including uncomplicated small and ileocolonic disease, colon resections, complex CD, stricturoplasty, intracorporeal anastomosis, and natural orifice specimen extraction.

Transanal surgery

Transanal TME was initially used as a surgical technique to treat rectal cancer. Recently, this technique is also used in patients with IBD located in the rectal area. The most appropriate example is patients with rectal stenosis or extensive perianal disease, in whom removal of the rectum is indicated. The technical description is beyond the scope of this review, but it can be asserted with certainty that its application avoids injury to the pelvic nerves and internal iliac vessels. A good overview of the lower pelvis is possible while helping to overcome the difficulties of the anatomical surgical field of the pelvis.

In general, the developments of minimally invasive surgery that refer to the use of single port surgery together with transanal rectal surgery make it even more effective. In 2016, de Buck van Overstraeten *et al*[81] described a technical modification regarding single stapled anastomoses in patients with UC undergoing transanal completion proctectomy and IAPA. Regarding the technical part, they report that all 11 patients included in the study underwent total colectomy with terminal ileostomy in the first phase. Colectomy was performed by multiport laparoscopy in six patients, while in 5 patients the ileostomy site was used as single port access. For the construction of the pouch, the stoma was used to mobilize the root of the mesentery and transfigure the pouch. Completion of the proctectomy was performed transanally. All patients underwent simple suture anastomosis. This technique appears to greatly reduce the invasive character in UC patients undergoing IAPA[81].

Robotic surgery

All types of surgeries required in UC patients (subtotal colectomy and ileostomy, robotic IAPA anastomosis, total proctocolectomy) can be successfully performed using robotic surgery. The so-called "straight-stick" laparoscopy presents some

disadvantages which contribute, among others, to the failure of IAPA. The robotic platform aims to overcome these disadvantages. As a result, robotic subtotal colectomy presents lower conversion rates as well as a quick return to normal intestinal function. Robotic subtotal colectomy requires a longer operating time compared to laparoscopic subtotal colectomy, while it has satisfactory safety in experienced hands, even when performed urgently. Finally, it is accompanied by less blood loss and hospital stay[82]. The advantages mentioned above are particularly evident in surgical interventions involving the pelvic cavity, especially in men and obese patients in whom it offers satisfactory function of the genitourinary system. The disadvantages consist of the high cost of the method and the increase in surgical time compared to conventional laparoscopy.

In conclusion, minimally invasive surgery seems to become more and more popular over time. The inevitable need for the existence of specialized surgeons in the surgical treatment of patients with IBD also contributed to this. All data indicate the need for laparoscopic surgery to be performed by specialized and experienced surgeons. Gaining experience should be done gradually, starting with, for example, simpler technical procedures such as resection of strictures of the terminal ileum and expanding the indications to more complex situations, as experience increases. The decision to treat a patient with minimally invasive surgery should be made, based on the clinical characteristics of the patient and the level of expertise possessed by the surgeon. There is a need to conduct studies with a larger number of patients to adequately document the advantages of the method.

SPECIAL TOPICS IN THE SURGICAL TREATMENT OF UC

Haemorrhoidectomy in patients with UC: Should it be performed?

In a systematic review of 10 retrospective studies that included 222 patients, (54% with CD and 46% with UC) who underwent surgical hemorrhoidectomy (open or closed, elastic band ligation, resection or transection of thrombosed hemorrhoid, and doppler hemorrhoidal artery ligation in 70%, 18%, 6%, and 6%, respectively), some type of complication occurred in 9% (23 patients). The complication rate was more than twice as high in CD patients compared to UC patients. Existing data support that surgical treatment of hemorrhoids in patients with IBD and especially in patients with CD should be done with caution and in inactive disease. Further studies are needed to investigate the effect of applying other techniques[83].

IBD in pregnancy

Recent data suggest that all previous surgical procedures performed in female patients with IBD to treat the underlying intestinal disease including IAPA can affect pregnancy outcomes. Of interest is the finding that assisted reproductive technology in female IBD patients does not differ from that of normal women. However, existing data recommend that conception should be attempted during periods of remission. The gastroenterologist should ensure the maintenance of remission throughout pregnancy, a fact that will ensure the smooth progress of pregnancy and delivery[84].

Quality of life in operated IBD patients

It is proven that the quality of life of patients with IBD is significantly lower than in the general population and that the prevalence of depression and anxiety is higher, especially during disease flares. Repeated surgical interventions are not uncommon in the course of the disease resulting in further impairment of the quality of life of the patients. Patient-reported outcome measures are used to determine the degree of impact of the chronic disease on the patient's quality of life. The same approach can be used in the group of patients undergoing surgery, which is believed to help to more accurately assess the effect of different types of surgery on quality of life and also to assess postoperative improvement or deterioration[85].

Relationship between treatment with biological agents and occurrence of postoperative complications

The question regarding the relationship between the occurrence of postoperative complications and previous treatment with biological agents remains unanswered to some extent[86]. A meta-analysis of 20 studies, which included a total of 12494 patients of which 2254 received treatment with biological agents before surgery, attempts to answer this question. The odds ratios of infection-related complications (n = 8067) and total complications (n = 11869) were 0.98 and 1.14, respectively, suggesting that there was no statistically significant association between the use of biologic agents before surgery and the occurrence of postoperative complications. It was also found that the time interval between the last dose of the biologic agent and the time of surgery did not increase the risk of postoperative infection[87].

CONCLUSION

Surgical treatment of patients with CD and UC represents a life-saving way out for a large proportion of them. Epidemiological data concerning UC show that the overall colectomy rate has decreased over the last three decades by a significant percentage. It is argued that the introduction of biological agents into our pharmaceutical quiver has played a role in reducing the risk of colectomy. The indications for surgical treatment of UC primarily include cases of failure of conventional treatment as well as cases of the appearance of complications (perforation, severe bleeding, toxic megacolon) or high-degree dysplasia and cancer. Indications for surgical treatment of CD include acute and chronic complications (abscesses, peritonitis, fistulas) and cases of failure of the available conservative treatment. Elective surgery

is applied to patients resistant to medical treatment or patients with an obstructive phenotype. In patients with stenotic phenotype, surgery is indicated. In these patients, segmental resection and stricturoplasty have advantages and disadvantages. Kono-S anastomosis appears to be superior to conventional anastomosis. Surgical management of perianal CD is important for the patient's outcome. Drainage of the abscesses before immunosuppressive therapy and a seton placement are important therapeutic modalities. Subsequently, the decision for definitive surgical management of fistulae, advancement flaps, and ligation of intersphincteric fistula tract procedures is made, after the patient's inflammatory burden is removed. Realistic therapeutic goals and a patient-oriented therapeutic approach are vital factors in treating perianal CD. The use of risk stratification models is important to guide management decisions. Early postoperative medical prophylaxis with current therapeutic manipulations is important in preventing disease recurrence. Penetrating CD requires a broad multidisciplinary approach. Particular emphasis should be placed on nutrition, skincare, and management of intestinal failure. Early surgical treatment is currently desirable. Appropriate preoperative imaging, good conservative management and surgical decision-making based on the surgeon's experience and available evidence play a key role in the success of surgery. It is emphasized that a multidisciplinary medical approach to the patient by a team including surgeons, gastroenterologists, radiologists, nutritionists, and nurses specialized in stoma care is required to achieve the optimal therapeutic outcome. The management of emergencies should be individualized based on the patient's age, the type and duration of the disease, and the objective treatment goals of the specific patient.

FOOTNOTES

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EDITORIAL

Management of early oesophageal cancer: An overview

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Abstract

The incidence of esophageal cancer, namely the adenocarcinoma subtype, continues to increase exponentially on an annual basis. The indolent nature of the disease renders a significant proportion inoperable at first presentation, however, with the increased utilisation of endoscopy, many early lesions are now being identified which are suitable for endotherapeutic approaches. This article details the options available for dealing with early esophageal cancer by endoscopic mean obviating the need for surgery thereby avoiding the potential morbidity and mortality of such intervention.

Key Words: Esophageal cancer; Endotherapy; Endoscopic submucosal resection; Endoscopic mucosal resection; Endoscopy

Core Tip: Endoscopic treatment approaches have been adopted in managing early esophageal cancer in recent years. Endoscopic mucosal resection and endoscopic submucosal dissection are now considered at multidisciplinary discussions. Both are viable options and have replaced esophagectomy as the preferred treatment modality in certain cases as they are associated with reduced morbidity and mortality rates. Endotherapy is now the key treatment for early esophageal cancer with no compromise to oncological outcomes.

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INTRODUCTION

Oesophageal cancer poses a significant global health challenge with over 600000 new diagnoses and 540000 deaths annually[1]. In recent years, there has been a shift in the histological subtype seen in Europe and North America from squamous cell carcinoma (SCC) to adenocarcinoma[2]. The overall 5-year relative survival rate is around 20% but, if diagnosed early, outcomes can be significantly improved with cure rates of successfully treated early oesophageal cancer of over 80%[3,4]. Traditionally, oesophagectomy was the treatment modality of choice but is associated with high morbidity rates and potential mortality[5]. In recent years endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have offered a more favourable approach where suitable with comparable oncological outcomes[6]. This scientific paper provides an overview of the current literature surrounding the management of early oesophageal cancer. We aim to shed light on recent developments in diagnostic modalities, treatment strategies, and prognostic factors influencing the management of this disease.

Clinical work-up is required to accurately diagnose and stage oesophageal cancer to determine an appropriate treatment plan. Pre-treatment evaluation includes locoregional staging to assess the extension of the tumour into the oesophageal wall along with lymph nodes. Before employing an endoscopic treatment approach, it is important that there is negligible lymph node metastasis (LNM) and that an *en bloc* resection with negative margins is achievable. There is a significantly increased incidence of nodal disease with advancing T stage[7]. The oesophagus consists of three mucosal layers (epithelium, lamina propria, and muscularis mucosa) and a deeper submucosal layer made of connective tissue. The submucosa connects the mucosa to the muscularis propria. This consists of an inner circular muscle layer, outer longitudinal muscle layer and the Auerbach plexus. Invasion of the mucosa and submucosa is described as T1a and T1b disease respectively. T1a tumours have a negligible rate of regional disease on pathology compared with 16%-41% in T1b tumours[8-10]. Therefore, it is paramount to establish the exact level of invasion of the oesophageal wall. T1a invasion is further subcategorised into the deepest layer of mucosa involved; epithelium (m1), lamina propria (m2), and muscularis propria (m3). Likewise, T1b is subcategorised into inner third (sm1), middle third (sm2), and outer third (sm3) invasion of the submucosa.

As alluded to already, surgical resection has been the traditional curative treatment method in oesophageal cancer for years but endoscopic therapy is now increasingly the established gold standard in early carcinomas if there is no lymph node involvement. Other factors associated with LNM include tumour size > 2 cm and poor differentiation[9] and these would be considered along with the extent of oesophageal wall invasion at multidisciplinary discussions. Scoring algorithms have been described to predict patients most at risk of LNM to aid the decision-making process for endoscopic resection in patients with T1 oesophageal adenocarcinoma[11].

Clinically apparent regional and distant disease often require investigations such as cross-sectional imaging, positron emission tomography (PET) scans and endoscopic ultrasound (EUS) to appropriately stage the disease. The Society of Thoracic Surgeons published guidelines on staging oesophageal cancer[12]. PET scans detect metastatic disease in 15%-20% of patients and supplements computed tomography imaging in this regard[13]. Moreover, PET imaging has been shown to have prognostic value and aids treatment decision-making. EUS aids locoregional staging in the absence of distant metastasis and can guide treatment planning. This is particularly relevant in early oesophageal cancer as EUS has a reported sensitivity and specificity of 81.6% and 99.4% respectively for staging T1 tumours[14]. This is enhanced by the use of fine-needle aspiration or fine-needle biopsy along with EUS[15]. Chromoendoscopy and advanced endoscopic imaging techniques may also be employed where appropriate. For example, dye stains such as Lugol's iodine and acetic acid may be used for SCC and Barrett's esophagus respectively, while Narrow Band Imaging enables detailed evaluation of lesions.

EMR is one of the main endoscopic treatment options in early oesophageal cancer. It has replaced oesophagectomy as the treatment approach of choice in high-grade dysplastic Barrett's oesophagus, intramucosal cancer and sometimes in early invasive cancer if there is a low risk of LNM[16]. Although higher cure rates are achieved with oesophagectomy, the significant incidence of morbidity and mortality associated with this procedure must be considered at multidisciplinary discussions. Moreover, patients with a number of co-morbidities may not be suitable candidates for surgery. Curative endoscopic resection is achievable for mucosal carcinomas with comparable outcomes in adenocarcinomas and early SCCs and is now the first line treatment option in 'superficial' cancers as seen on endoscopy. EMR is limited by its inability to resect large lesions *en bloc* but is a simpler and faster technique than ESD. This is because there is a high rate of recurrence if EMR is performed on large lesions[17]. Moreover, histopathologic evaluation of tissue specimens to accurately stage a lesion and assess for R0 resection can be quite difficult.

EMR is highly efficacious in treating Barrett's oesophagus-related adenocarcinoma and thus, there is a limited role for ESD in these cases. Endoscopic ablation of Barrett's oesophagus is employed in patients with high-grade dysplasia with no visible lesion. However, EMR is the treatment of choice where this a visible neoplasia. This is because there is no significant difference between EMR and ESD in local recurrence rates, positive margins, LNM, complications, or need for surgery despite the limitations of EMR[18,19].

Endoscopic resection is the preference in m1 to m3 adenocarcinomas but this approach is chosen in patients with more favourable factors[20,21]. In sm1 carcinomas, endoscopic resection and oesophagectomy are both considered. The Japan Esophageal Society suggests performing endoscopic resection for m1 and m2 carcinomas. In m3 tumours, surgical, endoscopic or chemo/radiotherapy may be used and the general condition of the patient determines the treatment modality regardless of histopathological type or grade[22].

ESD was developed as an alternative to EMR facilitating *en bloc* resection and histopathologic assessment[23]. Despite being a more technically challenging procedure, ESD has *en bloc* resection rates of 83%-100%, complete resection rates of 78%-100%, and local recurrence rates of 0%-2.6% in superficial SCCs, and is now recommended in the European Society of Gastrointestinal Endoscopy guidelines[24]. Consequently, it is the preferred treatment approach in m1 and m2 disease.

Tumour morphology is important in selecting patients suitable for ESD. Paris classification of 0-IIa, 0-IIb, and 0-IIc are typically intramucosal and the Japan Esophageal Society have advocated Paris 0-II lesions with m1/m2 invasion and < 2/3 circumferential extent as absolute indications for endoscopic resection. This is due to the low risk of LNM in m1 and m2 tumours along with the previously mentioned morbidity and mortality associated with oesophagectomy.

Endoscopic treatment approaches are associated with some potential complications. Bleeding can occur immediately during the procedure or as a delayed consequence following the procedure. Prophylactic coagulation and prompt identification and treatment are essential for successful outcomes. All ESD knives have haemostatic capabilities. However, the hybrid knives have been shown to reduce the need for haemostatic devices and regular haemostasis compared with conventional knives[25]. Specific haemostatic devices may be necessary in larger vessels. Clips are reserved for uncontrolled bleeding as they may interfere with further dissection. ESD is associated with a higher risk of perforation when compared with EMR and has a reported incidence of 0%-6.9%[26]. Conservative decompression with a nasogastric tube and nutritional support may be required for successful management. Small defects of less than 1cm can be treated with by through the scope clips while defects of up to 2 cm may require over-the-scope clips[27]. Self-expanding metallic stents can also be used as a salvage option. Similarly, strictures are more common following ESD with those having dissection of more than a 75% circumference at higher risk. The treatment of a stricture includes endoscopic balloon dilatation which may be performed in conjunction with local steroid injection or temporal oesophageal stent placement.

Following endoscopic resection, prognosis and further management is based on histologic type, lesion depth, lesion size, lymphovascular or venous invasion and cut margin status. Any case with positive margins should be considered for an oesophagectomy[28]. There is no guidelines of the role of surveillance endoscopy in such cases but a watch and wait approach may be appropriate in patients with several co-morbidities.

CONCLUSION

In conclusion, endoscopic resection is a feasible treatment approach in early oesophageal cancers. Appropriate staging of lesions is crucial for judicious patient selection. ESD is associated with higher rates of *en bloc*, curative resections and lower recurrence rates compared to EMR. However, EMR is a perfectly viable option in some cases and has fewer complications. Hybrid techniques are being evaluated to combine the advantages of ESD and EMR.

FOOTNOTES

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ORIGINAL ARTICLE

Case Control Study

Clinical characteristics and risk factors of post-operative intestinal flora disorder following laparoscopic colonic surgery: A propensity-score-matching analysis

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Abstract

BACKGROUND

Intestinal flora disorder (IFD) poses a significant challenge after laparoscopic colonic surgery, and no standard criteria exists for its diagnosis and treatment.

AIM

To analyze the clinical features and risk factors of IFD.

METHODS

Patients with colon cancer receiving laparoscopic surgery were included using propensity-score-matching (PSM) methods. Based on the occurrence of IFD, patients were categorized into IFD and non-IFD groups. The clinical characteristics and treatment approaches for patients with IFD were analyzed. Multivariate regression analysis was performed to identify the risk factors of IFD.

RESULTS

The IFD incidence after laparoscopic surgery was 9.0% (97 of 1073 patients). After PSM, 97 and 194 patients were identified in the IFD and non-IFD groups, respectively. The most common symptoms of IFD were diarrhea and abdominal, typically occurring on post-operative days 3 and 4. All patients were managed conservatively, including modulation of the intestinal flora (90.7%), oral/intravenous application of vancomycin (74.2%), and insertion of a gastric/ileus tube for decompression (23.7%). Multivariate regression analysis identified that preoperative intestinal obstruction [odds ratio (OR) = 2.79, 95%CI: 1.04–7.47, P = 0.041] and post-operative antibiotics (OR = 8.57, 95%CI: 3.31–23.49, P < 0.001)

were independent risk factors for IFD, whereas pre-operative parenteral nutrition (OR = 0.12, 95%CI: 0.06–0.26, P < 0.001) emerged as a protective factor.

CONCLUSION
A stepwise approach of probiotics, vancomycin, and decompression could be an alternative treatment for IFD. Special attention is warranted post-operatively for patients with pre-operative obstruction or early use of antibiotics.

Key Words: Colon cancer, Laparoscopy; Intestinal flora disorder; Clinical characteristics; Risk factors

Core Tip: Intestinal flora disorders (IFD) pose challenges in laparoscopic colonectomy. This study provides a detailed analysis of IFD-related factors, offering valuable insights to improve clinical strategies. The results of this study have certain clinical practical significance. We summarized the clinical characteristics, management strategies, and prognosis of IFD in patients receiving laparoscopic colonectomy. The risk factors associated with IFD was also identified. This will help us focus on the subgroup of patients combined with risk factors during clinical practice and implement targeted preventive measures.

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INTRODUCTION

Laparoscopic radical surgery has been established as the standard of care for colon cancer[1,2]. The safety and efficacy of laparoscopic surgery are well demonstrated in several randomised controlled trials[3,4]; however, post-operative complications (POCs) continue to pose a major problem in clinical practice[5,6]. These POCs prolong hospitalisation, increase healthcare costs, and adversely affect subsequent treatments, thereby compromising therapeutic outcomes[6,7].

Paralytic ileus is one of the common POCs in abdominal surgery[8,9]. We observed in clinical practice that some patients initially present with diarrheal symptoms, which later progress to abdominal distention, nausea and vomiting, fever, and cessation of gas and stool passage. In fact, the above mention symptoms are actually different from the classic features of paralytic ileus. Based on clinical practice and experience, we therefore defined these clinical syndromes as intestinal flora disorder (IFD). IFD might thus contribute to the development of paralytic ileus.

The composition and function of the intestinal flora may influence the development and progression of colon cancer [10,11]. Alterations in the abundance of certain bacteria in the intestine have shown a potential association with colon cancer, with a significant reduction in the population of probiotics such as *Bifidobacteria* and *lactobacilli*, and an increase in the abundance of harmful bacteria[11,12]. This imbalance in bacteria types and populations of probiotics and harmful flora, caused by the tumour itself, surgery, and the application of antibiotics, is defined as IFD.

As a result, it might be promising to detect the association of IFD with paralytic ileus in the perspective of the alterations in intestinal flora. The absence of specific diagnostic standards for IFD necessitates a comprehensive evaluation based on clinical manifestations, laboratory tests, and imaging examinations. Despite numerous studies focused on POCs after laparoscopic colon surgery, those specifically addressing IFD are scarce. This retrospective study used propensity score matching (PSM) to analyse the clinical features and risk factors associated with IFD after laparoscopic colonic surgery at our hospital, in an effort to offer valuable insights for the diagnosis and treatment of IFD.

MATERIALS AND METHODS

Study design and patients

This retrospective PSM study included eligible patients with colon cancer admitted to the Department of General Surgery at Peking Union Medical College Hospital from January 2019 to October 2023. The inclusion criteria were: Histologically confirmed adenocarcinoma, including caecum, ascending, transverse, descending, or sigmoid colon cancer, and laparoscopic radical surgery. Exclusion criteria were: Simultaneous resection of hepatic metastatic lesions, concurrent occurrence of two or more POCs, open or conversion to open surgery, and incomplete clinical data. The patients were categorised into IFD and non-IFD groups based on the occurrence of POCs (Figure 1). This study was approved by the Ethics Committee of Peking Union Medical College Hospital (Approval No, I-23PJ157) and informed consent was

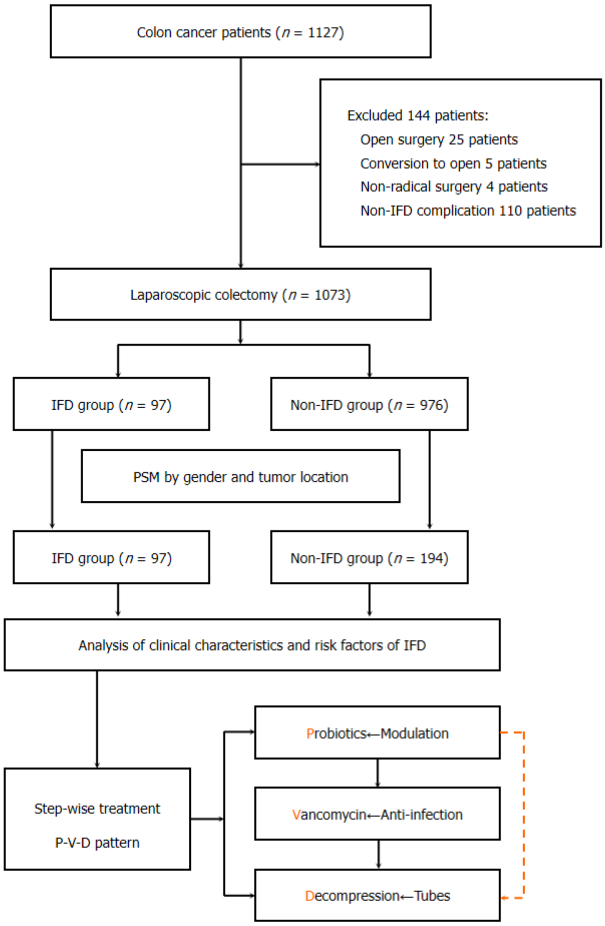

Figure 1 The flowchart of this study. P-V-D: Probiotics-Vancomycin-Decompression; PSM: Propensity score matching; IFD: Intestinal flora disorder.

obtained from all patients. The design and conduction of the study was strictly carried out according to the STROBE guidelines.

Clinical characteristics

Symptoms of intestinal obstruction were manifestations of incomplete ileus characterised by defecation issues, constipation, or abdominal pain observed during the patient's initial medical consultation. Computed tomography (CT) confirmed intestinal obstruction, revealing classic radiological features, including bowel dilation, gas accumulation, and fluid retention. Pre-operative colonoscopy was performed on the day of surgery or the day before for tumour re-localization or endoscopic removal of colonic polyps. All patients underwent mechanical bowel preparation using one to three packages of polyethylene glycol electrolyte solution. During mechanical bowel preparation, fluid replacement was administered to all patients the day before surgery. Fluid replacement options included enteral nutrition, parenteral nutrition, and glucose-sodium chloride solution. The post-operative use of antibiotics was confined to the day of surgery until the occurrence of IFD; any incidences of the application of oral or intravenous vancomycin for IFD were excluded.

Surgery

All patients underwent laparoscopic radical surgery for colon cancer, including right hemicolectomy, transverse colectomy, left hemicolectomy, or sigmoid colon resection. The surgeries were performed by the chief attending physician and their specialised team, with quality control ensured through a review of the surgical videos by two doctors.

IFD

The diagnostic criteria for IFD were based on a previous study by our team: (1) clinical manifestations: Symptoms included abdominal distension, diarrhoea (or a significant increase in colostomy output, appearing as a large volume of dark green "seawater-like stool"), fever, abdominal pain, nausea, and vomiting (with vomitus characterised by dark green or azure gastric contents). Additionally, some patients with diarrhoea may develop paralytic ileus, leading to reduced gas and stool passage, aggravated abdominal distension, and, in severe cases, sepsis and septic shock; (2) laboratory examinations: The stool test may reveal increased white blood cells. Stool smears may show an inversion in the ratio of rod-shaped bacteria and testing for *Clostridium difficile* toxins (A and B) may be positive. Routine blood examinations may indicate increased neutrophils and their ratio, along with elevated procalcitonin and C-reactive protein levels; and (3) imaging examinations: Abdominal radiography or CT scans may reveal significant dilatation of the intestinal lumen, intestinal wall oedema, and other features, such as multiple air-fluid levels. Some patients may develop ascites.

Radiologists reviewed all imaging findings of patients suspected of paralytic ileus owing to IFD, those with severe conditions of intestinal torsion or ischaemia were excluded. Typical images of patients with IFD are shown in Figure 2A-F [13].

IFD was graded using the Clavien–Dindo classification: Grade I: Requiring symptomatic treatment only; Grade II: Requiring antibiotics, blood transfusion, total parenteral nutrition, or placement of a gastric tube; Grade III: Requiring an intestinal obstruction tube. All patients had follow-up appointments within 1 month post-operatively to assess their recovery status upon discharge, conducted through outpatient visits and WeChat communication[14].

Treatment of IFD primarily involved conservative approaches[13]. Depending on the severity, therapeutic interventions included modulating the intestinal flora using probiotics, such as *Bifidobacteria* and *Licheniformis bacillus,* administration of oral or intravenous vancomycin for anti-infective treatment, or fasting, nutrition support, and gastrointestinal decompression. If symptoms persisted, interventional measures involves placing an ileus tube. The timing and duration of a gastric or ileus tube placement were documented.

Statistical analysis

Statistical analyses and graphical representations were conducted using SPSS 25.0 and R version 4.3.0. Categorical data were reported as counts and percentages *n* (%). Between-group comparisons were performed using the chi-squared test, as appropriate. Variables with a *P*-value less than 0.1 in the univariate analysis were included in the logistic regression analysis to calculate the odds ratio (OR) and 95%CI. A *P* value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Overall, 1127 patients with colon cancer were initially identified from our hospital's colorectal disease database. After excluding 144 ineligible patients, 1073 patients who underwent laparoscopic surgery were included, comprising 97 patients (9.0%) in the IFD group and 976 patients (91.0%) in the non-IFD group. Final enrolment comprised of 97 patients in the IFD group and 194 patients in the non-IFD group. After PSM, no differences were observed regarding baseline characteristics between the two groups (Table 1).

Characteristics of IFD

Among the 97 patients with IFD, the common symptoms were diarrhoea (51.6%) and abdominal distension (39.1%). In total, 49.6% of patients experienced IFD on post-operative days 3 and 4. Clavien–Dindo grades for IFD were as follows: I, 10 patients (10.3%); II, 76 patients (78.4%); and III, 11 patients (11.3%). Among these, 32 patients (50.7%) had faecal white blood cell counts exceeding 5/HPF. The positivity rate for detecting *C. difficile* toxins was 29.4% (15/51). All patients recovered after conservative treatment, with no secondary surgeries performed. Treatment measures included intestinal microbiota modulation by probiotics (88/97, 90.7%), oral vancomycin (72/97, 74.2%), and intravenous vancomycin administration (33/97, 34.0%). The most common application duration of vancomycin was 1 to 4 d.

Among the patients, 23.7% (23 of 97 patients) continued to experience unimproved symptoms despite the aforementioned treatments, necessitating gastrointestinal decompression. Gastric tube placement most commonly occurred on post-operative days 4–6, constituting approximately 73.9% of cases (17 of 23 patients). Additionally, symptom improvement within 3 d of gastric tube insertion was observed in 69.6% of patients (16 of 23 patients). Ileus tubes were required in 11.3% of patients (11 of 97 patients), with the most frequent placement timing on post-operative days 7–12. Among these patients, 63.6% (7 of 11 patients) experienced smooth removal after approximately 4 d of adequate drainage (Table 2). The colour of the tube drainage varied among patients, with dark brown, cerulean, and grass-green drainages observed. The signs mentioned above might be a clinical indication to consider the possibility of IFD after laparoscopic surgery (Figure 2G-I).

Additionally, we observed that the drainage volume gradually increased within the first 5 d following gastric tube placement, reaching its peak on the fifth day. Subsequently, the drainage volume in some patients gradually decreased to < 50 mL after symptom relief (Figure 3A). However, despite a reduction in drainage volume in a subset of patients, no apparent symptom alleviation was observed. In such cases, the placement of an ileus tube was deemed necessary. Following ileus tube placement, the drainage volume gradually decreased. For most patients, the drainage volume decreased to approximately 100 mL on the fourth to fifth days after the insertion of the ileus tube, prompting its removal (Figure 3B).

Univariate analysis

The characteristics such as age, symptoms of intestinal obstruction, pre-operative colonoscopy, polyp removal, operative time, blood loss, and stoma had no significant impact on IFD after laparoscopic surgery (all $P > 0.05$; Table 3).

Patients with pre-operative intestinal obstruction (OR = 0.29, 95%CI: 0.12–0.69, $P = 0.004$), pre-operative use of metronidazole (OR = 0.46, 95%CI: 0.28–0.75, $P = 0.002$), or post-operative antibiotics (OR = 0.16, 95%CI: 0.07–0.41, $P < 0.001$) were significantly associated with an increased risk of IFD. Compared to pre-operative enteral nutrition, initiating parenteral nutrition before surgery significantly reduced the risk of IFD (OR = 6.61, 95%CI: 3.35–13.03, $P < 0.001$).

Multivariate regression analysis

Multivariate analysis indicated that pre-operative intestinal obstruction (OR = 2.79, 95%CI: 1.04–7.47, $P = 0.041$) and post-

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

Factors	Before PSM				After PSM			
	Non-IFD (*n* = 976)	IFD (*n* = 97)	χ^2	*P* value	Non-IFD (*n* = 194)	IFD (*n* = 97)	χ^2	*P* value
Gender			6.831	0.009			0.000	1.000
Female	426 (43.6)	29 (29.9)			58 (29.9)	29 (29.9)		
Male	550 (56.4)	68 (70.1)			136 (70.1)	68 (70.1)		
Tumor locations			8.131	0.043			0.000	1.000
Asending colon	402 (41.2)	51 (52.6)			102 (52.6)	51 (52.6)		
Transverse colon	63 (6.5)	7 (7.2)			14 (7.2)	7 (7.2)		
Descending colon	395 (40.5)	25 (25.8)			50 (25.8)	25 (25.8)		
Sigmoid colon	116 (11.8)	14 (14.4)			28 (14.4)	14 (14.4)		
Age (yr)			2.060	0.151			0.063	0.801
< 65	499 (51.1)	57 (58.7)			111 (57.2)	57 (58.7)		
≥ 65	477 (48.9)	40 (41.3)			83 (42.8)	40 (41.3)		
ASA grade			1.336	0.248			0.248	0.619
I-II	888 (84.2)	86 (88.7)			168 (86.6)	86 (88.7)		
III-IV	154 (15.8)	11 (11.3)			26 (13.4)	11 (11.3)		
CEA			1.212	0.271			1.457	0.227
< 5 ng/mL	715 (73.3)	66 (68.1)			145 (77.7)	66 (68.1)		
≥ 5 ng/mL	261 (26.7)	31 (31.9)			49 (22.3)	31 (31.9)		
CA19-9			0.039	0.844			1.155	0.282
< 34 U/mL	852 (87.3)	84 (86.6)			176 (90.8)	84 (86.6)		
≥ 34 U/mL	124 (22.7)	13 (13.5)			18 (9.2)	13 (13.5)		
Hypertension (yes)	316 (32.4)	33 (34.0)	1.109	0.742	63 (32.5)	33 (34.0)	0.070	0.791
DM (yes)	198 (19.9)	18 (18.6)	0.098	0.755	26 (13.4)	18 (18.6)	1.339	0.247
CHD (yes)	98 (10.0)	10 (10.3)	0.007	0.933	10 (5.2)	10 (10.3)	2.685	0.101
Antiplatelet (yes)	89 (9.1)	9 (9.3)	0.003	0.956	10 (5.2)	9 (9.3)	1.802	0.179
Abdominal surgery (yes)	99 (10.1)	12 (12.4)	0.477	0.490	33 (17.1)	12 (12.4)	1.065	0.302

PSM: Propensity score matching; IFD: Intestinal flora disorder; ASA: American society of anesthesiologist; CEA: Carcino embryonic antigen; CA19-9: Carbohydrate antigen 19-9; DM: Diabetes mellitus; CHD: Coronary heart diseases.

operative antibiotics (OR = 8.57, 95%CI: 3.31–23.49, $P < 0.001$) were independent risk factors for IFD following laparoscopic colon surgery. Conversely, pre-operative parenteral nutrition support emerged as a protective factor against IFD after laparoscopic surgery (OR = 0.12, 95%CI: 0.06–0.26, $P < 0.001$; Figure 4).

DISCUSSION

IFD is a common complication of radical laparoscopic surgery for colon cancer. It manifests as a clinical syndrome with symptoms such as diarrhoea, abdominal distension, increased stoma output, intestinal obstruction, and fever[13,15,16]. The diagnosis of IFD lacks a gold standard, and relies on a comprehensive evaluation of clinical presentations, laboratory tests, and imaging examinations. IFD, particularly leading to paralytic ileus, prolongs hospitalisation, increases healthcare costs, and affects post-operative recovery and subsequent treatment[5,6]. Early identification, accurate diagnosis, and timely intervention are crucial for effective IFD management[17].

IFD predominantly emerges approximately the 3rd to 4th post-operative days, and it typically manifested within 1–2 wk [13]. Clinical presentations include abdominal distension, gas and stool passage cessation, reduced or absent of bowel sounds, and widespread intestinal dilation visible on abdominal CT scans with gas and fluid[18,19]. Given their significant role in post-operative paralytic ileus, early detection, accurate diagnosis, and prompt intervention are crucial

Table 2 The clinical features and treatment strategies of intestinal flora disorder, *n* (%)

Clinical features	Statistics
The first symptoms at the diagnosis of IFD	
Abdominal distension	38 (39.1)
Diarrhea	50 (51.6)
Fever	8 (8.3)
Septic shock	1 (1.0)
The occurrence timepoint of IFD	
POD 1-2	15 (15.4)
POD 3-4	48 (49.6)
POD 5-6	34 (36.0)
The routin stool tests (Yes/No)	63/34
The results of stool test (WBC/HPF)	
0-1	23 (36.6)
2-5	8 (12.7)
6-10	10 (15.9)
11-15	5 (7.9)
> 15	17 (26.9)
The detection of Clostridium difficile (Yes/No)	51/47
The results of Clostridium test (Positive/Negative)	15/36
Intestinal flora treatment (Yes/No)	88/9
Oral norvancomycin (Yes/No)	72/25
The duration of oral rvancomycin	
1-4 d	41 (56.9)
5-7 d	21 (29.2)
> 7 d	10 (13.9)
Venous vancomycin (Yes/No)	33/64
The duration of venous vancomycin	
1-4 d	15 (45.4)
5-7 d	13 (39.4)
> 7 d	5 (15.2)
The insertion of gastric tube (Yes/No)	23/74
The timepoint of insertion	
POD 1-3	6 (26.1)
POD 4-6	17 (73.9)
The duration of gastric tube	
1-3 d	16 (69.6)
4-7 d	7 (30.4)
The insertion of ileus tube (Yes/No)	11/86
The timepoint of insertion	
POD 5-7	4 (36.4)
POD 7-12	7 (63.6)
The duration of ileus tube	

4 d	7 (63.6)
6 d	2 (18.2)
≥ 7 d	2 (18.2)

IFD: Intestinal flora disorder; PSM: Propensity score matching; POD: Post-operative day; WBC: White blood cell; HPF: High power field.

Table 3 Uni-variate analysis after propensity score matching

Factors	IFD (*n* = 97)	Non-IFD (*n* = 194)	χ^2	OR (95%CI)	*P* value
Age (< 65/≥ 65 yr)	57/40	110/84	0.112	1.09 (0.66-1.78)	0.737
BMI (< 24/≥ 24 kg/m^2)	51/46	105/89	0.062	0.94 (0.58-1.53)	0.803
The systom of obstruction (No/Yes)	70/27	153/41	1.622	0.69 (0.40-1.22)	0.203
Total colonscopy (No/Yes)	43/54	73/121	1.211	1.32 (0.80-2.16)	0.271
The CFR occupation (≥ 1/2/< 1/2)	63/34	131/63	0.193	0.89 (0.53-1.49)	0.660
Neoadjuvant therapy (No/Yes)	91/6	181/11	0.031	0.91 (0.33-2.54)	0.860
Colonscopy pre-surgery (No/Yes)	71/26	151/43	0.769	0.78 (0.44-1.37)	0.380
Re-location pre-surgery (No/Yes)	76/21	166/28	2.405	0.61 (0.33-1.14)	0.121
Polypectomy pre-surgery (No/Yes)	83/14	172/22	0.571	0.76 (0.37-1.56)	0.450
Obstruction pre-surgery (No/Yes)	83/14	185/9	8.521	0.29 (0.12-0.69)	0.004
PGEP (1-2/3 packages)	63/34	139/55	1.368	1.36 (0.81-2.30)	0.243
Cephingosporins pre-surgery (No/Yes)	87/10	159/35	2.957	1.92 (0.90-4.05)	0.085
Metronidazole pre-surgery (No/Yes)	49/48	134/60	9.541	0.46 (0.28-0.75)	0.002
Operation duration (≥ 130/< 130 min)	48/49	102/92	0.248	0.88 (0.54-1.44)	0.619
Total blood loss (≥ 20/< 20 mL)	66/31	138/56	0.295	0.86 (0.51-1.46)	0.587
Stoma (No/Yes)	93/4	192/2	1.723	0.24 (0.04-1.35)	0.189
Antibotics post-surgery (No/Yes)	79/18	187/7	18.401	0.16 (0.07-0.41)	< 0.001
Nutrition supply pre-surgery, *n* (%)			33.880		< 0.001
EN	42 (43.3)	37 (19.1)		1 (Refrence)	
PN	17 (17.5)	99 (51.0)		6.61(3.35-13.03)	
GNS	38 (39.2)	58 (29.9)		1.73 (0.95-3.16)	

IFD: Intestinal flora disorder; BMI: Body mass index; CFR: Circumferential range; PGEP: Polyethylene glycol electrolytes powder; EN: Enteral nutrition; PN: Parenteral nutrition; GNS: Glucose and sodium chloride injection.

for IFD management.

Currently, laboratory tests for diagnosing IFD lack high specificity. Common methods include routine stool examination and testing for *C. difficile* toxins; however, the overall detection rates and clinical relevance are limited[20,21]. In this study, the positivity rate for *C. difficile* toxins in patients was only 29.4%, slightly higher than rates reported in previous studies[22]. However, this positivity did not correlate significantly with disease severity, post-operative length of stay, or gastric or intestinal obstruction tube insertion. Besides, though the positivity rate of *C. difficile* toxins was as low as 30%, most of the patients could benefit from the administration of vancomycin, suggesting the important role of anti-infectious in the management of IFD. This emphasises the constraints associated with relying exclusively on these diagnostic measures.

IFD should primarily be managed conservatively to prevent progression to the point of surgical intervention[23]. Additionally, we observed that the drainage volume gradually increased within the first 5 d following gastric tube placement, reaching its peak on the fifth day. Our team developed a three-step treatment approach involving the modulation of intestinal flora through the application of *Bifidobacteria* and *L. bacillus*, anti-infectious therapy with oral or intravenous vancomycin, and decompression drainage with a nasal gastric tube or ileus tube[13,24]. Consequently, the aforementioned treatment measures can be summarised as "P (Probiotics)-V (Vancomycin)-D (Decompression)". This stepwise approach of P-V-D, tailored to disease severity, has demonstrated satisfactory outcomes.

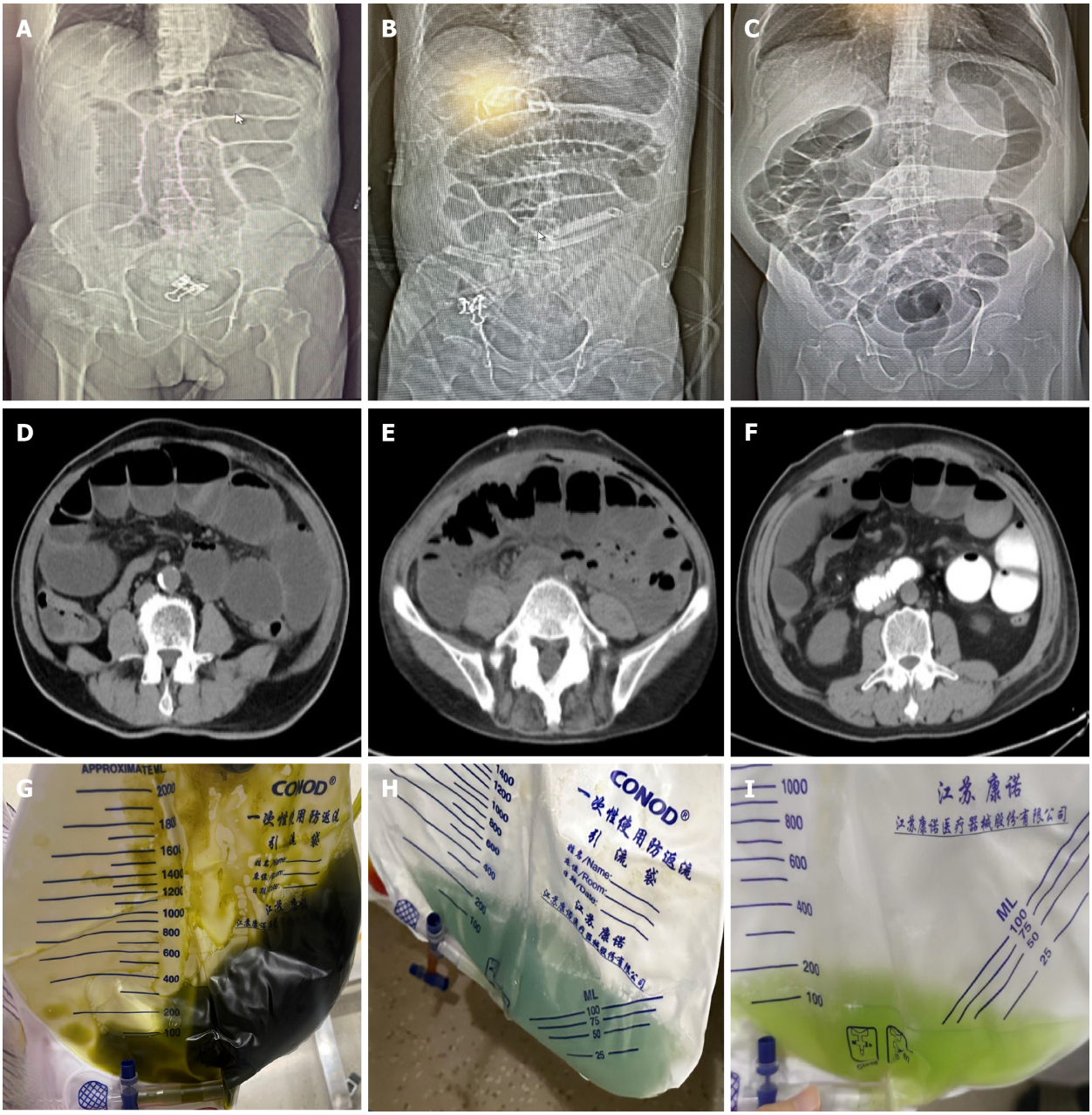

Figure 2 The typical images of patients with intestinal flora disorder. A-C: Depict typical abdominal X-ray findings of intestinal flora disorder patients, with extremely enlarged intestine; D-F: Represent classic computed tomography images, extensive intestinal gas and fluid accumulation are evident within the small bowel, accompanied by the presence of an air-fluid level; G-I: Represent the typical colour of the tube drainage, that are dark brown, cerulean blue and grass green.

Early recognition of IFD risk factors is clinically significant[25]. Our study revealed that pre-operative intestinal obstruction and early post-operative antibiotics significantly increased the risk of IFD after laparoscopic surgery. Conversely, pre-operative parenteral nutritional support during mechanical bowel preparation significantly reduced the risk of post-operative IFD, compared to enteral nutrition.

Colon cancer, primarily presenting as a mass, often occupies more than half of the intestinal lumen at the time of diagnosis[26]. Patients with pre-operative intestinal obstruction resulting from tumour-induced luminal obstruction may experience bacterial overgrowth and increased intestinal pressure, potentially leading to bacterial translocation[27,28]. Surgical removal of the tumour can alleviate the obstruction, causing a sudden metabolic shift and disrupting the epithelial barrier, resulting in microbial dysbiosis. Alterations in the gut microbiota microenvironment during the early stages of disease contribute to IFD[29]. Previous studies have demonstrated an association between pre-operative intestinal obstruction and post-operative IFD[25,30]. A retrospective study involving 1366 patients with colorectal cancer reported a post-operative ileus rate of 5.1%, with multivariate analysis indicating that pre-operative intestinal obstruction was an independent risk factor for post-operative ileus[30].

Mechanical bowel preparation, which is effective in clearing faeces and cleaning the bowel, may alter the composition and quantity of the gut microbiota. Pre-operative parenteral nutrition during the bowel preparation period provides the intestinal mucosa with adequate nutrition, preventing mucosal malnutrition owing to prolonged fasting post-operatively [31,32]. This approach avoids disrupting the microbial colonisation of the mucosa. Perioperative antibiotics are

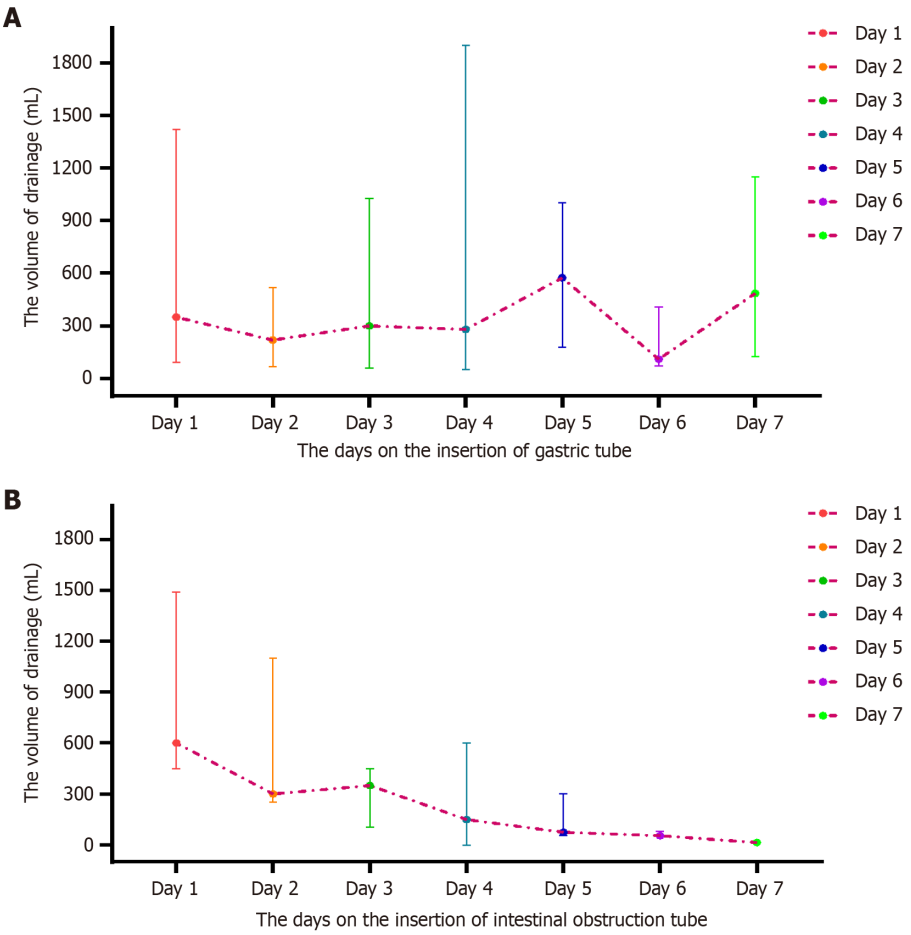

Figure 3 The overall drainage volume of patients receiving decompression. A: Gastric tube; B: The intestinal obstruction tube.

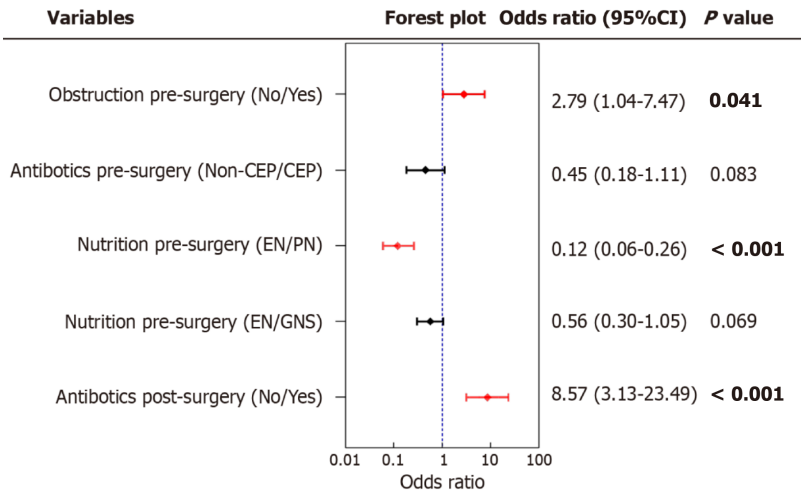

Figure 4 The multivariate analysis of factor affecting the incidence of intestinal flora disorder. CEP: Cephalosporin; EN: Enteral nutrition; PN: Parenteral nutrition; GNS: Glucose and sodium chloride injection.

recommended in the 0.5-2 h before surgery and are not routinely administered as prophylactic antimicrobial therapy. Multivariate analysis revealed that early post-operative application of antibiotics was an independent risk factor for IFD, possibly associated with the impact of broad-spectrum antibiotics on the distribution and composition of the gut microbiota.

The study also had certain limitations. First, as a retrospective study, despite ensuring an extent of baseline data consistency through PSM, we could not completely avoid potential inclusion bias. Further clarification is necessary through prospective cohort studies. Second, we were limited by the current lack of a gold standard for the clinical diagnosis of IFD, leading to a lack of uniform criteria among researchers when assessing IFD. Finally, establishing a clear

causal relationship between IFD and postoperative paralytic ileus is challenging through specific examinations or tests.

CONCLUSION

In conclusion, patients with pre-operative intestinal obstruction, or those exposed to early post-operative antibiotics, should be monitored for potential IFD occurrence. Administering parenteral nutrition before surgery may reduce the risk of IFD. A stepwise and comprehensive "P-V-D" treatment approach of focusing on "modulating intestinal flora, anti-infectious therapy, decompression by applying a gastric or ileus tube", demonstrated clinical efficacy and can be applied to IFD management.

FOOTNOTES

Author contributions: Li GB and Wang CT contributed equally to this study, they are co-first authors of this manuscript. Li GB, Wang CT and Lin GL conceptualized and designed the research; Li GB, Wang CT, Zhang X, Qiu XY, Lu JY, Xu L, Wu B, Xiao Y, and Lin GL screened patients and acquired clinical data; Li GB, Wang CT, Zhang X, and Chen WJ collected the clinical data; Li GB and Wang CT performed Data analysis, wrote the paper. All the authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Comparing short-term outcomes of robot-assisted and conventional laparoscopic total mesorectal excision surgery for rectal cancer in elderly patients

Hao Yang, Gang Yang, Wen-Ya Wu, Fang Wang, Xue-Quan Yao, Xiao-Yu Wu

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Abstract

BACKGROUND

Da Vinci Robotics-assisted total mesorectal excision (TME) surgery for rectal cancer is becoming more widely used. There is no strong evidence that robotic-assisted surgery and laparoscopic surgery have similar outcomes in elderly patients with TME for rectal cancer.

AIM

To determine the improved oncological outcomes and short-term efficacy of robot-assisted surgery in elderly patients undergoing TME surgery.

METHODS

A retrospective study of the clinical pathology and follow-up of elderly patients who underwent TME surgery at the Department of Gastrointestinal Oncology at the Affiliated Hospital of Nanjing University of Chinese Medicine was conducted from March 2020 through September 2023. The patients were divided into a robot-assisted group (the R-TME group) and a laparoscopic group (the L-TME group), and the short-term efficacy of the two groups was compared.

RESULTS

There were 45 elderly patients (≥ 60 years) in the R-TME group and 50 elderly patients (≥ 60 years) in the L-TME group. There were no differences in demo-

graphics, conversion rates, or postoperative complication rates. The L-TME group had a longer surgical time than the R-TME group [145 (125, 187.5) *vs* 180 (148.75, 206.25) min, $P = 0.005$), and the first postoperative meal time in the L-TME group was longer than that in the R-TME (4 *vs* 3 d, $P = 0.048$). Among the sex and body mass index (BMI) subgroups, the R-TME group had better out-comes than did the L-TME group in terms of operation time ($P = 0.042$) and intraoperative assessment of bleeding ($P = 0.042$). In the high BMI group, catheter removal occurred earlier in the R-TME group than in the L-TME group (3 *vs* 4 d, $P = 0.001$), and autonomous voiding function was restored.

CONCLUSION
The curative effect and short-term efficacy of robot-assisted TME surgery for elderly patients with rectal cancer are similar to those of laparoscopic TME surgery; however, robotic-assisted surgery has better short-term outcomes for individuals with risk factors such as obesity and pelvic stenosis. Optimizing the learning curve can shorten the operation time, reduce the recovery time of gastrointestinal function, and improve the prognosis.

Key Words: Robotic surgery; Laparoscopy; Rectal cancer; Total mesorectal excision; Elderly

Core Tip: Previous studies have shown that laparoscopic total mesorectal excision (TME) surgery for rectal cancer has been widely used worldwide. Robotic-assisted systems are capable of achieving finer anatomical manipulation and better surgical outcomes with high-definition cameras, but TME surgery has not been widely promoted in elderly rectal cancer patients. In this retrospective study, we enrich the evidence that robotic-assisted systems deserve to be widely used over laparoscopy.

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INTRODUCTION

Colorectal cancer has the third highest incidence and second highest mortality rate in the world[1]. The incidence rate in elderly patients is also gradually increasing. The treatment of choice for rectal cancer is surgical resection. Total mesorectal excision (TME), defined by sharp dissection and complete removal of the rectal mesentery envelope in the rectum, is the gold standard surgical treatment for rectal cancer, and it provides excellent control of local recurrence and overall survival[2,3]. To date, TME surgery has been frequently performed with the aid of laparoscopic techniques[4]. However, the evaluation of laparoscopic rectal cancer resection is not comprehensive and remains controversial. The main concerns are damage to adjacent tissues and the fact that tumor clearance and the number of dissected lymph nodes, which are markers of surgical su-ccess, may not be comparable to those of open surgery[5]. With robot-assisted surgery, the patient's vision becomes in-creasingly wider, which may effectively remedy the limitations of laparoscopy. Pigazzi *et al*[6] first described robot-assisted laparoscopic TME surgery for rectal cancer in 2006, and since then, robot-assisted laparoscopic surgery for rectal cancer has been widely used. However, there is still a lack of large, multicenter, randomized, controlled clinical trials demonstrating the clear superiority of robotic assistance over laparoscopic techniques in TME surgery. Moreover, due to the unique physical characteristics of elderly patients, they may have poor cardiopulmonary function, and there is still a lack of evidence demonstrating the advantages of these two surgical methods for resection of elderly rectal cancer patients. Therefore, we enrolled elderly rectal cancer patients from the Department of Gastrointestinal Oncology at the Affiliated Hospital of Nanjing University of Chinese Medicine from March 2020 to April 2023 and observed and com-pared the short-term outcomes of robotic-assisted and conventional laparoscopy in geriatric TME surgery.

MATERIALS AND METHODS

This retrospective cohort study was approved by the Institutional Review Board of Nanjing University of Chinese Medicine Hospital. Due to the retrospective nature of the study, the requirement for informed consent was waived.

Patients

The study reviewed the data of elderly patients who underwent rectal TME between March 2020 and September 2023 using laparoscopic or robotic approaches. The inclusion criteria for patients were as follows: (1) Rectal adenocarcinoma confirmed by preoperative or postoperative pathology; (2) aged ≥ 60 years; and (3) had a preoperative examination ex-

cluding distant metastasis. Exclusion criteria: (1) emergency surgical treatment due to acute intestinal obstruction; (2) multiple primary colorectal malignancies; (3) local resection; (4) history of other malignant tumors; (5) the American society of anesthesiologists [American Society of Anesthesiologists (ASA)] score > III; (6) preoperative treatment other than neoadjuvant therapy; (7) palliative resection; and (8) transvaginal surgery. Patients were divided into robot and laparoscopic groups according to the surgical treatment equipment.

The patient data used in this study came from the medical records of our hospital. These data were retrospectively analyzed and included information on patient characteristics, perioperative data, severity of complications according to the Clavien–Dindo classification, and pathology. Finally, 95 elderly patients with rectal cancer were enrolled in this study. Forty-five patients were assigned to the R-TME group, and another 50 were assigned to the L-TME group.

Surgical methods

This study was performed at a single center, and both the conventional laparoscopic and robotic approaches were managed by the same surgical team, who performed more than 2000 Laparoscopic-assisted surgeries. All patients voluntarily chose the surgical approach to which they wanted to be subjected. All patients included in the study underwent TME, abdominal lymph node dissection, and pelvic autonomic nerve preservation. The scope of surgery was the same for robot-assisted and laparoscopic procedures, and all procedures were performed in the colonic and pelvic stages. The colon phase includes submesenteric artery and vein ligation and left mesenteric mobilization; the pelvic phase includes pelvic dissection using TME or tumor-specific mesenterectomy principles and enterostomy with double anastomosis or hand-stitched coloanal suture; and when incisions are made for any reason other than specimen extraction, open surgery may be considered instead. Preventive ostomy was performed at the discretion of the surgeon.

Outcome measures

In this study, the outcome parameters were: operation time, conversion to laparotomy, transfusion, intraoperative bleeding, stoma condition, number of lymph node dissection, nature of pathological circumferential margin, time to recovery of intestinal function was assessed by first eating a liquid diet, postoperative hospital stay, drainage tube removal time, Foley catheter removal time, postoperative complications. Postoperative complications, reoperations, and mortality were defined as events that occurred during postoperative hospitalization or within 30 days after surgery. Postoperative complications were classified by the Clavien-Dindo (CD) classification. All of these events were assessed by clinicians and recorded in a database.

Statistical analyses

All statistical analyses were performed using SPSS (statistical Product and Service Solutions version 25.0; IBM Corporation, Armonk, NY, United States). Quantitative data that conformed to normal distribution were expressed as mean ± SD, and quantitative data that did not conform to normal distribution were expressed as Md (Q1, Q3) (Md stands for the median, Q1 for the 25th percentile of all values in the sample ranked in descending order, and Q3 for the 75th percentile of all values in the sample ranked in descending order), and the hypotheses of the above data were tested using the *t*-test and rank-sum test, respectively. Categorical data are presented as the number of cases and percentages, and chi-square (χ^2) or Fisher's exact tests were used to test the hypothesis. Univariate and multifactorial logistic analyses were used to correct for confounders and to predict factors influencing complications. Statistical significance was considered to exist when $P < 0.05$.

RESULTS

Comparison of baseline data between two groups of patients

There were 95 patients who met the criteria, 45 in the R-TME group and 50 in the L-TME group. Table 1 The baseline characteristics of the overall cohort are shown. There were no significant differences ($P > 0.05$) between the two groups in terms of age, sex, BMI, hemoglobin (HGB), albumin (ALB), tumor level from the anal verge, history of cardiopulmonary disease, history of neoadjuvant therapy or ASA level. With regard to baseline characteristics, the R-TME and L-TME groups were comparable.

Perioperative and pathological data between the two groups of patients

Table 2 shows that neither group of patients underwent a switch to laparotomy during surgery, and there was no positive surgical margin according to postoperative pathology. Moreover, there were no significant differences between the two groups in terms of intraoperative bleeding, transfusion volume, stoma rate, lymph node clearance, postoperative hospital stay, drainage tube removal time, or Foley catheter removal time ($P > 0.05$). The operation time in the R-TME group was significantly shorter than that in the L-TME group ($P < 0.05$). In terms of the time to first meal, the R-TME group was significantly better than the L-TME group ($P = 0.005$). However, the cost of R-TME was significantly greater than that of L-TME ($P < 0.005$).

Postoperative complications

Table 3 shows a comparison of postoperative complications between the two groups. The incidence of postoperative complications was 8.89% in the R-TME group compared with that in the L-TME group. Among them, L-TME had 1 patient with intestinal obstruction combined with abdominal infection and 1 patient with intestinal obstruction combined

Table 1 Baseline data between the two groups of patients

	R-TME (*n* = 45)	L-TME (*n* = 50)	*t*/*Z*/χ^2 value	*P* value
Age [yr, Md (IQR)]	68 (64, 71)	69 (65, 75)	-1.763[1]	0.078
Gender, *n* (%)			0.68[2]	0.409
Male	26 (57.7)	33 (66.0)		
Female	19 (42.3)	17 (34.0)		
BMI (kg/m^2, mean ± SD)	23.43 ± 2.52	23.85 ± 3.02	-0.73[3]	0.467
Tumor level from anal verge (cm), *n* (%)			0.818[2]	0.664
5-10	25 (55.6)	24 (48.0)		
11-15	14 (31.1)	20 (40.0)		
> 15	6 (13.3)	6 (12.0)		
History of cardiopulmonary disease, *n* (%)			0.068[2]	0.794
Yes	21 (46.7)	22 (44.0)		
No	24 (53.3)	28 (56.0)		
HGB (g/L, mean ± SD)	125.22 ± 12.31	127.22 ± 17.86	-0.628[3]	0.532
ALB (g/L, mean ± SD)	39.82 ± 2.77	39.19 ± 3.18	1.02[3]	0.31
History of abdominal surgery, *n* (%)			3.214[2]	0.073
Yes	9 (20.0)	17 (34.0)		
No	36 (80.0)	33 (66.0)		
History of neoadjuvant therapy, *n* (%)			0.253[2]	0.615
Yes	7 (15.6)	6 (12.0)		
No	38 (84.4)	44 (88.0)		
ASA level, *n* (%)			1.133[2]	0.287
II	30 (66.7)	28 (56.0)		
III	15 (33.3)	22 (44.0)		

[1]*Z* value.
[2]χ^2 value.
[3]*t* value.
R-TME: Robot-assisted total mesorectal excision; L-TME: Laparoscopic-assisted total mesorectal excision; BMI: Body mass index; HGB: Hemoglobin; ALB: Albumin; ASA: American Society of Anesthesiologists.

with pulmonary infection, and there was no significant difference in the incidence of various complications or CD grade between the two groups.

Univariate and multifactorial analysis of complications

Table 4 shows the analysis of factors related to postoperative complications, including age; sex; distance of the tumor from the anal margin; history of cardiopulmonary disease; history of abdominal surgery; BMI; HGB; ALB; history of neoadjuvant chemotherapy; surgical path; intraoperative blood loss; operation time; and whether or not to have a stoma. The results suggested that the operative time and degree of intraoperative bleeding were related to the occurrence of complications. On this basis, the results of multifactor analysis showed that there was no significant relationship between operation time and the occurrence of intraoperative bleeding or complications.

DISCUSSION

Compared with open surgery, laparoscopy has the advantages of being minimally invasive and allowing rapid recovery in the treatment of colorectal cancer[7], and laparoscopic surgery has been widely used to treat rectal cancer surgery. However, laparoscopic surgery also has limitations. Laparoscopic surgery is limited by the pelvis and operation angle, and surgical instruments can easily interfere with each other, which affects the separation of the local tissue in the surgical area. It is easy to injure the ureter and pelvic nerve to maintain urinary and sexual function, and suturing, knot-

Table 2 Perioperative and pathological data between the two groups of patients

	R-TME (*n* = 45)	L-TME (*n* = 50)	*t*/*Z*/χ^2 value	*P* value
Operation time [min, Md (IQR)]	145 (125, 187.5)	180 (148.75, 206.25)	-2.805[1]	0.005
Intraoperative bleeding [mL, Md (IQR)]	80 (40, 100)	100 (30, 162.5)	-0.98[1]	0.327
Conversion to laparotomy, *n* (%)	0	0	-	-
Transfusion, *n* (%)	0 (0)	1 (2)	-	1.0
Ostomy, *n* (%)	16 (35.56)	26 (52.0)	2.806[2]	0.246
No	29	24		
Ileostomy	12	21		
Colostomy	4	5		
Positive rate of cutting edge, *n* (%)	0	0	-	-
Number of lymph node dissection [*n*, Md (IQR)]	16 (12, 20)	15 (12, 17)	1.093[1]	0.278
Postoperative hospitalization days [d, Md (IQR)]	8 (7, 9)	7 (7, 10)	-0.566[1]	0.571
Time of first liquid feeding [d, Md (IQR)]	3 (3, 4)	4 (3, 5)	-1.977[1]	0.048
Drainage tube removal time [d, Md (IQR)]	6 (6, 7)	6 (5, 7)	-0.17[1]	0.865
Foley catheter removal time [d, Md (IQR)]	3 (3, 4.5)	4 (3, 5)	-1.667[1]	0.096
Expenditure [RMB, Md (IQR)]	77528.84 (67871.24, 92400.57)	61756.95 (54587.1, 71251.51)	-5.231[1]	< 0.005

[1]Z value.
[2]χ^2 value.
R-TME: Robot-assisted total mesorectal excision; L-TME: Laparoscopic-assisted total mesorectal excision.

ting, and other surgeries are difficult, thus affecting the short-term efficacy of surgery[8]. In terms of the selection of surgical procedures, TME is currently the main surgical treatment for rectal cancer, and some studies have noted that TME has a high long-term survival rate after surgery and can also reduce damage to pelvic nerves and blood vessels and destruction of anal function; however, TME also has disadvantages, such as increased intraoperative bleeding, high need for surgical techniques, a long postoperative hospital stay, and a high incidence of complications. Moreover, the risk of anesthesia, cardiovascular accidents, obesity, and other factors affecting the treatment of elderly patients with rectal cancer increase the uncertainty of the curative effect of laparoscopic TME surgery. With the development of minimally invasive surgery, Da Vinci robots have been used in TME surgery; however, evidence of their clinical superiority in terms of short-term outcomes over conventional rectal surgery conducted by expert surgeons is still lacking[9].

In this study, we compared the short-term efficacy of robot-assisted and laparoscopic TME surgery for elderly patients to determine the advantages of robot-assisted TME surgery for elderly patients. After a comprehensive evaluation of intraoperative and postoperative rehabilitation and pathological radical treatment, it was found that robot-assisted TME surgery had a similar or better short-term prognosis than laparoscopic surgery.

The completeness of TME specimen data reflects the quality of the tumor anatomy during rectal cancer surgery. Neither the robot-assisted surgery group nor the laparoscopic surgery group reported incomplete TME specimens (the results were not shown), which is similar to the conclusion of the prospective study conducted by Kim *et al*[10]. Therefore, it is not difficult to see that the robot can better complete the tumor results required by TME surgery and has sufficient tumor safety. Because patients who are transferred from minimally invasive surgery to open surgery are more prone to postoperative complications and local recurrence, the conversion rate of surgery is one of the key indicators for demonstrating the progress of surgical technology[11]. In this study, there was no conversion to open surgery in either group, which is similar to the findings of Yamanashi *et al*[12]. This benefits from the rich expertise of the surgical team in treating rectal cancer, which also proves the surgical safety of robot-assisted surgery.

The number of lymph node dissections and the positive margin of tumor specimens are the main indicators used to evaluate whether rectal cancer surgery is radical[13]. The results of this study showed that there was no significant difference in the number of lymph node dissections or positive margins of tumor specimens between the R-TME group and L-TME group ($P > 0.05$), which is consistent with the results of Grosek *et al*[14], Feroci *et al*[15] and other studies. In terms of operation time, in contrast to the findings of previous studies, the operation time of the robotic group was significantly shorter than that of the laparoscopic group ($P < 0.05$), which was attributed to the following reasons: (1) The scrub nurses in the robot group needed extensive experience in Da Vinci robot installation and working with the surgeon, had a higher degree of cooperation with the surgeon, and completed more quickly. Studies have shown[16,17] that skilled Da Vinci robotic surgery experience can significantly shorten operation time; and (2) The ostomy rate in the laparoscopic group (51.06%) was greater than that in the robotic group (41.03%), which affected the operation time.

Table 3 Postoperative complications, *n* (%)

Intraoperative complication	R-TME (*n* = 45)	L-TME (*n* = 50)	*P* value
Ureteral injury	0	0	-
Acute cardiovascular disease	0	0	-
Postoperative complication	4 (8.89)	6 (12.0)	0.874
Postoperative complication	0	0	-
Significant blood loss	0	0	-
Ileus	2 (4.44)	4 (8.0)	0.773
Abdominal infection	1 (2.22)	2 (4.0)	1
Pneumonia	0	1 (2.0)	1
Acute cerebral infarction	0	0	-
Urinary retention	1 (2.22)	1 (2.0)	1
Acute cardiovascular disease	0	0	-
Acute respiratory failure	0	0	-
Ureteral fistula	0	0	-
Chylous fistula	0	0	-
Complication Clavien-Dindo			0.644
II	4 (4.44)	5 (10.0)	0.854
III	0	1 (2.0)	0.343
IV	0	0	-
V	0	0	-

R-TME: Robot-assisted total mesorectal excision; L-TME: Laparoscopic-assisted total mesorectal excision.

In terms of treatment expenditure, we compared the cost of treatment between the two groups, mainly by calculating the cost before the use of health insurance. The cost of R-TME was significantly greater than that of L-TME ($P < 0.005$), which may be due to the maintenance of the machine and the failure of widespread popularity of the machine. Additionally, the price will be correspondingly greater, but we can observe that after the use of health insurance, the cost will be greatly reduced, which reduces the burden of the treatment to a certain extent.

Several studies have reported that the pelvis is an associated factor affecting TME operation[18]. The male pelvis is significantly different from the female pelvis. We believe that due to the special physiological structure of male and female patients, surgical data may be different; therefore, we used sex as a variable to investigate the intraoperative and postoperative conditions of male and female patients in the two groups. There were 26 males (57.8%) and 19 females (42.2%) in the R-TME group and 33 males (66%) and 17 females (34%) in the L-TME group, with no significant difference in demographic characteristics at baseline. We also conducted multivariate ANOVA for intraoperative conditions and postoperative recovery. Moreover, there were no significant differences in operation time, intraoperative bleeding, or hospitalization days. However, in terms of the individual statistics for males, the R-TME group had significant differences in operation time ($P = 0.042$) and intraoperative bleeding evaluation ($P = 0.042$) compared with the L-TME group, and the robot-assisted effect was significantly better than that of laparoscopy. Although the number of people is small, this may also indicate that robot-assisted surgery does not cause a difference in the outcome of surgery according to sex and may even be more advantageous.

A meta-analysis revealed that a considerable number of elderly patients are at risk for obesity, which significantly affects the quality of surgery and increases the risk of postoperative complications[19]. Therefore, we defined obese patients with a BMI ≥ 25 kg/m^2 as obese and subdivided them into 13 (28.9%) patients in the R-TME group and 15 (30%) patients in the L-TME group. In this subgroup, there were no significant differences between the two groups in terms of baseline characteristics, operation time or intraoperative bleeding. In terms of postoperative rehabilitation, there were no significant differences in length of stay, intestinal recovery time or postoperative complications. However, in terms of catheter removal time, catheter removal occurred significantly earlier in the R-TME group than in the L-TME (3 *vs* 4 d, $P = 0.001$), which was also reflected in Fleming *et al*'s[19] meta-analysis. This is because the Da Vinci robotic system has a better field of view, can eliminate tremors and movements caused by internal wrist instruments, and allows for more precise anatomical tissue, even in the case of individuals with a high BMI, rich visceral fat and a small operating space; moreover, this system effectively avoids damage to the genitourinary system.

Table 4 Univariate and multifactorial analysis of postoperative complications

Factors	Single factor analysis			Multiple factor analysis		
	OR	95%CI	*P* Value	OR	95%CI	*P* Value
Age	1.054	0.961-1.157	0.263			
Gender	0.375	0.075-1.874	0.232			
Tumor level from anal verge	0.26	0.06-1.121	0.071			
History of cardiopulmonary disease	2.074	0.502-8.563	0.313			
BMI	1.123	0.893-1.413	0.321			
History of abdominal surgery	0.674	0.133-3.411	0.633			
HGB	1.028	0.985-1.074	0.2			
ALB	0.974	0.78-1.217	0.818			
History of neoadjuvant therapy	0	0	0.999			
Operation time	1.016	1.004-1.028	0.009	1.007	0.989-1.025	0.461
Surgical path	0.715	0.188-2.718	0.623			
Intraoperative bleeding	1.009	1.002-1.015	0.006	1.008	0.999-1.018	0.075
Ostomy	2.279	0.915-5.68	0.077			

BMI: Body mass index; HGB: Hemoglobin; ALB: Albumin.

In terms of postoperative recovery, the time of the first postoperative liquid food intake reflects the recovery of intestinal function to a certain extent. This study showed that the time to first postoperative fluid intake in the robotic group was significantly earlier than that in the laparoscopic group ($P < 0.05$), which was similar to the results obtained by Feng *et al*[20]. This was mainly because, relative to laparoscopic surgery, robotic surgery was performed through a smaller incision, which reduced the stimulation of abdominal organ tissues and the degree of body damage, and the patients recovered their gastrointestinal function faster after surgery. In contrast, there was no significant difference between the two groups in terms of observational indicators, such as postoperative hospitalization time, drain removal, or catheter removal time ($P > 0.05$). In terms of complications, there were no serious complications or anastomotic fistulas in either group. The complication rate in the robotic group (8.9%) was lower than that in the laparoscopic group (12.0%). These findings are similar to the results of the retrospective analysis by Xu *et al*[21], which may be a consequence of the precision of the technique through improved vision and tremorless motion[22].

CONCLUSION

The overall radical outcome and short-term efficacy of robot-assisted TME in the treatment of elderly rectal cancer are similar to those of laparoscopic TME in the treatment of elderly rectal cancer, but robot-assisted TME is better than laparoscopic TME to a certain extent and is not effective in elderly patients; however, the former can shorten the operation time and reduce the recovery time of gastrointestinal function by optimizing the learning curve, which is beneficial for patient prognosis. There are several limitations in this study. The surgical efficacy, occurrence of complications, and prognosis of rectal cancer patients can also be affected by other factors, such as the enrollment of a small number of patients and the lack of comprehensive clinical data; moreover, there are several factors that cannot be evaluated, resulting in a certain bias. In the future, further comprehensive collection of clinical data from patients is needed, expanding the sample size of validation studies. The survival rate and quality of life of elderly patients also need to be considered. Future follow-up studies of these patients will continue to observe the long-term efficacy of robot-assisted surgery to enrich the evidence-based basis of robot-assisted TME surgery for elderly patients.

FOOTNOTES

Author contributions: Yang H, Yang G, Wu WY, Wang F, Yao XQ and Wu XY designed the research; Yang H, Yang G, Wu WY and Wang F performed the research; Yang H, Yang G and Wu WY contributed analytic tools and analyzed the data; Yang H, Yao XQ and Wu XY wrote the manuscript; Yao XQ and Wu XY provided help with project funding; all authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. Yao XQ and Wu XY contributed equally to this work as co-corresponding authors. The reasons for designating Yao XQ and Wu XY as co-corresponding authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures

effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of co-corresponding authors best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, Yao XQ and Wu XY contributed efforts of equal substance throughout the research process. The choice of these researchers as co-corresponding authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Yao XQ and Wu XY as co-corresponding authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Robotic *vs* laparoscopic abdominoperineal resection for rectal cancer: A propensity score matching cohort study and meta-analysis

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Abstract

BACKGROUND

Robotic surgery (RS) is gaining popularity; however, evidence for abdominoperineal resection (APR) of rectal cancer (RC) is scarce.

AIM

To compare the efficacy of RS and laparoscopic surgery (LS) in APR for RC.

METHODS

We retrospectively identified patients with RC who underwent APR by RS or LS from April 2016 to June 2022. Data regarding short-term surgical outcomes were compared between the two groups. To reduce the effect of potential confounding factors, propensity score matching was used, with a 1:1 ratio between the RS and LS groups. A meta-analysis of seven trials was performed to compare the efficacy of robotic and laparoscopic APR for RC surgery.

RESULTS

Of 133 patients, after propensity score matching, there were 42 patients in each group. The postoperative complication rate was significantly lower in the RS group (17/42, 40.5%) than in the LS group (27/42, 64.3%) (P = 0.029). There was

no significant difference in operative time (P = 0.564), intraoperative transfusion (P = 0.314), reoperation rate (P = 0.314), lymph nodes harvested (P = 0.309), or circumferential resection margin (CRM) positive rate (P = 0.314) between the two groups. The meta-analysis showed patients in the RS group had fewer positive CRMs (P = 0.04), lesser estimated blood loss (P < 0.00001), shorter postoperative hospital stays (P = 0.02), and fewer postoperative complications (P = 0.002) than patients in the LS group.

CONCLUSION

Our study shows that RS is a safe and effective approach for APR in RC and offers better short-term outcomes than LS.

Key Words: Robotic surgery; Laparoscopic surgery; Abdominoperineal resection; Postoperative complications; Propensity score

Core Tip: This study compared the efficacy of robotic surgery (RS) and laparoscopic surgery (LS) in abdominoperineal resection (APR) for rectal cancer (RC). Our results showed that RS patients had fewer positive circumferential resection margins, less estimated blood loss, shorter postoperative hospital stays, and fewer postoperative complications than did LS patients. Our findings demonstrate that RS is a safe and effective approach for APR in RC and offers better short-term outcomes than LS. This study contributes to the existing evidence base and can assist surgeons and healthcare providers in making informed decisions on using RS in APR for RC.

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INTRODUCTION

Colorectal cancer is the third most common cancer and one of the most common causes of cancer-related deaths worldwide. Nearly 40% of colorectal cancers occur in the rectum[1]. Surgery is the primary treatment for rectal cancer (RC)[2]. Common surgical procedures for RC include intersphincteric resection, low anterior resection (LAR), anterior resection, and abdominoperineal resection (APR)[3]. APR, also known as Miles's procedure, was first reported by Miles [4] in 1908. With the increasing use of LAR for lower RC, the application of APR has gradually declined. However, APR remains the best choice for RC cases in lower locations, cases with perianal muscle invasion, or cases where sphincter-preserving techniques are unsuitable for radical resection[5].

Laparoscopic minimally invasive surgery for colorectal cancer was first reported in the 1990s[5]. Compared with traditional open surgery, laparoscopic surgery (LS) has been widely used in RC surgery due to its advantages of shorter hospital stays, reduced blood loss, and faster postoperative recovery[6,7]. However, some limitations of LS, such as a two-dimensional field of view, amplification of operative tremors, and poor flexibility, may affect its efficacy in radical surgery[6,8]. These limitations are further amplified in the narrow pelvic cavity. However, robotic surgery (RS) offers a three-dimensional view, a stable camera platform, and flexible operating instruments[9]. The development of RS provides a potential approach that overcomes the limitations of LS. Several studies have compared the efficacy of laparoscopic and robotic APR for RC. However, the benefits of robotic APR remain controversial. Feng *et al*[10] showed that robotic APR significantly reduced the incidence of postoperative complications, rate of conversion to laparotomy, and length of hospital stay. However, some retrospective studies[11,12] have shown no significant difference in postoperative complication rates between robotic and laparoscopic APR.

Therefore, we conducted a retrospective cohort study to evaluate the effects of RS on postoperative complications, pathological findings, and postoperative recovery in RC patients undergoing APR. Propensity score matching (PSM) was performed to reduce the influence of imbalanced factors between the two groups. In addition, we performed a meta-analysis of all previous studies evaluating the efficacies of robotic and laparoscopic APR for RC surgery and combined the results of this trial.

MATERIALS AND METHODS

Study population

This retrospective study included 133 patients with pathologically confirmed RC who underwent APR *via* RS or LS at the First Affiliated Hospital of Chongqing Medical University from April 2016 to June 2022. This study was ethically ap-

proved by the Institutional Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. All patients provided informed consent. Patients undergoing surgery for local recurrence after rectal resection, with malignant melanoma, younger than 18 years, or undergoing combined resection of other organs were excluded.

Patient demographics [age, sex, body mass index (BMI), the American Society of Anesthesiologists physical status classification (ASA) scores, comorbidity, tumor distance from the anal verge, and neoadjuvant therapy], surgical information (surgical approach, operative time, blood loss, and conversion to open surgery), postoperative outcomes [length of stay, reoperation, complications within 30 d, readmissions, mortality, time to first flatus, first defecation time, lymph nodes harvested, circumferential resection margin (CRM), and cost] were obtained from the electronic medical record system.

Surgical procedure

All laparoscopic and robotic procedures were performed by the same experienced surgeon. Robotic and laparoscopic approaches were used only for abdominal procedures. The perineal portion of the procedure was performed manually by the surgeon. All surgical procedures were performed in accordance with the principle of total mesorectal excision, which included resection of the entire mesorectum to the pelvic floor, ligation of the inferior mesenteric artery at the origin of the inferior mesenteric artery, and lymph node dissection. Perineal resection involved the removal of the internal and external anal sphincters and a part of the levator ani muscle. Extended resection of the levator ani muscle, posterior vaginal wall, and surrounding tissues was performed, if necessary, for tumor invasion. No procedure was taken to fill the pelvic cavity.

Primary and secondary endpoints

The primary endpoint was postoperative complications within 30 postoperative days. The secondary endpoints included operative time, blood loss, time to first flatus and defecation, conversion rate, intensive care rate, histological examination, morbidity, reoperation rate, transfusion rate, and length of hospital stay.

Statistical analysis

Data were presented as frequencies (percentages), means (standard deviation), or medians (interquartile range). Differences in categorical variables between the groups were examined by the Pearson χ^2 test. Meanwhile, differences in continuous variables between the two groups were analyzed using the Student's *t*-test or Mann-Whitney *U* test, as appropriate. PSM analysis based on patient demographics (male, age, BMI, neoadjuvant therapy, tumor location, and stage) and comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes mellitus, coronary artery disease, and ASA) was performed to reduce potential confounders resulting from differences in baseline characteristics between the groups. The matching ratio was established as 1:1 using the nearest neighbor matching algorithm. Calipers were set to 0.05 times the standard deviation of the logarithm of the estimated propensity score. All statistical analyses were performed with IBM SPSS version 26. A P-value < 0.05 was considered statistically significant.

Meta-analysis

We conducted a meta-analysis of all published cohort studies, case-control studies, and randomized controlled trials (RCTs) following the PRISMA guidelines, comparing RS with LS in APR for RC. The PubMed, Embase, Web of Science, and Cochrane databases were searched from inception until December 7, 2022. Studies were included if they met the following criteria: (1) Patients undergoing APR for RC; (2) intervention with RS; (3) comparison with LS; (4) outcomes included postoperative complications, completeness of resection, operative time, length of hospital stay, mortality, conversion rate, lymph nodes harvested, and blood loss; and (5) cohort studies, case-control studies, or RCTs. The risk of bias in RCTs was assessed independently by two authors (Tang G and Song L) based on the Cochrane risk-of-bias tool. The quality of non-RCTs was assessed based on the Newcastle-Ottawa Scale. Data extracted from each eligible study were as follows: First author, year, country, study design, sample, age, sex, and outcomes. Heterogeneity between studies was assessed using the I^2 statistic[13]. Mean differences (MD) or odds ratios (OR) across studies were combined using the random effects model[14]. One-study exclusion test was used to examine the impact of each study on the pooled effect size. Analyses were conducted using Review Manager (RevMan) Version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration 2014; Copenhagen, Denmark). A P-value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

In total, 133 patients (96 males and 37 females) who underwent APR for RC were included. The median (interquartile range: 25th-75th percentile) age and mean BMI of the patients were 63.0 (55.5-70.0) years and 22.53 ± 2.43 kg/m^2, respectively. Robotic APR was performed in 49 patients and laparoscopic APR in 84 patients. There were no significant differences in the ASA grade, sex, age, diabetes mellitus, chronic obstructive pulmonary disease, coronary artery disease, BMI, and tumor stage between the two groups. However, the proportion of patients with hypertension was higher in the RS group than in the LS group (P = 0.011).

Surgical results

After matching, 42 patients were included in each group (Table 1). Operative times were similar between the two groups

Table 1 Baseline characteristics after propensity score matching, *n* (%)

	Group RS (*n* = 42)	Group LS (*n* = 42)	*P* value
Age (yr)[1]	63.5 (55-69)	65 (57.8-72.3)	0.211
Sex			1.000
Male	32 (76.2)	32 (76.2)	
Female	10 (23.8)	10 (23.8)	
BMI[2]	22.5 (2.03)	22.6 (2.41)	0.815
COPD	8 (19)	8 (19)	1.000
Hypertension	11 (26.2)	9 (21.4)	0.608
Diabetes mellitus	2 (4.8)	4 (9.5)	0.397
Coronary artery disease	1 (2.4)	2 (4.8)	0.557
ASA Grade			0.890
1	5 (11.9)	4 (9.5)	
2	22 (52.4)	24 (57.1)	
3	15 (35.7)	14 (33.3)	
Neoadjuvant therapy received	9 (21.4)	8 (19)	0.786
Distance between tumor and AV (cm)[1]	3 (2-5)	3 (2.5-4)	0.996
Stage			0.969
I	10 (23.8)	10 (23.8)	
II	16 (38.1)	15 (35.7)	
III	16 (38.1)	17 (40.5)	

[1]Values are median (interquartile range: 25th-75th percentile).
[2]Values are mean (SD).
Values in parentheses are percentages, unless indicated otherwise. ASA: American Society of Anesthesiologists physical status classification; AV: Anal verge; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; RS: Robotic surgery; LS: Laparoscopic surgery.

(P = 0.564), with a median of 245 min for RS and 230 min for LS. The estimated blood loss was significantly lower in the RS group than in the LS group (P = 0.012). No significant differences in the rate of intraoperative blood transfusion were observed between the two groups (P = 0.314). In addition, there was no conversion to open surgery in either group (Table 2).

Postoperative complication rate was significantly lower in the RS group (17/42, 40.5%) than in the LS group (27/42, 64.3%) (P = 0.029). There were no significant differences observed in pneumonia (P = 1.000), urinary infection rate (P = 0.557), ileus rate (P = 1.000), wound infection rate (P = 0.057), abdominal infection rate (P = 0.365), reoperation rate (P = 0.314), urinary retention (P = 0.557), or intensive care rate (P = 0.152) between the two groups, and no deaths were recorded in both groups. There was no significant difference between the two groups in the number of examined lymph nodes (P = 0.309) and CRM positive rate (P = 0.314). Median hospitalization costs were significantly higher in the RS group (81886.5 RMB) than in the LS group (70102.8 RMB; P = 0.040).

Regarding intestinal function recovery, the time to first flatus in the robotic group (P = 0.023) was significantly shorter than that in the laparoscopic group. However, there was no significant difference in the time to first defecation between the two groups (P = 0.679). In addition, the median postoperative hospital stay was significantly shorter in the RS group (9.0 d) than in the LS group (11.0 d; P = 0.044).

Meta-analysis

Our literature search yielded 810 potential records, of which 11 published articles were completely reviewed. In addition to our study, six trials[10-12,15-17] published between 2015 and 2022 were included. Details of the seven eligible trials are summarized in Table 3. The risk of bias was low in all seven studies included in the review.

