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MINIREVIEWS

Minimally invasive surgery for post cholecystectomy biliary stricture: current evidence and future perspectives

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Abstract

Postcholecystectomy bile duct injury (BDI) remains a devastating iatrogenic complication that adversely impacts the quality of life with high healthcare costs. Despite a decrease in the incidence of laparoscopic cholecystectomy-related BDI, the absolute number remains high as cholecystectomy is a commonly performed surgical procedure. Open Roux-en-Y hepaticojejunostomy with meticulous surgical technique remains the gold standard surgical procedure with excellent long-term results in most patients. As with many hepatobiliary disorders, a minimally invasive approach has been recently explored to minimize access-related complications and improve postoperative recovery. Since patients with gallstone disease are often admitted for a minimally invasive cholecystectomy, laparoscopic and robotic approaches for repairing postcholecystectomy biliary stricture are attractive. While recent series have shown the feasibility and safety of minimally invasive post-cholecystectomy biliary stricture management, most are retrospective analyses with small sample sizes. Also, long-term follow-up is avail-able only in a limited number of studies. The principles and technique of minimally invasive repair resemble open repair except for the extent of adhesiolysis and the suturing technique with continuous sutures commonly used in minimally invasive approaches. The robotic approach overcomes key limitations of laparoscopic surgery and has the potential to become the preferred minimally invasive approach for the repair of postcholecystectomy biliary stricture. Despite increasing use, lack of prospective studies and selection bias with available evidence precludes definitive conclusions regarding minimally invasive surgery for managing postcholecystectomy biliary stricture. High-volume prospective studies are required to confirm the initial promising outcomes with minimally invasive surgery.

Key Words: Robotics; Laparoscopy; Surgery; Biliary stricture; Cholecystectomy; Gallstones

Core Tip: Minimally invasive postcholecystectomy biliary stricture repair is an attractive and controversial option to manage this iatrogenic injury with serious health and litigation consequences. Recent evidence suggests a potential role of minimally invasive approaches especially robotic surgery. Refinements in minimally invasive techniques can widen the scope of minimally invasive surgery. Future studies should overcome the current evidence's limitations and help choose the most suitable method for repair in a patient with bile duct injury.

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INTRODUCTION

Iatrogenic post-cholecystectomy bile duct injury (BDI) resulting in biliary stricture is a devastating complication for any patient who experiences it and can be a nightmare to the surgeon responsible for it. The incidence of BDI following laparoscopic cholecystectomy is about 0.2% to 0.6% and slightly less following an open cholecystectomy (0.1%-0.2%)[1,2]. Recent series have shown comparable incidences of BDI between open and laparoscopic cholecystectomy[2,3]. However, considering the number of cholecystectomies done for gallstone disease worldwide, even this lower incidence turns into a substantial absolute number. On admission for elective laparoscopic cholecystectomy, often done as an outpatient procedure, the patient expects a prompt postoperative recovery. Hence, consequences of BDI like large abdominal incisions, the need for multiple drains and stents, a prolonged hospital stay, and the inability to continue routine work make it difficult for the patient to accept, often ending with litigations against the operating surgeon[4,5].

The implication of postcholecystectomy biliary stricture on quality of life mandates a meticulous surgical repair with utmost care. Roux-en-Y hepaticojejunostomy (RYHJ) is the gold standard surgical treatment for benign biliary stricture[5,6]. The reported success rate at 30 mo follow up period is as high as 80%-90%[6]. Conventionally, an open approach is used for performing RYHJ in postcholecystectomy biliary stricture patients. A minimally invasive approach for repairing postcholecystectomy biliary stricture is considered controversial as often the injury is a consequence of a laparoscopic approach. However, in recent years, the application of laparoscopy has yielded promising results in managing complex biliary tract diseases, including the repair of iatrogenic bile duct injuries[7-10]. Also, the robotic platform with a stable camera, tremor filtration, immersive 3-dimensional imaging, intuitive movement of surgeon's wrist, and enhanced dexterity allow the performance of complex procedures with increased precision[11-13]. Better cosmetic outcomes and early postoperative recovery with laparoscopic and robotic approaches could decrease the patient's attitude towards litigations[11]. However, literature on laparoscopic and robotic approaches for managing postcholecystectomy biliary stricture is still limited. The current evidence is reviewed to give an overview of the minimally invasive management of postcholecystectomy biliary strictures and future perspectives.

SEARCH STRATEGY

Both authors independently did a PubMed search of relevant articles. Further, the reference lists of selected manuscripts were searched for additional appropriate studies. The keywords and combinations included in the search were: "Bile leak"; OR "hepaticojejunostomy"; OR "biliary anastomosis"; OR "bile duct injury repair"; OR "iatrogenic bile duct injury"; OR "biliary anastomosis," OR "laparoscopic cholecystectomy"; "hepaticojejunostomy" AND "laparoscopic"; "hepaticojejunostomy" AND "robotic". The search was limited to publications in English literature till March 2023. Case reports and case series with less than five patients were not included in the review. All the authors agreed that the articles selected for review were relevant.

SURGICAL TECHNIQUE: IS MINIMALLY INVASIVE SURGERY DIFFERENT FROM OPEN SURGERY

The fundamental principles of surgical repair in a patient with postcholecystectomy biliary stricture are exposure of well-vascularized ducts, tension-free anastomosis and drainage of all segments[6]. While the principles of surgical repair remain the same in both open and minimally invasive approaches, the critical differences in operative steps between both approaches are highlighted in this section. In most series, elective repair is undertaken after a waiting period of 6-10 wk or even longer if an uncomplicated external biliary fistula is present[10-12]. Several case studies report applying minimally invasive methods for the on-table repair of BDI[10-12]. However, the availability of expert Hepato-Pancreato-Biliary surgeons to repair BDI is a challenge and can be considered in the presence of adequate expertise. Also, the rate of

conversion to open surgery is high (31%) for on-table BDI repair[11,12]. As a minimally invasive approach is still not a standard technique to repair benign biliary stricture, appropriate informed consent and shared decision making is imperative.