Meta-analysis of the six studies[10-12,16,17] showed no significant difference in operative time [MD = 17.86 min; 95%CI: -2.33 to 38.05; P = 0.08, with high heterogeneity (I^2 = 75%)] (Figure 1A and Table 4). Intraoperative blood loss was significantly lower in the RS group than in the LS group (MD -26.36 mL, 95%CI: -32.02 to -20.70; I^2 = 0%, P = 0.47) (Figure 1B). A total of 6290 participants in the seven studies[10-12,15-17] had postoperative complications. The incidence of postoperative complications was lower in the RS group than in the LS group (OR 0.69, 95%CI: 0.55-0.88; I^2 = 14%, P = 0.32) (Figure 1C). There was no significant difference (OR, 0.71; 95%CI: 0.26-1.94; P = 0.50) in the postoperative mortality between the RS and LS groups, with low heterogeneity between studies (I^2 = 0%, P = 0.60) (Figure 1D). Data on reope-

Table 2 Operative outcomes and postoperative complication after propensity score matching, *n* (%)

	Group RS (*n* = 42)	Group LS (*n* = 42)	*P* value
Duration of surgery (min)[1]	245 (191.5-295)	230 (200-286.3)	0.564
Intraoperative blood loss (ml)[1]	60 (50-100)	100 (50-200)	0.012
Transfusion	1 (2.4)	0 (0)	0.314
Days to first flatus[1]	2 (1-2)	2 (2-3)	0.023
Days to first defecation[1]	3 (2.8-4.3)	3 (2.8-4.3)	0.679
Reoperation	0 (0)	1 (2.4)	0.314
Mortality	0 (0)	0 (0)	-
Intensive care	0 (0)	2 (4.8)	0.152
Conventional open	0 (0)	0 (0)	-
Circumferential resection margin positive	0 (0)	1 (2.4)	0.314
Lymph nodes harvested[1]	15 (11-18)	13 (9-18.3)	0.309
Perineural invasion	1 (2.4)	1 (2.4)	1.000
Lymphovascular invasion	2 (4.8)	2 (4.8)	1.000
Hospital stay (d)[1]	9 (7.8-13)	11 (8-18)	0.044
Postoperative complications	17 (40.5)	27 (64.3)	0.029
Urinary infection	2 (4.8)	1 (2.4)	0.557
Pneumonia	1 (2.4)	1 (2.4)	1.000
Ileus	3 (7.1)	3 (7.1)	1.000
Wound infection	5 (11.9)	12 (28.6)	0.057
Intraabdominal infection	5 (11.9)	8 (19)	0.365
Urinary retention	1 (2.4)	2 (4.8)	0.557
Hospital charge (RMB)[1]	81886.5 (70540.5-109854.2)	70102.8 (60308.6-109415.4)	0.040

[1]Values are median (interquartile range: 25th-75th percentile).
Values in parentheses are percentages, unless indicated otherwise. RS: Robotic surgery; LS: Laparoscopic surgery.

ration rates were reported in four studies[10,12,17]. The RS and LS groups were comparable in terms of reoperation rate (OR, 0.40; 95%CI: 0.16-1.03; P = 0.06; I^2 = 0%) (Figure 1E). Furthermore, no significant differences were observed between RS and LS in terms of conversion to open surgery (OR, 0.45; 95%CI: 0.07-2.89; P = 0.40; I^2 = 54%), estimated at 1.8% for RS and 5.0% for LS (Figure 1F). The overall effect of the seven studies[10-12,15-17] reporting the length of stay showed that RS was associated with reduced length of hospital stay (MD -1.51 d; 95%CI: -2.80 to -0.21), with significant heterogeneity (I^2 = 89%, P < 0.00001) between studies (Figure 1G). Five studies[10-12,16] described the number of lymph nodes harvested, and there was no significant difference in the number of lymph nodes harvested between the RS and LS groups, with low heterogeneity (MD, 0.33; 95%CI: -1.03 to 1.69; P = 0.64; I^2 = 14%) (Figure 1H). Data on CRM positive rates were reported in five studies[10-12,16]. Surgery with the robotic-assisted technique for APR reduced the CRM positive rate (OR, 0.39; 95%CI: 0.16-0.95; P = 0.04; I^2 = 0%) (Figure 1I).

The results of the sensitivity analysis showed that the total effect size of intraoperative blood loss, postoperative complications, postoperative mortality, reoperation rate, conversion to open surgery, and number of lymph nodes harvested was not affected by the elimination of any one study. However, the total effect size for operative time changed (MD, 24.05 min; 95%CI: 3.71-44.40; I^2 = 0%, P = 0.47) when the study by Kasai *et al*[11] was excluded. Sensitivity analysis indicated that studies by Gorgun *et al*[12] (OR, 0.41; 95%CI: 0.16-1.06; I^2 = 0%, P = 0.96) and Feng *et al*[10] (OR, 0.38; 95%CI: 0.08-1.84; I^2 = 0%, P = 0.94) and the present study (OR, 0.40; 95%CI: 0.16-1.00; I^2 = 0%, P = 0.94) prominently affected the total effect size of the CRM positive rate. The total effect size of the length of hospital stay was changed by the exclusion of the study by Kasai *et al*[11] (MD, -1.27 d; 95%CI: -2.59 to 0.05), the present study (MD, -1.24 d; 95%CI: -2.60 to 0.12), and the study by Feng *et al*[10] (MD, -1.28 d; 95%CI: -2.68 to 0.12).

Table 3 Characteristics of trials included in the meta-analysis

Ref.	Country	Study design	Sample	Age	Gender (M/F)	Outcomes	NOS
Moghadamyeghaneh *et al*[15], 2015	United States	Retrospective cohort study	R: 872; L: 4737	R: 64; L: 62	R: 556/316; L: 2844/1893	Hospital stay, postoperative complications, mortality	7
Kamali *et al*[16], 2017	United Kingdom	Retrospective case-control study	R: 11; L: 11	R: 71; L: 57	R: 7/4; L: 9/2	Postoperative complications, mortality, CRM, operating time, hospital stay, lymph nodes harvested, conversion rate	8
Gavrila *et al*[17], 2021	Romania	Retrospective case-control study	R: 46; L: 63	R: 62; L: 62	R: 34/12; L: 32/31	Postoperative complications, mortality, operating time, blood loss, hospital stay, conversion rate, reoperation rate	8
Kasai *et al*[11], 2022	Japan	Retrospective cohort study	R: 33; L: 20	R: 74; L: 78	R: 20/13; L: 16/4	Postoperative complications, CRM, operating time, blood loss, hospital stay, conversion rate, lymph nodes harvested	8
Feng *et al*[10], 2022	China	Randomized controlled trial	R: 174; L: 173	R: 58; L: 60	R: 108/66; L: 113/60	Postoperative complications, mortality, CRM, operating time, blood loss, hospital stay, conversion rate, reoperation rate, lymph nodes harvested	-
Gorgun *et al*[12], 2022	United States	Retrospective PSM	R: 34; L: 34	R: 66; L: 66	R: 25/9; L: 25/9	Postoperative complications, CRM, operating time, blood loss, hospital stay, conversion rate, reoperation rate, lymph nodes harvested	9
Current study, 2022	China	Retrospective PSM	R: 34; L: 34	R: 34; L: 34	R: 34; L: 34	Lymph nodes harvested, postoperative complications, mortality, CRM, operating time, blood loss, hospital stay, conversion rate, reoperation rate	9

CRM: Circumferential resection margin; F: Female; L: Laparoscopic abdominoperineal resection; M: Male; NOS: Newcastle-Ottawa Scale; PSM: Propensity score matching; R: Robotic abdominoperineal resection.

Table 4 Summary of results from all outcomes

Indicators	No. of studies	Events for RS	Events for LS	Effect size	95%CI
Operative time	6	-	-	17.86 min	-2.33, 38.05
Intraoperative blood loss	5	-	-	-26.36 mL	-32.02, -20.70
Postoperative complications	7	315/1211	1651/5079	0.69	0.55, 0.88
Postoperative mortality	5	4/1144	29/5025	0.71	0.26, 1.94
Reoperation	4	5/296	15/312	0.40	0.16, 1.03
Conversion to open surgery	6	6/339	17/342	0.45	0.07, 2.89
The length of stay	7	-	-	-1.51 d	-2.80, -0.21
Lymph nodes harvested	5	-	-	0.33	-1.03, 1.69
Circumferential resection margin positive	5	7/294	17/280	0.39	0.16, 0.95

RS: Robotic surgery; LS: Laparoscopic surgery.

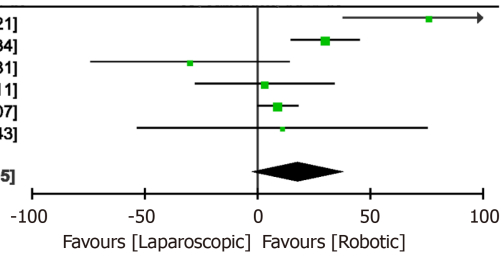
DISCUSSION

With advancements in technology, LS is gradually becoming the preferred technique for colorectal surgery. LS is safe and effective in the short and long term[9]. However, laparoscopic RC surgery has some inherent limitations, especially in patients with low RC[18]. In addition, neoadjuvant use can lead to pelvic tissue fibrosis, which increases the difficulty of surgery and affects the efficacy of LS[9]. RS is another surgical technique that is under development. Compared with LS, RS has several major advantages, including a wider surgical field, more flexible surgical instruments, and less fatigue for doctors[19]. In addition, LS is difficult to perform on the pelvic floor and requires a long learning curve, whereas RS has a shorter learning period, making this technique easier for younger doctors to learn[20,21]. A recently published meta-analysis[21] showed that robotic rectal surgery had similar long-term outcomes as LS, with shorter operative time, lower incidence of postoperative complications, shorter hospital stays, and lower conversion to open surgery rates. However, there are few related studies on RS for APR, and the efficacy is still controversial. Postoperative complications of minimally invasive surgery for RC are as high as 27%[3]. In addition, the incidence of postoperative complications was higher

A

Study or subgroup	Robotic Mean	SD	Total	Laparoscopic Mean	SD	Total	Weight	Mean difference IV, random, 95%CI
2017, Kamali	327	34	11	251	55	11	13.9%	76.00 [37.79, 114.21]
2021, Gavrila	221	42	46	191	38	63	23.9%	30.00 [14.66, 45.34]
2021, Kasai	277.59	82.96	33	307.44	77.35	20	11.9%	-29.85 [-74.01, 14.31]
2022, Current study	249.31	63.22	42	246.14	80.44	42	16.8%	3.17 [-27.77, 34.11]
2022, Feng	206.76	18.69	174	197.81	58.31	173	26.2%	8.95 [-0.17, 18.07]
2022, Gorgun	319	132	34	308	139	34	7.3%	11.00 [-53.43, 75.43]
Total (95% CI)			**340**			**343**	**100.0%**	**17.86 [-2.33, 38.05]**

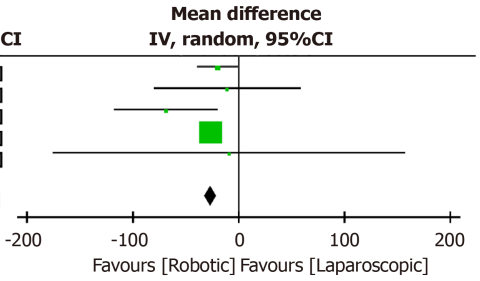
Heterogeneity: Tau² = 382.98; Chi² = 19.69, df = 5 (*P* = 0.001); I² = 75%
Test for overall effect: Z = 1.73 (*P* = 0.08)



B

Study or subgroup	Robotic Mean	SD	Total	Laparoscopic Mean	SD	Total	Weight	Mean difference IV, random, 95%CI
2021, Gavrila	150	50	46	170	50	63	8.9%	-20.00 [-39.01, -0.99]
2021, Kasai	99.12	120.72	33	110.04	126.86	20	0.7%	-10.92 [-80.11, 58.27]
2022, Current study	85.37	51.68	42	154.05	152.86	42	1.3%	-68.68 [-117.48, -19.88]
2022, Feng	100	14.95	174	126.49	37.38	173	89.0%	-26.49 [-32.49, -20.49]
2022, Gorgun	324	316	34	333	381	34	0.1%	-9.00 [-175.38, 157.38]
Total (95% CI)			**329**			**332**	**100.0%**	**-26.36 [-32.02, -20.70]**

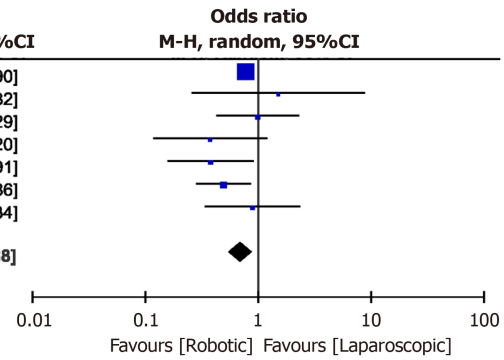
Heterogeneity: Tau² = 0.00; Chi² = 3.55, df = 4 (*P* = 0.47); I² = 0%
Test for overall effect: Z = 9.13 (*P* < 0.00001)



C

Study or subgroup	Robotic Events	Total	Laparoscopic Events	Total	Weight	Odds ratio M-H, random, 95%CI
2015, Moghadamyeghaneh	235	872	1537	4737	59.9%	0.77 [0.65, 0.90]
2017, Kamali	5	10	4	10	1.8%	1.50 [0.26, 8.82]
2021, Gavrila	13	46	18	63	7.3%	0.98 [0.42, 2.29]
2021, Kasai	9	33	10	20	4.0%	0.38 [0.12, 1.20]
2022, Current study	17	42	27	42	6.7%	0.38 [0.16, 0.91]
2022, Feng	23	174	41	173	14.8%	0.49 [0.28, 0.86]
2022, Gorgun	13	34	14	34	5.6%	0.88 [0.33, 2.34]
Total (95% CI)		**1211**		**5079**	**100.0%**	**0.69 [0.55, 0.88]**
Total events	315		1651			

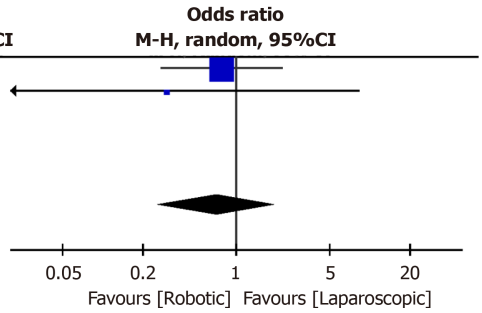
Heterogeneity: Tau² = 0.02; Chi² = 6.98, df = 6 (*P* = 0.32); I² = 14%
Test for overall effect: Z = 3.03 (*P* = 0.002)



D

Study or subgroup	Robotic Events	Total	Laparoscopic Events	Total	Weight	Odds ratio M-H, random, 95%CI
2015, Moghadamyeghaneh	4	872	28	4737	90.9%	0.78 [0.27, 2.22]
2017, Kamali	0	10	1	10	9.1%	0.30 [0.01, 8.33]
2021, Gavrila	0	46	0	63		Not estimable
2022, Current study	0	42	0	42		Not estimable
2022, Feng	0	174	0	173		Not estimable
Total (95% CI)		**1144**		**5025**	**100.0%**	**0.71 [0.26, 1.94]**
Total events	4		29			

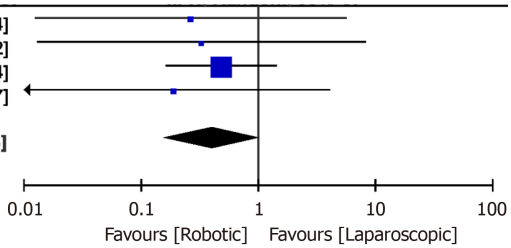
Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 1 (*P* = 0.60); I² = 0%
Test for overall effect: Z = 0.67 (*P* = 0.50)



E

Study or subgroup	Robotic Events	Total	Laparoscopic Events	Total	Weight	Odds ratio M-H, random, 95%CI
2021, Gavrila	0	46	2	63	9.3%	0.26 [0.01, 5.64]
2022, Current study	0	42	1	42	8.4%	0.33 [0.01, 8.22]
2022, Feng	5	174	10	173	73.0%	0.48 [0.16, 1.44]
2022, Gorgun	0	34	2	34	9.3%	0.19 [0.01, 4.07]
Total (95% CI)		**296**		**312**	**100.0%**	**0.40 [0.16, 1.03]**
Total events	5		15			

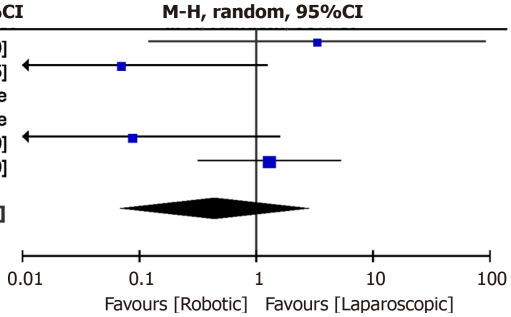
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 3 (*P* = 0.93); I² = 0%
Test for overall effect: Z = 1.90 (*P* = 0.06)



F

Study or subgroup	Robotic Events	Total	Laparoscopic Events	Total	Weight	Odds ratio M-H, random, 95%CI
2017, Kamali	1	10	0	10	18.9%	3.32 [0.12, 91.60]
2021, Gavrila	0	46	8	63	22.1%	0.07 [0.00, 1.25]
2021, Kasai	0	33	0	20		Not estimable
2022, Current study	0	42	0	42		Not estimable
2022, Feng	0	174	5	173	21.9%	0.09 [0.00, 1.60]
2022, Gorgun	5	34	4	34	37.1%	1.29 [0.32, 5.30]
Total (95% CI)		**339**		**342**	**100.0%**	**0.45 [0.07, 2.89]**
Total events	6		17			

Heterogeneity: Tau² = 1.91; Chi² = 6.57, df = 3 (*P* = 0.09); I² = 54%
Test for overall effect: Z = 0.84 (*P* = 0.40)



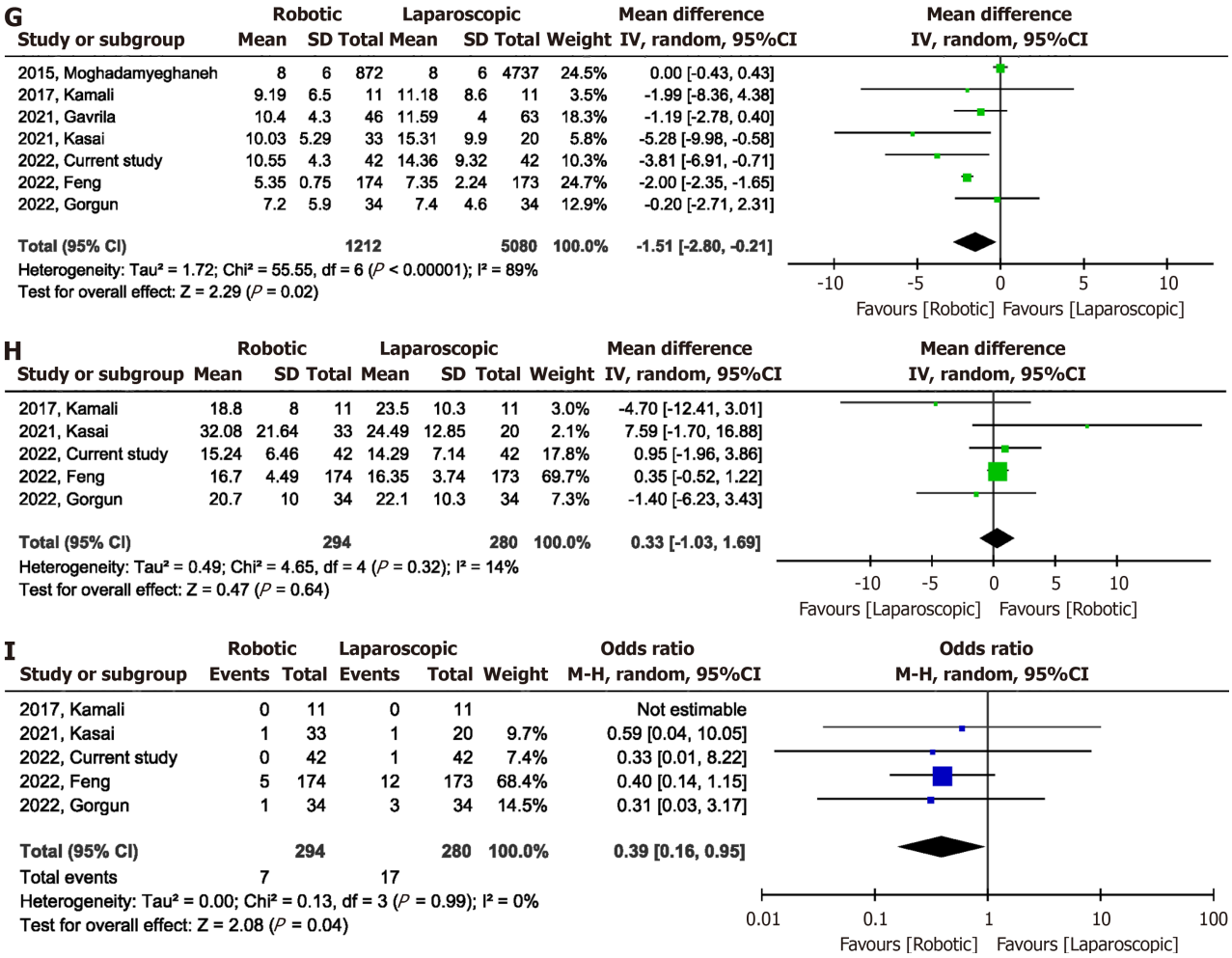


Figure 1 Forest plots. A: Forest plots of the operation time for robotic *vs* laparoscopic abdominoperineal resection; B: Forest plots of the intraoperative blood loss for robotic *vs* laparoscopic abdominoperineal resection; C: Forest plots of postoperative complications for robotic *vs* laparoscopic abdominoperineal resection; D: Forest plots of postoperative mortality for robotic *vs* laparoscopic abdominoperineal resection; E: Forest plots of the reoperation rates for robotic *vs* laparoscopic abdominoperineal resection; F: Forest plots of the rate of conversion to open surgery for robotic *vs* laparoscopic abdominoperineal resection; G: Forest plots of the length of stay for robotic *vs* laparoscopic abdominoperineal resection; H: Forest plots of the number of lymph nodes harvested for robotic *vs* laparoscopic abdominoperineal resection; I: Forest plots of the circumferential resection margin positive rates for robotic *vs* laparoscopic abdominoperineal resection.

with APR than with LAR[22]. The overall complication rate after APR in our study was 31%. Our retrospective study and meta-analysis showed that RS was effective in reducing the overall incidence of complications after APR. This result is consistent with that of a previous RCT involving patients undergoing LAR and APR procedures[23]. Postoperative complications not only increase the cost and length of hospital stay but also negatively affect long-term prognosis[24,25]. Gamboa *et al*[26] found that major complications after proctectomy were associated with shortened overall and recurrence-free survival. Thus, our findings have significant clinical implications, as we provide evidence supporting the benefit of RS in reducing complications after APR.

In addition, the advantages of the RS could theoretically bring benefits in terms of conversion to open surgery. A meta-analysis of 42 studies[21] showed that RS reduced the conversion rate. A recent large RCT[23] showed that robotics was associated with a lower conversion rate. However, in our study, there was no difference in the rate of conversion to open surgery between the RS and LS groups. After meta-analysis, conversion rates between RS and LS groups remained comparable. However, our analysis included a limited number of studies; more high-quality studies are needed to evaluate the effect of robotics on conversion to open surgery in APR. In addition, our meta-analysis showed that RS did not reduce the reoperation rate.

In RC surgery, surgeons focus on the quality of tumor resection. The number of harvested lymph nodes is related to the accuracy of tumor staging and oncologic radicality. In addition, it affects the patient's oncologic prognosis[27]. Being CRM positive, defined as having a minimum distance between the tumor and the CRM of 1 mm or less[28], is associated with tumor recurrence and shorter survival[18]. Studies have reported that being CRM positive leads to a 1- to 5-fold increased risk of local recurrence and a 1- to 4-fold increased risk of distant metastasis[23,29-32]. In traditional LS, surgical instruments need to enter the pelvic cavity in a nearly vertical direction, and their operation in the horizontal direction is limited. In addition, the narrow space in the pelvic cavity can lead to interference between instruments. Lower rectal surgery requires the cooperation of experienced assistants[23]. These factors may affect the quality of LS. RS has better three-dimensional vision and more flexible tools. In addition, the operating arm of the robot can be controlled by the

surgeon, which can replace the role of the assistant in LS. These factors allow the robot to perform precise surgical manipulations in a narrow space and improve the quality of tumor specimens[21,23]. Although there was no benefit of RS in terms of the number of lymph nodes harvested, our meta-analysis showed that RS significantly reduced the CRM positive rate. However, the sensitivity analysis showed that the total effect of the CRM positive rate was not robust. More studies are needed to explore the effect of RS on the quality of APR in the future.

Minimally invasive surgery is characterized by a rapid recovery of bowel function and a short hospital stay[19]. Postoperative recovery of gastrointestinal function is an important part of enhanced recovery after gastrointestinal tumor surgery, which has important clinical significance. The time to first flatus and time to first defecation after surgery are key indicators of gastrointestinal dysfunction[33]. Our study showed that although RS, compared to LS, did not shorten the time to first defecation, it reduced the time to first flatus. This is similar to the results of a recent meta-analysis[21] in which the time to first flatus after RC surgery was significantly shorter in the RS group (2.5 ± 1.4 d) than in the LS group (2.9 ± 2.0 d). In addition, our retrospective study and meta-analysis observed a significantly shorter hospital stay in the RS group than that in the LS group. This may be related to the faster recovery of intestinal function and fewer incidences of complications.

Regarding safety, some researchers have expressed concerns that RS will lead to longer operation times[3]. However, our retrospective study and meta-analysis suggest that RS does not lead to longer operation times. This is similar to the results of several previous studies[23,34,35]. In addition, we found that intraoperative blood loss was significantly lower in the RS group than that in the LS group. This may be due to the technical advantages of the robotic system providing a better surgical field of view, clearer anatomy, and easier suture manipulation, helping to prevent more bleeding[15,18].

A significant limitation of RS is its high cost[23]. Moghadamyeghaneh *et al*[15] used the nationwide inpatient sample database from 2009 to 2012 and found that the average total hospitalization cost of robotic APR was 37% higher than that of laparoscopy. Similar to previous studies, in the present study, we found a 17% increase in median hospitalization costs in the RS group compared with that in the LS group. Recently, Gorgun *et al*[12] reported an increase in direct costs of robotic APR compared with those of laparoscopic APR (26% increase in mean cost and 43% increase in median cost); however, the difference was not significant. The increase in hospitalization costs is an important factor hindering the routine application of RS[12]. Increased complication rates and longer hospital stays are associated with increased treatment costs[11]. Compared with LS, the lower complications and shorter hospital stays observed in the robotic group may be beneficial in reducing the high costs of RS treatment. Furthermore, as the use of RS becomes more widespread and the volume of such procedures increases, the cost of robotic devices will likely decrease over time. In the future, conducting further research to explore the cost-effectiveness of RS compared to that of LS will be important.

Our study had some limitations. First, our study was retrospective and may have been subject to some confounding factors. Therefore, we performed a PSM analysis, and the post-PSM RS and LS groups had similar underlying characteristics. Second, it was difficult to compare the effects of the two surgical techniques on long-term survival because the postoperative follow-up time was too short. However, given the concern about the impact of postoperative complications on survival and the lower incidence of postoperative complications in the RS group compared with that in the LS group, it is necessary to evaluate the long-term efficacy of the two surgical methods. Finally, this study was a single-center study, and all operations were performed by the same surgeon, which was not representative of the skill level of most colorectal surgeons. Therefore, we conducted a meta-analysis of data from other previous studies to further confirm the reliability of the results. To the best of our knowledge, this is the first meta-analysis comparing the short-term efficacy of robotic *vs* laparoscopic APR.

CONCLUSION

RS is a safe and effective treatment for APR in RC. Although RS is more expensive than LS, RS offers better short-term outcomes including fewer complications, fewer positive CRMs, less blood loss, and a faster postoperative recovery. More high-quality prospective studies are warranted to confirm the benefits of RS in APR.

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FOOTNOTES

Author contributions: Song L, Xu WQ, Wei ZQ, and Tang G made substantial contributions to conception and design; Xu WQ, Wei ZQ, and Tang G contributed to the acquisition of data, analysis, and interpretation; Song L and Tang G wrote the manuscript; Song L, Xu WQ, Wei ZQ, and Tang G supervised the work and edited the manuscript.

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Informed consent statement: Considering that the research was retrospective, the need for patients' informed written consent was waived.

Conflict-of-interest statement: All the authors have no conflict of interest related to the manuscript.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Preoperative prognostic nutritional index predicts long-term outcomes of patients with ampullary adenocarcinoma after curative pancreatoduodenectomy

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Abstract

BACKGROUND

The prognostic nutritional index (PNI), a marker of immune-nutrition balance, has predictive value for the survival and prognosis of patients with various cancers.

AIM

To explore the clinical significance of the preoperative PNI on the prognosis of ampullary adenocarcinoma (AC) patients who underwent curative pancreaticoduodenectomy.

METHODS

The data concerning 233 patients diagnosed with ACs were extracted and analyzed at our institution from January 1998 to December 2020. All patients were categorized into low and high PNI groups based on the cutoff value determined by receiver operating characteristic curve analysis. We compared disease-free survival (DFS) and overall survival (OS) between these groups and assessed prognostic factors through univariate and multivariate analyses.

RESULTS

The optimal cutoff value for the PNI was established at 45.3. Patients with a PNI ≥ 45.3 were categorized into the PNI-high group, while those with a PNI < 45.3 were assigned to the PNI-low group. Patients within the PNI-low group tended to

be of advanced age and exhibited higher levels of aspartate transaminase and total bilirubin and a lower creatinine level than were those in the PNI-high group. The 5-year OS rates for patients with a PNI ≥ 45.3 and a PNI < 45.3 were 61.8% and 43.4%, respectively, while the 5-year DFS rates were 53.5% and 38.3%, respectively. Patients in the PNI- low group had shorter OS (P = 0.006) and DFS (P = 0.012). In addition, multivariate analysis revealed that the PNI, pathological T stage and pathological N stage were found to be independent prognostic factors for both OS and DFS.

CONCLUSION

The PNI is a straightforward and valuable marker for predicting long-term survival after pancreatoduodenectomy. The PNI should be incorporated into the standard assessment of patients with AC.

Key Words: Ampullary carcinoma; Prognostic nutritional index; Prognosis; Pancreaticoduodenectomy

Core Tip: In light of emerging evidence that has substantiated the correlation between malnutrition and immune suppression with poor prognosis across various cancer types, we examined the prognostic significance of the preoperative prognostic nutritional index (PNI) in patients with ampullary adenocarcinoma (AC) who underwent curative pancreaticoduodenectomy (PD). Our findings revealed that the PNI, pathological T stage and pathological N stage were independent prognostic factors for both overall survival and disease-free survival in AC patients who underwent curative PD.

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INTRODUCTION

Ampullary adenocarcinoma (AC) accounts for only 0.2% of all gastrointestinal malignancies and is exceedingly rare[1,2]. Owing to the distinctive anatomical structure and biliary obstruction of AC, discernible clinical symptoms often appear at an early stage in patients, making surgical interventions feasible. Ordinarily, pancreaticoduodenectomy (PD) is the preferred therapeutic approach[3]. Although ampullary carcinoma exhibits a higher rate of radical resection and a more favorable prognosis compared to other periampullary malignancies, the long-term survival rate beyond five years after radical resection remains modest, ranging from 30% to 53% for these patients[4,5].

The prognostic nutritional index (PNI), which is calculated from the albumin concentration and lymphocyte count, was initially proposed to evaluate the perioperative immune-nutritional status and surgical risk in patients undergoing gastrointestinal surgery[6]. Emerging evidence has shown that malnutrition and immune suppression, which are assessed by the PNI, serve as independent predictors of poor prognosis in various types of cancer[7-10]. Moreover, Sun *et al*[11] conducted a pooled analysis and revealed that a low PNI was associated with poor overall survival (OS) [pooled odds ratio (OR): 1.80; 95% confidence interval (95%CI): 1.59-2.04] and the presence of postoperative complications (pooled OR: 2.45; 95%CI: 1.31-4.58) in cancer patients. In the context of AC, however, only a limited number of studies have explored this aspect[12], leaving the clinical significance and prognostic value of this marker uncertain.

Therefore, the primary objective of this study was to evaluate the prognostic value of the PNI and investigate its correlation with clinicopathological characteristics in patients diagnosed with AC.

MATERIALS AND METHODS

Patients

This retrospective study included patients with pathologically confirmed AC who underwent PD for curative resection at the China National Cancer Center between January 1998 and December 2020. Peripheral blood tests were conducted by the laboratory of the center preoperatively. The exclusion criteria were as follows: (1) Patients using anti-inflammatory or immunosuppressive medications; (2) patients with hematological disorders; (3) patients diagnosed with secondary tumors; (4) patients lacking clinicopathological information; and (5) patients lost to follow-up. According to these criteria, a cohort of 233 patients were enrolled in the study. The surgical informed consent forms of these patients were signed, and the study was approved by the institutional review board of the China National Cancer Center.

Clinical data extraction

The clinicopathological characteristics were retrospectively obtained from the medical records and assessed as prognostic factors. These included patient age, sex, tumor size, tumor differentiation, vascular invasion status, TNM stage, number of dissected lymph nodes, postoperative complications, and postoperative adjuvant therapy. AC was classified according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM classification system. Additionally, data from preoperative blood tests, including platelet count, neutrophil cell count, lymphocyte cell count, monocyte count, and serum albumin level, were collated.

Follow-up

At hospital discharge, patients were followed up every 3 months for up to 2 years after surgery, every 6 months for up to 5 years, and thereafter every year or until death. Postoperative follow-up data were collected through telephone reviews, outpatient follow-up, and the death registry system. OS was defined as the duration from the date of surgery to death from any cause or censoring at the time of the last follow-up. Disease-free survival (DFS) was calculated from the date of surgery to the onset of tumor recurrence or death.

Inflammatory indicator definitions

(1) PNI: Peripheral serum albumin level (g/L) + 5 × absolute lymphocyte count in peripheral blood (10^9/L); (2) neutrophil-to-lymphocyte ratio (NLR): Absolute neutrophil count in peripheral blood (10^9/L)/absolute lymphocyte count in peripheral blood (10^9/L); (3) platelet-to-lymphocyte ratio (PLR): Absolute platelet count in peripheral blood (10^9/L)/absolute lymphocyte count in peripheral blood (10^9/L); and (4) systemic immune-inflammation index (SII): Absolute neutrophil count in peripheral blood (10^9/L) × absolute platelet count in peripheral blood (10^9/L)/absolute lymphocyte count in peripheral blood (10^9/L).

Statistical analysis

Statistical analysis was performed using SPSS version 26 (SPSS Inc., Chicago, IL, United States) and R software (version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria). All categorical variables are expressed as frequencies (percentages), and the χ^2 test or Fisher's exact test was used for comparisons of different groups. DFS and OS curves were constructed using the Kaplan-Meier method. The optimal cutoff values of the Inflammatory indicators including PNI, NLR, PLR, and SII were determined by receiver operating characteristic (ROC) analysis. Furthermore, both univariate and multivariate Cox proportional hazard regression analyses were performed to ascertain the independent prognostic factors. Covariates demonstrating $P < 0.05$ in univariate analyses were incorporated into the subsequent multivariate analysis. All the statistical tests were two-sided, and P values < 0.05 were considered to indicate statistical significance.

RESULTS

Patient characteristics

After screening according to the inclusion and exclusion criteria, a total of 233 eligible AC patients were enrolled in the study. The median age of the patients was 57 years (range from 14 to 78 years), and the ratio of males to females was 1.33. Overall, lymphatic metastasis was observed in 71 patients (30.5%) and at least 17 lymph nodes were resected in 77 patients (33.0%). After surgery, complications were observed in 91 patients (39.1%), and postoperative adjuvant therapy was administered to 63 patients (27.0%). Analysis of these details revealed that biliary/pancreatic fistula (36.3%), gastric emptying disorder (28.5%), and hemorrhage (16.4%) were the most prevalent postoperative complications. In terms of postoperative therapy, the majority of patients (88.8%) received gemcitabine-based chemotherapy as an adjuvant treatment. The baseline characteristics of the patients are summarized in Table 1.

The optimal cutoff values for systemic inflammatory response biomarkers

The predictive efficacy of the PNI was evaluated through ROC curve analysis, and the PNI was compared with other inflammatory biomarkers (PLR, NLR, and SII). The results showed that the PNI exhibited superior precision for OS, with an area under the curve (AUC) of 0.535, surpassing the AUC values of the PLR (0.518), NLR (0.522), and SII (0.501). The recommended PNI cutoff, optimized for both sensitivity and specificity, was determined to be 45.3. Patients were subsequently stratified into PNI-high (PNI ≥ 45.3) and PNI-low (PNI < 45.3) groups.

PNI and clinicopathological characteristics of patients

No statistically significant differences were observed in sex, tumor size, tumor differentiation, vascular invasion or adjuvant therapy between the two groups. Patients aged 60 years or older were more prevalent in the PNI-low group. The incidence of postoperative complications and the severity of the disease (pT, pN, and pTNM stage) were comparable between the two groups ($P > 0.05$). Patients in the PNI-low group were more likely to exhibit higher aspartate transaminase (AST) and total bilirubin (TBIL) levels and lower creatinine (Cr) levels than were those in the PNI-high group (Table 1).

Analysis of independent prognostic factors for OS

The median OS for the entire cohort was 70 months, with estimated 1-year, 3-year, and 5-year OS rates of 91.6%, 68.4%, and 53.5%, respectively. Patients with a PNI ≥ 45.3 had a significantly greater 5-year OS rate than did those with a PNI <

Table 1 Comparison of the baseline characteristics of different groups of patients with ampullary adenocarcinoma, *n* (%)

Characteristic		Total (*n* = 233)	PNI-low (*n* = 100)	PNI-high (*n* = 133)	*P* value
Gender	Male	133 (57.1)	56 (56.0)	77 (57.9)	0.772
	Female	100 (42.9)	44 (44.0)	56 (41.1)	
Age, yr	≤ 60	141 (60.5)	52 (52.0)	89 (66.9)	0.021
	> 60	92 (39.5)	48 (48.0)	44 (33.1)	
Tumor size, cm	≤ 2	112 (48.1)	42 (42.0)	70 (52.6)	0.108
	> 2	121 (51.0)	58 (58.0)	63 (47.4)	
Tumor differentiation	Poor differentiation	88 (37.8)	43 (43.0)	45 (33.8)	0.063
	Moderate differentiation	96 (41.2)	43 (43.0)	53 (39.8)	
	Well differentiation	49 (21.0)	14 (14.0)	35 (26.4)	
Lymph nodes resection	< 17	156 (67.0)	64 (41.0)	92 (59.0)	0.406
	≥ 17	77 (33.0)	36 (46.8)	41 (53.2)	
Vascular invasion	No	182 (78.1)	74 (74.0)	108 (81.2)	0.188
	Yes	51 (21.9)	26 (26.0)	25 (18.8)	
pT	T1	31 (13.3)	13 (13.0)	18 (13.5)	0.829[1]
	T2	86 (36.9)	34 (34.0)	52 (39.1)	
	T3	110 (47.2)	50 (50.0)	60 (45.1)	
	T4	6 (2.6)	3 (3.0)	3 (2.3)	
pN	N0	162 (69.5)	64 (64.0)	98 (73.7)	0.193
	N1	58 (24.9)	28 (28.0)	30 (22.6)	
	N2	13 (5.6)	8 (8.0)	5 (3.7)	
TNM stage	I	97 (41.6)	36 (36.0)	61 (45.9)	0.213
	II	65 (27.9)	28 (28.0)	37 (27.8)	
	III	71 (30.5)	36 (36.0)	35 (26.3)	
Postoperative complication	No	142 (60.9)	40 (40.0)	51 (38.3)	0.798
	Yes	91 (39.1)	60 (60.0)	82 (61.6)	
Postoperative adjuvant therapy	No	152 (65.2)	29 (29.0)	34 (25.6)	0.597
	Yes	63 (27.0)	64 (64.0)	88 (74.4)	
	Unknow	18 (7.8)			
CA199, U/mL	≤ 59.67	107 (45.9)	38 (38.0)	69 (51.9)	0.053
	> 59.67	107 (45.9)	52 (52.0)	55 (48.1)	
	Unknow	19 (8.2)			
ALT, U/L	≤ 52.0	118 (50.6)	47 (47.0)	71 (53.4)	0.335
	> 52.0	115 (49.4)	53 (53.0)	62 (46.6)	
AST, U/L	≤ 55.0	122 (52.4)	44 (44.0)	78 (58.6)	0.027
	> 55.0	111 (47.6)	56 (56.0)	55 (41.4)	
TBIL, μmol/L	≤ 51.3	117 (50.2)	42 (42.0)	75 (56.4)	0.030
	> 51.3	116 (49.8)	58 (58.0)	58 (43.6)	
Cr, μmol/L	≤ 62.0	115 (49.4)	61 (61.0)	54 (40.6)	0.002
	> 62.0	118 (50.6)	39 (39.0)	79 (59.4)	

[1]Fisher exact test.

PNI: Prognostic nutritional index; CA199: Carbohydrate antigen 199; ALT: Alanine transaminase; AST: Aspartate transaminase; TBIL: Total bilirubin; Cr: Creatinine.

45.3 (61.8% *vs* 43.4%, $P = 0.006$; Figure 1A). According to the stratified analyses involving pT stage, pN stage, and TNM stage, patients with pT3 or pT4 tumors in the PNI-low group had a poorer prognosis ($P = 0.008$, Figure 1B). Similarly, patients with stage III disease, characterized by lymph node metastasis without distant spread, exhibited worse outcomes in the PNI-low group ($P = 0.035$, Figure 1C and D). Nonetheless, there were no statistically significant differences between the two groups in the remaining stratified analyses (Supplementary Figure 1).

Univariate analysis for OS showed that pT and pN, but not age, sex, postoperative complications, or adjuvant chemotherapy, were associated with OS. Multivariate analyses revealed that PNI [Hazard ratio (HR): 0.569; 95%CI: 0.383-0.846; $P = 0.005$], pT stage (HR: 1.901; 95%CI: 1.257-2.876; $P = 0.002$), and pN stage (HR: 1.851; 95%CI: 1.209-2.834; $P = 0.005$) were independent factors associated with OS (Table 2).

Analysis of independent prognostic factors for DFS

The estimated 1-year, 3-year, and 5-year DFS rates for all patients were 81.0%, 59.8%, and 52.7%, respectively, with a median DFS of 71 months. Patients with a PNI ≥ 45.3 also had a significantly greater 5-year DFS rate than did those with a PNI < 45.3 (53.5% *vs* 38.3%, $P = 0.012$; Figure 2A). After stratified analyses were performed, it was observed that among patients with stage pT3 or pT4 disease, those with a lower PNI tended to experience shorter DFS ($P = 0.002$; Figure 2B). No statistically significant differences were observed between the two groups in the remaining stratified analyses (Supplementary Figure 2).

The results of univariate survival analysis for DFS indicated associations with vascular invasion, pT stage, pN stage, and postoperative adjuvant therapy. Multivariate analysis identified PNI (HR: 0.674; 95%CI: 0.464-0.980; $P = 0.039$), pT stage (HR: 1.819; 95%CI: 1.215-2.723; $P = 0.004$) and pN stage (HR: 1.793; 95%CI: 1.130-2.846; $P = 0.013$) as independent predictors of DFS (Table 3).

DISCUSSION

The prognostic and clinicopathological significance of the PNI has been investigated in various malignancies. However, its specific role in patients with AC remains unclear. To the best of our knowledge, this is the first retrospective study in which the prognostic significance of the PNI and its correlation with clinicopathological characteristics in AC patients has been comprehensively examined. Our findings indicated that a high preoperative PNI was a significant predictor of improved OS and DFS, which might have a favorable impact on AC patients who underwent curative surgical resection.

The PNI serves as a biomarker for evaluating the nutritional and inflammatory status of patients. It was initially developed by Onodera *et al*[6] to evaluate the nutritional status of surgical patients, predict surgical risk, and determine prognosis. Subsequent studies have illuminated the predictive utility of the PNI across diverse tumor types. Okadome *et al*[13] reported that the PNI was valuable for assessing survival in patients with esophageal cancer. Yang *et al*[14] indicated that the preoperative PNI serves as a valuable predictor of postoperative complications and survival outcomes in patients diagnosed with gastric cancer. Park *et al*[15] also substantiated that the PNI, an indicator of immune-nutritional status, could predict the long-term outcome of non-small cell lung cancer patients. Our present study revealed that the OS and DFS rates of patients in the PNI-low group were significantly lower than those in the PNI-high group (both $P < 0.05$) and the predictive efficacy of the PNI was superior to that of other inflammatory biomarkers (PLR, NLR, and SII), with an AUC value of 0.535. Multivariate analysis revealed that the prognostic significance of the PNI paralleled that of lymph node metastasis (N stage) and infiltration depth (T stage). A diminished PNI was independently linked to a less favorable prognosis for individuals afflicted with AC. According to the stratified analysis, the PNI-low group exhibited significantly lower OS and DFS rates than did the PNI high-group among patients with T3 or T3 stage disease, while only an OS rate difference was observed between the PNI-high and PNI-low groups with lymph node metastasis.

Several factors contribute to the association between a low PNI and poor prognosis in patients with AC. First, the serum albumin concentration not only reflects nutritional status but also serves as a biomarker for systemic inflammation [16]. Some inflammatory factors may impede albumin synthesis, while oxidative stress can lead to the denaturation of albumin, both of which contribute to the swift reduction in serum albumin levels among patients in an inflammatory state[17-19]. Malnutrition and systemic inflammation are important factors driving tumor progression and metastasis[20-22]. Lymphocytes are essential components of the immune system with the capacity to eradicate cancer cells, making them indicative of immunological status. Research has indicated a significant association between reduced serum lymphocytes and adverse prognosis among cancer patients[23-25]. Therefore, the PNI reflects both the nutritional and immunological status of the host and can be a predictor of prognosis in patients with cancer. Second, we noted a close correlation between the PNI and age, TBIL, and AST. This observation aligns with the findings of Konishi *et al*[7], who noted a significantly higher PNI among younger patients undergoing gastrectomy compared to older patients. In our investigation, we found that the proportion of patients aged 60 years or older was higher in the PNI-low group than in the PNI-high group ($P = 0.021$). Numerous studies have corroborated that advanced age serves as an independent adverse prognostic factor for cancer patients[26,27]. In addition, the elevated levels of TBIL and AST in the PNI-high group may be attributed to biliary obstruction and impaired liver function, which have also been confirmed to be associated with poor prognosis in colorectal[28] and breast cancer patients[29]. Third, considering the established adverse

Table 2 Univariate and multivariate analysis of overall survival in patients with ampullary adenocarcinoma

Variate	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Gender (male *vs* female)	0.882	0.593-1.313	0.537			
age (≤ 60 *vs* > 60)	1.147	0.769-1.713	0.501			
Tumor size (≤ 2 *vs* > 2)	1.142	0.773-1.689	0.504			
Tumor differentiation (non-well *vs* well)	0.667	0.407-1.094	0.109			
Lymph nodes resection (< 17 *vs* ≥ 17)	1.161	0.761-1.771	0.488			
Vascular invasion (No *vs* Yes)	1.318	0.846-2.053	0.222			
pT (T1, T2 *vs* T3, T4)	2.114	1.417-3.153	< 0.001	1.901	1.257-2.876	0.002
pN (N0 *vs* N1, N2)	2.197	1.454-3.319	< 0.001	1.851	1.209-2.834	0.005
Postoperative complication (No *vs* Yes)	1.043	0.695-1.567	0.838			
Postoperative adjuvant therapy (No *vs* Yes)	1.432	0.934-2.195	0.100			
PNI (< 45.3 *vs* ≥ 45.3)	0.584	0.393-0.866	0.007	0.569	0.383-0.846	0.005

PNI: Prognostic nutritional index; 95%CI: 95% confidence interval; HR: Hazard ratio.

Table 3 Univariate and multivariate analysis of disease-free survival in patients with ampullary adenocarcinoma

Variate	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Gender (male *vs* female)	0.945	0.653-1.367	0.764			
Age (≤ 60 *vs* > 60)	1.048	0.723-1.518	0.806			
Tumor size (≤ 2 *vs* > 2)	1.213	0.844-1.745	0.297			
Tumor differentiation (non-well *vs* well)	0.666	0.420-1.056	0.084			
Lymph nodes resection (< 17 *vs* ≥ 17)	1.061	0.711-1.583	0.771			
Vascular invasion (No *vs* Yes)	1.523	1.012-2.291	0.044	1.063	0.677-1.668	0.792
pT (T1, T2 *vs* T3, T4)	1.975	1.363-2.861	< 0.001	1.819	1.215-2.723	0.004
pN (N0 *vs* N1, N2)	2.113	1.440-3.101	< 0.001	1.793	1.130-2.846	0.013
Postoperative complication (No *vs* Yes)	1.022	0.701-1.491	0.909			
Postoperative adjuvant therapy (No *vs* Yes)	1.591	1.072-2.360	0.021	0.958	0.590-1.557	0.863
PNI (< 45.3 *vs* ≥ 45.3)	0.631	0.438-0.909	0.013	0.674	0.464-0.980	0.039

PNI: Prognostic nutritional index; 95%CI: 95% confidence interval; HR: Hazard ratio.

effect of severe postoperative complications on long-term outcomes[30], the poorer OS and DFS in the low PNI group could be attributed to a greater incidence of postoperative complications. However, our present study revealed comparable incidences of severe postoperative complications between the two groups, with no statistically significant difference. Sakurai *et al*[31] reported a lack of significant correlation between the preoperative PNI and postoperative complications, probably because recent improvements in perioperative management have enhanced the safety of surgery.

Therefore, maintaining and/or increasing the preoperative PNI appears to be crucial for improving the outcomes of AC patients. Migita *et al*[32] found that oral nutritional supplementation did not increase the PNI in gastric cancer patients with low PNI values (baseline *vs* before surgery: 44.0 ± 3.9 *vs* 43.0 ± 4.4, $P = 0.049$). Similarly, Gunsel-Yildirim *et al*[33] observed that despite providing lung cancer patients with oral immunonutritional support twice daily, PNI levels significantly decreased in the postoperative period compared to those in the preoperative period. However, in a study involving patients undergoing PD, Tsukagoshi *et al*[34] reported that preoperative nutritional support (enteral nutrition) and prehabilitation (resistance or aerobic exercises) prevented a decrease in the PNI in patients with skeletal muscle loss. Paccagnella *et al*[35] also found that perioperative supplementation with arginine can reduce the incidence of complications and significantly increase long-term survival. Due to potential differences in patient characteristics and

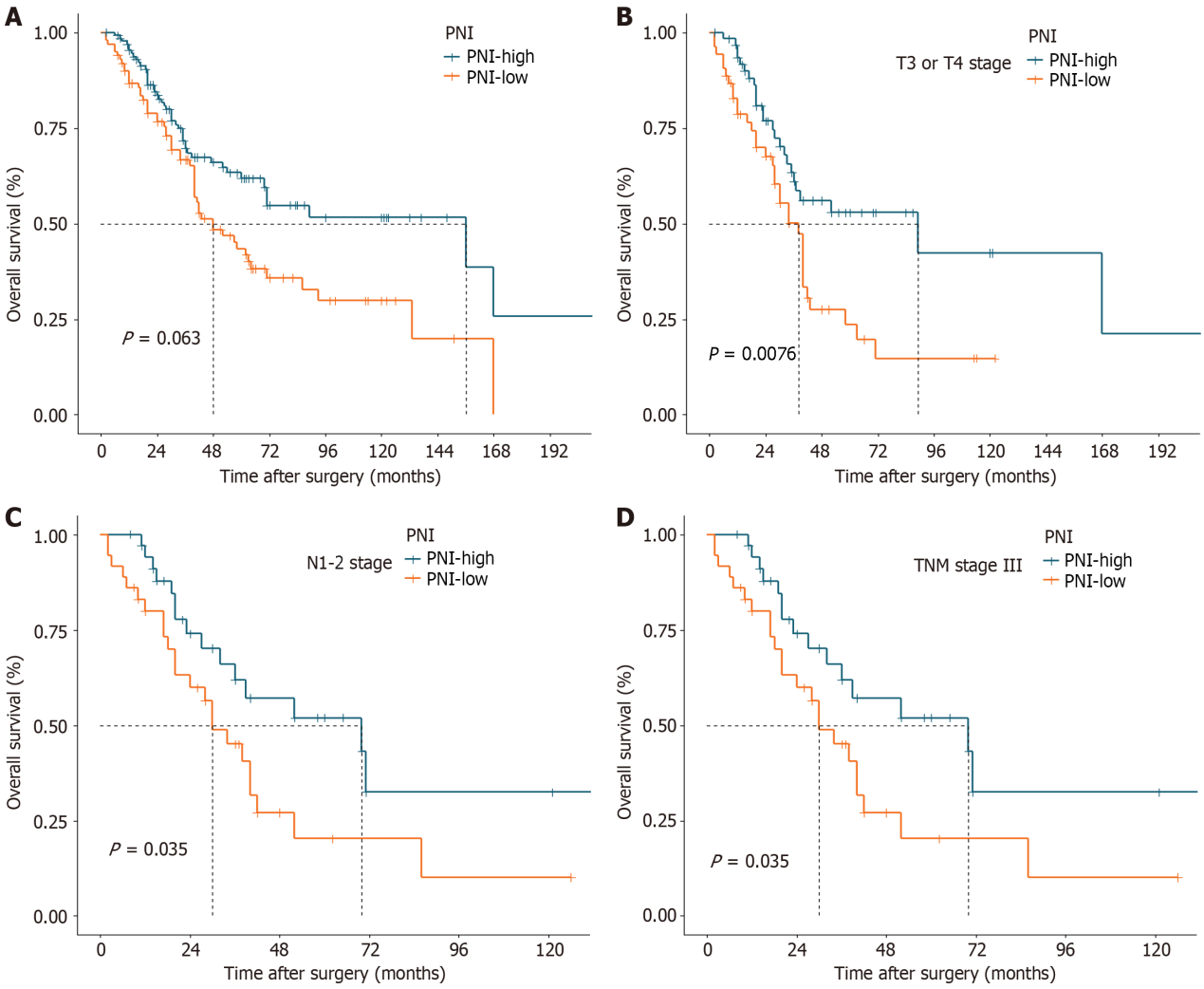

Figure 1 Comparison of the overall survival curves of different groups divided by the prognostic nutritional index. A: For all patients. The 5-year overall survival rates were 61.8% and 43.4% in the prognostic nutritional index (PNI)-high group and PNI-low group, respectively ($P = 0.006$); B: For patients with stage T3 or T4 disease ($P = 0.001$); C: For patients with lymph node metastasis (stage N1-3, $P = 0.035$); D: For patients with stage TNM III disease ($P = 0.035$). PNI: Prognostic nutritional index.

interventions across various studies, the results may exhibit heterogeneity. Nevertheless, it remains important for physicians to pay special attention to perioperative care for patients with low PNI values.

Furthermore, the optimal cutoff value for the PNI to effectively predict long-term outcomes remains uncertain. According to a meta-analysis focused on gastric cancer, the PNI cutoff value in the included studies varied between 40.0 and 49.7[14]. Okamura *et al*[36] found that the optimal cutoff value for the PNI for prognosis differs among TNM stages. Initially, this value was established at 45 because resection and anastomosis of the gastrointestinal tract can be safely performed when the PNI is > 45[6]. In our present study, we conducted an ROC curve analysis and identified the optimal PNI cutoff value as 45.3, where the Youden index was maximal. However, whether this cutoff value is the optimal prognostic value remains unknown, requiring further well-designed studies for clarification.

The strength of our study lies in being the first to establish a significant correlation between the PNI and the prognosis of patients with ampullary carcinoma following PD. The use of perioperative immunonutrition may improve early postoperative nutritional status and reduce postoperative complications for patients with ampullary carcinoma. Furthermore, the inclusion of data on DFS in our follow-up strengthens the validity of our research findings. Nevertheless, we must admit the limitations of the current study. First, this retrospective study is subject to selection bias due to inherent limitations in sample selection and data collection. Second, the follow-up time of some patients was relatively short, which is a limitation when pushing the results into clinical practice. Third, due to the lack of postoperative peripheral blood testing, we were unable to further assess the impact of dynamic changes in PNI on prognosis.

CONCLUSION

In this study, the preoperative PNI could be clinically utilized as a straightforward and valuable marker for predicting

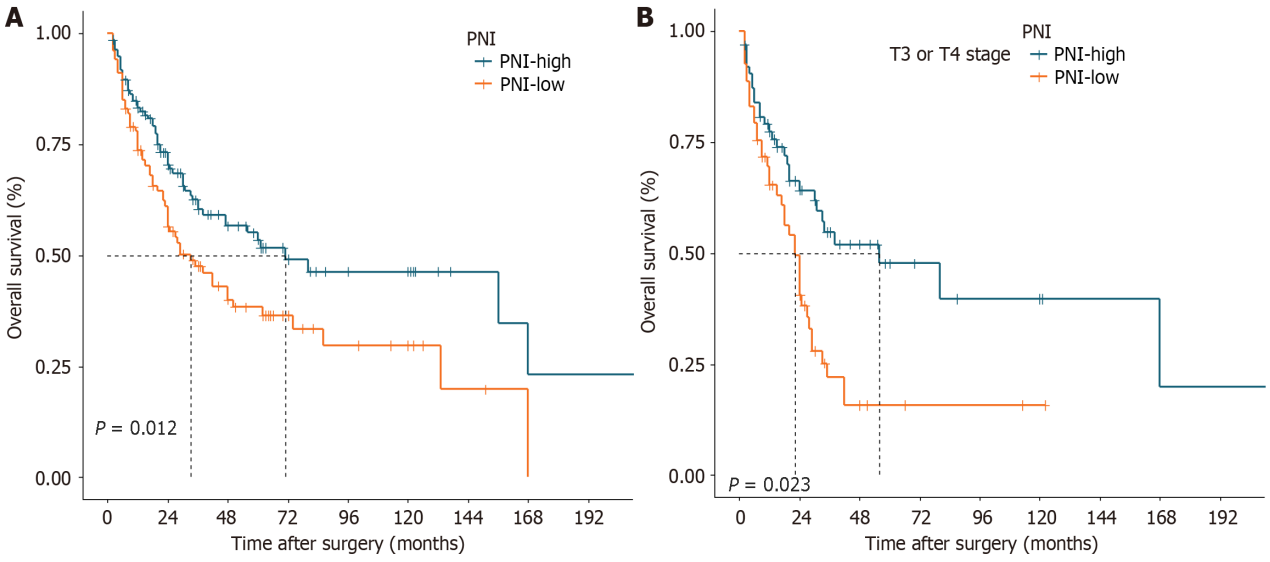

Figure 2 Comparison of the disease-free survival curves of different groups divided by the prognostic nutritional index. A: For all patients, the 5-year disease-free survival rates were 53.5% and 38.3% in the prognostic nutritional index (PNI)-high group and PNI-low group, respectively (P = 0.012); B: For patients with stage T3 or T4 disease (P = 0.002). PNI: Prognostic nutritional index.

long-term survival after surgery. Physicians should enhance perioperative management for patients with low preoperative PNI.

FOOTNOTES

Author contributions: Sun SC and Zhang XJ contributed equally to this work; Zhao DB designed the research study, who is the corresponding authors of this paper; Sun SC and Zhang XJ analyzed the data; and all authors wrote the manuscript and have approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Development and validation of a predictive model for acute-on-chronic liver failure after transjugular intrahepatic portosystemic shunt

Wei Zhang, Ya-Ni Jin, Chang Sun, Xiao-Feng Zhang, Rui-Qi Li, Qin Yin, Jin-Jun Chen, Yu-Zheng Zhuge

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Abstract

BACKGROUND

Transjugular intrahepatic portosystemic shunt (TIPS) is a cause of acute-on-chronic liver failure (ACLF).

AIM

To investigate the risk factors of ACLF within 1 year after TIPS in patients with cirrhosis and construct a prediction model.

METHODS

In total, 379 patients with decompensated cirrhosis treated with TIPS at Nanjing Drum Tower Hospital from 2017 to 2020 were selected as the training cohort, and 123 patients from Nanfang Hospital were included in the external validation cohort. Univariate and multivariate logistic regression analyses were performed to identify independent predictors. The prediction model was established based on the Akaike information criterion. Internal and external validation were conducted to assess the performance of the model.

RESULTS

Age and total bilirubin (TBil) were independent risk factors for the incidence of

ACLF within 1 year after TIPS. We developed a prediction model comprising age, TBil, and serum sodium, which demonstrated good discrimination and calibration in both the training cohort and the external validation cohort.

CONCLUSION

Age and TBil are independent risk factors for the incidence of ACLF within 1 year after TIPS in patients with decompensated cirrhosis. Our model showed satisfying predictive value.

Key Words: Acute-on-chronic liver failure; Transjugular intrahepatic portosystemic shunt; Influencing factor analysis; Risk prediction model; Nomogram

Core Tip: Previous studies have proposed several models for predicting the prognosis of patients with acute-on-chronic liver failure (ACLF). However, to date, no such prediction model exists for forecasting the occurrence of ACLF following transjugular intrahepatic portosystemic shunt (TIPS). This study provides an internally and externally validated nomogram model, as well as an easy-to-use risk score scale for predicting the risk of ACLF within 1 year after TIPS. This information could enable physicians to effectively communicate the risks and benefits of the procedure to patients, facilitating shared decision-making.

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INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a clinical syndrome characterized by acute liver failure on underlying chronic liver disease. It manifests as jaundice, coagulation dysfunction, and hepatic encephalopathy. Currently, medical therapy, including pharmacological treatment and artificial liver therapy, is the main treatment for patients with ACLF. For those who do not respond to routine medical treatment, liver transplantation is the only curative treatment[1]. However, the use of liver transplantation is limited by the number of donors and the high cost of the procedure. Despite aggressive therapy, the short-term mortality remains very high among patients with ACLF, usually over 30%[2,3]. Therefore, it is crucial to identify the risk factors of ACLF, identify high-risk patients in the early stages, and improve the management of high-risk patients to delay or prevent the progression of liver damage to ACLF[4]. In recent years, several risk score models have been developed to predict the prognosis of patients with ACLF, such as the model for end-stage liver disease (MELD) score, chronic liver failure-sequential organ failure assessment score, and the Asian Pacific Association for the Study of the Liver (APASL) ACLF research consortium score[5]; however, studies predicting the incidence of ACLF are relatively rare.

Transjugular intrahepatic portosystemic shunt (TIPS) is an interventional strategy that reduces portal venous pressure. It is mostly used to treat the complications of portal hypertension, such as esophagogastric variceal bleeding and refractory ascites, in patients with cirrhosis[6]. Although the TIPS procedure can effectively reduce portal venous pressure and relieve the complications of portal hypertension, it may also deteriorate liver function and induce ACLF in some patients[7]. A previous study showed that within 3 months after TIPS, liver failure occurred in 9.2% of patients with cirrhosis with MELD ≤ 12 points[8].

Currently, there are no studies on ACLF after TIPS. Predicting the risk of ACLF after TIPS in patients with cirrhosis may help clinicians make more accurate treatment decisions. Therefore, we investigated independent predictors of ACLF within 1 year after TIPS and developed an effective predictive model to predict the risk of ACLF after TIPS. This predictive model can help physicians identify patients at high risk of postoperative ACLF before conducting the TIPS procedure.

MATERIALS AND METHODS

Patients

In total, 828 consecutive patients with cirrhosis who underwent TIPS at Nanjing Drum Tower Hospital and Nanfang Hospital, Southern Medical University, between January 2017 and December 2020, were screened based on the inclusion and exclusion criteria. Inclusion criteria were as follows: (1) Age more than or equal to 18 years; (2) meeting the diagnostic criteria of cirrhosis based on medical history, laboratory, and imaging studies; and (3) successful TIPS procedure.

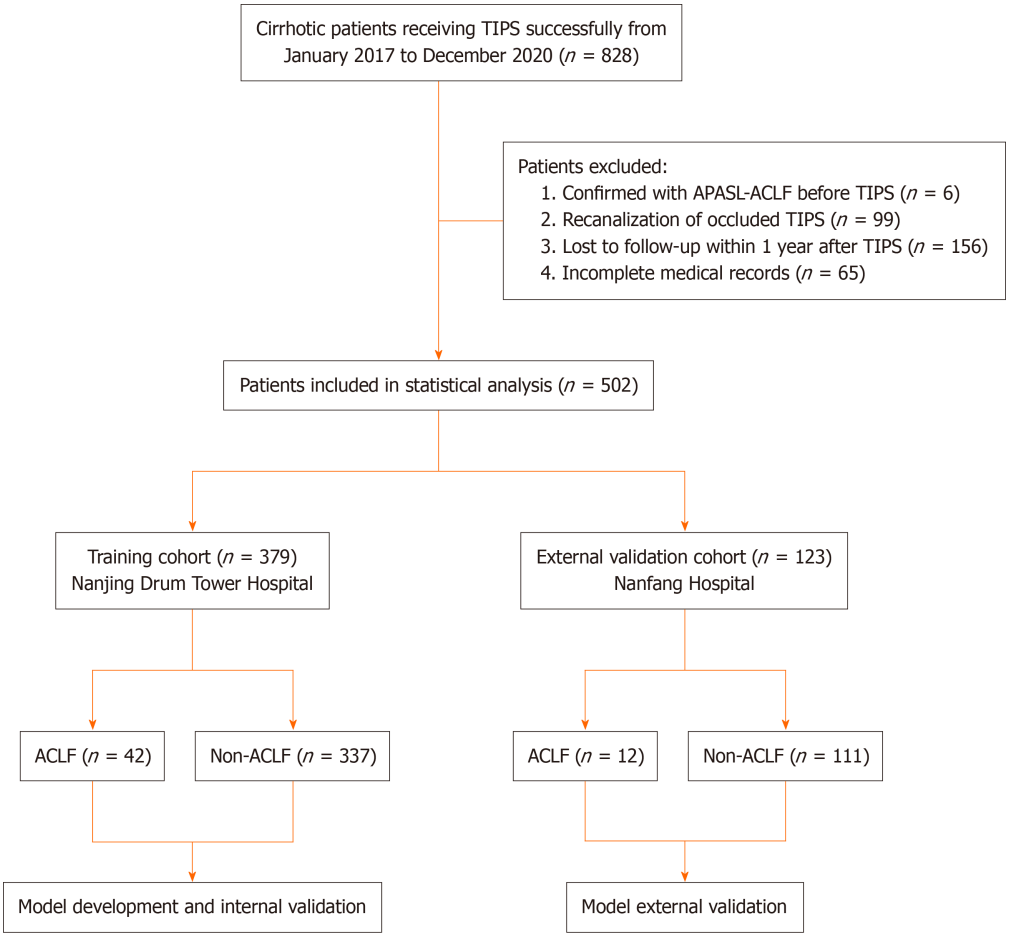

Figure 1 Patients' flowchart. TIPS: Transjugular intrahepatic portosystemic shunt; APASL: Asian Pacific Association for the Study of the Liver; ACLF: Acute-on-chronic liver failure.

Exclusion criteria were as follows: (1) Confirmed APASL-ACLF before TIPS; (2) undergoing recanalization for occluded TIPS; (3) lost to follow-up within 1 year after TIPS; (4) absence of preoperative clinical data; (5) concomitant cancer; and (6) heart, kidney, and other major organ failure. In total, 502 patients were included in the final analysis. First, 379 patients at Nanjing Drum Tower Hospital, including 42 patients in the ACLF group and 337 patients in the non-ACLF group, were enrolled as the training cohort and were enrolled to develop the model. Then, 123 patients at Nanfang Hospital, Southern Medical University, including 12 patients in the ACLF group and 111 patients in the non-ACLF group, were enrolled in the external validation group. This study complies with the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement. The flow chart is shown in Figure 1. This study followed the ethical principles reported in the Declaration of Helsinki and Istanbul. The protocol of this study was approved by the Ethics Committee of The Affiliated Drum Tower Hospital of Nanjing University Medical School (approval No. 2022-596-02). Verbal informed consent was obtained from all participants *via* telephone.

Data collection

Preoperative and intraoperative variables were recorded for each patient. Preoperative variables included gender, age, history of diabetes mellitus, history of portal vein thrombosis, history of splenectomy, etiology of cirrhosis, and TIPS indication. Four liver function scores, including the Child-Pugh score, MELD score, MELD-Na score, and CLIF-C acute decompensation (AD) score, were recorded. Preoperative laboratory indicators included white blood cell (WBC) count, platelet count, alanine transaminase (ALT), serum total bilirubin (TBil), serum albumin (Alb), serum creatinine, serum sodium (Na), international normalized ratio (INR), and fibrinogen, which were measured within 1 wk before surgery. Intraoperative variables included stent diameter and puncture site.

Study endpoints and follow-up

The primary endpoint was the incidence of ACLF within 1 year after TIPS. Postoperative death, postoperative rebleeding, and postoperative stent stenosis were secondary endpoints. All patients were followed in clinic or *via* telephone at 1, 3, and 6 months after TIPS and every 6 months thereafter until August 31, 2022.

Definition of ACLF

There is no universal definition of ACLF globally; therefore, we used the definition of APASL because its study popu-

lation was similar to ours. According to the APASL ACLF consensus of 2019, ACLF is defined as an acute hepatic injury manifesting as jaundice (serum bilirubin ≥ 5 mg/dL or 85 umol/L) and coagulopathy (INR ≥ 1.5 or prothrombin activity < 40%) developing within 4 wk and accompanied by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis. Previously, it was shown that ACLF is associated with a high 28-d mortality rate.

Statistical analysis

R 4.2.1 was used for data processing and development and validation of the nomogram model. Continuous variables are expressed as mean ± SD or median (interquartile range), and statistical differences were estimated using the independent sample *t*-test or the Mann-Whitney *U* test. Count data are expressed as the number of cases and percentage (%). We used the χ^2 test or Fisher's exact probability method to compare groups. Univariate regression analysis was conducted using binary logistic regression, and variables with $P < 0.10$ in univariate analysis were included in multivariate logistic regression analysis. We used the Akaike Information Criterion (AIC) as a stopping criterion and selected the model with the lowest AIC using the backward stepwise method. The nomogram model was then plotted. We performed a bootstrap internal validation procedure with 1000 bootstrap resamples. Additionally, a geographically independent cohort was used for external validation. Model performance was measured using discrimination and calibration. The model's discrimination ability was assessed by calculating the area under the receiver operating characteristic (ROC) curve, and calibration was assessed using the Hosmer-Lemeshow test and calibration plots. Using ROC curves in the entire cohort, we assessed the predictive performance of the nomogram model compared to four commonly used liver function scoring systems (*i.e.*, MELD score, Child-Pugh score, CLIF-C AD score, and MELD-Na score). The ROC curves were compared using DeLong's test. To facilitate clinical application, we integrated the regression coefficients of each variable in the model and assigned values to these variables to develop a risk score model. Survival analysis was conducted using the Kaplan-Meier method, and differences between groups were measured using the log-rank test. A P value < 0.05 was considered statistically significant.

RESULTS

In the entire cohort, 828 patients were successfully treated with TIPS from January 2017 to December 2020. Of them, 6 patients who were diagnosed with APASL-ACLF before TIPS procedure, 99 patients who underwent TIPS for shunt dysfunction, 156 patients who were lost to follow-up within 1 year after TIPS, and 65 patients with notable missing data were excluded based on the exclusion criteria. In total, 502 patients were enrolled in the final analysis, including 379 patients in the training cohort and 123 patients in the external validation cohort. The training cohort consisted of 219 men and 160 women, with a median age of 59 years (range: 18-86 years). The median follow-up time was 629 d in the ACLF group and 722 d in the non-ACLF group. The external validation cohort consisted of 100 men and 23 women, with a median age of 51 years (range: 22-74 years). The median follow-up time was 364 d in the ACLF group and 542 d in the non-ACLF group.

Overall, 54 patients (10.76%) developed ACLF within 1 year after TIPS. Among those who developed ACLF within 1 year after TIPS, 23 (42.60%) developed ACLF within 28 d and 17 (31.50%) developed ACLF between day 29 and day 180. In the entire cohort, the incidence of ACLF within 28 d, 180 d, and 1 year after the TIPS procedure was 4.68%, 7.97%, and 10.76%, respectively. The baseline characteristics of the training cohort and the external validation cohort are shown in Supplementary Table 1.

Univariate and multivariate analysis for the incidence of ACLF within 1 year after the TIPS procedure. In total, 17 variables were included in a univariate regression analysis to investigate the predictors of ACLF within 1 year after TIPS. Variables with a P value of less than 0.10 in the univariate analysis were selected for multivariate logistic regression analysis. The model was built using a backward conditional method, which identified age [age ≥ 65 years, odds ratio (OR): 2.649, 95% confidence interval (95%CI): 1.263-5.558, $P = 0.010$] and TBil (TB: 17.1-34.2 umol/L, OR: 2.944, 95%CI: 1.151-7.528, $P = 0.024$; TB: 34.2-51.2 umol/L, OR: 11.632, 95%CI: 4.068-33.259, $P < 0.001$; TB ≥ 51.3 umol/L, OR: 28.746, 95%CI: 6.969-118.579, $P < 0.001$) as independent risk factors for ACLF within 1 year after TIPS procedure (Table 1).

Establishment and validation of the nomogram model

Serum sodium level was included in the final prediction model based on the minimum AIC. Therefore, we developed a predictive model including three variables: Age, TBil, and serum sodium. We compared the area of the curve (AUC) of this model with other models using data from the entire cohort (Supplementary Table 2). Considering the simplicity and predictive power of the model, it was determined to be the optimal choice compared to other models. Figure 2 displays a predictive nomogram based on the three variables. In addition, the nomogram is available through a free browser-based online calculator at https://jyn1212.shinyapps.io/DynNomapp/. Using this calculator, the risk of developing ACLF within 1 year after TIPS can be estimated and displayed.

In the training cohort, the AUC of this prediction model was 0.800 (95%CI: 0.731-0.868) with a cutoff value of 0.112, corresponding to a sensitivity and specificity of 0.700 and 0.775, respectively (Figure 3A). We conducted a bootstrap internal validation procedure with 1000 bootstrap repetitions. The AUC was 0.774, indicating good discrimination power. The calibration curve showed that the predicted probability of ACLF based on the nomogram model aligned well with the actual probability (Figure 3C), with a Brier score of 0.084 and a Hosmer-Lemeshow test $\chi^2 = 3.950$, $P = 0.915$. These findings suggest that the model has good calibration ability. In the external validation cohort, the AUC of the nomogram prediction model was 0.761 (95%CI: 0.607-0.914), and the cutoff value of the ROC curve was 0.288, corresponding to a

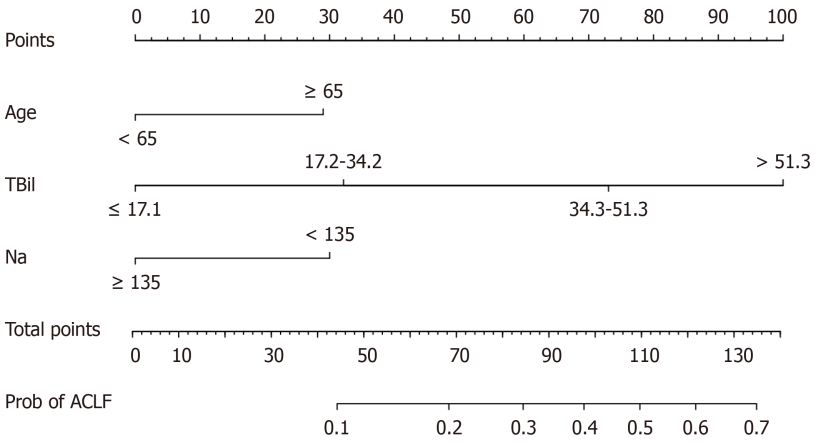

Figure 2 The nomogram model for predicting the incidence of acute-on-chronic liver failure within 1 year after transjugular intrahepatic portosystemic shunt. ACLF: Acute-on-chronic liver failure; TBil: Total bilirubin; Na: Sodium.

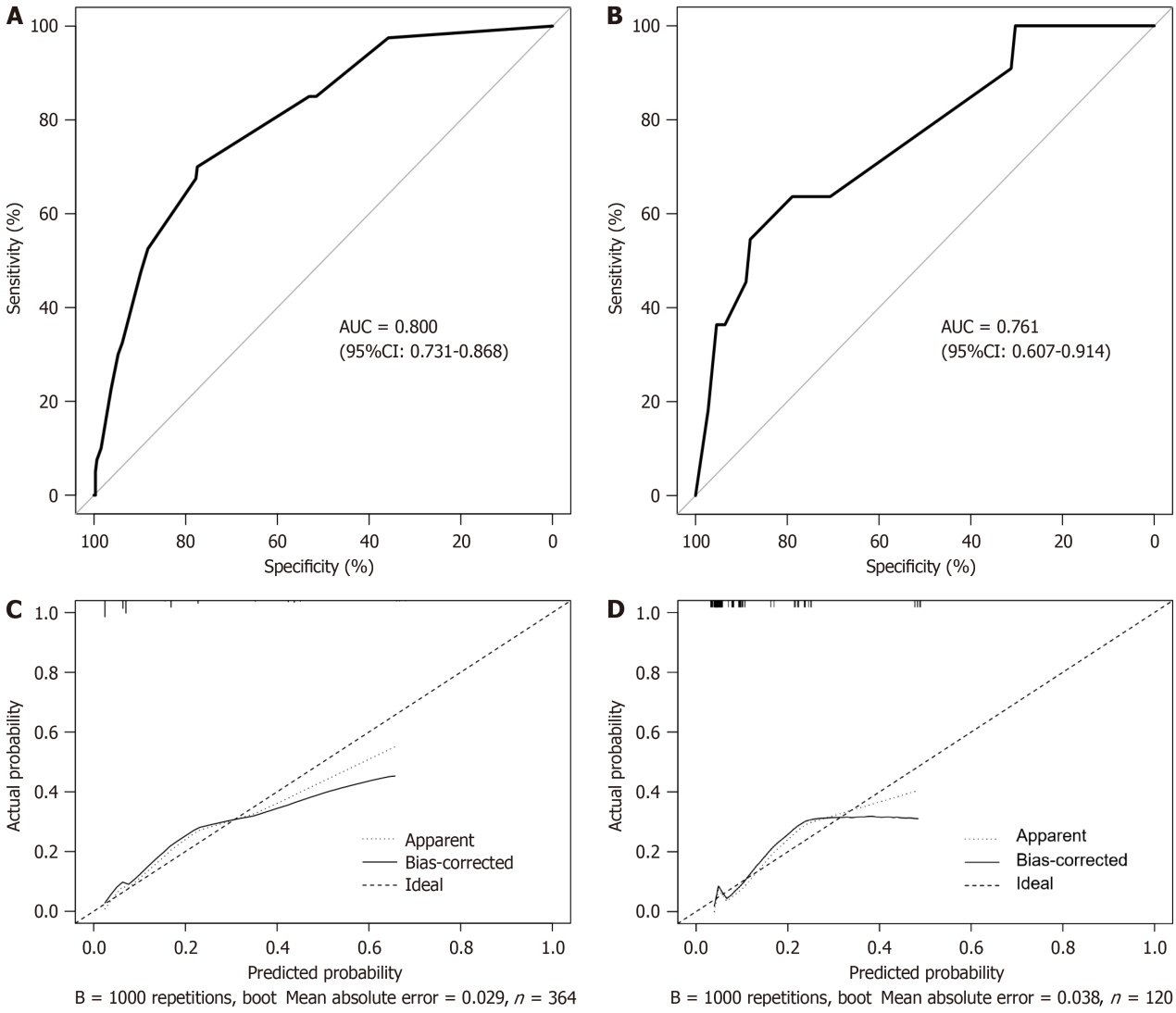

Figure 3 Receiver operating characteristic curves and the calibration plots of the model for predicting the incidence of acute-on-chronic liver failure within 1 year after transjugular intrahepatic portosystemic shunt. A: In the training cohort, the area under the receiver operating characteristic curve (AUC) of the model was 0.800 [95% confidence interval (95%CI): 0.731-0.868]; B: In the validation cohort, the AUC of the model was 0.761 (95%CI: 0.607-0.914); C and D: The calibration plots in the training and validation cohorts. The predicted probability of the model was plotted on the x-axis; the actual probability was plotted on the y-axis. An ideal calibration plot is indicated by a 45° diagonal line. AUC: Area under the receiver operating characteristic curve; 95%CI: 95% confidence interval.

Table 1 Univariate and multivariate logistic regression analyses of variables in predicting the incidence of acute-on-chronic liver failure within 1 year after transjugular intrahepatic portosystemic shunt in the training cohort

Variables	OR comparison	Univariate analysis			Multivariate analysis		
		OR	95%CI	*P* value	OR	95%CI	*P* value
Gender	Male *vs* female	0.922	0.471-1.802	0.811			
Age	≥ 65 yr *vs* < 65 yr	2.086	1.074-4.055	0.030	2.649	1.263-5.558	0.010[a]
DM	Yes *vs* No	1.847	0.905-3.769	0.092			
Portal vein thrombosis	Yes *vs* No	0.809	0.411-1.590	0.539			
Splenectomy	Yes *vs* No	0.426	0.146-1.240	0.117			
Etiology of cirrhosis	Viral hepatitis *vs* other	1.174	0.609-2.265	0.631			
TIPS indication	EGVB *vs* refractory ascites	1.304	0.477-3.563	0.605			
WBC	< 4.0 × 10^9/L *vs* ≥ 4.0 × 10^9/L	0.578	0.297-1.123	0.106			
PLT	< 100 × 10^9/L *vs* ≥ 100 × 10^9/L	2.085	0.930-4.674	0.075			
ALT	> 40 U/L *vs* ≤ 40 U/L	2.000	0.856-4.673	0.109			
TBil	17.1-34.1 μmol/L *vs* < 17.1 μmol/L	3.064	1.212-7.742	0.018	2.944	1.151-7.528	0.024[a]
	34.2-51.2 μmol/L *vs* < 17.1 μmol/L	12.357	4.433-34.443	0	11.632	4.068-33.259	< 0.001[a]
	≥ 51.3 μmol/L *vs* < 17.1 μmol/L	24.714	6.342-96.315	0	28.746	6.969-118.579	< 0.001[a]
Alb	≥ 35.0 g/L *vs* < 35.0 g/L	1.651	0.758-3.596	0.206			
Na	< 135 mmol/L *vs* ≥ 135 mmol/L	3.606	1.402-9.275	0.008	2.741	0.960-7.821	0.060[1]
Scr	≥ 133 μmol/L *vs* < 133 μmol/L	1.368	0.295-6.349	0.689			
INR	< 1.5 *vs* ≥ 1.5	2.363	1.001-5.575	0.050			
FIB	< 2.0 g/L *vs* ≥ 2.0 g/L	1.542	0.726-3.273	0.259			
Stent diameter	≥ 8 mm *vs* < 8 mm	0.787	0.392-1.581	0.501			
Puncture site	Right branch *vs* left branch	1.000	0.373-2.680	1.000			
	Bifurcation *vs* left branch	1.067	0.437-2.602	0.887			
	Trunk *vs* left branch	0.889	0.352-2.246	0.803			

[a]$P < 0.05$.

[1]Included on the basis of a minimized Akaike Information Criterion value.

OR: Odd ratio; 95%CI: 95% confidence interval; DM: Diabetes mellitus; TIPS: Transjugular intrahepatic portosystemic shunt; EGVB: Esophagogastric variceal bleeding; WBC: White blood cell; PLT: Platelet; ALT: Alanine transaminase; TBil: Total bilirubin; Alb: Albumin; Na: Sodium; Scr: Serum creatinine; INR: International normalized ratio; FIB: Fibrinogen.

sensitivity and specificity of 0.545 and 0.881, respectively (Figure 3B). These findings indicate that the model showed good discrimination in the external validation cohort. The calibration in the external validation cohort was also good, with a Brier score of 0.082 and a Hosmer-Lemeshow test $\chi^2 = 5.793$, $P = 0.760$. The calibration plot is shown in Figure 3D.

We also assigned scores to each variable based on the regression coefficients of the variables in the model and compiled a risk score (Table 2). The total score was 8, with a cutoff value of 4.5. In the entire cohort, the AUC of the risk score was 0.787 (95%CI: 0.729-0.845) (Figure 4), which was comparable to that of the nomogram model ($P = 0.645$) (Supplementary Table 2). The probability of ACLF for each score is shown in Supplementary Table 3. Patients were then stratified into three groups based on their scores: Low risk (total score of 3-4), medium risk (total score of 5-6), and high risk (total score of 7-8) group. In the whole cohort, the actual incidence of ACLF was 4.7% among patients with a total score of 3-4, 24.1% among patients with a total score of 5-6, and 50.0% among patients with a total score of 7-8.

The predictive ability of the proposed nomogram model was compared with that of four commonly used liver function scoring systems using ROC curve analysis (Figure 4) for the entire cohort of 502 patients. The discriminatory ability of the nomogram model had an AUC of 0.792 (95%CI: 0.730-0.853), which was superior to MELD score (AUC: 0.696, 95%CI:

Table 2 Risk score scale for prediction of the incidence of acute-on-chronic liver failure within 1 year after transjugular intrahepatic portosystemic shunt

Variable	1 point	2 points	3 points	4 points
Age (yr)	< 65.0	≥ 65.0		
TBil (μmol/L)	≤ 17.1	17.2-34.2	34.3-51.3	> 51.3
Na (mmol/L)	≥ 135.0	< 135.0		

TBil: Total bilirubin; Na: Sodium.

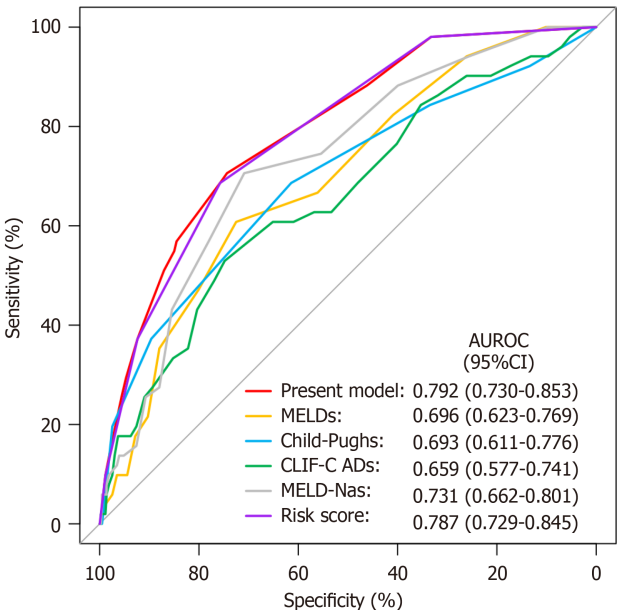

Figure 4 Receiver operating characteristic curves of the prediction model, risk score, and four liver function scoring systems for the prediction of the incidence of acute-on-chronic liver failure within 1 year after transjugular intrahepatic portosystemic shunt in the entire cohort. MELDs: Model for end-stage liver disease score; Child-Pughs: Child-Pugh score; CLIF-C ADs: Chronic Liver Failure Consortium acute decompensation score; MELD-Nas: MELD-Na score; AUROC: Area under the receiver operating characteristic curve; 95%CI: 95% confidence interval.

0.623-0.769, P = 0.002), Child-Pugh score (AUC: 0.693, 95%CI: 0.611-0.776, P = 0.018), CLIF-C AD score (AUC: 0.659, 95%CI: 0.577-0.741, P = 0.002), and MELD-Na score (AUC: 0.731, 95%CI: 0.662-0.801, P = 0.022).

Survival analysis

During the follow-up period, 34 deaths occurred in the ACLF group, of which 27 were associated with liver disease. The cumulative survival rates at 28 d, 180 d, and 1 year were 88.7%, 64.2%, and 38.0%, respectively. The Kaplan-Meier survival curve showed that the cumulative survival rate in the ACLF group was significantly lower than that in the non-ACLF group (Figure 5A). Furthermore, the incidence of liver disease-related deaths was significantly higher in the ACLF group than in the non-ACLF group (both P values < 0.001) (Figure 5B), suggesting that the incidence of ACLF was associated with a poor prognosis. Regarding postoperative complications, the cumulative postoperative rebleeding rate was significantly higher in the ACLF group than in the non-ACLF group (P < 0.001) (Figure 5C), but there was no statistically significant difference in the incidence of postoperative stent stenosis between the two groups (Figure 5D).

DISCUSSION

ACLF is an acute deterioration of chronic liver disease characterized by high short-term mortality. Early diagnosis and treatment of potential precipitating events are crucial in preventing ACLF[9]. These precipitating events include hepatitis B infection, acute viral hepatitis, alcohol consumption, hepatotoxic drugs, and acute variceal bleeding[1]. Based on the CANONIC study in 2011, the TIPS procedure, as an invasive transhepatic treatment strategy, may increase the risk of ACLF[3]. After the TIPS procedure, the portal blood flow enters directly into the systemic circulation without passing through the liver, reducing blood flow to the liver. In addition, the puncture process causes direct mechanical damage to the liver. In addition, the stent compresses the surrounding liver tissue and affects bile excretion, impairing liver function.

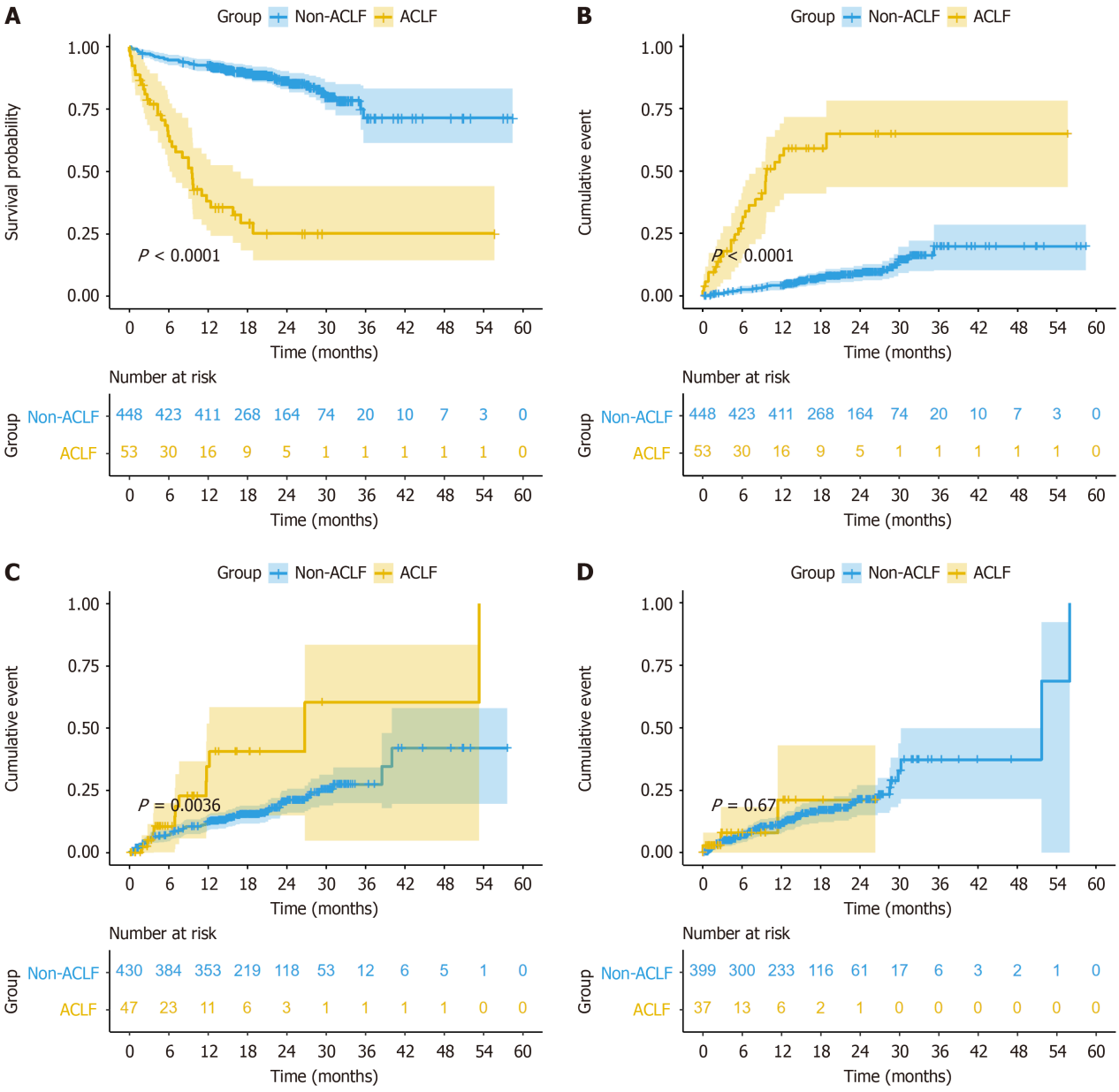

Figure 5 The prognosis between the acute-on-chronic liver failure group and the non-acute-on-chronic liver failure group. A: The Kaplan-Meier curve shows the probability of survival; B: The Kaplan-Meier curve shows the liver disease-related mortality rates; C: The Kaplan-Meier curve shows the rebleeding rates; D: The Kaplan-Meier curve shows the probability of stent stenosis. ACLF: Acute-on-chronic liver failure.

Considering these mechanisms, the main purpose of this study was to establish a predictive model based on the risk factors of ACLF after TIPS to help clinicians select appropriate patients for TIPS procedures and reduce the risk of ACLF after TIPS. To date, several studies have been conducted to predict ACLF, but none of them were conducted on post-TIPS patients; thus, their results are not suitable for predicting ACLF after TIPS. Xiao *et al*[10] proposed the first prediction model of APASL-ACLF based on outpatients with compensated cirrhosis. The independent predictors included hazardous drinking behaviors, age, baseline Alb, INR, TBil, creatinine, and hemoglobin. The incidence of ACLF 1 year after the baseline assessment was 1.36%. Similarly, Yu *et al*[11] developed a prediction model for ACLF in patients with chronic hepatitis B and severe acute exacerbation. Yu *et al*[11] proposed a PATA model comprising prothrombin time, age, TBil, and ALT. The above-mentioned studies together confirm the predictive ability of age and TBil for ACLF.

Similar to previous studies, in our study, TBil and age were found to be independent predictors of ACLF after TIPS. TBil is often used to assess the severity of liver impairment, and higher levels of TBil indicate more severe hepatic damage. In addition, TBil is an important parameter in several liver function evaluation models, such as the Child-Pugh score and MELD score. Our study confirmed that TBil can also be used to predict the incidence of ACLF after TIPS, and patients with high TBil levels before TIPS are more likely to develop ACLF after surgery. Age is also an independent risk factor for ACLF after TIPS, which may be related to the aging of the liver. With aging, the liver undergoes significant changes at the tissue-organ and cellular levels, resulting in decreased reserve and regeneration capacity[12]. Therefore, elderly patients are more likely to exhibit abnormal liver function under internal or external stresses. Hyponatremia is common in ACLF and predicts a poor prognosis[13,14]. A previous study has shown that a lower level of serum sodium

is an independent risk factor for developing severe ACLF in patients with cirrhosis and bacterial infection[15].

Previous studies have confirmed that a severe systemic inflammatory state is the major driver of extensive tissue and organ damage in patients with acute decompensated cirrhosis who develop ACLF[16]. Compared to cirrhotic patients without ACLF, patients with ACLF have higher WBC counts and plasma levels of C-reactive protein[3]. However, our study did not find a correlation between WBC count and the development of ACLF. This could be because our data were the baseline data of patients, which were collected before TIPS, and patients did not exhibit a severe systemic inflammatory state before developing ACLF.

Based on the minimum AIC, we developed a risk prediction model that can predict the incidence of ACLF within 1 year after the TIPS procedure. The model showed good discrimination and calibration in both the training cohort and the external validation cohort. Furthermore, the discriminatory ability of the nomogram model was superior to that of the MELD score, Child-Pugh score, CLIF-C AD score, and MELD-Na score. Based on this model, we also constructed other models, and after comparison, we found that there was no significant improvement in the AUC. Therefore, we finally chose the first model as it was simpler. To facilitate its clinical application, we also transformed the nomogram model into a risk score. The predictive ability of the risk score was comparable to that of the nomogram model. Patients with a score of 3-4 are at low risk of ACLF, and for such patients, TIPS can be actively performed in the presence of an indication for TIPS. In contrast, patients with a score of 7-8 are at higher risk of ACLF, and clinicians should be cautious and adopt active treatment to reduce patients' scores before the TIPS procedure. Other treatments or liver transplantation should be considered if patients' risk scores remain high. For patients with a score of 5-6, we should assess the benefit-risk of TIPS and fully consider patients' willingness to undergo the procedure.

Limitations: First, selection bias may exist as this study was a retrospective study with a limited sample size. Additionally, a notable number of patients were lost to follow-up, indicating that the number of patients was possibly underestimated. However, the incidence of ACLF was comparable between the two cohorts. Second, as our findings were based on patients with APASL-ACLF, whether the model can be applied to other populations needs more studies.

CONCLUSION

In conclusion, the incidence of ACLF within 1 year after TIPS was independently associated with age and TBil. Our model and risk score can help predict the incidence of ACLF after TIPS, providing a reference for clinical decision-making. Prospective validation in larger cohorts is needed to assess the generalizability of our findings.

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FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Evaluating the use of three-dimensional reconstruction visualization technology for precise laparoscopic resection in gastroesophageal junction cancer

Dan Guo, Xiao-Yan Zhu, Shuai Han, Yu-Shu Liu, Da-Peng Cui

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Abstract

BACKGROUND

Laparoscopic gastrectomy for esophagogastric junction (EGJ) carcinoma enables the removal of the carcinoma at the junction between the stomach and esophagus while preserving the gastric function, thereby providing patients with better treatment outcomes and quality of life. Nonetheless, this surgical technique also presents some challenges and limitations. Therefore, three-dimensional reconstruction visualization technology (3D RVT) has been introduced into the procedure, providing doctors with more comprehensive and intuitive anatomical information that helps with surgical planning, navigation, and outcome evaluation.

AIM

To discuss the application and advantages of 3D RVT in precise laparoscopic resection of EGJ carcinomas.

METHODS

Data were obtained from the electronic or paper-based medical records at The First Affiliated Hospital of Hebei North University from January 2020 to June 2022. A total of 120 patients diagnosed with EGJ carcinoma were included in the study. Of these, 68 underwent laparoscopic resection after computed tomography (CT)-enhanced scanning and were categorized into the 2D group, whereas 52 underwent laparoscopic resection after CT-enhanced scanning and 3D RVT and were categorized into the 3D group. This study had two outcome measures: the deviation between tumor-related factors (such as maximum tumor diameter and infiltration length) in 3D RVT and clinical reality, and surgical outcome indicators

(such as operative time, intraoperative blood loss, number of lymph node dissections, R0 resection rate, postoperative hospital stay, postoperative gas discharge time, drainage tube removal time, and related complications) between the 2D and 3D groups.

RESULTS

Among patients included in the 3D group, 27 had a maximum tumor diameter of less than 3 cm, whereas 25 had a diameter of 3 cm or more. In actual surgical observations, 24 had a diameter of less than 3 cm, whereas 28 had a diameter of 3 cm or more. The findings were consistent between the two methods (χ^2 = 0.346, P = 0.556), with a kappa consistency coefficient of 0.808. With respect to infiltration length, in the 3D group, 23 patients had a length of less than 5 cm, whereas 29 had a length of 5 cm or more. In actual surgical observations, 20 cases had a length of less than 5 cm, whereas 32 had a length of 5 cm or more. The findings were consistent between the two methods (χ^2 = 0.357, P = 0.550), with a kappa consistency coefficient of 0.486. Pearson correlation analysis showed that the maximum tumor diameter and infiltration length measured using 3D RVT were positively correlated with clinical observations during surgery (r = 0.814 and 0.490, both P < 0.05). The 3D group had a shorter operative time (157.02 ± 8.38 *vs* 183.16 ± 23.87), less intraoperative blood loss (83.65 ± 14.22 *vs* 110.94 ± 22.05), and higher number of lymph node dissections (28.98 ± 2.82 *vs* 23.56 ± 2.77) and R0 resection rate (80.77% *vs* 61.64%) than the 2D group. Furthermore, the 3D group had shorter hospital stay [8 (8, 9) *vs* 13 (14, 16)], time to gas passage [3 (3, 4) *vs* 4 (5, 5)], and drainage tube removal time [4 (4, 5) *vs* 6 (6, 7)] than the 2D group. The complication rate was lower in the 3D group (11.54%) than in the 2D group (26.47%) (χ^2 = 4.106, P < 0.05).

CONCLUSION

Using 3D RVT, doctors can gain a more comprehensive and intuitive understanding of the anatomy and related lesions of EGJ carcinomas, thus enabling more accurate surgical planning.

Key Words: Gastroesophageal junction cancer; Endoscopy; Tumor resection; Three-dimensional reconstruction visualization; Two-dimensional imaging; computed tomography

Core Tip: Three-dimensional reconstruction visualization technology (3D RVT) provides a more comprehensive and intuitive understanding of the anatomy and related lesions at the gastroesophageal junction. This study compared the 2D group, which underwent laparoscopic resection surgery after computed tomography (CT)-enhanced scanning, with the 3D group, which underwent laparoscopic resection surgery after CT-enhanced scanning and 3D RVT. Our findings highlight the benefits of using 3D RVT to improve surgical outcomes and reduce complications in patients with gastroesophageal junction cancer.

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INTRODUCTION

Esophagogastric junction (EGJ) carcinoma is a malignant tumor that occurs at the junction of the esophagus and stomach [1]. Current research has indicated a global increase in the incidence of EGJ carcinoma[2], with a nearly 2.5-fold increase since the early 1970s[3]. The development of EGJ carcinoma is complex and associated with various factors, such as diet, smoking, alcohol consumption, chronic gastritis, and *Helicobacter pylori* infection.

Due to its unique anatomical location and highly invasive nature, it is the primary choice for most patients with EGJ carcinomas to achieve long-term survival. Compared with traditional open surgery, laparoscopic resection offers advantages such as less surgical trauma, fewer complications, and higher safety while providing comparable lymph node clearance and survival benefits[4]. However, owing to the unique location and biological behavior of EGJ carcinomas, there are significant challenges in achieving precise surgical visualization, selecting the appropriate surgical approach, improving lymph node clearance, and achieving good digestive tract reconstruction while minimizing intraoperative and postoperative complications.

With the advancement of medical imaging technology, three-dimensional reconstruction visualization technology (3D RVT) has become increasingly important for accurately assessing tumors before surgery, planning individualized surgical approaches, and facilitating the application of minimally invasive laparoscopic techniques in the treatment of EGJ carcinomas. Additionally, 3D RVT provides clear and detailed information regarding the location, size, infiltration, adjacent relationships, and lymphatic metastasis range of tumors[5].

With the emergence of clinical techniques and the widespread use of 3D RVT, studies have explored their application in preoperative evaluation, treatment planning, intraoperative complication guidance, and postoperative recovery for various diseases such as liver[6] and gastric cancers[7]. However, to the best of our knowledge, research on the use of 3D RVT in the context of EGJ carcinomas is limited. Comprehensive research on the application of this technology in the preoperative planning of EGJs is crucial. Therefore, this study aimed to evaluate the application and advantages of 3D RVT in precise laparoscopic resection of EGJ carcinomas.

MATERIALS AND METHODS

Patient characteristics

This study enrolled patients with EGJ carcinoma who were hospitalized at The First Affiliated Hospital of Hebei North University from January 2020 to June 2022. Data were obtained from electronic or paper-based medical records.

The inclusion criteria were as follows: Age between 18 and 75 years; preoperative diagnosis of Siewert type II or III EGJ carcinoma confirmed by gastroscopy, abdominal plain and enhanced computed tomography (CT) scan, and magnetic resonance imaging (MRI) with preoperative gastroscopic biopsy[8]; postoperative pathological confirmation of EGJ carcinoma; and eligibility and willingness to undergo surgery.

The exclusion criteria were as follows: severe comorbidities, such as severe heart disease and liver or kidney failure; advanced or distant metastasis before surgery; a tumor diameter of 10 cm or more; severe adhesions in the abdominal cavity discovered during surgery, with tumor infiltration into other organs; patients who received other treatment modalities before surgery; incomplete clinical data or relevant test results; and pregnant women.

According to different preoperative imaging guidelines for surgical decision-making, the 3D group (n = 52) underwent laparoscopic resection surgery based on 3D RVT after CT-enhanced scanning, while the 2D group (n = 68) underwent laparoscopic resection surgery after CT-enhanced scanning.

Specific methods

2D group: Before surgery, patients underwent comprehensive physical examinations and evaluations, including gastroscopy, gastrointestinal barium meal, CT scans, and other imaging examinations, to determine their surgical plan. The surgeon planned laparoscopic total gastrectomy preoperatively. The patients underwent standard preoperative protocols, including fasting and intestinal preparations, and received general anesthesia under the guidance of an anesthesiologist. After the surgery began, the surgeon used laparoscopy and endoscopy for intraoperative localization of tumor position and extent before its removal. This included resection of the gastric wall and esophageal mucosa to ensure complete tumor removal. Subsequently, the surgeon reconstructed the stomach and esophagus to restore gastrointestinal function. After surgery, frozen section examination was performed on the surgical margins to ensure the absence of residual cancer cells. The patients entered the postoperative recovery period and underwent stan-dardized postoperative care and rehabilitation training.

3D group: 3D reconstruction was performed using Mimics software (Materialise Corp., Belgium), which is an interactive medical image-control system. The CT-enhanced scan data of the EGJ were saved as "DICOM" format files and imported into the 3D visualization software for editing and optimization of the 3D model. In the 3D visualized model of reconstruction, the position and size of the tumor, morphology and density of the tumor, lymph node metastasis, veins and surrounding veins, and abnormalities of other structures (such as the esophagus, stomach, liver, lung, and spleen) were clearly displayed. 3D RVT can display tumor position, vascular course, and adjacent relationships in a 360° stereo view. The software allows the doctor to rotate, zoom in and out, measure distances, and observe and analyze the anatomical data of tumors in relation to the surrounding tissues from various angles. This helps evaluate the extent of tissue resection, range of lymph node dissection, and difficulty of digestive tract reconstruction, thereby enabling more accurate surgical planning and better surgical path planning, such as thoracotomy, laparotomy, or a combined approach. The 3D model and 3D RVT guide the preoperative planning of laparoscopic resection surgery and assist with intraoperative procedures. After the surgery was completed, the patients entered the postoperative recovery period and underwent standardized postoperative care and rehabilitation training.

Observation indicators

Observation indicators included the deviation between tumor-related information based on 3D RVT and clinical practice. Indicators included the maximum tumor diameter and infiltration length. It also included a comparison of surgical outcomes between the 3D and 2D groups.

Intraoperative indicators were the operative time, intraoperative blood loss, number of lymph node dissections, and R0 resection rate. Postoperative indicators were the postoperative hospital stay, postoperative gas evacuation time, drainage tube removal time, and complications such as incision infection, anastomotic fistula, lung infection, adhesive intestinal obstruction, and anastomotic bleeding.

Statistical analysis

Statistical analyses were performed using SPSS software version 32.0 (IBM Corp., New York, United States). Normally distributed continuous data were presented as mean ± SD; a t-test was used for analysis when comparing two groups. Non-normally distributed continuous data were expressed as interquartile ranges (IQRs); the Mann-Whitney U test was used for analysis when comparing two groups. Categorical data were reported as frequencies and percentages, and the χ^2

test was used for analysis when comparing two or more groups. The kappa test was used for consistency analysis, with higher values indicating better consistency. In this study, a Pearson's correlation analysis was employed. A P value of less than 0.05 was considered statistically significant.

RESULTS

This study consisted of two parts: the deviation between tumor-related information based on 3D RVT and clinical practice and the surgical outcome indices between the 3D and 2D groups (Figure 1).

Clinical characteristics

A total of 112 patients were enrolled in the study. There were no statistically significant differences between the clinical characteristics of the two groups (all $P > 0.05$), suggesting that the data were well-balanced and the study results were reliable and comparable (Table 1).

3D RVT of the tumor and clinical practice

Among 52 patients who underwent 3D RVT, 27 had a maximum tumor diameter of less than 3 cm, whereas 25 had a maximum diameter of 3 cm or more. In actual surgical observations, 24 patients had a maximum tumor diameter of less than 3 cm, whereas 28 had a maximum diameter of 3 cm or more. For the infiltration length in the 3D RVT, 23 patients had a length of less than 5 cm, while 29 had a length of 5 cm or more. In the actual surgical observations, 20 had a length of less than 5 cm, while 32 had a length of 5 cm or more. These findings were consistent between the two methods ($P > 0.05$). The kappa consistency coefficients were 0.808 and 0.486, respectively. Pearson's correlation analysis showed a positive correlation, with a coefficient of 0.814 for one set and 0.490 for the other set (Table 2 and Figure 2).

Intraoperative indices in the 3D and 2D groups

The 3D model group had a shorter operative time and less intraoperative blood loss than the 2D model group; however, the number of lymph node dissections and the R0 resection rate were higher in the 3D model group ($P < 0.05$) (Table 3).

Postoperative indices in the 3D and 2D groups

The 3D group had a significantly shorter hospitalization time, exhaust time, and drainage tube removal time than the 2D group ($P < 0.05$) (Table 4).

Complications

A total of 18 patients in the 2D group experienced complications such as incision infection, anastomotic fistula, lung infection, adhesive intestinal obstruction, and anastomotic bleeding. Six patients in the 3D group developed postoperative complications; hence, the percentage of complications in the 3D group (11.54%) was lower than that in the 2D group (26.47%) (Figure 3).

DISCUSSION

The factors influencing radical resection of EGJ carcinomas can be summarized as anatomical, physiological, and biological characteristics of the tumor and choice of surgical approach. The anatomical location of the EGJ determines the difficulty and feasibility of the surgery. The biological properties of the tumor such as tumor size, extent of invasion, and lymph node metastasis also influence the feasibility of surgery. Moreover, the choice of surgical approach and the specific location of the tumor has a significant impact on its complete resection, radical lymph node clearance, and gastrointestinal reconstruction. Therefore, accurate preoperative assessment of patients with EGJ carcinomas and selection of the appropriate surgical approach to ensure the effectiveness and safety of the surgery has become both the focus and difficulty in their treatment.

Since the 1970s, new imaging technologies have provided effective methods for observing tissue and organ function. Traditional 2 imaging methods lack the ability to provide precise preoperative assessment and planning, limiting their use in qualitative disease analysis. In contrast, 3D reconstruction utilizes computer image processing technology to analyze, calculate, segment, extract, and merge data from 2D imaging. This advanced technology offers accurate and visually intuitive data support, thereby enabling improved surgical planning and evaluation[5,9,10]. 3D reconstruction uses computer image-processing technology to analyze, calculate, segment, extract, and fuse traditional 2D imaging data. More importantly, this technology provides virtual surgical demonstration and 3D image measurement capabilities, allowing surgeons to use medical 3D surgical simulations, intraoperative navigation systems, and other operating systems for accurate surgical assessment and planning[11,12].

The results of this study indicate that 3D RVT provides accurate measurements of tumor characteristics and extent of infiltration, which is consistent with actual surgical observations. This is in line with previous studies[13] suggesting that 3D RVT have high reliability and accuracy in tumor diagnosis and surgical planning. Zeng *et al*[14] demonstrated that preoperative 3D RVT can shorten surgical time and reduce intraoperative blood loss. These positive outcomes can be attributed to the improved localization of tumors and enhanced understanding of their interactions with the surrounding tissues provided by 3D reconstruction[14,15]. We observed similar results in this study, with the 3D group exhibiting a

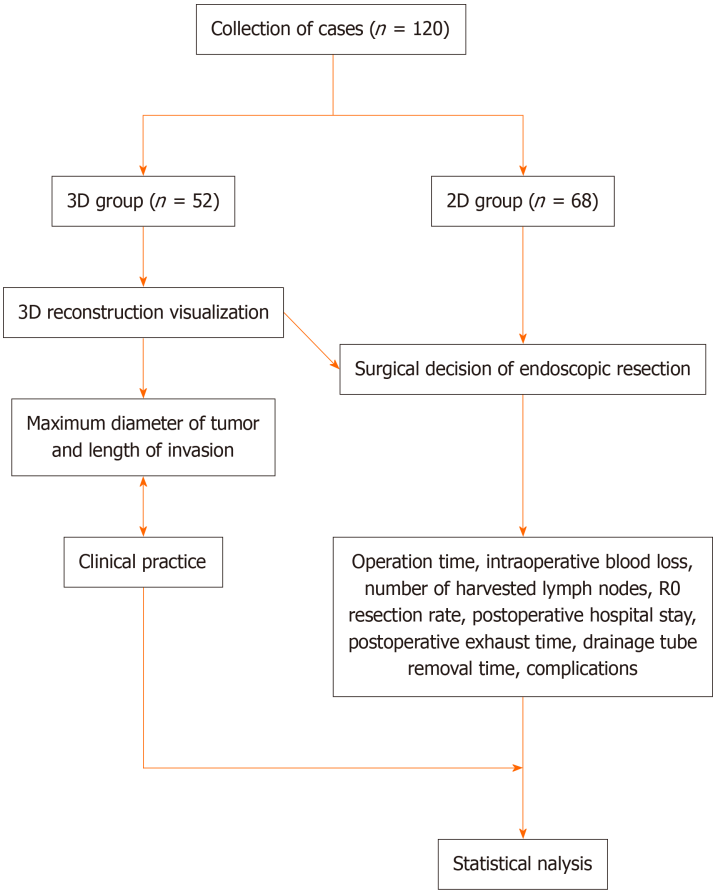

Figure 1 Flowchart of the research scheme. 3D: Three-dimensional; 2D: Two-dimensional.

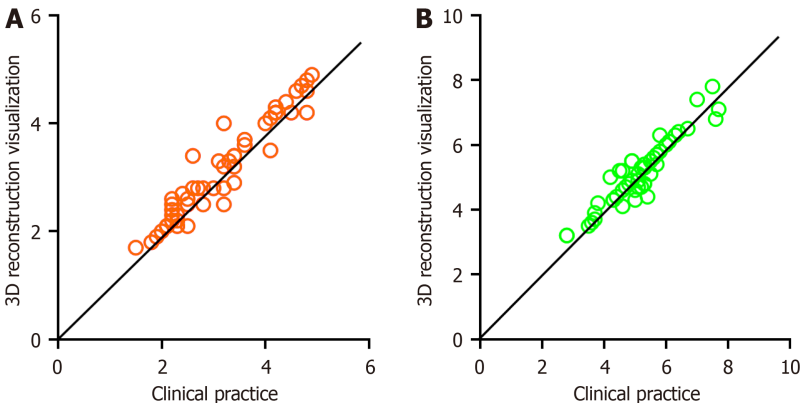

Figure 2 Actual tumor conditions under three-dimensional reconstruction visualization and in clinical practice. A: Maximum tumor diameter; B: infiltration length. 3D: Three-dimensional; 2D: Two-dimensional.

shorter operative time, less intraoperative blood loss, a higher R0 resection rate, and a lower incidence of complications. This confirms the guiding and predictive capabilities of 3D RVT. Possible reasons for these findings include the fact that 3D RVT can provide more comprehensive anatomical information and allow for virtual surgical rehearsals preoperatively, helping surgeons to become familiar with the surgical steps and operative pathways, thereby reducing the operative time. Furthermore, 3D RVT can provide more comprehensive information on vascular structures, enabling surgeons to preoperatively understand the distribution and location of blood vessels, thereby reducing the risk of vascular injury and intraoperative blood loss. Additionally, 3D RVT can accurately display the location and quantity of lymph nodes, helping surgeons in determining the extent of lymph node dissection, and enhancing the precision of resection.

A meta-analysis conducted on the use of 3D RVT in tumor surgery demonstrated significant reductions in operative time, intraoperative blood loss, and incidence of complications[16]. In addition, previous studies on liver cancer and hilar cholangiocarcinoma showed that 3D RVT improved the accuracy and safety of surgery while reducing intraoperative blood loss and complications, shortening the postoperative intestinal gas discharge time, and increasing the rates of R0

Table 1 Analysis of patient characteristics in each group, *n* (%)

Variables	3D group (*n* = 52)	2D group (*n* = 68)	χ^2/t value	*P* value
Age (yr, mean ± SD)	51.96 ± 8.30	50.28 ± 9.10	1.042	0.300
BMI (kg/m^2, mean ± SD)	21.68 (19.62, 24.92)	22.06 (20.45, 23.92)	-0.172	0.863
Sex			2.631	0.105
Male	38 (73.08)	40 (58.82)		
Female	14 (26.92)	28 (41.18)		
Pathological pattern			0.502	0.778
Squamous cell carcinoma	15 (28.85)	18 (26.47)		
Adenocarcinoma	24 (46.15)	29 (42.65)		
Other	13 (25.00)	21 (30.88)		
Helicobacter pylori infection			0.900	0.343
Yes	12 (23.08)	21 (30.88)		
No	40 (76.92)	47 (69.12)		
Siewert type			1.222	0.269
II	23 (44.23)	37 (54.41)		
III	29 (55.77)	31 (45.59)		
Scope of resection			0.351	0.554
Whole stomach	27 (51.92)	39 (57.35)		
Proximal stomach	25 (48.08)	29 (42.65)		
Operative route			0.2115	0.643
Transthoracic approach	35 (67.31)	43 (63.24)		
Transabdominal	17 (32.69)	25 (36.76)		
Maximum tumor diameter			0.543	0.461
< 3 cm	24 (46.15)	36 (52.94)		
≥ 3 cm	28 (53.85)	32 (47.06)		
Infiltration length			1.211	0.271
< 5 cm	20 (38.46)	33 (48.53)		
≥ 5 cm	32 (61.54)	35 (51.47)		

BMI: Body mass index; 3D: Three-dimensional; 2D: Two-dimensional.

resection and lymph node dissection[17,18]. In our study, the incidence of complications was lower in the 3D group than in the 2D group (11.54% *vs* 26.47%). This finding may be attributed to the clearer and more stereoscopic views of anatomical structures provided by 3D RVT, which aided the surgeons to more accurately evaluate the surgical area prior to surgery and formulate more precise surgical plans, thereby reducing intraoperative accidents and complications. Additionally, 3D RVT enhanced the accuracy of surgery, potentially shortening the operative time, reducing surgical trauma, and lowering the risk of infection and complications. Patients recovered faster, leading to a shorter hospital stay, improved quality of life, and reduced postoperative discomfort and long-term health problems. Nevertheless, other studies have reported inconsistent results. A study on the repair of total extraperitoneal inguinal hernia reported that the use of 3D RVT did not significantly reduce the operative time, hospital stay, or pain score; however, there were fewer peritoneal tears[19]. Another study on complex lower lobe resection showed that the use of 3D RVT did not significantly affect intraoperative blood loss, postoperative drainage volume, postoperative hospital stay, pneumonia/pulmonary atelectasis, and hemoptysis but shortened the operative time[20]. This may be due to differences in tumor types and surgical procedures. We believe that the application prospects of 3D RVT in tumor surgery are very broad but require more time and financial investment. Moreover, for some complex surgeries, the effect of 3D RVT may not be as expected. Further research is required to confirm its application in surgeries of different types and complexities. Simultaneously, we need to explore more surgical techniques and methods to further improve the safety and accuracy of surgery.

Table 2 Tumor conditions under three-dimensional reconstruction visualization and clinical practice, *n* (%)

	3D (*n* = 52)	Clinical practice (*n* = 52)	χ^2/t value	*P* value
Maximum tumor diameter			0.346	0.556
< 3 cm	27 (51.92)	24 (46.15)		
≥ 3 cm	25 (48.08)	28 (53.85)		
Infiltration length			0.357	0.550
< 5 cm	23 (44.23)	20 (38.46)		
≥ 5 cm	29 (55.77)	32 (61.54)		

3D: Three-dimensional.

Table 3 Comparison of intraoperative indices between the three- and two-dimensional groups (mean ± SD)

Variables	3D group (*n* = 52)	2D group (*n* = 68)	χ^2/t value	*P* value
Operative time (min)	157.02 ± 8.38	183.16 ± 23.87	-8.381	< 0.001
Intraoperative blood loss (mL)	83.65 ± 14.22	110.94 ± 22.05	-8.212	< 0.001
Number of lymph node dissections (*n*)	28.98 ± 2.82	23.56 ± 2.77	10.539	< 0.001
R0 resection rate (%)	80.77% (42/52)	61.64% (42/68)	5.068	0.024

3D: Three-dimensional; 2D: Two-dimensional.

Table 4 Comparison of postoperative indices between the three- and two-dimensional groups

Variables	3D group (*n* = 52)	2D group (*n* = 68)	*Z* value	*P* value
Postoperative hospital stay (d, IQR)	8 (8, 9)	13 (14, 16)	-9.341	< 0.001
Postoperative gas evacuation time (d, IQR)	3 (3, 4)	4 (5, 5)	-7.402	< 0.001
Drainage tube removal time (d, IQR)	4 (4, 5)	6 (6, 7)	-8.413	< 0.001

IQR: Interquartile range; 3D: Three-dimensional; 2D: Two-dimensional.

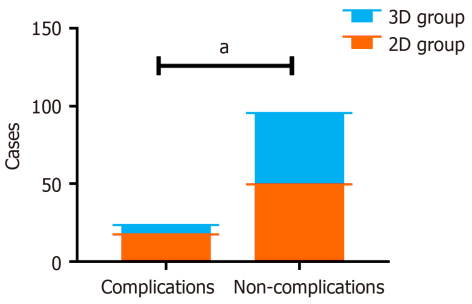

Figure 3 Stacking diagram of the proportion of complications in the three-dimensional and two-dimensional groups. [a]*P* < 0.05. 3D: Three-dimensional; 2D: Two-dimensional.

This study had certain limitations that should be acknowledged. First, the retrospective design restricted the exploration of data not routinely documented in medical records. Second, the use of specific inclusion criteria might have introduced selection bias, potentially affecting the generalizability of findings. Finally, the absence of long-term follow-up data hindered the assessment of long-term safety and surgical intervention outcomes. Further research is necessary to validate the results and address the limitations and challenges that may be encountered in practical applications. For instance, 3D RVT may require additional equipment and software support, which may increase the complexity and cost of surgeries. Physicians who are unfamiliar with this technology may also need additional training and time to master

such technology. The images generated by 3D RVT may require specialized knowledge to interpret them correctly, necessitating interdisciplinary collaboration between radiologists and surgeons. Nonetheless, these challenges can be overcome to realize the potential benefits by providing dedicated training courses and workshops for physicians to quickly learn 3D RVT. Developing standardized workflows for 3D RVT can aid physicians in utilizing these tools more effectively and ensure consistency in surgical planning. While there may be initial investments, 3D RVT may reduce the overall healthcare costs in the long run by reducing complications, shortening hospital stays, and improving surgical success rates.

CONCLUSION

The findings of this study align with those of previous studies and provide additional evidence for the efficacy of 3D RVT in surgery for EGJ carcinomas.

FOOTNOTES

Author contributions: Guo D performed the research and wrote the paper; Zhu XY, Han S, and Liu YS organized the data and contributed to data analysis; Cui DP designed the research and supervised the report.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Hebei North University.

Informed consent statement: Because this was a retrospective study, the requirement for informed consent was waived.

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

Data sharing statement: The data used in this study can be obtained from the corresponding author upon request.

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ORIGINAL ARTICLE

Retrospective Study

Comparative observation of the effectiveness and safety of remimazolam besylate versus dexmedetomidine in gastrointestinal surgery in obese patients

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Abstract

BACKGROUND

Surgery for obese patients carries a higher risk of anesthesia complications compared with surgery for nonobese patients. Thus, a safe and effective anesthesia strategy is necessary to improve the medical experience of such patients and ensure their safety.

AIM

To compared the effectiveness and safety of remimazolam besylate *versus* dexmedetomidine (DEX) in gastrointestinal surgery in obese patients.

METHODS

The study cohort included 60 obese patients undergoing gastrointestinal surgery between July 2021 and April 2023, comprising 30 patients who received DEX intervention (control group) and 30 patients who received remimazolam besylate intervention (research group). Heart rate (HR), respiratory rate (RR), mean arterial pressure (MAP), blood oxygen saturation (SpO_2), safety (nausea and vomiting, bradycardia, hypotension, and apnea), anesthesia and examination indices [induction time, anesthesia recovery time, and postanesthesia care unit (PACU) discharge time], sedation effect (Ramsay Sedation Scale), and postoperative pain visual analog scale were comparatively analyzed before anesthesia (T0), during anesthesia (T1), and after anesthesia (T2).

RESULTS

At T1, the research group showed significantly smaller changes in HR, RR, MAP, and SpO_2 than the control group, with a significantly lower adverse reaction rate and shorter induction, anesthesia recovery, and PACU discharge times. Additionally, the intra- and postoperative Ramsay Sedation Scale scores were statistically higher in the research group than in the control group.

CONCLUSION
Remimazolam besylate was significantly more effective than DEX in gastrointestinal surgery in obese patients and had a higher safety profile and value in clinical promotion.

Key Words: Remimazolam besylate; Dexmedetomidine; Obesity; Gastrointestinal surgery; Effectiveness; Safety

Core Tip: This study primarily compared the effectiveness and safety of remimazolam besylate versus dexmedetomidine (DEX) in gastrointestinal surgery for obese patients. Our findings confirmed that remimazolam besylate was significantly more effective than DEX in gastrointestinal surgery in obese patients, with a high safety profile and value in clinical promotion, thereby providing a reliable clinical reference for anesthesia management optimization in gastrointestinal surgery for obese patients.

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INTRODUCTION

Obesity is a disease of abnormal or excessive accumulation of body fat and is influenced by the interaction of dietary, genetic, cultural, and socioeconomic factors[1,2]. The risk of obesity has tripled over the past 3 decades, with a prevalence as high as 28.3% and 36.5% in men and women, respectively[3]. Obesity not only impairs patients' physical health but also increases the risk of complications, such as hypertension, diabetes, coronary artery disease, and cancer[4,5]. Current surgical treatments for obesity include gastric bypass, sleeve gastrectomy, adjustable gastric banding, and duodenal-jejunal bypass, but these all carry a higher risk of anesthesia complications compared with nonobese patients[6-9]. Therefore, the determination of a safe and effective anesthesia strategy for obese patients undergoing gastrointestinal surgery is crucial to improving their medical experience and ensuring their safety.

Dexmedetomidine (DEX), a central alpha-2 adrenergic agonist with analgesic, sedative, and antisympathetic effects, is a common clinical anesthetic[10] used in cardiac surgery, colorectal cancer surgery, and joint replacement in elderly patients. To a certain extent, it prevents postoperative delirium and improves the quality of arousal in patients under general anesthesia[11]. Zhang *et al*[12] reported that the use of DEX during bariatric surgery alleviated postoperative pain, thereby promoting postoperative rehabilitation. DEX also has the advantage of not causing respiratory depression, but it may cause adverse hemodynamic events, such as hypertension, hypotension, and bradycardia[13,14].

Remimazolam besylate is a novel benzodiazepine (BDZ) with faster onset and metabolism than remimazolam[15]. Its narcotic effect stems from its action on central γ-aminobutyric acid type A receptors, leading to the opening of channels and subsequent acceleration of chloride ion influx, which hyperpolarizes the nerve membrane and effectively inhibits neuronal activity[16]. Xu *et al*[17] reported that remimazolam besylate also had the advantages of a quick onset, fast recovery, high compatibility, safety, and comfortable and painless anesthesia in plastic surgery.

There are few comparative observational studies on the effectiveness and safety of remimazolam besylate and DEX in obese patients undergoing gastrointestinal surgery. Thus, this study aimed to conduct a more in-depth analysis of this aspect to contribute to anesthesia optimization in such patients.

MATERIALS AND METHODS

General information

The study cohort comprised 60 obese patients undergoing gastrointestinal surgery at Xiangtan Central Hospital between July 2021 and April 2023, including 30 cases receiving DEX intervention (control group, Con) and 30 cases receiving remimazolam besylate intervention (research group, Res).

Eligibility and exclusion criteria

Confirmed obese patients with a body mass index (BMI) > 28 kg/m^2, no contraindications for gastrointestinal surgery, American Society of Anesthesiologists (ASA) classification I or II, good cardiopulmonary function, no allergies to narcotic drugs, no intraoperative awareness, and intact medical records were included in our study.

The exclusion criteria were recent intermittent use of BDZs or opioids, preoperative diagnosis of difficult airway (Mallampati grade ≥ III) or sleep apnea syndrome, severe hypertension or hypotension, hepatorenal insufficiency, long-term use of sedative hypnotics, psychiatric disorders, and inability to communicate due to neuromuscular disorders.

Table 1 Background information on obese patients undergoing gastrointestinal surgery

Factors	Con (*n* = 30)	Res (*n* = 30)	χ^2 or *t*-test result	*P* value
Age (yr)	38.13 ± 6.05	39.38 ± 6.72	0.757	0.452
Sex (male/female)	13/17	14/16	0.067	0.795
BMI (kg/m^2)	32.05 ± 2.80	32.05 ± 2.80	0.673	0.504
ASA classification (I/II)	20/10	17/13	0.635	0.426
Educational level (below high school/high school and above)	22/8	17/13	1.832	0.176

Results are presented as mean ± SD or numbers and percentages. ASA: American Society of Anesthesiologists; BMI: Body mass index; Con: Control group; Res: Research group.

Treatment methods

Upper-limb venous access was established in all patients, and invasive blood pressure monitoring was performed, as well as monitoring of blood oxygen saturation (SpO_2), cardiac function *via* continuous electrocardiography, and the bispectral (BIS) index.

In the Con group, anesthesia was induced by DEX infusion at a dose of 0.5-1.0 μg/kg for 10-15 min and was maintained by continuous pump infusion at 0.2-0.7 μg/kg/h, with the BIS index kept at 45-60. Opioid analgesics and muscle relaxants were also used.

In the Res group, continuous pumping was used to induce anesthesia with remimazolam besylate at a rate of 6 mg/kg/h for ≤ 3 min, and anesthesia was maintained at 0.2-1.0 mg/kg/h. If the depth of anesthesia became insufficient, 12 mg/kg/h was added for 1 min. Opioid analgesics and muscle relaxants were also used during anesthesia induction.

Detection indicators

Patients' vital signs were monitored before anesthesia (T0), during anesthesia (T1), and after anesthesia (T2), including heart rate (HR), respiratory rate (RR), mean arterial pressure (MAP), and SpO_2. We also observed and recorded the incidence of postoperative adverse events (nausea and vomiting, bradycardia, hypotension, and apnea) and calculated the incidence rate. Anesthesia indices, including anesthesia induction, anesthesia recovery, and postanesthesia care unit (PACU) discharge times, were also compared. The sedation effect was scored according to the Ramsay Sedation Scale (1, agitated or restless; 2, cooperative and tranquil; 3, asleep and responding to commands; 4, asleep but can be aroused; 5, sluggish response to an auditory stimulus; 6, deep sleep and no response to an auditory stimulus). Pain severity was assessed at 2 and 12 h after surgery using a visual analog scale (VAS) ranging from 0-10, with the score directly proportional to the degree of pain.

Statistical analyses

SPSS 24.0 software was used for statistical analysis of the data, and statistical significance was set at $P < 0.05$. Age, BMI, and other measurement data were represented as mean ± SD. Independent sample *t*-tests were performed to identify between-group differences, and paired *t*-tests were used to determine differences between two time points. Sex, ASA classification, the incidence of adverse events, and other categorical variables were expressed by numbers and percentages, and intergroup comparisons were conducted using χ^2 tests.

RESULTS

Information on obese patients undergoing gastrointestinal surgery

There were no statistically significant differences between the Res and the Con groups in terms of age, sex, BMI, ASA classification, and educational level ($P > 0.05$; Table 1).

Vital signs of obese patients undergoing gastrointestinal surgery

Although there were no marked differences in HR, RR, MAP, and SpO_2 between the Res and the Con groups at T0 ($P > 0.05$), they all decreased at T1 to varying degrees ($P < 0.05$), with even smaller changes in the Res group ($P < 0.05$). At T2, the RR and MAP of both groups increased to varying degrees, but these were not significant compared with T0 or intergroup differences ($P > 0.05$). At T2, HR and SpO_2 showed further decreases ($P < 0.05$), with smaller reductions in the Res group but no evident intergroup differences ($P > 0.05$; Figure 1).

Safety of the two groups of obese patients undergoing gastrointestinal surgery

The incidence of postoperative complications (nausea and vomiting, bradycardia, hypotension, and apnea) in the Res and Con groups were 13.33% and 36.67%, respectively, and the difference between them was statistically significant ($P < 0.05$; Table 2).

Table 2 Safety of obese patients undergoing gastrointestinal surgery, *n* (%)

Adverse event	Con (*n* = 30)	Res (*n* = 30)	χ^2	*P* value
Nausea and vomiting	2 (6.67)	0 (0.00)		
Bradycardia	4 (13.33)	2 (6.67)		
Hypotension	3 (10.00)	1 (3.33)		
Apnea	2 (6.67)	1 (3.33)		
Total	11 (36.67)	4 (13.33)	4.356	0.037

Con: Control group; Res: Research group.

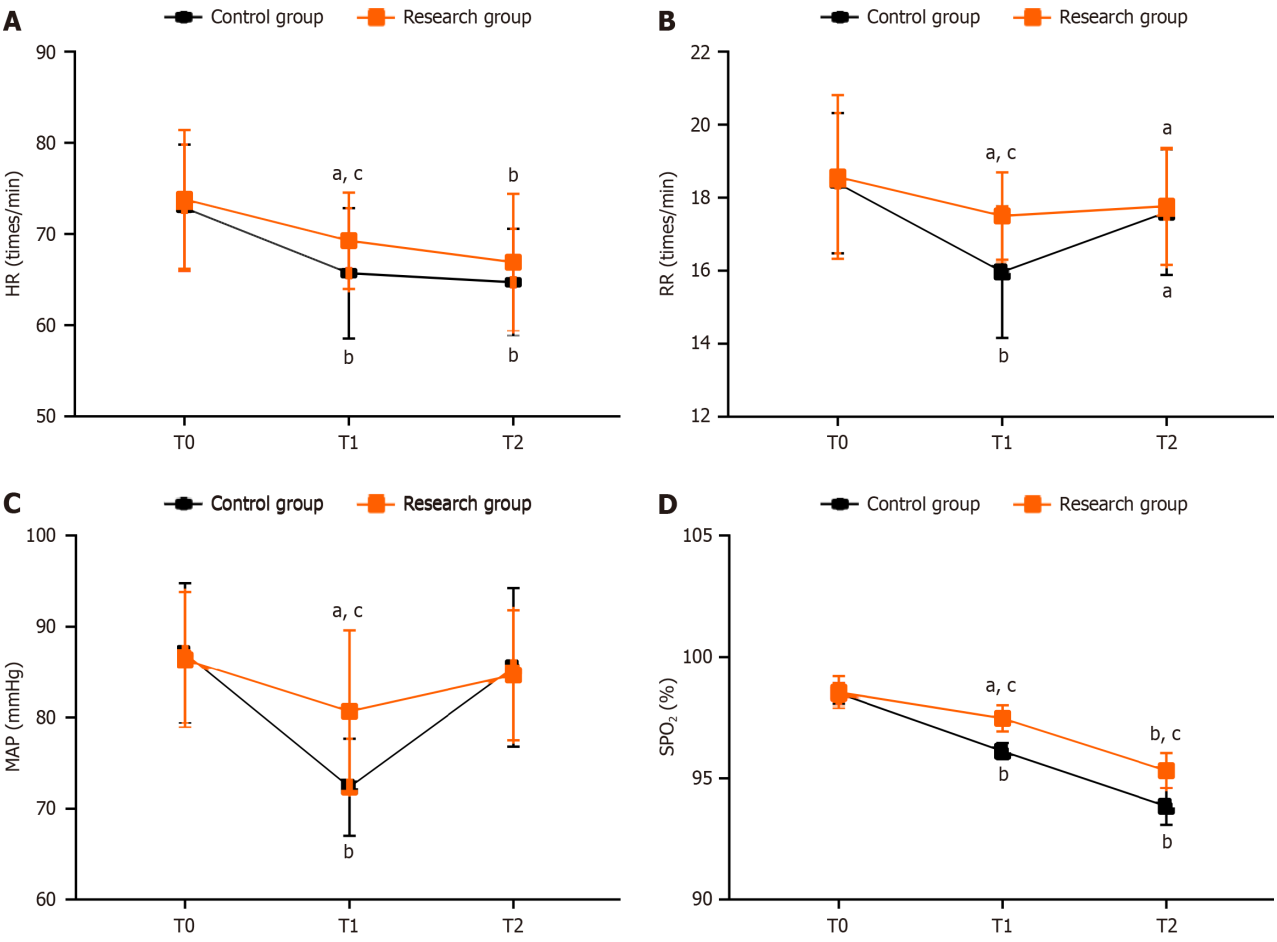

Figure 1 Vital signs of two groups of obese patients undergoing gastrointestinal surgery. A: Heart rate at different time points in the two groups; B: Respiratory rate at different time points in the two groups; C: Mean arterial pressure at different time points in the two groups; D: Blood oxygen saturation at different time points in the two groups. HR: Heart rate; RR: Respiratory rate; MAP: Mean arterial pressure; SpO_2: Blood oxygen saturation. $^aP < 0.05$, $^bP < 0.01$ *vs* T0; $^cP < 0.05$ *vs* Con.

Anesthesia indices of the two groups of obese patients undergoing gastrointestinal surgery

Patients in the Res group had shorter anesthesia induction, anesthesia recovery, and PACU discharge times compared with patients in the Con group ($P < 0.05$; Figure 2).

Sedative effects of two groups of obese patients undergoing gastrointestinal surgery

Both intraoperative and postoperative Ramsay scores were significantly increased in both groups compared with the preoperative score, with those in the Res group being significantly higher compared with the Con group ($P < 0.05$; Figure 3).

Postoperative pain scores of the two groups of obese patients undergoing gastrointestinal surgery

The VAS scores of the Res and Con groups were similar at 2 and 12 h after surgery ($P > 0.05$; Figure 4).

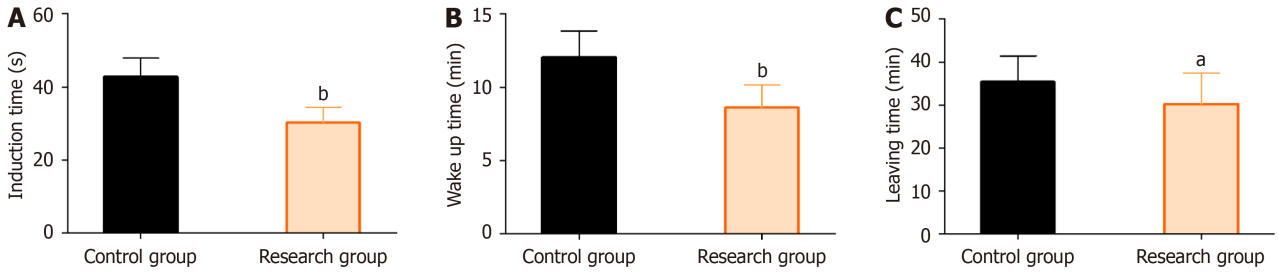

Figure 2 Anesthesia indices of the two groups of obese patients undergoing gastrointestinal surgery. A: The research group showed a markedly shorter anesthesia induction time than the control group; B: The research group showed a significantly shorter anesthesia recovery time than the control group; C: The research group showed an obviously shorter postanesthesia care unit discharge time than the control group. $^{a}P < 0.05$, $^{b}P < 0.01$ *vs* T0.

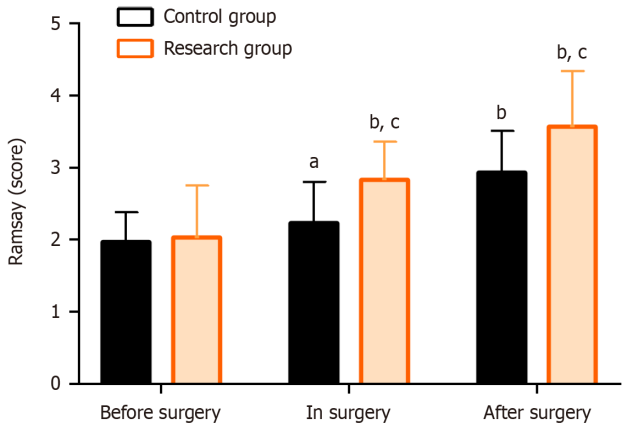

Figure 3 Sedative effects on the two groups of obese patients undergoing gastrointestinal surgery. $^{a}P < 0.05$, $^{b}P < 0.01$ *vs* T0; $^{c}P < 0.05$ *vs* Con.

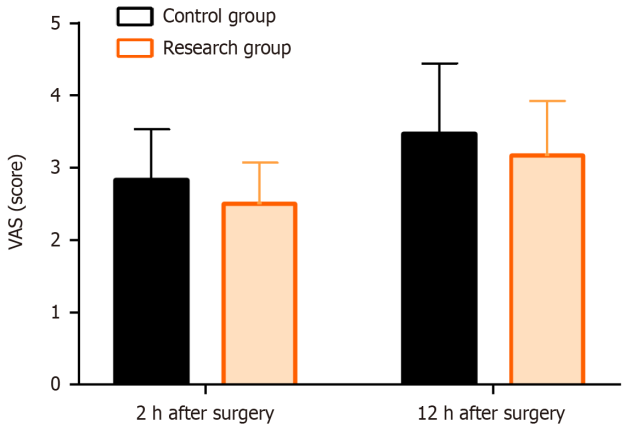

Figure 4 Postoperative pain visual analog scale scores of the two groups of obese patients undergoing gastrointestinal surgery. VAS: Visual analog scale.

DISCUSSION

This comparative observational analysis studied 60 obese patients who underwent gastrointestinal surgery. Of them, 30 underwent anesthesia with DEX (Con group), and 30 underwent anesthesia with remimazolam besylate (Res group). Remimazolam besylate was clearly advantageous over DEX in obese patients undergoing gastrointestinal surgery.

To ensure good anesthesia performance, it is important to maintain hemodynamic stability by avoiding overexcitation and inhibition of sympathetic and parasympathetic nerves[18-20]. Our analysis of the patients' vital signs (HR, RR, MAP, and SpO_2) revealed smaller fluctuations of these indices in the Res group compared with the Con group at T1. Furthermore, the only significant intergroup difference at T2 was SpO_2, suggesting that remimazolam besylate anesthetization exerted relatively little influence on patients' vital signs and maintained hemodynamic stability more effectively than DEX. Anesthesia using remimazolam besylate was reported to exert a minimal effect on the circulatory system and

contribute to slight HR and blood pressure fluctuations, with a certain stabilizing effect on hemodynamics[21], which agrees with our research findings. This may be because remimazolam besylate acts on γ-aminobutyric acid receptors, with rapid onset of action, fast counteraction, short half-life, high clearance rate, easy and rapid metabolism, and little variation in pharmacodynamic properties among individuals, making it more conducive to the recovery of hemodynamic stability[22]. In our study, the incidence of adverse effects (nausea and vomiting, bradycardia, hypotension, apnea, and other events) in the Res group was significantly lower than the incidence of adverse effects in the Con group, indicating a reduced risk of postoperative adverse events in obese patients undergoing gastrointestinal surgery under anesthesia with remimazolam besylate. Remimazolam besylate is metabolized by abundant plasma and nonspecific tissue esterases, independent of arbitrary organ metabolism and without significant negative effects on hemodynamics, which partially explains its high safety profile[23]. Liu *et al*[24] reported that remimazolam besylate exhibited a favorable safety profile in elderly outpatients undergoing colonoscopy, correlating with our research results. Yi *et al*[25] reported a relatively lower risk of bradycardia, nausea, vomiting, and chills in patients undergoing endoscopic retrograde cholangiopancreatography under anesthesia with remimazolam besylate, similar to our observations. Furthermore, De Cassai *et al*[26] pointed out that DEX caused lower blood pressure and HR after endotracheal intubation in adult patients, and these symptoms are closely related to hypotension and bradycardia, consistent with our findings. Additionally, the induction, anesthesia recovery, and PACU discharge times were significantly shorter in the Res group compared with the Con group, indicating that remimazolam besylate had a better anesthetic effect in obese patients undergoing gastrointestinal surgery. In terms of sedation effects, the Ramsay Sedation Scale scores were markedly high intra- and postoperatively in the Res group versus in the Con group, suggesting that the significant sedative effect of remimazolam besylate was better than DEX in obese patients undergoing gastrointestinal surgery. Deng *et al*[27] reported that remimazolam besylate used in nonintubated elderly patients after orthopedic surgery achieved sedation within the target range faster and for a longer duration compared with DEX, which supports our findings. This may be due to the readily metabolized ester composition of remimazolam besylate and its predictable pharmacokinetic and dose-dependent pharmacodynamic properties, which allow for rapid and deeper sedation shortly after injection[28,29]. Finally, the VAS scores between the two groups were comparable at 2 and 12 h after surgery, indicating that remimazolam besylate also exerted a considerable analgesic effect in obese patients undergoing gastrointestinal surgery. One study reported that remimazolam besylate was less likely to cause injection-related pain because of its water solubility[30].

This study had several limitations that require further consideration and improvement. First, the risk factors affecting the safety of obese patients undergoing gastrointestinal surgery were not thoroughly analyzed and discussed, and supplementing this analysis would help to avoid the occurrence of adverse events. Second, the sample size was limited, and potential biases or confounding factors may have affected our findings. If the study were to be extended to multiple centers and the sample size increased, the accuracy of the research results would be improved to some extent. Finally, to further enhance the understanding and management of narcotic drug regimens, it would be helpful to perform relevant animal experiments to explore the underlying mechanisms of anesthesia.

CONCLUSION

In summary, remimazolam besylate is more advantageous than DEX in the clinical application of gastrointestinal surgery in obese patients, which is reflected in its high safety profile, excellent anesthetic, sedative, and analgesic effects, and no significant impact on patients' vital signs, and it is deserving of clinical promotion. Additionally, our findings provide a new optimized choice and a reliable clinical reference for the anesthesia management of gastrointestinal surgery in obese patients while shedding new light on current anesthesia guidelines.

FOOTNOTES

Author contributions: Deng YF designed the research and wrote the first manuscript; Deng YF, Jiang XR and Feng ZG contributed to conceiving the research and analyzing data; Deng YF conducted the analysis and provided guidance for the research; all authors reviewed and approved the final manuscript.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Xiangtan Central Hospital.

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

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ORIGINAL ARTICLE

Retrospective Study

GLI1 and *PTTG1* expression in colorectal carcinoma patients undergoing radical surgery and their correlation with lymph node metastasis

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Abstract

BACKGROUND

Few studies have investigated the expression of *GLI1* and *PTTG1* in patients undergoing radical surgery for colorectal carcinoma (CRC) and their association with lymph node metastasis (LNM). Therefore, more relevant studies and analyses need to be conducted.

AIM

To explore *GLI1* and *PTTG1* expression in patients undergoing radical surgery for CRC and their correlation with LNM.

METHODS

This study selected 103 patients with CRC admitted to our hospital between April 2020 and April 2023. Sample specimens of CRC and adjacent tissues were collected to determine the positive rates and expression levels of *GLI1* and *PTTG1*. The correlation of the two genes with patients' clinicopathological data (*e.g.*, LNM) was explored, and differences in *GLI1* and *PTTG1* expression between patients with LNM and those without were analyzed. Receiver operating characteristic (ROC) curves were plotted to evaluate the predictive potential of the two genes for LNM in patients with CRC.

RESULTS

Significantly higher positive rates and expression levels of *GLI1* and *PTTG1* were

observed in CRC tissue samples compared with adjacent tissues. *GLI1* and *PTTG1* were strongly linked to LNM in patients undergoing radical surgery for CRC, with higher *GLI1* and *PTTG1* levels found in patients with LNM than in those without. The areas under the ROC curve of *GLI1* and *PTTG1* in assessing LNM in patients with CRC were 0.824 and 0.811, respectively.

CONCLUSION

GLI1 and *PTTG1* expression was upregulated in patients undergoing radical surgery for CRC and are significantly related to LNM in these patients. Moreover, high *GLI1* and *PTTG1* expression can indicate LNM in patients with CRC undergoing radical surgery. The expression of both genes has certain diagnostic and therapeutic significance.

Key Words: Colorectal carcinoma; *GLI1*; *PTTG1*; Radical resection; Lymph node metastasis

Core Tip: The main goal of radical surgery for colorectal carcinoma (CRC) is to completely remove the primary tumor and regional lymph nodes. Lymph nodes are essential in predicting patient prognosis and for determining the need for adjuvant chemotherapy after surgical resection. In this study, the expression of *GLI1* and *PTTG1* in patients with CRC undergoing radical surgery and their correlation with lymph node metastasis (LNM) were examined. Aberrant overexpression of *GLI1* and *PTTG1* was confirmed in patients undergoing radical surgery for CRC. In addition, both *GLI1* and *PTTG1* were significantly related to LNM and could be used as predictors of LNM, indicating their clinical significance in the evaluation of CRC cases and the development of treatment plans.

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INTRODUCTION

Colorectal carcinoma (CRC), which originates from the colon or rectum, is the third most common malignancy in both men and women worldwide[1]. Overweight, family history, tall stature, excessive intake of alcoholic beverages, and lack of regular exercise are the predisposing factors[2]. Etiologically, CRC is associated with excessive mucosal epithelial cell proliferation, distant tumor metastasis, long-term intestinal inflammatory responses, and abnormal changes in the gut microbiota[3,4]. The global number of new CRC cases in 2018 was 1.8 million, with nearly 900000 deaths[5]. Patients with CRC may present with clinical symptoms such as celialgia, abdominal mass, hemoproctia, abnormal weight loss, abnormal appetite loss, depression, and insomnia, which can seriously affect their physical and mental health and their quality of life[6,7]. Radical surgery for CRC is a common treatment option that aims for a complete resection of the primary tumor and regional lymph nodes. Lymph nodes are essential for predicting patient outcomes and determining the need for adjuvant chemotherapy after surgical resection[8].

GLI1 is a gene that mediates pathophysiological processes and changes in various tumors. It is involved in the proliferation, migration, invasiveness, growth, vascular invasion, and self-renewal of cancer stem cells in various malignancies [9,10]. According to Du *et al*[11], *GLI1*, as a component of the hedgehog (Hh)/GLI1 signaling pathway in CRC, can affect the inhibition of resveratrol on the growth and metastasis of HCT116 cells. Park *et al*[12] found that *GLI1* influences the survival of patients with CRC by participating in hypoxic mechanisms and interacting with *CCT2*. *PTTG1*, a carcinogenic agent closely associated with tumor metastasis, participates in organ development, metabolism, DNA damage/repair, and cell cycle regulation. It is aberrantly overexpressed in various tumors, including those in the pituitary gland, thyroid, breast, ovary, uterus, and colon[13,14]. The promotion by *PTTG1* of tumor metastasis and invasion has been linked to its direct regulation of basic fibroblast growth factor, epidermal growth factor, and β-catenin/transcription factor[15].

Research on the expression of *GLI1* and *PTTG1* in patients with CRC undergoing radical surgery and their correlation with lymph node metastasis (LNM) is limited. This study sought to bridge this gap to contribute to the improved clinical management of CRC.

MATERIALS AND METHODS

General information

We enrolled 103 patients who underwent radical surgery for CRC at Shanghai Zhangjiang Institute of Medical Innovation between April 2020 and April 2023. Samples of CRC and adjacent tissues were collected from all patients. Of the 103 patients, 53 were male and 50 were female. Furthermore, 42 were < 60 years old, and 61 were ≥ 60 years old. Tumors were

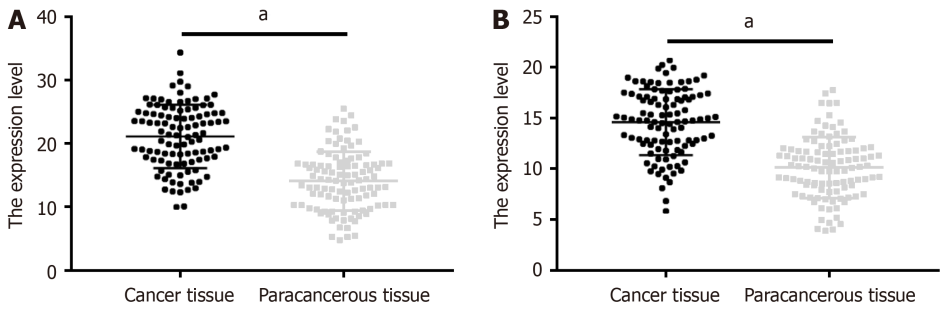

Figure 1 Comparison of *GLI1* and *PTTG1* expression between colorectal carcinoma tissue samples. A: Para-cancerous tissue; B: Adjacent tissues. [a]*P* < 0.05.

located in the colon in 43 cases and in the rectum in 60 cases. In 23 cases, tumors were well differentiated, whereas in 80 cases, they were moderately and poorly differentiated. Furthermore, 48 cases were pathologically staged I–II, whereas 55 were staged III–IV. LNM was observed in 58 cases.

Criteria for patient enrollment and exclusion

The inclusion criteria were as follows: Diagnosis of CRC by surgical pathology and colonoscopic biopsy; met corresponding indications for surgical treatment and underwent radical surgery, with complete cancer and para-cancer tissue specimens obtained; no mental and cognitive abnormalities; and intact clinical data.

The exclusion criteria were as follows: systemic inflammatory diseases; previous use of chemoradiotherapy or targeted therapy; presence of other malignant tumors; estimated survival < 3 months; inability to attend follow-up visits or loss to follow-up; lactating or pregnant women; infectious diseases or blood disorders.

Sample collection and testing methods

Samples of CRC and adjacent tissues of about 2–3 g were collected from all patients during the surgery and subsequently processed into sections (5–10 μm thick) after preliminary treatment. The specimen sections were placed in an electrothermal constant-temperature air-blowing drying oven at 50°C–60°C for 3–4 h to make them adhere to the slide. After baking, disodium hydrogen phosphate–sodium dihydrogen phosphate buffer was used for antigen retrieval, and mouse antihuman GLI1 and PTTG1 monoclonal antibodies were added overnight. Next, each tissue sample was stained by immunohistochemistry following the SP kit instructions. Then, the positive rates of *GLI1* and *PTTG1* expression in each tissue sample were observed using an automatic immunohistochemical staining instrument.

The criteria for judging the positive expression rate were as follows: (1) According to the product of the staining intensity and the number of positive cells in the field of view, a percentage of positive cells < 5% was counted as 0 points, 5%–25% as 1 point, 26%–50% as 2 points, 51%–75% as 3 points, and > 75% as 4 points; and (2) Based on dyeing intensity, 0, 1, 2, and 3 points were given for colorless, light yellow, brownish yellow, and tan, respectively. Positive expression was determined if the sum of the two results was greater than 3 points. The immunohistochemical staining instrument was set to counting mode in counting the number of *GLI1*- and *PTTG1*-positive cells in the visual field. Finally, the expression levels of *GLI1* and *PTTG1* were calculated.

Outcome measures

The positive expression rates and protein levels of *GLI1* and *PTTG1* in CRC and adjacent tissues were statistically compared. The correlations between *GLI1* and *PTTG1* expression and clinicopathological characteristics, such as sex, age, tumor location, degree of tumor differentiation, pathological stage, and LNM, were evaluated. The differences in *GLI1* and *PTTG1* expression levels between patients with and without LNM were examined.

Statistical analysis

All analyses were performed using SPSS 20.0 at a significance level of $P < 0.05$. Categorical variables were expressed as number (percentage) and comparatively analyzed using the χ^2 test. Continuous variables were expressed as mean ± SE and analyzed using the independent sample *t*-test, respectively.

RESULTS

Positive rates of GLI1 and PTTG1 expression in CRC tissue samples

The positive expression rates of *GLI1* in CRC and adjacent tissues were 63.11% and 12.62%, respectively, and the corresponding positive expression rates of *PTTG1* were 56.31% and 5.83%, respectively. Significantly higher positive rates of *GLI1* and *PTTG1* were observed in cancer tissues than in adjacent tissues ($P < 0.001$; Table 1).

Table 1 Positive rates of *GLI1* and *PTTG1* in colorectal carcinoma tissue samples

Grouping	*n*	Cancerous tissue	Para-cancerous tissue	χ^2	*P* value
GLI1 positive	103	65 (63.11)	13 (12.62)	55.792	< 0.001
PTTG1 positive	103	58 (56.31)	6 (5.83)	61.292	< 0.001

Table 2 Correlation of *GLI1* expression with clinicopathological data of patients undergoing radical surgery for colorectal carcinoma

Grouping	*n*	*GLI1* positive (*n* = 65), *n* (%)	*GLI1* negative (*n* = 38), *n* (%)	χ^2	*P* value
Sex				0.403	0.526
Male	53	35 (53.85)	18 (47.37)		
Female	50	30 (46.15)	20 (52.63)		
Age				3.504	0.061
< 60 yr old	42	22 (33.85)	20 (53.63)		
≥ 60 yr old	61	43 (66.15)	18 (47.37)		
Tumor location				0.221	0.638
Colon	43	26 (40.00)	17 (44.74)		
Rectum	60	39 (60.00)	21 (55.26)		
Differentiation degree				0.552	0.458
High differentiation	23	13 (20.00)	10 (26.32)		
Medium–low differentiation	80	52 (80.00)	28 (73.68)		
Pathological staging				3.086	0.079
I–II	48	26 (40.00)	22 (57.89)		
III–IV	55	39 (60.00)	16 (42.11)		
Lymph node metastasis				5.233	0.022
Positive	58	44 (67.69)	17 (44.74)		
Negative	45	21 (32.31)	21 (55.26)		

GLI1 and PTTG1 expression levels in CRC tissue samples

Significantly higher *GLI1* and *PTTG1* levels were observed in cancer tissue samples than in adjacent tissues ($P < 0.05$; Figure 1).

Correlation of GLI1 and PTTG1 with patients' clinicopathological data

Neither *GLI1* or *PTTG1* expression were strongly associated with sex, age, tumor location, degree of tumor differentiation, or pathological stage ($P > 0.05$). However, the expression of both genes was significantly associated with LNM ($P < 0.05$; Tables 2 and 3).

GLI1 and PTTG1 expression in patients with LNM

Patients with LNM showed obviously higher *GLI1* and *PTTG1* levels than those without. The area under the curve (AUC) of *GLI1* for predicting LNM in patients with CRC undergoing radical surgery was 0.824 (sensitivity: 75.56%; specificity: 84.48%), and the optimal cut-off was 19.76. The AUC, sensitivity, specificity, and the optimal cut-off of *PTTG1* for predicting LNM were 0.811, 68.89%, 82.76%, and 13.97, respectively (Figure 2 and Table 4).

DISCUSSION

Screening for CRC in patients based on early symptoms is difficult; imaging and pathological examination are often required[16]. However, in patients with CRC who underwent radical resection of the primary tumor, the accuracy of the said methods of disease assessment will be greatly affected[17]. To maximize the curative effect of radical surgery for CRC and promote patients' postoperative recovery, more accurate and effective means of predicting disease changes are needed.

Table 3 Association between *PTTG1* expression and clinicopathological data of patients undergoing radical surgery for colorectal carcinoma

Grouping	*n*	PTTG1 positive (*n* = 58), *n* (%)	*PTTG1* negative (*n* = 45), *n* (%)	χ^2	*P* value
Sex				2.728	0.099
Male	53	34 (58.62)	19 (42.22)		
Female	50	24 (41.38)	26 (57.78)		
Age				3.534	0.060
< 60 yr old	42	19 (32.76)	23 (51.11)		
≥ 60 yr old	61	39 (67.24)	22 (48.89)		
Tumor location				2.327	0.127
Colon	43	28 (48.28)	15 (33.33)		
Rectum	60	30 (51.72)	30 (66.67)		
Differentiation degree				0.867	0.352
High differentiation	23	11 (18.97)	12 (26.67)		
Low–moderate differentiation	80	47 (81.03)	33 (73.33)		
Pathological staging				0.616	0.433
I–II	48	29 (50.00)	19 (42.22)		
III–IV	55	29 (50.00)	26 (57.78)		
Lymph node metastasis				17.150	< 0.001
Positive	58	43 (74.14)	15 (33.33)		
Negative	45	15 (25.86)	30 (66.67)		

Table 4 Receiver operating characteristic analysis of the potential of *GLI1* and *PTTG1* expression to indicate lymph node metastasis in patients undergoing radical surgery for colorectal carcinoma

Grouping	AUC	95%CI	SE	Cut-off	Sensitivity (%)	Specificity (%)
GLI1	0.824	0.739–0.910	0.044	19.76	75.56	84.48
PTTG1	0.811	0.726–0.895	0.043	13.97	68.89	82.76

95%CI: 95% confidence interval.

This study included 103 patients with CRC who underwent radical surgery and analyzed samples of cancer and adjacent tissues. First, we observed a significantly higher positive rate and expression of *GLI1* in cancer tissue samples versus adjacent tissues, as well as a markedly higher positive rate and expression of *PTTG1*, suggesting the overexpression of *GLI1* and *PTTG1* and the possible involvement of both genes in tumorigenesis in CRC. Wu *et al*[18] found high *GLI1* expression in human small-cell lung cancer, which indicates that *GLI1* may mediate the onset and progression of small-cell lung cancer by activating the target gene downstream of Hh signaling. Chen *et al*[19] also reported high *GLI1* expression in hepatocellular carcinoma cells and found that downregulating its expression inhibited the adhesion, movement, migration, and invasion of hepatocellular carcinoma cells. Ding *et al*[20] further pointed out that *GLI1* substantially upregulated protein levels in colon cancer and colon tissue, and its expression was also helpful in predicting LNM, T stage, and postoperative metastasis-free survival, similar to our findings. *PTTG1* induces significantly increased mRNA and protein expression in CRC tissues and cell lines, and its overexpression is closely related to LNM[21]. Moreover, the influence of *PTTG1* on CRC cell migration and invasion is related to *FOXM1* (forkhead box M1)[22], and its promoting effect on CRC cell growth and motility is associated with its induction by *STAT3* (transcriptional activator 3)[14].

Analysis of the clinicopathological data showed that *GLI1* and *PTTG1* had no significant relationship with sex, age, tumor location, degree of tumor differentiation, and pathological stage but were significantly related to LNM. That is, patients with LNM had significantly higher expression rates of *GLI1* and *PTTG1*. Similarly, we found significantly elevated *GLI1* and *PTTG1* expression in patients with LNM, suggesting that both *GLI1* and *PTTG1* are deeply involved in the pathological process of LNM in these patients. Yang *et al*[23] confirmed the significant correlation between *GLI1* and distant metastasis in colorectal adenocarcinoma (CRAC) and clinical staging. Evidence has shown that *GLI1*-activated Hh signaling is strongly linked to poor clinicopathological status and low survival rate in patients with CRC, indicating the potential of *GLI1* to predict poor clinicopathological characteristics and prognosis in patients with CRC[24]. *GLI1* can also

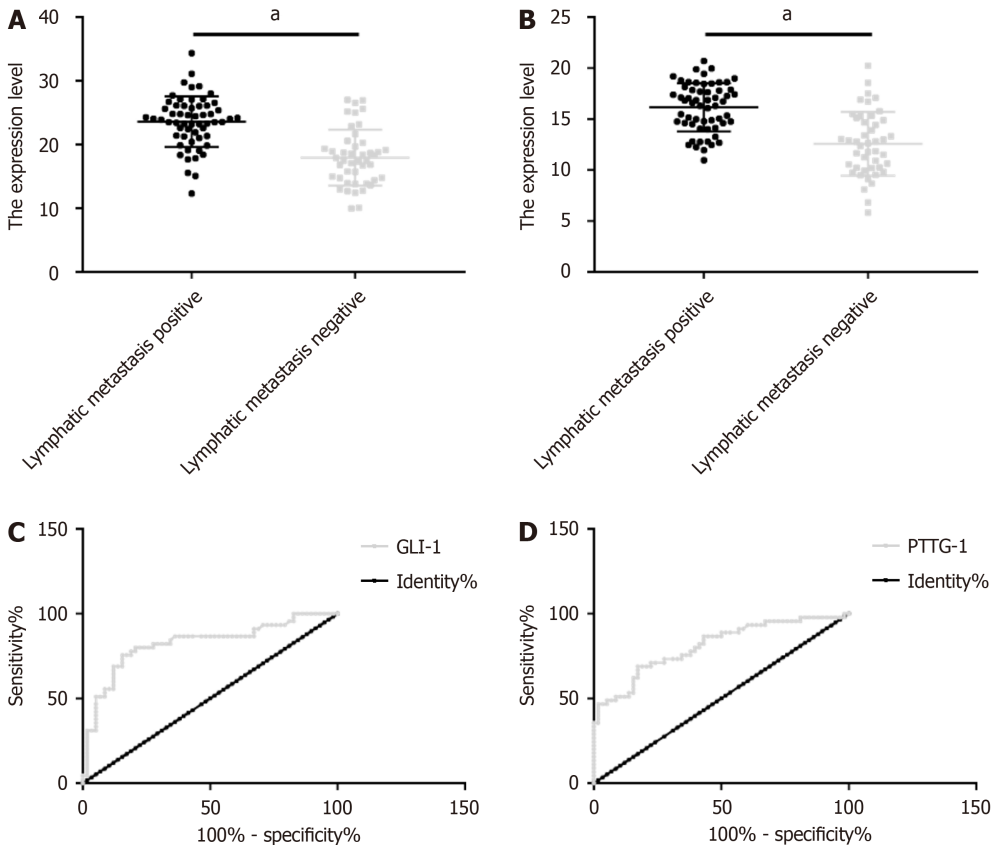

Figure 2 Comparison of *GLI1* and *PTTG1* expression in patients with and without lymph node metastasis. A: *GLI1* expression in patients with and without LNM; B: *PTTG1* expression in patients with and without lymph node metastasis; C and D: Receiver operating characteristic. $^{a}P < 0.05$.

predict survival in patients with CRAC to some extent, with positive *GLI1* expression indicating shorter survival. Besides indicating the presence of LNM, *GLI1* can also predict the pathological status of patients with tumor size ≥5 cm and venous and nerve invasion[25]. However, the research on the correlation between *PTTG1* and clinicopathological data in CRAC is limited. Another study also reported a significant positive correlation between PTTG1 protein levels and TNM staging in endometrial cancer but no significant correlation with other clinical parameters[26]. Furthermore, ROC analysis revealed that the AUC of both *GLI1* and *PTTG1* for predicting LNM was over 0.800, indicating that their expression can effectively predict LNM in patients undergoing radical surgery for CRC.

This study has several limitations. First, the single-center study design and small sample size would have affected the universality of the research results. Second, no basic investigation was conducted to explore the specific molecular mechanisms of *GLI1*, *PTTG1*, and LNM in CRC. Third, no analysis was performed to identify the risk factors that affect the efficacy of radical surgery or LNM in patients with CRC. Continuous optimization and supplementation should be implemented in future investigations to address the above deficiencies.

CONCLUSION

GLI1 and *PTTG1* were aberrantly overexpressed in patients undergoing radical surgery for CRC. The expression of both genes was significantly correlated with LNM and can be used as predictors of LNM. Furthermore, *GLI1* and *PTTG1* expression has certain clinical implications on the evaluation of cases and the development of treatment plans.

FOOTNOTES

Author contributions: Cao F and Chen YY contributed equally to this work and are co-first authors; Cao F and Chen YY designed the research and wrote the first manuscript; Cao F, Chen YY and Wang HC contributed to conceiving the research and analyzing data; Cao F and Chen YY 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 Shanghai Zhangjiang Institute of Medical Innovation.

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: Dr. Cao has nothing to disclose.

Data sharing statement: All data and materials are available from the corresponding author.

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ORIGINAL ARTICLE

Retrospective Study

Clinical feasibility of laparoscopic left lateral segment liver resection with magnetic anchor technique: The first clinical study from China

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Abstract

BACKGROUND

Magnetic anchor technique (MAT) has been applied in laparoscopic cholecystectomy and laparoscopic appendectomy, but has not been reported in laparoscopic partial hepatectomy.

AIM

To evaluate the feasibility of the MAT in laparoscopic left lateral segment liver resection.

METHODS

Retrospective analysis was conducted on the clinical data of eight patients who underwent laparoscopic left lateral segment liver resection assisted by MAT in our department from July 2020 to November 2021. The Y-Z magnetic anchor devices (Y-Z MADs) was independently designed and developed by the author of this paper, which consists of the anchor magnet and magnetic grasping apparatus. Surgical time, intraoperative blood loss, intraoperative accidents, operator ex-

perience, postoperative incision pain score, postoperative complications, and other indicators were evaluated and analyzed.

RESULTS

All eight patients underwent a MAT-assisted laparoscopic left lateral segment liver resection, including three patients undertaking conventional 5-port and five patients having a transumbilical single-port operation. The mean operation time was 138 ± 34.32 min (range 95-185 min) and the mean intraoperative blood loss was 123 ± 88.60 mL (range 20-300 mL). No adverse events occurred during the operation. The Y-Z MADs showed good workability and maneuverability in both tissue and organ exposure. In particular, the operators did not experience either a "chopstick" or "sword-fight" effect in the single-port laparoscopic operation.

CONCLUSION

The results show that the MAT is safe and feasible for laparoscopic left lateral segment liver resection, especially, exhibits its unique abettance for transumbilical single-port laparoscopic left lateral segment liver resection.

Key Words: Magnetosurgery/magnetic surgery; Magnetic anchor technique; Laparoscopic hepatectomy; Transumbilical single-port laparoscopy; Magnet

Core Tip: Magnetic anchor technique (MAT) can be used to assist in exposing tissues or organs during laparoscopic surgery, thereby effectively reducing the number of trocars and eliminating interference between laparoscopic instruments. This study retrospectively analyzed eight patients who underwent laparoscopic left lateral lobectomy using Y-Z magnetic anchor devices. The results showed that MAT is safe and feasible for transumbilical single-port laparoscopic left lateral hepatectomy.

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INTRODUCTION

Since the laparoscopic resection of benign liver tumors was first reported in 1991[1], laparoscopic liver resection has progressively developed and its safety and feasibility have gradually increased[2,3]. Laparoscopic hepatectomy has become a common operation in hepatobiliary surgery with the advantages being less trauma and faster recovery[4]. The unique anatomical structure of the left lateral hepatic lobe makes laparoscopic left lateral segment liver resection an earlier and more widely used laparoscopic hepatectomy. As a result, it has thus been considered to be the first "gold standard" laparoscopic procedure, replacing open left lateral lobectomy for liver resection[5-7].

Transumbilical single-port laparoscopic left lateral lobectomy has been reported[8-10]. However, the "chopstick" and "sword-fight" effects caused by the single-port not only confines the intraoperative maneuverability of the laparoscope instruments[11], but also hinders the interplay of traction and counter-traction between the instruments for effectively stretching and exposing the tissues and organs in the single-port laparoscopic operation. Taking this into account, in addition to the demand for laparoscopic surgeons to continuously improve their single-port operating skills, there is a need for developing better instruments for single-port laparoscopic operations.

The magnetic anchor technique (MAT) uses magnetic devices to perform non-contact spatial anchoring between the anchor magnet and the target magnet[12], which can be used to assist tissue or organ exposure in laparoscopic surgery [13], thereby feasibly reducing the number of inserted trocars, and eliminating the reciprocal interferences between laparoscopic instruments. Tentatively magnetic anchor devices have been used in laparoscopic cholecystectomy with port-reduction[14-16], but there are no reports on the use of magnetic anchor devices in laparoscopic hepatectomy. Herein we report our experiences on the clinical feasibility of a Y-Z magnetic anchor device (Y-Z MADs) in a laparoscopic left lateral hepatectomy.

MATERIALS AND METHODS

Y-Z MADs

The Y-Z MADs was designed by the authors (Yan XP and Zhang MM) and consists of an anchor magnet and a magnetic

grasping apparatus. The auxiliary operation instrument is a titanium alloy tissue grasping forceps. The anchor magnet is a cylindrical magnet with a diameter of 60 mm, a height of 160 mm, and a mass of 2242 g (Figure 1A), made of N50 sintered-type neodymium-iron-boron magnetized with axial saturation with 7500 gausses of the magnetic induction intensity on the surface of the magnet, and housed with a 10 mm thick plastic cover. The magnetic grasping apparatus that possesses a tissue clip connecting a target magnet with a silk thread has a total length of 55 mm and a mass of 18.5 g, and can smoothly pass through a 12 mm laparoscopic port (Figure 1B). Experimentally, the magnetic force curve showed that the maximum magnetic force can reach as high as 59.17 N when the anchor magnet and the target magnet are attracted together at zero distance (Figure 2).

Ethical statement

This single-center, retrospective clinical study was conducted at an academic medical center and approved by its ethics committee (No. 2018-W18). We conducted this study in accordance with the Declaration of Helsinki, and all methods were performed in accordance with the relevant guidelines and regulations. All patients or their authorized legal representatives signed the informed consent form for the use of MAT in their operations.

The inclusion and exclusion criteria

The included patients conformed to the following criteria: (1) A preoperative computerized tomography scan or magnetic resonance imaging of the upper abdomen gave a clear diagnosis, and if the malignant lesion was unveiled, it must be confined to the left lateral lobe of the liver; (2) Informed consent had been signed by the patient or their family members; and (3) Body mass index (BMI) should be no more than 30 kg/m^2. In addition, the patients were excluded from this study if they: (1) Presented with a history of upper abdominal surgery or severe intra-abdominal adhesions; (2) Were found to have any metastatic lesion, either intrahepatic or extrahepatic; (3) Had a cardiac pacemaker implanted; (4) Had a BMI over 30 kg/m^2; (5) Suffered severe cardiopulmonary diseases and were not able to tolerate general anesthesia during surgery and/or patients with pneumoperitoneum; and (6) Were considered inappropriate by the investigator for other reasons.

The clinical data of eight patients who underwent magnetic anchor-assisted laparoscopic left lateral hepatic lobectomy were retrospectively analyzed. Demographically, two patients were female and six were male in this study, aged between 23 and 75 years, with a median age of 49.5 years. Their BMI ranged from 19.26 to 26.30 kg/m^2, with a median of 23.19 kg/m^2. Diagnostically, three of the patients had hepatic hemangioma, one had primary liver cancer, two had primary liver cancer complicated with gallbladder stones, one had liver metastases, and one had focal hepatic steatosis.

Surgical procedure

Among the eight patients in this study, the first three underwent 5-port laparoscopic operations with the purpose of developing the stepwise procedure for the MAT-assisted laparoscopic left lateral hepatic lobectomy. Afterwards, based upon the practical experience gained from the first three patients, we performed transumbilical single-port laparoscopic left lateral hepatic lobectomy on the remaining five patients.

The MAT-assisted 5-port left lateral hepatic lobectomy was started once general anesthesia took effect. After the patients were placed in a lithotomy position with slight reverse trendelenburg tilting to left, five trocars were placed in the abdominal wall as shown in Figure 3A, and subsequently, the pneumoperitoneum was established with the pressure maintained at the level of 12 mmHg. The magnetic grasping forceps were delivered into the peritoneal cavity through the 12 mm port using the titanium alloy tissue grasping forceps, and then clamped on the edge of the left lateral lobe of the liver. The anchor magnet was then placed on the abdominal wall to attract the target magnet so that the liver could be pulled up following the movement of the anchor magnet (Figure 3B). Once this was completed, the coronary ligament and the left deltoid ligament were disconnected from their attachment to peritoneal wall, and the liver capsule and superficial liver parenchyma were opened with an ultrasonic scalpel by following the marking line made with an electric hook. Along the resection, titanium clips were used to close the smaller vascular branches before cutting, while the larger branches were clipped with vascular clips and freed until they were close to the hepatic pedicle of the left lateral lobe of the liver. At the same time, the left hepatic vein and the left lateral hepatic lobe of the liver were sequentially transected with two linear cutting and closure devices (Figure 3C). For the patient with cholecystolithiasis and chronic cholecystitis, his gallbladder was successfully removed by conventional methods during the operation. Before concluding the operation, the anchoring magnet was taken away from the abdominal wall, the magnetic grasping apparatus was retrieved with a titanium alloy grasping forceps, and the specimens were placed in a specimen bag and taken out through the extended incision below the umbilicus (Figure 3D). The abdominal cavity drainage tube was placed in the liver section, which was drawn out from the abdominal wall and fixed.