Patient positioning and port placement

The patient is positioned supine or supine with a leg split, with the operating surgeon standing on the left side of the patient or between the patient's legs. Trocar position is determined after creating the pneumoperitoneum and initial exploratory laparoscopy. In the laparoscopic approach, commonly, five trocars are placed in a semi-circular line at the level of the umbilicus[9,10]. In patients undergoing robotic repair, four robotic trocars are placed in a straight line at the level of the umbilicus, with an assistant trocar placed in the infraumbilical region.

Adhesiolysis

Most patients with postcholecystectomy biliary have dense intra-abdominal adhesions that require careful adhesiolysis. In open surgery, perihepatic adhesions are completely released before reaching the hepatic hilum. Whereas in minimally invasive surgery, perihepatic adhesions, if present, are left undisturbed because they serve as a natural source of liver retraction facilitating exposure and dissection of the hilum (Figure 1)[10]. In biliary stricture patients undergoing robotic repair, docking of the robotic arms is usually done after laparoscopic intra-abdominal adhesiolysis.

Identification of base of segment IV and left hepatic artery

The dissection started in the inferior surface of the liver to identify the base of segment four. Gastro hepatic ligament is taken down to facilitate the same. Dissection proceeds towards the umbilical fissure with careful identification and preservation of the left hepatic artery, as this may be the sole artery supplying the liver and bile duct in patients with associated right hepatic artery injury (Figure 1). The lack of tactile sensation of palpating blood vessels in minimally invasive surgery is compensated by visualization of pulsations under magnified vision[11,12]. While intravenous indocyanine green (ICG) can be used to identify the blood vessels, it is often used to determine the ductal anatomy.

Identification of hepatic duct and lowering the hilar plate

After delineation of the porta hepatis, the next step is identifying the left hepatic duct and lowering the hilar plate. In patients with internal fistula, frequently with the duodenum, dismantling the fistula facilitates duct identification (Figure 2). ICG is frequently used in minimally invasive approaches to identify the hepatic ducts (Figure 3). Identification of biliary anatomy is facilitated by intravenous injection at least 6 h before the procedure to minimize background liver fluorescence. However, background fluorescence interferes with ductal anatomy delineation once an intraoperative bile leak occurs.

Lowering the hilar plate is achieved by dissection between the Glissonean sheath surrounding portal structures and Laennec's capsule surrounding the liver (Figure 3). Magnified vision in a minimally invasive approach facilitates the identification of the correct plane to lower the hilar plate. Once the left hepatic duct is identified, it is widely opened, and its confluence with the right hepatic duct is defined (Figure 4). In patients with type IV and V stricture, coring of hilar liver tissue or partial resection of segment IV may be required to have good exposure to the ducts. Delineation of the distal bile duct is neither required nor recommended, as it may result in vascular injury.

Creation of Roux limb and performance of RYHJ

The loop of the jejunum about 30 cm from the duodenojejunal flexure is identified and divided using an endoscopic bowel stapler. Creation of a Roux limb can be technically challenging, especially in a robotic approach due to changes in the quadrant. Similarly, the creation of a mesocolic window in minimally invasive surgery is complex in patients with extensive periduodenal adhesions and inflammation. A wide side-to-side tension-free hepaticojejunostomy to the healthy bile duct, ensuring complete drainage of all the bile ducts, is a crucial step of the surgical procedure (Figure 5). Due to difficulty in handling multiple sutures, stay sutures on the hepatic duct are not commonly used in a minimally invasive approach. Also, continuous sutures are frequently used in minimally invasive surgery, especially the laparoscopic approach[8-10]. Absorbable suture materials are preferred for anastomosis. As in the open technique, 3-0 or 4-0 polydioxanone sutures are commonly used to create hepaticojejunostomy. Barbed sutures, initially used in tendon repair to reduce the need for knot tying and increase gripping strength, are increasingly used in minimally invasive pancreatobiliary surgeries, including BDI repair for anastomosis. Avoidance of repeated suture tightening and traction after each stitch during continuous suturing is the primary advantage of barbed sutures. However, more evidence is required regarding its safety in BDI repair, especially in patients with thin bile ducts.

Preservation of perihepatic adhesions, frequent use of ICG to delineate ducts and anastomosis technique are some of the critical technical differences in the minimally invasive repair of postcholecystectomy biliary stricture compared to open RYHJ.

LAPAROSCOPIC REPAIR OF POST-CHOLECYSTECTOMY BILIARY STRICTURE

The feasibility of laparoscopic repair of postcholecystectomy biliary stricture was first reported in 2002 by Crema *et al* [14]. Despite the encouraging results, the laparoscopic approach was not widely used, and publications were limited only to case reports. Apprehension of abdominal adhesion due to previous bile leak and technical challenges in dissecting the

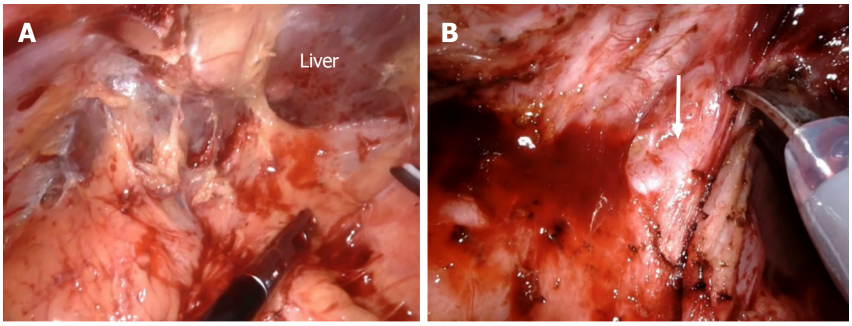

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Figure 1 Adhesiolysis and initial dissection phase. A: Perihepatic adhesions are left undisturbed to facilitate liver retraction and exposure of the hilum; B: Dissection proceeds towards the umbilical fissure with careful identification and preservation of the left hepatic artery (arrow).