For the MAT-assisted transumbilical single-port laparoscopic left lateral hepatic lobectomy, after a 4 cm arcuate incision was first made under the umbilicus as shown in Figure 4A, a single-port (Hangzhou Kangji Medical Instrument Co., Ltd.) was inserted, and the pneumoperitoneum was established with a pressure of 12 mmHg. After laparoscopically surveying the abdominal cavity, the magnetic grasping apparatus was introduced into the cavity through the single-port to clamp the edge of the left lateral lobe of the liver. At the same time, the anchoring magnet was placed outside the right upper abdominal wall of the patient to attract the target magnet to the magnetic grasping apparatus. After maneuvering the pulling direction and strength to create ample exposure to the operating field, the falciform ligament, left coronary ligament, and left deltoid ligament were sacrificed by ultrasonic scalpel, and the "two-step two-nail" technique was adopted to sequentially remove segment II and part of segment III of the left lateral lobe of the liver (Figure 4B and C). Following this, the anchoring magnet was removed from the abdominal wall, both the magnetic grasping apparatus and the bagged resected liver were taken out through the single-port, and the indwelling abdominal drainage tube in the liver

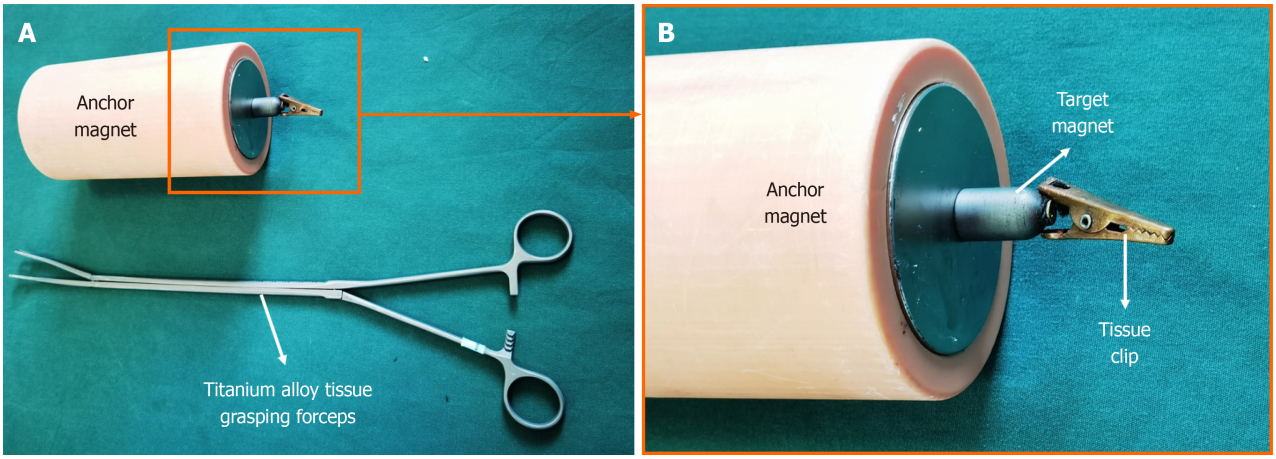

Figure 1 Y-Z magnetic anchor devices. A: Anchor magnet and the titanium alloy tissue grasping forceps; B: Magnetic grasping apparatus.

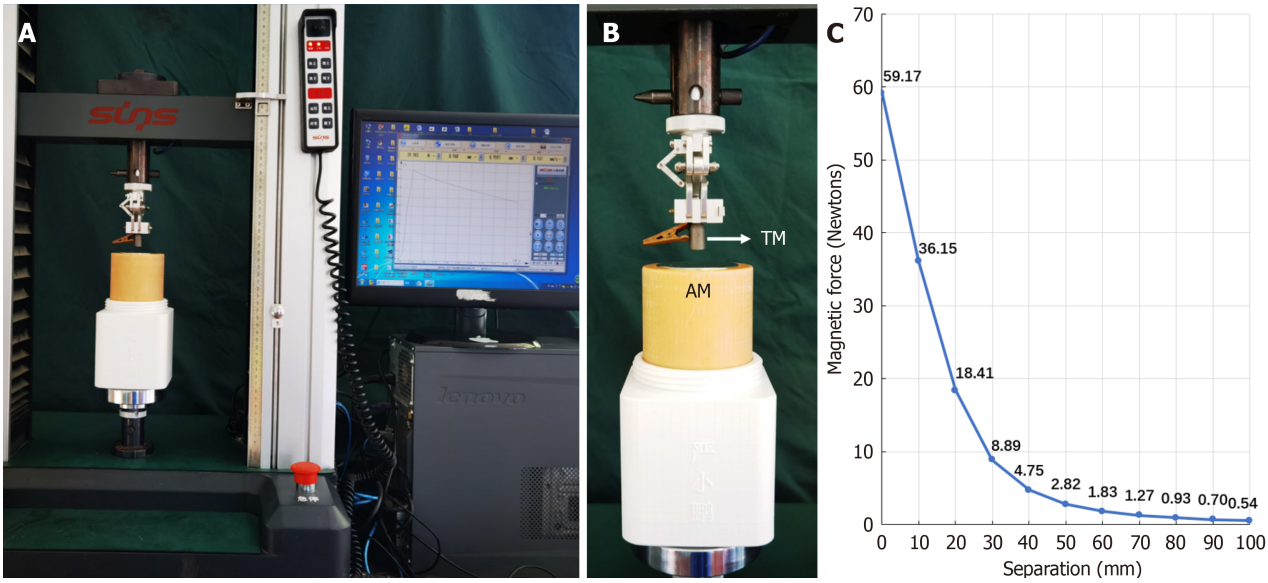

Figure 2 Magnetism test of the Y-Z magnetic anchor devices. A: Magnetism test equipment; B: The anchor magnet and target magnet in the test state; C: The magnetic force-displacement curve of the anchor and target magnet. AM: Anchor magnet; TM: Target magnet.

section was led out of the body from the umbilical incision and fixed (Figure 4D). The operation was then complete. The surgical procedure of patient 8 is shown in the Video.

Statistical analysis

Study parameter indicators included operating time, intraoperative blood loss, damage to the surrounding organ, failure of the magnetic anchoring device, the operating experience of the operator and assistants, postoperative incision pain score, postoperative hospital stay, perioperative complications, and other indicators. SPSS 20.0 software was used for statistical analysis. The measurement data of normal distribution were expressed as (mean ± SD), while the measurement data of skewed distribution were expressed as a median.

RESULTS

MAT-assisted laparoscopic left lateral hepatic lobectomy was successfully performed on all eight patients without the conversion to an open procedure or use of the Pringle maneuver. Five patients had successful single-port operations without the addition of any trocars in the abdominal wall. Intraoperatively, the Y-Z MADs made the surgical field exposed well so that none of the surrounding organs were accidentally damaged. Statistically, the mean operating time was 138 ± 34.32 min (range 95-185 min), and the mean intraoperative blood loss was 123 ± 88.60 mL (range 20-300 mL). Postoperatively, all patients had no bile leakage or bleeding after the operation, the abdominal drainage tube was removed 0-5 d after the operation, incisional pain scores were maintained at the level of less than 3, and hospital stay was

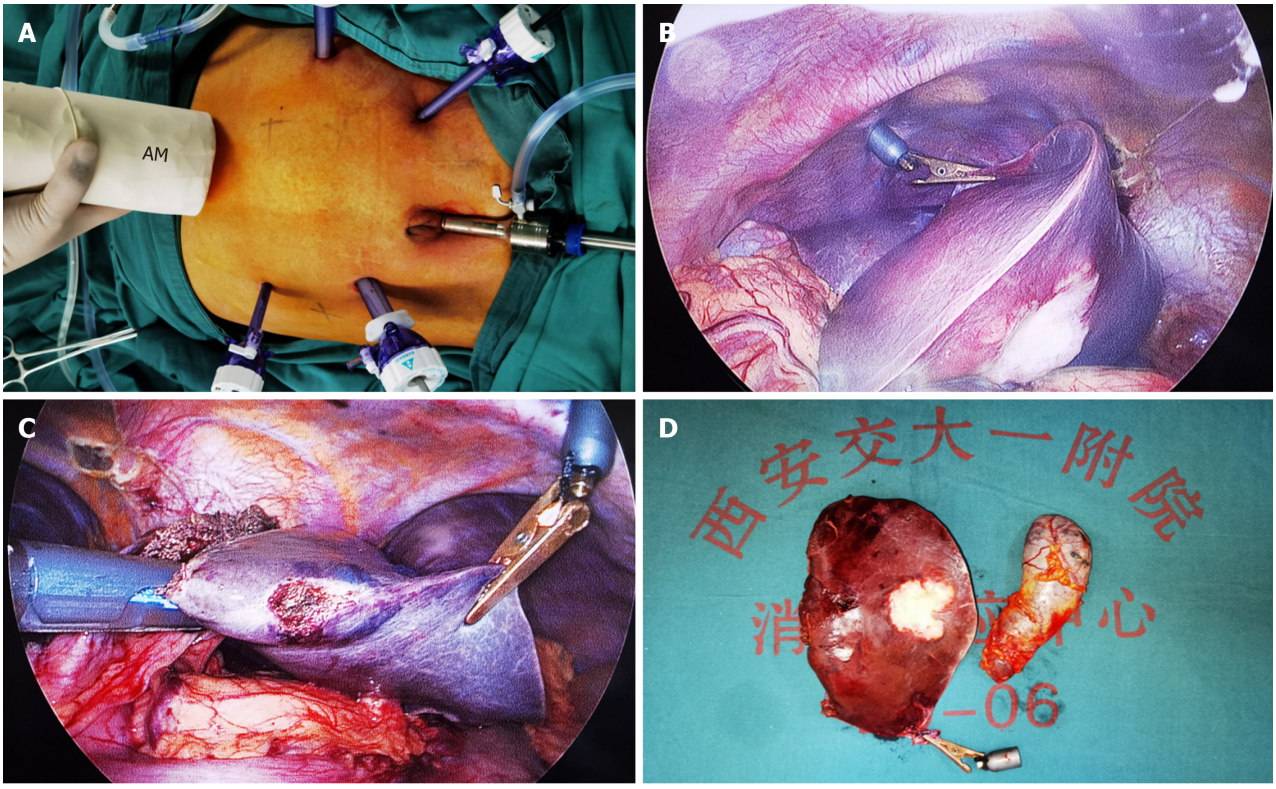

Figure 3 Magnetic anchor-assisted 5-port left lateral hepatic lobectomy operation procedure (patient 2). A: The layout of the abdominal wall port and the position of the anchor magnet; B: The magnetic anchoring device pulling the left lateral lobe of the liver to reveal the tumor lesion and the hepatogastric ligament; C: The left lateral lobe of the liver is shown under the magnetic anchoring device, which is transected at the hepatic pedicle of the left lateral lobe of the liver with a linear cutting and closure device; D: The left lateral hepatic lobe and gallbladder specimens that are resected. AM: Anchor magnet.

between 2-6 d. In the follow-up examinations one month after the operation, all patients presented with a good prognosis. Moreover, in the three transumbilical single-port laparoscopic left lateral lobectomies, both the operator and the scope driver had a positive operating experience with no complaint of either the "chopstick" or "sword fight" effect between the instruments. All the perioperative parameters are shown in Table 1.

DISCUSSION

Single-port laparoscopic surgery further reduces abdominal wall trauma and is of great significance for the development of minimally invasive surgery. However, both the "chopstick" and "sword-fight" effects in the single port laparoscopic operations seriously impair the operating experience of the surgeons and their assistants through increasing the difficulty of surgical field exposure and making the maneuverability of the laparoscopic instruments more awkward. Despite several methods being applied in practice, such as a reduction in the number of instruments or suture suspension[17], none of the modus operandi can workably expose the surgical field well. As a special traction technique, the MAT has been tentatively used in port-reduced laparoscopic surgery and endoscopic submucosal dissection. Mechanically, the magnetic anchor device can generate non-contact attraction outside the body cavity on the target magnet in the cavity, thus being able to create a traction and counter traction effect, which may pull the tissue or organs away from the surgical field and improve the visibility of the anatomical structures. The MAT has been piloted to assist thoracoscopic lung wedge resection and esophagectomy[18,19], laparoscopic cholecystectomy[14,15], and laparoscopic hysterectomy[20]. Moreover, in the endoscopic operation technique, the MAT has been shown to assist the lesion traction in endoscopic submucosal dissection[21,22].

We independently designed and developed Y-Z MADs suitable for laparoscopic surgery. The device has been clinically used for port-reducing and single-port laparoscopic cholecystectomy and has achieved promising clinical results in our clinics. In this study, the Y-Z MAD was used for the first time in a laparoscopic left lateral hepatic lobectomy. Since laparoscopic liver resection is more complex than laparoscopic cholecystectomy, the key aspects should be emphasized during the operation. Firstly, compared with the use of the MAT in laparoscopic cholecystectomy, transumbilical single-port laparoscopic left lateral hepatic lobectomy required a much stronger traction force to be applied to the left lateral lobe of the liver than the gallbladder. If the abdominal wall is too thick, it may mitigate the magnetic field for achieving a firm grasp of the liver, so we only performed the MAT-assisted single port liver procedure on the patients with a BMI less than 30 kg/m^2. Secondly, the assistant (magnetic palmist) should know how to dexterously move the anchor magnet to change the grasping direction or extent of tissue or organ exposure to accommodate the needs of the surgeon during the

Table 1 Clinical data of magnetic anchor-assisted laparoscopic left lateral hepatic lobectomy

Patient no.	Gender	Age (yr)	BMI (kg/m²)	Diagnosis	Child-Pugh scoring	Extent of resection	Tumor size	Number of ports	Operative (min)	Bleeding volume (mL)	Pain score[1]	Drainage tube retention time (d)	Postoperative hospital stay (d)
1	Male	61	26.30	Primary liver cancer	5	Left lateral lobe	45 mm × 45 mm × 32 mm	5	100	100	2/3/3	5	5
2	Male	51	21.67	Primary liver cancer, gallstone	5	Left lateral lobe + gallbladder	40 mm × 35 mm × 40 mm	5	170	110	3/3/3	4	5
3	Female	42	19.26	Hepatic hemangioma	6	S2 + partial S3	82 mm × 60 mm × 45 mm	5	110	100	3/3/2	4	6
4	Female	23	21.88	Focal hepatic steatosis	5	Left lateral lobe	25 mm × 23 mm × 20 mm	1	185	300	1/1/2	0	4
5	Male	48	24.91	Hepatic hemangioma	5	Left lateral lobe	62 mm × 50 mm × 43 mm	1	150	100	2/2/2	2	5
6	Male	75	24.24	Liver metastases	5	S2 + partial S3	55 mm × 45 mm × 60 mm	1	165	200	2/2/2	5	6
7	Male	37	22.65	Hepatic hemangioma	5	Left lateral lobe	72 mm × 55 mm × 45 mm	1	130	50	1/2/2	3	3
8	Male	57	23.72	Primary liver cancer, gallstone	5	S2 + gallbladder	25 mm × 20 mm × 13 mm	1	95	20	2/1/1	0	2

[1]Using the Wong-Banker facial expression pain score, the table lists the pain scores of the patients' surgical incisions on the 1st, 2nd, and 3rd d after the operation.
BMI: Body mass index.

operation. One important aspect to avoid is the large-scale rapid movement of the target magnet to eliminate the "de-anchoring", which can interrupt the continuity of the surgical operation. In addition, when the magnetic palmist cannot obtain satisfactory exposure by adjusting the anchor magnet, the surgeon should internally adjust the position of the grasping forceps in time in order to obtain a better traction effect. Thirdly, the MAT-assisted transumbilical single-port laparoscopic left lateral hepatic lobectomy is an innovative operating method, so both the surgeon and the assistant should not only master the knowledge of the MAT but also train themselves to improve operating finesses in order to perform the MAT-assisted single-port procedure(s).

CONCLUSION

This study preliminarily shows that the MAT can assist multiple-port as well as single-port laparoscopic left lateral hepatic lobectomy. The MAT indeed undermined the single-port-related "chopstick" and "sword-fight" effects so that it improved the surgeon's operating experience and contributed to abating postoperative pain at incisional sites. Of course, this study is a retrospective study with only eight cases, which is a limitation of this study. In future, we will conduct a

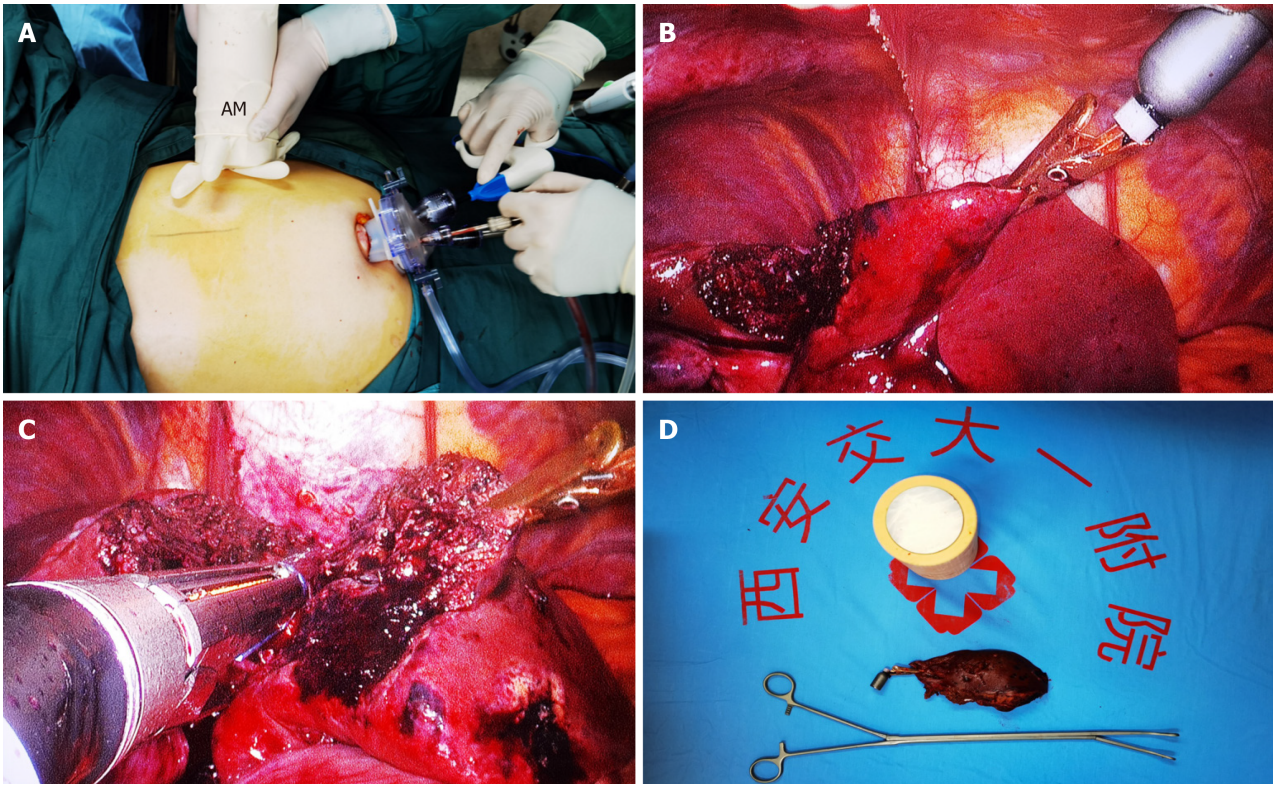

Figure 4 Magnetic anchoring-assisted transumbilical single-port laparoscopic left lateral hepatic lobectomy process (patient 5). A: The subumbilical single-port and the anchor magnet; B: The Y-Z magnetic anchor devices pulling the left lateral lobe of the liver to reveal the liver section; C: The linear cutting and closure device was used to cut off segment II and part of segment III of the left lateral lobe of the liver; D: The resected segment II and part of segment III of the left lateral lobe of the liver. AM: Anchor magnet.

prospective randomized controlled trial to continuously evaluate the safety and feasibility of the use of the MAT in transumbilical single port left lateral hepatectomy. In summary, this study showed that the MAT is safe and feasible for transumbilical single-port laparoscopic left lateral segment liver resection.

FOOTNOTES

Author contributions: Lyu Y and Yan XP designed and coordinated the study; Zhang MM and Yan XP designed the Y-Z magnetic anchor device and wrote the manuscript; Zhang MM, Bai JG, Zhang D, Tao J, Geng ZM, and Yan XP performed the research and acquired the data; Zhang MM, Li ZQ, Ren YX, and Zhang YH analyzed the data; Lyu Y and Yan XP conceived of the study and contributed to the study design, the interpretation of the results, and the critical revision of the manuscript; and all authors read and approved the final manuscript. The reasons for designating Yan XP and Lyu Y as co-corresponding authors are as follows: Yan XP and Lyu Y have equal contributions in study design and making critical revisions to the manuscript. The two co-corresponding authors ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Yan XP and Lyu Y contributed efforts of equal substance throughout the research process. Therefore, Yan XP and Lyu Y are designated as co-corresponding authors in this manuscript.

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Informed consent statement: All study participants provided their voluntary written informed consent prior to their inclusion.

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

Data sharing statement: The authors declare that the data supporting the findings of this study are available within the article or from the corresponding authors upon request.

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ORIGINAL ARTICLE

Retrospective Study

Prognostic prediction model of colorectal cancer based on preoperative serum tumor markers

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Abstract

BACKGROUND

Preoperative serum tumor markers not only play a role in the auxiliary diagnosis and postoperative monitoring in colorectal cancer (CRC), but also have been found to have potential prognostic value.

AIM

To analyze whether preoperative serum tumor markers, including carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), affect the prognosis of CRC.

METHODS

This was a retrospective study conducted in a single center. Patients with nonmetastatic CRC who underwent initial surgery between January 2011 and January 2020 were enrolled and divided into development site and validation site groups at a ratio of 7:3. The independent prognostic factors were screened by Cox regression analysis, and finally, a prognostic nomogram model was established. The newly developed model was tested by internal validation.

RESULTS

Eventually, 3526 postoperative patients with nonmetastatic CRC were included in the study. There were 2473 patients at the development site and 1056 patients at the validation site. Age ($P < 0.01$, HR = 1.042, 95%CI = 1.033-1.051), tumor node metastasis (TNM) classification ($P < 0.01$, HR = 1.938, 95%CI = 1.665-2.255), preoperative CEA ($P = 0.001$, HR = 1.393, 95%CI = 1.137-1.707) and CA19-9 ($P < 0.01$, HR = 1.948, 95%CI = 1.614-2.438) levels were considered independent prognostic factors for patients with nonmetastatic CRC and were used as variables in the nomogram model. The areas under the curve of the development and vali-

dation sites were 0.655 and 0.658, respectively. The calibration plot also showed the significant performance of the newly established nomogram.

CONCLUSION
We successfully constructed a nomogram model based on age, TNM stage, preoperative CEA, and CA19-9 levels to evaluate the overall survival of patients with nonmetastatic CRC.

Key Words: Colorectal cancer; Prognosis; Carcinoembryonic antigen; Carbohydrate antigen 19-9; Nomogram

Core Tip: The tumor markers carcinoembryonic antigen and carbohydrate antigen 19-9 are often used in the auxiliary diagnosis and postoperative monitoring of colorectal patients, but their role in prognosis needs to be further explored. Here, we retrospectively analyzed the clinical data and pathological characteristics of 3526 patients with nonmetastatic colorectal cancer (CRC), confirmed the negative correlation between preoperative serum tumor marker levels and prognosis, and established a nomogram model to evaluate the prognosis of CRC patients.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide[1,2]. Although the 5-year survival rate of CRC patients has improved due to continuous improvements in screening, chemoradiotherapy, immunotherapy, metastasis resection and other treatment measures[3,4], CRC is still the second leading cause of cancer death worldwide, accounting for 10% of all cancer deaths[5,6].

At present, the prognosis prediction and treatment decision of patients with CRC depend on traditional tumor node metastasis (TNM) staging (according to the degree of tumor invasion, lymph node status, and distant metastasis status) [7]. However, as the clinical outcomes of patients with the same stage of CRC vary greatly, it is often inaccurate to judge the prognosis by TNM staging alone, especially for patients with nonmetastatic CRC[8,9]. Therefore, it is necessary to identify biomarkers to help judge the prognosis of patients with CRC.

As serum tumor markers, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are often used for postoperative monitoring and auxiliary diagnosis of CRC. At present, CEA is the most commonly used biomarker for CRC. In addition to preoperative monitoring, monitoring every 3-6 months after surgery is recommended by guidelines [10,11]. Although there is some controversy regarding the clinical benefit of CA19-9, it is still considered useful for monitoring disease progression in CRC patients without elevated CEA[12]. Many studies have shown that the preoperative CEA level can help to predict the prognosis of patients with CRC[13-15], and the CA19-9 level is also considered to play a role in monitoring recurrence and evaluating prognosis[16-18].

Due to the existence of tumor heterogeneity, it is impractical to predict the prognosis of patients with CRC with a single factor. Therefore, this study combined tumor markers with TNM stage and clinical characteristics of patients to construct a prediction model for the prognosis of CRC patients using a nomogram in hopes of elucidating further prognostic insights.

MATERIALS AND METHODS

Enrollment of patients

In this retrospective study, we enrolled 3529 patients with nonmetastatic CRC who underwent surgical resection at the Department of Gastrointestinal Surgery, the First Affiliated Hospital of Chongqing Medical University, from January 2011 to January 2020. The inclusion criteria were as follows: (1) Aged ≥ 18 years; (2) diagnosed with primary CRC for the first time; (3) underwent radical surgery; and (4) had TNM stage I-III disease. The exclusion criteria were as follows: (1) Previous diagnosis of any malignant tumor; (2) distant metastasis at initial diagnosis of CRC; and (3) lack of clinical parameters and laboratory results. The study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University, and informed consent was obtained from the patients (2022-135-2).

Clinical variables selected for analysis

Clinical and pathological variables were obtained from 3526 selected patients, including age, sex, body mass index (BMI),

smoking history, drinking history, hypertension status, type 2 diabetes mellitus (T2DM) status, chronic heart disease status, tumor location, tumor size, TNM stage, surgical time, and the levels of the preoperative serum tumor markers CEA, CA19-9, and alpha-fetoprotein. Serum tumor markers were measured within one week before surgery, and normal and abnormal levels were distinguished based on the test results.

Statistical analyses

The independent sample t test was used to analyze the differences between groups for continuous variables, and the chi-square test or Fisher's exact test was used to analyze the differences between groups for categorical variables. Univariate analysis was used to test the relationships between various prognostic predictors and overall survival (OS). Variables with *P* values less than 0.05 in univariate analysis were used for Cox proportional hazard analysis. The nomogram model was constructed with R software 4.1.2, and then the newly established nomogram was evaluated in the validation site group. The ratio of participants in the development site group to those in the validation site group was 7:3. The areas under the curve (AUCs) and decision curve analysis (DCA)[19] were used to evaluate the performance of the nomogram model, and the accuracy of the model was further evaluated by comparing the predicted results with the actual observation results through the calibration curve[20,21].

RESULTS

Characteristics of the included patients

According to the inclusion criteria, 3529 patients were ultimately enrolled. Patients were randomized at a 7:3 ratio, with 2473 patients assigned to the development site group and 1056 to the validation site group (Table 1). In the development site group, males accounted for 58.4%, females accounted for 41.6%, and the average age was 63.1 years. Moreover, 47.3% of patients had colon cancer, and 60.1% of the patients had a tumor larger than 5 cm. Among them, 649 (25.1%) had hypertension, and 311 (11.5%) had T2DM. According to the TNM classification, 18.9% of patients were in stage I, 39.9% were in stage II, and 35.6% were in stage III. Preoperative CEA and CA19-9 levels were elevated in 36.8% and 20.2% of the patients, respectively.

Establishment of the nomogram

To predict the prognosis of CRC, univariate and Cox analyses were performed (Table 2). According to univariate analysis, age ($P < 0.01$, HR = 1.045, 95%CI = 1.037-1.055), BMI ($P = 0.001$, HR = 0.952, 95%CI = 0.924-0.981), tumor size ($P < 0.01$, HR = 1.426, 95%CI = 1.184-1.718), tumor stage ($P < 0.01$, HR = 2.105, 95%CI = 1.817-2.438), and preoperative CEA ($P < 0.01$, HR = 2.185, 95%CI = 1.812-2.633) and CA19-9 ($P < 0.01$, HR = 2.646, 95%CI = 2.185-3.204) levels all showed highly significant differences. Unhealthy lifestyle habits, such as smoking ($P = 0.706$, HR = 0.964, 95%CI = 0.795-1.168) and drinking ($P = 0.248$, HR = 0.884, 95%CI = 0.718-1.089), were not significantly associated with OS, and chronic diseases, such as hypertension ($P = 0.493$, HR = 0.926, 95%CI = 0.743-1.154) and T2DM ($P = 0.134$, HR = 1.231, 95%CI = 0.938-1.617), were also not associated with OS.

Next, we included variables with significant differences in the univariate analysis in the Cox analysis, which revealed that age ($P < 0.01$, HR = 1.042, 95%CI = 1.033-1.051), tumor stage ($P < 0.01$, HR = 1.938, 95%CI = 1.665-2.255), preoperative CEA ($P = 0.001$, HR = 1.393, 95%CI = 1.137-1.707) and CA19-9 ($P < 0.01$, HR = 1.948, 95%CI = 1.614-2.438) levels were independent risk factors for the prognosis of patients with CRC. A nomogram based on the Cox regression model was established (Figure 1). The score of each factor was obtained according to the patient's own condition, and the total score was obtained by adding the four scores. Then, the prognosis of patients with nonmetastatic CRC was estimated according to the total score.

Validation

To verify whether the nomogram was applicable to other datasets, we conducted a validation study using data from 1056 CRC patients at the validation site. Time-dependent receiver operating characteristic curves for the OS-associated nomograms were generated for predicting 1-, 3-, and 5-year survival rates (Figure 2). The AUCs for 5-year survival were 0.655 at the development site and 0.658 at the validation site, which both indicated good predictive ability. The nomogram calibration curve was obtained by comparing the predicted survival rate of the nomogram with the corresponding survival rate obtained by the Kaplan-Meier method (Figure 3). The calibration curves for both the training and validation sets revealed high-quality prediction results. Figure 4 shows the DCA curves, which further confirmed the net benefit of our nomogram model within a certain threshold probability range.

DISCUSSION

Relying only on the traditional TNM stage to judge the prognosis of patients with CRC[22], especially patients with nonmetastatic CRC, is difficult, and additional influencing factors should be considered[23-25]. Over the past two decades, many molecular biomarkers of CRC have been extensively investigated, but serum tumor markers remain the most commonly used. CEA and CA19-9, which are readily available serum tumor markers, are widely used in the diagnosis and postoperative monitoring of CRC[26,27]. Although previous studies have verified the use of high preoperative CEA and CA19-9 levels as independent predictors of OS and DFS[28-30], few studies have quantified their impact on

Table 1 Baseline information between the development and validation cohorts, *n* (%)

Characteristics	Development (2473)	Validation (1056)	*P* value
Age, yr	63.1 ± 12.0	61.7 ± 12.3	0.002[a]
Sex			0.930
Male	1448 (58.4)	620 (59.1)	
Female	1025 (41.6)	436 (40.9)	
BMI, kg/m^2	22.6 ± 3.2	22.8 ± 3.2	0.180
Smoking	942 (37.0)	395 (37.9)	0.700
Drinking	767 (30.8)	310 (29.8)	0.327
Hypertension	649 (25.1)	257 (25.4)	0.235
T2DM	311 (11.5)	123 (11.5)	0.442
CHD	98 (4.3)	52 (4.8)	0.195
Tumor location			0.217
Colon	1166 (47.3)	582 (46.9)	
Rectum	1307 (52.7)	474 (53.1)	
TNM stage			0.802
I	490 (18.9)	215 (18.4)	
II	1067 (39.9)	443 (40.4)	
III	916 (35.6)	398 (36.6)	
Tumor size			0.705
< 5 cm	1442 (60.1)	623 (60.9)	
≥ 5 cm	1031 (39.9)	433 (39.1)	
CEA			0.053
Normal	1562 (63.2)	703 (66.6)	
Abnormal	911 (36.8)	353 (33.4)	
CA199			0.823
Normal	1973 (79.8)	839 (79.5)	
Abnormal	500 (20.2)	217 (20.5)	
AFP			0.105
Normal	2366 (95.7)	997 (94.4)	
Abnormal	107 (4.3)	59 (5.6)	
Surgical time, min	224.5 ± 78.3	224.6 ± 78.3	0.967

[a]$P < 0.05$.

T2DM: Type 2 diabetes mellitus; BMI: Body mass index; CHD: Chronic heart disease; TNM: Tumor node metastasis; AFP: Alpha fetoprotein; CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen 19-9.

prognosis.

In this study, we attempted to establish a nomogram including serum tumor markers combined with traditional TNM staging to improve prognosis prediction in patients with CRC. A total of 15 variables were included in the study, and four variables (age, TNM stage, preoperative CEA level and CA19-9 level) were ultimately included in the nomogram. BMI and tumor size were also considered to be associated with prognostic outcome in the univariate analysis, but the association was not strong according to the Cox analysis. This might be because tumor size tends to indicate a greater tumor burden, which is positively correlated with tumor marker levels[31]. For BMI, an inverse association with CEA was considered, possibly due to the hemodilution effect of increased plasma volume observed in patients with high BMIs[32, 33]. Other factors, such as poor lifestyle habits and other chronic diseases, did not appear to be associated with prognosis.

Consistent with the results of other studies[34-37], we found that the CEA level was an independent predictor of survival. Compared with normal levels of CEA, elevated preoperative CEA resulted in a 62% increased risk of death[38].

Table 2 Univariate and multivariate analysis of overall survival

Risk factors	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age (yr)	1.045 (1.037-1.055)	< 0.01[a]	1.042 (1.033-1.051)	< 0.01[a]
Sex (male/female)	0.931 (0.770-1.126)	0.461		
BMI (kg/m^2)	0.952 (0.924-0.981)	0.001[a]	0.980 (0.952-1.008)	0.161
T2DM (yes/no)	1.231 (0.938-1.617)	0.134		
Tumor location (colon/ rectum)	1.179 (0.979-1.421)	0.083		
Tumor stage (III/II/I)	2.105 (1.817-2.438)	< 0.01[a]	1.938 (1.665-2.255)	< 0.01[a]
Smoking (yes/no)	0.964 (0.795-1.168)	0.706		
Drinking (yes/no)	0.884 (0.718-1.089)	0.248		
Hypertension (yes/no)	0.926 (0.743-1.154)	0.493		
Tumor size (≥ 5 cm/< 5 cm)	1.426 (1.184-1.718)	< 0.01[a]	1.117 (0.923-1.351)	0.255
CEA (abnormal/normal)	2.185 (1.812-2.633)	< 0.01[a]	1.393 (1.137-1.707)	0.001[a]
AFP (abnormal/normal)	1.108 (0.715-1.718)	0.645		
CA-199 (abnormal/normal)	2.646 (2.185-3.204)	< 0.01[a]	1.984 (1.614-2.438)	< 0.01[a]
Surgical time, min	1.001 (1.000-1.002)	0.069		

[a]*P* < 0.05.

BMI: Body mass index; T2DM: Type 2 diabetes mellitus; AFP: Alpha fetoprotein; CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen 19-9.

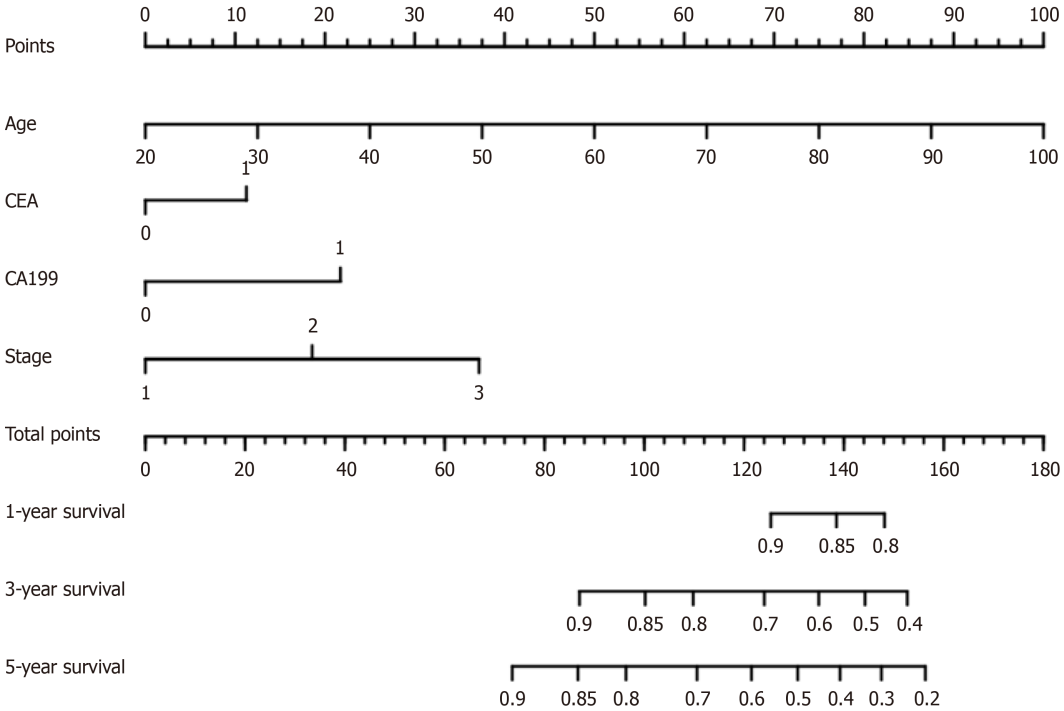

Figure 1 Nomogram for predicting the prognosis of patients with non-metastatic colorectal cancer. CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen 19-9.

The guidelines also recommend CEA as an effective predictor of OS[39,40]. Notably, previous reports have shown that the significance of postoperative CEA measurements depends on preoperative CEA levels. Almost all patients with high preoperative CEA levels had increased CEA levels at the time of CRC recurrence, but this increase was rarely observed in patients with normal preoperative CEA levels[17,41]. Therefore, we selected the preoperative CEA level as a prognostic predictor. In contrast, previous guidelines did not recommend the use of CA19-9 to assess prognosis[40,42]. However, similar to our findings, several recent studies have also demonstrated the prognostic value of CA19-9[31,43], especially in

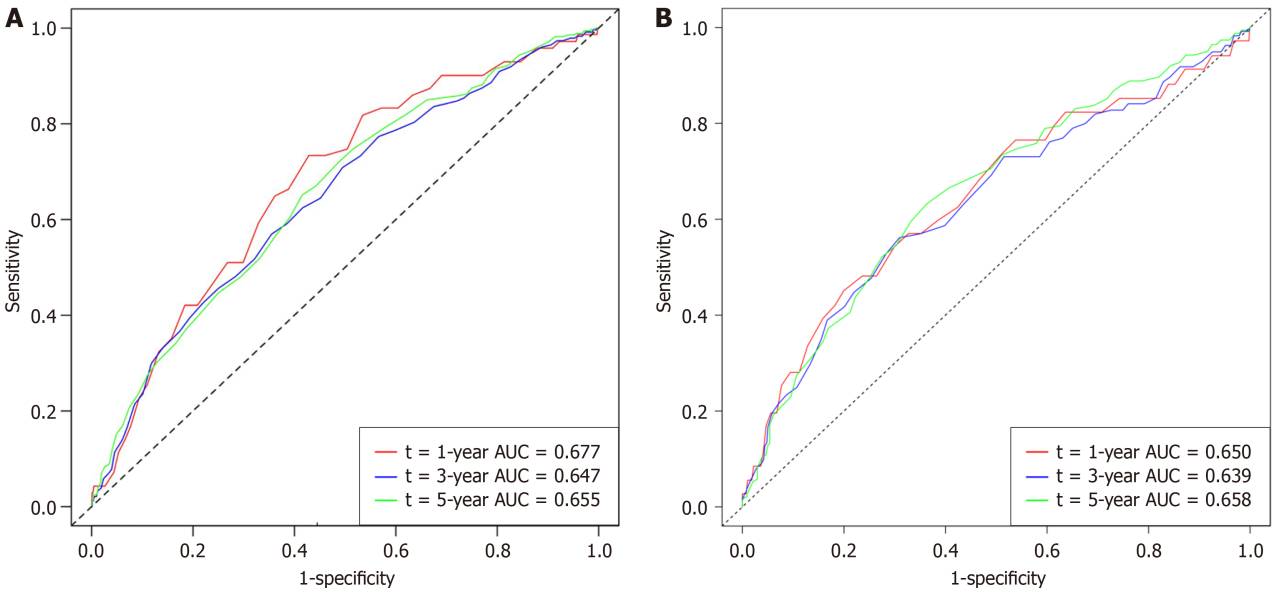

Figure 2 Receiver operating characteristic curves of the nomogram. A: 1-,3- and 5-year receiver operating characteristic (ROC) of nomogram using train set; B: 1-,3- and 5-year ROC of nomogram using validation set. AUC: Area under the curve.

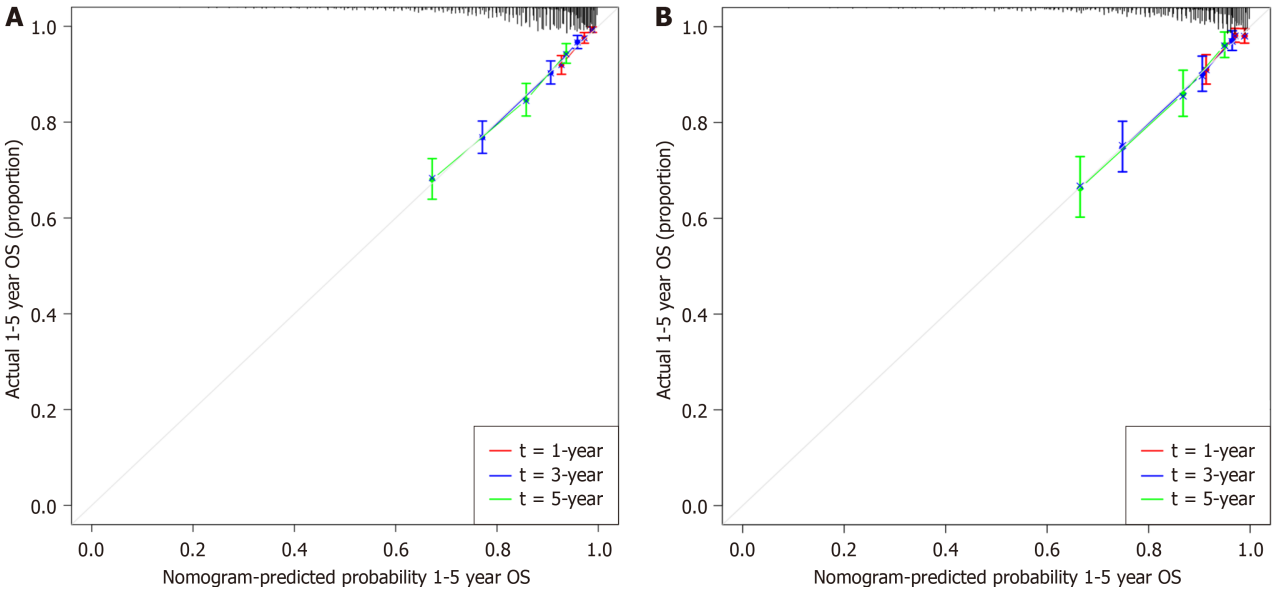

Figure 3 Calibration curves for the nomogram. A: 1-,3- and 5-year calibration curves of overall survival (OS) using training set; B: 1-,3- and 5-year calibration curves of OS using validation set. OS: Overall survival.

CRC patients with normal preoperative CEA levels[12,44]. Furthermore, some studies have reported that the combined assessment of preoperative serum CEA and CA19-9 may enhance the diagnostic prediction and prognosis prediction of CRC patients[45].

In our study, we successfully established a novel prognostic model for patients with nonmetastatic CRC. Compared with previous studies, our sample size was quite large, and after internal validation, our prediction model showed good performance. However, the current study has several limitations. First, our study was retrospective and was conducted at a single center, which might have caused selection bias. Second, while we performed internal validation of the prediction model, it would have been better if external validation could have been performed to verify whether our findings were generally applicable.

CONCLUSION

Our study demonstrated the prognostic impact of the tumor markers CEA and CA19-9 and established a more accurate and practical nomogram model for predicting the prognosis of patients with nonmetastatic CRC.

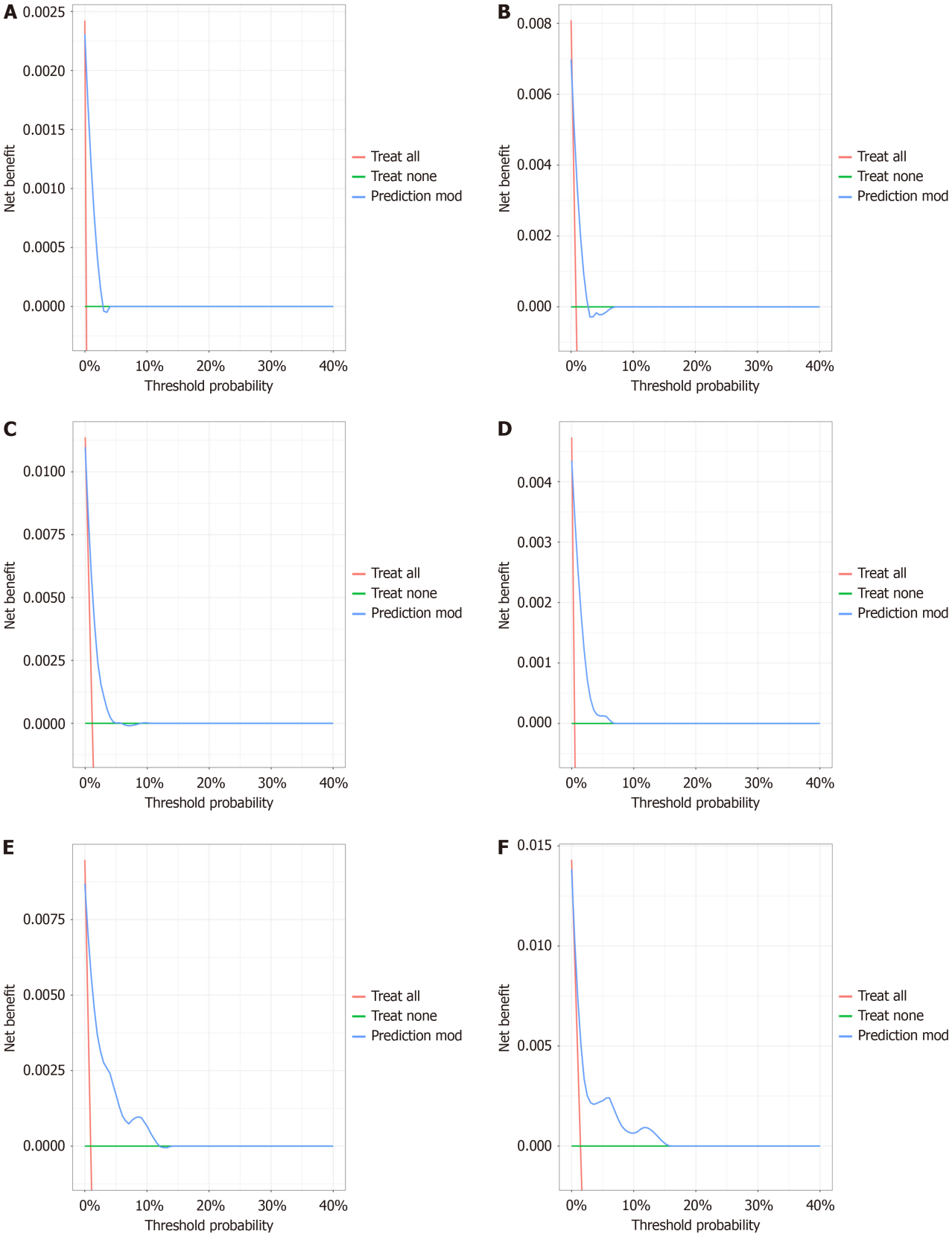

Figure 4 Decision curve analysis for the nomograms. A: Decision curve analysis (DCA) of 1-year survival nomogram using training set; B: DCA of 3-year survival nomogram using training set; C: DCA of 3-year survival nomogram using training set; D: DCA of 1-year survival nomogram using validation set; E: DCA of 3-year survival nomogram using validation set; F: DCA of 5-year survival nomogram using validation set.

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FOOTNOTES

Author contributions: Rao SQ was thanked for her significant contribution in revising the manuscript; Diao YH and Rao SQ contributed to the data analysis; Peng D led the quality assessments, Diao YH wrote the original draft; Shu XP and Cheng Y revised the manuscript. All authors have agreed on the manuscript to be submitted, provided final approval of the version to be published, and agree to be responsible for all elements of the work. Diao YH and Rao SQ contributed equally to this work.

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Institutional review board statement: This study was reviewed and approved by the Ethics Committee of The First Affiliated Hospital of Chongqing Medical University.

Informed consent statement: This study is a retrospective study, and the patients is come from a teaching hospital of the First Affiliated Hospital of Chongqing Medical University. When we deliver the ethics application, we have also delivered application for exemption of informed consent, and This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (2022-133-2).

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

Data sharing statement: The datasets generated and/or analyzed during the current study are not publicly available due but are available from the corresponding author upon reasonable request.

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ORIGINAL ARTICLE

Retrospective Study

Predictors of complications after prophylactic ileostomy reversal for rectal cancer: A retrospective study

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Abstract

BACKGROUND

Previous studies have analyzed the risk factors for complications after ileostomy reversal for rectal cancer (RC), but there were significant differences in the reported risk factors for complications after stoma reversal. No studies have analyzed the risk factors for stoma-related complications and overall postoperative com-plications separately.

AIM

To analyze the risk factors for overall complications and stoma-related complications after ileostomy reversal for patients with RC.

METHODS

This was a retrospective study of 439 patients who underwent ileostomy reversal at a clinical center and were followed up between September 2012 and September 2022. Continuous variables are expressed as the mean ± SD and were analyzed with independent-sample *t* tests, while frequency variables are expressed as *n* (%), and the χ^2 test or Fisher's exact test was used. Univariate and multivariate logistic regression analyses were used to identify predictors of overall complications and stoma-related complications.

RESULTS

The overall complication rate after ileostomy reversal was 11.4%. Patients with lower preoperative albumin concentration ($P < 0.01$), greater blood loss ($P = 0.017$), and longer operative times ($P < 0.01$) were more likely to experience

postoperative complications. The incidence of stoma-related complications was 6.4%. Analysis of the study showed that a higher body mass index (BMI) ($P < 0.01$), preoperative comorbid hypertension ($P = 0.049$), time from primary surgery to ileostomy reversal ($P < 0.01$) and longer operation time ($P = 0.010$) were more likely to result in stoma-related complications postoperatively. Multivariate logistic regression analysis revealed that a lower preoperative albumin level ($P < 0.01$, OR = 0.888, 95%CI: 0.828-0.958) was an independent risk factor for overall complications. Moreover, multivariate analysis revealed that BMI ($P < 0.01$, OR = 1.176, 95%CI: 1.041-1.330) and time from primary surgery to ileostomy reversal ($P < 0.01$, OR = 1.140, 95%CI: 1.038-1.252) were independent risk factors for stoma-related complications after stoma reversal.

CONCLUSION

The preoperative albumin level was a predictor of overall complications. Preoperative BMI and the time from primary surgery to ileostomy reversal were predictors of stoma-related complications.

Key Words: Ileostomy; Reversal; Risk factors; Complications; Rectal cancer

Core Tip: There were no studies that have analyzed the risk factors for stoma-related complications and overall postoperative complications after stoma reversal for rectal cancer (RC) separately. Our study showed that the preoperative serum albumin concentration was a predictor of overall complications. Preoperative body mass index and time between initial surgery and stoma reversal were predictors of stoma-related complications. Therefore, for RC patients undergoing ileostomy reversal, adequate albumin supplementation should be provided preoperatively to reduce the incidence of postoperative complications.

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INTRODUCTION

Colorectal cancer (CRC) is a common malignancy that ranks as the third most common cancer and the second leading cause of cancer-related death worldwide[1]. Current treatments for CRC include endoscopic and surgical resection, radiotherapy, immunotherapy, palliative chemotherapy, targeted therapy, extensive surgery, and local ablation of metastases[2-4]. However, with the continuous improvement of surgical techniques, postoperative complications of rectal cancer (RC) are still inevitable, and anastomotic leakage (AL) is one of the most dangerous postoperative complications in RC patients[5-8]. In high-risk resettable RC surgery, temporary ileostomy is often used to reduce the incidence of AL after RC surgery[9-11].

Although protective ileostomy reduced the incidence of AL after RC, the construction of an ileostomy was associated with potential complications, and it reduced the quality of life of patients[12-15]. The overall complication rate of ileostomy is as high as 20%, including dehydration, electrolyte imbalance, parastomal hernia, and peristomal infections, with postoperative bowel obstruction and surgical site infections (SSI) being the most common[16-19]. The risk of complications after stoma reversal can easily reach 17%-20%[20,21], including surgical SSI, AL, intestinal obstruction, postoperative intestinal obstruction, wound dehiscence, extraintestinal leakage and other complications[22,23]. Protective ileostomy was often performed at the expense of the patient's quality of life[24]. Therefore, correct identification of risk factors for postoperative complications after recovery of the peristomal stoma is necessary.

Previous studies have shown that age, operative time, preoperative comorbid diabetes mellitus and the time from primary surgery to ileostomy reversal are risk factors for complications after ileostomy reversal[25-27]. Li *et al*[28] reported that early reversal of the ileostomy before 3 months was both practical and safe, allowing sufficient time to recover from the initial resection and soften intra-abdominal adhesions. Ahmadi-Amoli H *et al*[29] concluded that early reversal of ileostomy was not better than late reversal, and there was no significant difference between the two groups in reducing the risk of stoma complications. There were significant differences in the reported risk factors for complications after stoma reversa and no studies have analyzed the risk factors for stoma-related complications and overall postoperative complications separately.

Based on the results of previous studies, we hypothesized that the time between initial surgery and ileostomy reversal was a risk factor for postoperative complications. The present study was aimed to analyze the risk factors for overall complications and stoma-related complications after ileostomy reversal for RC and to guide clinical practice.

MATERIALS AND METHODS

Patients

This was a retrospective study of 439 patients who underwent ileostomy reversal at a clinical center and were followed up between September 2012 and September 2022. The present study was performed according to the World Medical Association Declaration of Helsinki. Ethical approval from the institutional review board (K2024-002-01) was obtained. All patients signed the informed consent.

Inclusion and exclusion criteria

Patients with RC who underwent laparoscopic low anterior rectal resection with temporary ileostomy and concomitant ileostomy reversal were recruited for this study (n = 548). The exclusion criteria were as follows: (1) Incomplete perioperative medical information (n = 86); and (2) resection of the other organs (n = 23). Ultimately, a total of 439 patients were included in this study (Figure 1).

Criteria for prophylactic ileostomy reversal

The criteria for prophylactic ileostomy reversal were as follows: (1) Regular postoperative follow-up, no new tumor recurrence, or metastasis; (2) satisfactory assessment of anal and rectal function; (3) no anastomotic stenosis, no AL, and no improvement in anastomotic stenosis symptoms; and (4) exclusion of intestinal obstruction and other contraindications to surgery.

Anesthesia management

All patients underwent general intravenous anesthesia in accordance with Chinese anesthesiology guidelines and expert consensus.

Data collection

All clinical information was collected from both inpatient health care systems and outpatient systems. These data included age, sex, body mass index (BMI), smoking status, drinking status, hypertension status, type 2 diabetes mellitus (T2DM) status, hemoglobin level, albumin level, time from primary surgery to ileostomy reversal, operation time, blood loss, length of hospital stay, overall complications, and stoma-related complications.

Statistical analysis

According to the previous literature[20,21], the complication rate of ileostomy reversal is 20%. The significance level was 0.05, the data distribution was 0.10, the permissible error was 0.10, and a two-sided test was performed, which showed that at least 168 patients who underwent ileostomy reversal needed to be included in this study. A total of 439 ileostomy-returned patients were selected for this study, which meant adequate. PASS (version 11) software was used for sample size calculations. Continuous variables are expressed as the means ± SD, and independent-sample t tests were used to analyze the data. Moreover, frequency variables are expressed as n (%), and the χ^2 test or Fisher's exact test was used. A logistic regression model with a backward selection approach was constructed to predict overall complications and stoma-related complications predictors. $P < 0.05$ was considered to indicate significance. All the data analyses were performed with SPSS (version 22.0).

RESULTS

Clinical characteristics

Overall, 439 RC patients were included in the study (292 males and 147 females). The mean age of the participants was 61.6 ± 11.4 years, and the mean BMI was 22.3 ± 3.0 kg/m^2. There were 164 (37.4%) patients with a history of smoking, 144 (32.8%) with a history of drinking, 105 (23.9%) with a history of hypertension, and 42 (9.6%) with a history of T2DM. The mean hemoglobin concentration was 124.7 ± 17.3 g/L, and the mean albumin concentration was 40.5 ± 4.3 g/L. The time from primary surgery to ileostomy reversal was 4.6 ± 2.9 months, the mean operation time was 94.2 ± 41.7 min, the mean blood loss was 29.7 ± 34.5 mL, and the mean hospital stay was 5.7 ± 3.1 days. There was no 30-d mortality. Postoperative complications occurred in 50 (11.4%) patients, and stoma-related complications occurred in 28 (6.4%) patients. The clinical characteristics of the patients in the study groups are summarized in Table 1.

Statistical analysis of overall complications and stoma-related complications

The overall complication rate after ileostomy reversal was 11.4%. Patients with lower preoperative albumin concentration ($P < 0.01$), greater blood loss ($P = 0.017$), and longer operative times ($P < 0.01$) were more likely to experience postoperative complications (Table 2). The incidence of stoma-related complications was 6.4%. Analysis of the study showed that a higher BMI ($P < 0.01$), preoperative comorbid hypertension ($P = 0.049$), time from initial surgery to ileostomy reversal ($P < 0.01$) and longer operative time ($P = 0.010$) were more likely to result in stoma-related complications postoperativel (Table 3).

Table 1 Clinical characteristics of the whole cohort, *n* (%)

Characteristics	No. 439
Age (yr)	61.6 ± 11.4
Sex	
Male	292 (66.5)
Female	147 (33.5)
BMI (kg/m^2)	22.3 ± 3.0
Smoking	164 (37.4)
Drinking	144 (32.8)
Hypertension	105 (23.9)
T2DM	42 (9.6)
Hemoglobin (g/L)	124.7 ± 17.3
Albumin (g/L)	40.5 ± 4.3
The time from primary surgery to ileostomy reversal (months)	4.6 ± 2.9
Operation time (min)	94.2 ± 41.7
Blood loss (mL)	29.7 ± 34.5
Hospital stay (d)	5.7 ± 3.1
Overall complications	50 (11.4)
Stoma-related complications	28 (6.4)

T2DM: Type 2 diabetes mellitus; BMI: Body mass index.

Table 2 Comparison between the complication group and the no complication group, *n* (%)

Characteristics	Complication (50)	No complication (389)	*P* value
Age (yr)	63.2 ± 10.0	61.4 ± 11.5	0.300
Sex			0.579
Male	35 (53.2)	257 (64.0)	
Female	15 (46.8)	132 (36.0)	
BMI (kg/m^2)	22.5 ± 2.7	22.3 ± 3.1	0.710
Smoking	20 (35.3)	144 (39.2)	0.682
Drinking	16 (28.5)	128 (32.6)	0.898
Hypertension	10 (26.4)	95 (24.1)	0.490
T2DM	7 (12.8)	35 (10.2)	0.258
Hemoglobin (g/L)	122.6 ± 18.6	125.0 ± 17.1	0.366
Albumin (g/L)	38.8 ± 4.0	40.8 ± 4.2	< 0.01[a]
The time from primary surgery to ileostomy reversal (months)	5.0 ± 3.3	4.6 ± 2.8	0.369
Operation time (min)	103.6 ± 43.4	93.0 ± 41.4	0.090
Blood loss (mL)	40.7 ± 49.6	28.3 ± 31.8	0.017[a]
Hospital stay (d)	9.1 ± 6.0	5.3 ± 2.1	< 0.01[a]

[a]$P < 0.05$.
T2DM: Type 2 diabetes mellitus; BMI: Body mass index.

Table 3 Comparison between the stoma-related group and the no stoma-related complication group

Characteristics	Stoma-related Complication (28)	No stoma-related complication (411)	*P* value
Age, (yr)	64.8 ± 10.7	61.4 ± 11.4	0.133
Sex			0.277
Male	16 (53.2)	276 (64.0)	
Female	12 (46.8)	135 (36.0)	
BMI (kg/m^2)	23.8 ± 2.9	22.2 ± 3.0	< 0.01[a]
Smoking	10 (35.3)	154 (39.2)	0.853
Drinking	8 (28.5)	136 (32.6)	0.622
Hypertension	11 (26.4)	94 (24.1)	0.049[a]
T2DM	4 (12.8)	38 (10.2)	0.329
Hemoglobin	123.9 ± 21.9	124.8 ± 17.0	0.793
Albumin (g/L)	39.7 ± 4.0	40.6 ± 4.3	0.287
The time from primary surgery to ileostomy reversal (months)	6.3 ± 3.8	4.5 ± 2.8	< 0.01[a]
Operation time (min)	113.7 ± 60.3	92.9 ± 39.5	0.010[a]
Blood loss (mL)	39.6 ± 36.9	29.1 ± 34.3	0.116
Hospital stay (d)	5.3 ± 1.7	5.7 ± 3.1	0.452

[a]*P* < 0.05.
T2DM: Type 2 diabetes mellitus; BMI: Body mass index.

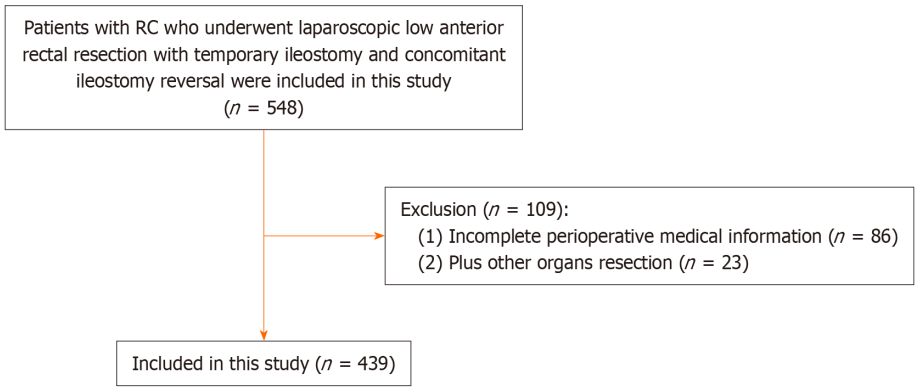

Figure 1 Flow chart of patient selection. RC: Rectal cancer.

Univariate and multivariate logistic regression analyses of overall complications

Univariate analysis suggested that patients with a lower preoperative albumin concentration ($P < 0.01$, OR = 0.887, 95%CI: 0.822-0.957) had a greater risk of ileostomy reversal complications, and multivariate analysis suggested that a lower preoperative albumin concentration ($P < 0.01$, OR = 0.888, 95%CI: 0.828-0.958) was an independent risk factor for overall complications. Other factors, including age, sex, BMI, T2DM status, smoking status, drinking status, hypertension status, hemoglobin, and the time from primary surgery to ileostomy reversal, had no predictive value for overall complications ($P > 0.01$) (Table 4).

Univariate and multivariate logistic regression analyses of stoma-related complications

Univariate analysis revealed that patients with a higher BMI ($P < 0.01$, OR = 1.175, 95%CI: 1.044-1.324) and a longer time from primary surgery to ileostomy reversal ($P < 0.01$, OR = 1.142, 95%CI: 1.041-1.253) had a greater risk of postoperative stoma-related complications. Multivariate analysis revealed that BMI ($P < 0.01$, OR = 1.176, 95%CI: 1.041-1.330) and the time from primary surgery to ileostomy reversal ($P < 0.01$, OR = 1.140, 95%CI: 1.038-1.252) were independent risk factors for stoma-related complications after stoma reversal. There was no association between age, sex, T2DM status, smoking status, drinking status, hypertension status, hemoglobin, or albumin concentration (Table 5).

Table 4 Univariate and multivariate logistic regression analysis of overall complications

Risk factors	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Age (yr)	1.014 (0.988-1.041)	0.300		
Sex (female/male)	0.834 (0.440-1.583)	0.579		
BMI (kg/m^2)	1.019 (0.924-1.122)	0.710		
T2DM (yes/no)	1.647 (0.689-3.934)	0.262		
Smoking (yes/no)	1.134 (0.621-2.071)	0.682		
Drinking (yes/no)	0.960 (0.511-1.803)	0.898		
Hypertension (yes/no)	0.774 (0.373-1.606)	0.491		
Hemoglobin (g/L)	0.992 (0.976-1.009)	0.365		
Albumin (g/L)	0.887 (0.822-0.957)	< 0.01a	0.888 (0.828-0.958)	< 0.01[a]
The time from primary surgery to ileostomy reversal (months)	1.042 (0.952-1.141)	0.371	1.030 (0.939-1.130)	0.534

[a]*P* < 0.05.

T2DM: Type 2 diabetes mellitus; BMI: Body mass index.

Table 5 Univariate and multivariate logistic regression analysis of stoma-related complications

Risk factors	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Age (yr)	1.027 (0.992-1.064)	0.134		
Sex (female/male)	1.533 (0.706-3.332)	0.280		
BMI (kg/m^2)	1.175 (1.044-1.324)	< 0.01[a]	1.176 (1.041-1.330)	< 0.01[a]
T2DM (yes/no)	1.636 (0.539-4.963)	0.385		
Smoking (yes/no)	0.927 (0.417-2.060)	0.853		
Drinking (yes/no)	0.809 (0.347-1.883)	0.623		
Hypertension (yes/no)	2.182 (0.988-4.820)	0.054		
Hemoglobin (g/L)	0.997 (0.975-1.019)	0.792		
Albumin (g/L)	0.951 (0.867-1.043)	0.287		
The time from primary surgery to ileostomy reversal (months)	1.142 (1.041-1.253)	< 0.01[a]	1.140 (1.038-1.252)	< 0.01[a]

[a]*P* < 0.05.

T2DM: Type 2 diabetes mellitus; BMI: Body mass index.

DISCUSSION

In the present study, we found that a lower preoperative albumin, intraoperative hemorrhage, and length of postoperative hospital stay were associated with overall complications after ileostomy. A higher preoperative BMI, preoperative combined hypertension, time from primary surgery to ileostomy reversal, and operative time were associated with stoma-related complications after ileostomy reversal. Pre-operative albumin level was a predictor of overall complications. Preoperative BMI and the time from primary surgery to ileostomy reversal were predictors of stoma-related complications.

Prophylactic ileostomy after low anterior resection is the preferred surgical procedure for patients with resettable and survivable RC, which could reduce the incidence of AL after RC[9-11]. However, the overall complication rate of stoma re-versal is as high as 20%, including dehydration, electrolyte imbalance, parastomal hernia, and peristomal infections, with postoperative bowel obstruction and SSI being the most common[16-18]. In our study, postoperative complications occurred in 50 (11.4%) patients, and stoma-related complications occurred in 28 (6.4%) patients; these rates are slightly lower than those previously reported in the literature[30,31].

Studies have shown that hypoalbuminemia negatively affects wound healing and disease severity[32]. In RC surgery, low preoperative protein levels significantly increase the incidence of postoperative complications[33,34]. Similarly, low albumin levels have been associated with postoperative complications in RC patients[35-37]. Our results were similar to those of a previous study showing that low preoperative albumin levels were an independent risk factor for overall complications after ileostomy reversal[30]. Moreover, preoperative albumin levels were not significantly associated with stoma-related complications. This might be related to the fact that the included patients all had normal preoperative albumin values.

Multivariate risk factor analysis revealed that obesity was a risk factor for stoma-related complications. Previous studies have shown that obesity is also a risk factor for AL after resection of RC resection[38], and obese patients are at increased risk of incisional hernia[39]. The postoperative healing process might also be impaired in obese patients due to the impaired visual field in overweight patients and the more complex release of adhesions during ileostomy reversal. Currently, there is no definitive conclusion on the optimal timing of stoma reversal. We found that prolonged time from initial surgery to stoma reversal was an independent risk factor for stoma-related complications, which was similar to the findings of previous studies[15,27].

In this study, we investigated for the first time the risk factors for overall complications and stoma-related complications after stoma reversal for RC. However, our study has several limitations. First, there was a lack of analysis of the long-term prognosis of the patients. Second, there was no categorical analysis of postoperative complications. Third, there was a lack of adequate preoperative baseline information on patients and tumor staging studies. In the future, we hope to collect more clinical information and evaluate more variables through multicenter collaborations.

CONCLUSION

In summary, the preoperative serum albumin concentration was a predictor of overall complications. Preoperative BMI and time between initial surgery and stoma reversal were predictors of stoma-related complications. Therefore, for RC patients undergoing ileostomy reversal, adequate albumin supplementation should be provided preoperatively to reduce the incidence of postoperative complications.

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FOOTNOTES

Author contributions: Peng D contributed to the data analysis; Lv Q and Xiang Z led the quality assessments; Lv Q and Shu XP wrote the original draft; Xiang Z and Shu XP revised the manuscript. All authors have agreed on the journal to which the manuscript will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work. Both Lv Q and Shu XP have played important and indispensable roles in the experimental design, data interpretation and manuscript preparation as the co-first authors.

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ORIGINAL ARTICLE

Retrospective Study

Effect of the extrahepatic bile duct anatomy on choledocholithiasis and its clinical significance

Zheng Cao, Jia Zhou, Li Wei, Hai-Yu He, Jun Li

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Abstract

BACKGROUND

A comprehensive understanding of the extrahepatic bile duct anatomy is vital to guide surgical procedures and perform endoscopic retrograde cholangiography. Anatomical irregularities within the extrahepatic bile duct may increase susceptibility to bile duct stones.

AIM

To investigate the anatomical risk factors associated with extrahepatic bile ducts in patients diagnosed with choledocholithiasis, with a specific focus on preventing stone recurrence after surgical intervention and endoscopic lithotomy.

METHODS

We retrospectively analyzed the medical records of 124 patients without choledocholithiasis and 108 with confirmed choledocholithiasis who underwent magnetic resonance cholangiopancreatography examinations at our center between January 2022 and October 2022. Logistic regression analyses were conducted to identify the anatomical risk factors influencing the incidence of common bile duct stones.

RESULTS

Multivariate logistic regression analysis revealed that several factors independently contributed to choledocholithiasis risk. Significant independent risk factors for choledocholithiasis were diameter of the common hepatic [adjusted odds ratio (aOR) = 1.43, 95% confidence interval (CI): 1.07-1.92, adjusted *P* value = 0.016] and common bile (aOR = 1.68, 95%CI: 1.27-2.23, adjusted *P* value < 0.001) ducts, length of the common hepatic duct (aOR = 0.92, 95%CI: 0.84-0.99, adjusted *P* value = 0.034), and angle of the common bile duct (aOR = 0.92, 95%CI: 0.89–0.95, adjusted *P* value < 0.001).

CONCLUSION
The anatomical features of the extrahepatic bile duct were directly associated with choledocholithiasis risk. Key risk factors include an enlarged diameter of the common hepatic and bile ducts, a shorter length of the common hepatic duct, and a reduced angle of the common bile duct.

Key Words: Bile ducts; Extrahepatic; Choledocholithiasis; Cholangiopancreatography; Magnetic resonance; Cholangiopancreatography; Endoscopic retrograde

Core Tip: Comprehensive understanding of the extrahepatic bile duct anatomy is imperative to guide surgical procedures and perform endoscopic retrograde cholangiography. This study aimed to investigate the anatomical risk factors associated with the extrahepatic bile ducts in patients diagnosed with choledocholithiasis, specifically focusing on preventing stone recurrence after surgical intervention and endoscopic lithotomy. Several independent risk factors for choledocholithiasis were identified in our retrospective analysis of medical records. Noteworthy factors include an enlarged diameter of the common hepatic and bile ducts, a shorter length of the common hepatic duct, and a reduced angle of the common bile duct. Our findings underscore the significance of these anatomical features in the incidence of common bile duct stones. Our findings provide valuable insights into the relationship between extrahepatic bile duct anatomy and choledocholithiasis risk.

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INTRODUCTION

Cholelithiasis frequently leads to biliary and pancreatic complication-related hospitalizations, with approximately 622000 individuals hospitalized annually in the United States, and approximately 15% of cases are attributed to choledocholithiasis[1,2]. Despite the identification of the various risk factors associated with gallstones, the precise mechanisms underlying their formation remain poorly understood. Significant risk factors, often referred to as the "5 Fs" (Forty years of age, Female, Fatty, Fair, and Fertile), are recognized contributors. Independent studies have implicated type 2 diabetes as an additional risk factor for gallstones[3]. A study by Chen *et al*[4] further supported this perspective, proposing that lower total cholesterol levels may independently contribute to gallstone formation[3-5]. Furthermore, evidence suggests that abnormalities in the extrahepatic bile duct anatomy may increase the susceptibility to gallstones. A study by Choi *et al*[6] demonstrated that low cystic duct insertion and the angle of the common bile duct are independent risk factors for the recurrence of common bile duct stones. Similarly, Ji *et al*[7,8] found that the recurrence rate was the highest in the S-type common bile duct morphology, followed by the polyline and straight-line types.

Anatomically, the extrahepatic bile duct includes the left and right hepatic ducts, common hepatic and bile ducts, gallbladder, and cystic duct[9]. Contributors to the risk of choledocholithiasis recurrence include specific anatomical factors of the extrahepatic bile duct, including the shape and insertion mode of the cystic duct, as well as the diameter, angle, and shape of the common bile duct[6,7,10,11].

Both endoscopic ultrasonography (EUS) and magnetic resonance cholangiopancreatography (MRCP) serve as effective diagnostic methods for choledocholithiasis. Although EUS and MRCP exhibit higher specificity, EUS is notable for its increased sensitivity in the diagnosis of choledocholithiasis[12].

However, because proficiency in EUS may not be universal among endoscopists and MRCP has good sensitivity and is noninvasive for suspected biliary tract lesions[13,14], MRCP remains the primary method for clinically diagnosing choledocholithiasis owing to its ability to accurately visualize the bile duct anatomy.

This study aimed to assess the extrahepatic bile duct anatomy through MRCP examinations in patients with suspected choledocholithiasis. Additionally, we sought to explore the relationship between various anatomical characteristics of the extrahepatic bile duct and choledocholithiasis risk. The insights reported in this study are expected to provide valuable guidance for preventing stone recurrence after surgical and endoscopic lithotomy.

MATERIALS AND METHODS

Patients and study design

We collected MRCP data from individuals aged ≥ 18 years hospitalized with suspected choledocholithiasis at our medical center between January 2022 and October 2022. Exclusions were made for patients with chronic liver disease, abnormal liver function tests associated with chronic liver conditions or hemolytic anemia, known hepatobiliary diseases (*e.g.*, cho-

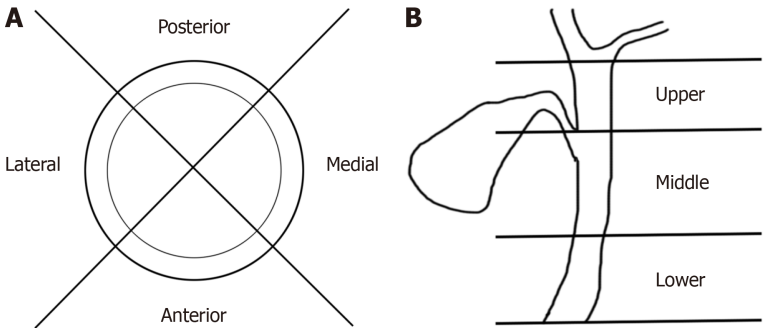

Figure 1 Cross-section of the bile duct and insertion height of the cystic duct is divided into three equal segments. A: Insertion position of the cystic duct is divided into anterior, posterior, medial, and lateral segments; B: Insertion height of the cystic duct is divided into upper, middle, and lower segments.

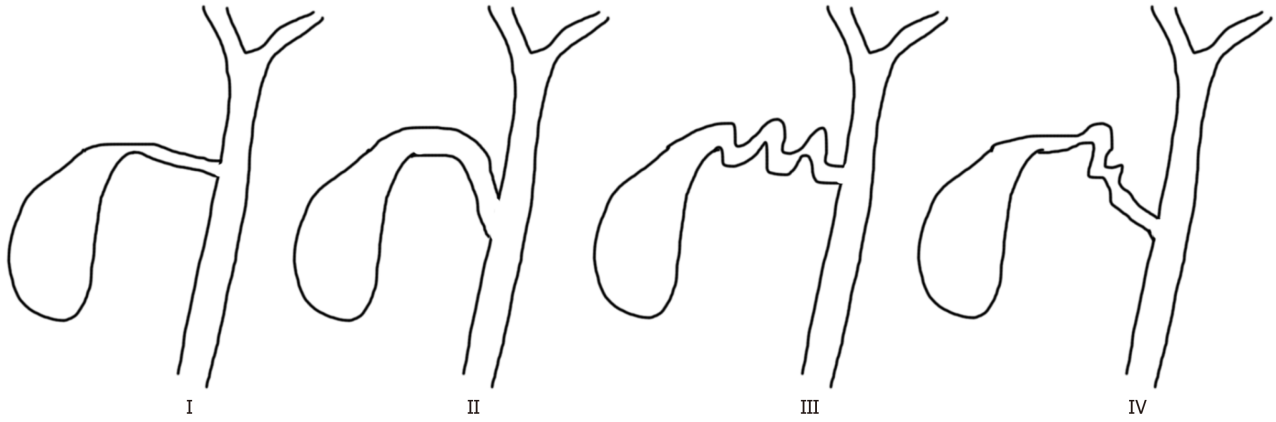

Figure 2 Cystic duct typing. I: Linear type; II: Curve type; III: Spiral type; IV: Complex type.

ledochal stricture, malignant tumor, or cholecystectomy), suboptimal MRCP imaging, history of biliary surgery, hepatectomy, congenital biliary system abnormalities (such as choledochal cysts), and pregnant women.

Patient records provided information on the following: Demographic details: Age, sex, body mass index (BMI), and history of hypertension, diabetes, and hyperlipidemia; laboratory tests: Alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), direct bilirubin (DBil), and indirect bilirubin (IBil); MRCP assessment: Anatomical evaluation of the extrahepatic bile duct; and measurement of the length and dia-meter of the common hepatic, bile, and cystic ducts. Connections between the cystic and bile ducts were noted and divided into anterior, posterior, medial, and lateral sections, whereas those between the left and right hepatic ducts and the common hepatic duct to the ampulla were categorized into upper, middle, and lower segments (Figure 1). The cystic duct route was classified as linear, curved, spiral, or complex (Figure 2). The morphology of the common bile duct, from the connection between the left and right hepatic ducts to the distal common bile duct duodenum, was considered polyline or S type [7] (Figure 3). Additionally, the oblique angle of the common bile duct (*i.e.*, the angle formed between the first bend of the common bile duct and the horizontal line) was recorded[11] (Figure 4). Angulation of the common bile duct (*i.e.*, the first angle between the common bile duct and the ampulla) was also noted[6] (Figure 4).

MRCP anatomical data, demographic features, and laboratory results of patients with and without choledocholithiasis were compared. Given the retrospective and nonintrusive nature of this study, our ethics committee granted approval for the exemption from obtaining written informed consent.

Statistical analysis

Statistical analyses were performed using SPSS version 25.0. Categorical data are shown as frequencies (%), and continuous data as median (range) or mean ± SD. Continuous variables were assessed using Student's *t*-test, and categorical variables using Fisher's exact test or χ^2 test. Independent risk factors for choledocholithiasis were identified using multivariate logistic regression, with $P < 0.05$ considered significant.

RESULTS

From January 2022 to October 2022, a thorough assessment of 2239 suspected choledocholithiasis cases was conducted using MRCP. Following stringent exclusion criteria, 232 patients were deemed eligible for the study, including 124 without choledocholithiasis and 108 with confirmed choledocholithiasis.

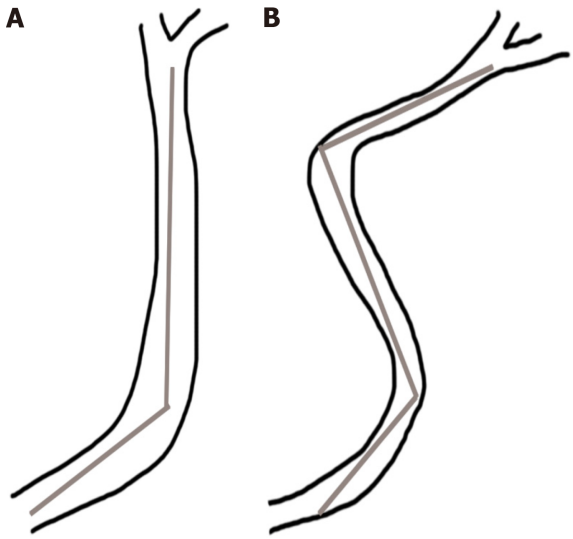

Figure 3 Morphology of the common bile duct. A: Polyline type; B: S type.

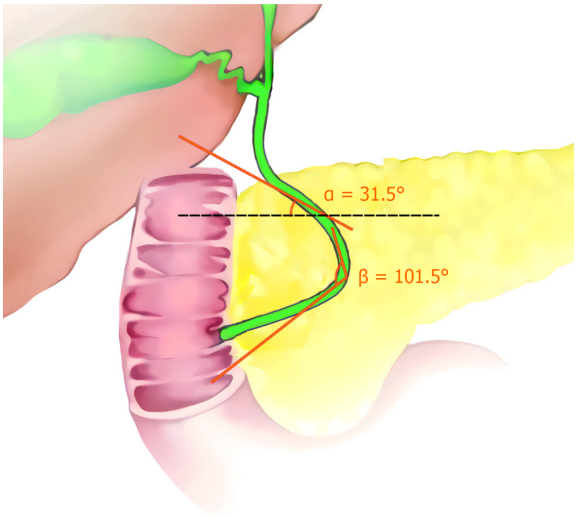

Figure 4 Oblique angle of the common bile duct and angle of the common bile duct. α indicates the oblique angle of the common bile duct: Angle between the first bend of the common bile duct and the horizontal line; β indicates the angle of the common bile duct: First angle between the common bile duct and the ampulla.

In the examination of general data, hyperlipidemia, ALT, AST, ALP, GGT, and DBil were associated with the occurrence of choledocholithiasis in both the noncholedocholithiasis and common bile duct stone groups (Table 1). Exploring the anatomical factors of the extrahepatic bile duct revealed various variables linked to the incidence of choledocholithiasis, including the diameter and length of the common hepatic and bile ducts, diameter and diverse insertion points of the cystic duct, and angle and tilt angle of the common bile duct (Table 2).

Independent risk factors for choledocholithiasis, including the diameter [adjusted odds ratio (aOR) = 1.43, 95% confidence interval (CI): 1.07-1.92, adjusted *P* value = 0.016] and length (aOR = 0.92, 95%CI: 0.84-0.99, adjusted *P* value = 0.034) of the common hepatic duct and diameter (aOR = 1.68, 95%CI: 1.27-2.23, adjusted *P* value < 0.001) and angulation (aOR = 0.92, 95%CI: 0.89-0.95, adjusted *P* value < 0.001) of the common bile duct, were identified using multivariate logistic regression (Table 3).

DISCUSSION

In this study, we explored the impact of various risk factors on choledocholithiasis using univariate and multivariate logistic regression analyses.

Contrary to the common consideration of age as a predictor in other studies[15,16], our research did not establish statistical significance in this aspect. However, Govindan *et al*[17] suggested a potential correlation between age and common bile duct diameter, with an annual expansion rate of 0.07 mm. Nevertheless, the designation of age as an in-

Table 1 Univariate analysis for general data

Variable	Without CBD stones (*n* = 124)	With CBD stones (*n* = 108)	*P* value
Age (yr)	50.88 ± 15.60	55.06 ± 18.00	0.060
Sex, *n* (%)			0.575
Female	70 (56.45)	57 (52.78)	
Male	54 (43.55)	51 (47.22)	
BMI (kg/m^2)	23.79 ± 3.78	23.62 ± 3.71	0.732
Hypertension, *n* (%)	19 (15.32)	9 (8.33)	0.103
Diabetes, *n* (%)	12 (9.68)	5 (4.63)	0.141
Hyperlipidemia, *n* (%)	23 (18.55)	6 (5.56)	0.003
ALT (U/L)	24.50 (16.00, 45.25)	100.45 (32.00, 216.25)	< 0.001
AST (U/L)	24.00 (19.00, 39.25)	53.00 (26.00, 130.75)	< 0.001
ALP (U/L)	84.50 (70.00, 116.50)	160.80 (104.50, 275.25)	< 0.001
GGT (U/L)	43.00 (23.00, 118.25)	251.50 (121.50, 576.50)	< 0.001
DBil (μmol/L)	4.25 (2.98, 6.60)	10.00 (4.90, 29.48)	< 0.001
IBil (μmol/L)	9.35 (6.47, 13.38)	10.70 (7.50, 15.20)	0.167

BMI: Body mass index; ALT: Alanine transaminase; AST: Aspartate transaminase; ALP: Alkaline phosphatase; GGT: γ-glutamyl transferase; DBil: Direct bilirubin; IBil: Indirect bilirubin; CBD: Common bile duct.

dependent contributor to choledocholithiasis may be unreliable. Liver biochemical indicators such as ALT, AST, DBil, and GGT, recognized as choledocholithiasis risk factors, were significant only in the univariate analysis. This discrepancy could be attributed to secondary changes in these indicators after the occurrence of choledocholithiasis, rendering them unsuitable as reliable risk indicators.

Our findings demonstrate no significant variations in the course of the cystic duct. However, Deenitchin *et al*[10] reported a high incidence of gallstones associated with cystic duct malformations. Currently, a comprehensive understanding of the causes of these abnormalities and their interactions with other factors is lacking. Moreover, due to the absence of long-term follow-up data, our study's single observation does not permit the determination of a causal relationship between cystic duct abnormality and gallstone formation.

In contrast to previous studies[6], our multivariate logistic regression analysis indicated no significant differences in the position, direction, or route of cystic duct insertion. This suggests that cystic duct insertion characteristics may not be a substantial risk factor for choledocholithiasis. Nevertheless, we hypothesize that the development of primary and secondary choledocholithiasis is affected by disparities in the course and position of the cystic duct. For instance, a more twisted and folded cystic duct may impede gallstone entry into the common bile duct, potentially reducing the risk of secondary choledocholithiasis. Further studies are required to validate these hypotheses.

We identified several significant anatomical factors of the extrahepatic bile duct. Additionally, we assessed the common bile duct route, oblique angle, and shape (polyline or S-shaped). Unlike Ji *et al*'s study using endoscopic retrograde cholangiopancreatography (ERCP)[7,8], we categorized bile ducts into polyline and S-shaped and observed no straight-line insertion into the duodenum. This divergence may be attributed to differing presentations of the extrahepatic bile ducts observed on MRCP and ERCP. However, the duct's course and oblique angle showed no statistically significant differences.

Regarding diameters of the common hepatic and bile duct, diameter of the common hepatic duct increased with dilation of the common bile duct. Additionally, gallbladder dilation through the cystic duct can alleviate pressure and reduce dilatation.

No statistically significant relationship was found between low cystic duct insertion and choledocholithiasis risk. However, as the common hepatic duct length increased, choledocholithiasis risk decreased, which is consistent with the findings of Kao *et al*[18]. Reduced choledocholithiasis risk has been reported with an increased choledochal angle, consistent with the findings related to recurrence risk factors[6,19,20]. This suggests decreased choledocholithiasis risk with an increasing choledochal angle, both in primary and recurrent cases. Furthermore, the biliary tract is not a sterile environment[21,22], and a smaller common bile duct angle may lead to shape distortion, causing a twisted common bile duct. This increases the risk of bile stagnation, bacterial infection, and stone formation.

While ERCP and endoscopic sphincterotomy are widely used to treat choledocholithiasis, the post-treatment recurrence rate remains notably elevated, ranging from 4% to 25%[23]. During ERCP and surgery, potential choledocholithiasis recurrence should be considered in patients with these anatomical characteristics. Further investigations are warranted to explore whether early drug interventions or modifications to the anatomical structure of the extrahepatic bile duct can reduce the occurrence of stones.

Table 2 Univariate analysis for anatomical factors of the extrahepatic bile duct

Variable	Without CBD stones (*n* = 124)	With CBD stones (*n* = 108)	*P* value
CHD diameter (mm)	4.10 (3.20, 6.03)	9.40 (6.88, 12.50)	< 0.001
CD diameter (mm)	3.10 (2.40, 4.93)	5.85 (3.70, 8.50)	< 0.001
CBD diameter (mm)	5.00 (3.80, 6.70)	10.35 (8.10, 13.00)	< 0.001
CHD length (mm)	20.51 ± 8.88	25.12 ± 12.58	0.002
CD length (mm)	26.10 ± 12.76	35.83 ± 21.69	< 0.001
CBD length (mm)	50.46 ± 12.87	52.65 ± 13.84	0.212
CBD angulation (°)	138.94 ± 19.19	112.79 ± 19.12	< 0.001
Oblique angle of the CBD (°)	60.12 ± 18.54	47.08 ± 19.85	< 0.001
Insertion position of CD, *n* (%)			
Anterior	15 (12.10)	21 (19.44)	0.123
Posterior	8 (6.45)	33 (30.56)	< 0.001
Lateral	95 (76.61)	50 (46.30)	< 0.001
Medial	6 (4.84)	4 (3.70)	0.920
Upper	85 (68.55)	57 (52.78)	0.014
Middle	38 (30.65)	48 (44.44)	0.030
Lower	1 (0.81)	3 (2.78)	0.519
Route of CD, *n* (%)			
Linear type	15 (12.10)	8 (7.41)	0.233
Curved type	92 (74.19)	80 (74.07)	0.983
Spiral type	8 (6.45)	14 (12.96)	0.091
Complex type	9 (7.26)	6 (5.56)	0.599
Route of CBD, *n* (%)			
Polyline type	118 (95.16)	98 (90.74)	0.185
S type	6 (4.84)	10 (9.26)	0.185

CHD: Common hepatic duct; CD: Cystic duct; CBD: Common bile duct.

Table 3 Independent risk factors for common bile duct stones in multivariate analysis

Variable	aOR (95%CI)	Adjusted *P* value
CHD diameter	1.43 (1.07-1.92)	0.016
CBD diameter	1.68 (1.27-2.23)	< 0.001
CHD length	0.92 (0.84-0.99)	0.034
CBD angulation	0.92 (0.89-0.95)	< 0.001

aOR: Adjusted odds ratio; CHD: Common hepatic duct; CBD: Common bile duct.

The primary limitation of our study lies in the single-time-point assessment of extrahepatic bile duct anatomical changes without long-term patient follow-up. Consequently, we could not ascertain the temporal trends of these changes or their correlations with underlying diseases. Additionally, our two-dimensional measurement method for the extrahepatic bile duct anatomy limits the precise calculation of various anatomical values. It is crucial to note that this was a single-hospital study, potentially introducing limitations specific to the geographical location and population.

CONCLUSION

In conclusion, individuals with a broader diameter of the extrahepatic bile duct, shorter length of the common hepatic duct, and smaller angle of the common bile duct are at an elevated risk of developing choledocholithiasis. Moreover, these patients are more prone to stone recurrence after surgical or endoscopic lithotomy. Thus, vigilance regarding the potential for stone recurrence is crucial in managing such cases.

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FOOTNOTES

Author contributions: Cao Z designed and performed the research and wrote the paper; Zhou J designed the research and supervised the report; Wei L and He HY designed the research and contributed to the analysis; Li J supervised the report.

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Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Kunming Medical University (Approval No. 2023-234).

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

Randomized Controlled Trial

Effects of oral probiotics on inflammation and intestinal function in adult patients after appendectomy: Randomized controlled trial

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Abstract

BACKGROUND

Appendectomy is an acute abdominal surgery that is often accompanied by severe abdominal inflammation. Oral probiotics are one of the postoperative treatments for rapid rehabilitation. However, there is a lack of prospective studies on this topic after appendectomy.

AIM

To investigate whether the postoperative probiotics can modulate the inflammatory response and restore intestinal function in patients following appendectomy.

METHODS

This was a prospective, randomized trial. A total of 60 emergency patients were randomly divided into a control group (n = 30) and a probiotic group (n = 30). Patients in the control group started to drink some water the first day after surgery, and those in the probiotic group were given water supplemented with *Bacillus licheniformis* capsules for 5 consecutive days postsurgery. The indices of inflammation and postoperative conditions were recorded, and the data were analyzed with RStudio 4.3.2 software.

RESULTS

A total of 60 participants were included. Compared with those in the control group, the C-reactive protein (CRP), interleukin 6 and procalcitonin (PCT) levels were significantly lower in the probiotic group at 2 d after surgery (P = 2.224e-05, P = 0.037, and P = 0.002, respectively, all P < 0.05). This trend persisted at day 5 post-surgery, with CRP and PCT levels remaining significantly lower in the probiotic group (P = 0.001 and P = 0.043, both P < 0.05). Furthermore, probiotics

resulted in a shorter time to first flatus and a greater percentage of gram-negative bacilli in the feces (P = 0.035, P = 0.028, both P < 0.05).

CONCLUSION
Postoperative oral administration of probiotics may modulate the gut microbiota, benefit the recovery of the early inflammatory response, and subsequently enhance recovery after appendectomy.

Key Words: Probiotics; Gut microbiota; Appendectomy; Inflammatory markers; Intestinal function; Enhanced recovery after surgery; Postsurgical infections

Core Tip: This research examines the impact of administering oral probiotics postoperatively on inflammation responses and intestinal function in patients undergoing appendectomy procedures. Our findings reveal that orally administered probiotics effectively decrease postoperative inflammatory indicators and enhance intestinal functionality, thereby resulting in reduced hospitalization durations. These insights highlight the potential contribution of probiotics in expediting post-surgical recovery and offer novel approaches for clinical application.

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INTRODUCTION

Appendectomy is an acute abdominal surgery that is often accompanied by severe abdominal inflammation. Inflammation will continue even after surgery for almost a week. Severe inflammation can increase the translocation of endotoxin and pathogenic bacteria, leading to intestinal mucosal barrier dysfunction[1-3]. Therefore, inflammatory intestinal obstructions and abdominal abscesses often appear after surgery[2]. Oral probiotics are one of the postoperative treatments for rapid rehabilitation. Several studies have demonstrated that probiotics can reduce the inflammatory response and incidence of postoperative infections and promote the recovery of gastrointestinal function after gastrointestinal surgery[2-7]. Probiotics administered orally can modulate the intestinal mucosal barrier function, thereby enhancing the stability and balance of gut microbiota[8]. Thus, the role of probiotics after gastrointestinal surgery has attracted increasing amounts of attention[4,8-15]. However, there is a lack of prospective studies on this topic after appendectomy. In our study, whether the oral administration of postoperative probiotics can effectively modulate the inflammatory response and restore intestinal function in patients following appendectomy was investigated.

MATERIALS AND METHODS

We conducted a randomized controlled trial comprising 60 emergency adult patients who underwent laparoscopic appendectomy and were admitted to Zigong Fourth People's Hospital in Sichuan Province, China, between June 1st, 2023 and August 31st, 2023. This study was approved by the Institutional Ethics Committee and adhered to the ethical guidelines laid down by them.

Sixty adult patients were randomly divided into a control group (n = 30) and a probiotic group (n = 30). The process of assigning participants or experimental units into different groups has been carried out using the Random Number Table Method. In the control group, 15 patients were male, 15 were female, and the mean age was 44.5 ± 15.91 years. In the probiotics group, there were 13 males and 17 females aged 43.17 ± 15.73 years. All patients underwent computerized tomography and were diagnosed by an experienced attending doctor. The exclusion criteria for patients were as follows: Periappendiceal abscess, diabetes mellitus, severe organ dysfunction, or conversion to laparotomy. General data such as sex and age were comparable between the two groups. Before surgery, all patients or guardians signed informed consent.

Patients in the control groups started to drink some water the first day after surgery, and those in the probiotic group received *Bacillus* licheniformis capsules with water (Northeast Pharmaceutical Group Co., Ltd., Liaoning Province, China) for 5 consecutive day postsurgery. After surgery, the patients were treated with antibiotics (ceftazidime; Qilu Pharmaceutical Co., Ltd., Shandong Province, China).

Detection indices

The following indices were detected after admission to the hospital before surgery and at 2 and 5 d after surgery.

Table 1 C-reactive protein/interleukin/procalcitonin and white blood cell count before and after surgery in both groups

Items	Groups	Before surgery	2 d after surgery	5 d after surgery
WBC (× 10^9/L)	Control group	13.09 ± 2.98	10.44 ± 2.17	7.82 ± 1.98
	Probiotics group	12.72 ± 2.87	9.41 ± 2.19	7.69 ± 1.95
CRP (mg/L)	Control group	32.83 ± 56.11	102.07 ± 73.49	33.03 ± 28.56
	Probiotics group	30.89 ± 33.52	31.49 ± 26.57[a]	13.46 ± 10.49[a]
IL (pg/mL)	Control group	24.73 ± 12.73	36.55 ± 45.58	9.32 ± 7.64
	Probiotics group	30.31 ± 20.29	16.85 ± 18.2[a]	8.71 ± 5.72
PCT (ng/mL)	Control group	0.143 ± 0.2	0.895 ± 1.2	0.521 ± 1.19
	Probiotics group	0.216 ± 0.29	0.155 ± 0.26[a]	0.051 ± 0.07[a]

[a]$P < 0.05$ in the comparison between the two groups.
CRP: C-reactive protein; WBC: White blood cell count; IL: Interleukin; PCT: Procalcitonin.

C-reactive protein (CRP) and interleukin 6 (IL-6) were detected using the enzyme-linked immunosorbent assay method. Procalcitonin (PCT) was detected by a Roche E411 automatic electrochemiluminescence analyzer.

The white blood cell (WBC) count and neutrophil percentage (NE%) were detected using a Labospect003 full-automatic biochemical analyzer (Hitachi).

Body temperature was measured every four hours with a mercury thermometer (axillary temperature < 37.4 °C), and the average heart rate was recorded by the electrocardiogram monitor and nurse. In addition, the time of the first anal exsufflation was recorded.

Statistical analysis

Based on the approximate means and standard deviations of various inflammation indicators, the sample size was determined. RStudio 4.3.2 software was used for statistical analysis. The quantitative data are presented as the mean ± SD. A *t* test was used to compare differences between two groups. The categorical data are presented as numbers and were compared by the chi-square test. $P < 0.05$ was considered to indicate statistical significance ([a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$).

RESULTS

A comparison of WBC and NE% pre- and post-surgery among the two groups revealed that WBC levels in both groups were reduced following surgery and no significant difference was observed between the groups post-operatively ($P > 0.05$). The NE% was lower than that before surgery in both groups and was similar in both groups ($P > 0.05$). These findings indicate that the preoperative application of postoperative probiotics cannot significantly reduce the WBC and NE% after appendectomy (Table 1).

Comparison of CRP, IL, and PCT between two groups pre- and post-surgery. In the control group, CRP levels rose 2 d post-surgery, subsequently declining gradually towards the normal range by day 5, whereas in the probiotics group, this decrease was notably more pronounced. At 2 d post-surgery, the CRP increase was marginal in the probiotics group, resulting in statistically significant differences between the groups at both the 2-d ($P = 2.224e-05$) and 5-d ($P = 0.001$) marks, all with *P* values less than 0.05. The trend for PCT mirrored that of CRP: In the control group, it increased post-surgery at 2 d, later reducing gradually to normal levels by day 5, yet again experiencing a more evident decline within the probiotics group. The PCT levels also exhibited a slight decrease 2 d after surgery in the probiotics group, leading to statistically significant inter-group differences at both 2-d ($P = 0.002$) and 5-d ($P = 0.043$) assessments, all with *P* values below 0.05. As for IL levels, they followed a similar pattern in the control group, rising at 2 d post-surgery and gradually returning to normal levels by day 5. However, there was a statistically significant difference between the two groups solely at the 2-d post-surgical mark ($P = 0.037$, $P < 0.05$). These findings collectively suggest that the administration of probiotics significantly enhances the attenuation of the systemic inflammatory response following surgery (Table 1 and Figure 1).

Comparison of the percentage of gram-negative bacilli (GNB) in the feces after surgery between the two groups. The percentage of GNB in the feces was greater in the probiotics group than in the control group ($P = 0.028$, $P < 0.05$). These findings suggest that probiotics can modulate the gut microbiota (Table 2 and Figure 1).

Comparison of the postoperative conditions between the two groups. The incidence rates of postoperative fever and average heart rate were similar in both groups ($P > 0.05$). The first exhaust time was shorter in the probiotic group than in the control group ($P = 0.035$, $P < 0.05$; Table 2 and Figure 1).

Table 2 Comparison of the postoperative general conditions between the two groups at 7 d after surgery

Groups	Fever (%)	Heart rate	First exhaust, time (d)	GNB%
Control group	16.6	74 ± 10.93	2.16 ± 0.69	67.2 ± 11.01
Probiotics group	13.3	76.4 ± 12.09	1.8 ± 0.6[a]	73.3 ± 9.65[a]

[a]$P < 0.05$ in the comparison between the two groups.
GNB%: The percentage of gram-negative bacilli.

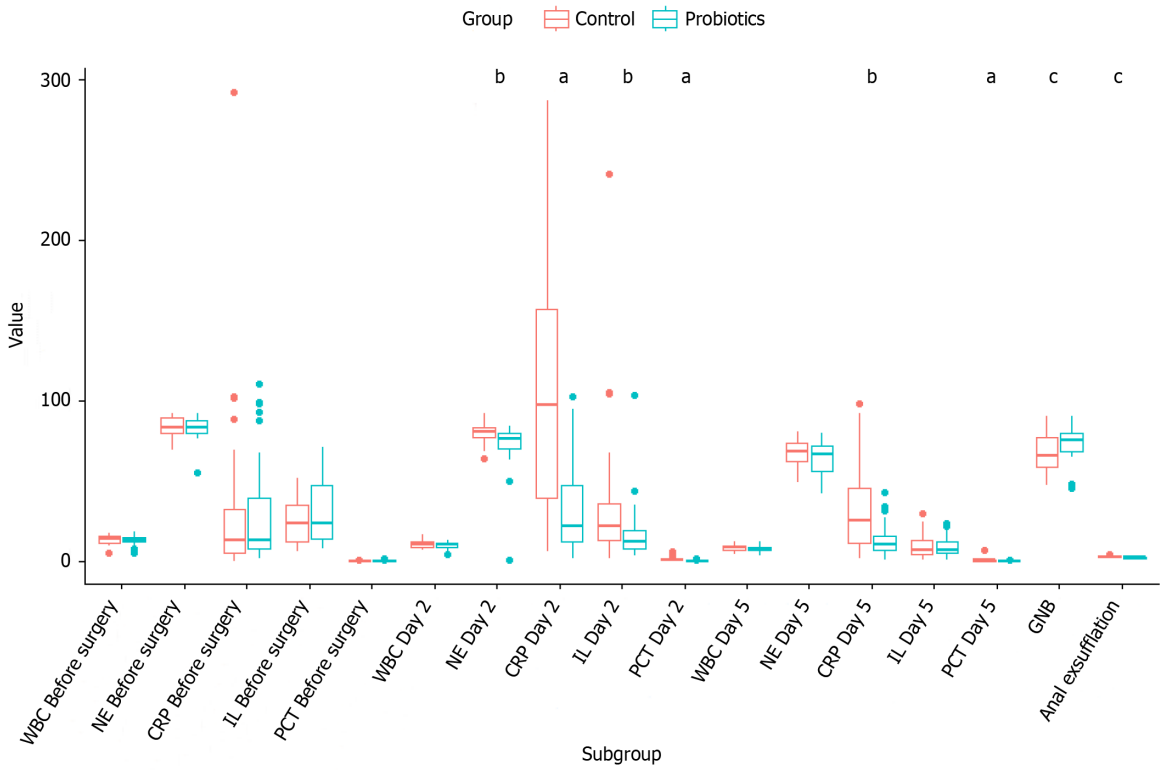

Figure 1 Various test indicator before and after surgery in both groups. [a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$. NE: Neutrophil; GNB: Gram-negative bacilli; CRP: C-reactive protein; WBC: White blood cell count; IL: Interleukin; PCT: Procalcitonin.

DISCUSSION

There is increasing interest in the relationship between the gut microbiota and human immunity[1,5,8]. In our study, we found that the CRP, IL-6 and PCT levels were significantly lower in the probiotic group after appendectomy. This outcome is consistent with findings reported in articles related to postoperative oral probiotics administration in colorectal cancer patients. Gastrointestinal surgery alters the gut microbiota due to surgical trauma and inflammation. Microbiota changes and intestinal barrier damage may cause systemic inflammation. According to previous studies[3,11,12,14,15], probiotics can be used to modulate the gut microbiota and have beneficial effects on humans. Perioperative probiotic administration during colorectal surgery can reduce infectious complications. Additionally, probiotics can reduce the levels of inflammatory markers and cytokines, such as CRP and IL[1,5,8,12].

In our study on appendicitis, it revealed that in the control group, CRP levels escalated 2 d post-surgery, thereafter gradually diminishing to reach normal levels by the fifth day post-procedure. Remarkably, this reduction was even more pronounced in the probiotics group. The inflammatory marker PCT was also similar to the CRP. Differences in the IL-6 concentration at 2 d after surgery were statistically significant between the two groups. This finding showed that postoperative probiotic administration may accelerate the duration of inflammation reduction after appendectomy. However, the WBC and NE% were lower after surgery than before surgery in both groups and were similar in both groups. This result was dissimilar to that obtained for inflammatory markers. This could be because inflammatory markers, such as CRP levels, are more sensitive than WBC counts are.

A comparison of the postoperative conditions between the two groups revealed that the time to first exhaust was shorter in the probiotics group than in the control group. These findings showed that postoperative probiotic administration after appendectomy may accelerate the recovery of intestinal function, contributing to enhanced recovery after surgery.

However, our study unfortunately did not include markers of intestinal mucosal barrier function. This will be our next step. Due to the wide fluctuations in CRP values, our study may suffer from inadequate sample size, and in future in-depth investigations, increasing the sample size should be taken into consideration.

CONCLUSION

In conclusion, postoperative oral administration of probiotics may modulate the gut microbiota, improve the recovery of the early inflammatory response, and subsequently enhance recovery after appendectomy.

FOOTNOTES

Author contributions: Lan K designed this study; Lan K, Zeng KR, Zhong FR, Tu SJ and Luo JL collected and analyzed the data; Lan K drafted the manuscript and Lu K gave final approval of the version to be published; Shu SL, Peng XF and Yang H took part in this study as endoscopic operators or assistants.

Institutional review board statement: This study was approved by the Ethics Committee of Zigong Fourth People's Hospital and adhered to the ethical guidelines laid down by them (Approval No. 2023012).

Clinical trial registration statement: This study has already undergone retrospective registration for the clinical trial at https://www.chictr.org.cn/. The registration identification number is ChiCTR2400083131.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Clinical study on microscopic syndrome differentiation and traditional Chinese medicine treatment for liver stomach disharmony in chronic gastritis

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Abstract

BACKGROUND

Chronic gastritis (CG) is a common gastrointestinal disorder characterized by inflammation of the stomach lining. Liver-stomach disharmony (LSD) syndrome is believed to contribute to CG symptoms.

AIM

To evaluate the efficacy and safety of microcosmic syndrome differentiation and Chinese herbal medicine (CHM) treatment in patients with CG and LSD syndrome.

METHODS

Sixty-four patients with CG and LSD syndrome were randomly divided into two groups: The treatment group received CHM based on microcosmic syndrome differentiation and the control group received conventional Western medicine. The treatment course lasted 12 wk. The primary outcome was improvement in dyspeptic symptoms, measured using the Nepean Dyspepsia Index. The secondary outcomes included the improvement rate of endoscopic findings, histopathological findings, and microcosmic syndrome scores and the incidence of adverse events.

RESULTS
After 12 wk of treatment, the treatment group showed significantly greater improvement in dyspeptic symptoms than the control group (93.75% *vs* 65.63%, $P < 0.01$). The treatment group also showed a significantly higher improvement rate in endoscopic findings than the control group (81.25% *vs* 53.13%, $P < 0.05$). The improvement rates of histopathological findings and microcosmic syndrome scores were not significantly different between the two groups ($P > 0.05$). No serious adverse events were observed in either group.

CONCLUSION
Microcosmic syndrome differentiation and CHM treatment can effectively improve dyspeptic symptoms and endoscopic findings in patients with CG and LSD syndrome and have a good safety profile. Further studies with larger sample sizes and longer follow-up periods are required to confirm the long-term efficacy and mechanism of action of this treatment.

Key Words: Chronic gastritis; Liver-stomach disharmony; Microcosmic syndrome differentiation; Chinese herbal medicine; Randomized controlled trial; Microcosmic syndrome scores

Core Tip: Microcosmic syndrome differentiation and Chinese herbal medicine treatment effectively improve dyspeptic symptoms and endoscopic findings in patients with chronic gastritis and liver-stomach disharmony syndrome. Long-term efficacy and mechanisms of this treatment require further investigation through larger-scale studies with extended follow-up periods.

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INTRODUCTION

Chronic gastritis (CG) is a prevalent digestive disorder marked by persistent inflammation and mucosal damage in the stomach[1]. It leads to various dyspeptic symptoms, including abdominal pain, bloating, nausea, vomiting, loss of appetite, and belching[2]. Furthermore, CG augments the risk of developing gastric ulcers, cancer, and other severe complications. The prevalence of CG is high in China, affecting approximately 42.5% of the population[3]. The etiology and pathogenesis of CG are intricate and multifaceted, encompassing *Helicobacter pylori* (*H. pylori*) infection as well as environmental, genetic, immunological, and psychological factors[4]. Conventional Western medicine (CWM) treatments for CG involve antibiotics, proton pump inhibitors, histamine receptor antagonists, and mucosal protective agents[5]. Nevertheless, these medications exhibit certain limitations, such as a low eradication rate of *H. pylori*, drug resistance, adverse effects, and recurrence. Chinese herbal medicine (CHM) has a long history and rich experience in CG treatment. CHM can regulate the functions of the stomach and spleen, harmonize the liver and stomach, eliminate dampness and heat, promote blood circulation, and eliminate blood stasis[6]. CHM can also modulate the immune system, inhibit the growth of *H. pylori*, protect the gastric mucosa, and improve the quality of life of patients with CG[7]. Microcosmic syndrome differentiation is a novel method of syndrome differentiation based on Traditional Chinese Medicine (TCM)[8]. It combines macroscopic observation of the tongue, pulse, and symptoms with microscopic examination of blood, urine, and stool[9]. Microcosmic syndrome differentiation can reveal subtle changes in the internal environment of the body and provide more accurate and individualized guidance for CHM prescription[10]. Liver-stomach disharmony (LSD) syndrome is a common CG syndrome in TCM[11]. It is characterized by the liver qi invading the stomach, causing the stomach qi to rebel upward and disturb the spleen. The primary symptoms of LSD syndrome include abdominal pain, acid regurgitation, belching, nausea, vomiting, poor appetite, irritability, and depression. The main pathological factors of LSD syndrome include emotional stress, improper diet, and chronic inflammation. This study aimed to evaluate the efficacy and safety of microcosmic syndrome differentiation and CHM treatment in patients with CG and LSD syndrome compared to CWM treatment. We hypothesized that microcosmic syndrome differentiation and CHM treatment could improve dyspeptic symptoms and endoscopic findings in patients with CG and LSD syndrome, with a good safety profile.

MATERIALS AND METHODS

Study design

This randomized controlled clinical trial was conducted from January 2021 to December 2022 at the Rehabilitation Medicine Department of Beijing Aerospace General Hospital. The research plan has been approved by the Medical Ethics Committee of Beijing Aerospace General Hospital. All participants sign an informed consent form before registration.

Participants

The inclusion criteria were as follows: (1) Age 18-65 years; (2) diagnosis of CG according to the Sydney System; (3) diagnosis of LSD syndrome according to the Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in TCM; (4) dyspeptic symptoms for more than 3 months; (5) Nepean Dyspepsia Index (NDI) score of more than 25; and (6) willingness to comply with the study protocol.

The exclusion criteria were as follows: (1) Gastric ulcer, gastric cancer, or other organic diseases of the digestive system; (2) severe liver, kidney, heart, lung, or blood diseases; (3) mental disorders or cognitive impairment; (4) history of allergy to CHM or CWM; (5) pregnancy or lactation; (6) use of other drugs or therapies for CG during the study period; and (7) participation in other clinical trials within 3 months before enrollment.

Randomization and allocation concealment

Eligible participants were randomly assigned to either the treatment or control group in a 1:1 ratio, using a computer-generated random number table. The randomization sequence was maintained by an independent statistician who was not involved in the recruitment, intervention, or assessment. The allocation was concealed in sealed opaque envelopes that were opened by the researchers after the participants signed the consent forms.

Intervention

The treatment group received CHM based on the microcosmic syndrome differentiation, whereas the control group received CWM alone. The treatment course lasted for 12 wk in both the groups.

The CHM prescription was composed of the following herbs: Radix Bupleuri (Chaihu), 10 g; Radix Paeoniae Alba (Baishao), 10 g; Rhizoma Cyperi (Xiangfu), 10 g; Fructus Aurantii (Zhiqiao), 10 g; Radix Glycyrrhizae (Gancao), 6 g; Rhizoma Atractylodis Macrocephalae (Baizhu), 10 g; Rhizoma Pinelliae (Banxia), 10 g; Pericarpium Citri Reticulatae (Chenpi), 6 g; and Fructus Amomi (Sharen), 6 g. The herbs were decocted in water twice daily, and the decoction was divided into two doses administered before breakfast and dinner. The dosage of the herbs was adjusted according to microcosmic syndrome differentiation, which was performed by the researchers before each prescription. Microcosmic syndrome differentiation was based on the following indicators: Tongue color, tongue coating, pulse condition, blood routine, urine routine, and stool routine. Indicators were scored according to the Microcosmic Syndrome Differentiation Scoring System, and the total score was calculated. The higher the score, the more severe the syndrome. The herbs were added or subtracted according to the following rules: (1) If the score of tongue color was more than 3, Radix Salviae Miltiorrhizae (Danshen), 15 g, was added; (2) if the score of tongue coating was more than 3, Cortex Magnoliae Officinalis (Houpo), 10 g, and Fructus Forsythiae (Lianqiao), 15 g, were added; (3) if the score of pulse condition was more than 3, Radix Scutellariae (Huangqin), 10 g, and Rhizoma Coptidis (Huanglian), 6 g, were added; (4) if the score of blood routine was more than 3, Radix Angelicae Sinensis (Danggui), 10 g, and Radix Rehmanniae (Shengdi), 15 g, were added; (5) if the score of urine routine was more than 3, Herba Lysimachiae (Jinqiancao), 15 g, and Herba Desmodii (Jinqiancao), 15 g, were added; and (6) if the score of stool routine was more than 3, Radix et Rhizoma Rhei (Dahuang), 6 g, and Semen Plantaginis (Cheqianzi), 15 g, were added.

The CWM treatment consisted of the following drugs: Amoxicillin, 1 g, twice a day; clarithromycin, 500 mg, twice a day; and omeprazole, 20 mg, twice a day for the first 14 d; and omeprazole, 20 mg, once a day for the remaining 10 wk. Drugs were orally administered after meals.

Outcome measures

The primary outcome was the improvement rate of dyspeptic symptoms, as measured using the NDI. The NDI is a validated instrument used to assess the severity and impact of dyspepsia on the quality of life[11]. It consists of two parts: Part A evaluates the frequency and intensity of 15 dyspeptic symptoms and Part B evaluates the impairment of 25 aspects of daily life. Each item is scored on a 5-point Likert scale, ranging from 0 (none or not applicable) to 4 (extremely). The total score for Part A ranges from 0 to 60, while the total score for Part B ranges from 0 to 100. The higher the score, the more severe the dyspepsia. The improvement rate of dyspeptic symptoms was calculated as follows: (Baseline NDI score-follow-up NDI score)/baseline NDI score × 100%. The NDI was administered at baseline, 4, 8, and 12 wk.

The secondary outcomes included the improvement rates of endoscopic findings, histopathological findings, and microcosmic syndrome scores and the incidence of adverse events.

The improvement rate of endoscopic findings was measured using the modified Lanza score (MLS)[12]. The MLS is a widely used scoring system for evaluating the degree of gastric mucosal damage. It grades mucosal lesions into four levels: 0 (normal), 1 (petechiae or hemorrhagic spots), 2 (erosions), and 3 (ulcers). The total score ranges from 0 to 12, with each level scored as follows: 0 (no lesion), 1 (one lesion), 2 (two lesions), 3 (more than two lesions), and 4 (confluent lesions). The improvement rate of endoscopic findings was calculated as follows: (baseline MLS score-follow-up MLS score)/baseline MLS score × 100%. Endoscopy was performed by experienced gastroenterologists who were blinded to the group allocation at baseline and 12 wk.

Table 1 Baseline characteristics of the two groups

	Treatment group (*n* = 64)	Control group (*n* = 64)	*P* value
Age (yr)	46.3 ± 11.2	45.6 ± 10.8	0.68
Sex (male/female)	32/32	33/31	0.82
Body mass index (kg/m^2)	23.5 ± 3.2	23.7 ± 3.4	0.76
Duration of disease (months)	27.4 ± 15.6	26.8 ± 16.2	0.84
Helicobacter pylori status (positive/negative)	38/26	37/27	0.88
NDI score	42.7 ± 8.9	43.1 ± 9.2	0.79
MLS score	6.4 ± 2.1	6.5 ± 2.2	0.87
USS score	9.3 ± 3.4	9.5 ± 3.6	0.81
Microcosmic syndrome score	12.6 ± 4.8	12.8 ± 4.9	0.83

NDI: Nepean Dyspepsia Index; MLS: Modified Lanza score; USS: Updated Sydney system.

The improvement rate of histopathological findings was measured using the updated Sydney system (USS)[13]. The USS is a standardized system for assessing the histological features of CG, including chronic inflammation, activity, atrophy, intestinal metaplasia, and *H. pylori* density. Each feature is graded from 0 (absent) to 3 (marked). The improvement rate of histopathological findings was calculated as follows: (Baseline USS score-follow-up USS score)/baseline USS score × 100%. Histopathological examination was performed by experienced pathologists who were blinded to the group allocation, using biopsy specimens obtained from the antrum and body of the stomach at baseline and 12 wk.

The improvement rate of microcosmic syndrome scores was measured using the Microcosmic Syndrome Differentiation Scoring System[14]. The system consists of six indicators: Tongue color, tongue coating, pulse condition, blood routine, urine routine, and stool routine. Each indicator is scored from 0 (normal) to 4 (severe) according to the reference values and criteria. The total score ranges from 0 to 24. The higher the score, the more severe the syndrome. The improvement rate of microcosmic syndrome scores was calculated as follows: (Baseline microcosmic syndrome score–follow-up microcosmic syndrome score)/baseline microcosmic syndrome score × 100%. Microcosmic syndrome differentiation was performed at baseline and at 4, 8, and 12 wk.

The incidence of adverse events was recorded throughout the study period. An adverse event was defined as any undesirable or unintended sign, symptom, or disease that occurred during or after the intervention, regardless of its causal relationship with the intervention. The severity of adverse events was graded as mild, moderate, or severe according to the Common Terminology Criteria for Adverse Events. The causality of adverse events was assessed as definite, probable, possible, unlikely, or unrelated according to the World Health Organization-Uppsala Monitoring Centre criteria. Participants were instructed to report any adverse events to the researchers as soon as possible. The researchers also monitored the vital signs, physical examination, and laboratory tests of the participants at baseline and at 12 wk and recorded any abnormal findings.

Statistical analysis

The sample size calculation was based on the primary outcome of the improvement rate of dyspeptic symptoms. Assuming a mean improvement rate of 50% in the treatment group and 30% in the control group, with a standard deviation of 20%, two-sided alpha of 0.05, and power of 0.8, the required sample size was 64 participants per group. The final sample size was 80 participants per group, with a dropout rate of 20%.

Statistical analysis was performed by an independent statistician who was blinded to the group allocation, using SPSS 22.0. Data are expressed as mean ± SD for continuous variables and as frequency and percentage for categorical variables. Normality of the data were tested using the Kolmogorov-Smirnov test. The baseline characteristics of the two groups were compared using the independent *t*-test or Mann-Whitney *U* test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. The within-group and between-group differences in the outcome measures were analyzed using the paired *t*-test or Wilcoxon signed-rank test for continuous variables and the McNemar test or Cochran's *Q* test for categorical variables. A two-sided *P* value of less than 0.05 was considered statistically significant.

RESULTS

Participant flow and baseline characteristics

A total of 160 participants were screened for eligibility; 128 met the inclusion criteria and were randomized into the treatment group (*n* = 64) or the control group (*n* = 64). Twelve participants in the treatment group and ten in the control group dropped out during the study period, mainly because of loss to follow-up, withdrawal of consent, or protocol violation. The final analysis included 52 and 54 participants in the treatment and control groups, respectively. The

Table 2 Improvement rate of dyspeptic symptoms of the two groups at different time points

Time point	Treatment group improvement rate of dyspeptic symptoms (%)	Control group improvement rate of dyspeptic symptoms (%)	*P* value
4 wk	48.7 ± 15.3	24.6 ± 12.4	< 0.01
8 wk	67.4 ± 18.2	35.7 ± 16.7	< 0.01
12 wk	93.8 ± 12.6	65.6 ± 19.4	< 0.01

baseline characteristics of the two groups were comparable, with no significant differences in age, sex, body mass index, disease duration, *H. pylori* status, NDI score, MLS score, USS score, and microcosmic syndrome score. The baseline characteristics of the two groups are presented in Table 1.

Efficacy outcomes

The primary outcome of the improvement rate of dyspeptic symptoms was that the treatment group had a significantly higher improvement rate than the control group at 4, 8, and 12 wk ($P < 0.01$). The mean improvement rates of the treatment group were 48.7%, 67.4%, and 93.8%, respectively, whereas those of the control group were 24.6%, 35.7%, and 65.6%, respectively. The improvement rates of dyspeptic symptoms of the two groups at different time points are shown in Table 2.

The secondary outcome of the improvement rate of endoscopic findings was that the treatment group had a significantly higher improvement rate of 81.3% ± 21.4% compared to 53.1 ± 28.6% in the control group at 12 wk ($P = 0.03$).

The secondary outcome of the improvement rate of histopathological findings showed no significant difference between the two groups at 12 wk ($P = 0.67$). The improvement rate in the treatment group was 52.1% ± 23.7%, whereas in the control group it was 48.9% ± 25.4%.

The secondary outcome of the improvement rate of microcosmic syndrome scores showed no significant difference between the two groups at 4, 8, and 12 wk ($P > 0.05$). The mean improvement rates of the treatment group were 28.6%, 46.8%, and 64.3%, respectively, whereas those of the control group were 25.4%, 40.6%, and 58.9%, respectively. The improvement rates of the microcosmic syndrome scores of the two groups at different time points are shown in Table 3.

Safety outcomes

The incidence of adverse events was similar between the two groups, but the difference was not significant ($P > 0.05$). The most common adverse events were diarrhea, nausea, headache, and rashes. All adverse events were mild or moderate in severity and resolved spontaneously or with symptomatic treatment. No serious adverse events or deaths occurred during the study period. The incidence and types of adverse events in the two groups are shown in Table 4.

DISCUSSION

The main finding of this study was that microcosmic syndrome differentiation and CHM treatment were more effective and safe than CWM treatment in patients with CG and LSD syndrome. The treatment group had a significantly higher improvement rate in dyspeptic symptoms and endoscopic findings than the control group and a similar improvement rate in histopathological findings and microcosmic syndrome scores. The incidence of adverse events was similar between the two groups, and no serious adverse events or deaths occurred during the study period. These results suggest that microcosmic syndrome differentiation and CHM treatment can regulate stomach and spleen function, harmonize the liver and stomach, eliminate dampness and heat, promote blood circulation, and eliminate blood stasis, thus alleviating dyspeptic symptoms and repairing gastric mucosal damage in patients with CG and LSD syndrome[15]. Moreover, microcosmic syndrome differentiation and CHM treatment can modulate the immune system, inhibit the growth of *H. pylori*, protect the gastric mucosa, and improve the quality of life of patients with CG and LSD syndrome[16]. The possible mechanisms of microcosmic syndrome differentiation and CHM treatment for patients with CG and LSD syndrome are as follows: (1) Radix Bupleuri, Radix Paeoniae Alba, Rhizoma Cyperi, and Fructus Aurantii can soothe the liver qi, relieve the LSD, and reduce the abdominal pain, acid regurgitation, belching, nausea, and vomiting of patients with CG and LSD syndrome[17]; (2) Radix Glycyrrhizae, Rhizoma Atractylodis Macrocephalae, Rhizoma Pinelliae, Pericarpium Citri Reticulatae, and Fructus Amomi can strengthen the spleen and stomach, regulate the qi movement, and improve the appetite, bloating, and diarrhea of patients with CG and LSD syndrome[18]; (3) Radix Salviae Miltiorrhizae, Radix Scutellariae, Rhizoma Coptidis, Radix Angelicae Sinensis, and Radix Rehmanniae can nourish the blood, clear the heat, and eliminate the blood stasis, thus improving the tongue color, pulse condition, and blood routine of patients with CG and LSD syndrome[19]; (4) Cortex Magnoliae Officinalis, Fructus Forsythiae, Herba Lysimachiae, and Herba Desmodii can dispel the dampness and heat and enhance diuresis, thus improving the tongue coating, urine routine, and stool routine of patients with CG and LSD syndrome[16]; (5) Radix et Rhizoma Rhei and Semen Plantaginis can purge the heat and toxins and moisten the intestines, thus improving the constipation and stool routine of patients with CG and LSD syndrome[20]; and (6) microcosmic syndrome differentiation and CHM treatment can also modulate the immune system, inhibit the growth of *H. pylori*, protect the gastric mucosa, and improve the quality of life of patients with CG and LSD syndrome, by affecting the cytokines, inflammatory mediators, oxidative stress, and mucosal barrier[21,22]. The strengths

Table 3 Improvement rate of microcosmic syndrome scores of the two groups at different time points

Time point	Treatment group improvement rate of microcosmic syndrome scores (%)	Control group improvement rate of microcosmic syndrome scores (%)	*P* value
4 wk	28.6 ± 14.5	25.4 ± 13.6	0.42
8 wk	46.8 ± 18.7	40.6 ± 17.9	0.26
12 wk	64.3 ± 21.3	58.9 ± 22.4	0.37

Table 4 Incidence and type of adverse events in the two groups, *n* (%)

Adverse events	Treatment group (*n* = 64)	Control group (*n* = 64)	*P* value
Total adverse events	6 (9.4)	8 (12.5)	0.57
Diarrhea	2 (3.1)	3 (4.7)	0.89
Nausea	1 (1.6)	2 (3.1)	0.85
Headache	2 (3.1)	1 (1.6)	0.79
Rash	1 (1.6)	2 (3.1)	0.81

of this study are as follows: (1) It was a clinical randomized controlled trial with a large sample size and high follow-up rate; (2) the intervention was based on microcosmic syndrome differentiation, which is a novel and individualized method of syndrome differentiation in TCM; (3) the outcome measures were comprehensive and objective, including the NDI, MLS, USS, and microcosmic syndrome scores; and (4) adverse events were monitored and recorded throughout the study period, and no serious adverse events or deaths occurred. The limitations of this study include the following: (1) The duration of the intervention was relatively short, and the long-term effects and recurrence rate of microcosmic syndrome differentiation and CHM treatment for patients with CG and LSD syndrome were not evaluated; (2) the mechanism of microcosmic syndrome differentiation and CHM treatment for patients with CG and LSD syndrome was not fully elucidated, and the biomarkers and pathways involved were not explored; (3) the blinding of the participants and researchers was not feasible because of the nature of the intervention; and (4) the generalizability of the results may be limited, as the study was conducted in a single center and only included patients with CG and LSD syndrome.

CONCLUSION

In conclusion, this study demonstrated that microcosmic syndrome differentiation and CHM treatment were more effective and safe than CWM treatment in patients with CG and LSD syndrome. Microcosmic syndrome differentiation and CHM treatment can improve the dyspeptic symptoms and endoscopic findings of patients with CG and LSD syndrome and have a similar effect on histopathological findings and microcosmic syndrome scores. Microcosmic syndrome differentiation and CHM treatment can also modulate the immune system, inhibit the growth of *H. pylori*, protect the gastric mucosa, and improve the quality of life of patients with CG and LSD. Further studies are needed to confirm the long-term effects and recurrence rate of microcosmic syndrome differentiation and CHM treatment in patients with CG and LSD syndrome and to explore the mechanism and biomarkers of microcosmic syndrome differentiation and CHM treatment in patients with CG and LSD syndrome.

FOOTNOTES

Author contributions: Bai CY and Tian W proposed the concept of this study; Zhang Q verified the effectiveness of this study; Bai CY and Zhang Q jointly wrote the first draft; Tian W has made contributions in data collection; Zhang Q contributes to formal analysis; Bai CY and Tian W participated in the research; Zhang Q contributed to the visualization of this study. All authors jointly guide the research, review, and edit the manuscript. Bai CY and Tian W as co-first authors, have made equal contributions to this research work.

Institutional review board statement: The study was reviewed and approved by the Beijing Aerospace General Hospital.

Clinical trial registration statement: This study is registered at the Clinical Registry. https://www.researchregistry.com (Researchregistry9837).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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ORIGINAL ARTICLE

Basic Study

Establishment of acquired tracheoesophageal fistula using a modified magnetic compression technique in rabbits and its postmodeling evaluation

Han Meng, Fu-Yao Nan, Na Kou, Qin-Yan Hong, Ming-Sheng Lv, Ju-Bo Li, Bao-Jie Zhang, Hang Zou, Lei Li, Hong-Wu Wang

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Abstract

BACKGROUND

Previous studies have validated the efficacy of both magnetic compression and surgical techniques in creating rabbit tracheoesophageal fistula (TEF) models. Magnetic compression achieves a 100% success rate but requires more time, while surgery, though less frequently successful, offers rapid model establishment and technical maturity in larger animal models.

AIM

To determine the optimal approach for rabbit disease modeling and refine the process.

METHODS

TEF models were created in 12 rabbits using both the modified magnetic compression technique and surgery. Comparisons of the time to model establishment, success rate, food and water intake, weight changes, activity levels, bronchoscopy findings, white blood cell counts, and biopsies were performed. In response to the failures encountered during modified magnetic compression modeling, we increased the sample size to 15 rabbit models and assessed the repeatability and

stability of the models, comparing them with the original magnetic compression technique.

RESULTS

The modified magnetic compression technique achieved a 66.7% success rate, whereas the success rate of the surgery technique was 33.3%. Surviving surgical rabbits might not meet subsequent experimental requirements due to TEF-related inflammation. In the modified magnetic compression group, one rabbit died, possibly due to magnet corrosion, and another died from tracheal magnet obstruction. Similar events occurred during the second round of modified magnetic compression modeling, with one rabbit possibly succumbing to aggravated lung infection. The operation time of the first round of modified magnetic compression was 3.2 ± 0.6 min, which was significantly reduced to 2.1 ± 0.4 min in the second round, compared to both the first round and that of the original technique.

CONCLUSION

The modified magnetic compression technique exhibits lower stress responses, a simple procedure, a high success rate, and lower modeling costs, making it a more appropriate choice for constructing TEF models in rabbits.

Key Words: Tracheoesophageal fistula; Modified magnetic compression technique; Post-modeling evaluation; Pneumonia; Malnutrition

Core Tip: Tracheoesophageal fistula (TEF) is a complex condition with both congenital and acquired forms and presents a significant clinical challenge. Despite its importance, the methods for creating TEF models have limitations, particularly in terms of success rates and practicality. We compared the modified magnetic compression technique with the conventional surgical method for creating TEF models in rabbits.

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INTRODUCTION

Tracheoesophageal fistula (TEF) is a pathological communication between the esophagus and trachea and is the most common digestive-respiratory tract fistula. Congenital TEF often accompanies esophageal atresia[1,2], while acquired TEF can result from factors such as tumors, surgeries, infections, trauma, or foreign objects[3-11]. Untreated, TEF leads to recurrent pneumonia or malnutrition in a short span[12].

Surgery is the preferred method for treating benign fistulas[13], although it can be traumatic, necessitating multiple surgeries, with feasibility and safety hinging on the patient's condition. Malignant TEF patients may opt for interventional treatment due to overall health constraints[12]. Effective postoperative airway management and complication prevention are essential for therapeutic success[14]. Alternative methods include endoscopic closure, vacuum therapy, fibrin glue, and cardiac occluders, but conclusive research on their clinical efficacy is lacking[12].

Establishing suitable animal models is crucial for exploring minimally invasive treatments. In 2003, Kiyan *et al*[15] surgically created a rabbit TEF model[15]. However, there have been no subsequent reports of successful surgical TEF model establishment in rabbits. In 2019, Gao *et al*[16] used a nonsurgical magnetic compression technique in rabbits, achieving a 100% success rate[16]. To further explore the best method for modeling TEF in rabbits and validate its repeatability and stability, our team conducted this study. This involved simplifying some of the original procedures, conducting controlled studies comparing the magnetic compression technique with surgical modeling (SM), and investigating potential adverse reactions during the process.

MATERIALS AND METHODS

Ethical statement

This study was approved by the Ethical Committee of Animal Experiments at Nongnong (Beijing) Biotechnology Co., Ltd. (No. 202307001). Twenty-seven adult New Zealand rabbits (3-4 kg, conventionally graded) from the Beijing Fangyuanyuan Breeding Farm were subjected to one week of adaptive feeding before the experiments (26 °C, 12 h/12 h light/dark, 50% humidity, with ad libitum access to food and water). Twelve rabbits were designated for comparison of

the modified magnetic compression (MMC) technique and SM (6 per group). Fifteen rabbits were employed to validate the repeatability and stability of the MMC technique for modeling.

Experimental equipment and reagents

The experimental equipment used in this study included a tracheal intubation device (Guangzhou AMK Equipment Co., Ltd., Guangdong Medical Device Registration No. 20172660258), an X-ray machine (GE OEC Medical Systems, Inc., OEC 9900 Elite), a flexible bronchoscope (Zhejiang UE Medical Corp., EBC-380C), a laryngoscope (Shenzhen Teslong Technology Co., Ltd., TSL2080845), a puncher (Beijing Lab Anim Tech Development Co., Ltd., LAT-DK), nonabsorbable surgical sutures (Johnson & Johnson MedTech, National Medical Device Registration No. 20192022154), an anesthesia machine (Beijing Aerospace Changfeng Co., Ltd., 17-608-10-027), a monitor (Shenzhen Mindray Bio-Medical Electronics Co., Ltd., CM-74153659), and an upside-down integrated fluorescence microscope (Revolve FL microscope, Echo-labs, San Diego, CA, United States).

The experimental reagents included pentobarbital sodium (Shanghai Pharma New Asia Pharma Co., Ltd.), methylene blue (Jumpcan Pharmaceutical Group Co., Ltd.), sodium penicillin for injection (Huabei Pharmaceutical Co., Ltd.), Tolfedine CS (Vétoquinol SA, France), potassium chloride (China Otsuka Pharmaceutical Co., Ltd.), 4% paraformaldehyde fixative solution (Shanghai Beyotime Biotech. Co., Ltd.), and hematoxylin-eosin staining (Shanghai Klamar Reagent Co., Ltd.).

Magnets

The magnets utilized included a parent magnet (PM, cylinder, diameter 5 mm, thickness 3 mm), a daughter magnet (DM, cylinder, diameter 3 mm, thickness 3 mm), and an anchor magnet (cylinder, diameter 8 mm, thickness 10 mm). All magnets were constructed from N52 NdFeB permanent magnetic material with zinc electroplating for corrosion resistance.

Study procedures

After 12 h of fasting and water restriction, the rabbits were weighed, and blood was collected. Anesthesia was induced *via* injection of 1.5% pentobarbital sodium (2 mL/kg) through the marginal ear vein. Once the rabbits were anesthetized, they were placed in a supine position and securely fastened to the operating table.

MMC technique (Figure 1): The rabbits' heads were fully extended, and the glottis was visualized using a laryngoscope. Tracheal and esophageal intubation tubes (3.5 and 5.5 mm, respectively) were inserted 4 cm below the glottis, each with a magnet (DM and PM) (Supplementary Figure 1). The PM was pushed out using a guide wire and automatically connected to the DM by magnetic force, and then the guide wire and tracheal intubation tubes were removed, and magnet placement was confirmed by X-ray. Daily checks were conducted using an anchor magnet. If the magnet moved away from its target position, X-rays were repeated. Their entry into the digestive tract indicated suc-cessful establishment of the model (Figure 2). The time to successful model establishment was recorded.

SM technique: Rabbits underwent tracheal intubation to provide artificial respiration, and were connected to an anesthesia machine and a monitor. A longitudinal incision was made 3-5 cm below the larynx, cutting through the skin and subcutaneous tissues. The surrounding tissues of the trachea and esophagus were separated. Using a 3 mm puncher, two holes were made adjacent to the trachea and esophagus. Once the two holes were aligned, the trachea and esophagus were sutured together. The subcutaneous tissues and skin were sutured in layers, and the operation time was recorded. Methylene blue was injected into the esophagus and observed under a bronchoscope to confirm successful model establishment (Figure 3A).

After the procedures, each rabbit received prophylactic antibiotics (25000 U/kg) to prevent infection and xylazine (4 mg/kg) for 3 d for pain relief. The model success rate, general observations (food and water intake, respiration, activity level), and survival duration were compared between the groups. To address modeling failures and adverse reactions, the sample size was increased to further clarify the feasibility and success rate of the MMC technique.

Specimen collection and histological analysis

On the 3rd day after successful model establishment, blood samples were collected. After 5 d, the rabbits were weighed, anesthetized with pentobarbital sodium, placed in a supine position, and the morphology of the fistula was observed under a bronchoscope. Subsequently, euthanasia was performed using a large dose of 10% potassium chloride solution, and the fistula tissues were excised. After gross examination, the specimens were fixed in 4% paraformaldehyde, and the sections were stained with hematoxylin and eosin for light microscopy to assess histological changes. In the event of mortality during the experiment, fistula tissues were collected promptly for gross observation and histological analysis. The Smith score method was used for semiquantitative analysis of pulmonary inflammation: No injury (0), lesion range < 25% (1), lesion area 25% Mel 50% (2), lesion range 50% Mel 75% (3), and lesion range > 75% (4). Five nonrepetitive regional visual fields were observed for each animal, and the average value was taken.

Statistical analysis

Data analysis was conducted using SPSS 26.0 statistical software. Quantitative data are presented as the mean ± SD. Group comparisons were performed using one-way ANOVA for quantitative data. For quantitative data that met the normal distribution, Pearson correlation analysis was employed. Spearman correlation analysis was used to analyze the relationship between the quantitative and qualitative data. A P value less than 0.05 was considered to indicate statistical significance. Graphs and plots were generated using GraphPad Prism 8.0.

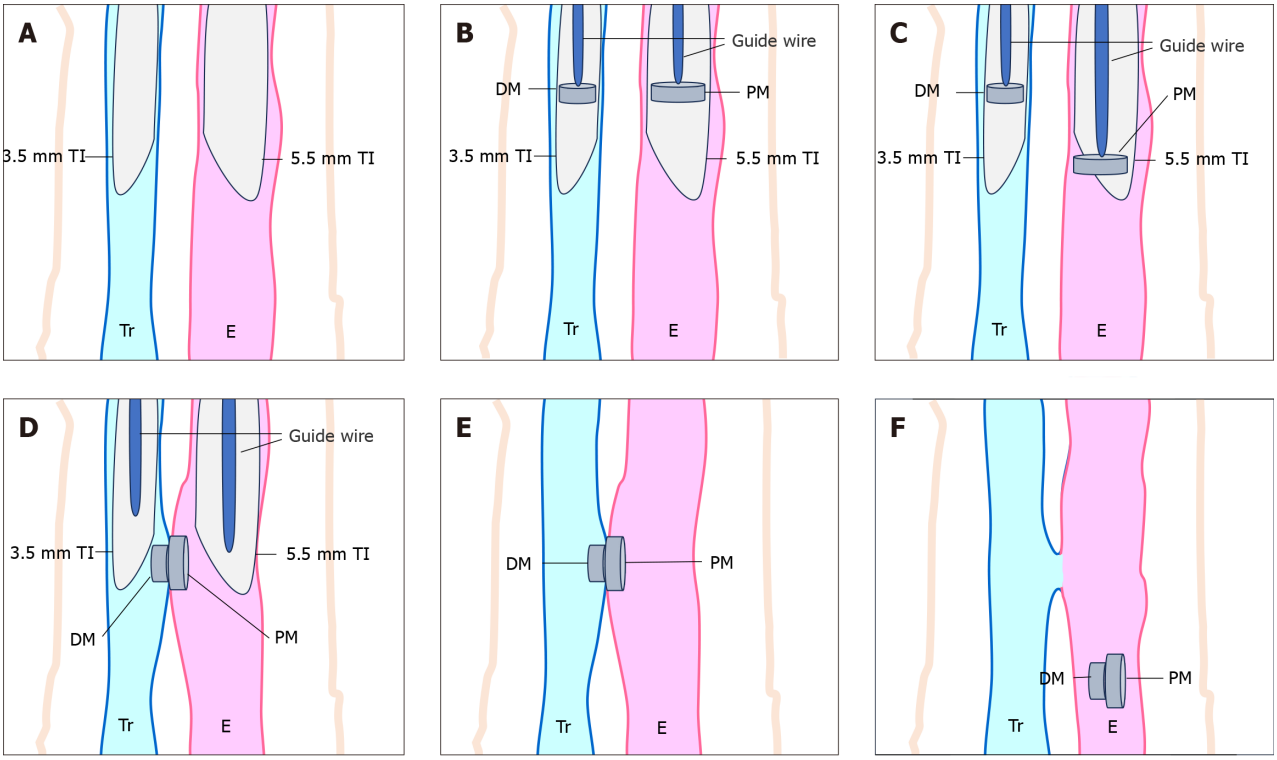

Figure 1 Schematic of the modified magnetic compression technique. A: Inserting 3.5 mm and 5.5 mm tracheal intubation into the trachea and esophagus respectively; B: Placing the daughter magnet (DM) and parent magnet (PM) inside the tracheal intubation and pushing them to the intubation's end using a guide wire; C: Gently pushing the PM towards the end using the guide wire; D: Under the influence of magnetic force, the DM and PM attract each other, detach from tracheal intubation, and adhere to the tracheal and esophageal mucosa; E: Removing the tracheal intubation and guide wire; F: Separation of the magnets, entry into the esophagus, and expulsion from the body through the digestive tract. Tr: Trachea; TI: Tracheal intubation; E: Esophagus; DM: Daughter magnet; PM: Parent magnet.

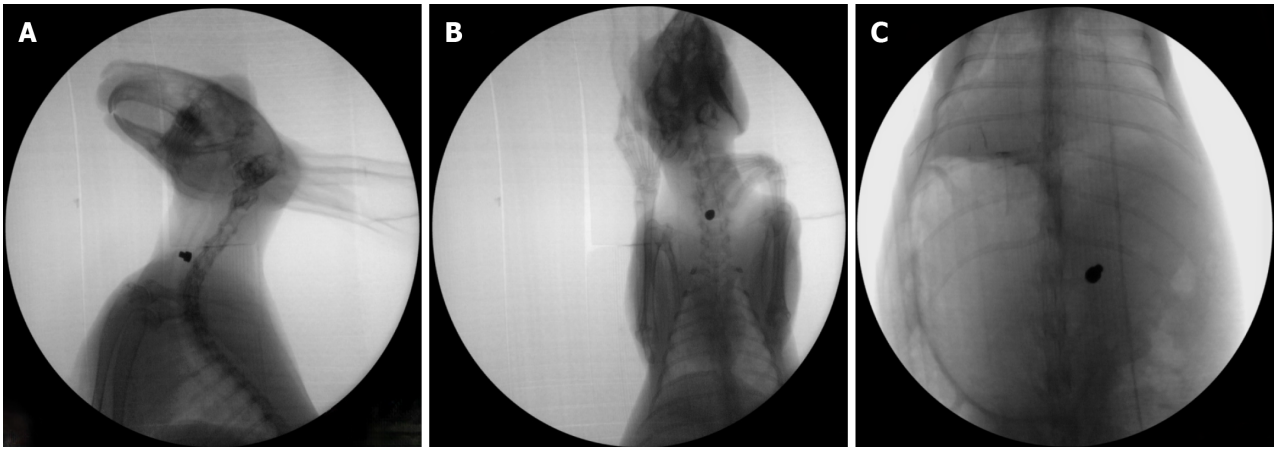

Figure 2 X-ray images of the rabbit neck after magnet implantation. A: Lateral view; B: Anteroposterior view; C: Magnet entering the digestive tract.

RESULTS

Comparison between the MMC technique and SM technique

Model conditions: In the MMC group, the average operation time was 3.2 ± 0.6 min. Some rabbits showed reduced food and water intake. One rabbit died on the 6th day. In this rabbit, the magnet was still in the target position, and the tissue between the DM and PM was necrotic, the lungs were congested and the spleen vessels were bruised; changes in the color of the tracheal and esophageal mucosa were also observed (Supplementary Figure 2). Another rabbit experienced breathing difficulties, and bronchoscopy revealed that the magnets had entered the trachea on the 9th day. Attempts to remove the magnets were unsuccessful (Supplementary Figure 3). For the remaining 4 rabbits, the average time for the magnets to move away from the target position was 8.0 ± 1.4 d. These rabbits were able to eat and drink normally and showed good general activity, resulting in a model success rate of 66.7%.

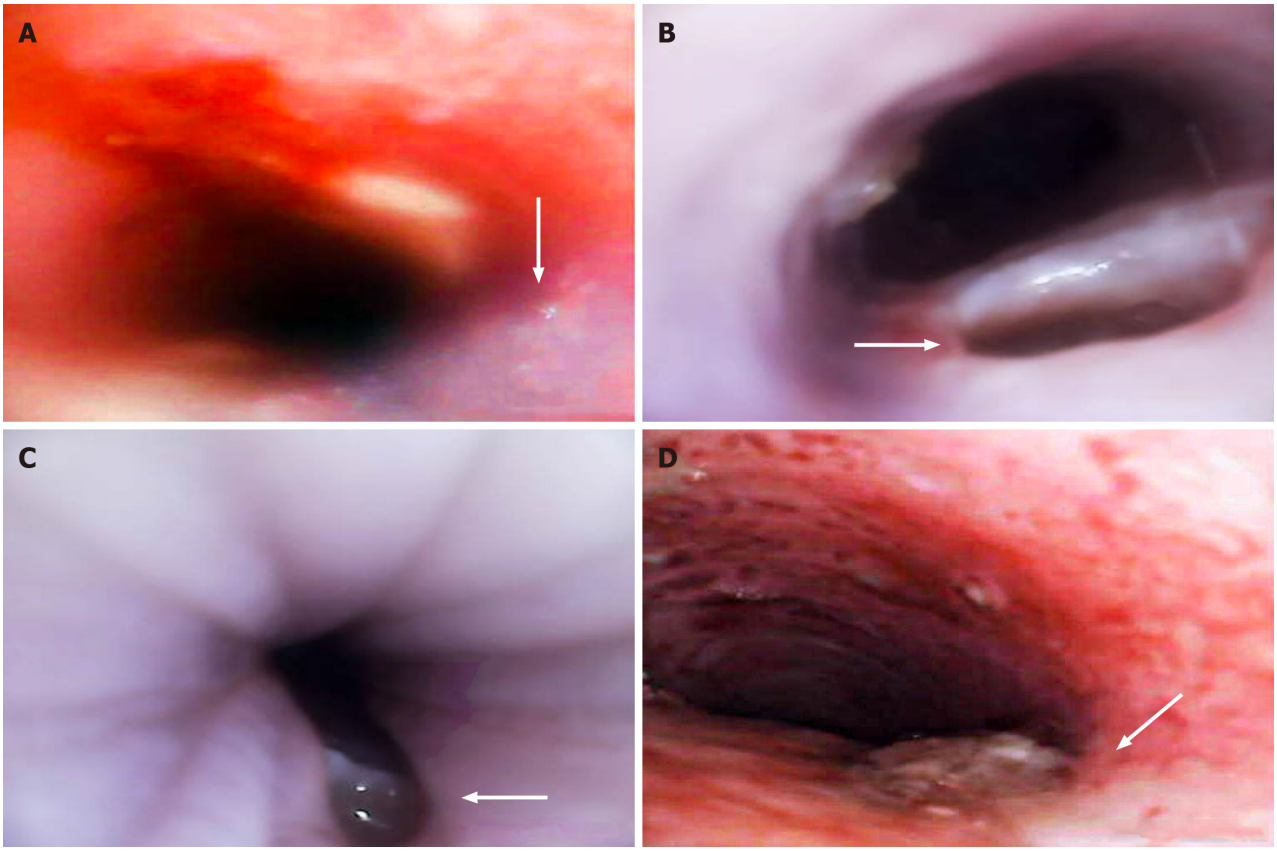

Figure 3 Endoscopic findings after modeling with the surgical modeling technique and modified magnetic compression technique. A: In the surgical modeling (SM) group, methylene blue was immediate injected into the esophagus, leading to overflow into the trachea (indicated by the arrow); B: 5 d after successful modeling with modified magnetic compression (MMC) technique, the fistula on the tracheal side was observed (indicated by the arrow); C: 5 d after successful modeling with MMC technique, the fistula on the esophageal side was observed (indicated by the arrow); D: 5 d after successful modeling with SM, the fistula and surrounding tracheal mucosa were observed (indicated by the arrow).

In the SM group, the average operation time was 17.8 ± 3.2 min. The process of establishing the model was uneventful, but the condition of the rabbits deteriorated after model establishment. The rabbits did not eat or drink, showed rapid breathing, and some exhibited labored breathing. Within 3 d of model establishment, 4 rabbits died. One rabbit remained lethargic and did not eat or drink water. The final rabbit gradually improved and exhibited good activity. This group had a model success rate of 33.3%.

After model establishment, the MMC group showed a slight decrease in weight, while the SM group, with only 2 successful model cases, exhibited significant weight loss (Supplementary Table 1). Analysis highlighted a significant correlation (coefficient of 0.828, $^{a}P < 0.05$) between the premodel weight in the SM group and model success, whereas no such correlation was observed in the MMC group.

Three days after successful establishment of the model, blood analysis revealed no significant differences in the white blood cell (WBC) count or WBC composition between the two groups. However, both groups exhibited significant differences from their premodel WBC counts.

Gross and histological observations: In the MMC group, the tracheal mucosa of the rabbits appeared pale red, and the mucosa around the fistula was smooth. The anatomical structure of the esophagus and trachea was intact, with no signs of adhesions or scar formation. Pathologically, the tracheal mucosa displayed a clear structure with neutrophil infiltration, and the inflammation score of the lung tissue was 2.7 ± 0.7 (Figures 3B, C and 4; Supplementary Figure 4).

Conversely, in the SM group, the tracheal mucosa appeared congested and rough. The junction of the esophagus and trachea exhibited adhesions, and a dirty moss-like appearance was observed on the surface of the fistula. Pathologically, the tracheal mucosa exhibited swelling, a disrupted anatomical structure, and significant neutrophil infiltration. The inflammation score of the lung tissue was 3.6 ± 0.5, which was significantly greater than that of the MMC group ($^{b}P < 0.01$; Figures 3D and 5; Supplementary Figure 5).

Study on the feasibility and success rate of the MMC technique

In the second round of MMC modeling, 15 rabbits were employed, with an average weight of 3.458 ± 0.221 kg. The process of model establishment was smoother, averaging 2.1 ± 0.4 min, which was significantly shorter than that of the first round ($^{c}P < 0.001$). After placing the magnets, some rabbits exhibited reduced food and water intake. One rabbit died on the 6th day, with no apparent changes in the tracheal or esophageal mucosa, lung or spleen. Two rabbits experienced magnet detachment into the trachea; the magnet was successfully removed using an external magnet in one of the rabbits,

Figure 4 Gross anatomy and pathology of the tracheoesophageal fistula model established by the modified magnetic compression method in rabbits. A: Longitudinal section of the trachea; B: Longitudinal section of the esophagus; C: Tracheal mucosa around the fistula (hematoxylin & eosin staining, 20 ×).

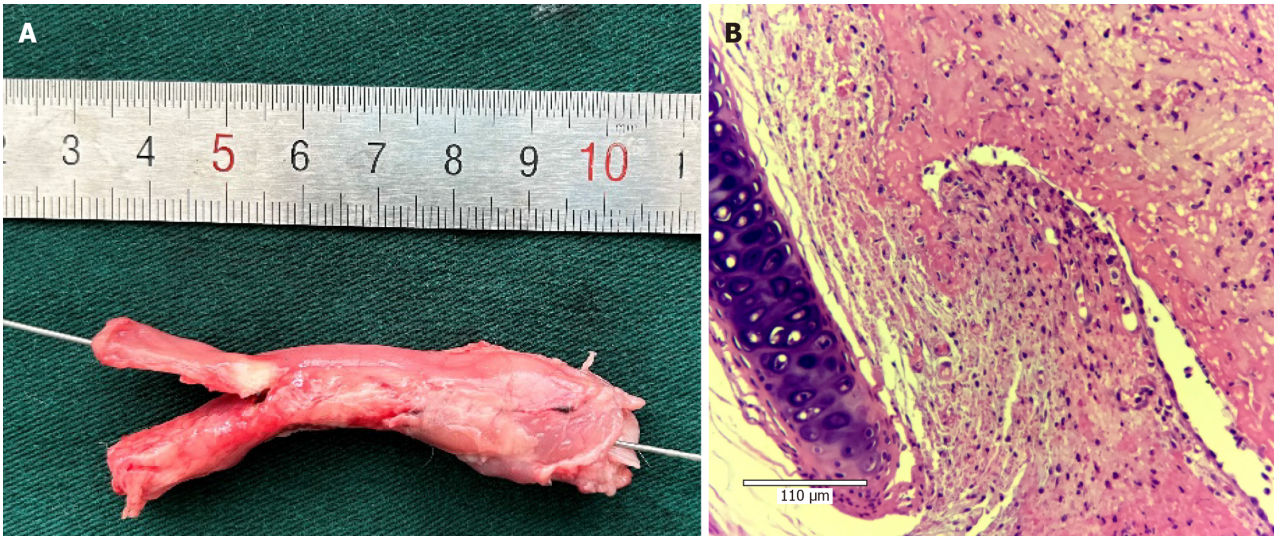

Figure 5 Gross anatomy and pathology of the tracheoesophageal fistula model established by the surgical method in rabbits. A: Guidewire inserted from the tracheal side, allowing access to the esophagus through the fistula; B: Tracheal mucosa around the fistula (hematoxylin & eosin staining, 20 ×).

and the other rabbit died. The model success rate was 86.7%, and the time to magnet detachment averaged 6.2 ± 1.3 d, which was significantly less than that of the first round ($^{d}P < 0.05$); however, the magnet detachment time was not significantly correlated with body weight, model establishment time, or other factors.

On the 2nd day after successful establishment of the model, one rabbit died; this rabbit exhibited normal during model establishment but displayed decreased food and water intake and lethargy after magnet detachment. Pathological sections revealed tracheal mucosa edema and extensive neutrophil infiltration (Supplementary Figure 6A-C), and pulmonary pathological sections revealed significant neutrophil infiltration, with near complete obstruction of the small and tiny bronchi. The inflammation score of the lung tissue was 2.9 ± 0.8 (Supplementary Figure 6D-F).

On the 5th day after successful establishment of the model, the average body weight of the rabbits was 3.419 ± 0.276 kg, and there were no significant differences in body weight between before and after establishment of the model. Tracheal pathological biopsies revealed a clear mucosal structure with neutrophil infiltration (Supplementary Figure 7).

After modeling, the WBC and neutrophil% increased, while the lymphocyte% decreased; these values were significantly different from those at baseline but were not significantly different from those of the first round (Supplementary Table 2 and Figure 6).

DISCUSSION

MMC technique

Gao *et al*[16,17] successfully created TEF models in New Zealand rabbits and beagles using the magnetic compression technique[16,17]. They achieved this by utilizing external anchoring magnets to pinpoint the target location and

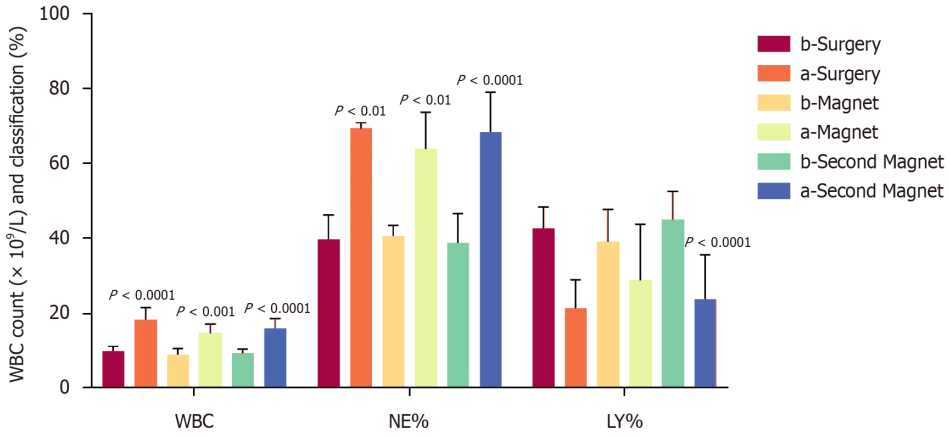

Figure 6 Changes in peripheral blood white blood cell counts and classification in rabbits before and after modeling using different methods. b-Surgery: Premodeling-surgical method (SM); a-Surgery: Postmodeling-SM; b-Magnet: Premodeling-modified magnetic compression (MMC); a-Magnet: Postmodeling-MMC; b-Second Magnet: Premodeling-second-round MMC; a-Second Magnet: Postmodeling-second-round MMC. *P* values represent comparisons with premodeling within the same method. WBC: White blood cell; NE%: Neutrophil%; LY%: Lymphocyte%.

employed a transportation magnet to introduce the DM and PM into the body. After model establishment, X-rays were taken every other day. As the diameter of the trachea and esophagus in rabbits is relatively small, prolonged modeling procedures could affect ventilation, posing a risk to animal safety. Therefore, we aimed to shorten the model establishment time as much as possible. Drawing from our extensive experience in endotracheal interventional research and clinical practice, we modified this technique by using tracheal intubation as the conduit for transporting the magnets. This modification not only ensured proper ventilation but also reduced the production costs of the modeling tools. In the first round of model establishment, the operation time was similar to that of the original method. However, in the second round, the operation time was significantly shorter. This reduction in time is attributed to increased experience and proficiency with the technique, demonstrating that the MMC method is more convenient. Additionally, the modified method still involved the use of anchoring magnets, primarily to confirm whether the magnets had moved from the target location. This approach minimizes the frequency of X-rays, thereby reducing the number of times the animal is anesthetized and the potential radiation exposure risks for both the animals and researchers.

Comparison between the MMC technique and SM technique

The SM technique is considered one of the most convenient methods for constructing TEF models, and it has been successfully applied to large animals such as small pigs and beagles[18,19]. In 2003, Kiyan *et al*[15] reported the only known case of a TEF model in rabbits in which a surgical approach was used[15]. The experimental results indicate that the success rate of SM is only 33.3%, which is half that of MMC. Although 2 rabbits successfully underwent the SM procedure, significant weight loss occurred, and one of the rabbits may not have been able to be used for subsequent experiments due to its short survival time. Moreover, SM requires a high level of surgical expertise. While the use of a puncher may ensure a consistent fistula size between the trachea and esophagus, the suturing process might alter the original anatomical relationship of the two structures and the size of the fistula. Surgical procedures can be highly stressful for experimental animals, affecting their postoperative food and water intake. Since providing long-term nutritional support for rabbits can be challenging, this approach increases the experimental difficulty. If SM is chosen, it is recommended that rabbits with greater starting weights be selected because these rabbits may have greater stress tolerance.

The MMC technique has a minimal impact on food and water intake, causes only mild local inflammatory reactions, and is suitable for conducting follow-up research. However, unexpected deaths occurred during the initial round of model establishment, which has not been reported before. This incident might be related to corrosion of the magnets within the body, which the organism could not tolerate. NdFeB magnets are prone to oxidation and have poor corrosion resistance. Although the magnets are zinc-plated, they may still experience varying degrees of corrosion in complex biological environments. Research has shown that magnets coated with epoxy resin, a highly polymeric material, exhibit the highest resistance to gastric juice corrosion[20].

Additionally, rabbits typically use all four limbs for movement, and their trachea is situated below the esophagus when in a normal position. When the DM and PM are dislodged from their target location, certain movements, such as neck extension and jumping, could lead to a misalignment or tilting of the PM. This may cause it to slide out of the esophageal smooth muscle tissue and enter the trachea under the influence of gravity, causing airway obstruction. The combined thickness of the DM and PM is 6 mm, and when combined with secretions and necrotic mucosal tissue, there is a potential for complete blockage of the airway, leading to rapid asphyxiation. Although the rabbits were promptly identified when they were experiencing respiratory distress, the unforeseeable nature of this situation delayed intervention and resulted in death.

WBC count analysis for both methods revealed that both techniques could lead to infectious diseases associated with TEF, such as pneumonia. However, the surgical group cannot avoid the infection or inflammation associated with the surgical procedure. In summary, compared to the SM method, the MMC method is simpler, more practical, and induces

less stress response. The MMC technique is conducive to the experimental exploration of treatment methods for TEF in animals.

Study on the feasibility and success rate of the MMC technique

Due to the number of failed cases and to further verify the repeatability and stability of the MMC technique, we increased the sample size and continued our research. Nevertheless, the success rate of the second round of model establishment still did not reach 100%, and similar incidents were encountered. However, based on the experience gained from the first round of modeling, we were fortunate to save one rabbit by removing the magnets that had fallen into the trachea, and it subsequently remained in good condition. Unfortunately, another rabbit suffocated at midnight, as its respiratory issues were not detected in time. Upon necropsy of the rabbits that did not survive the establishment of the model, no significant pathological changes were observed, and the tracheal and esophageal mucosa appeared normal. The exact cause of death remains unclear. The analysis indicated that the modeling success rate was not significantly correlated with the baseline weight or weight changes. The incidences of unexpected death or entry of the magnets into the trachea seemed to be random. A rabbit's weight gradually increases with age, and the diameter of the trachea and esophagus also increases accordingly. This allows for placement of a larger PM, increasing the diameter difference between the DM and PM, which may reduce the occurrence of airway obstruction.

Our work showcases the potential of the MMC technique as a reliable and efficient method for creating TEF models, which can facilitate research on therapeutic interventions, airway management, and the development of novel endoscopic procedures. In clinical practice, patients with TEF often remain asymptomatic following the formation of a fistula. These patients cannot seek immediate medical attention, and many present with symptoms of pneumonia, such as cough, sputum production, and fever, after food or drink enters the airway. Diagnosis typically requires a chest computed tomography scan, gastrointestinal contrast, or bronchoscopy. Among various treatment options, the use of anti-infective therapy is essential[12]. During the second round, it is understandable that one rabbit died on the 2nd day after successful model establishment. Due to the presence of the fistula, food and water can enter the trachea, leading to pneumonia and, in severe cases, systemic inflammatory responses that can be life-threatening. Although the magnets were successfully removed from the target site, the rabbit could not be used for subsequent experiments. Specifically, the success rate of the second round of MMC model established was 80%. Analysis of the WBC count and classification indicated that the rabbits developed infections related to TEF, with no significant difference compared to the first round of modeling. Therefore, it is recommended that animals be observed for several days after successful model establishment before the intervention treatment is employed to simulate the actual clinical diagnosis and treatment.

Method for modeling acquired malignant TEF

Acquired malignant TEF is more common in the clinic and significantly impacts the survival and quality of life of patients with esophageal cancer and other malignancies. Using a transplantable tumor animal model to establish a fistula may involve the local injection of tumor cells to simulate the response of a TEF to various treatment methods in the tumor microenvironment. Nevertheless, this method still has several limitations. First, animals are not immune deficient, and their immune system may eliminate the tumor cells. Second, the time required for tumor growth is relatively long, and the criteria for assessing the success of a malignant TEF model need further clarification. Third, the timing of tumor and fistula model establishment raises questions. If the fistula is created first, the waiting time for tumor growth may be extended, potentially increasing mortality without therapeutic intervention. Conversely, if the tumor model is established first, inserting the magnets may be more difficult. Tumor invasion can render the esophageal mucosa fragile and prone to ulceration, increasing the occurrence of adverse reactions such as magnets falling into the trachea. Therefore, further theoretical exploration and practical research are needed to address these issues.

CONCLUSION

In summary, the MMC method offers the advantages of being noninvasive, precise, and simple, making it more suitable than the SM technique for the establishment of TEF models in small animals. However, it is important to be aware of potential complications that may arise during the magnetic compression procedure, such as magnet blockage in the trachea. These complications can be managed by adjusting the diameter difference between the DM and PM and promptly addressing any issues that arise, which can help improve the model success rate.

FOOTNOTES

Author contributions: Meng H, Kou N, Lv MS, Li JB and Li L designed the research; Meng H, Kou N, Li JB, Nan FY, Hong QY and Zhang BJ performed the research; Meng H wrote the paper, performed data analysis and prepared the first draft of the manuscript; Zou H and Wang HW provided technical support; Li L and Wang HW proofread and revised the manuscript; All the authors have read and approved the final manuscript. Both Wang HW and Li L have played important and indispensable roles in the experimental design, data interpretation and manuscript preparation as the co-corresponding authors. Wang HW conceptualized, designed, and supervised the whole process of the project. He searched the literature, revised and submitted the early version of the manuscript with the focus on how to improve magnetic compression technique. Li L was instrumental and responsible for data re-analysis and re-interpretation, figure plotting, comprehensive literature search, preparation and submission of the current version of the manuscript with a new focus on model evaluation. This collaboration between Wang HW and Li L is crucial for the publication of this manuscript and other manuscripts

still in preparation.

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ORIGINAL ARTICLE

Basic Study

Mesenchymal-epithelial transition factor amplification correlates with adverse pathological features and poor clinical outcome in colorectal cancer

Qiu-Xiao Yu, Ping-Ying Fu, Chi Zhang, Li Li, Wen-Ting Huang

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Abstract

BACKGROUND

Colorectal cancer (CRC) is the third most common cancer and the second most common cause of cancer-related mortality worldwide. Mesenchymal-epithelial transition factor (*MET*) gene participates in multiple tumor biology and shows clinical potential for pharmacological manipulation in tumor treatment. *MET* amplification has been reported in CRC, but data are very limited. Investigating pathological values of *MET* in CRC may provide new therapeutic and genetic screening options in future clinical practice.

AIM

To determine the pathological significance of *MET* amplification in CRC and to propose a feasible screening strategy.

METHODS

A number of 205 newly diagnosed CRC patients undergoing surgical resection without any preoperative therapy at Shenzhen Cancer Hospital of Chinese Academy of Medical Sciences were recruited. All patients were without *RAS/RAF* mutation or microsatellite instability-high. *MET* amplification and c-MET protein expression were analyzed using fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC), respectively. Correlations between *MET* aberration and pathological features were detected using the chi-squared test. Progression free survival (PFS) during the two-year follow-up was detected using the Kaplan-Meier method and log rank test. The results of *MET* FISH and IHC were com-

pared using one-way ANOVA.

RESULTS

Polysomy-induced *MET* amplification was observed in 14.4% of cases, and focal *MET* amplification was not detected. Polysomy-induced *MET* amplification was associated with a higher frequency of lymph node metastasis (LNM) ($P < 0.001$) and higher tumor budding grade ($P = 0.02$). In the survival analysis, significant difference was detected between patients with amplified- and non-amplified *MET* in a two-year follow-up after the first diagnosis ($P = 0.001$). C-MET scores of 0, 1+, 2+, and 3+ were observed in 1.4%, 24.9%, 54.7%, and 19.0% of tumors, respectively. C-MET overexpression correlated with higher frequency of LNM ($P = 0.002$), but no significant difference of PFS was detected between patients with different protein levels. In terms of concordance between *MET* FISH and IHC results, *MET* copy number showed no difference in c-MET IHC 0/1+ (3.35 ± 0.18), 2+ (3.29 ± 0.11) and 3+ (3.58 ± 0.22) cohorts, and the *MET*-to-*CEP7* ratio showed no difference in three groups (1.09 ± 0.02, 1.10 ± 0.01, and 1.09 ± 0.03).

CONCLUSION

In CRC, focal *MET* amplification was a rare event. Polysomy-induced *MET* amplification correlated with adverse pathological characteristics and poor prognosis. IHC was a poor screening tool for *MET* amplification.

Key Words: Colorectal cancer; *MET*; Amplification; Pathological features; Prognosis; Fluorescence *in situ* hybridization

Core Tip: This study aimed to investigate pathological significance of mesenchymal-epithelial transition factor (*MET*) amplification in therapy-naïve colorectal cancer (CRC) and to propose a feasible screening strategy in clinical practice. In CRC harboring no *RAS/RAF* mutation or microsatellite instability, focal *MET* amplification was a rare event, while polysomy-caused *MET* amplification was observed in 14.4% of patients. Polysomy-caused *MET* amplification significantly correlated with frequent lymph node metastasis and higher tumor budding grade, which were two independent predictors of unfavorable CRC survival. Consistently, we discovered that *MET* amplification predicted poor outcome in a two-year follow-up. To our knowledge, this study firstly proved that c-MET immunohistochemistry (IHC) was not a suitable screening tool for *MET* amplification in CRC, and we recommend that tissue should be prioritized for fluorescence in situ hybridization over IHC to determine *MET* amplification.

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INTRODUCTION

The mesenchymal-epithelial transition factor gene (*MET*) is a proto-oncogene located on chromosome 7q21-31 and encodes the receptor for hepatocyte growth factor[1,2]. The aberrant interaction between c-MET and HGF regulates cell survival, proliferation, migration, and differentiation by stimulating the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathways[2,3]. *MET* amplification is relevant to the clinical oncogenesis of diverse tumor types, including lung cancer, gastric cancer and papillary renal cell carcinoma[4,5]. The recognition of *MET* alterations has enhanced the development of *MET* tyrosine kinase inhibitors (TKIs), antibodies, and antibody-drug conjugates, which were actively investigated in numerous clinical trials and showed great potential[6]. Therefore, the identification of tumors that are oncogenically related to *MET* is crucial.

Colorectal cancer (CRC) ranks third in terms of incidence and second in mortality globally[7]. *MET* amplification has been identified in CRC, and the prevalence varies greatly from 2% to 18% due to different detection techniques and criteria applied[8,9]. Moreover, tumor status (therapy-naïve/therapy-resistant, primary/metastasis, mutated/wide-type) are important variables that must be considered. In CRC, the most commonly discussed function of *MET* amplification is an acquired feedback of the activation of PI3K/AKT and MAPK cascades in patients with resistance to anti-epidermal growth factor receptor (EGFR) therapies[10,11]. However, data on *de novo MET* amplification in therapy- naïve CRC biology are very limited. The incidence of *de novo MET* amplification and clinical values in newly diagnosed CRC patients need to be investigated.

In this study, we examined the incidence, pathological and prognostic significance of *de novo MET* amplification and c-MET expression in therapy- naïve CRC patients. We also investigated the correlation between *MET* fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC) results to propose an efficient screening strategy for future clinical gene detection.

MATERIALS AND METHODS

Patients

From May 2020 to December 2021, 205 newly diagnosed CRC patients who underwent complete surgical resection without any preoperative therapy at Shenzhen Cancer Hospital of Chinese Academy of Medical Sciences were recruited. The criteria for selecting these patients were: (1) Diagnosed as having primary malignant CRC with relevant clinicopathological features; (2) being without other tumors diagnosed simultaneously; and (3) being *RAS/RAF* wild-type and microsatellite stable. The study was performed in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the ethics committee of Shenzhen Cancer Hospital of Chinese Academy of Medical Sciences. Informed consent was obtained from all patients.

Assessment of histological features

The pathological profiles of patients were obtained from medical records, including gender, age, primary tumor site, histological tumor type, differentiation grade, tumor stage, presence, or absence of lymphovascular invasion (LVI), perineural invasion (PNI), extramural venous invasion (EMVI), lymph node metastasis (LNM), poorly differentiated clusters (PDC), and tumor budding (TB). All samples were sliced at 4 μm to obtain histological sections that were further stained with haematoxylin and eosin (H&E). All H&E slides were reviewed by two experienced pathologists. LVI was defined by the presence of tumor cells within endothelium-lined lymphatic or vascular channels[12]. PNI was defined as tumor cells found within the perineural space or the infiltration of cancer cells into the endoneurium[13]. EMVI was defined as the presence of tumor cells within an endothelium-lined space that was either surrounded by a rim of muscle or contains red blood cells[14]. PDC was defined as small group of more than five cancer cells in tumor stroma without gland formation[15]. TB was defined as the presence of cancer cells detached from the main tumor either as single cells or as clusters of fewer than five cells[16]. According to the three-tier system proposed by the ITBCC, all samples were divided into three categories: 0-4 buds (BD1), 5-9 buds (BD2) and 10 or more buds (BD3) based on the quantification of the buds at the hotspot (in a field measuring 0.785 mm^2)[17].

FISH assay and interpretation

After reviewing H&E slides, representative formalin-fixed-paraffin-embedded (FFPE) tumor blocks were selected to determine *MET* amplification following the manufacturer's protocol[18]. Briefly, the FFPE slides were pretreated using the Vysis paraffin pretreatment IV & post-hybridisation wash buffer kit (Abbott Molecular, Inc.; 01N31-005) after dewaxing and dehydration. A mixture of the *MET* (7q31) probe and centromere 7q (*CEP7*) probe (Abbott Molecular, Inc.; 06N05-020, 06J37-007) was added to the target tissue areas, and the slides were processed using the ThermoBrite Denaturation/Hybridization System (Abbott Molecular, Inc.). FISH signals were reviewed under a fluorescence microscope at a magnification of 600 × (Leica Microsystems GmbH). Two major methods were used to define *MET* amplification. A: *MET* amplification was classified as the presence of 5 or more copies of *MET* signal per cell [*MET* gene copy number (GCN) ≥ 5] using the Cappuzzo criteria[19]; B: Tumors with a *MET*/*CEP7* ≥ 2 were defined as *MET* amplification using PathVysion criteria, which is also termed focal amplification[20].

IHC staining and evaluation

Same blocks were selected for c-MET IHC staining. The experiment was performed using the CONFIRM anti-total c-MET (SP44) rabbit monoclonal primary antibody (Ventana Medical Systems, Tucson, AZ; 790-4430) with a Ventana BenchMark XT automated slide processing system according to the manufacturer's protocol. A pathologist without knowing the clinical information independently evaluated all stained slides. C-MET IHC was evaluated according to the scoring criteria established by Spigel *et al*[21] based on staining intensity (negative, weak, moderate, or strong) and the prevalence of these intensities in tumor cells. The following four subgroups were defined: 0 (no staining or < 50% of tumor cells with any intensity); 1+ (≥ 50% of tumor cells with weak or higher staining but < 50% with moderate or higher intensity); 2+ (≥ 50% of tumor cells with moderate or higher staining but < 50% with strong intensity); and 3+ (≥ 50% of tumor cells staining with strong intensity)[21].

Statistical analysis

The relationships between clinicopathological features and *MET* amplification or c-MET protein expression were detected using the chi-squared test in SPSS software version 15.0 (SPSS, Inc). Progression free survival (PFS) was determined using the Kaplan-Meier method, and survival curves were compared using log rank test. The comparison of *MET* GCN and *MET/CEP7* between different c-MET IHC groups was performed using one-way ANOVA with GraphPad Prism software version 5.0 (GraphPad Software, Inc.). *P* values < 0.05 were considered significant.

RESULTS

General information

A total of 205 CRC patients were included in this study, and all patients had surgical resection tissue samples that were adequate for FISH and IHC analyses. The pathological characteristics of the patients are summarized in Table 1. The median age of disease onset was 60 years (range: 24 to 93 years), and the male-to-female ratio was 1.2. A total of 140 (68.3%) tumors occurred in the colon, and 65 (31.7%) occurred in the rectum. There were 151 (73.7%) tumors defined as

exophytic type, and 54 (26.3%) as ulcerative type. The incidences of LVI, PNI, EMVI, LNM, and PDC in our cohort were 31.2%, 28.3%, 15.1%, 43.4%, and 74.1% respectively. In terms of TB, 117 (57.1%) were categorized into BD1, 40 (19.5%) were BD2, and 48 (23.4%) were BD3. Fifty-three (25.9%) CRC patients had poorly differentiated or mucinous carcinoma. According to the criteria of TNM staging after surgery, there were 34 (16.6%) patients with stage I disease, 72 (35.1%) patients with stage II, 80 (39.0%) patients with stage III, and 19 (9.3%) patients with stage IV.