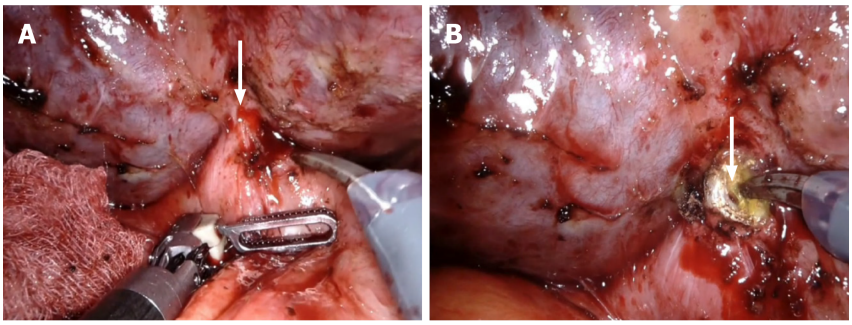

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Figure 2 Identification of hepatic duct. A: Internal fistula between the hepatic duct and duodenum (arrow); B: Division of the fistula facilitates visualization of the hepatic duct (arrow).

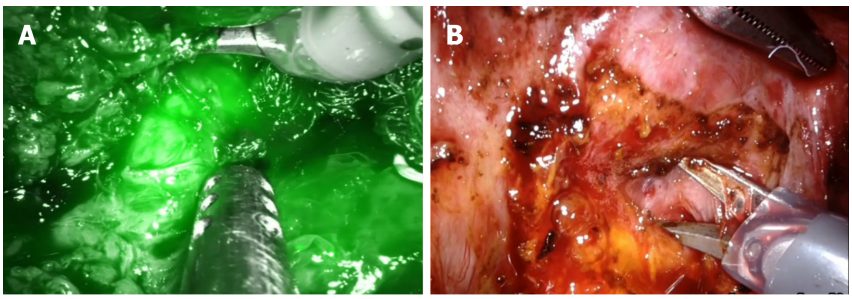

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Figure 3 Lowering the hilar plate. A: Indocyanine green fluorescence facilitates hepatic duct identification; B: Hilar plate lowered by dissection between the Glissonean sheath and Laennec's capsule.

scarred tissues were the primary reasons for surgeon's hesitation to adopt a minimally invasive approach. In 2016, Cuendis-Velázquez *et al*[7] published the first laparoscopic reconstruction series, which included 29 patients with post-cholecystectomy biliary strictures. The authors have given a detailed description of the procedure and reported excellent outcomes with minimal morbidity. During a median follow-up of 36 mo, one patient developed hepatico-jejunostomy stricture requiring endoscopic intervention. While most laparoscopic series had a single study arm, Javed *et al*[10], in a retrospective study, compared the outcomes of 29 patients who underwent laparoscopic repair with 34 patients who underwent open RYHJ. More than three fourth of patients in both groups had high strictures (Strasberg E3, E4 and E5 types). While median operative time was comparable between the two groups (210 *vs* 200 min, $P = 0.93$), the mean blood loss (50 *vs* 200 mL, $P = 0.001$), time to resume oral diet (2 *vs* 4 d, $P = 0.023$), and duration of hospital stay (6 *vs* 8 d, $P = 0.04$) were significantly less in the laparoscopic group. While all patients in the open group underwent RYHJ, hepaticoduodenostomy for biliary reconstruction was used in more than half of the patients included in the laparoscopic group. Median operative time (190 *vs* 230 min, $P = 0.034$) was significantly less in the laparoscopic hepaticoduodenostomy group as it requires single anastomosis compared to additional small bowel anastomosis with hepaticojejunostomy.

Hepaticoduodenostomy is commonly used for reconstruction following choledochal cyst excision in the pediatric age group[15-17]. However, its use in postcholecystectomy biliary stricture is documented only in a single series[10]. Authors

Table 1 Studies on laparoscopic repair of postcholecystectomy biliary stricture

Ref.	Year	Patients	Strasberg injury type	Method of reconstruction	Mean operative time (min)	Blood loss (mL)	Conversion to open	Overall morbidity	Specific biliary complications	Length of stay (d)	Follow up
Cuendis-Velázquez *et al* [7]	2016	29	C, E1-E4	HJ	240	200	1	31.03	Bile leak–5 patients. One patient required laparotomy and drainage of bile collection	8	36 (range 7-36) mon, Anastomotic patency rate 96.6%
Gomez *et al*[9]	2020	20	E1-E4	HJ	146.5	15-50	None	10%	One patient had bile leak and was managed conservatively	4.5 (mean)	5 yr–no long-term complications
Sahoo *et al*[8]	2021	16		HJ	280	176	None	12.5%	Two patients had bile leak and were managed conservatively	8.5	28 mo
Javed *et al*[10]	2021	29	E1-E5	HJ-13 patients, HD-16 patients	210	50	None	20%	Four patients had bile leak and were managed conservatively	6	9 mo–one patient had anastomotic strictest and managed with repeater dilations

HJ: Hepaticojejunostomy; HD: Hepaticoduodenostomy.