MET amplification and c-MET expression in CRC patients

Of all the 205 cases detected, 195 showed interpretable FISH results. Following Cappuzzo criteria, 28 (14.4%) cases were defined as *MET* amplification (*MET* copy number ≥ 5) (Figure 1A and B). The PathVysion criteria indicated that the *MET*/*CEP7* ratio was less than 2.0 in all 195 cases (Table 1). These data suggested that chromosome 7 polysomy, rather than focal gene amplification, was preferentially detected in primary lesions of therapy- naïve CRC patients. C-MET IHC was successfully performed in all 205 samples, and immunoreactivity was predominantly observed in the cytoplasm and membrane (Figure 1C-F). C-MET scores of 0, 1+, 2+, and 3+ were observed in 3 (1.4%), 51 (24.9%), 112 (54.7%), and 39 (19.0%) tumors, respectively (Table 1).

Correlation between *MET* amplification, c-MET expression, and clinicopathological features in CRC patients

Polysomy-induced *MET* amplification significantly correlated with frequent LNM ($P < 0.001$) and higher grade of TB ($P = 0.02$), while there were no significant differences regarding gender, age, tumor site, tumor type, LVI, PNI, EMVI, and PDC ($P > 0.05$) (Table 2).

In terms of c-MET expression, significant correlation was detected between high c-MET IHC scores and occurrence frequency of LNM ($P = 0.002$), while there was no significant difference regarding other pathological features (Table 3).

The significance of *MET* amplification and c-MET expression for patients' survival

During a two-year follow-up after first diagnosis, 7 out of 28 (25%) CRC patients with *de novo MET* amplification experienced tumor recurrence or metastasis, while 11 patients were lost to follow up. In 167 patients with non-amplified *MET*, 13 (7.8%) had tumor recurrence or metastasis, and 58 were lost to follow up. In Kaplan-Meier analysis, significant difference in PFS was found between patients with positive-FISH and negative-FISH in our cohort ($P = 0.003$) (Figure 2A). The relationship between c-MET expression level and PFS was also investigated, and the recurrence/metastasis rates in group 0/1+, 2+ and 3+ were 11.8% (6/51), 10% (11/110), and 7.9% (3/38) respectively. No significant difference was detected between three IHC groups ($P = 0.863$) (Figure 2B).

c-MET IHC is a poor screening tool for *MET* amplification in CRC

Of the 28 (14.4%) patients with polysomy-induced *MET* amplification, 9 (32%), 10 (36%), and 9 (32%) patients had c-MET immunoscore of 0/1+, 2+ and 3+, respectively. *MET* FISH was negative in 167 (85.6%) patients, and 41 (24.0%), 98 (59.0%), and 28 (17.0%) were defined as c-MET IHC 0/1+, 2+ and 3+ (Figure 3A). The mean ± SEM of *MET* copy number showed no difference in the c-MET IHC 0/1+ (3.35 ± 0.18), 2+ (3.29 ± 0.11) and 3+ (3.58 ± 0.22) cohorts (Figure 3B). The *MET*-to-*CEP7* ratio showed no difference in these three groups (1.09 ± 0.02, 1.10 ± 0.01, and 1.09 ± 0.03) (Figure 3C).

DISCUSSION

Dysregulated *MET* signalling participates in tumor biology and may occur *via* various mechanisms, including protein overexpression, gene amplification and mutation[22]. In non-small cell lung cancer (NSCLC), *de novo MET* amplification occurs in 2%-4% of patients as primary oncogenic driver[4], and acquired *MET* amplification was detected in 10%-15% as a response to anti-EGFR drugs[23-25]. Various clinical guidelines recommended *MET* amplification as an actionable molecular target in the genetic profiling of NSCLC[26]. In CRC, *MET* amplification is less discussed. Cremolini *et al*[27] observed *MET* amplification in 8.5% of resistant CRC cases and suggested that acquired *MET* amplification might drive resistance to anti-EGFR antibodies in CRC patients. However, the role of *de novo MET* amplification in primary lesions of therapy-naïve CRC patients remains elusive, and validation of *MET* amplification in this cohort is critical to this field.

Our study detected *MET* amplification using FISH, the gold standard for gene copy detection. Currently, there is no consensus on the standardized cut-off value of *MET* amplification. In clinical trials, two major methods are commonly used. The first one by Cappuzzo *et al*[19] defines *MET* amplification as *MET* GCN ≥ 5, while other studies use GCN ≥ 6 [28] or ≥ 15[29] as cut-offs. In our study, 14.4% of CRC had *MET* amplification (GCN range: 5.05-6.25) based on Cappuzzo criteria. Another research using PCR assay reported a *MET* amplification rate of 9% in primary CRC lesions[9]. This PCR-based method defined tumor as amplified when the GCN was ≥ 3 times the mean of the corresponding normal tissue. The data discrepancy between this study and ours may be explained by the different methodologies and interpretation criteria. One drawback of the GCN method is that focal amplification cannot be distinguished from polysomy. The second method calculates the ratio of *MET*-to-*CEP7* and identifies focal *MET* amplification as *MET*/*CEP7* ≥ 2.0[30,31]. Some clinical trials categorize amplified degree more accurately into three groups: Low (≥ 1.8 to ≤ 2.2); intermediate (> 2.2 to < 5.0); and high (≥ 5.0)[32]. The *MET*/*CEP7* ratio in our cohort ranged from 0.60 to 1.64, and no sample had focal amplification. Our data indicated that in primary CRC lesions exposed to no treatment, *MET* amplification occurred primarily *via* polysomy instead of focal gene duplication. Consistently with our data, Raghav *et al*[11] reported that the rate of focal *MET* amplification was 0% and 1.9% in resected liver metastases of two therapy-naïve CRC cohorts, indicating that focal *MET* amplification was a rare event in therapy-naïve CRC.

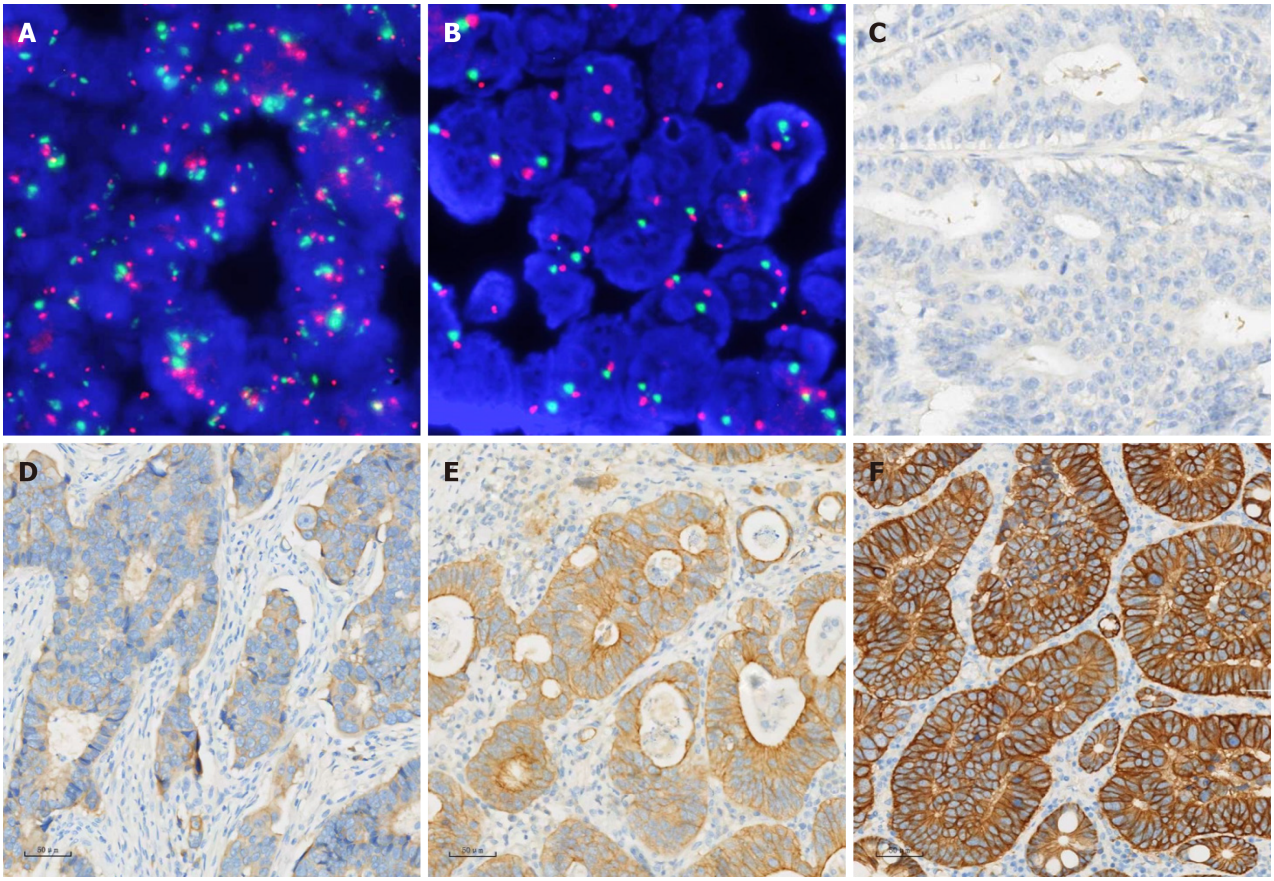

Figure 1 C-mesenchymal-epithelial transition factor immunohistochemistry (20 ×) and mesenchymal-epithelial transition factor fluorescence in situ hybridization (100 ×) results. A: Mesenchymal-epithelial transition factor (*MET*) fluorescence in situ hybridization (FISH) positive (*MET* gene copy number ≥ 5 and *MET*/*CEP7* < 2); B: *MET* FISH negative (*MET* gene copy number < 5 and *MET*/*CEP7* < 2); C: Immunohistochemistry (IHC) 0; D: IHC 1+; E: IHC 2+; F: IHC 3+.

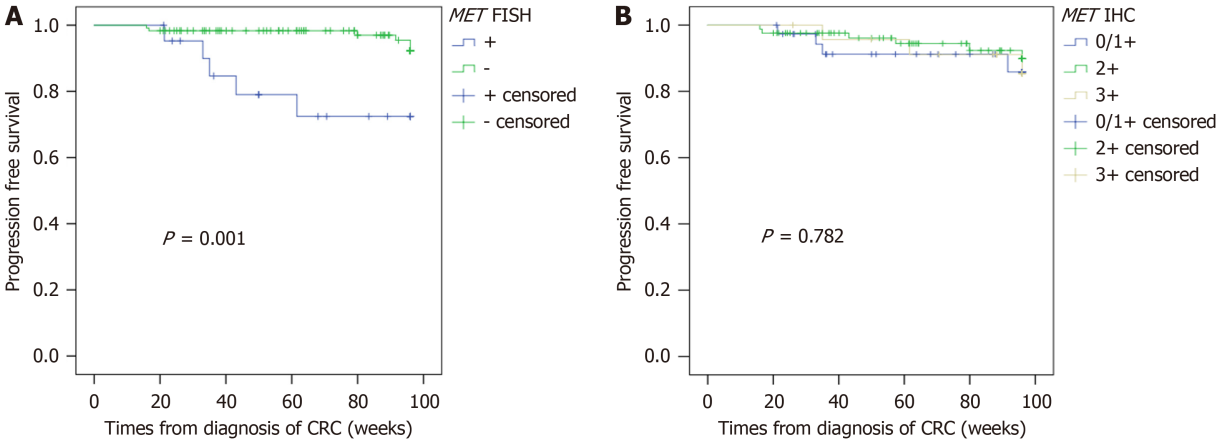

Figure 2 Kaplan-Meier curve of progression free survival for colorectal cancer patients in a two-year follow-up. A: Progression free survival (PFS) in colorectal cancer (CRC) patient with amplified-mesenchymal-epithelial transition factor (*MET*) and non-amplified *MET*; B: PFS in CRC patient with different c-MET protein levels. *MET*: Mesenchymal-epithelial transition factor; FISH: Fluorescence *in situ* hybridization; IHC: Immunohistochemistry.

Our study demonstrated that polysomy-induced *MET* amplification significantly correlated with LNM and TB, which were two independent predictors of unfavorable survival in CRC patients[33]. Consistently, during the two-year follow up in our study, we found that the recurrence/metastasis rate in *MET*-amplified CRC was higher in *MET*-non-amplified CRC, and the Kaplan-Meier curve also showed significant difference between these two populations. Hence, we suggested that *MET* amplification was considered to predict a poor prognosis in CRC without *RAS/RAF* mutation or microsatellite instability-high (MSI-H). In terms of c-MET protein, our data revealed a correlation between c-MET overexpression and high frequency of LNM, but no significant difference was detected in patients' outcome during the two-year

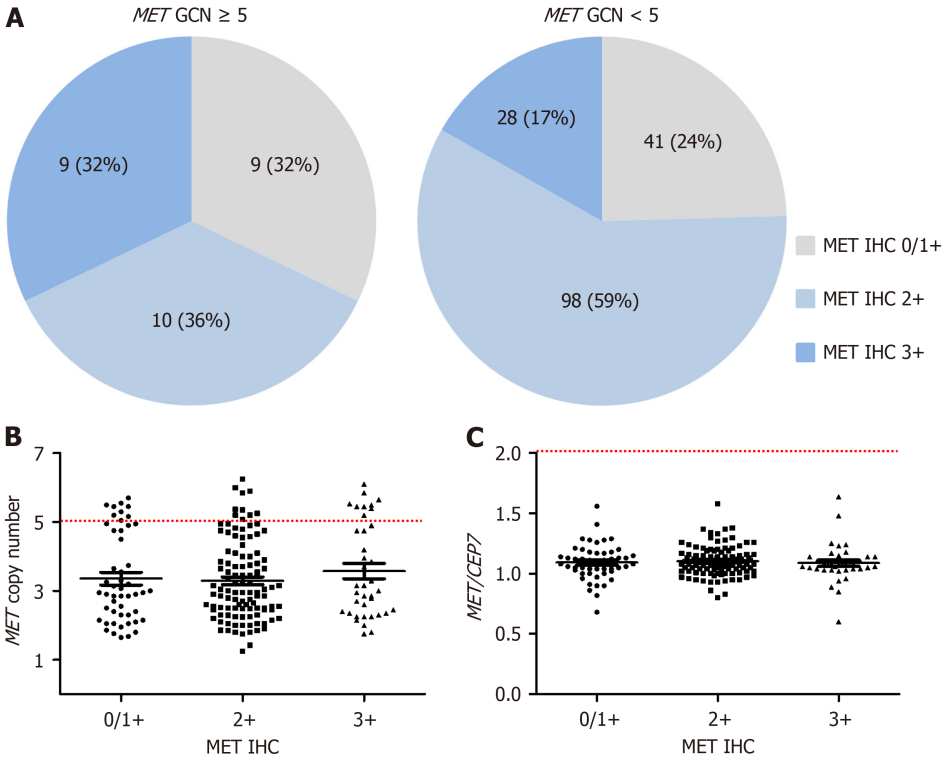

Figure 3 Comparison between mesenchymal-epithelial transition factor fluorescence in situ hybridization and immunohistochemistry results. A: The c-mesenchymal-epithelial transition factor (MET) immunohistochemistry (IHC) status in *MET* fluorescence in situ hybridization positive and negative cases; B: The scatter plot representations of *MET* gene copy number in different c-MET IHC groups; C: The scatter plot representations of *MET*/*CEP7* ratios in different c-MET IHC groups. *MET*: Mesenchymal-epithelial transition factor; GCN: Gene copy number; IHC: Immunohistochemistry.

follow-up. Currently, the prognostic value of c-MET still remains controversial. A systematic review of 11 retrospective studies found that high c-MET expression significantly predicted poor OS and PFS in 1895 CRC patients[34]. Another study conducted by Lai *et al*[35] demonstrated no significant difference in overall survival time between c-MET-high and c-MET-low tumors, which was similar to our finding. The contradiction between these studies may be attributed to different IHC scoring system applied and cohorts studied. In our study, we chose clinical score system established by Spigel *et al*[21], which was applied in multiple clinical trials investigating drug efficacy of *MET* inhibitors[36-38].

MET amplification may be an efficient indicator in future targeted therapies in CRC patients, therefore a feasible screening strategy should be established. IHC can be adopted as a screening tool in clinical practice for certain gene amplifications[39]. For example, HER-2 protein overexpression using IHC shows high concordance with gene amplification by FISH[40,41]. Therefore, we tried to figure out whether c-MET IHC was a predictive marker for amplification. No clear association between FISH and IHC was observed based on our data, indicating that IHC is not a screening tool for *MET* amplification in CRC. Similar conclusions were presented in lung cancer. A study of 81 lung sarcomatoid carcinomas showed that c-MET IHC correlated poorly with *MET* amplification (GCN ≥ 5 or *MET*/*CEP7* ≥ 2)[42]. Another tri-institutional study tested 181 lung adenocarcinoma tissues and demonstrated that most c-MET IHC-positive cases were negative for *MET* amplification, and IHC missed patients with *MET* amplification, indicating that IHC was not a reliable screening tool for *MET* amplification in lung cancer[25]. The discordance between c-MET overexpression and amplification may be explained in two aspects: (1) *MET* amplification caused by low-level polysomy does not result in substantial protein expression; and (2) other than gene amplification, hypoxia or inflammation also induces c-MET protein expression by amplifying HGF signalling, including increasing autocrine or paracrine HGF, or stimulating an HGF activator or other epigenetic regulations[43-45].

Our study has some limitations. Firstly, patients were retrospectively recruited from single institution and the two years of follow-up was not long enough to fully assess the prognostic values of either *MET* amplification or c-MET overexpression. In addition, the pharmacological significance of polysomy-induced *MET* amplification in CRC patients still remains unclear. Therefore, future research directions could be: (1) The long-term prognostic significance of *MET* amplification and c-MET overexpression in CRC patients harboring no other classic gene mutations (*RAS/RAF* or MSI-H); and (2) the drug efficacy of *MET*-TKIs and other *MET* inhibitors in CRC patients with *MET* GCN ≥ 5.

CONCLUSION

Focal *MET* amplification was a rare event in primary lesions of therapy-naïve CRC, and polysomy-caused *MET* amplification was observed in 14.4% of this population. Both *MET* amplification and c-MET overexpression correlated with

Table 1 Histological and clinical characteristics of colorectal cancer patients, *n* (%)

Variable	Value
Gender	
Male	112 (54.6)
Female	93 (45.4)
Age (yr)	
≥ 60	106 (51.7)
< 60	99 (48.3)
Primary site	
Colon	140 (68.3)
Rectum	65 (31.7)
Tumor type	
Exophytic type	151 (73.7)
Ulcerative type	54 (26.3)
LVI	
Present	64 (31.2)
Absent	141 (68.8)
PNI	
Present	58 (28.3)
Absent	147 (71.7)
EMVI	
Present	31 (15.1)
Absent	174 (84.9)
LNM	
Present	89 (43.4)
Absent	116 (56.6)
PDC	
Present	152 (74.1)
Absent	53 (25.9)
TB	
BD1	117 (57.1)
BD2	40 (19.5)
BD3	48 (23.4)
Histologic differentiation	
P/D or mucinous	53 (25.9)
M/D	142 (69.3)
W/D	10 (4.9)
Tumor stage	
I	34 (16.6)
II	72 (35.1)
III	80 (39.0)
IV	19 (9.3)
c-MET immunohistochemistry	

0	3 (1.4)
1+	51 (24.9)
2+	112 (54.7)
3+	39 (19.0)
MET FISH (Cappuzzo criteria)	
MET GCN ≥ 5	28 (14.4)
MET GCN < 5	167 (85.6)
MET FISH (PathVysion criteria)	
MET/*CEP7* ≥ 2	0 (0.0)
MET/*CEP7* < 2	195 (100.0)

EMVI: Extramural venous invasion; GCN: Gene copy number; LNM: Lymph node metastasis; LVI: Lymphovascular invasion; M/D: Moderately differentiated; P/D: Poorly differentiated; PDC: Poorly differentiated clusters; PNI: Perineural invasion; TB: Tumor budding; W/D: Well differentiated.

Table 2 Correlations between polysomy-caused mesenchymal-epithelial transition factor amplification and clinicopathological characteristics of colorectal cancer patients, *n* (%)

Characteristic	*MET* FISH			*P* value
	Positive *MET* GCN ≥ 5 (*n* = 28)	Negative *MET* GCN < 5 (*n* = 167)	Total (*n* = 195)	
Gender				0.975
Male	15 (53.60)	90 (53.90)	105 (53.80)	
Female	13 (12.90)	77 (46.21)	90 (46.20)	
Age (yr)				0.085
≥ 60	19 (67.90)	84 (50.30)	103 (52.80)	
< 60	9 (32.10)	83 (49.70)	92 (47.20)	
Primary site				0.077
Colon	23 (82.10)	109 (65.30)	132 (67.70)	
Rectum	5 (17.90)	58 (34.70)	63 (32.30)	
Tumor type				0.187
Exophytic type	18 (64.30)	127 (76.00)	145 (74.40)	
Ulcerative type	10 (35.70)	40 (24.00)	50 (25.60)	
LVI				0.261
Present	11 (39.30)	48 (28.70)	59 (30.30)	
Absent	17 (60.70)	119 (71.30)	136 (69.70)	
PNI				0.377
Present	10 (35.70)	46 (27.50)	56 (28.70)	
Absent	18 (64.30)	121 (72.50)	139 (71.30)	
EMVI				0.500
Present	6 (21.40)	24 (14.40)	30 (15.40)	
Absent	22 (78.60)	143 (85.60)	165 (84.60)	
LNM				< 0.001
Present	21 (75.00)	60 (35.90)	81 (41.50)	
Absent	7 (25.00)	107 (64.10)	114 (58.50)	

PDC				0.153
Present	24 (85.70)	122 (73.10)	146 (74.90)	
Absent	4 (14.30)	45 (26.90)	49 (25.10)	
TB				0.020
BD1	10 (35.70)	99 (59.30)	109 (55.9)	
BD2/3	18 (64.30)	68 (40.70)	86 (44.10)	
Histologic differentiation				0.933
P/D or mucinous	7 (25.00)	43 (25.70)	50 (25.60)	
W/D or M/D	21 (75.00)	124 (74.30)	145 (74.40)	

MET: Mesenchymal-epithelial transition factor; EMVI: Extramural venous invasion; GCN: Gene copy number; LNM: Lymph node Metastasis; LVI: Lymphovascular invasion; M/D: Moderately differentiated; P/D: Poorly differentiated; PDC: Poorly differentiated clusters; PNI: Perineural invasion; TB: Tumor budding; W/D: Well differentiated.

Table 3 Correlations between c-mesenchymal-epithelial transition factor protein expression and clinicopathological characteristics of colorectal cancer patients, *n* (%)

Characteristic	C-MET IHC				*P* value
	0/1+ (*n* = 54)	2+ (*n* = 112)	3+ (*n* = 39)	Total (*n* = 205)	
Gender					0.525
Male	33 (61.1)	58 (51.8)	21 (53.8)	112 (54.6)	
Female	21 (38.9)	54 (48.2)	18 (46.2)	93 (45.4)	
Age (yr)					0.138
≥ 60	33 (61.1)	51 (45.4)	22 (56.4)	106 (51.7)	
< 60	21 (38.9)	61 (54.5)	17 (43.6)	99 (48.3)	
Primary site					0.805
Colon	38 (70.4)	77 (68.8)	25 (64.1)	140 (68.3)	
Rectum	16 (29.6)	35 (31.3)	14 (35.9)	65 (31.7)	
Tumor type					0.656
Exophytic type	39 (72.2)	81 (72.3)	31 (79.5)	151 (73.7)	
Ulcerative type	15 (27.8)	31 (27.7)	8 (20.5)	54 (26.3)	
LVI					0.941
Present	17 (31.5)	34 (30.4)	13 (33.3)	64 (31.2)	
Absent	37 (68.5)	78 (69.6)	26 (66.7)	141 (68.8)	
PNI					0.897
Present	15 (27.8)	33 (29.5)	10 (25.6)	58 (28.3)	
Absent	39 (72.2)	79 (70.5)	29 (74.4)	147 (71.7)	
EMVI					0.252
Present	5 (9.3)	21 (18.8)	5 (12.8)	31 (15.1)	
Absent	49 (90.7)	91 (81.3)	34 (87.2)	174 (84.9)	
LNM					0.002
Present	18 (33.0)[1]	56 (50.0)[1]	25 (64.1)[1]	89 (43.4)	
Absent	36 (67.0)[1]	56 (50.0)[1]	14 (35.9)[1]	116 (56.6)	
PDC					0.188
Present	35 (64.8)	87 (77.7)	30 (76.9)	152 (74.1)	

Absent	19 (35.2)	25 (22.3)	9 (23.1)	53 (25.9)	
TB					0.148
BD1	34 (63.0)	66 (58.9)	17 (43.6)	117 (57.1)	
BD2/3	20 (37.0)	46 (41.1)	22 (56.4)	88 (42.9)	
Histologic differentiation					0.541
P/D or mucinous	17 (31.5)	27 (24.1)	9 (23.1)	53 (25.9)	
W/D or M/D	37 (68.5)	85 (75.9)	30 (76.9)	152 (74.1)	

[1]Each superscript letter denotes a subset of MET mesenchymal-epithelial transition factor immunohistochemistry categories whose column proportions do not differ significantly from each other at the 0.05 level.
MET: Mesenchymal-epithelial transition factor; EMVI: Extramural venous invasion; LNM: Lymph node metastasis; LVI: Lymphovascular invasion; M/D: Moderately differentiated; P/D: Poorly differentiated; PDC: Poorly differentiated clusters; PNI: Perineural invasion; TB: Tumor budding; W/D: Well differentiated.

adverse clinicopathological features in CRC. *MET* amplification predicted poor clinical outcome. C-MET IHC was not a suitable tool for *MET* amplification screening, and we firstly recommend that tissue should be prioritised for FISH over IHC to determine *MET* amplification in CRC.

FOOTNOTES

Author contributions: Yu QX and Li L designed the research study; Yu QX performed the research; Fu PY and Zhang C contributed new reagents and analytic tools; Yu QX analyzed the data; Yu QX and Huang WT wrote the manuscript; and all authors have read and approve the final manuscript.

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META-ANALYSIS

Evaluating effectiveness and safety of combined percutaneous transhepatic gallbladder drainage and laparoscopic cholecystectomy in acute cholecystitis patients: Meta-analysis

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Abstract

BACKGROUND

Acute cholecystitis (AC) is a common disease in general surgery. Laparoscopic cholecystectomy (LC) is widely recognized as the "gold standard" surgical procedure for treating AC. For low-risk patients without complications, LC is the recommended treatment plan, but there is still controversy regarding the treatment strategy for moderate AC patients, which relies more on the surgeon's experience and the medical platform of the visiting unit. Percutaneous transhepatic gallbladder puncture drainage (PTGBD) can effectively alleviate gallbladder inflammation, reduce gallbladder wall edema and adhesion around the gallbladder, and create a "time window" for elective surgery.

AIM

To compare the clinical efficacy and safety of LC or PTGBD combined with LC for treating AC patients, providing a theoretical basis for choosing reasonable surgical methods for AC patients.

METHODS

In this study, we conducted a clinical investigation regarding the combined use of PTGBD tubes for the treatment of gastric cancer patients with AC. We performed searches in the following databases: PubMed, Web of Science, EMBASE, Cochrane Library, China National Knowledge Infrastructure, and Wanfang Database. The search encompassed literature published from the inception of these databases to the present. Subsequently, relevant data were extracted, and a meta-analysis was conducted using RevMan 5.3 software.

RESULTS

A comprehensive analysis was conducted, encompassing 24 studies involving a

total of 2564 patients. These patients were categorized into two groups: 1371 in the LC group and 1193 in the PTGBD + LC group. The outcomes of the meta-analysis revealed noteworthy disparities between the PTGBD + LC group and the LC group in multiple dimensions: (1) Operative time: Mean difference (MD) = 17.51, 95%CI: 9.53-25.49, $P < 0.01$; (2) Conversion to open surgery rate: Odds ratio (OR) = 2.95, 95%CI: 1.90-4.58, $P < 0.01$; (3) Intraoperative bleeding loss: MD = 32.27, 95%CI: 23.03-41.50, $P < 0.01$; (4) Postoperative hospital stay: MD = 1.44, 95%CI: 0.14-2.73, $P = 0.03$; (5) Overall postoperative compli-cation rate: OR = 1.88, 95%CI: 1.45-2.43, $P < 0.01$; (6) Bile duct injury: OR = 2.17, 95%CI: 1.30-3.64, $P = 0.003$; (7) Intra-abdominal hemorrhage: OR = 2.45, 95%CI: 1.06-5.64, $P = 0.004$; and (8) Wound infection: OR = 0. These find-ings consistently favored the PTGBD + LC group over the LC group. There were no significant differences in the total duration of hospitalization [MD = -1.85, 95%CI: -4.86-1.16, $P = 0.23$] or bile leakage [OR = 1.33, 95%CI: 0.81-2.18, $P = 0.26$] between the two groups.

CONCLUSION

The combination of PTGBD tubes with LC for AC treatment demonstrated superior clinical efficacy and enhanced safety, suggesting its broader application value in clinical practice.

Key Words: Acute cholecystitis; Laparoscopic cholecystectomy; Percutaneous transhepatic gallbladder drainage; Meta-analysis; Efficacy

Core Tip: Laparoscopic cholecystectomy (LC) is the standard surgical procedure for treating acute cholecystitis (AC), but postoperative complications and patient mortality are relatively high. Percutaneous transhepatic gallbladder drainage (PTGBD) can quickly drain infected bile, reduce gallbladder tension, and is often used in combination with delayed LC in clinical practice, but PTGBD is associated with more adverse long-term outcomes. The meta-analysis results of this study showed that the combination of PTGBD and LC for the treatment of AC has short surgical time, low conversion rate to open surgery, less intraoperative bleeding, and low overall incidence of complications, which is worthy of promotion.

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INTRODUCTION

Acute cholecystitis (AC) is a prevalent acute abdominal pathology in general surgery and is predominantly attributed to etiologies such as gallstones, bile stasis, and bacterial infections. With the rapid advancements in laparoscopic technologies, laparoscopic cholecystectomy (LC) has emerged as the standard surgical approach, superseding open cholecystectomy for gallbladder pathologies. Despite this progress, mortality rates in high-risk cohorts remain substantial, ranging between 3.7% and 41.0%[1]. Percutaneous transhepatic gallbladder drainage (PTGBD) is an expedited method for draining infected bile, thereby alleviating gallbladder tension and reducing the risk of rupture due to bile-induced chemical irritation. This approach effectively diminishes toxin absorption, mitigates gallbladder obstruction, and stabilizes the disease trajectory, with some patients attaining complete resolution[2]. LC is the preferred modality for uncomplicated, low-risk patients[3]. However, in moderate AC scenarios, characterized by potential organ failure and significant local inflammatory adhesions, the combination of PTGBD with delayed LC appears more judicious[4]. Despite its utility, PTGBD is not an unequivocal therapeutic modality and is linked to less favorable long-term results, including prolonged hospitalization periods and heightened rates of readmission[5,6]. International guidelines exhibit variability in recommending LC over PTGBD for AC management[3,7,8]. Additionally, most of the current domestic and international research on the combination of PTGBD and LC for treating AC has involved single-center studies with small sample sizes. In this study, we sought to perform a comparative evaluation of the clinical effectiveness and safety of LC and the combination of PTGBD and LC in the management of AC by employing an evidence-based medicine framework. This comparison was intended to provide a theoretical basis for appropriately selecting surgical methods for patients with AC.

MATERIALS AND METHODS

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Study type: Clinical randomized controlled trials (RCTs); (2) Subjects: Patients

diagnosed with AC; (3) Intervention: Control group receiving LC; Experimental group receiving PTGBD combined with LC; and (4) Outcome measures: Clinical efficacy indicators, including operative time, intraoperative blood loss, conversion to open surgery rate, postoperative and total hospital stay; safety indicators, including overall postoperative complication rate, and incidence of bile leakage, bile duct injury, intra-abdominal hemorrhage, and wound infection. The exclusion criteria were as follows: (1) Basic research, abstracts, conference papers, reviews, meta-analyses, systematic reviews, or case reports; (2) Literature not in Chinese or English; (3) Duplicate publications, including studies that were republished or similar in research direction by the same author; (4) Studies with a sample size of fewer than 20 subjects; and (5) Literature where the full text was unavailable, inappropriate statistical methods were used, data could not be extracted, or data were incomplete.

Literature search strategy

Through computerized searches, we conducted an extensive exploration across a multitude of databases, including PubMed, Web of Science, EMBASE, Cochrane Library, China National Knowledge Infrastructure, and Wanfang, with the aim of identifying RCTs pertaining to the combined management of AC using PTGBD and LC. Our search strategy included specific English terms, including "acute cholecystitis" or "AC", "laparoscopic cholecystectomy" or "LC" and "percutaneous transhepatic gallbladder" or "PTGBD". The corresponding Chinese search terms included: Acute cholecystitis, laparoscopic cholecystectomy, percutaneous transhepatic gallbladder puncture and drainage, alongside others. Our search efforts spanned from the inception of these databases to the present day. This manuscript was meticulously crafted in accordance with the directives set forth in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Furthermore, our systematic review has been officially registered with PROSPERO under Registration No. 2023110106.

Data extraction

Two researchers carried out a thorough and independent literature screening process following preestablished inclusion and exclusion criteria. Initially, they meticulously scrutinized the titles and abstracts to exclude studies that were evidently unrelated to the research focus. Following this initial screening, the full texts of potentially relevant studies underwent a comprehensive review to validate their eligibility. Any discrepancies that emerged during this process were resolved through consultation with a third researcher. The data extraction procedure encompassed critical details, including the titles of the included literature, authors, publication journals, publication year, study sample size, inclusion periods for samples, treatment modalities, outcome measures, and other pertinent information.

Quality assessment of the included studies

We utilized the Newcastle-Ottawa scale (NOS) to evaluate the methodological quality of the included studies. The NOS assessment criteria encompass the following dimensions: The selection of study groups (comprising 4 items with a maximum score of 4 points), comparability of the groups (1 item with a potential score of up to 2 points), and assessment of outcomes (comprising 3 items with a potential score of up to 3 points). The highest achievable score was 9 points, with a score of ≥ 6 points indicating high-quality literature.

Statistical analysis

The data were analyzed utilizing RevMan 5.3 software for meta-analysis. For dichotomous variables, odds ratios (ORs) in combination with 95%CI were utilized as the primary outcome measures. For continuous variables, the mean difference (MD) and 95%CI were used. The assessment of study heterogeneity was performed using the I^2 statistic. A fixed-effects model was adopted when P was ≥ 0.1 and I^2 was < 50%, while a random-effects model was utilized when P was < 0.1 and I^2 was ≥ 50%. The sources of heterogeneity were meticulously investigated, and publication bias was evaluated through funnel plot analysis. A P value < 0.05 was considered to indicate statistical significance.

RESULTS

Literature search results

According to the literature search strategy, a comprehensive search across various databases was conducted. Initially, 672 articles were identified. After removal of duplicates, 235 articles were excluded. After scrutinizing the titles and abstracts, 369 articles were subsequently excluded. After thorough examination of the full texts and additional assessment, 43 articles were eliminated due to inappropriate intervention measures or data that could not be extracted. Overall, a total of 24 articles were included in this study. The details of the literature selection process and its outcomes are depicted in Figure 1.

Basic characteristics of the included studies

In the course of this investigation, of the 24 articles that were included, 7 were published in Chinese, while the remaining 17 were published in English. These articles collectively encompassed a cohort of 2564 patients, with 1371 allocated to the control group and 1193 to the experimental group. Table 1 provides a comprehensive overview of the fundamental characteristics of the studies included in this analysis.

Table 1 Overview of the included study characteristics

Ref.	Country	LC	Timing of LC after admission	PTGBD + LC	Time of LC after PTGBD	NOS
Duan and Li[9], 2021	China	44	Immediately	48	Within 1-3 months	8
Hao and Fan[10], 2022	China	82	Within 24 h	118	Within 1-3 months	8
Liu[11], 2018	China	40	Not specified	40	Simultaneous	8
Ma *et al*[12], 2020	China	57	Not specified	57	After 1 month	7
Wu and Kuang[13], 2017	China	20	Within 3 months	14	Within 3 months	8
Zhan *et al*[14], 2023	China	38	Not specified	38	4-6 wk	8
Zhou *et al*[15], 2019	China	47	Within 3 h	47	3-9 wk	8
El-Gendi *et al*[16], 2017	Egypt	75	After 72 h	75	6 wk	8
Chikamori *et al*[17], 2002	Japan	9	Not specified	31	Not specified	7
Choi *et al*[18], 2012	Korea	63	Within 72 h	40	Average 7.9 d	8
Hu *et al*[19], 2015	China	35	Not specified	35	6-10 wk	8
Jung and Park[20], 2017	Korea	166	Not specified	128	2-23	8
Karakayali *et al*[21], 2014	Turkey	48	Within 72 h	43	4-8 wk	8
Ke and Wu *et al*[22], 2018	China	47	After 72 h	49	1-1096 d	8
Kim *et al*[23], 2009	Korea	60	Not specified	35	Within 7 d	8
Kim *et al*[24], 2011	Korea	147	Mean time interval 42.2 h	97	Mean time interval 188.4 h	8
Lee *et al*[25], 2017	Korea	41	36 had LC within 24 h, 3 had LC 1-3 d, 2 had LC > 7 d	44	Mean 30 d	8
Liu *et al*[26], 2020	China	45	57.6 ± 12.2 h	58	62.4 ± 11.5 h	8
Na *et al*[27], 2015	Korea	77	Not specified	39	Not specified	7
Ni *et al*[28], 2015	China	33	Not specified	26	Within 1 year	8
Pan *et al*[29], 2023	Taiwan	67	Immediately	23	Not specified	8
Tsumura *et al*[30], 2004	Japan	73	Within 24 h	60	Not specified	8
Yamazaki *et al*[31], 2023	Japan	22	Immediately	13	After 2 months	8
Yang and Tian[32], 2022	China	35	After 7 d	35	After 40 d	8

PTGBD: Percutaneous transhepatic gallbladder puncture drainage; LC: Laparoscopic cholecystectomy; NOS: Newcastle-Ottawa scale.

Clinical efficacy meta-analysis results

Operative time: In this comprehensive analysis, all 24 studies[9-32] included a comparative assessment of operative times across the two groups. The heterogeneity test indicated a highly significant variance ($P < 0.00001$, $I^2 = 94\%$), thus indicating the application of a random-effects model for the analysis. The meta-analysis demonstrated a significantly shorter operative duration in the PTGBD + LC group than in the LC group, with an average decrease of 17.51 min (95%CI: 9.53-25.49, $P < 0.0001$). For a visual depiction of these results, please refer to Figure 2A.

Conversion to open surgery rate: Twenty-two studies[9,10,12-28,30-32] compared the rate of conversion to open surgery between the two groups. The heterogeneity test results showed $P = 0.005$ and $I^2 = 50\%$, indicating significant heterogeneity. Consequently, a random effects model was employed for the analysis. The outcomes of the meta-analysis revealed a statistically notable difference: In comparison to the LC group, the PTGBD + LC group displayed a decreased conversion rate to open surgery, with an average reduction of 2.95%. This reduction was statistically significant, with a 95%CI of 1.90 to 4.58, and the P value was less than 0.00001 (Figure 2B).

Intraoperative blood loss: Seventeen studies[9-16,18,19,22,26-28,30-32] compared intraoperative blood loss between the two groups. The heterogeneity test results showed $P < 0.00001$ and $I^2 = 97\%$, necessitating the use of a random-effects model for the analysis. The meta-analysis revealed that the PTGBD + LC group exhibited a significant reduction in intraoperative blood loss compared to the LC group, with an average decrease of 32.27 mL, which was statistically significant (95%CI: 23.03-41.50, $P < 0.00001$; Figure 2C).

Total hospital stay: Fifteen studies[10,11,15,17-20,23-28,31,32] conducted a comparative assessment of the total hospital stay between the two groups. Heterogeneity testing produced significant results ($P < 0.00001$, $I^2 = 98\%$), which necessitated the adoption of a random-effects model for the analysis. The meta-analysis revealed that the PTGBD + LC group

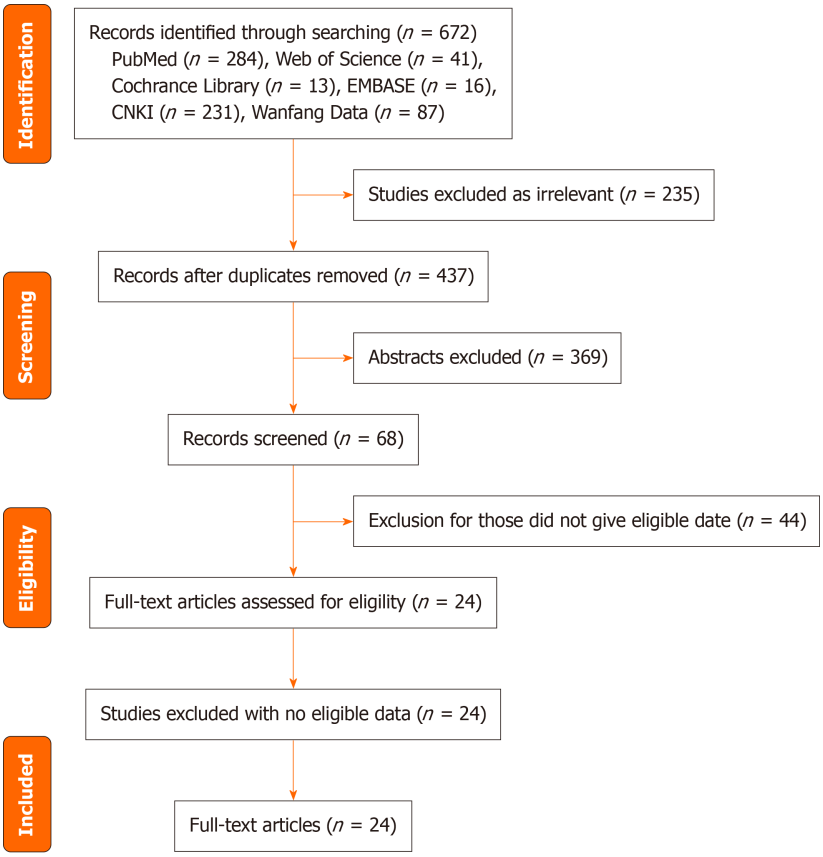


Figure 1 Flow diagram depicting the screening and inclusion process of the studies. CNKI: China National Knowledge Infrastructure.

had a marginally longer total hospital stay than did the LC group, with an average increase of 1.85 d; however, it is important to note that this difference did not achieve statistical significance (95%CI: -4.86-1.16, P = 0.23; Figure 2D).

Postoperative hospital stay: Thirteen studies[9,12-14,17,20-22,24,25,27,30,31] conducted a comparative analysis of postoperative hospital stays between the two groups. The heterogeneity test results showed P < 0.00001 and I^2 = 94%, necessitating the application of a random-effects model for the analysis. The meta-analysis revealed a statistically significant difference: The PTGBD + LC group demonstrated a noteworthy reduction in postoperative hospital stay compared to the LC group, with an average decrease of 1.44 d (95%CI: 0.14-2.73, P = 0.03; Figure 2E).

Safety meta-analysis results

Postoperative complication rate: Twenty-two studies[9-24,26-29,31,32] compared the overall postoperative complication rates between the groups. The heterogeneity test showed P = 0.0001 and I^2 = 61%, which necessitated the adoption of a random-effects model for the analysis. A significant reduction in the overall incidence of complications was observed in the PTGBD + LC group compared to the LC group. This reduction amounted to an average of 1.88 patients (95%CI: 1.45-2.43, P < 0.00001; Figure 2F).

Bile leakage: Seventeen studies[9,13-16,18-23,26,27,29-32] compared the incidence of postoperative bile leakage between the two groups. The heterogeneity test showed P = 0.40 and I^2 = 5%, confirming the use of a fixed-effects model for the analysis. After conducting the meta-analysis, it was evident that the PTGBD + LC group exhibited a lower incidence of postoperative bile leakage than did the LC group, with an average reduction of 1.33 patients. Nevertheless, it is noteworthy that this disparity did not reach statistical significance, as indicated by the 95%CI: 0.81-2.18, P = 0.26 (Figure 2G).

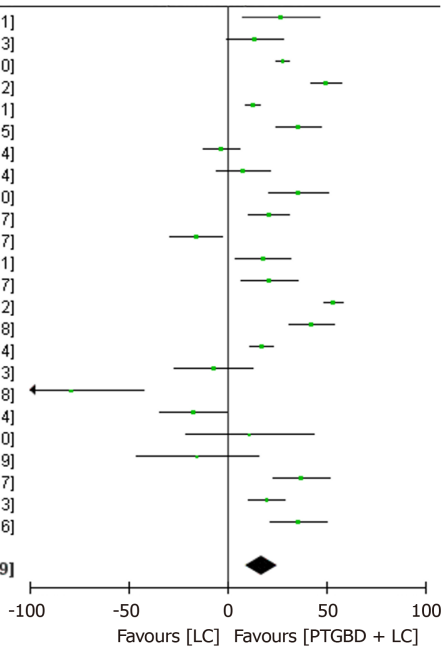
Wound infection: Sixteen studies[9,10,12,14-16,19-21,23,25,26,28-31] compared the incidence of postoperative wound infection between the two groups. The results of the heterogeneity test demonstrated P = 0.67 and I^2 = 0%, indicating minimal heterogeneity. Consequently, a fixed-effects model was employed for the analysis. The meta-analysis findings demonstrated a statistically significant reduction in postoperative wound infections in the PTGBD + LC group compared with the LC group, with an average decrease of 2.17 patients (95%CI: 1.30-3.64, P = 0.003; Figure 2H).

Intra-abdominal hemorrhage: Ten studies[9,10,13,15-17,20,26,27,32] compared the incidence of postoperative intra-abdominal hemorrhage between the groups. The heterogeneity test results, with P = 0.67 and I^2 = 0%, supported the application of a fixed-effects model for the analysis. The meta-analysis revealed a notable difference: The PTGBD + LC group exhibited a significantly lower incidence of postoperative intra-abdominal hemorrhage than did the LC group,

A

Study or subgroup	LC Mean	LC SD	LC Total	PTGBD + LC Mean	PTGBD + LC SD	PTGBD + LC Total	Weight	Mean difference IV, random, 95%CI
Chikamori et al. 2002	116	24	9	89	33	31	3.8%	27.00 [7.49, 46.51]
Choi et al. 2012	99.84	45.37	63	85.88	28.01	40	4.2%	13.96 [-0.21, 28.13]
Duan and Li. 2021	65.42	9.74	44	37.29	6.21	48	4.9%	28.13 [24.76, 31.50]
El-Gendi et al. 2017	87.8	33.06	75	38.09	8.23	75	4.7%	49.71 [42.00, 57.42]
Hao and Fan. 2022	82.64	15.09	82	69.83	11.78	118	4.8%	12.81 [8.91, 16.71]
Hu et al. 2015	91.4	25.1	35	55.6	23.3	35	4.5%	35.80 [24.45, 47.15]
Jung et al. 2017	78.8	39.3	166	82	40.7	128	4.6%	-3.20 [-12.44, 6.04]
Karakayali et al. 2014	114	38	48	106	27	43	4.3%	8.00 [-5.44, 21.44]
Ke and Wu. 2018	119	37	47	83	38	49	4.2%	36.00 [21.00, 51.00]
Kim et al. 2009	75.8	23.2	60	54.7	25.8	35	4.5%	21.10 [10.73, 31.47]
Kim et al. 2011	104	48.7	147	119.6	53.4	97	4.3%	-15.60 [-28.83, -2.37]
Lee et al. 2017	91.4	35.6	41	73.4	28.7	44	4.3%	18.00 [4.19, 31.81]
Liu et al. 2020	139.6	37.2	45	118.3	34.7	58	4.2%	21.30 [7.23, 35.37]
Liu. 2018	116.98	13.43	40	63.24	6.18	40	4.8%	53.74 [49.16, 58.32]
Ma et al. 2020	89.5	38.2	57	46.9	23.8	57	4.4%	42.60 [30.92, 54.28]
Na et al. 2015	120.17	15.07	77	102.96	16.31	39	4.8%	17.21 [11.08, 23.34]
Ni et al. 2015	110	47	33	116.7	30.8	26	3.7%	-6.70 [-26.63, 13.23]
Pan et al. 2023	114	47	67	193	85	23	2.4%	-79.00 [-115.52, -42.48]
Tsumura et al. 2004	107	48	73	124	51	60	4.0%	-17.00 [-33.96, -0.04]
Wu and Kuang. 2017	85.6	46.83	20	74.18	48.31	14	2.7%	11.42 [-21.16, 44.00]
Yamazaki et al. 2023	116.68	56.82	22	131.89	36.08	13	2.8%	-15.21 [-46.01, 15.59]
Yang and Tian. 2022	120.56	30.55	35	83.15	31.17	35	4.2%	37.41 [22.95, 51.87]
Zhan et al. 2023	84.4	23.7	38	64.4	16.2	38	4.6%	20.00 [10.87, 29.13]
Zhou et al. 2019	119	36.4	47	83.2	34.1	47	4.2%	35.80 [21.54, 50.06]
Total (95% CI)			**1371**			**1193**	**100.0%**	**17.51 [9.53, 25.49]**

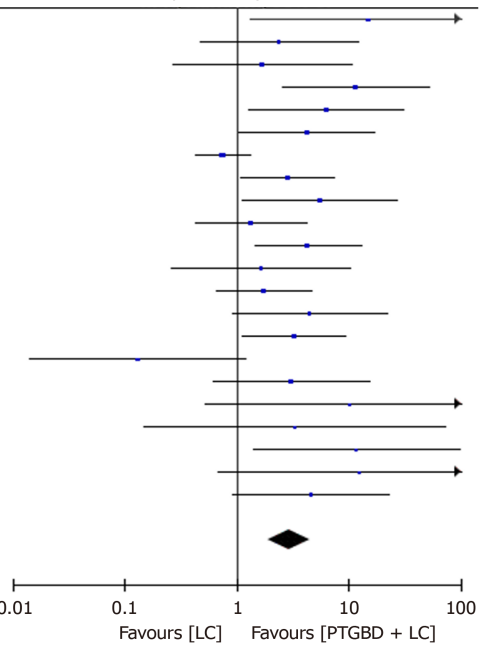
Heterogeneity: Tau² = 338.86; Chi² = 411.61, df = 23 (*P* < 0.00001); I² = 94%
Test for overall effect: Z = 4.30 (*P* < 0.0001)



B

Study or subgroup	LC Events	LC Total	PTGBD + LC Events	PTGBD + LC Total	Weight	Odds ratio M-H, random, 95%CI
Chikamori et al. 2002	3	9	1	31	2.5%	15.00 [1.32, 169.87]
Choi et al. 2012	7	63	2	40	4.3%	2.38 [0.47, 12.06]
Duan and Li. 2021	3	44	2	48	3.7%	1.68 [0.27, 10.58]
El-Gendi et al. 2017	18	75	2	75	4.8%	11.53 [2.57, 51.73]
Hao and Fan. 2022	8	82	2	118	4.5%	6.27 [1.30, 30.34]
Hu et al. 2015	10	35	3	35	5.2%	4.27 [1.06, 17.17]
Jung et al. 2017	32	166	31	128	9.1%	0.75 [0.43, 1.31]
Karakayali et al. 2014	19	48	8	43	7.1%	2.87 [1.10, 7.50]
Ke and Wu. 2018	9	47	2	49	4.5%	5.57 [1.13, 27.31]
Kim et al. 2009	11	60	5	35	6.2%	1.35 [0.43, 4.26]
Kim et al. 2011	23	147	4	97	6.4%	4.31 [1.44, 12.89]
Lee et al. 2017	3	41	2	44	3.7%	1.66 [0.26, 10.46]
Liu et al. 2020	11	45	9	58	6.9%	1.76 [0.66, 4.71]
Ma et al. 2020	8	57	2	57	4.4%	4.49 [0.91, 22.16]
Na et al. 2015	25	77	5	39	6.6%	3.27 [1.14, 9.37]
Ni et al. 2015	1	33	5	26	2.9%	0.13 [0.01, 1.20]
Tsumura et al. 2004	7	73	2	60	4.4%	3.08 [0.61, 15.40]
Wu and Kuang. 2017	5	20	0	14	1.8%	10.29 [0.52, 203.06]
Yamazaki et al. 2023	2	22	0	13	1.7%	3.29 [0.15, 74.06]
Yang and Tian. 2022	9	35	1	35	3.1%	11.77 [1.40, 98.85]
Zhan et al. 2023	5	38	0	38	1.9%	12.64 [0.67, 237.19]
Zhou et al. 2019	8	47	2	47	4.4%	4.62 [0.92, 23.04]
Total (95% CI)		**1264**		**1130**	**100.0%**	**2.95 [1.90, 4.58]**
Total events	227		90			

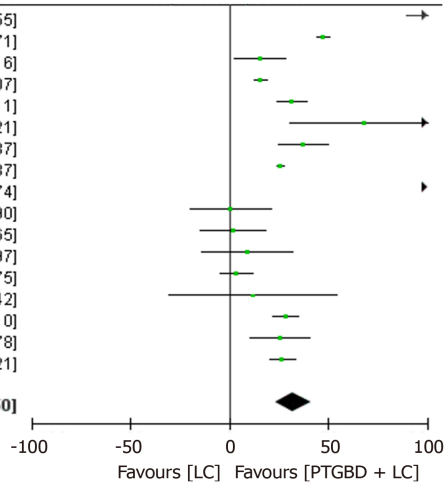
Heterogeneity: Tau² = 0.48; Chi² = 41.73, df = 21 (*P* = 0.005); I² = 50%
Test for overall effect: Z = 4.81 (*P* < 0.00001)



C

Study or subgroup	LC Mean	LC SD	LC Total	PTGBD + LC Mean	PTGBD + LC SD	PTGBD + LC Total	Weight	Mean difference IV, random, 95%CI
Choi et al. 2012	361.67	218.45	63	186.14	216.21	40	1.0%	175.53 [89.51, 261.55]
Duan and Li. 2021	62.86	10.2	44	15.32	3.49	48	7.4%	47.54 [44.37, 50.71]
El-Gendi et al. 2017	41.73	51.09	75	26.33	23.86	75	6.5%	15.40 [2.64, 28.16]
Hao and Fan. 2022	77.58	12.16	82	61.75	10.43	118	7.4%	15.83 [12.59, 19.07]
Hu et al. 2015	60.4	16.4	35	28.7	15.2	35	7.1%	31.70 [24.29, 39.11]
Ke and Wu. 2018	101	125	47	33	37	49	3.4%	68.00 [30.79, 105.21]
Liu et al. 2020	109.4	33.6	45	72.1	30.5	58	6.6%	37.30 [24.73, 49.87]
Liu. 2018	52.43	5.68	40	26.48	2.51	40	7.5%	25.95 [24.03, 27.87]
Ma et al. 2020	179.6	64.5	57	26.1	15.8	57	5.9%	153.50 [136.26, 170.74]
Na et al. 2015	108.67	56.14	77	108.16	51.25	39	5.5%	0.51 [-19.88, 20.90]
Ni et al. 2015	34.8	24.6	33	32.9	37.7	26	6.0%	1.90 [-14.85, 18.65]
Tsumura et al. 2004	26	85	73	17	48	60	5.1%	9.00 [-13.97, 31.97]
Wu and Kuang. 2017	21.57	10.7	20	18.16	13.17	14	7.0%	3.41 [-4.93, 11.75]
Yamazaki et al. 2023	53.25	65.46	22	41.3	59.77	13	2.9%	11.95 [-30.52, 54.42]
Yang and Tian. 2022	61.01	15.54	35	32.54	12.61	35	7.2%	28.47 [21.84, 35.10]
Zhan et al. 2023	47.6	41.3	38	21.9	23.3	38	6.2%	25.70 [10.62, 40.78]
Zhou et al. 2019	60.4	16.7	47	33.7	15.5	47	7.2%	26.70 [20.19, 33.21]
Total (95% CI)			**833**			**792**	**100.0%**	**32.27 [23.03, 41.50]**

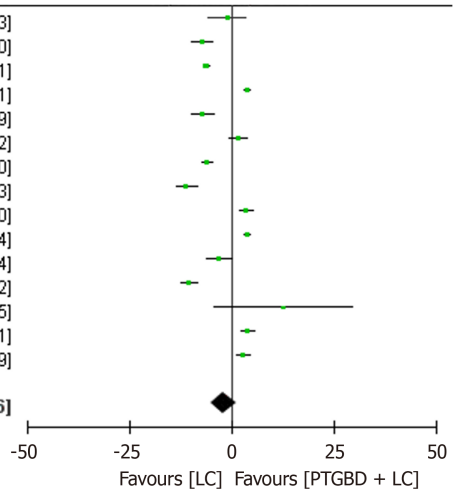
Heterogeneity: Tau² = 296.87; Chi² = 483.62, df = 16 (*P* < 0.00001); I² = 97%
Test for overall effect: Z = 6.85 (*P* < 0.00001)



D

Study or subgroup	LC Mean	LC SD	LC Total	PTGBD + LC Mean	PTGBD + LC SD	PTGBD + LC Total	Weight	Mean difference IV, random, 95%CI
Chikamori et al. 2002	14	6	9	15	7	31	6.2%	-1.00 [-5.63, 3.63]
Choi et al. 2012	12.92	5.63	63	20.08	7.33	40	6.9%	-7.16 [-9.82, -4.50]
Hao and Fan. 2022	9.85	1.73	82	16.02	3.02	118	7.2%	-6.17 [-6.83, -5.51]
Hu et al. 2015	7	1.7	35	3	1.3	35	7.2%	4.00 [3.29, 4.71]
Jung et al. 2017	10.6	7	166	17.6	14.4	128	6.9%	-7.00 [-9.71, -4.29]
Kim et al. 2009	15.9	6.4	60	14.2	5	35	7.0%	1.70 [-0.62, 4.02]
Kim et al. 2011	9	4.5	147	14.9	6	97	7.2%	-5.90 [-7.30, -4.50]
Lee et al. 2017	6.3	3.5	41	17.3	7.9	44	6.9%	-11.00 [-13.57, -8.43]
Liu et al. 2020	18	4.8	45	14.3	4.4	58	7.1%	3.70 [1.90, 5.50]
Liu. 2018	16.87	1.89	40	12.86	1.43	40	7.2%	4.01 [3.28, 4.74]
Na et al. 2015	13.43	6.56	77	16.38	9.02	39	6.7%	-2.95 [-6.14, 0.24]
Ni et al. 2015	8.2	3.9	33	18.5	4.5	26	7.0%	-10.30 [-12.48, -8.12]
Yamazaki et al. 2023	29.79	37.96	22	16.95	10.76	13	2.2%	12.84 [-4.07, 29.75]
Yang and Tian. 2022	11.95	4.15	35	7.98	3.24	35	7.1%	3.97 [2.23, 5.71]
Zhou et al. 2019	11.2	4.7	47	8.3	3	47	7.1%	2.90 [1.31, 4.49]
Total (95% CI)			**902**			**786**	**100.0%**	**-1.85 [-4.86, 1.16]**

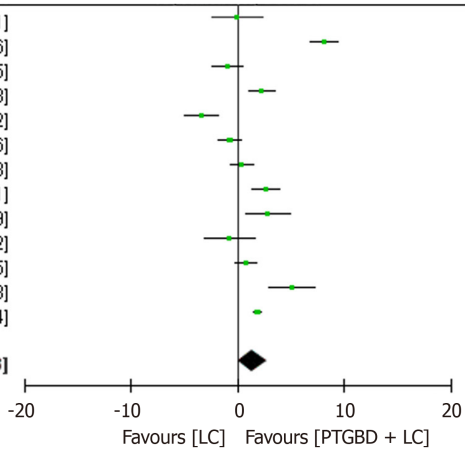
Heterogeneity: Tau² = 32.46; Chi² = 898.84, df = 14 (*P* < 0.00001); I² = 98%
Test for overall effect: Z = 1.21 (*P* = 0.23)



E

Study or subgroup	LC Mean	LC SD	LC Total	PTGBD + LC Mean	PTGBD + LC SD	PTGBD + LC Total	Weight	Mean difference IV, random, 95%CI
Chikamori et al. 2002	9	3	9	9	4	31	6.7%	0.00 [-2.41, 2.41]
Duan and Li. 2021	19.57	3.54	44	11.45	2.36	48	8.0%	8.12 [6.88, 9.36]
Jung et al. 2017	6.4	4.7	166	7.3	7.3	128	7.8%	-0.90 [-2.35, 0.55]
Karakayali et al. 2014	5.3	3.3	48	3	2.4	43	8.1%	2.30 [1.12, 3.48]
Ke and Wu. 2018	8.2	3.2	47	11.6	4.6	49	7.7%	-3.40 [-4.98, -1.82]
Kim et al. 2011	6.5	4.2	147	7.2	4.1	97	8.2%	-0.70 [-1.76, 0.36]
Lee et al. 2017	5.4	2.5	41	5	2.6	44	8.2%	0.40 [-0.68, 1.48]
Ma et al. 2020	8.6	4.8	57	5.9	1.6	57	7.9%	2.70 [1.39, 4.01]
Na et al. 2015	8.94	5.98	77	6.08	5.27	39	7.0%	2.86 [0.73, 4.99]
Tsumura et al. 2004	11.1	7.1	73	11.8	7.1	60	6.6%	-0.70 [-3.12, 1.72]
Wu and Kuang. 2017	4.9	1.8	20	4.1	1	14	8.3%	0.80 [-0.15, 1.75]
Yamazaki et al. 2023	10.42	3.93	22	5.29	2.69	13	6.9%	5.13 [2.93, 7.33]
Zhan et al. 2023	5.3	0.8	38	3.4	0.7	38	8.6%	1.90 [1.56, 2.24]
Total (95% CI)			**789**			**661**	**100.0%**	**1.44 [0.14, 2.73]**

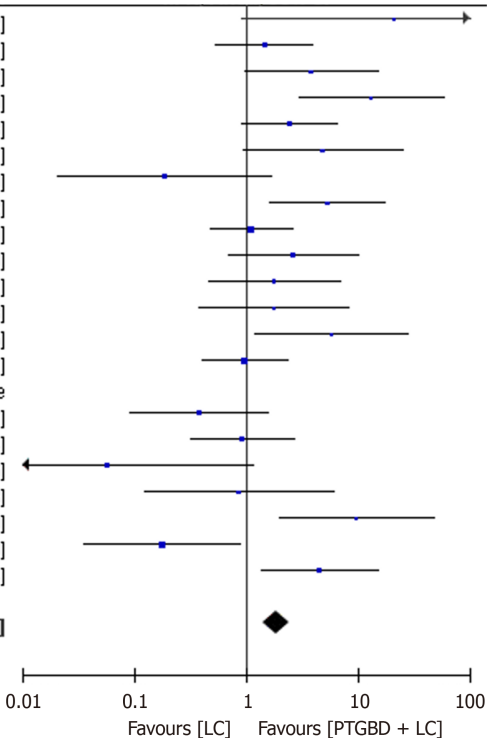
Heterogeneity: Tau² = 5.08; Chi² = 204.50, df = 12 (*P* < 0.00001); I² = 94%
Test for overall effect: Z = 2.16 (*P* = 0.03)



F

Study or subgroup	LC Events	LC Total	PTGBD + LC Events	PTGBD + LC Total	Weight	Odds ratio M-H, fixed, 95%CI
Chikamori et al. 2002	2	9	0	31	0.2%	21.00 [0.91, 484.72]
Choi et al. 2012	15	63	7	40	7.5%	1.47 [0.54, 4.01]
Duan and Li. 2021	9	44	3	48	2.6%	3.86 [0.97, 15.32]
El-Gendi et al. 2017	20	75	2	75	1.7%	13.27 [2.98, 59.19]
Hao and Fan. 2022	11	82	7	118	5.7%	2.46 [0.91, 6.63]
Hu et al. 2015	8	35	2	35	1.8%	4.89 [0.96, 24.97]
Jung et al. 2017	1	166	4	128	5.1%	0.19 [0.02, 1.70]
Karakayali et al. 2014	17	48	4	43	3.1%	5.35 [1.63, 17.52]
Ke and Wu. 2018	31	47	31	49	11.8%	1.13 [0.49, 2.60]
Kim et al. 2009	12	60	3	35	3.5%	2.67 [0.70, 10.20]
Kim et al. 2011	8	147	3	97	3.9%	1.80 [0.47, 6.97]
Liu et al. 2020	4	45	3	58	2.7%	1.79 [0.38, 8.43]
Ma et al. 2020	10	57	2	57	1.9%	5.85 [1.22, 28.05]
Na et al. 2015	57	77	29	39	11.5%	0.98 [0.41, 2.37]
Ni et al. 2015	0	33	0	26		Not estimable
Pan et al. 2023	5	67	4	23	6.3%	0.38 [0.09, 1.57]
Tsumura et al. 2004	8	73	7	60	7.8%	0.93 [0.32, 2.74]
Wu and Kuang. 2017	0	20	4	14	5.9%	0.06 [0.00, 1.16]
Yamazaki et al. 2023	3	22	2	13	2.5%	0.87 [0.13, 6.03]
Yang and Tian. 2022	13	35	2	35	1.4%	9.75 [2.00, 47.50]
Zhan et al. 2023	2	38	9	38	9.8%	0.18 [0.04, 0.89]
Zhou et al. 2019	14	47	4	47	3.2%	4.56 [1.37, 15.14]
Total (95% CI)		**1290**		**1109**	**100.0%**	**1.88 [1.45, 2.43]**
Total events	250		132			

Heterogeneity: Chi² = 51.43, df = 20 (*P* = 0.0001); I² = 61%
Test for overall effect: Z = 4.78 (*P* < 0.00001)



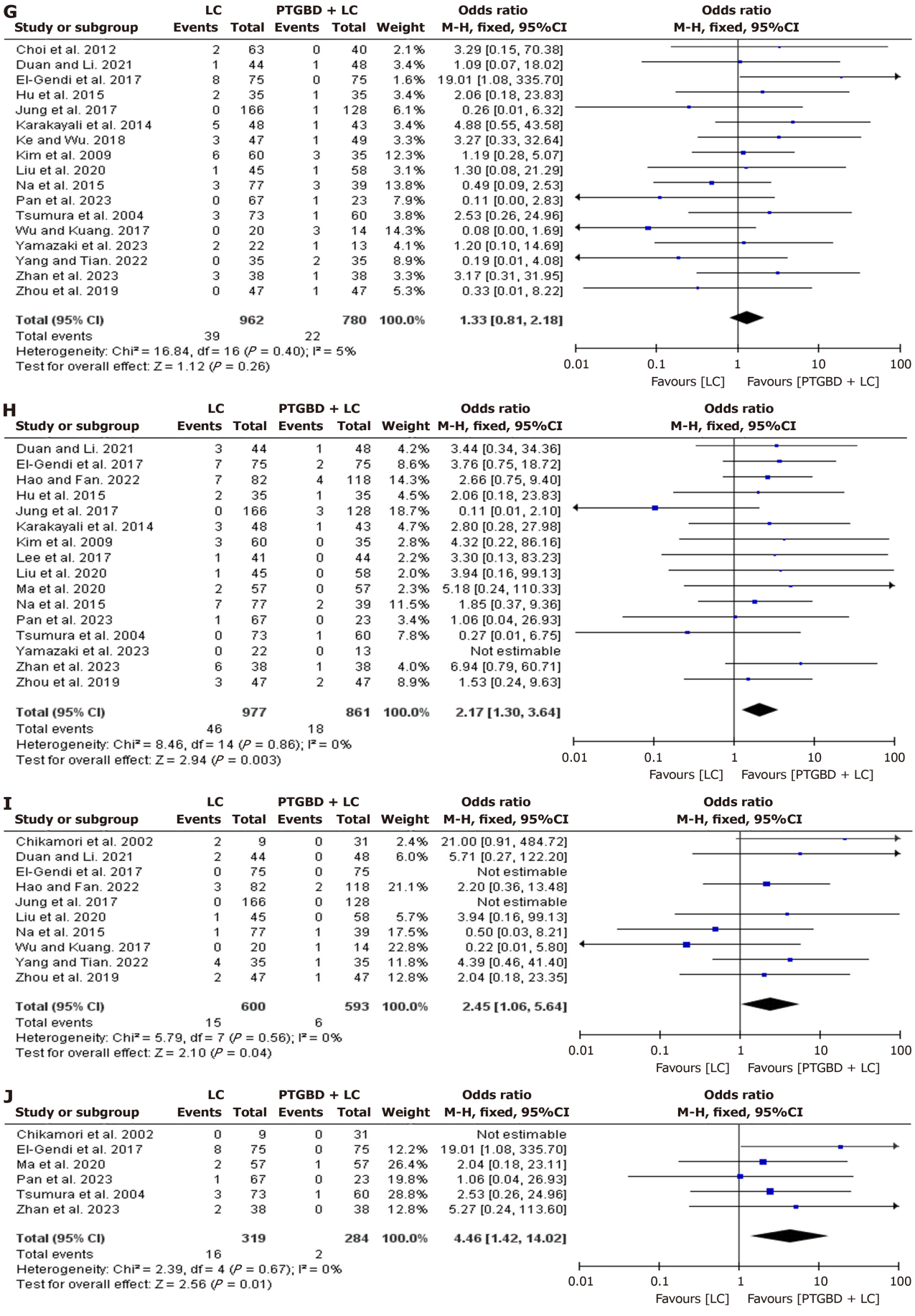


Figure 2 Forest plot depicting comparison between the percutaneous transhepatic gallbladder puncture drainage + laparoscopic

cholecystectomy group and the laparoscopic cholecystectomy group. A: Forest plot depicting the operation time comparison between the percutaneous transhepatic gallbladder puncture drainage (PTGBD) + laparoscopic cholecystectomy (LC) group and the LC group; B: Forest plot illustrating the comparison of the conversion rate to open surgery between the PTGBD + LC group and the LC group; C: Forest plot illustrating the comparison of intraoperative bleeding between the PTGBD + LC group and the LC group; D: Forest plot depicting the comparison of overall hospital stay between the PTGBD + LC group and the LC group; E: Forest plot depicting the comparison of postoperative hospital stay between the PTGBD + LC group and the LC group; F: Forest plot illustrating the comparison of postoperative complications between the PTGBD + LC group and the LC group; G: Forest plot illustrating the comparison of bile leakage rates between the PTGBD + LC group and the LC group; H: Forest plot depicting the comparison of wound infection rates between the PTGBD + LC group and the LC group; I: Forest plot depicting intraperitoneal hemorrhage in the PTGBD + LC group compared to the LC group; J: Forest plot comparing bile duct injury incidence between the PTGBD + LC group and the LC group. PTGBD: Percutaneous transhepatic gallbladder puncture drainage; LC: Laparoscopic cholecystectomy.

with an average reduction of 2.45 patients (95%CI: 1.06-5.64, $P = 0.004$; Figure 2I).

Bile duct injury: Six studies[12,14,16,17,29,30] compared the incidence of postoperative bile duct injury between the two groups. The heterogeneity test results showed $P = 0.67$ and $I^2 = 0\%$, thus confirming the use of a fixed-effects model for the analysis. The meta-analysis demonstrated that the PTGBD + LC group exhibited a significantly lower incidence of postoperative bile duct injuries than did the LC group, with an average reduction of 4.46 patients (95%CI: 1.42-14.02, $P = 0.01$; Figure 2J).

Publication bias: Publication bias analysis was conducted using funnel plots for various outcomes, which included operative time, conversion to open surgery rate, intraoperative blood loss, total hospital stay, postoperative hospital stay, overall postoperative complication rate, postoperative bile leakage, bile duct injury, intra-abdominal hemorrhage, and incidence of wound infection. The results indicated good symmetry in the funnel plots, suggesting that the study results are minimally influenced by publication bias (Figure 3).

DISCUSSION

A meta-analysis refers to the use of statistical methods to analyze and summarize multiple collected research studies, providing a quantified average effect to answer research questions. Its advantage lies in increasing the credibility of the conclusions by enlarging the sample size. This study included 24 articles and included a meta-analysis aimed at comparing the clinical effectiveness and safety of LC combined with PTGBD and LC for the treatment of AC, providing valuable clinical insights. The meta-analysis revealed that compared with the LC group, the PTGBD + LC group had a shorter surgery time (MD = 17.51, 95%CI: 9.53-25.49, $P < 0.01$), a lower rate of conversion to open surgery (OR = 2.95, 95%CI: 1.90-4.58, $P < 0.01$), less intraoperative bleeding (MD = 32.27, 95%CI: 23.03-41.50, $P < 0.01$), a shorter postoperative hospital stay (MD = 1.44, 95%CI: 0.14-2.73, $P = 0.03$), and a lower overall postoperative complication rate (OR = 1.88, 95%CI: 1.45-2.43, $P < 0.01$). There were also lower incidences of postoperative bile duct injury (OR = 14.46, 95%CI: 1.42-14.02, $P = 0.01$), intra-abdominal bleeding (OR = 2.45, 95%CI: 1.06-5.64, $P = 0.004$), and wound infection (OR = 2.17, 95%CI: 1.30-3.64, $P = 0.003$), indicating that PTGBD combined with LC is more effective and safer for treating AC than LC alone.

The short surgical time in the PTGBD + LC group may be related to the relief of local inflammation after PTGBD. As a minimally invasive surgery, PTGBD reduces gallbladder swelling, gallbladder wall edema, and inflammation around the gallbladder[33]. PTGBD can immediately alleviate the clinical symptoms of AC in patients in good preoperative condition [34]. In addition, PTGBD can be used for cholangiography to display the anatomical structure of the biliary tract and provide clear information on the surgical site[35].

Previous studies have concluded that the fundamental reason for transitioning to open surgery is recurrent and progressive inflammation accompanied by gallbladder wall swelling and edema[36,37]. The low rate of conversion to open surgery in the PTGBD + LC group may be attributed to PTGBD, as PTGBD has the ability to alleviate inflammatory gallbladder adhesion. After PTGBD, patients have a reduced gallbladder wall thickness, clearer anatomical structure of the gallbladder triangle, reduced intraoperative bleeding, and a reduced risk of biliary tract injury.

Our analysis of intraoperative bleeding revealed less bleeding in the PTGBD + LC group than in the LC group. PTGBD can immediately alleviate the decompression of swollen gallbladders and inflammation around the gallbladder, preventing the development of fibrosis in the Calot triangle[34]. With the help of PTGBD, the surgical field of view of the Calot triangle is clearer, which facilitates LC and reduces intraoperative bleeding.

Our analysis of hospitalization time revealed that the postoperative hospitalization time of the PTGBD + LC group was significantly shorter than that of the LC group. It is possible that the patient's gallbladder wall congestion, edema, and inflammation caused by gallbladder inflammation gradually subside in the short term after PTGBD, making it easier to distinguish anatomy and thereby reducing surgical difficulty and shortening surgical time[25,33]. Our analysis revealed that the total incidence of postoperative complications in the PTGBD + LC group was low, possibly because PTGBDD was associated with minimal trauma. At the same time, supportive treatment, such as systemic anti-infection therapy, can quickly alleviate clinical symptoms, prevent further deterioration of the condition, and provide sufficient time for the treatment of complications[38].

The results of the meta-analysis indicated that the combined hospital stay in the PTGBD + LC group was slightly longer than that in the PTGBD + LC group, but the difference did not reach statistical significance (MD = -1.85, 95%CI:

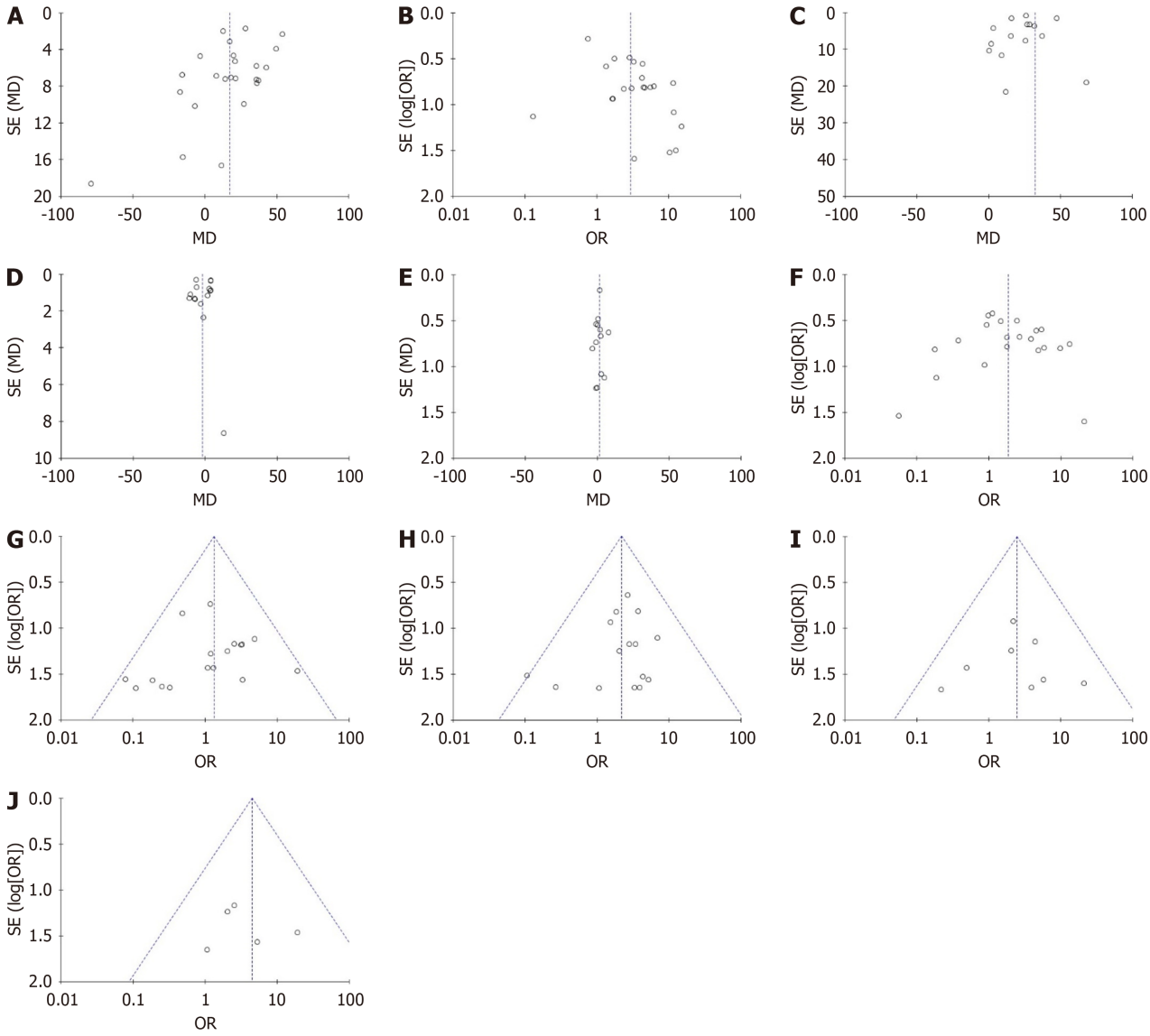


Figure 3 Funnel plots of each outcome. A: Operative time; B: Conversion rate to open surgery; C: Intraoperative bleeding; D: Overall hospital stay; E: Postoperative hospital stay; F: Postoperative complications; G: Bile leakage; H: Wound infection; I: Intraperitoneal hemorrhage; J: Bile duct injury. MD: Mean difference; OR: Odds ratio.

-4.86-1.16, P = 0.23). The extended total hospital stay in the PTGBD + LC group can be attributed to the requirement for a longer duration or even two hospital admissions to complete the treatment, which may be considered the sole drawback of PTGBD.

The presence of publication bias is indicated by the observed asymmetry in the funnel plot. Significant heterogeneity was also observed in some studies, possibly related to variations in surgical experience, surgical instruments, severity grading of AC, and discharge criteria. The interval between PTGBD tube placement and LC was another important factor contributing to heterogeneity. The optimal timing for delayed LC after PTGBD remains controversial, with different experiences and policies at various centers leading to varied optimal timing. Jia *et al*[39] noted that patients who underwent LC within 5 d after PTGBD had significantly less surgical time, bleeding, postoperative peritoneal drainage duration, postoperative oral intake time, and postoperative complications than those who exceeded 5 d. Finally, most of the included studies were performed in Asia, and the data regarding LC and PTGBD in Europe and America were unclear. RCTs and multicenter studies with large sample sizes are needed to verify the outcomes of this meta-analysis.

Meta-analysis is an observational study type and inevitably possesses biases in its design. The limitations of this study include the following: (1) The inclusion of a restricted number of research articles with small sample sizes has implications for the generalizability of conclusions and increases the vulnerability to publication bias; (2) Variability in the interval from PTGBD to LC in the included studies; and (3) The focus on only English and Chinese literature, neglecting gray literature and other languages, which might introduce certain biases in the results.

CONCLUSION

In summary, this meta-analysis revealed that the amalgamation of PTGBD combined with LC conspicuously enhances clinical efficacy while concurrently mitigating the frequency of postoperative complications in individuals afflicted with AC.

FOOTNOTES

Author contributions: Li Y and Xiao WK are co-first authors and contributed equally to this work, including design of the study, acquiring and analyzing data from experiments, and writing of the manuscript; Li Y, Xiao WK and Dong HY designed the experiments and conducted clinical data collection; Li Y, Xiao WK and Li XJ performed postoperative follow-up and recorded the data, conducted the collation and statistical analysis, and wrote the original manuscript and revised the paper; all authors read and approved the final manuscript.

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META-ANALYSIS

Prognostic factors associated with gastrointestinal dysfunction after gastrointestinal tumor surgery: A meta-analysis

Jia Song, Cong Zhou, Tian Zhang

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Abstract

BACKGROUND

Explore the risk factors of gastrointestinal dysfunction after gastrointestinal tumor surgery and to provide evidence for the prevention and intervention of gastrointestinal dysfunction in patients with gastrointestinal tumor surgery.

AIM

To investigate the potential risk factors for gastrointestinal dysfunction following gastrointestinal tumor surgery and to present information supporting the prevention and management of gastrointestinal dysfunction in surgery patients.

METHODS

Systematically searched the relevant literature from PubMed, Web of Science, Cochrane Library, Embase, CNKI, China Biomedical Database, Wanfang Database, and Weipu Chinese Journal Database self-established until October 1, 2022. Review Manager 5.3 software was used for meta-analysis after two researchers independently screened literature, extracted data, and evaluated the risk of bias in the included studies.

RESULTS

A total of 23 pieces of literature were included, the quality of which was medium or above, and the total sample size was 43878. The results of meta-analysis showed that the patients were male (OR = 1.58, 95%CI: 1.25-2.01, $P = 0.002$) and ≥ 60 years old (OR = 2.60, 95%CI: 1.76-2.87, $P < 0.001$), physical index ≥ 25.3 kg/m^2 (OR = 1.6, 95%CI: 1.00-1. 12, $P = 0.040$), smoking history (OR = 1.89, 95%CI: 1.31-2.73, $P < 0.001$), chronic obstructive pulmonary disease (OR = 1.49, 95%CI: 1.22-

1.83, $P < 0.001$), enterostomy (OR = 1.47, 95%CI: 1.26-1.70, $P < 0.001$), history of abdominal surgery (OR = 2.90, 95%CI: 1.67-5.03, $P < 0.001$), surgical site (OR = 1.2, 95%CI: 1.40-2.62, $P < 0.001$), operation method (OR = 1.68, 95%CI: 1.08-2.62, $P = 0.020$), operation duration (OR = 2.65, 95%CI: 1.92-3.67, $P < 0.001$), abdominal adhesion grade (OR = 2.52, 95%CI: 1.90-3.56, $P < 0.001$), postoperative opioid history (OR = 5.35, 95%CI: 3.29-8.71, $P < 0.001$), tumor TNM staging (OR = 2.58, 95%CI: 1.84-3.62, $P < 0.001$), postoperative blood transfusion (OR = 2.92, 95%CI: 0.88-9.73, $P = 0.010$) is a risk factor for postoperative gastrointestinal dysfunction in patients with gastrointestinal tumors.

CONCLUSION

There are many factors affecting gastrointestinal dysfunction in gastrointestinal patients after surgery. Clinical staff should identify relevant risk factors early and implement targeted intervention measures on the basis of personalized assessment to improve the clinical prognosis of patients.

Key Words: Gastrointestinal tumor surgery; Postoperative gastrointestinal dysfunction; Intestinal paralysis; Risk factors; Meta-analysis

Core Tip: Our study conducted meta-analysis to investigate prognostic factors associated with gastrointestinal dysfunction after surgery for gastrointestinal tumors. Through systematic integration of existing literature, we will further study the survival rate, quality of life, complication rate, and other indicators of patients after surgery and analyze the relationship between them and factors such as patient age, tumor type, and surgical method. It is helpful to provide clinicians with more accurate postoperative management strategies to promote patients' recovery and quality of life. Our study will also provide an important reference basis to enhance the understanding and attention given to the postoperative recovery process.

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INTRODUCTION

Gastrointestinal tract refers to the digestive tube from the stomach to the anus, including the stomach, small intestine, large intestine and other parts, which is the longest and most important part of the digestive tube[1-3]. Postoperative gastrointestinal dysfunction (POGD), also known as postoperative gastro-anthralgia, is an acute pathophysiological change of the gastrointestinal tract, mainly characterized by gastrointestinal mucosal damage, barrier dysfunction and gastrointestinal motility disorders, manifested by nausea, vomiting, abdominal distension, delayed exhaust or defecation, and may even cause intestinal infection and sepsis. Prolong the hospital stay of patients and increase the economic burden of patients. Studies[4-6] have shown that almost all medium and above surgery (especially abdominal surgery), anesthesia, fluid load, analgesic drugs, postoperative inflammatory response, *etc*., will have varying degrees of influence on postoperative gastrointestinal function. Among them, the incidence of POGD after abdominal surgery ranges from 4% to 32%, and the incidence of gastrointestinal surgery is even higher. Rapid and effective identification of risk factors for POGD is of great importance for formulating prevention and treatment interventions, reducing the incidence of POGD, and reducing the medical burden of patients[7].

Through meta-analysis, this study summarized the risk factors of POGD in patients undergoing gastrointestinal surgery, providing a theoretical basis for early assessment and identification of high-risk groups of POGD in patients undergoing gastrointestinal surgery.

MATERIALS AND METHODS

Literature retrieval strategy

Using the combination of subject words and free words, we searched PubMed, Web of Science, Cochrane Library, Embase, CNKI, China Biomedical Database, Wanfang Database, WiP Chinese Journal, and other databases for relevant studies on the influencing factors of gastrointestinal dysfunction after gastrointestinal surgery. The references included in the literature were also retroactively searched, and the search time range was from the establishment of the database to October 1, 2023.

The search strategies were (Colorectal Neoplasms OR Ileal Neoplasms OR Duodenal Neoplasms OR Stomach Neoplasms OR Jejunal Neoplasms) AND (colorectal neoplasms or ileal neoplasms or duodenal neoplasms or stomach neoplasms or jejunal neoplasms). Surgery OR Opera OR Perioperative Period OR Postoperative) AND (Postoperative

gastrointestinal dysfunction OR ileus OR postoperative ileus OR prolonged ileus OR intestinal paralysis) AND (Factors OR relatives).

Document inclusion criteria

(1) Age of the study subjects was ≥ 18 years old; (2) Patients with gastrointestinal tumors undergoing elective surgery; (3) The content of the literature studies was the influencing factors or risk factors of postoperative POGD; (4) The study type was cohort study; and (5) Outcome indicators were the risk factors associated with POGD after gastrointestinal tumor surgery.

Document exclusion criteria

(1) Repeated publication; (2) Unable to obtain the full text; only abstracts; incomplete data literature; (3) Literature with a score of < 7 on the Newcastle-Ottawa Scale (NOS); and (4) Literature on the diagnosis of POGD is not clear.

Literature screening and data extraction

Two researchers independently searched and screened the literature strictly according to the inclusion and exclusion criteria, extracted data for cross-checking, and, in cases of disagreement, the third researcher arbitrated or discussed it in a group. The main contents of data extraction include the first author, publication years, research location, research type, manual location, sample size, POGD incidence, research factors, etc.

Literature quality evaluation

NOS was used independently by two researchers to evaluate the quality of the included documents, and a third researcher was jointly assessed when disagreements arose. A total of 8 items were included in 3 aspects, including the selection of research objects, the comparability between groups, and the evaluation of exposure and outcome. The full score was 9, and ≥ 7 was classified as high-quality research, which was included.