suggested that in patients with choledochoduodenal fistula or those with dense adhesion of the duodenum to the hilum, hepaticoduodenostomy can be safely performed without difficulties in mobilizing the duodenal knuckle. Hepaticoduodenostomy is primarily used in Strasberg E1-2 and some E3 strictures. In addition to the single anastomosis, the feasibility of the endoscopic intervention in patients with postoperative stricture is an added advantage of hepaticoduodenostomy. More severe presentation of anastomotic leak compared to hepaticojejunostomy is the primary risk with hepaticoduodenostomy. As the current evidence is limited, more studies are required to document the safety of hepaticoduodenostomy in patients with a postcholecystectomy biliary stricture. A few other series published from high-volume centres with significant experience in advanced laparoscopic hepatobiliary procedures report that the laparoscopic approach may be equivalent, if not better, for managing post-cholecystectomy biliary strictures[18-21]. Published laparoscopic case series with at least ten patients included in the analysis are summarized in Table 1.

ROBOTIC REPAIR OF POST-CHOLECYSTECTOMY BILIARY STRICTURE

With the development of Devol's first robotic machines using a magnetic process controller in the 1940s, robotic surgery made immense progress in recent years[22]. Since the first robotic cholecystectomy performed by Himpens in 1997, the use of robotics in hepatobiliary and pancreatic surgery, including complex surgeries, has shown noticeable growth[23,24]. The initial case series on the use of robots for biliary stricture repair was published by Giulianotti *et al*[11] in 2018, which analyzed fourteen patients. Interestingly, 42.9% of included patients had Bismuth type II injuries underscoring the careful selection of patients for the robotic approach in the initial phase. However, complex reconstructions were also performed in their series. Two patients, one with isolated right hepatic duct stricture and the other with type IV stricture because of small duct size, underwent Robotic assisted Kasai procedure. One patient with previous Roux en-y gastric bypass underwent dismantling of gastric bypass, sleeve gastrectomy of the remnant stomach, and an anastomosis between the

Table 2 Studies on robotic repair of postcholecystectomy biliary stricture

Ref.	Year	Patients	Strasberg injury type	Method of reconstruction	Operative time (min)	Blood loss (mL)	Overall morbidity	Length of stay (d)	Specific complications	Follow up
Giulianotti *et al*[11]	2018	14	E1-E5	HJ-12 patients, Kasai procedure-2 patients	280.6	135	28.6%	8.4	Bile leak-two patients and 1 patient required pigtail catheter insertion. Subhepatic abscess-one patient	36.1 mo, 2 patients had mild HJ stenosis and cholangitis. Managed by PTBD and multiple transhepatic dilatations
Marino *et al*[12]	2019	12	E1-E4	HJ	260	252	16.7%	9.4	1 patient developed subhepatic abscess and required pigtail catheter insertion	12 mo–1 patient had anastomotic stenosis and revision robotic HJ was done
Sucandyet al[13]	2021	8		HJ	259	50	14%	8	None	22 mo–1 patient had anastomotic stenosis at 10 mo and required transhepatic dilatation

HJ: Hepaticojejunostomy; PTBD: Percutaneous transhepatic biliary drainage.

gastric pouch and sleeve gastrectomy portion with the use of Roux limb for biliary anastomosis. The authors highlighted the potential advantage of the robotic approach over the laparoscopic repair of bile duct injuries: improved magnification (10X), enhanced range of motion, ambidextrous handling with precise dissection and tremor filtration with better ergonomics. The study concluded that robot-assisted biliary reconstruction for postcholecystectomy biliary stricture is feasible and safe in expert hands[11]. Marino *et al*[12] published the only prospective series on Robotic assisted repair of biliary stricture in 2019. Twelve patients who underwent robotic repair from 2014 to 2017 were analyzed. However, the duration of follow-up was only 12 mo. Sucandy *et al*[13] compared the robotic approach with open surgery and reported less blood loss in the robotic group (50 *vs* 150 mL). However, the study had only eight patients in the robotic arm. Since then, a few other series have documented the usefulness of the robotic approach, although the number of patients included was small with a short follow-up period[25-27]. Published robotic case series with at least five patients included in the analysis are summarized in Table 2[12].

ROBOTIC VERSUS LAPAROSCOPIC REPAIR OF POST-CHOLECYSTECTOMY BILIARY STRICTURE

Only one study compared the outcomes of two minimally invasive approaches for biliary reconstruction in post-cholecystectomy biliary stricture patients[28]. Of the 75 patients included in the study 40 were managed laparoscopically, and 35 underwent robotic reconstruction. The BDI types were as follows: E1 (7.5% *vs* 14.3%), E2 (22.5% *vs* 14.3%), E3 (40% *vs* 42.9%), E4 (22.5% *vs* 28.6%), and E5 (7.5% *vs* 0), for laparoscopic hepaticojejunostomy and robotic-assisted hepaticojejunostomy respectively. The blood loss, operative times, length of hospital stay and anastomotic patency rate at the 90-day index period were comparable between the two groups (Table 3). Though overall morbidity and anastomotic patency rate were slightly superior in the robotic group, the difference was not statistically significant. The authors concluded that both minimally invasive approaches are safe and effective for biliary reconstruction in a high-volume centre[28]. However robotic approach has technical superiority over the laparoscopic approach. As the duration of follow-up was different in the two groups, the 90-day-index treatment period rather than the actuarial anastomotic patency rate was compared, which is a limitation of the study. Also, the selection of patients for the robotic and laparoscopic approach was based on the availability of the equipment, which could result in selection bias. A cost-effective analysis between the two

Table 3 Study comparing laparoscopic and robotic repair of postcholecystectomy biliary stricture

Ref.	Year	Patients	Strasberg injury type	Method of reconstruction	Mean operative time (min)	Blood loss (mL)	Conversion to open	Overall morbidity	Specific complications	Length of stay (d)	Follow up (mo)
Cuendis-Velázquez *et al*[28]	2019	75 (laparoscopic–40, robotic–35)	E1-E5	Roux-en-Y hepaticojejunostomy	Laparoscopic–240, Robotic–270	Laparoscopic–215, Robotic–150	1 patient in laparoscopic group due to dense adhesions	Laparoscopic–27.5, Robotic–22.8	Bile leak, laparoscopic–2 patients, robotic–1 patient, one patient in each group underwent laparotomy, lavage with additional drain placement for bile leak	Laparoscopic–7, Robotic–6	Laparoscopic–49, anastomotic patency rate–92.5%, robotic–16, anastomotic patency rate–100%

approaches was not performed as the robot adds cost to the surgical procedure.