Statistical analysis

Meta-analysis was performed using Review Manager 5.3 software. According to the OR value and 95%CI of the original data in the literature, the combined effect size (ES), ES = LN (OR), and standard error of effect size (SE) = LN (upper limit of interval - lower limit of interval)/3.92. I^2 was used to test the heterogeneity of the included literature. If $I^2 \leq 50\%$ and $P \geq 0.1$, it indicated that there was no significant heterogeneity among the studies, and a fixed-effect model was selected for analysis. If I^2 is greater than 50% and $P < 0.01$, it indicates heterogeneity among studies. After analyzing the source of heterogeneity, a random effects model is selected for analysis. Sensitivity analysis was conducted by comparing the consistency of the results of the two models and eliminating the literature that had a great influence on the combined results. The funnel plot method was used to analyze the existence of publication bias.

RESULTS

Literature retrieval results and included research characteristics

A total of 922 literatures were obtained through the initial examination of the database; 130 literatures were supplemented by other means; 102 duplicated literatures were removed; 125 literatures that were obviously inconsistent with the theme were excluded by reading the abstract and title; 30 literatures were included in the preliminary screening; 7 literatures were excluded after reading the full text; and the full text was carefully read according to the inclusion and exclusion criteria. Finally, a total of 23 eligible pieces of literature were included[4,8-29]. The specific literature screening process is shown in Figure 1.

Basic features of the included literature

A total of 23 cohort studies were included[4,8-29], with a total sample size of 43878 cases and 5300 cases of POGD, and the incidence of POGD ranged from 4.5% to 71.2 percent. The NOS scores of the included literature were all ≥ 7 points, and the quality of the literature met the requirements (Figure 2). The basic characteristics and quality evaluation results of the included literature are shown in Table 1.

Meta-analysis results

A fixed-effect model was used to analyze 10 factors, including body mass index (BMI) (≥ 25.3 kg/m^2), age, smoking history, chronic obstructive pulmonary disease, enterostomy, history of abdominal surgery, surgical site, duration of surgery, abdominal adhesion grade, and TNM stage of tumors. Statistical heterogeneity was not found among the included literatures. A random effects model was used for analysis, and gender, operation mode, postoperative opioid history, postoperative blood transfusion, postoperative body temperature, and preoperative albumin low heterogeneity test were statistically significant ($P < 0.05$). The results showed that, in addition to postoperative body temperature and preoperative hypoalbumin, the other 14 factors were risk factors for postoperative POGD in patients with gastrointestinal tumors (Table 2 and Figure 3).

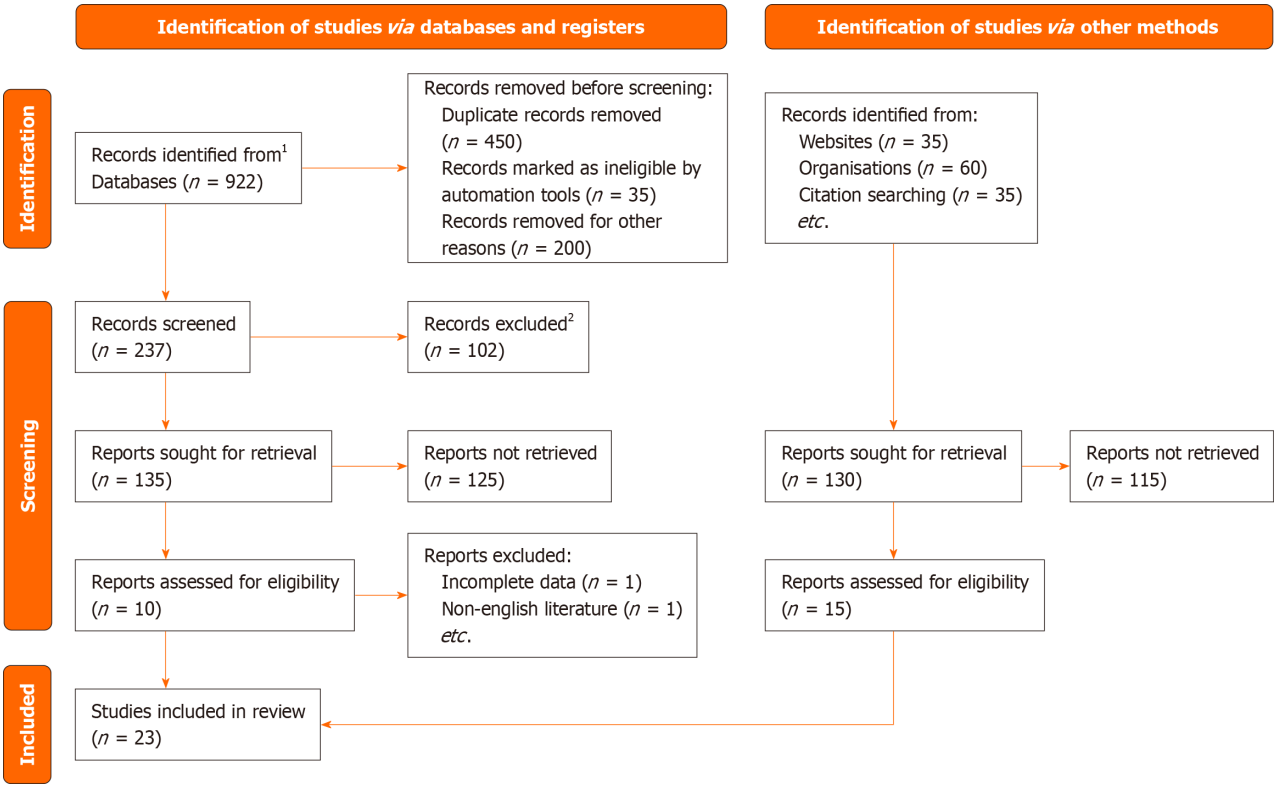

Figure 1 Flow chart of the literature screening. [1]Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). [2]If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Sensitivity analysis

For risk factors with large heterogeneity ($I^2 \geq 50\%$), the source of heterogeneity was further explored by excluding individual studies one by one. The results showed that after the exclusion of individual studies, the statistical heterogeneity among all literature was reduced, and the research results were relatively stable compared with before and after the exclusion, as shown in Table 3.

Publication bias assessment

The funnel plot method was used to conduct bias analysis for the meta-analysis, with a large number of included studies. The results showed that the distribution of the funnel plot of age was asymmetrical, and there was publication bias. The gender, enterostomy funnel plot distribution is symmetrical; there is no bias in the distribution table. These results indicate that there is a certain publication bias in the literature included in this study, which may be related to the small number of studies included for each risk factor (Figure 4).

DISCUSSION

The latest expert consensus on the prevention and treatment of POGD points out that once POGD occurs, it will prolong the hospital stay of patients and increase the financial burden of patients[30]. Understanding the risk factors of POGD is of great significance to preventing its occurrence. In this study, 23 studies on the risk factors of POGD after gastrointestinal tumor surgery were analyzed, and the results showed that the risk factors affecting POGD involved individual factors including gender, age, BMI, and smoking history. The associated factors of disease and treatment history included chronic obstructive pulmonary disease, a history of abdominal surgery, and the grade of abdominal adhesion. The factors related to surgery included the operation site, operation mode, operation duration, enterostomy, and TNM grade of the tumor[31]. Treatment-related factors included postoperative opioid use history and postoperative blood transfusion[32]. The correlation between risk factors and the risk of POGD was summarized.

Effects of pathophysiological factors on POGD in patients undergoing surgery for gastrointestinal tumors. The incidence of POGD is higher in men than in women, which is consistent with the conclusion of one study. The reason may be that the hypogastric nerve, pelvic nerve, and spermatic cord may be damaged in male patients during the operation[33]. At the same time, studies have shown that the pain threshold of male patients is higher than that of female patients, and pain leads to increased release of catecholamines, which act on the gastrointestinal tract and inhibit gastrointestinal peristalsis function. The incidence of POGD is higher in patients with a BMI > 25.3 kg/m^2, which is consistent with another study on the cause of POGD after colon surgery. Patients with a high BMI may have hyper-

Table 1 Basic characteristics and quality evaluation results of the included literatures

Ref.	Country	Research type	Surgical site	Cases	Incidence of POGD (%)	NOS score
Xu *et al*[13]	China	Retrospective cohort study	Colorectal cancer	187	16. 6	7
Huang *et al*[14]	China	Prospective cohort study	Gastric cancer	296	32. 4	7
Wang *et al*[17]	China	Retrospective cohort study	Gastric cancer	83	26. 5	8
Pu *et al*[24]	China	Retrospective cohort study	Colorectal cancer	404	18. 3	7
Wu *et al*[25]	China	Retrospective cohort study	Gastric cancer	312	41. 03	8
Liu *et al*[26]	China	Retrospective cohort study	Colorectum	260	31. 6	8
Tian *et al*[29]	China	Retrospective cohort study	Small intestine	247	40. 5	7
Franko *et al*[8]	America	Retrospective cohort study	Colorectum	820	4. 5	8
Kronberg *et al*[9]	America	Retrospective cohort study	Colorectum	413	10.2	7
Millan *et al*[10]	Spain	Retrospective cohort study	Colorectal cancer	773	15.96	7
Chapuis *et al*[11]	Australia	Retrospective cohort study	Colorectum	3393	14. 0	8
Kim MG *et al*[12]	Korea	Retrospective cohort study	Gastric cancer	389	1.8	7
Moghadamyeghaneh *et al*[15]	America	Retrospective cohort study	Colon	27560	12.7	7
Wolthuis *et al*[16]	Belgium	Retrospective cohort study	Colorectum	523	15. 9	7
Courtot *et al*[18]	France	Retrospective cohort study	Right colon cancer	637	17.7	8
Kim *et al*[19]	Korea	Retrospective cohort study	Ileum	220	8.1	8
Weng *et al*[20]	Russia	Prospective cohort study	Colorectal cancer	300	13. 0	8
Sugawara *et al*[21]	Japan	Prospective cohort study	Gastrointestinal tract	841	8.8	7
Aktaş *et al*[22]	Turkey	Prospective cohort study	Ileum	79	9. 0	7
Sapci *et al*[23]	America	Retrospective cohort study	Colorectal cancer	5369	16. 6	8
Greenberg *et al*[27]	America	Retrospective cohort study	Ileum	261	32.6	8
Namba *et al*[28]	Japan	Retrospective cohort study	Colorectal cancer	356	13. 5	7
Watkins *et al*[4]	South Africa	Retrospective cohort study	Colorectal cancer	155	36. 0	8

POGD: Postoperative gastrointestinal dysfunction; NOS: Newcastle-Ottawa Scale.

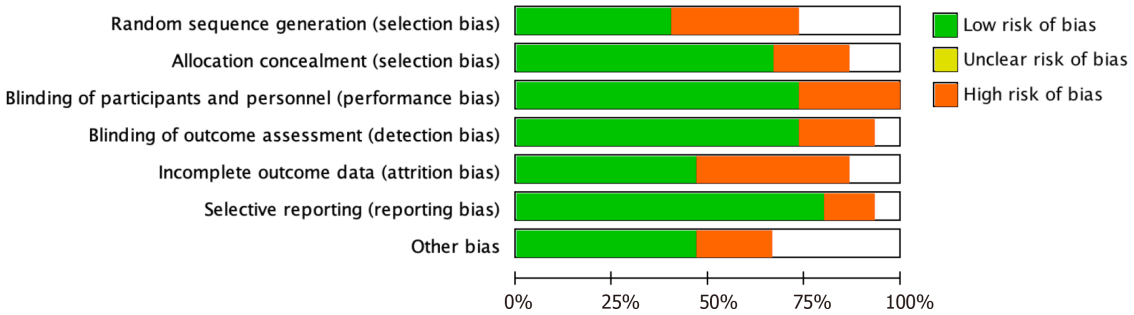

Figure 2 Literature quality evaluation chart.

glycemia, glucose metabolism disorder, intestinal epithelial cell dysfunction, and thus intestinal infection susceptibility and mucosal barrier dysfunction. At the same time, studies[34-36] have shown that the higher the BMI, the higher the incidence of POGD and the greater the impact on the postoperative recovery of patients. This study shows that age ≥ 60 years old is one of the risk factors for POGD, which is consistent with the results of the meta-analysis of the study. The reason may be that the older the patients, the autoimmune function will be relatively lower, and the recovery ability of the body will be reduced after surgery. The study's conclusion was that people who had smoked in the past were more likely to have POGD. This was in line with the findings of other relevant studies. This could be because smoking increased the release of reactive oxygen species, which damaged cell and tissue levels and harmed normal tissue perfusion. At the same time, increasing oxidative stress induces blood tube damage and further leads to the occurrence of

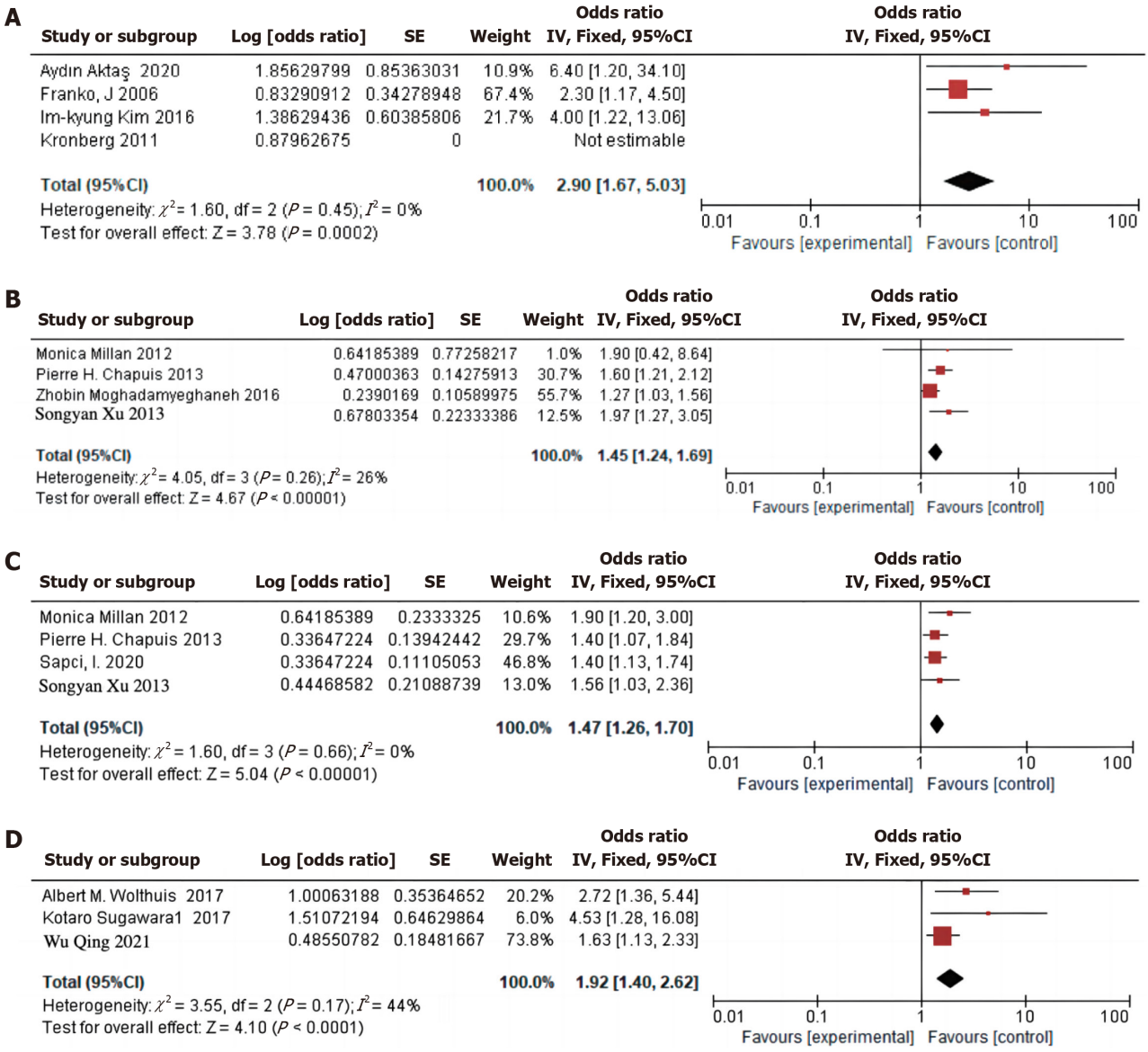

Figure 3 Meta-analysis of the effects of gastrointestinal dysfunction after gastrointestinal tumor surgery. A: Meta-analysis of the correlation between abdominal surgery history and postoperative postoperative gastrointestinal dysfunction (POGD) for gastrointestinal tumors; B: Meta-analysis of postoperative POGD in patients with chronic obstructive pulmonary disease and gastrointestinal tumors; C: Meta-analysis of the correlation between POGD after enterostomy and gastrointestinal tumors; D: Meta-analysis of the correlation between surgical site and postoperative POGD in gastrointestinal tumors.

POGD[37].

Effect of combined disease and treatment history on POGD in patients undergoing surgery for gastrointestinal tumors. The incidence of postoperative POGD is higher in patients with chronic obstructive pulmonary disease, which may be due to the fact that patients with this history need to take drugs for a long time, which may lead to gastrointestinal dysfunction[38]. Patients with a history of abdominal surgery have a higher incidence of POGD, which is consistent with the results of a study on the occurrence of postoperative POGD in patients with gastric cancer. In patients with a history of abdominal surgery, the normal intestinal anatomical structure is destroyed, and intestinal adhesions are present. Meanwhile, the more serious intestinal adhesions are, the longer the operation time needs to be removed and the intestinal cavity opening time will increase, and the incidence of POGD will increase[39].

Effect of surgery-related factors on POGD in patients undergoing surgery for gastrointestinal tumors. At present, surgical treatment is the primary treatment for gastrointestinal tumors, and the risk of POGD occurrence in patients undergoing open surgery is higher than that in patients undergoing laparoscopic surgery. The possible reason is that laparoscopic surgery is minimally invasive and less traumatic, which can reduce the exposure time of patients' intestinal cavities and the stimulation of viscera in the abdominal cavity during surgery[40]. The results of the study showed that the incidence of POGD was higher in patients with TNM stage ≥ III, which was consistent with the results of another study. The later the TNM stage of the tumor, the bigger the resection area, which meant it was more likely to damage abdominal tissue and cause infections and adhesions. People with stage III or higher had to have extensive lymph node dissection[41]. It not only prolongs the operation time but also easily damages lymphatic vessels, leading to obstruction of lymphatic reflux and increasing the risk of POGD[42]. At the same time, different tumor locations have different effects

Table 2 Meta-analysis of factors affecting gastrointestinal dysfunction in patients after gastrointestinal surgery

Research factor	Inclusion study	Heterogeneity test		Effect model	Meta-analysis results	
		P value	I^2 (%)		OR (95%CI)	*P* value
Body mass index (≥ 25.3 kg/m^2)	4 studies[14,20,23,27]	0.59	0	Immobilization	1.06 (1.00-1.12)	0.040
Age	9 studies[9,14,15,20,22,23,25-27]	0.17	40	Immobilization	2.25 (1.76-2.87)	< 0.001
Smoking history	4 studies[4,10,13,21]	0.56	0	Immobilization	1.89 (1.31-2.73)	< 0.001
Chronic obstructive pulmonary disease	4 studies[10,11,13,15]	0.26	26	Immobilization	1.45 (1.24-1.69)	< 0.001
Enterostomy	4 studies[10,11,13,23]	0.66	0	Immobilization	1.47 (1.26-1.70)	< 0.001
History of abdominal operation	6 studies[8,9,14,19,20,22]	0.45	0	Immobilization	2.90 (1.67-5.03)	< 0.001
Surgical site	7 studies[10,13,14,16,21-23]	0.17	44	Immobilization	1.92 (1.40-2.62)	< 0.001
Operation duration	7 studies[11,14,15,25,27-29]	0.21	36	Immobilization	2.65 (1.92-3.67)	< 0.001
Grade of abdominal adhesion	4 studies[20,22,27,29]	0.33	0	Immobilization	2.52 (1.90-3.56)	< 0.001
Tumor TNM staging	2 studies[14,25]	0.78	0	Immobilization	2.58 (1.84-3.62)	< 0.001
Gender (male)	15 studies[4,10-13,15-18,20,21,23,25,27,28]	< 0.001	81	Random	1.58 (1.25-2.01)	0.002
Mode of operation	9 studies[14-16,21-26]	0.35	87	Random	1.68 (1.08-2.62)	0.020
Postoperative opioid use history	7 studies[9,14,17,20,25-27]	0.13	51	Random	5.35 (3.29-8.71)	< 0.001
Postoperative transfusion	6 studies[11,18,20,22,28,29]	0.09	64	Random	2.92 (0.88-9.73)	< 0.001
Postoperative body temperature	2 studies[17,25]	< 0.001	99	Random	5.72 (0.76-42.96)	0.090
Preoperative low albumin (< 30 g/L)	6 studies[9,13-15,24,29]	< 0.001	96	Random	0.37 (0.08-1.72)	0.210

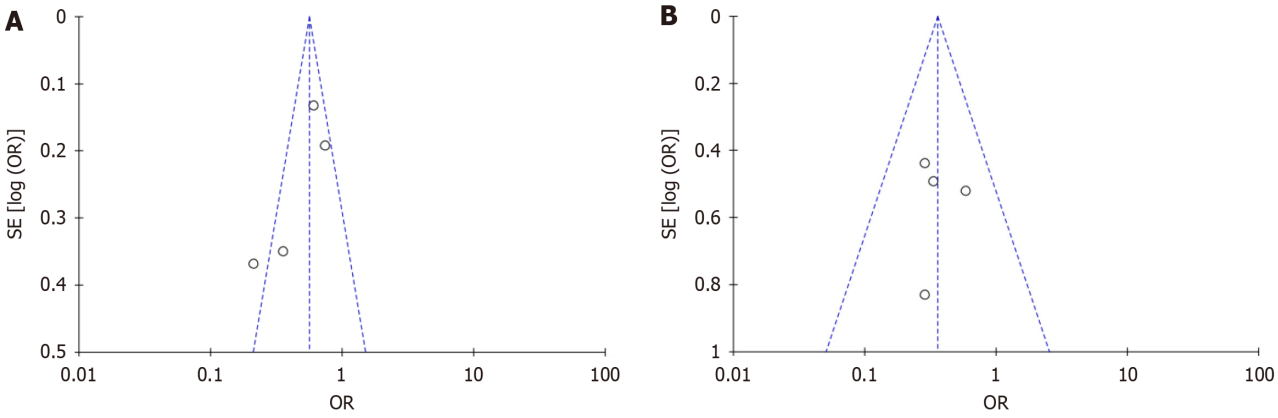

Figure 4 Publication bias analysis. A: Publication bias funnel plot of abdominal surgery history and postoperative postoperative gastrointestinal dysfunction (POGD) for gastrointestinal tumors; B: Publication bias funnel plot of postoperative POGD in patients with chronic obstructive pulmonary disease.

on the occurrence of postoperative POGD. The lower the tumor, the more likely it is that the middle rectal artery and lower rectal artery will be damaged when they are free from the mesocentery. This means that the intestine and anastomosis won't get enough blood after surgery, which slows down the recovery of gastrointestinal function[43].

This study showed that preoperative low albumin (< 30 g/L) and postoperative body temperature ≥ 38 °C were not correlated with the occurrence of postoperative POGD after gastrointestinal tumors, which was consistent with the results of a study on the risk factors of postoperative POGD after gastric cancer. Preoperative low albumin (< 30 g/L) was a risk factor in some studies, but it could not be identified as a risk factor for POGD in this study, perhaps because the association between the two became statistically insignificant when more studies were included. However, because of its association with advanced age, this risk factor suggested a decline in nutrition and bodily function. Postoperative body temperature ≥ 38 °C is mostly caused by the absorption of inflammatory factors, postoperative infection, and drug allergy; its normal condition will not exceed 38.5 °C, and it can subside after a period of time. Therefore, more high-quality related studies are needed to explore whether these two indicators are risk factors.

Table 3 Exclusion of risk factors of postoperative postoperative gastrointestinal dysfunction for gastrointestinal tumors

Risk factor	Before exclusion			After exclusion		
	Model	OR (95%CI)	*P* value	Model	OR (95%CI)	*P* value
Gender	Random	1. 65 (1.36-2.00)	0. 002	Immobilization	1.41 (1.29-1.54)	< 0. 001
Mode of operation	Random	1. 68 (1.08-2.62)	0. 020	Immobilization	2.73 (1.96-3.81)	< 0. 001
Opioid use history	Random	4. 78 (2.30-9.92)	< 0. 001	Immobilization	1.47 (1.17-1.92)	0. 010
Hemorrhage	Random	2. 92 (0.88-9.73)	< 0. 001	Random	2.92 (0.88-9.73)	0. 080

CONCLUSION

In summary, males, age ≥ 60 years old, BMI ≥ 25.3 kg/m^2, history of smoking, history of chronic obstructive pulmonary disease, TNM stage III or above, enterostomy, history of abdominal surgery, surgical site, surgical method, surgical duration, abdominal adhesion grade, and postoperative blood transfusion were risk factors for postoperative POGD for gastrointestinal tumors. However, due to the limited number and quality of the included studies, the above conclusions need to be verified by more high-quality studies.

FOOTNOTES

Author contributions: Song J wrote the manuscript; Zhou C collected the data; Zhang T guided the study. All authors reviewed, edited, and approved the final manuscript and revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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CASE REPORT

Multi-modal imaging for the diagnosis of spontaneous visceral artery dissection: A case report

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Abstract

BACKGROUND

Spontaneous visceral artery dissection (SVAD) is a rare condition that affects the visceral arteries, such as the celiac, superior mesenteric, and inferior mesenteric arteries, without involving the aorta. Organ ischemia or hemorrhage from vessel rupture can occur in SVAD; therefore, prompt detection and management is essential. Contrast-enhanced computed tomography (CECT) has been used to diagnose most of the previous cases, but few studies have explored the potential of contrast-enhanced ultrasound (CEUS) for early detection of this disease.

CASE SUMMARY

A 53-year-old male presented with complaints of poor appetite and abnormal liver function for the past 6 months. He had previously undergone transabdominal splenectomy, esophagogastric devascularization, and cholecystectomy for gallstones and severe portal hypertension. Liver ultrasound was performed in our department to assess liver status. An abnormal hepatic artery spectrum was observed, and dissection involving both the celiac artery and the common hepatic artery was observed. A CEUS was then performed and clearly showed the entry site of the intimal tear and the false lumen, and dissection was subsequently confirmed by CECT. The patient was asymptomatic; therefore, treatment to control the blood pressure was provided, and follow-up was recommended. After 6 months of follow-up, the celiac artery was found to be dilated with an adherent thrombus visible in the wall, and the common hepatic artery was occluded with the presence of collateralization. Despite these findings, no significant changes in liver function were observed.

CONCLUSION

Multi-modal imaging is effective in diagnosing SVAD, and conservative treatment is a choice for asymptomatic patients.

Key Words: Spontaneous visceral artery dissection; Celiac artery dissection; Contrast-

enhanced computed tomography; Contrast-enhanced ultrasound; Case report

Core Tip: Spontaneous visceral artery dissection (SVAD) is a rare condition. Imaging examinations play an important role in the diagnosis of SVAD. Contrast-enhanced computed tomography has been used to diagnose most of the previous cases, but few studies have explored the potential of contrast-enhanced ultrasound (CEUS) for early detection of this disease. In our case, CEUS was used for early detection of the dissection, which was confirmed using other imaging modalities, and the condition was successfully managed with conservative therapy. This case demonstrates the diagnostic value of multi-modal imaging for this uncommon disease.

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INTRODUCTION

Artery dissection is a life-threatening condition that occurs when a tear or rupture in the arterial lining allows blood to enter the arterial wall, separating its layers, and disrupting blood flow. Aortic dissection is a severe and fatal vascular disease with an annual incidence of 3.5-6/100000 per year[1]. Spontaneous visceral artery dissection (SVAD), which occurs without accompanying aortic dissection, is a rare condition. According to a recent systematic review, the main risk factors for SVAD are middle-aged male, hypertension or dyslipidemia, and smoking[2]. Additionally, SVAD may be caused by compression of the median arcuate ligament or a history of abdominal surgery[3,4]. Treatment for SVAD varies depending on the patient's condition. Asymptomatic patients usually receive conservative treatment, whereas patients with persistent abdominal pain, ruptured aneurysm, or organ ischemia need urgent intervention, such as endovascular treatment[5].

Most of the previous cases have been diagnosed by contrast-enhanced computed tomography (CECT)[2,6], but the potential of contrast-enhanced ultrasound (CEUS) for early detection of this disease remains underexplored. We used CEUS to identify a case of artery dissection involving the celiac and common hepatic arteries at an early stage.

CASE PRESENTATION

Chief complaints

A 53-year-old male was admitted to our hospital with complaints of poor appetite and abnormal liver function during the previous 6 months.

History of present illness

Blood tests at the local hospital showed abnormalities in liver and renal functions, and ultrasound showed a hypoechoic nodule in the liver. The patient was transferred to our hospital for further diagnosis and treatment.

History of past illness

The patient had a history of viral hepatitis B for more than 20 years and had undergone transabdominal splenectomy, esophagogastric devascularization, and cholecystectomy 4 years earlier at our hospital for gallstones and severe portal hypertension. The patient had no history of hypertension, diabetes mellitus, or other abdominal surgery.

Personal and family history

There was no other personal or family history of acute or chronic disease.

Physical examination

The patient showed no jaundice on visual examination and no tenderness, rebound tenderness, or muscle tension on abdominal palpation.

Laboratory examinations

Liver function tests were performed at baseline, 3 months, and 6 months. Alanine aminotransferase was 45, 46, and 34 IU/L, respectively (reference range, < 50 IU/L). Aspartate aminotransferase was 38, 35, and 36 IU/L, respectively (reference range, < 40 IU/L). Total bilirubin was 31.9, 32.7, and 34.4 μmol/L, respectively (reference range, 5 μmol/L to 28

μmol/L).

Imaging examinations

Color Doppler imaging showed that the flow of blood in the common hepatic artery was slowed, and the resistance index was reduced. Additionally, right hepatic artery blood flow accelerating time was significantly prolonged, and blood flow was slowed (Figure 1A and B). A dissection of the celiac artery was detected, with two opposite flow signals in the lumen (Figure 1C and D). In the CEUS imaging, the contrast agent extravasated the vessel wall, and the common hepatic artery was narrowed (Figure 1E and F). The CECT images revealed a linear low-density area in the celiac artery wall, heterogeneous thickening of the celiac artery, and thinning of the common hepatic artery, with low-density material attached to their walls (Figure 2A and B); at 3 months of follow-up, the low-density material increased, and the common hepatic artery was narrowed (Figure 2C and D); at 6 months of follow-up, the celiac artery wall had more low-density material, and the common hepatic artery was occluded with evidence of collateralization (Figure 2E and F).

FINAL DIAGNOSIS

Based on the analysis of multiple imaging information, the patient was finally diagnosed with SVAD.

TREATMENT

The patient chose conservative treatment rather than surgical intervention. During follow-up, the patient was treated with a daily oral dose of 0.5 mg entecavir, 12.5 mg carvedilol, and 5 mg amlodipine besylate.

OUTCOME AND FOLLOW-UP

During the follow-up period of 6 months, the patient did not experience any symptoms (*e.g.*, abdominal pain), and the liver function tests did not show any significant abnormal changes.

DISCUSSION

The three main branches of the visceral arteries are the celiac, superior mesenteric, and inferior mesenteric arteries. An SVAD is a condition in which these arteries experience a tear or rupture in their lining without affecting the aorta. Superior mesenteric artery dissection is the most prevalent among the SVADs, followed by celiac artery dissection (CAD) [6]. CAD may propagate along the vessel wall and compromise its branches, such as the splenic and common hepatic arteries. With advancement and wider use of diagnostic imaging modalities in clinical settings, the detection rate of SVAD is increasing[7], but spontaneous celiac artery and common hepatic artery dissections are still extremely rare. When it occurs, SVAD requires prompt diagnosis and treatment, otherwise organ ischemia or vascular rupture causing massive bleeding may occur.

According to a recent systematic review, approximately 60% of patients with CAD exhibited nonspecific clinical symptoms, such as abdominal pain, malaise, and vomiting[2]. However, SVAD is a potential diagnosis of an acute abdomen that warrants clinical concern among patients who present with persistent abdominal pain[8]. The etiology of CAD is obscure. A systematic review revealed that hypertension, smoking, and hyperlipidemia were the top three risk factors for this patient group[2]. Furthermore, one possible cause is the compression of the median arcuate ligament, which exerts constant friction or stress on the celiac artery from the diaphragm during respiration[3]. Additionally, it was implicated that surgical manipulation may be a risk factor for celiac or hepatic artery dissection[4,9]. Our patient had a long history of alcohol consumption and smoking without confirmed hypertension. He had also undergone transabdominal splenectomy, esophagogastric devascularization and cholecystectomy 4 years earlier. He reported no other history of abdominal surgery. We hypothesize that the past trauma from abdominal surgery and the hemodynamic changes might have triggered the dissection of the celiac and common hepatic arteries.

Imaging plays a crucial role in the diagnosis of CAD, which has increased in prevalence with the advancement of imaging modalities[7]. The preferred diagnostic method for CAD is CECT/Computed tomography angiography, while magnetic resonance angiography and ultrasound are also viable options. Digital subtraction angiography is the gold standard for diagnosis; however, it is invasive. Previous studies have shown that most patients were diagnosed by CECT of the abdomen[2,6]. However, in our case, the patient had an ultrasound of the liver, and the physician observed abnormalities in the spectrum of the hepatic artery. He then traced the examination backward along the arterial course and finally located the artery dissection in the common hepatic artery and the celiac trunk. A CEUS was then performed on the patient. By dynamically observing the distribution of microbubbles in the celiac and common hepatic arteries, the site of the peritoneal rupture in the celiac artery was clearly identified, as well as the blood flow in the true and false lumens. In contrast to the static images of computed tomography, ultrasound imaging not only has the advantage of dynamically observing vessel movement, but has several other advantages. Color Doppler ultrasound can measure the velocity of

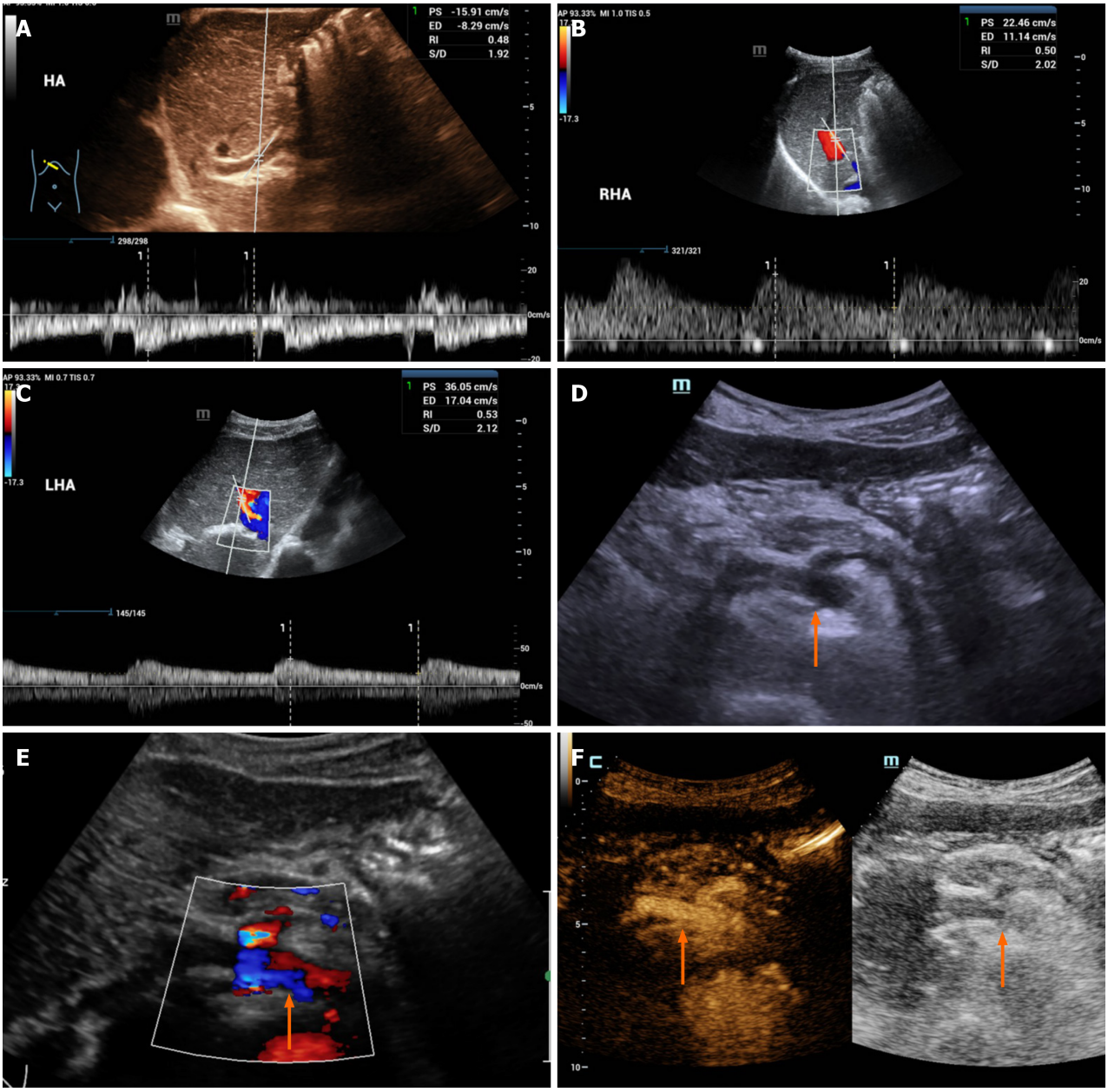

Figure 1 Ultrasound images of the patient. A and B: Hepatic artery and right hepatic artery flow spectrum; C: Rupture of the vessel wall (orange arrow); D: Color Doppler flow imaging of the celiac artery; E and F: Contrast-enhanced ultrasound imaging shows contrast agent extravasation outside the vessel wall and narrowing of the common hepatic artery (orange arrow).

blood flow at the most significant point of luminal narrowing, thereby indirectly determining the presence of organ ischemia. By observing the distribution of microbubbles, the location of the intimal tear can be visualized, and blood flow and thrombosis in the false lumen can be assessed. When blood flow was slow and could not be visualized on Color Doppler ultrasound, blood flow could be determined by observing the flow or absence of microbubbles, suggesting that CEUS was more sensitive in determining blood flow in the pseudo cavity. Therefore, it was suggested that CEUS be used as an imaging modality for long-term follow-up of patients with CAD[10].

The rates of conservative and surgical treatments for CAD vary widely, largely because of its unpredictable natural course[11]. For asymptomatic patients, doctors mostly recommend conservative treatment or regular follow-up. Conservative treatment consists mainly of antihypertensive, anticoagulant, and/or antiplatelet therapy[7]. Anticoagulation or antiplatelet therapy can help prevent thrombosis and maintain organ perfusion; however, the criteria for use of these agents are unclear. CAD can lead to thrombus formation at the entry site or in the false lumen, which can cause stenosis of the true lumen and obstruct blood flow, resulting in organ ischemia[12]. In our case, even though the hepatic artery was occluded, we did not provide surgical treatment because the liver is an organ with a dual blood supply. The CECT suggested that collateral circulation had formed around the occluded artery, and laboratory tests suggested that the patient did not have significant liver function abnormalities. A significant change in liver function would have been an indication that the CAD may have involved the hepatic artery, resulting in inadequate blood supply to the liver, which did not occur in our case. An additional concern was the possibility of splenic infarction if inhomogeneous splenic per-

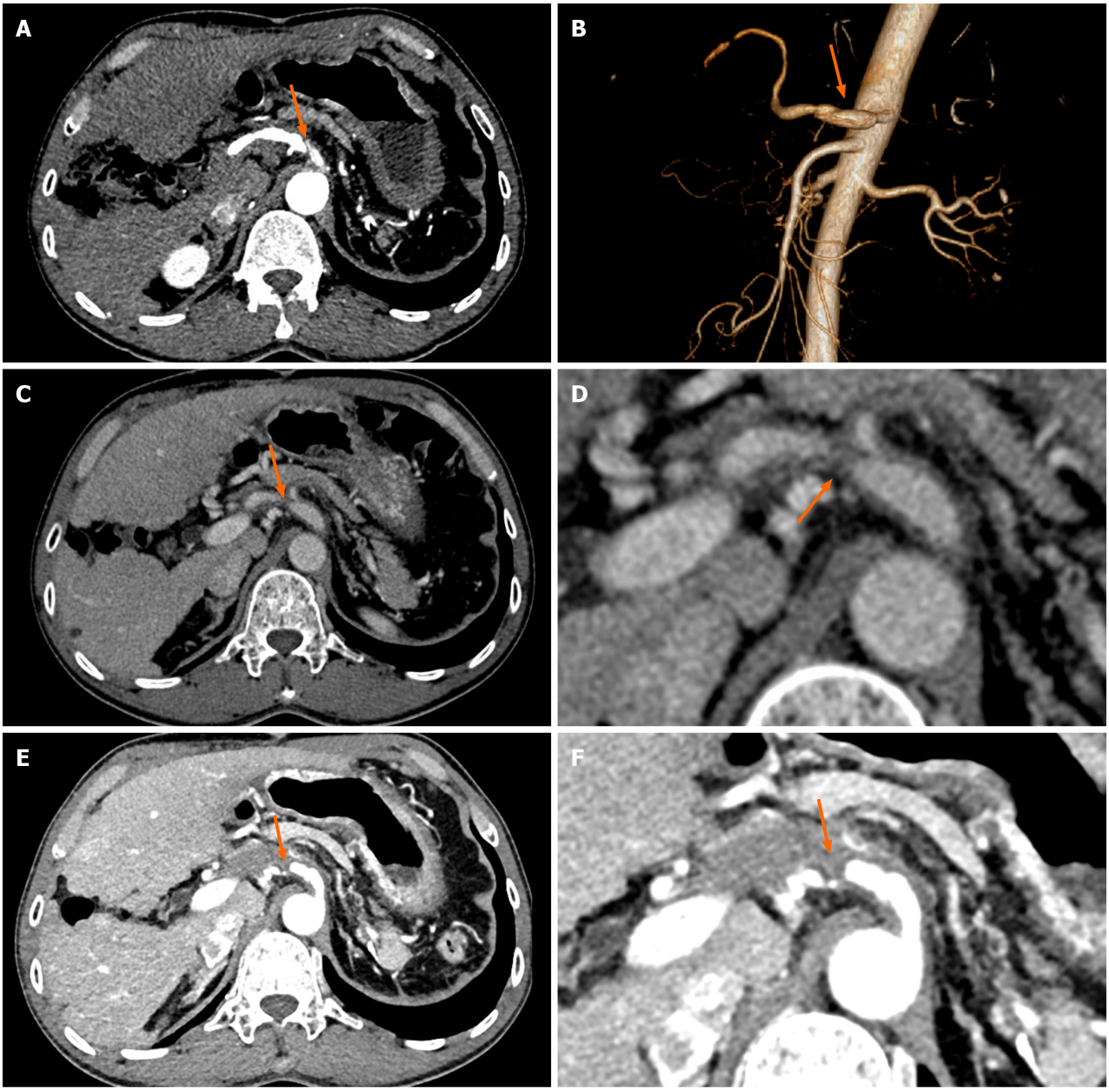

Figure 2 Contrast-enhanced computed tomography images of the patient. A and B: Artery dissection is shown in the first computed tomography examination (orange arrow); C and D: Narrowing of the common hepatic artery at the 3-month follow-up (orange arrow); E and F: Occlusion of the common hepatic artery with collateralization at the 6-month follow-up (orange arrow).

fusion was observed[13], which also was not an issue in our case. Endovascular treatment such as stenting is recommended if symptoms persist, dissection progresses, or the aneurysm continues to enlarge, and surgery is the last option if complications are severe or endovascular treatment fails[14-16].

CONCLUSION

SVAD is a rare condition that requires prompt diagnosis and treatment to prevent organ ischemia or vascular rupture that results in massive bleeding. We identified this case early *via* CEUS, confirmed the diagnosis with other imaging modalities, and successfully managed it with conservative therapy. This case demonstrated the diagnostic value of multi-modal imaging for this uncommon disease. Conservative treatment is a reasonable choice for asymptomatic patients.

FOOTNOTES

Author contributions: Pu Y supported the data collection and wrote the manuscript; Luo Y supervised the writing and revision of the

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CASE REPORT

Metastatic stomach lymphoepithelioma-like carcinoma and immune checkpoint inhibitor therapy: A case report

Guo-Feng Chen, Jun Wang, Yu Yan, Song Xu, Jian Chen

Specialty type: Gastroenterology and hepatology

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Abstract

BACKGROUND

Pulmonary lymphoepithelioma-like carcinoma (PLELC) is a rare type of non-small-cell lung cancer. Stomach lymphoepithelioma-like carcinoma (LELC) metastasis secondary to PLELC has not been reported recently.

CASE SUMMARY

A 64-year-old female was admitted to our hospital for a regular gastroscopy examination with a 6-year history of surgical resection for left PLELC. Positron emission tomography/computed tomography suggested high accumulation of 18F-fludeoxyglucose in the gastric cardia region. Upper gastrointestinal endoscopy confirmed a large mass at the stomach fundus. Immunohistochemistry (IHC) of the biopsy suggested metastatic stomach LELC. Proximal gastrectomy showed that this 6.5 cm × 5.0 cm mass was located in the stomach fundus near the cardia. Histopathological examination showed a poorly differentiated carcinoma with prominent lymphoplasmacytic infiltration. IHC demonstrated that the tumor was positive for CK (AE1/AE3), p63, p40, p53, Ki-67 (70%), and EGFR (3+) and negative for CK7, CK20, Her2, and CD10. *In situ* hybridization analysis showed positive staining Epstein-Barr virus-encoded RNA. Tumor programmed cell death ligand 1 (PD-L1) expression score was 98%, and the combined positive score was

100, with no evidence of microsatellite instability. Thus, the patient was unequivocally diagnosed with metastatic stomach LELC secondary to pulmonary LELC. After discharge, this patient underwent PD-1 inhibitor treatment (toripalimab, 240 mg) every 3 wk for ten cycles, and she has had no tumor recurrence.

CONCLUSION
For gastric LELC metastasis, PD-1 inhibitor therapy could become a new therapeutic approach, though there is still no evidence from large data sets to support this.

Key Words: Stomach neoplasm; Pulmonary lymphoepithelioma-like carcinoma; Metastasis; Immune checkpoint inhibitor; Case report

Core Tip: Pulmonary lymphoepithelioma-like carcinoma (PLELC) is a rare type of non-small-cell lung cancer. Stomach lymphoepithelioma-like carcinoma (LELC) metastasis secondary to PLELC has not been reported recently. We present a 64-year-old female patient who was admitted to our hospital for a regular gastroscopy examination with a 6-year history of surgical resection for left PLELC. After proximal gastrectomy, histopathological examination showed a poorly differentiated carcinoma with prominent lymphoplasmacytic infiltration, suggesting stomach LELC metastasis. Tumor programmed cell death ligand 1 (PD-L1) expression showed a tumor proportion score of 98% and a combined positive score of 100. After discharge, this patient underwent PD-1 inhibitor treatment for ten cycles and has not experienced tumor recurrence. These findings suggest that for gastric LELC metastasis, PD-1 inhibitor therapy could become a potential therapeutic approach.

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INTRODUCTION

Pulmonary lymphoepithelioma-like carcinoma (PLELC) is a rare type of non-small cell lung cancer that tends to occur in young, nonsmoking, and Asian populations[1]. It has unique clinical and pathological features that are similar to those of undifferentiated nasopharyngeal carcinoma[2,3]. PLELC is characterized by Epstein-Barr virus (EBV) infection. According to whole-exome sequencing, targeted deep sequencing and single-nucleotide polymorphism arrays, the genetic lesions affect several critical pathways, including the NF-κB, JAK/STAT, and cell cycle pathways[4]. Along with conventional surgical resection, immunotherapy has become a focus of attention[5,6]. Although lymphoepithelioma-like carcinoma (LELC) metastasis has been reported, including subcutaneous[7], endotracheal[8], and lung door and mediastinal lymph nodes[9], stomach LELC secondary to PLELC has not been reported recently, nor have treatments for it.

CASE PRESENTATION

Chief complaints

A 64-year-old female patient was admitted to our hospital for a regular gastroscopy examination.

History of present illness

There is no history of present illness.

History of past illness

The patient had a 6-year history of surgical resection for left PLELC. She underwent four cycles of gemcitabine plus cisplatin chemotherapy, four cycles of pemetrexed plus carboplatin chemotherapy, and 30 cycles of radiotherapy (Figure 1).

Personal and family history

The patient denied any chronic medical history, such as hypertension, diabetes, heart disease, or tobacco or alcohol (illicit drug) use.

Physical examination

On physical examination, the patient reported no obvious discomfort.

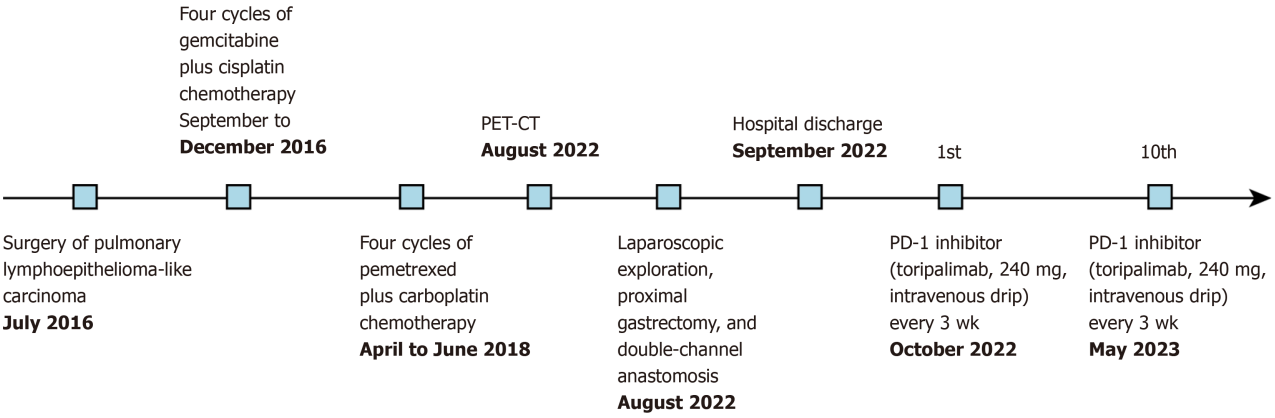

Figure 1 Timeline of history of past illnessthe, initial diagnosis, surgical intervention, postoperative adjuvant therapy, and follow-up period. PET-CT: Positron emission tomography/computed tomography; PD-1: programmed cell death 1.

Laboratory examinations

Laboratory findings included increased levels of tumor markers, such as carbohydrate antigen 125 (CA125) (36.9 U/mL; reference range, < 35 U/mL) and CA211 (5.9 ng/mL; reference range, < 5 ng/mL). A stool occult blood test was positive.

Imaging examinations

Gastroscopy revealed a space-occupying lesion in the cardia/fundus region of the stomach. A whole-abdominal contrast-enhanced computed tomography (CT) scan showed an irregular mass in the gastric cardia. Positron emission tomography/CT was also performed, which suggested high levels of 18F-fludeoxyglucose accumulation in the gastric cardia region (a maximum standardized uptake value of 20.03), indicating malignant tumors (Figure 2). Upper gastrointestinal endoscopy further confirmed a large mass of about 5 cm × 4 cm at the stomach fundus, and this submucosal bulge broke into the stomach cavity (Figure 3A). According to the immunohistochemistry (IHC) of the biopsy, the pathological diagnosis was a metastatic stomach lymphoepithelioma-like carcinoma.

FINAL DIAGNOSIS

Based on all the findings, the patient was diagnosed with metastatic LELC of the stomach.

TREATMENT

Based on the above diagnosis, we performed laparoscopic exploration, proximal gastrectomy, and double-channel anastomosis between the esophagus, residual stomach, and jejunum. Surgical resection of the tumor revealed a large mass located in the stomach fundus near the cardia, presenting as a type of ulcer infiltrate with a size of 6.0 cm × 5.0 cm (Figure 3B). Pathology after surgery showed a poorly differentiated carcinoma of the gastric fundus of 6.5 cm × 5.0 cm. Only one perigastric LN showed positive metastasis (1/24). Histopathological examination by hematoxylin and eosin staining of the stomach tumor sections showed a poorly differentiated carcinoma with prominent lymphoplasmacytic infiltration (Figure 4A). IHC analysis demonstrated that the tumor was positive for CK (AE1/AE3), p63, p40, p53, Ki-67 (70%), and EGFR (3+) and negative for CK7, CK20, Her2, Muc-5AC, Muc-6, Muc-2, and CD10. *In situ* hybridization showed positive staining for EBV -encoded RNA (Figure 4B). Moreover, the ICH results of the positive LN were consistent with those of the stomach lesions. When we analyzed tumor programmed cell death ligand 1 (PD-L1) expression, we found a tumor proportion score of 98% and a combined positive score of 100, with no evidence of microsatellite instability. The pathological findings were consistent with those reported for pulmonary LELC. Thus, the patient was unequivocally diagnosed with stomach LELC metastatic secondary to pulmonary LELC. After 16 d of routine treatment following gastrectomy, the patient was discharged.

OUTCOME AND FOLLOW-UP

The patient underwent immune checkpoint inhibitor (ICI) treatment with a PD-1 inhibitor (toripalimab, 240 mg, intravenous drip) every 3 wk after discharge (September 6, 2022). On outpatient follow-up, the patient stayed on schedule for ten cycles of PD-1 inhibitor treatment. So far, no adverse events and no tumor recurrence have occurred.

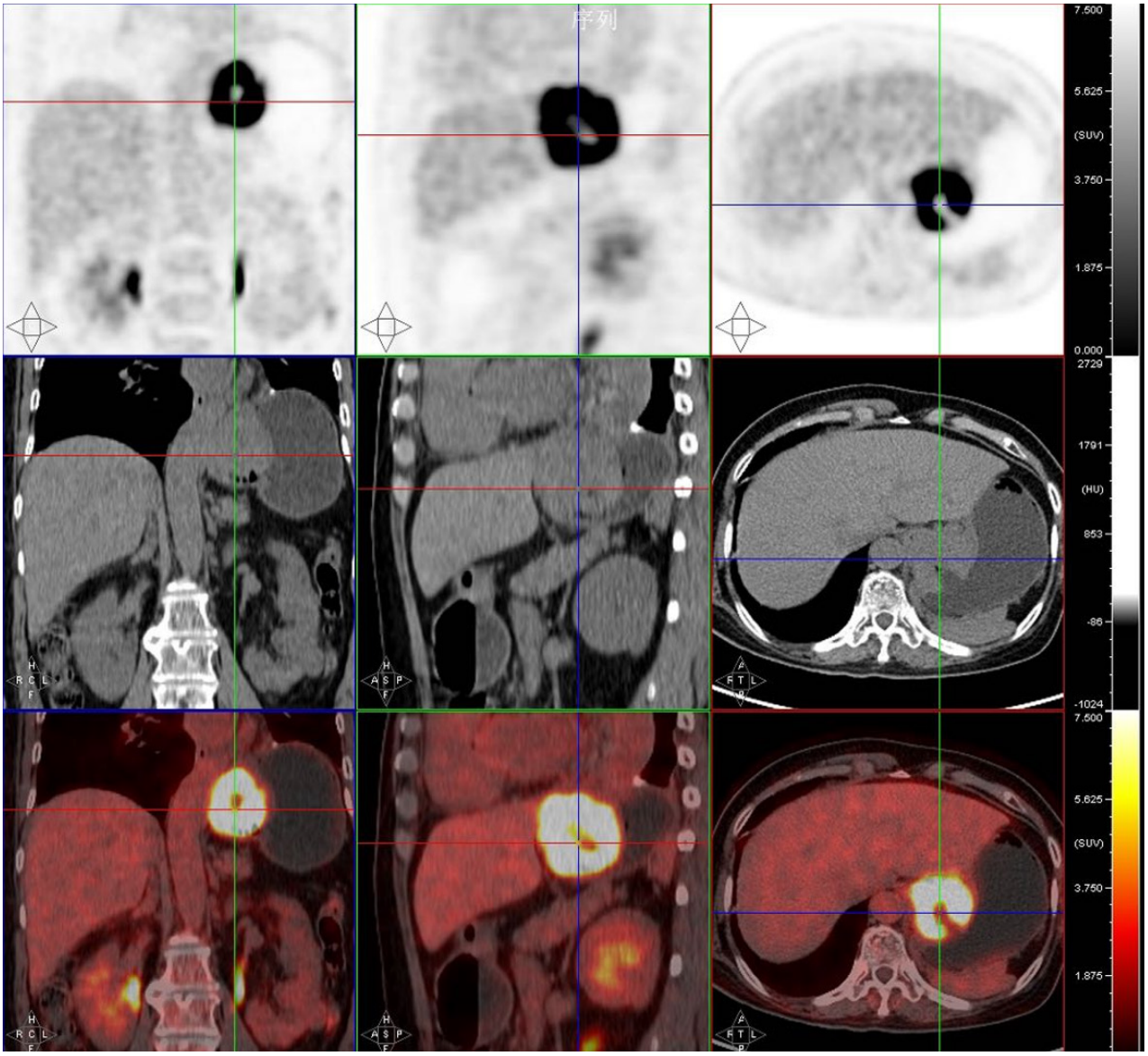

Figure 2 Positron emission tomography/computed tomography showing high accumulation of ^{18}F-fludeoxyglucose in the gastric cardia region. A maximum standardized uptake value of 20.03.

DISCUSSION

Pulmonary LELC is a rare type of non-small-cell lung cancer. Cases of pulmonary or metastatic LELC have been reported recently, but to our knowledge, this is the first report of stomach LELC metastasis secondary to a pulmonary tumor.

The most common approach for treating LELC is multimodal therapy. The expression of PD-1/PD-L1 may be related to the prognosis of LELC[10]. Growing evidence shows that ICIs are effective against pulmonary LELC[5]. One study reviewed 36 patients with PLELC treated with PD-1/PD-L1 inhibitors[6]. The objective response rate of all 36 patients was 57.6%, and the patients with higher PD-L1 expression were more likely to have a tumor response. In another study in which patients received multiple treatments that were ineffective, including surgery, chemotherapy and radiotherapy, ICIs proved to be a feasible option[11]. The efficacy of ICI therapy in patients with metastatic stomach LELC is unknown.

In one metastasis study[9], the patient was diagnosed with PLELC as well as metastasis to the mediastinal lymph nodes and liver. After five cycles of nivolumab, the tumor and the lesions in the liver became smaller. The values of CYFRA21-1 and NSE dramatically decreased. Another study found advanced thymic LELC with bone marrow metastases[12]. This patient responded well to toripalimab after 10 months of therapy. Based on the above evidence, we gave our patient a PD-1 inhibitor (toripalimab, 240 mg, intravenous drip) every 3 wk after discharge for ten cycles, with no radiographical evidence of tumor recurrence.

For this case, two questions are worth considering. First, what is the pathway through which lung cancer metastasizes to the stomach? Although gastric metastasis from lung cancer is rare, it can spread to the gastrointestinal tract through hematogenous and lymphatic routes[13]. Based on the findings in the positive LN, which was consistent with those in the stomach lesions, we believe that this patient's gastric metastasis was through the lymphatic pathway. Second, do we have better treatment options, such as PD-1 inhibitor treatment, before surgery? Because of the growing evidence about PD-1

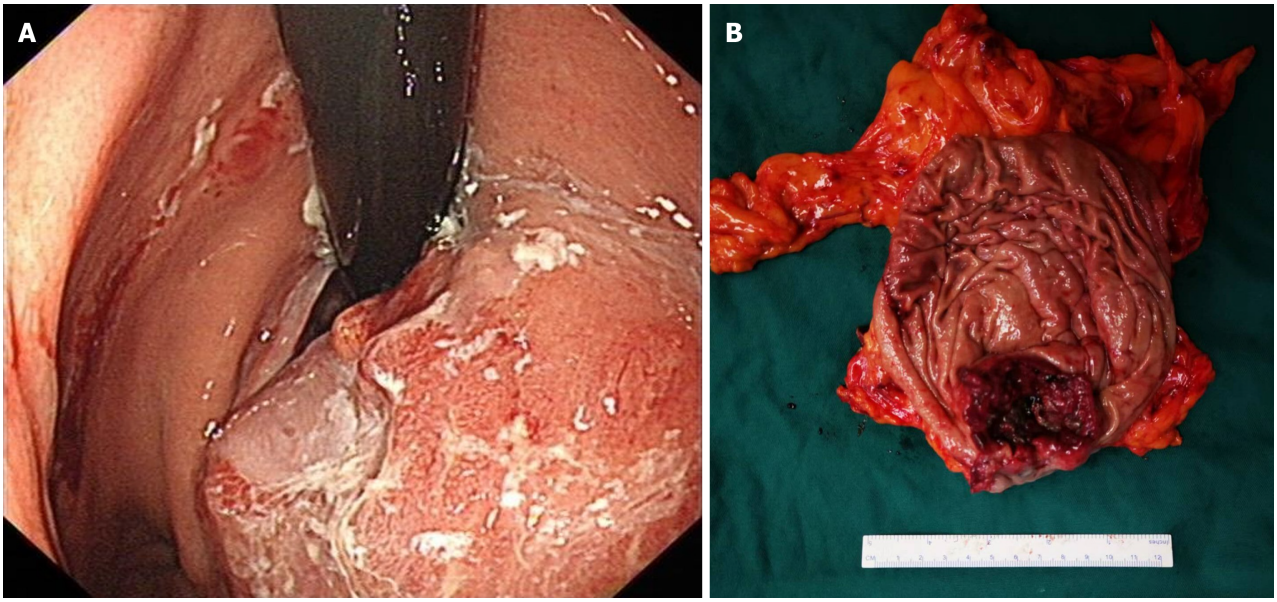

Figure 3 Upper endoscopy and surgical resection. A: The presence of a large mass of about 5 cm × 4 cm at the stomach fundus was confirmed by upper endoscopy; B: Surgical resection of the tumor revealed a large mass located in the stomach fundus near the cardia, showing a type of ulcer infiltrate measuring 6 cm × 5 cm.

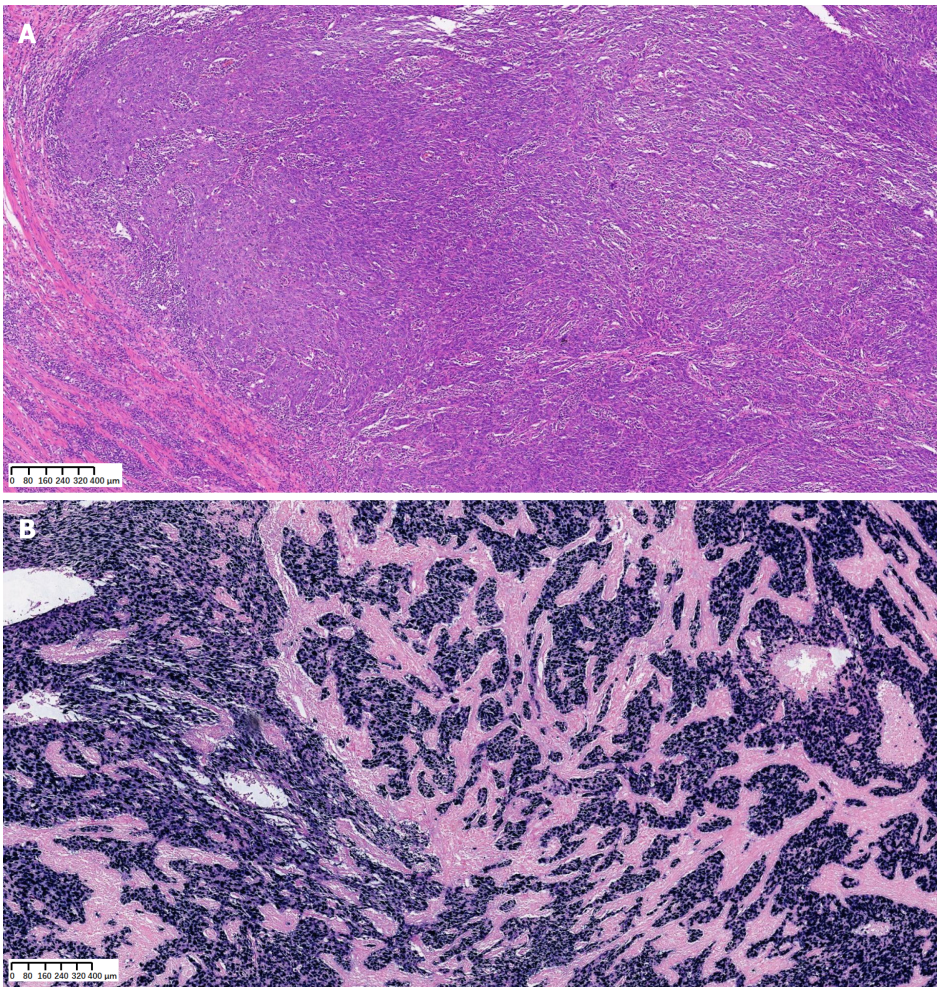

Figure 4 Hematoxylin and eosin staining and *in situ* hybridization. A: Histopathological examination of a stomach tumor section by hematoxylin and eosin staining, showing poorly differentiated carcinoma with prominent lymphoplasmacytic infiltration; B: *In situ* hybridization analysis showing positive staining for Epstein-Barr virus-encoded RNA.

inhibitors in pulmonary or metastatic LELC, we may prioritize PD-1 inhibitors in later-stage cases, especially for patients who cannot undergo surgical resection.

In conclusion, the present case presents a rare type of stomach tumor secondary to pulmonary LELC. This case demonstrates the necessity of IHC for differential diagnosis. ICIs such as PD-1 inhibitors may play an important role in the treatment of metastatic LELC.

CONCLUSION

The case suggested that for metastatic gastric LELC, PD-1 inhibitor therapy can become a potential therapeutic approach. However, there is still a lack of evidence from large data and large samples to support this.

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FOOTNOTES

Author contributions: Chen GF and Wang J contributed equally to this work; Chen GF and Wang J wrote draft of the manuscript and participated in the patient's treatment; Xu S performed the gastroscopy and provided the images; Yan Y, as a pathologist, performed the histological findings; Chen J supervised the study, developed the concept and edited the paper; and all authors have approved the final version of the manuscript.

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CASE REPORT

Treatment of anastomotic stricture after rectal cancer operation by magnetic compression technique: A case report

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Abstract

BACKGROUND

The treatment of postoperative anastomotic stenosis (AS) after resection of colorectal cancer is challenging. Endoscopic balloon dilation is used to treat stenosis in such cases, but some patients do not show improvement even after multiple balloon dilations. Magnetic compression technique (MCT) has been used for gastrointestinal anastomosis, but its use for the treatment of postoperative AS after colorectal cancer surgery has rarely been reported.

CASE SUMMARY

We report a 72-year-old man who underwent radical resection of colorectal cancer and ileostomy one year ago. An ileostomy closure was prepared six months ago, but colonoscopy revealed a narrowing of the rectal anastomosis. Endoscopic balloon dilation was performed three times, but colonoscopy showed no significant improvement in stenosis. The AS was successfully treated using MCT.

CONCLUSION

MCT is a minimally invasive method that can be used for the treatment of postoperative AS after colorectal cancer surgery.

Key Words: Rectostenosis; Magnetic surgery; Magnetic Surgery Clinic; Rectal cancer; Magnetic compression technique; Case report

Core Tip: Endoscopic balloon dilation of postoperative anastomotic stenosis (AS) after colorectal cancer surgery is not always effective. Repeated balloon dilation can aggravate the stenosis. Magnetic compression technique (MCT) has been used for gastrointestinal anastomosis, but its use for the treatment of postoperative AS of colorectal cancer has rarely been reported. This article reports the treatment process and outcomes of MCT for the treatment of postoperative AS after colorectal cancer surgery. Our experience suggests that MCT can be an effective treatment for postoperative AS in this setting.

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INTRODUCTION

The reported incidence of anastomotic stenosis (AS) after radical resection of colorectal cancer is about 3%-30%[1]. Anastomotic fistula, infection, and ultra-low anal preservation operation are risk factors for AS[2]. The typical symptoms of rectal AS include difficulty in defecation, bloating, and anal pain[3]. As a minimally invasive treatment, endoscopic balloon dilatation is routinely performed in clinical settings[4]. However, this technique is effective only in approximately 20% of patients[5]. Repeated endoscopic balloon dilatation in patients who show poor response may aggravate stenosis. The occurrence of AS prevents ileostomy closure, greatly reducing the quality of life of patients. For patients who do not respond to endoscopic balloon dilation, we propose an endoscopy-assisted magnetic compression technique (MCT) to treat AS, which achieved satisfactory therapeutic effect after initial clinical application.

CASE PRESENTATION

Chief complaints

A 72-year-old man who underwent radical resection of rectal cancer one year ago presented with rectal stenosis for the past 6 months.

History of present illness

The patient underwent radical resection of rectal cancer and ileostomy one year ago for rectal cancer. A colonoscopy performed six months ago revealed a narrow rectal anastomosis, which did not meet the indications for ileostomy reduction surgery. After endoscopic balloon dilation was performed three times, colonoscopy showed no improvement in the rectal stenosis (Figure 1A). The patient was recommended by the endoscopist to visit the Magnetic Surgery Clinic of the First Affiliated Hospital of Xi'an Jiaotong University for further treatment.

History of past illness

The past medical history was unremarkable.

Personal and family history

There was no family history of this condition.

Physical examination

The patient's vital signs were stable, and auscultation of the heart and lungs was normal. The abdomen was flat and soft with no tenderness. There was no mobile dullness and bowel sounds were normal. Ileostomy was visible in the lower right quadrant of the abdomen, and the intestinal mucosa of ileostomy was normal.

Laboratory examinations

There were no significant abnormalities in the patient's hematological examination.

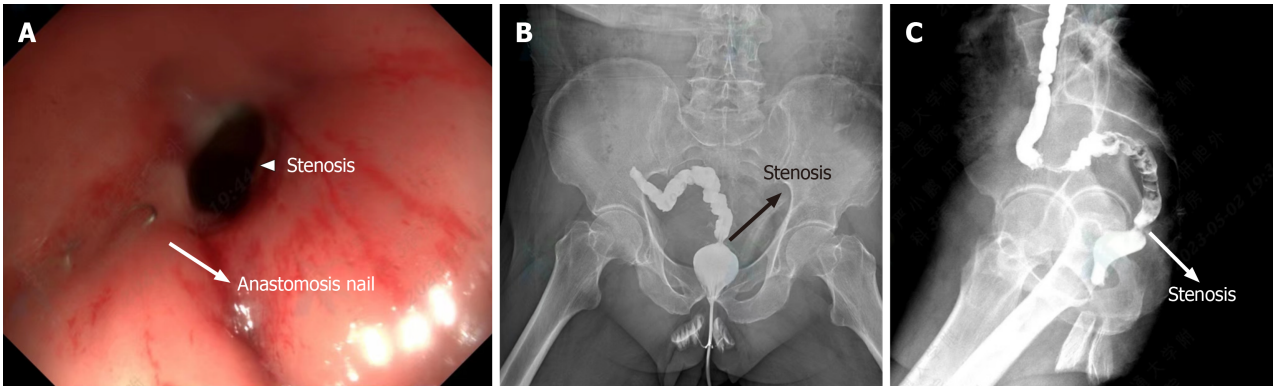

Figure 1 Preoperative examination. A: Colonoscopy; B and C: Colonography.

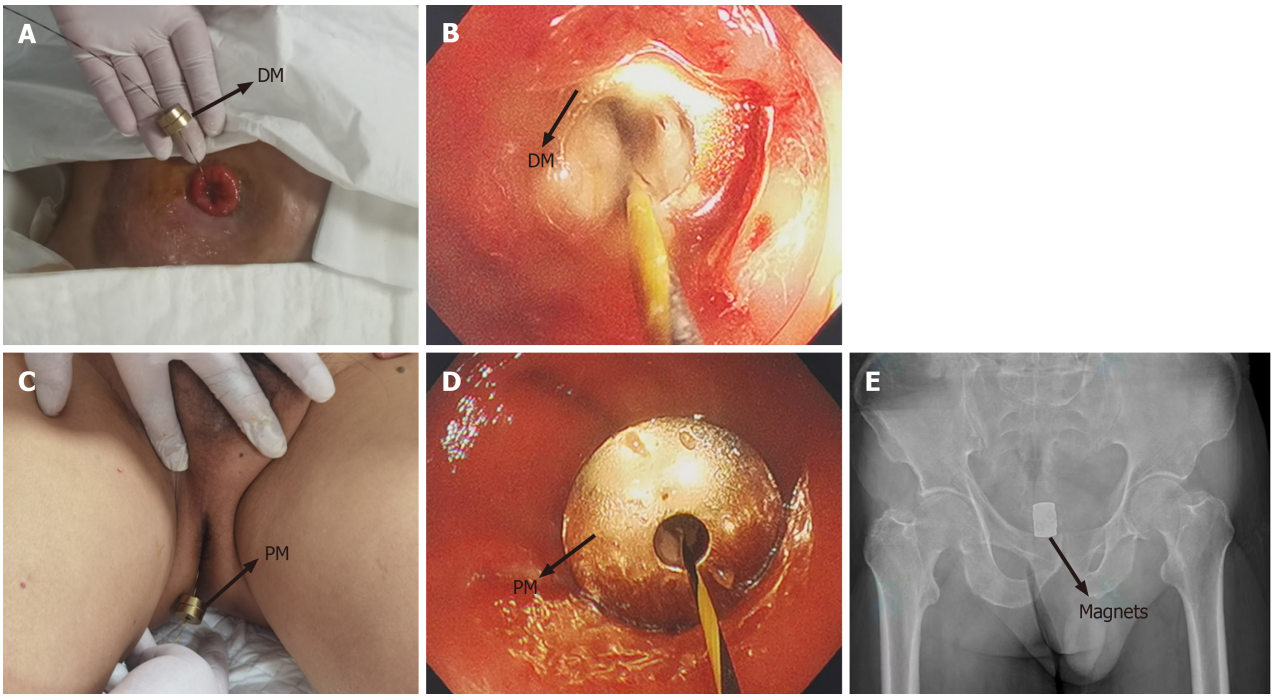

Figure 2 Magnet placement process. A: The daughter magnet (DM) was inserted along the zebra guide wire *via* ileostomy; B: Colonoscopy pushed the DM to the proximal end of the rectum stenosis; C: The parent magnet (PM) was inserted through the anus along the zebra wire; D: The PM reached the distal end of the rectum stenosis; E: The X-ray indicates the apposition of the daughter magnet and the PM. DM: Daughter magnet; PM: Parent magnet.

Imaging examinations

A 14Fr nasogastric tube was inserted through the anus and 80 mL iodohexol was injected. Rectal stenosis was observed by colonography (Figure 1B and C).

FINAL DIAGNOSIS

Based on the colonoscopy and colonography findings, the patient was diagnosed as having rectal AS.

TREATMENT

The patient signed an informed consent form for treatment. After intravenous anesthesia, the patient was placed supine. The colonoscope was inserted through the ileostomy and reached above the rectal stenosis. The zebra guide wire was inserted through the colonoscopy biopsy hole, and the zebra guide wire tip was adjusted to pass through the rectal stenosis and extrude from the anus. Two magnets with a 20-mm diameter and 6-mm height were used as daughter magnets (DM) having a 4-mm central hole. The central hole of the DM was inserted into the zebra guide wire on the side of the

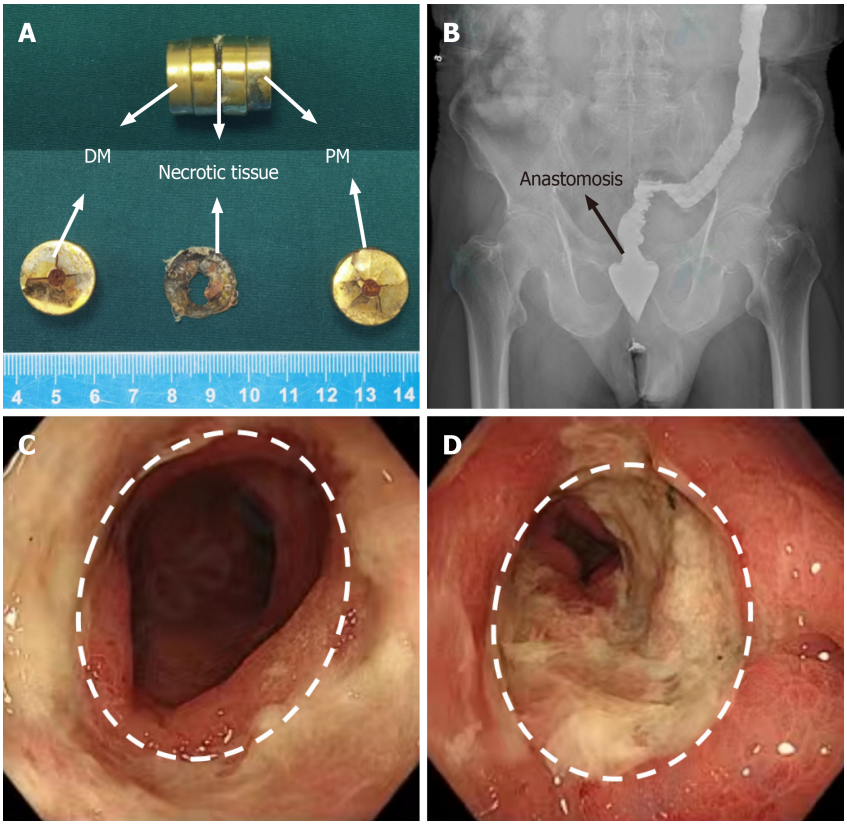

Figure 3 Postoperative examination. A: The daughter and parent magnets were discharged on the 11th d after surgery; B: X-ray shows good rectal patency; C and D: Colonoscopic images showing good patency at the site of anastomosis. DM: Daughter magnet; PM: Parent magnet.

ileostomy (Figure 2A), and the colonoscope was used to push the DM along the zebra guide wire to the upper part of the rectum stenosis (Figure 2B). Two magnetic rings with an outer diameter of 20 mm, an inner diameter of 4 mm, and a height of 6 mm were superimposed as the parent magnet (PM). The central hole of the PM was inserted into the zebra guide wire on the anal side (Figure 2C), and the colonoscope was used to push the PM along the zebra guide wire to the lower part of the rectum stenosis (Figure 2D). At this time, the DM and the PM automatically attracted each other, and the colonoscope and zebra guide wire were removed. X-ray was performed immediately to confirm that the magnets were in a good position (Figure 2E).

The patient recovered from anesthesia and resumed normal activities and oral intake. The patient was asked to pay attention to the discharge of the magnets. On the 11th day after surgery, the magnets were discharged through the anus, with detached necrotic tissue visible between the DMs and PMs (Figure 3A). An immediate colonography showed good patency of the lower rectum (Figure 3B). Colonoscopy showed good patency of the rectal anastomosis, and no ulcers, bleeding, or erosion at the magnetic anastomosis site (Figure 3C and D).

OUTCOME AND FOLLOW-UP

After discharge, the patient was asked to self-dilate with an 18-mm diameter anal dilator stick three times a day. The ileostomy closure surgery was completed one month later. The patient has been followed up for six months and has good bowel status.

DISCUSSION

MCT was first reported in 1978 for nonsuture microvascular anastomosis in experimental animals[6]. Later, this technique was used in coronary artery bypass surgery[7-9]. With further development, MCT has been used in digestive tract anastomosis[10-12], therapeutic fistula[13-15], and ureteral stenosis anastomosis[16,17]. The combination of MCT and endoscopic technology has greatly expanded its application for the treatment of digestive tract lesions[18,19].

The application of MCT in the digestive tract mainly focuses on gastrointestinal anastomosis. MCT has also been used for postoperative AS of colorectal cancer[20], but such studies have been rare, mainly due to the limited knowledge of surgeons and endoscopists about this technique. Previously, we reported the use of MCT for treating radiation-induced sigmoid stenosis with good long-term outcomes[21].

The MCT for the treatment of this patient had the following characteristics: First, this patient had an ileostomy, which can provide convenience for magnet placement. This patient had an easier procedure than those with rectal stenosis who did not have an ostomy. Second, the patient showed no response to repeated endoscopic balloon dilation, indicating a heavy scar in the stenosed area. Therefore, the magnet superposition scheme was adopted to increase the magnetic force between the DM and the PM. Third, there have been limited case reports of postoperative AS treated with MCT after rectal cancer surgery, and its long-term effect is unknown. Therefore, despite the good patency of the anastomosis after the discharge of magnets, in order to prevent restenosis, we recommended the patient to continue anal dilation.

CONCLUSION

This case indicates that MCT can be used as a new treatment method for patients with postoperative AS in whom endoscopic balloon dilation is not effective. It is a simple and minimally invasive treatment. The favorable outcome demonstrates that it is worth promoting.

FOOTNOTES

Author contributions: Yan XP and Lyu Y designed the operation and revised the manuscript; Zhang MM, Sha HC, Xue HR, Qin YF, and Yan XP performed the operation and drafted this manuscript; Dong FF and Zhang L assisted in perioperative care; and all authors have read and approved the final manuscript.

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CASE REPORT

Neuroendocrine carcinoma of the common hepatic duct coexisting with distal cholangiocarcinoma: A case report and review of literature

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Abstract

BACKGROUND

Neuroendocrine carcinoma (NEC) of the extrahepatic bile duct is very rare, and the treatment and prognosis are unclear. Herein, we report the case of a middle-aged female with primary large cell NEC (LCNEC) of the common hepatic duct combined with distal cholangiocarcinoma (dCCA). Additionally, after a review of the relevant literature, we summarize and compare mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) and pure NEC to provide a reference for selecting the appropriate treatment and predicting the prognosis of this rare disease.

CASE SUMMARY

A 62-year-old female presented to the hospital due to recurrent abdominal pain for 2 months. Physical examination showed mild tenderness in the upper abdomen and a positive Courvoisier sign. Blood tests showed elevated liver transaminase and carbohydrate antigen 199 levels. Imaging examination revealed

a 1-cm tumour in the middle and lower segments of the common bile duct. Pancreaticoduodenectomy + lymph node dissection was performed, and hepatic duct tumours were unexpectedly found during surgery. Pathology suggested poorly differentiated LCNEC (approximately 0.5 cm × 0.5 cm × 0.4 cm), Ki-67 (50%), synaptophysin+, and chromogranin A+. dCCA pathology suggested moderately differentiated adenocarcinoma. The patient eventually developed lymph node metastasis in the liver, bone, peritoneum, and abdominal cavity and died 24 months after surgery. Gene sequencing methods were used to compare gene mutations in the two primary bile duct tumours.

CONCLUSION
The prognosis of MiNEN and pure NEC alone is different, and the selection of treatment options needs to be differentiated.

Key Words: Neuroendocrine carcinoma; Mixed neuroendocrine-non-neuroendocrine neoplasm; Cholangiocarcinoma; Extrahepatic bile duct; Case report

Core Tip: We reported a rare case of primary large cell neuroendocrine carcinoma (NEC) of the hepatic duct combined with distal cholangiocarcinoma (dCCA). The overall survival was 24 months, and the prognosis was relatively good, which may be related to the early stage and low Ki-67 index of NEC and the early stage and moderate differentiation of the coexisting dCCA. To explore genetic causes, gene sequencing was performed on the two types of cancer tissue. A total of 35 gene mutations were detected in NEC tissue, and 7 gene mutations were detected in adenocarcinoma tissue.

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INTRODUCTION

Neuroendocrine carcinoma (NEC) is a malignant tumour that originates from peptidergic neurons and neuroendocrine cells and expresses neuroendocrine markers. NEC can occur in the whole body, especially the gastrointestinal (GI) tract, lung, pancreas, and thymus. NEC of the extrahepatic bile duct (EBNEC) is very rare, accounting for only 0.32% of NEC cases[1]. The patient in the reported case had primary large cell NEC (LCNEC) of the hepatic duct combined with distal cholangiocarcinoma (dCCA), which is even rarer. After a literature search, we believe that this is the first such case reported in the world. The common locations of EBNEC are the common hepatic duct and the distal end of the common bile duct (19.2%), the middle section of the common bile duct (17.9%), the cystic duct (16.7%), and the proximal end of the common bile duct (11.5%), and the median age of patients is 47.04 years. EBNEC is likely to occur in females, with a male to female ratio of 1.0:1.6[2]. The cause of EBNEC remains unclear. Chronic inflammation of the bile duct can lead to metaplasia of endocrine cells scattered on the bile duct epithelium, which may be the initial stage of NEC development [3].

In 1959, Davies was the first to report neuroendocrine tumours (NETs), which were then called carcinoids. In 2000, the World Health Organization (WHO) officially adopted the term NET. Studies have confirmed that the incidence of NEC is showing an upwards trend. The results of the National Epidemiological Survey in the United States showed that the annual standardized incidence of NETs increased from 1.09/100000 in 1973 to 6.98/100000 in 2012, a 6.4-fold increase in the age-adjusted incidence rate[4]. The results of the Cancer Registry of Norway showed that the prevalence of NEC increased from 7.4/100000 in 1993 to 21.56/100000 in 2021[5]. Currently, the 2019 WHO standards for digestive system tumours are used for classification and grading, and NEC is divided into LCNEC, small cell NEC and mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN); the 8th edition of the American Joint Committee on Cancer is often used for staging.

CASE PRESENTATION

Chief complaints

A 62-year-old female presented to the hospital due to recurrent abdominal pain for 2 months.

History of present illness

The pain location was identified as the middle upper quadrant. She reported that the pain was a feeling of swelling and did not radiate. She denied nausea, vomiting, chills, fever or jaundice. She had no previous history of hepatitis, tuberculosis, or special drug use, and she had no family history of cancer.

History of past illness

She was healthy and had no previous history of hepatitis, tuberculosi.

Personal and family history

She had no previous history of special drug use, and she had no family history of cancer.

Physical examination

Specialist examination at admission showed stable vital signs, no swollen superficial lymph nodes throughout the body, no yellow staining of skin and sclera, flat and soft abdomen, mild tenderness in the middle and upper abdomen, no rebound tenderness, no muscle guarding, positive Courvoisier sign, negative percussion pain in the liver and kidney region, nonpalpable liver and spleen under the ribs, negative movement dullness, and bowel sounds at 4 times/min.

Laboratory examinations

The results of a liver function examination at another hospital were as follows: Alanine aminotransferase, 174 U/L; aspartate aminotransferase, 125 U/L; alkaline phosphatase, 195 U/L; and gamma-glutamyl transferase 1036 U/L. Regarding tumour indicators, carbohydrate antigen 199 was 151.50 U/mL, and carcinoembryonic antigen and alpha-fetoprotein were normal.

Imaging examinations

Total abdominal computed tomography (CT) showed slight dilatation of the intrahepatic bile duct; the gallbladder was full in shape, with no obvious abnormal shadows. Magnetic resonance cholangiopancreatography (MRCP) showed local discontinuity of the middle segment of the common bile duct, mild dilatation of the upper segment of the common bile duct and intrahepatic bile duct, and a full gallbladder (Figure 1A). Enhanced magnetic resonance imaging of the upper abdomen showed slight thickening of the local wall of the middle and lower segments of the common bile duct with mild dilatation of the upper segment of the common bile duct and intrahepatic bile duct and an enlarged gallbladder. After admission, the IgG4 test was negative. Endoscopic ultrasound (EUS) showed a hypoechoic mass in the middle and lower segments of the common bile duct, with a size of approximately 1.02 cm × 0.9 cm and an irregular boundary (Figure 1B). EUS-guided fine needle aspiration was not performed due to the small mass.

FINAL DIAGNOSIS

In summary, the preoperative diagnosis was cholangiocarcinoma.

TREATMENT

After preoperative preparation, pancreaticoduodenectomy was performed. During the surgery, another exophytic tumour (approximately 0.5 cm × 0.5 cm and hard in texture) was accidentally found in the common hepatic duct, and the surrounding tissues were not infiltrated. Postoperative pathology and immunohistochemistry suggested poorly differentiated LCNEC, with a size of approximately 0.5 cm × 0.5 cm × 0.4 cm, Ki-67 (50%), synaptophysin (Syn)+, and chromogranin A (CgA)+. dCCA pathology suggested moderately differentiated adenocarcinoma (Figure 2). The size of the tumour was 1.0 cm × 1.0 cm × 0.4 cm, and it infiltrated the full thickness of the bile duct wall, with nerve invasion (+) and vascular tumour thrombus (-). No residual cancer was found in the margin, and no cancer metastasis was found in lymph nodes 8, 12, and 13. The operation, which lasted for approximately 5 h, went smoothly.