LIMITATIONS OF MINIMALLY INVASIVE SURGERY FOR REPAIR OF POST-CHOLECYSTECTOMY BILIARY STRICTURE

Although minimally invasive surgery has gained immense popularity in recent years for treating various hepatobiliary and pancreatic disorders, it has limitations, especially in complex procedures[29]. The technical drawbacks related to the laparoscopic approach are an unsteady surgical field, restricted degrees of freedom of movement, a steep learning curve and difficulties in complex suturing[30]. The complexity of the surgery and the steep learning curve comes from the fact that most patients with BDI would have suffered a bile leak and peritonitis, resulting in extensive adhesions, and altered anatomy[30,31]. Also, most patients with BDI have complex strictures (Strasberg E3-E5 types). The need to anastomose delicate and supple lobar ducts to the jejunum necessitates steady vision and a high degree of laparoscopic suturing skills. Difficulty in handling multiple sutures during minimally invasive surgery results in increased usage of continuous suture technique. While meta-analysis comparing two suture techniques has reported comparable outcomes, the evidence in the setting of postcholecystectomy biliary stricture is limited[32]. Hence, the long-term patency rate with the continuous suture technique commonly used in minimally invasive surgery must be analyzed. As documented in most studies, laparoscopic repair of postcholecystectomy biliary stricture was performed by surgeons who have completed more than 30 complex hepatopancreatobiliary surgeries, including laparoscopic Whipple's procedure[18]. On the other hand, the robotic repair of biliary strictures has documented advantages over the laparoscopic approach in terms of magnification, stable vision, and a greater degree of freedom of movement with ease of intracorporeal suturing[11]. However, robotic repair of biliary stricture is not without limitations, the foremost being the availability of equipment, high equipment and maintenance costs restricting its availability to a few centres. Undoubtedly robotic approach increases the treatment cost for patients with severe economic hardships due to the disease.

Regarding drawbacks in the published literature on minimally invasive surgery, most studies were retrospective analyses with several reporting biases. The diagnostic criteria for postoperative complications, timing, and duration of follow-up were non-homogenous. It eventually translated to difficulty in acquiring raw data for some long-term follow-

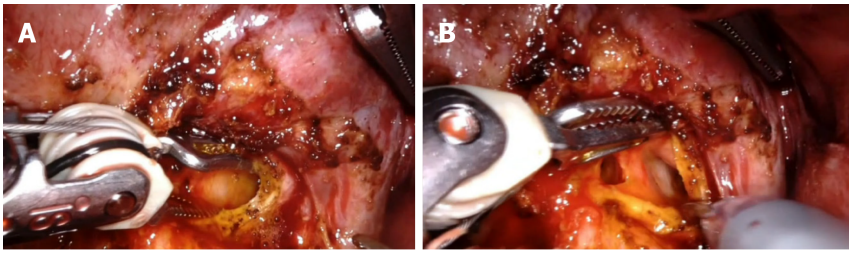

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Figure 4 Opening the hepatic duct. A: Identification and opening of the left hepatic duct; B: Confluence of left hepatic duct with right hepatic duct identified.

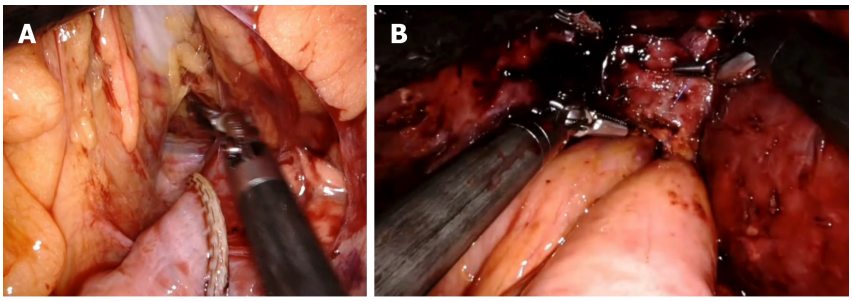

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Figure 5 Roux-en-Y hepaticojejunostomy. A: Roux limb of jejunum taken to the supracolic compartment through the mesocolic window; B: Completed hepaticojejunostomy.

up parameters, including the anastomotic patency rate. Upcoming studies have to consider reporting long-term follow-up and ten year patency rates of bilio-enteric anastomosis, which could confirm the better quality of life with the minimally invasive repair of BDI.

FUTURE PERSPECTIVE – A NEW ERA OF BILE DUCT REPAIR

Studies published in the last five years, despite their limitations, provide hope that minimally invasive procedures could play a greater role in the management, thereby offering short- and long-term advantages to patients experiencing this devastating complication. The availability and expertise of a hepatobiliary surgeon are of prime importance in managing BDI patients, and the application of minimally invasive procedures would complement the surgery results. As minimally invasive surgery can be relatively easily employed in patients with Strasberg E1-E3 strictures, future prospective trials should compare open and minimally invasive approaches in this subgroup of patients. As postcholecystectomy biliary stricture repair requires fine dissection in a small, narrow operating field along with extreme accuracy in suture placement, robotic surgery could have a greater role. In the economic foreground, the robotic approach can increase the total cost of BDI management compared to the laparoscopic approach. However, with the availability of new robotic platforms, the cost of the robotic approach is expected to decrease in the near future. While three-dimensional (3D) laparoscopy could overcome some of the limitations of conventional laparoscopy, more studies are required to compare the outcomes of BDI repair done with 3D laparoscopic and robotic approaches. There is significant potential for artificial intelligence and computer-guided technology in surgery for postcholecystectomy biliary stricture. Lopez-Lopez *et al*[33] demonstrated the use of machine learning to develop a risk-scoring model and improve the accuracy of predicting the success of surgical repair in managing iatrogenic BDI. Also, artificial intelligence and computer-guided technology could avoid misidentifying critical structures during minimally invasive BDI repair. Future advancements could widen the application of minimally invasive surgery, offering patients a better quality of life and psychological benefits in addition to the traditional benefits of the minimal access approach. Upcoming studies have to consider reporting long-term follow-up and ten-year patency rates of bilio-enteric anastomosis, which could confirm the better quality of life with the minimally invasive repair of BDI. Early referral to high-volume centres with expertise in advanced minimally invasive hepatopancreatobiliary procedures could widen the scope of minimally invasive surgery. Also, multiple benefits to patients could preclude them from filing lawsuits against surgeons thereby benefitting the surgical community.

CONCLUSION

Open surgical repair remains the gold standard for managing postcholecystectomy biliary stricture, a dreadful compli-

cation with severe health and litigation consequences. However, the available evidence suggests that minimally invasive surgery in carefully selected patients could help eliminate the trauma and devastation suffered by these patients, thereby offering superior quality of life. With its unique advantages, the robotic approach can potentially become the preferred minimally invasive approach for repairing postcholecystectomy biliary stricture. Experts from high-volume centres should take the lead in conducting prospective trials to compare different approaches for managing postcholecystectomy biliary stricture with long-term follow-up.

FOOTNOTES

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MINIREVIEWS

From basic to clinical: Anatomy of Denonvilliers' fascia and its application in laparoscopic radical resection of rectal cancer

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Abstract

The total mesorectal excision (TME) approach has been established as the gold standard for the surgical treatment of middle and lower rectal cancer. This approach is widely accepted to minimize the risk of local recurrence and increase the long-term survival rate of patients undergoing surgery. However, standardized TME causes urogenital dysfunction in more than half of patients, thus lowering the quality of life of patients. Of note, pelvic autonomic nerve damage during TME is the most pivotal cause of postoperative urogenital dysfunction. The anatomy of the Denonvilliers' fascia (DVF) and its application in surgery have been investigated both nationally and internationally. Nevertheless, controversy exists regarding the basic to clinical anatomy of DVF and its application in surgery. Currently, it is a hotspot of concern and research to improve the postoperative quality of life of patients with rectal cancer through the protection of their urinary and reproductive functions after radical resection. Herein, this study systematically describes the anatomy of DVF and its appli-cation in surgery, thus providing a reference for the selection of surgical treatment modalities and the enhancement of postoperative quality of life in patients with middle and low rectal cancer.

Key Words: Denonvilliers' fascia; Total mesorectal excision; Middle and low rectal cancer; Laparoscopic surgery; Dissect

Core Tip: Denonvilliers' fascia, an influential separating and barrier structure surrounding the rectum, is of paramount significance to the quality of life and the protection of pelvic autonomic nerves following surgery for rectal cancer.

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INTRODUCTION

Rectal cancer, one of the most common cancers worldwide[1], is currently treated with a complete surgical approach. Heald *et al*[2,3] proposed that total mesorectal excision (TME) is the gold standard for the surgical treatment of middle and low rectal cancer and that the integrity of mesorectal specimens can be utilized as an essential criterion for evaluating surgical quality and has the function of predicting tumor recurrence.

As reported[2], the most frequent postoperative complications of rectal cancer are urination disorder and sexual dysfunction caused by intraoperative pelvic autonomic nerve (PAN) damage. These two complications have an incidence rate of 30%-60% and 50%-70%, respectively, and severely affect the postoperative quality of life of patients. The precise separation of planes in front of the rectum was not overemphasized in the early surgical description of Heald. Importantly, recent years have witnessed the constant development of TME technology for rectal cancer and the increasing requirements for PAN preservation, which enables the selection of scope of radical resection for rectal cancer and the better preservation of postoperative urinary, reproductive, and defecation functions of patients to become an important issue that must be solved urgently. It has been extensively demonstrated that the removal of Denonvilliers' fascia (DVF) during TME is a primary contributor to postoperative urogenital dysfunction in patients with rectal cancer [4]. Nonetheless, there is currently a paucity of long-term follow-up results on DVF-preserving TME (iTME), and it is yet to be reported on the results of long-term research on whether DVF preservation affects the long-term survival rate and increased local recurrence rate of patients. At the moment, it is a consensus to free the posterior and lateral anatomical levels of the rectum during TME, that is, freeing along the fascia propria of the rectum. However, the freeing of the anterior rectal wall and DVF-related levels is still debatable[5]. Accordingly, this study explores the anatomy of DVF and its use in surgery in greater detail and analyzes the comprehension of DVF and its preservation or not, thus providing a further reference for the selection of surgical treatment modes for middle and low rectal cancer.