OUTCOME AND FOLLOW-UP

However, severe pancreatitis occurred after surgery (Figure 1C). The patient was discharged after 2 months of treatment. The disease course was accompanied by long-term pancreatic fistula and recurrent abdominal abscess, and adjuvant chemoradiotherapy had to be delayed. Follow-up data showed that multiple metastases in the liver 12 months after surgery, multiple metastases in the pelvis and bilateral femur, peritoneal metastasis and abdominal lymph node metastasis developed in the patient 21 months after surgery. The patient died 24 months after surgery.

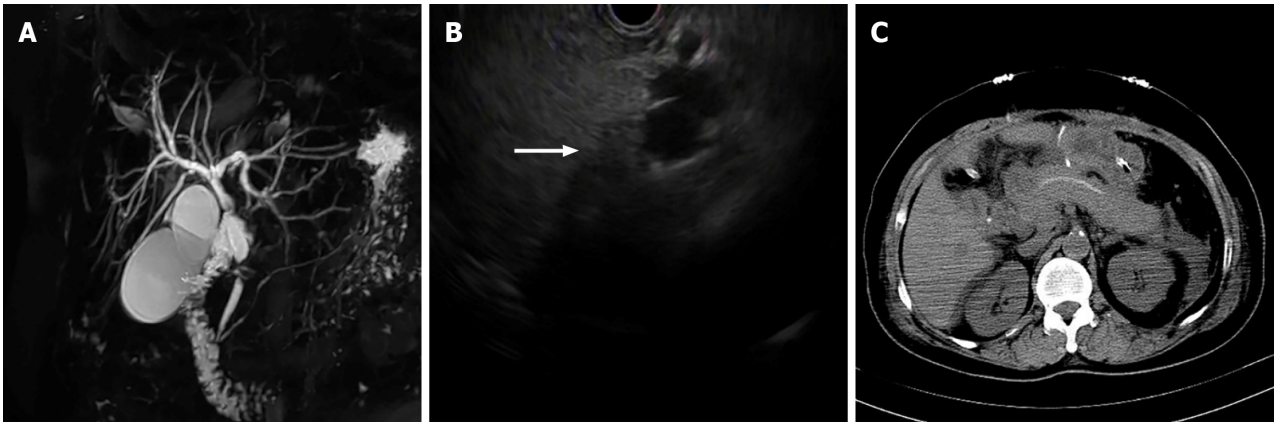

Figure 1 Imaging findings. A: Magnetic resonance cholangiopancreatography showed severe stenosis at the mid-portion of bile duct; B: Endoscopic ultrasound found a hypoechoic mass in the mid-portion and inferior portion of the common bile duct (white arrows); C: Computed tomography 3 d after surgery revealed significant pancreatic necrosis and exudation.

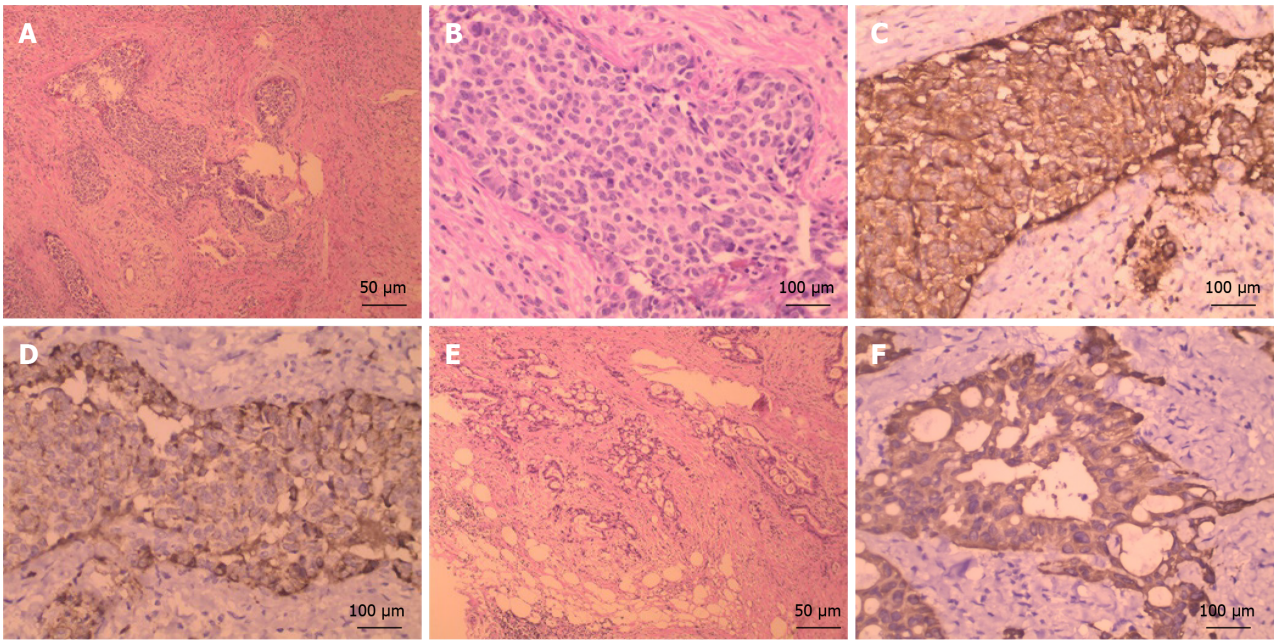

Figure 2 Histopathologic features in neuroendocrine carcinoma of the common hepatic duct coexisting with distal cholangiocarcinoma. A: The neuroendocrine carcinoma (NEC) showed a nested organoid growth pattern [hematoxylin and eosin (HE), × 100]; B: The NEC cells were round or oval, hyperchromatic nuclei and scant cytoplasm (HE, × 400); C: Immunohistochemically, the NEC cells were positive for synaptophysin(HE, × 400); D: Immunohistochemically, the NEC cells were positive for chromogranin A (HE, × 400); E: The distal cholangiocarcinoma (dCCA) cells arranged in irregular tubular and papillary structures (HE, × 100); F: Immunohistochemically, the dCCA cells were positive for cytokeratin 19 (HE, × 400).

DISCUSSION

The majority of extrahepatic CCA is adenocarcinoma; other types, especially NEC, are very rare[6]. A literature search in the PubMed and Web of Science databases was conducted, and articles on NEC of the intrahepatic bile duct, gallbladder, and ampulla of Vater and articles with incomplete data were excluded. A total of 48 English articles on EBNEC were obtained (Table 1)[1,7-52]. The main clinical and pathological features of MiNEN and pure NEC were briefly summarized and compared (Table 2), and the baseline characteristics of the two groups, including age, sex, tumour location, tumour size, and Ki-67, were not significantly different.

A total of 48 EBNEC cases (including this case) were included in this study, but the case reported by Edakuni *et al*[53] was excluded because the Ki-67 index was < 10%, below the threshold for NEC according to the latest WHO classification and grading system. The median age of the patients was 68.50 years (range 61.75-75.75), the majority of patients were men, and the male to female ratio was 2:1. Due to the lack of obvious early manifestations, the lack of clinically detectable serum markers, and the fact that most patients do not have carcinoid syndrome, EBNEC is usually not diagnosed in its early stage. Nonspecific manifestations, such as jaundice, fever, abdominal pain, and abdominal distension, may occur in the middle and late stages of EBNEC, and patients often only start to pay attention to these symptoms at this time. The

Table 1 Neuroendocrine carcinoma of the extrahepatic bile duct, review of the literature

Ref.	Age	Sex	Location	Symptom	Pathology	Size (mm)	Ki-67 index (%)	Treatment	Metastasis	Prognosis
van der Wal *et al*[7], 1990	55	Male	Bm	Jaundice, abdominal pain	SCNEC + AC	40	NA	SR	NA	12 months, alive
Nishihara *et al*[8], 1993	64	Male	Bh-Bs	Jaundice, weight loss	SCNEC + AC	19	NA	SR	NA	8 months, alive
Oikawa *et al*[9], 1998	70	Male	Bh-Bs	Jaundice	NEC	25	NA	SR	Liver	6 months, dead
Yamamoto *et al*[10], 1998	71	Female	Bh	Jaundice, fever	SCNEC + AC	60	NA	SR	Liver, bone	7 months, dead
Kim *et al*[11], 2000	64	Male	Bm	Abdominal pain	SCNEC + AC	30	NA	SR	NA	1 months, alive
Kuraoka *et al*[12], 2003	75	Male	Bi	Jaundice	SCNEC	45	90	SR	LN	5 months, alive
Hazama *et al*[13], 2003	60	Male	Bi	Jaundice	SCNEC	3	NA	SR	Brain, LN	17 months, dead
Park *et al*[14], 2004	60	Female	Bs-Bm	Jaundice	SCNEC	30	NA	SR	Brain, LN	17 months, dead
Thomas *et al*[15], 2005	54	Male	Bh-Bm	Jaundice	SCNEC	NA	NA	SR	Brain	6 months, alive
Kaiho *et al*[16], 2005	66	Female	Bi	Abdominal pain	SCNEC + AC	35	NA	SR + chemo	Liver	8 months, dead
Viana Miguel *et al*[17], 2006	76	Male	Bm	Jaundice	SCNEC	NA	NA	SR + chemo + radio	NA	5 months, alive
Jeon *et al*[18], 2006	65	Male	Bs-Bm	Jaundice	SCNEC	20	NA	SR + chemo	Liver	12 months, dead
Sato *et al*[19], 2006	68	Male	Bi	Jaundice	LCNEC + AC	20	71.4	SR	Liver	3 months, dead
Nakai *et al*[20], 2008	32	Male	Bs-Bi	Abdominal pain	SCNEC	NA	NA	NA	Liver, lung	18 d, dead
Hosonuma *et al*[21], 2008	69	Female	Bh-Bs	Jaundice	SCNEC	30	NA	NA	NA	2 months, dead
Arakura *et al*[22], 2008	75	Male	Bh-Bm	Jaundice	SCNEC	65	NA	Chemo + radio	Peritoneal, pleural, LN	10 months, dead
Okamura *et al*[23], 2009	62	Male	Bm	Abdominal, pain, fever	SCNEC	30	NA	SR + chemo + radio	Bone, LN	23 months, dead
Kohashi *et al*[24], 2009	77	Male	Bi	Jaundice	LCNEC	18	67	SR	Liver, lung, local	3 months, dead
Cho *et al*[25], 2009	59	Female	Bh	Jaundice, abdominal pain	SCNEC	30	NA	SR	NA	6 months, alive
Demoreuil *et al*[26], 2009	73	Male	Bs	Jaundice, abdominal pain, weight loss	LCNEC + AC	30	50	SR + chemo	Lung, peritoneal	12 months, dead
Masui *et al*[27], 2011	82	Male	Bm	Jaundice, anorexia	MANEC	25	35	SR	Liver	6 months, dead
Takahashi *et al*[28], 2012	28	Female	Bm	Pruritus	NEC	30	89.8	SR	None	36 months, alive
Ninomiya *et al*[29], 2013	74	Female	Bm	Jaundice	SCNEC	30	NA	SR	NA	14 months, alive
Sasatomi *et al*[30], 2013	76	Male	Bh	Jaundice	LCNEC	50	75	SR	LN	21 d, dead
Linder *et al*[31], 2013	82	Male	Bi	Jaundice, abdominal pain, weight loss	MANEC	19	NA	SR	None	6 months, alive

Park *et al*[32], 2014	75	Female	Bm	Nausea, jaundice	LCNEC	27	NA	SR + chemo	Local	12 months, dead
Lee *et al*[33], 2014	75	Male	Bs	Jaundice	SCNEC + AC	20	NA	SR	None	11 months, alive
Wysocki *et al* [34], 2014	65	Male	Bm	Jaundice, vomit, weight loss	LCNEC + AC	36	80	SR	NA	5 months, dead
Aigner *et al* [35], 2015	61	Male	Bm	Abdominal pain, jaundice, nausea, pruritus	SCNEC	27	90	SR + chemo	Liver, LN, bone	3 months, alive
Kihara *et al* [36], 2015	70	Female	Bh	Jaundice	SCNEC	30	70	SR + chemo	None	10 months, alive
Nakamaru *et al* [37], 2015	75	Male	Bh-Bm	Jaundice	SCNEC	40	NA	SR + chemo	NA	16 months, alive
Oshiro *et al* [38], 2016	72	Male	Bs	Jaundice	LCNEC	30	56.2	SR + chemo	Liver	7 months, alive
Katada *et al* [39], 2016	78	Male	Bh	Jaundice	SCNEC	30	NA	SR + chemo	NA	5 months, alive
Murakami *et al* [40], 2016	80	Male	Bm	Jaundice, anorexia	LCNEC + AC	24	72	SR	Liver, lung, peritoneal	3 months, dead
Priyanka Akhilesh *et al* [41], 2016	76	Male	Bh	Jaundice, weight loss	MANEC	14	90	SR	NA	NA
Izumo *et al*[42], 2017	66	Male	Bi	Jaundice, anorexia, fatigue	LCNEC + AC	10	30	SR	None	30 months, alive
Komo *et al*[43], 2017	82	Male	Bi	Liver dysfunction	MANEC	18	37	SR	None	7 months, alive
Park and Jeon [44], 2018	59	Male	Bh	Jaundice	LCNEC	62	20	SR + chemo	None	10 months, alive
Zhang *et al*[45], 2018	62	Male	Bh	Jaundice	SCNEC	20	80	SR	Liver	6 months, dead
Koo *et al*[46], 2019	77	Female	Bh	Jaundice, abdominal pain	LCNEC	10	60	Radio	Liver	1.5 months, alive
Zhang *et al*[47], 2019	60	Male	Bh-Bs	Abdominal pain	LCNEC + AC	17	70	SR	NA	NA
Zhang *et al*[48], 2019	64	Female	Bi	Jaundice, abdominal pain	MANEC	45	50	SR	Liver, lung	12 months, dead
Kamiya *et al* [49], 2020	84	Male	Bm	Jaundice, abdominal pain	MANEC	25	80	SR	Liver	3 months, dead
Kiya *et al*[50], 2021	29	Female	Bm	Abdominal pain	LCNEC	50	90	SR + chemo	NA	16 months, alive
Sugita *et al*[51], 2022	62	Female	Bi	Jaundice	SCNEC + AC	19	80	SR	NA	4 months, alive
Han *et al*[52], 2023	84	Female	Bs	Abdominal pain	SCNEC	17	85	NA	NA	NA
Jevdokimov *et al*[1], 2023	42	Female	Bs	Jaundice	NEC	30	75	SR + chemo	NA	4 months, alive
This study	62	Female	Bh	Abdominal pain	LCNEC	5	50	SR	Liver, LN, bone	24 months, dead

AC: Adenocarcinoma; NEC: Neuroendocrine carcinoma; SCNEC: Small cell neuroendocrine carcinoma; LCNEC: Large cell neuroendocrine carcinoma; MANEC: Mixed adenoneuroendocrine carcinoma; SR: Surgical resection; Chemo: Chemotherapy; Radio: Radiotherapy; Bh: Hilar bile duct; Bs: Superior portion of common bile duct; Bm: Mid-portion of common bile duct; Bi: Inferior portion of common bile duct; LN: lymph node(s); NA: not available.

main clinical manifestations of the 48 EBNEC patients included jaundice (37/48), abdominal pain (16/48), weight loss (5/48), anorexia (3/48), nausea (2/48), pruritus (2/48), fever (2/48), fatigue (1/48), vomiting (1/48), and liver dysfunction (1/48). A small number of EBNECs are nonfunctional tumours in the early stage and transition into functional tumours as the disease progresses. Therefore, dynamic observation and evaluation of clinical manifestations are helpful for diagnosis.

Table 2 Comparison of neuroendocrine-non-neuroendocrine neoplasm and pure neuroendocrine carcinoma in the extrahepatic biliary tract

	MiNEN	Pure NEC
Number of cases	19	29
Age, yr	70.47 ± 8.67	64.07 ± 14.88
Sex		
Male	15	17
Female	4	12
Location		
CHD	2	8
CBD	15	5
CHD + CBD	2	16
Symptom		
Jaundice/pruritus	15	24
Abdominal pain	8	8
Anorexia/nauseas/vomit/fatigue/weight loss/ fever	9	3
Size, mm	26.63 ± 12.22	30.15 ± 15.08
Ki-67 index, %	62.12 ± 20.61	69.42 ± 20.75
Treatment		
SR	17	12
SR + chemo/radio	2	12
Chemo/radio	0	2
Metastasis		
Liver	7	9
Lymph node	0	8
Lung	3	2
Bone	1	3
Brain	0	3
Peritoneal/pleural/local	2	3

MiNEN: Mixed neuroendocrine-non-neuroendocrine neoplasm; NEC: Neuroendocrine carcinoma; CHD: Common hepatic duct; CBD: Common bile duct; SR: Surgical resection; Chemo: Chemotherapy; Radio: Radiotherapy.

Using colour Doppler ultrasound, CT, MRCP, and positron emission tomography-CT to preoperatively diagnose EBNEC is still difficult, and EBNEC is especially difficult to differentiate from other CCAs; however, these techniques are helpful for determining positioning and the presence of liver invasion, lymph node and distant metastasis, *etc*. NEC is a malignant tumour with a strong metastatic tendency. Studies have reported that more than half of patients with GI-NEC have distant metastasis when newly diagnosed[45]. Percutaneous transhepatic cholangiography (PTC), endoscopic brushing examination and needle biopsy can be used to obtain preoperative pathological results for diagnosis, but the positivity rate is low. In this study, 2 patients were pathologically confirmed by preoperative PTC[13,23], and 8 patients were pathologically confirmed by endoscopic biopsy[1,14,35-37,42,43,46]. The diagnosis of NEC often relies on immunohistochemistry, and there are a specific set of markers, such as neuron-specific enolase, CgA, Syn, and Ki-67, and cluster of differentiation 5.

Due to the low incidence, effective treatment guidelines for EBNEC are lacking, and radical surgical resection is considered the preferred treatment. In this study, 43 of 48 patients underwent surgery. The surgical method was determined based on the location of the tumour: Extrahepatic CCA resection was chosen for NEC of the common hepatic duct and upper segment of the common bile duct, and pancreatoduodenectomy was chosen for NEC of the middle and lower segments of the common bile duct; regional lymph node dissection was also recommended. For patients with focal liver metastasis, partial hepatectomy can be used to remove primary and metastatic lesions as much as possible; this approach was used in 7 of 48 patients in this study. To date, adjuvant therapy for EBNEC lacks standardization, and the

roles of chemotherapy, radiotherapy and immunotherapy are still unclear. Commonly used chemotherapy regimens include cisplatin and etoposide[17,22,26,38,44] and cisplatin and irinotecan[37,39,50]. As neoadjuvant chemotherapy regimens, these two regimens can successfully achieve conversion. In this study, 4 patients received subsequent surgical treatment and achieved an overall survival (OS) of 16-23 months[13,14,23,37]. For NEC recurrence or metastasis, radiotherapy, transarterial chemoembolization, and ablation therapy should be considered. Studies have found that the expression of programmed death-ligand 1 in poorly differentiated NET cells is higher than that in well-differentiated NET cells, indicating that when applying the most appropriate settings, combinations and treatment sequences, immunotherapy may become a powerful treatment for NEC in the future[54].

EBNEC is poorly differentiated and invasive and has a poor prognosis. A recent retrospective study using the Surveillance, Epidemiology, and End Results database to perform propensity score matching of 62 EBNEC and 3215 CCA patients showed that the overall prognosis of EBNEC was better than that of CCA and that neuroendocrine components could be used as a favourable prognostic factor for CCA patients. Kaplan-Meier analysis of 45 EBNEC patients with survival follow-up data showed that the median OS was 12 months (Figure 3A); the survival of MiNEN patients was worse than that of patients with pure NEC; and the median survival of patients with MiNEN and pure NEC was 12 months and 17 months, respectively (Figure 3B), but the difference was not statistically significant (P = 0.20). We believe that the confounding non-NEC components of MiMEN may be more malignant than those of ENC, which may explain the poorer prognosis of MiMEN than pure NEC.

The OS of the patient in this study was 24 months, and the prognosis was relatively good, which may be related to the early stage and low Ki-67 index of NEC and the early stage and moderate differentiation of the coexisting dCCA. To explore genetic causes, gene sequencing was performed on two types of cancer tissue, primary LCNEC of the hepatic duct and dCCA. High-throughput sequencing was performed using the Illumina NextSeq 500/550 next-generation sequencing platform and the NGS-Panel 639 developed by high-efficiency hybridization capture technology (AllNGSTM) independently developed by Yunying Medical Inspection Institute. The sequencing results are shown in Table 3. A total of 35 gene mutations were detected in NEC tissue, and 7 gene mutations were detected in adenocarcinoma tissue; additionally, the number of gene mutations in NEC was significantly higher than that in adenocarcinomas. In addition, the types and loads of gene mutations in these two types of tumours were also quite different. We speculate that different gene mutations and different loads could affect the targeted drugs and the prognosis of tumours, but the specific mechanism of action still needs to be elucidated.

This study has limitations. The main limitation is the small number of reported cases. Therefore, in future clinical work, a multidisciplinary team is needed to summarize more case reports, carry out multimodal treatment and pathogenesis studies, and establish more standardized and unified guidelines and consensus to prolong the life of EBNEC patients.

CONCLUSION

Herein, we reported a rare case of primary LCNEC of the hepatic duct combined with dCCA. The number of gene mutations in primary LCNEC of the hepatic duct in this patient was significantly greater than that in dCCA. EBNEC is very rare and invasive, making preoperative diagnosis difficult; treatment options are not uniform, and the prognosis is poor. We believe that the prognoses of MiMEN and pure NEC are different and, thus, that the selection of treatment options needs to be differentiated.

Table 3 Comparison of gene mutations in the two primary bile duct tumours

Gene	LCNEC	dCCA
ERBB2	14.10%, exon17, c.2033G>A, p.R678Q	3.70%, exon17, c.2033G>A, p.R678Q
	10.80%, exon17, c.1970C>T, p.A657V	
ERBB3	20.10%, exon3, c.310G>A, p.V104M	3.60%, exon3, c.310G>A, p.V104M
LCE1F	43.40%, exon2, c.244C>T, p.R82W	41.70%, exon2, c.244C>T, p.R82W
MSH6	47.80%, exon5, c.3173-3C>G	47.30%, exon5, c.3173-3C>G
	18.00%, exon6, c.3514dup, p.R1172fs	
FCAMR	47.00%, exon4, c.250C>T, p.R84W	47.90%, exon4, c.250C>T, p.R84W
BRAF	No	1.30%, exon11, c.1391G>T, p.G464V
CREBBP	45.10%, exon28, c.4711G>A, p.A1571T	52.90%, exon28, c.4711G>A, p.A1571T
ARID1A	17.20%, exon5, c.2077C>T, p.R693*	No
	17.20%, exon20, c.5842_5843del, p.S 1948fs	
KMT2C	13.30%, exon46, c.11878C>T, p.R3960	No

	19.80%, exon36, c.5668C>T, p.R1890	
KMT2D	21.30%, exon12, c.3318del, p.S1107fs	No
KRAS	18.50%, exon2, c.38G>A, p.G13D	No
CDKN2A	22.20%, exon2, c.238C>T, p.R80	No
ATR	19.30%, exon7, c.1544G>A, p.R515H	No
NTRK1	15.30%, exon11, c.1330C>T, p.R444W	No
CDC73	12.40%, exon6, c.439C>T, p.R147C	No
FOXP1	29.40%, exon12, c.952G>A, p.E318K	No
FBXW7	30.10%, exon10, c.1514G>A, p.R505H	No
MAP3K1	25.10%, exon3, c.746G>A, p.R249H	No
CTNNA1	13.50%, exon7, c.943G>A, p.G315R	No
PRKDC	15.30%, exon73, c.10241C>T, p.T3414M	No
RUNX1T1	23.10%, exon8, c.1084G>A, p.A362T	No
RIC8A	21.30%, exon3, c.568C>T, p.R190C	No
CBL	8.90%, exon14, c.2222C>T, p.A741V	No
KDM5A	15.60%, exon26, c.4400G>A, p.R1467Q	No
	19.80%, exon23, c.3470G>A, p.R1157H	
RB1	15.10%, exon8, c.763C>T, p.R255*	No
	15.30%, exon18, c.1735C>T, p.R579*	
TP53	2.20%, exon5, c.473G>A, p.R158H	No
BCOR	15.10%, exon4, c.1754G>T, p.R585M	No
STAG2	19.60%, exon9, c.775C>T, p.R259*	No
BCORL1	21.80%, exon4, c.1279G>A, p.A427T	No
	18.10%, exon8, c.4258C>T, p.R1420*	

LCNEC: Large cell neuroendocrine carcinoma; dCCA: Distal cholangiocarcinoma.

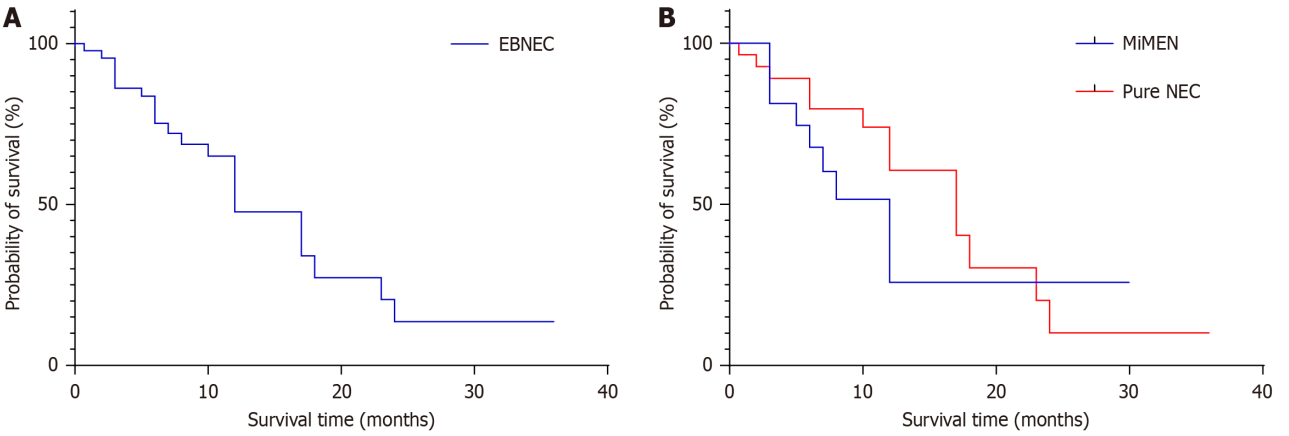

Figure 3 Kaplan-Meier survival curve of the 45 neuroendocrine carcinomas of the extrahepatic bile duct patients with survival follow-up data. A: The median overall survival was 12 months; B: Kaplan-Meier survival curves of extrahepatic bile duct patients with neuroendocrine-non-neuroendocrine neoplasm and pure neuroendocrine carcinoma were compared and log-rank test were assessed for significance (P = 0.20). MiNEN: Mixed neuroendocrine-non-neuroendocrine neoplasm; EBNEC: Extrahepatic bile duct patients with neuroendocrine-non-neuroendocrine neoplasm; NEC: Neuroendocrine carcinoma.

FOOTNOTES

Author contributions: Chen F, Li WW, Mo JF, Yang SY, and Song ZW designed the research; Chen F, Li WW, and Mo JF performed the research; Chen MJ and Wang SH contributed new reagents/analytic tools; Chen F, Li WW, and Mo JF analyzed the data; Chen F, Li WW,

Mo JF, and Yang SY wrote the paper. Chen F and Li WW contributed equally and shared co-first authorship. Yang SY and Song ZW contributed equally and shared corresponding author.

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CASE REPORT

Hem-o-lok clip migration to duodenal bulb post-cholecystectomy: A case report

Hong-Yan Liu, Ai-Hong Yin, Zhi Wei

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Abstract

BACKGROUND

Hem-o-lok clips are typically used to control the cystic duct and vessels during laparoscopic cholecystectomy (LC) and common bile duct exploration for stones in the bile duct and gallbladder. Here, we report a unique example of Hem-o-lok clip movement towards the duodenal bulb after LC, appearing as a submucosal tumor (SMT). Additionally, we provide initial evidence of gradual and evolving endoscopic manifestations of Hem-o-lok clip migration to the duodenal bulb wall and review the available literature.

CASE SUMMARY

A 72-year-old man underwent LC for gallstones, and Hem-o-lok clips were used to ligate both the cystic duct and cystic artery. Esophagogastroduodenoscopy (EGD) 2 years later revealed an SMT-like lesion in the duodenal bulb. Due to the symptomatology, the clinical examination did not reveal any major abnormalities, and the patient was followed up as an outpatient. A repeat EGD performed 5 months later revealed an SMT-like lesion in the duodenal bulb with raised edges and a central depression. A third EGD was conducted, during which a Hem-o-lok clip was discovered connected to the front side of the duodenum. The clip was extracted easily using biopsy forceps, and no complications occurred. Two months after the fourth EGD, the scar was surrounded by normal mucosa.

CONCLUSION

Clinicians should be aware of potential post-LC complications. Hem-o-lok clips should be removed if symptomatic.

Key Words: Hem-o-lok clip; Migration; Duodenum; Laparoscopic cholecystectomy; Laparoscopic common bile duct exploration; Case report

Core Tip: Migration of Hem-o-lok clips to the duodenal bulb may manifest as a slightly raised lesion resembling a submucosal tumor in the duodenal bulb. A gradual alteration in the endoscopic view of the lesion could be seen as the Hem-o-lok clip migrates through the wall of the duodenal bulb. Although Hem-o-lok clip migration to the duodenal bulb is infrequent, clinicians must be highly attentive and vigilant regarding these complications to avoid misdiagnosis.

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INTRODUCTION

Migration of a Hem-o-lok clip to the duodenal bulb after laparoscopic cholecystectomy (LC) is rare in clinical practice[1]. Herein, we report on a gradual and evolving process of Hem-o-lok clip movement towards the duodenal bulb subsequent to LC. In addition, we have examined the research papers on the migration of Hem-o-lok clips to the duodenal bulb post-LC that were indexed in the PubMed database. We conducted the search using keywords including "Hem-o-lok clip", "migration", "duodenum", "laparoscopic cholecystectomy", and "laparoscopic common bile duct exploration". Approximately 6 cases were retrieved, and we provide a summarization and analysis of them in detail.

CASE PRESENTATION

Chief complaints

A 72-year-old man presented with a complaint of abdominal pain, which had persisted over the previous 10 d.

History of present illness

The patient had undergone LC for symptomatic gallstone disease 2 years previously and presented to the hospital complaining of the persistent abdominal pain. Hem-o-lok clips had been used to control the cystic duct and artery during the LC. An adhesion in the gallbladder triangle and an inflamed and dilated bile duct had been discovered during surgery, and the operation had been difficult. Two years after the LC, he underwent a screening esophagogastroduodenoscopy (EGD), which revealed a submucous tumor (SMT)-like lesion in the duodenal bulb with normal overlying mucosa (Figure 1A). Nevertheless, he remained asymptomatic after the EGD and was monitored as an outpatient. After 5 months, he underwent a second EGD, which revealed an SMT-like lesion in the duodenal bulb with raised edges and a central depression (Figure 1B). Physical examination revealed no major abnormalities. Therefore, he continued with outpatient follow-up. After 5 months, he was hospitalized due to the 10 d of abdominal discomfort.

History of past illness

The patient had a clinical history of primary esophageal, hypopharyngeal, and lung cancers. Additionally, he had hypertension and coronary artery disease.

Personal and family history

The patient had a history of excessive tobacco use and consumption of alcoholic beverages.

Physical examination

Vital signs were stable for the patient. He also showed no tenderness or rebound tenderness upon palpation, and the abdomen was flat and soft.

Laboratory examinations

Routine coagulation test and tumor marker test results were within normal limits.

Imaging examinations

An SMT-like lesion, with a fixed foreign body, covered by white exudates, was observed in the duodenal bulb during the third EGD (Figure 1C). Around the lesion, erosions and edema were observed in the duodenum. When the biopsy forceps were used to touch the lesion, it was hard and active. Abdominal computed tomography (CT) revealed that the foreign body had migrated into the duodenal bulb (Figure 2).

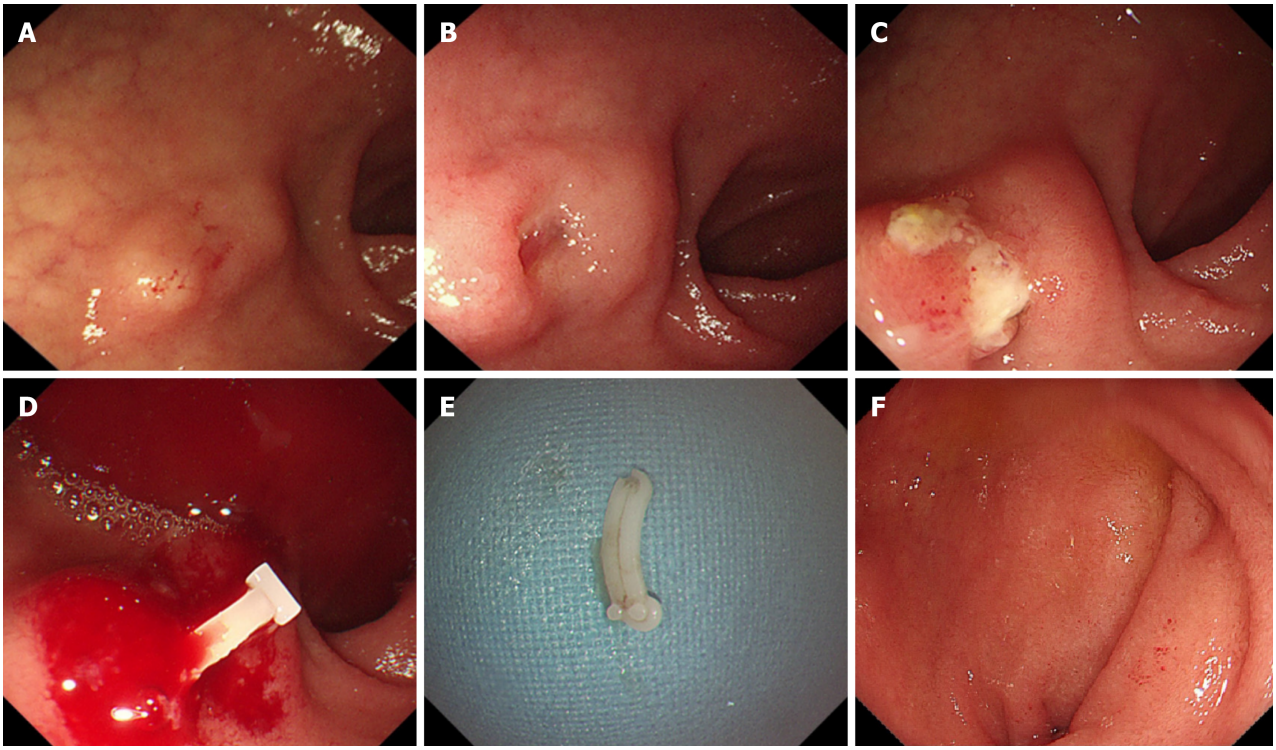

Figure 1 The esophagogastroduodenoscopy results. A: The first esophagogastroduodenoscopy (EGD) revealed a submucosal tumor (SMT)-like lesion in the duodenal bulb with normal overlying mucosa; B: The second EGD revealed an SMT-like lesion in the duodenal bulb with raised edges and central depression; C: The third EGD revealed an SMT-like lesion, covered by white exudates, with erosions and edema. The lesion was active and hard when touched with biopsy forceps; D: Olympus grasping forceps removed the foreign body; E: The foreign body was a Hem-o-lok clip; F: The fourth EGD revealed the duodenum was covered with normal mucosa.

Figure 2 Computed tomography scan examination. Computed tomography scan shows a foreign body in the duodenum.

FINAL DIAGNOSIS

The patient was diagnosed as foreign body in duodenal bulb.

TREATMENT

Olympus grasping forceps were used to remove the foreign body (Figure 1D), which was the Hem-o-lok clip (Figure 1E). The patient was discharged from the hospital the next day without complications such as hemorrhage and perforation.

OUTCOME AND FOLLOW-UP

After 2 months, we performed another EGD. The clip was no longer visible, and the duodenum exhibited a healthy

Table 1 Review of case reports of Hem-o-lok clip migration to the duodenal bulb post-cholecystectomy

Ref.	Patients, *n*	Age in yr	Sex	Clips	Type of surgery	Time from surgery	Symptoms	Diagnosis	Treatment
Mantoo *et al*[13], 2010	1	57	F	Hem-o-lok	LC	1 yr	Melena	EGD	Endoscopic removal
Seyyedmajidi *et al*[14], 2013	1	41	M	Hem-o-lok	LC	8 months	Abdominal pain	EGD	Endoscopic removal
Soga *et al*[15], 2016	1	66	F	Hem-o-lok	LC	13 months	Asymptomatic	EGD + CT	PPI/spontaneous detachment
Padmanabhan *et al*[18], 2016	1	59	F	Hem-o-lok	LC	2 yr	Melena	EGD + CT	ND
Zheng *et al*[19], 2018	1	54	M	Hem-o-lok	LC + LCBDE	4 months	Abdominal pain	EGD	Observation
Yang *et al*[20], 2023	1	67	F	Hem-o-lok	LC	ND	Abdominal pain	EGD + CT	Endoscopic removal

CT: Computed tomography; EGD: Esophagogastroduodenoscopy; LC: Laparoscopic cholecystectomy; LCBDE: Laparoscopic common bile duct exploration; ND: Not described; PPI: Proton pump inhibitor.

mucosal covering (Figure 1F).

DISCUSSION

Since the Hem-o-lok clip's inception in 1999, it has been used for a wide variety of applications in the urinary tract, hepatobiliary, and gastrointestinal surgeries. Complications associated with postoperative Hem-o-lok clip displacement have been reported[2-5]. Postoperative clip displacement can lead to various complications, such as rectal elevated lesion caused by Hem-o-lok clip migration after prostate cancer surgery, abscess in the fallopian tube caused by Hem-o-lok clip migration after laparoscopic appendectomy, and dysphagia caused by Hem-o-lok clip migration into the esophagus subsequent to clamping of the azygous vein after radical resection of distal esophageal cancer[6-8]. LC and laparoscopic common bile duct exploration (LCBDE) are the most effective way to treat gallbladder stones, gallbladder polyps, and cholecystitis[9,10]. Hem-o-lok clips are commonly utilized for clamping the arteries and ducts of the gallbladder during LC and LCBDE. Although several previous reports have described Hem-o-lok clip migration in the biliary system, which can lead to stones, bile leakage, and cholangitis, very few reports have described the Hem-o-Lok clip's postoperative migration to the duodenal bulb[11-13].

Migration of the Hem-o-Lok clip to the duodenal bulb can manifest as various endoscopic findings, including ulcers, erosions of the mucosa, and lesions resembling SMTs[14,15]. In this particular instance, the Hem-o-lok clip migrated to the duodenal bulb following LC and presented as a lesion resembling an SMT, requiring differentiation from polyps, cysts, stromal tumors, ectopic pancreatic lipomas, and carcinoids. Initially, the patient exhibited a gradual and evolving endoscopic presentation of Hem-o-lok clip movement towards the wall of the duodenal bulb.

After conducting a thorough search in the PubMed database, we discovered a total of 6 cases (4 women/2 men) since 2010 where Hem-o-lok clip migration to the duodenal bulb occurred following a LC. These cases are documented in Table 1 with corresponding references. The latest migration occurred 2 years post-LC and LCBDE, and the earliest occurred at nearly at 4 months. Minimum and maximum ages were 41 years and 67 years, respectively[14]. Of these, 1 patient was asymptomatic and 5 were symptomatic (*e.g.*, melena or abdominal pain). The clinical manifestations of clip migration to duodenal bulb were also atypical, including abdominal pain, nausea, vomiting, gastrointestinal bleeding, and anemia. It is easy to miss diagnosis and misdiagnosis[1,15]. The clip was discharged spontaneously without complication in 1 case.

However, there is no clear etiology or exact incidence for clip migration[16-18]. We considered three possible mechanisms for clip migration into the duodenum. First, due to the anatomical proximity between the cystic duct ligation site and the duodenum, a fistula could form around the cystic duct clip and extend into the duodenum through a rejection-response mechanism. Second, in the case of severe cholecystitis combined with Calot's triangle severe inflammation and adhesion, the severe inflammation around the anastomosis would gradually erode the duodenal wall near the anastomosis and ultimately cause the Hem-o-lok clip to enter the duodenal wall. Third, when an undiagnosed duodenal ulcer persists, the duodenum may adhere to the gallbladder fossa, causing inflammation. In our case, the migration of the Hem-o-lok clip to the duodenum could potentially be accounted for by the second mechanism.

There is no clear consensus on the management of clip migration to the duodenal bulb after LC. According to earlier findings, the majority of Hem-o-lok clips that migrated postoperatively were typically extracted using endoscopic methods. In 2010, a 57-year-old male patient, who had previously undergone LC, experienced migration of a Hem-o-lok clip to the duodenal bulb at 1-year post-LC. This case was reported by Mantoo *et al*[13] and the clip was successfully removed using biopsy forceps. Similar treatments were reported by Seyyedmajidi *et al*[14]. In addition, a few cases also showed

that displaced clips dislodged spontaneously over time. A 66-year-old man experienced a natural separation of a Hem-o-lok clip that had moved into the duodenum, as documented by Soga *et al*[15]. Likewise, Zheng *et al*[19] also adopted a watch-and-wait strategy after postoperative clip displacement. The migration of clips can lead to various complications such as abdominal pain, ulcers, bleeding, and anemia. In addition, due to most patients being asymptomatic and detection occurring during physical examination, the incidence of postoperative clip migration is likely to be overlooked. Clinicians should be mindful of the potential for migration of Hem-o-lok clips in patients with recurring abdominal pain who have undergone LC or LCBDE, and consider arranging CT scans and gastroscopy. Based on the above, clinicians can adopt a watch-and-wait strategy post-LC if no clip-related complications are observed. Once symptomatic, however, clips should be removed in a timely manner.

CONCLUSION

Migration of the Hem-o-lok clip to the duodenal bulb after LC is uncommon in clinical practice and may manifest as a lesion resembling SMT, slightly protruding in the duodenal bulb. Clinicians need to be aware of the potential complications post-LC. While the Hem-o-lok clip has migrated, clinicians can adopt a watch-and-wait strategy post-LC if the patient is asymptomatic. Clips should be removed if symptomatic.

FOOTNOTES

Author contributions: Liu HY performed the manuscript writing and editing; Yin AH collected the patient's clinical data; Wei Z provided the report conceptualization and supervision; and all authors have read and approved the final manuscript.

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LETTER TO THE EDITOR

Resection and reconstruction in high-grade pancreatic head injuries

Jake Krige, Eduard Jonas, Andrew John Nicol, Pradeep Harkson Navsaria

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Abstract

This study by Chui *et al* adds further important evidence in the treatment of high-grade pancreatic injuries and endorses the concept of the model of pancreatic trauma care designed to optimize treatment, minimize morbidity and enhance survival in patients with complex pancreatic injuries. Although the authors have demonstrated favorable outcomes based on their limited experience of 5 patients who underwent a pancreaticoduodenectomy (PD), including 2 patients who were "unstable" and did not have damage control surgery (DCS), we would caution against the general recommendations promoting index PD without DCS in "unstable" grade 5 pancreatic head injuries.

Key Words: Pancreas; Injury; Surgery; Pancreaticoduodenectomy

Core Tip: This study by Chui *et al* adds further important evidence in the treatment of high-grade pancreatic injuries and endorses the concept of the model of pancreatic trauma care designed to optimize treatment, minimize morbidity and enhance survival in patients with complex pancreatic injuries.

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TO THE EDITOR

We read with interest the article by Chui *et al*[1] reporting their 20-year experience in Sydney with 14 patients who had undergone surgery for high-grade pancreatic injuries. The authors are to be congratulated on their excellent results with a 92.9% survival rate in a cohort of pancreatic injuries with predominantly blunt trauma. The authors report that 7 patients in their series had grade III and 7 had either grade IV or V pancreatic injuries; 9 underwent a distal pancreatectomy, and 5 required a pancreaticoduodenectomy (PD). Three patients were hemodynamically unstable at presentation, two of whom underwent damage control laparotomies, followed by a distal pancreatectomy[1]. Notably, all 5 patients who underwent a PD had the operation as the primary index procedure, despite the fact that two were "unstable" and had received 2 and 7 units pRBC pre-operatively[1].

There is universal recognition that grade IV and V pancreatic injuries are notoriously difficult to handle and challenge even the most experienced surgeons in well-resourced high-volume trauma referral centers[2,3]. In view of their impressive results, it would be important for the authors to clarify their decision to perform a primary PD in a "unstable" patient as their management deviates from accepted practice and norms. The crux of our concern is that the prevailing surgical sentiment recommends that initial abbreviated damage control surgery (DCS) is preferable and more expedient under these circumstances.

In our experience with 19 pancreaticoduodenectomies for trauma we found that DCS was necessary in 5 patients in whom complex pancreatic injuries were aggravated by severe associated injuries and major blood loss, acidosis, coagulopathy, hypothermia and persisting hypotension in spite of vigorous resuscitation[4]. These five patients had a median Apache II score of 11 and received a median of 10 u (range 8–12) pRBC[4]. Two factors may however reflect institutional bias. Firstly, in a geographically large country such as South Africa where distances are vast, the "tyranny of distance" impacts on decisions and trauma management. Under these circumstances DCS in a small rural hospital becomes imperative in a shocked patient to control bleeding and contamination before a 600 mile Air Ambulance flight to a Level One Trauma Centre for definitive care. Secondly, despite optimal resources and involvement of an experienced pancreatic surgical team, patient physiology may be depleted after staunching massive blood loss and multiple transfusions, especially after major venous and other essential organ repairs. To then embark on a PD after stabilizing a patient *in extremis* is counterintuitive to surgical principles and practice. This situation may of course not pertain in Sydney where spatial and transport logistics may differ from ours. In addition, their description and definition of "unstable" may be temporal and measured prior to effective pre-operative resuscitation and surgery and may not encompass or include shocked or exsanguinating patients. A patient who required two units pRBC pre-operatively would not be classified as "unstable" after resuscitation in our series.

Severe injuries involving the pancreas head continue to be a considerable cause of morbidity and mortality[2,4]. We agree with the authors' assessment that an individualized and multidisciplinary approach using modern resuscitation and expert consultation when needed is the most prudent treatment model for complicated high grade V pancreatic patients. We have previously recommended that our own facility practice with close collegial cooperation between trauma and HPB surgeons in complex injuries with a low threshold to involve an experienced HPB surgical team day or night should be central in the modern pancreatic trauma management paradigm[5]. Familiarity with and competence in pancreatic head surgery bring essential special organ-specific surgical skills and expertise, including IOUS, endoscopic proficiencies, both for the experienced operative assessment and the technical dexterities required for resection and reconstruction of complex pancreatic injuries[3,5].

We have grappled with the problem of deficiencies in scoring models when comparing pancreatic injury data between institutions in order to make meaningful assessments and accurate interpretations for the benefit of patient management and improved outcome, *i.e.*, comparing like with like in pancreaticodudenectomies for trauma. We developed and validated a novel pancreatic injury mortality score (PIMS), calculated from five variables identified from stepwise logistic regression analyses (age > 55, shock on admission, associated vascular injury, number of associated injuries and AAST pancreatic injury scale) to identify patients at greatest risk of in-hospital mortality after a major pancreatic injury[6]. Cut-off scores were used to generate three risk groups and the rate of mortality within low (PIMS 0-4), medium (PIMS 5-9), and high risk (PIMS 10-20) groups. PIMS is simple, quick and easily understandable, increases clinical risk prediction for patients with complex pancreatic and can be used as a benchmark for survival and for comparative institutional and international studies[6]. Validating this score in trauma patients undergoing PD in Sydney may add clinically valuable information in these challenging and high-risk patients.

This study by Chui *et al*[1] adds further important evidence in the treatment of high-grade pancreatic injuries and endorses the concept of the model of pancreatic trauma care designed to optimize treatment, minimize morbidity and enhance survival in patients with complex pancreatic injuries. Although the authors have demonstrated favourable outcomes based on their limited experience of 5 patients who underwent a PD, including 2 patients who were unstable and did not have DCS, we would still caution against the general recommendations promoting index PD and limiting DCS in "unstable" Grade 5 pancreatic head injuries.

FOOTNOTES

Author contributions: Krige JE and Jonas E contributed equally to this work; Krige JE and Jonas EG designed the research study; Krige JE, Jonas EG, Nicol AJ and Navsaria PH analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

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LETTER TO THE EDITOR

Should we perform decompressive laparotomy during severe acute pancreatitis with intra-abdominal hypertension below 25 mmHg: Only the gut knows

Thibault Vieille, Melissa Crotet, Celia Turco, Paul Monasterolo, Hadrien Winiszewski, Gael Piton

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Abstract

We suggest that during severe acute pancreatitis (SAP) with intra-abdominal hypertension, practitioners should consider decompressive laparotomy, even with intra-abdominal pressure (IAP) below 25 mmHg. Indeed, in this setting, non-occlusive mesenteric ischemia (NOMI) may occur even with IAP below this cutoff and lead to transmural necrosis if abdominal perfusion pressure is not promptly restored. We report our experience of 18 critically ill patients with SAP having undergone decompressive laparotomy of which one third had NOMI while IAP was mostly below 25 mmHg.

Key Words: Acute pancreatitis; Abdominal compartment syndrome; Decompressive laparotomy; Mesenteric ischemia; Intra-abdominal pressure; Abdominal perfusion pressure

Core Tip: In a recent review, Nasa *et al* discussed the optimal timing for decompressive laparotomy during severe acute pancreatitis. In line with the authors, we think that practitioners should not only focus on intra-abdominal pressure (IAP) levels to consider laparotomy but should also consider the gut viability. Indeed, intra-abdominal hypertension may decrease bowel perfusion pressure and precipitate non-occlusive mesenteric ischemia even with IAP below 25 mmHg. The objective of decompressive laparotomy is to restore mesenteric blood flow and prevent from transmural necrosis from occurring.

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TO THE EDITOR

We have read with great interest the review recently published by Nasa *et al*[1] in which they focused on decompressive laparotomy for abdominal compartment syndrome following severe acute pancreatitis (SAP). In this review, included studies reported patients with intra-abdominal pressure (IAP) > 25 mmHg at the time of laparotomy. The authors concluded that in the absence of strong evidence, surgical decompression may be considered in patients with increasing IAP and/or with progressive cardio-respiratory compromise when medical management fails. They also suggested that the development of irreversible visceral ischemia could explain the poor prognosis of these patients and that the optimal cutoff of IAP is not strongly established.

We agree with Nasa *et al*[1] that considering visceral ischemia is the cornerstone of the decision of performing decompressive laparotomy among these patients. Indeed, based upon our clinical experience, we suggest that decompressive laparotomy should be considered even among patients with IAP below 25 mmHg in whom non-occlusive mesenteric ischemia (NOMI) is highly suspected. We would like to report here our experience of laparotomy in patients with SAP and abdominal hypertension in which NOMI with irreversible bowel ischemia was found one third of the time.

Between January 2006 and March 2022, 18 patients (median age 60, 89% males) with SAP and intra-abdominal hypertension (IAH) (*i.e.*, IAP > 12 mmHg) underwent exclusive decompressive laparotomy in our intensive care unit (ICU) (Table 1). Decision of surgery was guided by both worsening organ failures and IAH. However, IAP above 25 mmHg was not mandatory. At the time of surgery, median SOFA and IAP were 10 (9-12), and 20 (17-24) mmHg, respectively. For 6 out of 18 patients, initial macroscopic examination of the colon and small bowel during surgery showed acute mesenteric ischemia with transmural bowel necrosis. In all of them, mesenteric ischemia was non-occlusive. Lesions were localized in the colon for two patients and were diffused (colon and ileum/jejunum) for 4 patients (Table 1). Among these 6 patients, median IAP before surgery was 20 mmHg, and 5 out of 6 had IAP below 25 mmHg. Four out of six patients with transmural necrosis underwent resection. For 2 patients, the surgeon has considered that the resection was futile because of extensive transmural bowel necrosis. Four of the six patients with transmural necrosis died. Among the five patients with IAP below 25 mmHg, three died.

Table 1 Patients characteristics

Characteristics	Population	Ischemia	No ischemia
	n = 18	*n* = 6	*n* = 12
Baseline characteristics			
Age (yr)	60 [43; 67]	59 [54; 60]	60 [39; 70]
Male sex	16/18 (89%)	5/6 (83%)	11/12 (92%)
BMI (kg/m^2)	31.7 [29.8; 35.7]	35.3 [32.2; 37.2]	30.6 [29.3; 32.1]
CTSI score	6 [4; 8]	7 [6; 9]	6 [4; 8]
SOFA score at ICU admission	7 [4; 11]	8 [6; 13]	7 [4; 10]
Severity at the time of laparotomy			
IAP (mmHg)	20 [17; 24]	20 [18; 22]	21 [18; 25]
pH	7.26 [7.07; 7.30]	7.06 [6.93; 7.24]	7.27 [7.19; 7.32]
Lactate (mmol/L)	3.6 [2.9; 7.4]	10.4 [4.4; 15.0]	3.3 [2.8; 3.8]

SOFA	10 [9; 12]	14 [12; 17]	9 [8; 11]
P_aO_2/F_IO_2	174 [108; 227]	122 [108; 174]	206 [106; 258]
Norepinephrine dose (µg/kg/min)	0.71 [0.42; 0.88]	1.04 [0.50; 1.39]	0,63 [0.45; 0.72]
Non occlusive mesenteric ischemia			
Transmural necrosis	6/18 (33%)	6	0
NOMI location			
Localised-colon		2/6	
Diffuse- Ileum/jejunum + colon		4/6	
Surgical resection		4/6	
Surgical abstention for futility		2/6	
Outcome			
28-d mortality	6/18 (33%)	4/6 (66%)	2/12 (17%)
1-yr mortality	10/18 (56%)	4/6 (66%)	6/12 (50%)
ICU length of stay (d)	24 [8; 45]	5 [2; 11]	44 [20; 67]
Hospital length of stay (d)	40 [10; 58]	6 [3; 29]	51 [30; 116]

Data are median [IQR] or *n* (%). BMI: Body mass index; CTSI: Computed tomography severity score; SOFA: Sequential organ failure assessment; IAP: Intra-abdominal pressure; NOMI: Non occlusive mesenteric ischemia; ICU: Intensive care unit.

In the setting of SAP, NOMI may be secondary to both circulatory shocks related to hypovolemia, and IAH. This results in decreased abdominal perfusion pressure (*i.e.*, difference between mean arterial pressure and IAP) and decreased bowel perfusion pressure[2]. Indeed, the gut is particularly sensitive to ischemia, as mesenteric blood flow decreases as soon as IAP is above 10 mmHg[3].

A key point is that NOMI is a dynamic process. At the early phase, restoration of mesenteric blood flow may result in bowel recovery. In case of prolonged low abdominal perfusion pressure, transmural necrosis occurs, resulting in poor prognosis. A prolonged time with IAH, even if below 25 mmHg, may be deleterious.

In line with Nasa *et al*[1] and based on our experience, we suggest that during SAP with IAH, practitioners should consider decompressive laparotomy, even with IAP below 25 mmHg, when NOMI is clinically suspected. In this setting, NOMI may occur even with an IAP level lower than 25 mmHg, and waiting for such a cutoff before considering decompressive laparotomy may lead to delayed treatment and worse prognosis.

FOOTNOTES

Author contributions: Vieille T and Piton G drafted the manuscript; Crotet M, Turco C, Monasterolo P, and Winiszewski H have reviewed the manuscript and consistently improved its content; and all authors read and approved the final manuscript.

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LETTER TO THE EDITOR

Primary repair of esophageal atresia Gross type C *via* thoracoscopic magnetic compression anastomosis: Is it the best option?

Sonia Pérez-Bertólez, Jorge Godoy-Lenz

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Abstract

Magnetic compression anastomosis is a promising treatment option for patients with complex esophageal atresia; but, at the present time, should not be the first therapeutic option in those cases where the surgeon can perform a primary anastomosis of the two ends of the esophagus with acceptable tension.

Key Words: Esophageal atresia; Tracheoesophageal fistula; Thoracoscopy; Magnamosis; Magnetic anastomosis

Core Tip: Esophageal magnetic compression anastomosis or magnamosis consists of a non-surgical esophageal anastomosis performed with the use of magnets positioned into upper and lower esophageal pouches. The magnetic force applies compression on interposed tissues, resulting in spontaneous progressive esophageal anastomosis. It is a promising treatment option for patients with complex esophageal atresia; but, at the present time, should not be the first therapeutic option in those cases where the surgeon can perform a primary anastomosis of the two ends of the esophagus with acceptable tension.

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TO THE EDITOR

The use of magnets for the treatment of esophageal atresia (EA) was first described in 1975 by Hendren and Hale[1] and was initially proposed as lengthening procedure. In recent years, there is a renewed interest in magnetic compression for EA, focusing on magnetic compression force acting on interposed esophageal tissues, leading to simultaneous central necrosis and peripheral mucosal bridging, ultimately forming an esophageal anastomosis or "magnamosis"[2,3].

We have read with interest a case report by Zhang *et al*[4], who presented a case of thoracoscopic-assisted esophageal magnetic compression anastomosis. We would like to add some considerations on their paper.

The fundamental goal of EA repair remains the restoration of esophageal continuity, allowing for nutritional autonomy *via* oral intake. Thoracoscopic repair of EA represents one of the most challenging advanced pediatric endoscopic procedures. In general, minimally invasive surgery is preferred due to its association with reduced tissue trauma, decreased pain, shorter hospital stays, and comparable or even superior clinical outcomes compared to standard surgical approaches. Studies have shown that cerebral oxygenation remains stable within the normal range during and after thoracoscopic primary anastomosis for EA[5]. However, it is essential to recognize that the vast majority of senior pediatric surgeons are proficient in performing this surgery satisfactorily *via* thoracotomy.

In general terms, thoracotomy is more invasive than thoracoscopy, which, in turn, is more invasive than endoscopy. We disagree with the statement "open approaches are extremely invasive and there are many postoperative complications". A significant proportion of children develop musculoskeletal deformities after thoracotomy, but most of them are subclinical. An axillary muscle-sparing technique has been shown to significantly decrease the incidence of these deformities[6-10]. Other complications (leakage, dehiscence, stenosis…) are not directly related to the surgical approach, but are influenced by factors such as the type of EA, patient characteristics and technical details.

Although the patient comes from a county hospital, the delay in diagnosis is conspicuous, as the patient exhibited classic clinical signs of EA, including drooling of saliva, dyspnea, and vomiting immediately after feeding. Additionally, prenatal detection of polyhydramnios further highlights the need for early recognition and intervention.

The authors mention "angiography" in their paper, but the imaging technique they describe is more accurately termed an "esophagogram." Angiography is typically used to visualize vascular structures by detecting contrast injected into blood vessels. In this context, esophagograms are valuable for assessing the size and location of the proximal pouch. However, their systematic implementation is not recommended due to the risk of aspiration. An alternative approach involves insufflating air during X-rays, which is less hazardous.

The authors correctly placed a tube in the proximal esophageal pouch during physical examination. However, it is essential to clarify that this was not a "gastric tube" since it did not reach the stomach. Precise terminology ensures accurate communication.

The classification system used by the authors corresponds to that described by Robert E Gross, a revered pioneer in pediatric surgery. Given that it bears his surname, it should be written in capital letters: EA Gross type C.

The statement "To avoid the complications associated with open surgery" in the context of parental consent warrants clarification. Notably, a laparotomy (open surgery) was performed to access the stomach. Therefore, we recommend omitting this phrase to accurately reflect the surgical approach.

To validate the cosmetic outcome mentioned by the authors, we recommend including a photograph of the patient's abdominal scar. Visual evidence would enhance transparency and allow readers to assess the aesthetic impact of the procedure.

The authors should provide the code of approval from their hospital's ethics committee. Transparency in ethical considerations is essential for readers and ensures adherence to established guidelines.

While the authors describe their approach as less invasive, we respectfully disagree. The presented case of type C EA represents an ideal scenario for surgery, since it is a full-term newborn with a good weight (3500 g), without severe cardiopathy or other associated anomalies (if present, they should be described) and proximity of both pouches. In our opinion, the optimal procedure for this specific case would have been to close the tracheoesophageal fistula and perform an end-to-end esophageal anastomosis. This approach would have avoided an unnecessary laparotomy.

The authors meticulously describe their technique, including 3 ligatures (2 in the azygos vein and one in the fistula) and two purse strings (one in each esophageal pouch), the laparotomy, the measurement with the lower esophagus probes, the placement of the magnets, the progression of the transanastomotic probe through the magnets, the measurement of the ideal site for the placement of the silk stitch over the probe and its proper positioning, the closure of the stomach and the laparotomy… However, we question whether this multifaceted approach is indeed easier, faster, and superior to a straightforward termino-terminal esophageal anastomosis, which typically requires no more than ten stitches.

It would be valuable to include information on the anesthetic time and the overall duration of the surgical procedure. These details contribute to understanding the practical aspects of the technique.

Clarification is essential. Did the authors modify the patient's position for the laparotomy? Were the esophageal pouches overlapping? Did the authors fix both pouches together with sutures? Describing and discussing these technical aspects would enhance the reader's understanding and provide insights into surgical strategy.

A point of controversy lies in the preservation of the azygos vein. If not preserved, should it be ligated or coagulated? Addressing this topic would enrich the discussion.

Skilled surgeons proficient in thoracoscopic repair of EA can complete the procedure in less than an hour, as exemplified by Dr. Godoy's impressive 37-min timeframe[11].

We seek clarification on several critical points: How long was the patient intubated and under relaxation? What was the duration of NICU admission? How many days did the patient spend in the hospital postoperatively?

The decision not to administer enteral nutrition through the transanastomotic tube warrants discussion. By utilizing the transanastomotic catheter for enteral nutrition, the patient could have potentially avoided 23 days of parenteral nutrition. Why didn't they administer enteral nutrition through the transanastomotic tube? Were they trying to prevent a stomach leak of the gastrotomy? After a non-complicated procedure of tracheoesophageal fistula closure and an end-to-end esophageal anastomosis, the esophagogram is routinely performed on the 5th-7th postoperative day and can start oral feeding. In addition, the patient has previous received enteral nutrition through the transanastomotic catheter. This approach aligns with the goal of early enteral feeding.

The authors report a minor leak on postoperative day 15. However, several questions arise: Were any other studies performed before this point? How many days did the patient have a chest tube, and what was the drainage pattern? The images of the case reported by Zhang *et al*[4], reveal atelectasis and pachypleuritis in the right hemithorax, suggesting that the leak may have been initially more significant than observed. The images also depicts effusion in the right costophrenic angle. We disagree with the authors' statement that "the contrast agent did not enter the pleural cavity." Given the transpleural approach used, the mediastinum and pleura were indeed connected.

While the abstract aligns with the manuscript content, the absence of explicit mention of the leakage is concerning. The statement "No leakage existed when the transoral feeding started" could mislead readers into assuming there was no leak throughout the entire course. Anastomotic leakage is a serious complication in EA, although rarely reported in magnamosis[12,13]. Transparency in reporting complications is essential for advancing our understanding and improving patient care.

Thinking about potential causes of leak… Could the leak be related to an area where the esophageal tissue did not connect due to the interposed purse string suture? To mitigate a possible suture interposition, alternative strategies can be considered:

(1) Transanastomotic tube avoidance: If the transanastomotic tube is not going to be used for feeding, it would not be necessary. Thus, the opening and subsequent purse string suture of the proximal esophageal pouch could have been circumvented.

(2) Optimal magnet sizing: The choice of magnets with appropriate diameters (proximal magnet larger than distal esophagus) further reduces the likelihood of displacement into the stomach. In this scenario, the silk "plug" attached to the transanastomotic probe could also have been avoided.

And (3) Alternative approach: End-to-side anastomosis: To prevent interposition of the distal purse string suture, consider sectioning the tracheoesophageal fistula between two ligatures and placing the magnet to create an end-to-side anastomosis (Figure 1).

The authors removed the magnets on postoperative day 23, but the method of removal remains unspecified. Clarification on this critical step would enhance our understanding.

The image of the control esophagogram is suboptimal due to faint staining of the esophagus. Clearer visualization would provide more robust evidence.

An essential aspect missing from the manuscript is the patient's short, medium, and long-term evolution. Recalcitrant stenosis is a common complication after magnamosis[2,8,13-15], often manifesting at a later stage[16-19]. Reporting on the patient's progress beyond the immediate postoperative period would be valuable.

There are some radiation exposure considerations. Magnamosis involves increased exposure to ionizing radiation, as both magnet positioning and removal typically occur under pulsed fluoroscopy. Although the authors do not mention this data, direct viewing by thoracoscopy may have reduced radiation dose.

Although thoracoscopic repair of EA is one of the most challenging advanced pediatric endoscopic procedures, nowadays the availability of step-by-step descriptions and documented procedures facilitates learning and training. Simulation-based training offers a promising avenue for acquiring technical skills[20]. Although it is expected that this technique will become the gold standard as robotic surgery evolves and miniaturizes, reducing the challenges of the thoracoscopic approach.

We acknowledge that the use of magnets has its specific indications. Dr. Godoy's experience with 9 cases-comprising 2 type A long gap EA, 1 type B long gap EA, one congenital esophageal stenosis, and 5 severe esophageal strictures after prior EA surgery-provides valuable insights.

Based on this personal experience and an extensive review of the literature, we believe that magnamosis should be approached with caution and it is essential a proper patient selection. Magnamosis is not indicated nowadays when tension-free esophageal anastomosis surgery is feasible. However, we recognize that certain patients, particularly those with high-risk physiologic and anatomic comorbidities, may benefit from magnamosis.

We observed improved outcomes when both esophageal pouches are in contact with each other. However, for long gap EA cases, the choice of magnet type still needs to evolve, refining magnet design and optimizing the balance between attraction and tissue preservation. The ideal balance lies in creating an attraction between the magnets within the esophageal pouches, allowing for esophageal growth similar to tissue expanders. Excessive magnet force ultimately leads to severe stenosis, compromising patient outcomes. We hypothesize that the observed phenomenon may be due to two possible mechanisms. First, excessive traction may cause esophageal fissures, leading to the formation of fibrous and scar tissue, similar to cicatricial phimosis following forced preputial retraction. Second, the magnets may necrotize the ends of the distant esophageal pouches, and the path between the two pouches may resemble a fibrin sheath, without esophageal tissue, similar to the sheath that forms around a port-a-cath. In order to determine the true cause, anatomopathological studies of these tissues would be necessary.

Our best results emerged in the treatment of refractory strictures following EA repair[21]. By combining magnamosis with dynamic stents[22], we achieved definitive resolution of esophageal strictures in three patients. Long-term follow-up corroborates the efficacy of this strategy.

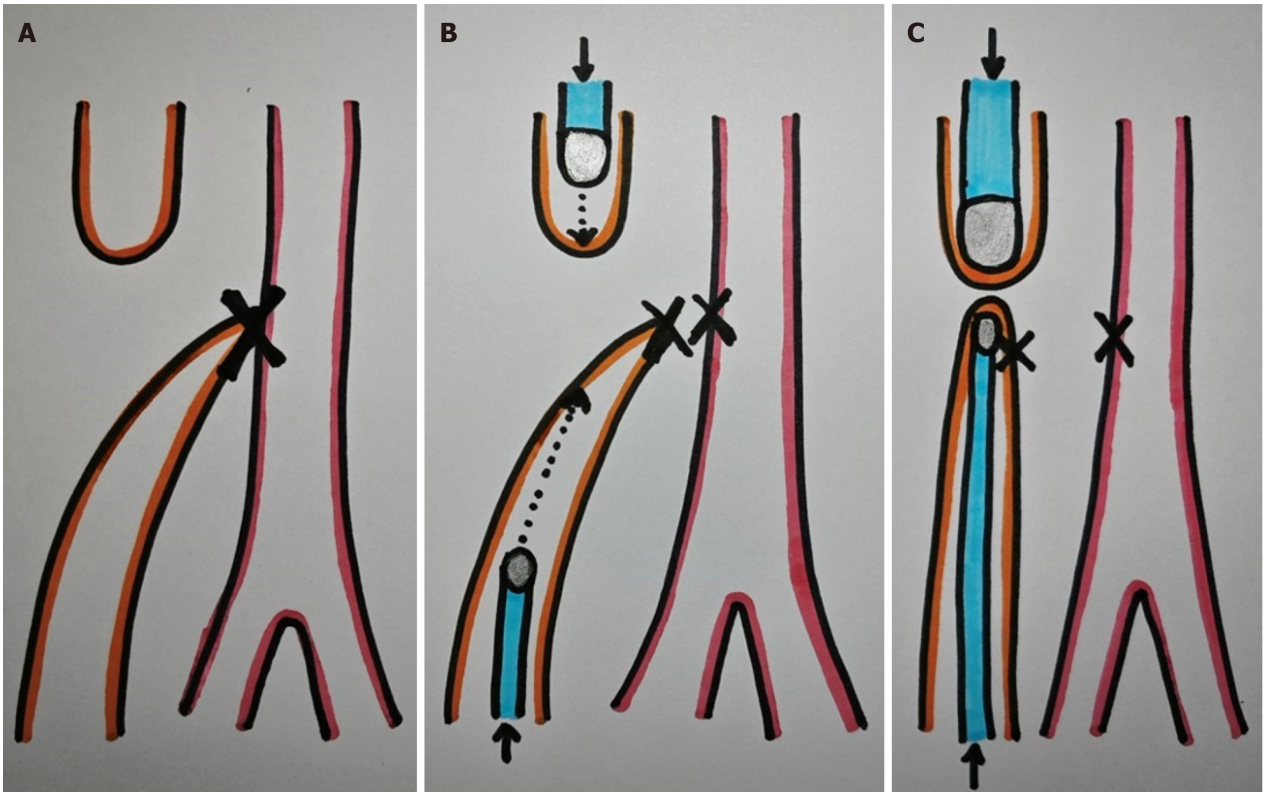

Figure 1 Alternative esophageal end-to-side anastomosis. A: Esophageal atresia Gross Type C: The X indicates the area of ligation and section of the distal tracheoesophageal fistula; B: Magnets Advancement: Magnets are carefully advanced through each esophageal pouch using catheters to push them; C: Avoiding Suture Interposition: To prevent suture interposition in the distal esophageal pouch, the distal magnet is positioned laterally to the stitches, creating an end-to-side anastomosis. The X denotes the area of suture in the trachea and distal esophagus.

Figure 2 Esophagogram showing complete obliteration of the anastomosis due to severe esophageal stricture.

We hypothesize that dynamic stents are an effective treatment option for esophageal cicatricial strictures because they bring together several therapeutic options for the treatment of postoperative scars[23], such as silicone gel sheets (the silicone is in direct contact with the stenotic scar), pressure dressings and scar massage with a moisturizing substance (with the patient's movement and esophageal peristalsis, direct pressure and massage is exerted on the scar and moisturized with the patient's own saliva).

Herein, we present a case of a 5-month-old boy with a multioperated type C long gap EA who developed a severe esophageal stricture with complete obliteration (Figure 2). The esophagus was repermeabilized by magnamosis (Figures 3-5), and subsequently, a dynamic stent was implanted for 2 months (Figure 6). Video 1 shows the patient eating normally

Figure 3 Placement of magnets in both esophageal pouches under endoscopic and fluoroscopic control.

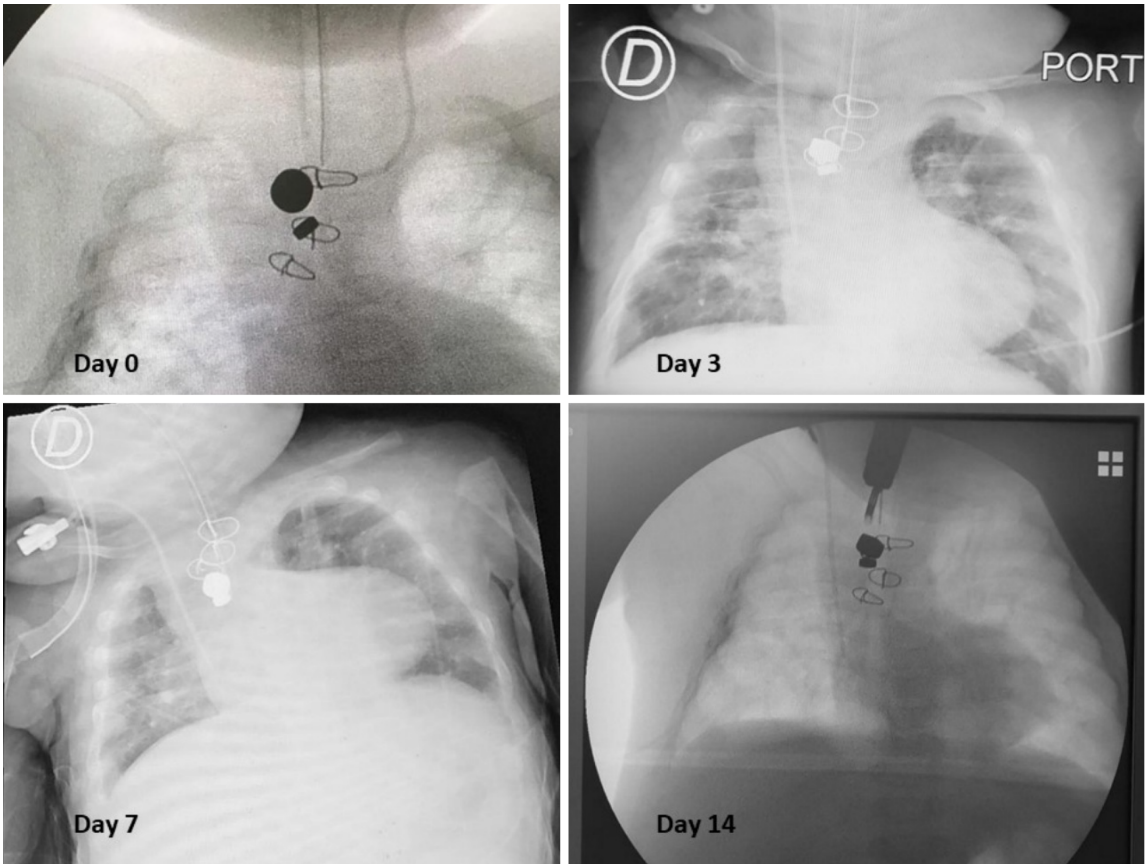

Figure 4 Radiological evolution while the magnets were in place. Progressive mobilization closer together of the magnets is observed until they were completely joined.

one year after the procedure (recorded by his mother; Supplementary material).

There has been no recurrence of the stricture or other complications after more than 3 years of follow-up (Figure 7).

We emphasize the importance of individualizing each case. Feasibility does not necessarily equate to the best or least invasive option for a patient. Considering patient-specific factors and tailoring the approach accordingly ensures optimal outcomes.

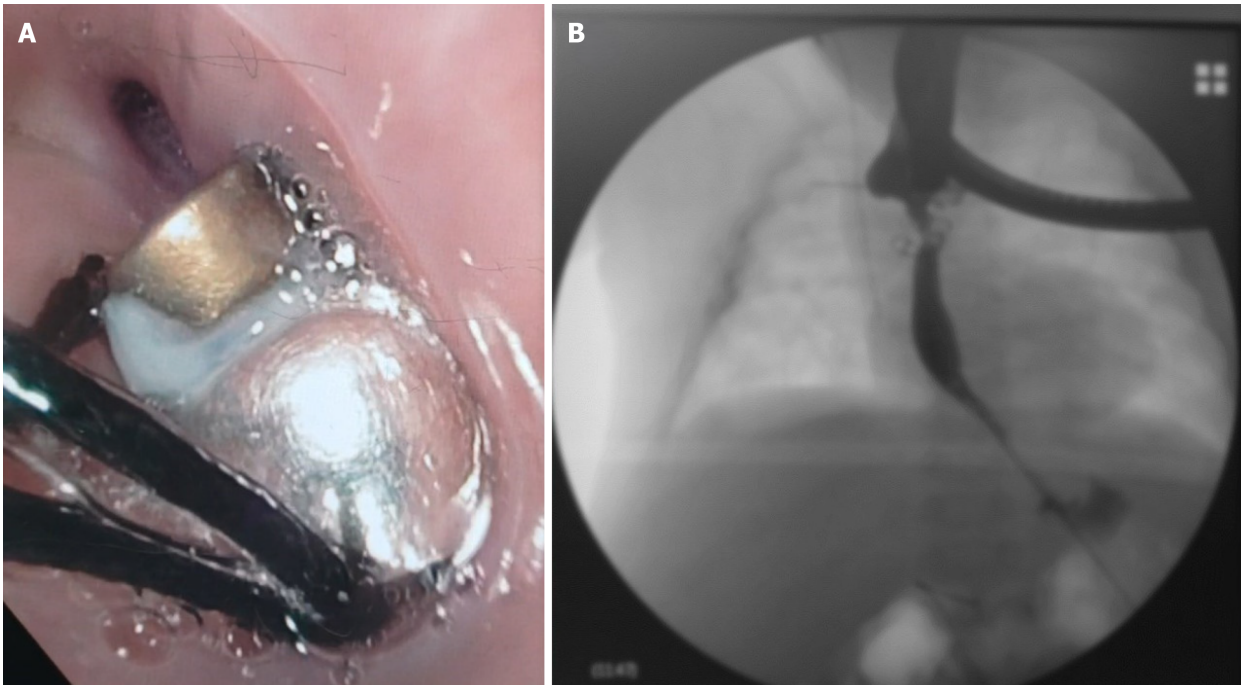

Figure 5 Inmediate results after magnets removal. A: Endoscopic removal of the magnets two weeks after placement; B: The esophagogram taken immediately after the procedure shows that the esophagus had been repermeabilized, but there is still some degree of stenosis at the anastomosis.

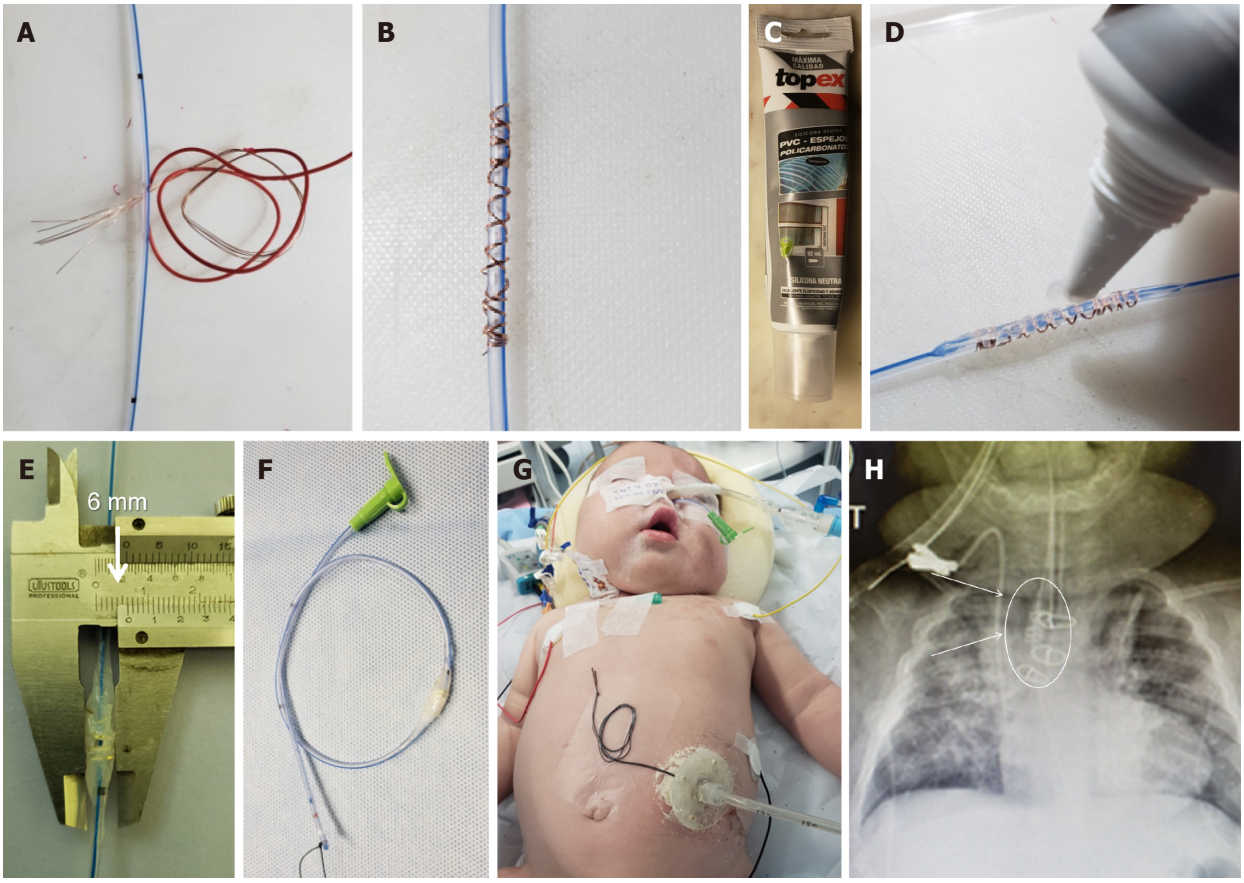

Figure 6 Custom-made dynamic stent. A and B: A radio-opaque metal wire is coiled in a nasogastric tube according to stricture length, and is tailored to exceed the extent of the stricture by at least 2 cm to avoid displacement of the stent above or below the area of interest; C-E: The wire is covered with silicone until it reaches the desired thickness (6 mm in this case); F: A silk stitch is placed at the distal end of the probe for distal stent fixation; G, H: The dynamic stent is inserted in a way that is similar to a nasogastric tube, with the radio-opaque zone positioned in the stenotic area. It is secured with adhesive tape at the skin in two places (the probe near the nostril entrance and the silk stitch exiting through the gastrostomy).

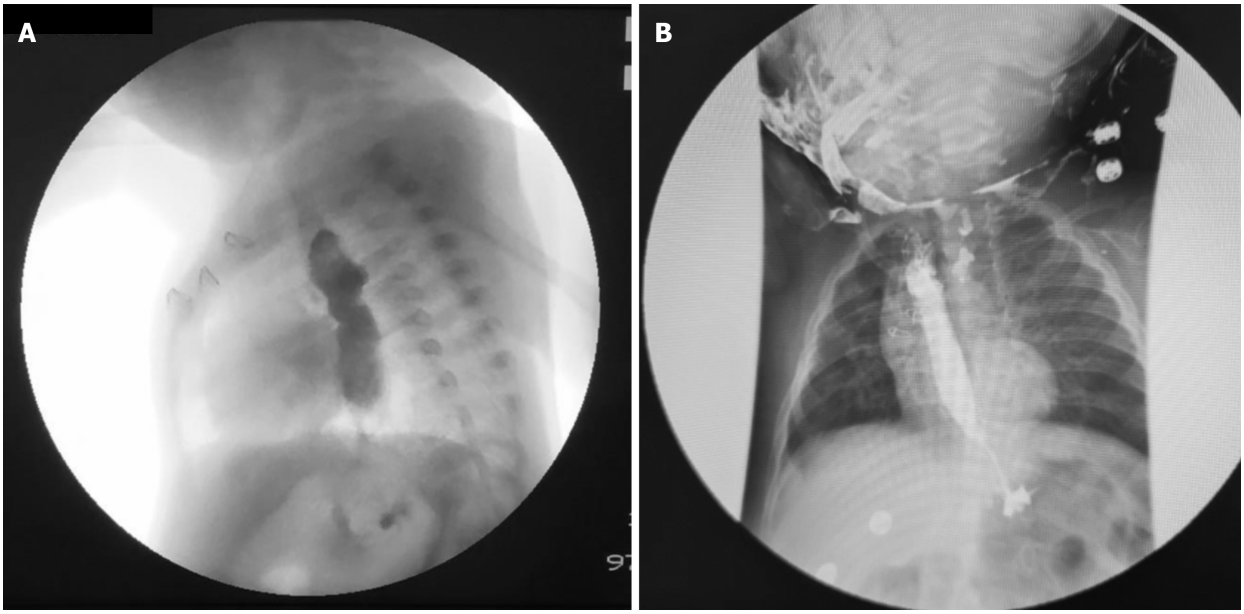

Figure 7 Absence of stricture recurrence after dynamic stent removal. A: Esophagogram after inmediate removal of dynamic stent; B: Esophagogram 6 months later.

In conclusion, while magnamosis holds promise, judicious patient selection, ongoing evaluation, and a commitment to individualized care remain paramount.

FOOTNOTES

Author contributions: Pérez-Bertólez S and Godoy-Lenz J designed and performed the research, analyzed the data and revised the letter; Pérez-Bertólez S wrote the letter.

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LETTER TO THE EDITOR

Exploring predictive markers for liver failure post-hepatectomy in hepatocellular carcinoma patients

Shi-Yan Zhang, Xiong-Jian Ma, Xue-Xia Zhu, Na Cai

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Abstract

This letter to the editor addresses the study titled "Predictive value of NLR, Fib4, and APRI in the occurrence of liver failure after hepatectomy in patients with hepatocellular carcinoma" by Kuang *et al* in the *World Journal of Gastrointestinal Surgery*. The study acknowledges the comprehensive patient data analysis while suggesting that there is a need for further discussion on the clinical applicability of these markers across diverse patient populations. This letter recommends prospective studies for validation and considers the influence of confounding factors. This finding underscores the significance of this study in improving hepatocellular carcinoma management.

Key Words: Neutrophil-to-lymphocyte ratio; Hepatocellular carcinoma; Liver failure; Hepatectomy; Letter to the Editor; Commentary

Core Tip: Acknowledges the study's comprehensive analysis and its contribution to hepatocellular carcinoma management. These findings suggest further exploration of the clinical applicability of the neutrophil-lymphocyte ratio, fibrosis index based on four factors, and aspartate aminotransferase-to-platelet ratio index in diverse patient groups. Prospective studies for the validation of these findings are recommended. This highlights the importance of considering the confounding factors in future research.

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TO THE EDITOR

We recently read the insightful study titled "Predictive value of NLR, Fib4, and APRI in the occurrence of liver failure after hepatectomy in patients with hepatocellular carcinoma" by Kuang *et al*[1], which was published in the *World Journal of Gastrointestinal Surgery*. The study's exploration of neutrophil-lymphocyte ratio (NLR), fibrosis index based on four factors (Fib4), and aspartate aminotransferase-to-platelet ratio index (APRI) as predictive markers for liver failure post-hepatectomy in hepatocellular carcinoma (HCC) patients is commendable.

The researchers' meticulous approach to developing and validating a column-line graph prediction model based on these markers is a significant advancement in predicting postoperative complications in HCC patients. The use of a large sample size and the division of patients into modeling and validation cohorts strengthens the study's validity. The high concordance between predicted and actual events in the study emphasizes the potential of these markers as tools for better clinical decision-making[2].

However, several aspects could be enhanced or explored further[3]. First, while the present study effectively established the predictive value of the NLR, Fib4 levels, and APRI, it primarily focused on a retrospective patient cohort. Prospective studies could further validate these findings and assess their applicability in real-time clinical settings.

Moreover, the study's focus on a single hospital's patient cohort may limit the generalizability of the findings. A multicenter study encompassing diverse demographic and genetic backgrounds could provide a more comprehensive understanding of the predictive value of these markers across different populations[4].

Additionally, the paper briefly touches upon the potential impact of confounding factors such as underlying liver diseases, other comorbidities, and different treatment regimens. A more detailed exploration of how these factors might influence the predictive accuracy of the NLR[5], Fib4, and APRI would be beneficial. Such an analysis could lead to a more nuanced understanding of the limitations and scope of these biomarkers in clinical practice.

Another aspect worth considering is the practicality of implementing these predictive models in clinical settings. While the study presents a robust statistical model, the translation of these findings into a simple, accessible format for routine clinical use would be a significant step forward. This could include the development of an easily interpretable scoring system or a digital tool that can be integrated into existing hospital information systems.

Finally, this study opens avenues for exploring the role of these biomarkers in the broader spectrum of liver diseases and surgeries[6]. Future research could focus on whether these markers can predict outcomes in other liver surgeries or liver-related conditions, potentially broadening the scope of their clinical utility.

In conclusion, the study by Kuang *et al*[1] is a valuable addition to the field of hepatology and surgical oncology. This study not only advances our understanding of postoperative complications in HCC patients but also sets the stage for further research that could ultimately enhance patient outcomes and personalized treatment approaches.

FOOTNOTES

Author contributions: Zhang SY and Ma XJ designed and performed research; Zhu XX wrote the comment; and Cai N revised the comment. All the authors listed have read and approved the final manuscript.

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