THE ORIGIN, BASIS, AND CLINICAL ANATOMY OF DVF

The anatomical position of DVF and its association with adjacent organs are responsible for its critical role in surgery for rectal cancer and influence the choice of surgical plane in front of the rectum during TME. This structure can be understood to some extent through anatomy and embryology (Figure 1A). At present, three basic hypotheses exist for the embryonic origin of DVF, including peritoneal fusion of embryo dead sac, condensation of embryo mesenchyme, and mechanical pressure. According to certain experts[5], DVF is formed through peritoneal fusion. Another opinion[4] holds that DVF formation is not derived from the occurrence of peritoneal fusion or pelvic dead sac of peritoneum. Moreover, DVF is a tension-induced structure, rather than a fascia fusion. DVF formation, whether caused by peritoneal fusion or tension, is the result of fusion or compression, which certainly results in its thickening structure. Under the light microscope, DVF is observed to have a single-layer, double-layer, multi-layer, or composite single-layer structure. Nevertheless, DVF has not been observed to be stratified to the naked eye in practically all individuals, and individual DVF is partially separated into two layers of vacuolated structures. Nonetheless, such individuals may also be particular. This structure has also been corroborated in the studies by Abdelrahman[6] and Wang *et al*[7].

The DVF structure was first discovered in male cadavers and then accepted by surgeons. However, the structure of DVF in females has not been thoroughly characterized, since physicians seldom find structures identical to DVF in males between the rectum and vagina after surgery. Hence, the presence of DVF in females has been controversial. However, mounting embryological, anatomical, and histological studies show the existence of DVF in females, including the structure of the rectovaginal septum. Despite no agreement on the embryonic origin of DVF, three theories including tension induction, mesenchyme, and peritoneal fusion all support the concept of DVF as a separate structure that neither belongs to the fascia propria of the rectum nor to the urogenital system[8-11]. Frizzell *et al*[12] observed that DVF fused with the anterior mesorectal fascia in imaging such as magnetic resonance imaging and therefore was difficultly differentiated and that the above two types of fascia exhibited a low-signal shadow of a single-layer linear structure after being reflected between the anterior rectal wall of the rectum and vagina, the seminal vesicle and the prostate, and peritoneum (Figure 1B). Another researcher discovered that intraoperative observations (endorectal ultrasound) were completely consistent with the anatomical course of DVF and that DVF divided the rectum and urogenital organs into posterior prostatic space and anterior rectal space, among which the latter existed objectively as the anatomical plane of separation plane during TME. A histological study[13] revealed that DVF was markedly stratified and varied among individuals,

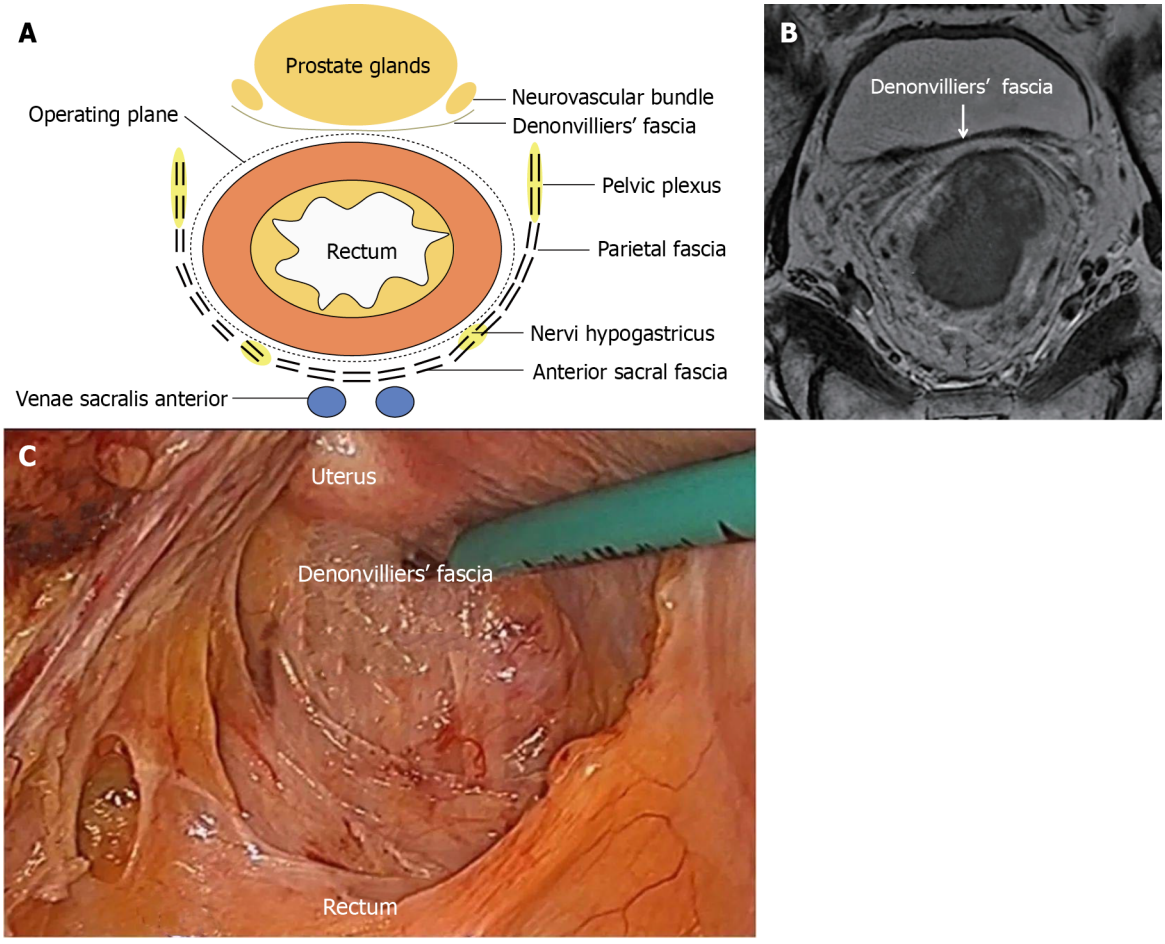

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Figure 1 The anatomical location of the Denonvilliers' fascia is shown in hand-drawn diagrams, images and surgical photographs. A: Diagram of the anatomical pattern of Denonvilliers' fascia (DVF); B: Magnetic resonance imaging-weighted image with DVF shown by arrow; C: Anatomical location and adjacency of DVF during laparoscopy.

manifesting as a variety of distinct configurations. Retrospective studies of laparoscopic surgery videos[14,15] demonstrated the obvious stratification of DVF (Figure 1C). A prior study[11] unraveled that the original structure of DVF was easily disrupted by intraoperative exploration. In addition, the loose porous tissue between the seminal vesicle and the DVF has been questioned as an artificial structure formed by the drawing tension generated by the surgical procedure[16]. As a result, further multi-center fundamental and clinical studies are warranted to identify whether the anatomical structure of DVF is stratified. Although the embryonic origin of DVF remains undetermined, the differences in the anatomical structure of DVF between males and females are recognized by most experts.

THE RELATIONSHIP BETWEEN DVF AND SURROUNDING TISSUES

The association of DVF with perirectal fascia and ligaments is barely reported in both domestic and foreign literature at present. Perirectal fascia and ligaments include the fascia propria of the rectum and the perirectal fat, nerves, and blood vessels, the presacral fascia and sacrococcygeal ligament behind the rectum, the DVF in front of the rectum, the rectal ligament on the side of the rectum, and some unclear fascia. Scholars at home and abroad have individually detailed the aforementioned structures in the past. Nevertheless, the relationship among these structures has been rarely described. This issue has been described by Zhang *et al*[17] in some detail: under peritoneal reflection, the anterior layer of DVF merges to both sides with the presacral fascia behind the rectum, forming the second cyclic structure of the rectum; the posterior layer of DVF directly merges with the rectum to generate the fascia propria of the rectum, constituting the first cyclic structure of the rectum; the pelvic parietal peritoneum and piriformis fascia form the third cyclic structure. The above discussion creatively provides a systematic overview of the overall association of perirectal mesentery. However, additional research on anatomy and histology is still currently necessary to further understand this topic.

DVF is a thin fascial layer that connects the rectum and its mesentery to the posterior wall of the seminal vesicle or prostate of males or the vagina of females, which originates upward from the peritoneal reflection to the prostate apex and the perineal central tendon, with some fibers forming the intramuscular fibers of the anal sphincter. DVF progressively thins to the sides and extends with the posterior pelvic fascia, separating the anterior rectal space into two

independent fascia spaces: the anterior rectal space and the posterior prostatic space[18]. The incision is conducted along the Denonvilliers line (the inverted thickening line of the pelvic floor peritoneum, that is, the projection of DVF on the peritoneal surface) from the lowest point of the pelvic floor peritoneum directly into the large anterior rectal space behind DVF. The Denonvilliers line extends laterally as a yellow-white borderline between the mesorectum and the pelvic fascia, which is a crucial anatomical landmark during TME[19]. During the surgery, DVF is closely connected with the seminal vesicle or prostate in males or the posterior wall of vagina in females, with numerous blood vessels in the space, which is difficult to separate during the surgery, particularly for patients who had underwent neoadjuvant chemotherapy.

Posteriorly to the rectum, the superior hypogastric plexus and hypogastric nerve of the PAN branch course between the inside (also named the anterior fascia of the hypogastric nerve) and outside of the pelvic fascia. In most individuals, the fascia propria of the rectum exhibits a complete columnar surface contour on the lateral side, from which the smooth interface may be separated. Some nerves and blood vessels course to the fascia propria of the rectum only at the "lateral ligament" position. The neurovascular bundle (NVB) in males is located below the seminal vesicle in the front and travels through DVF tissues *via* the anterolateral side, whose branches are distributed in the prostate and seminal vesicle[18]. Liang *et al*[20] investigated the association between autonomic nerves and the prerenal fascia-presacral fascia in 7 cadaveric specimens and 52 patients with rectal cancer who underwent laparoscopic excision and observed that the abdominal aortic plexus, superior hypogastric plexus, hypogastric nerve, and inferior hypogastric were located in the posterolateral side of the presacral fascia-presacral fascia. Histological examination unveiled that nerve fibers were located behind fascia, with some thinner fibers in the fascia. Hence, when the tissues behind the descending mesocolon and mesorectum are separated during the surgery for rectal cancer, the basic skills to protect nerves are as follows: maintaining the integrity of the prerenal fascia-presacral fascia (Gerota fascia) and dissection in the fusion space between it and mesentery. Accordingly, the maintenance of the fascia integrity is the anatomical basis and fundamental strategy for protecting the autonomic nerve in surgery for rectal cancer surgery.

APPLICATION OF DVF IN SURGERY FOR RECTAL CANCER

The anterior separation of DVF needs to be performed during the dissection of the anterior rectal space in laparoscopic surgery for rectal cancer, which is in accordance with the surgical protocol for rectal cancer optimized by Heald *et al*[21] and fulfills the standards of TME. Moszkowicz *et al*[22] proposed that anus-preserving surgery for rectal cancer primarily aims to improve the quality of life of patients and diminish the risk of local tumor recurrence, with the second goal of minimizing nerve damage and preserving organ function. As a result, DVF should not be separated in patients with tumor infiltration in the mesentery if the bottom of the seminal vesicle is not completely exposed but should be separated in front of the DVF. For patients with serious tumor infiltration, a portion of the seminal vesicle (male) or posterior vaginal wall (female) should be excised. Overall, the scope of alternative resection should be selected based on the extent of infiltration and specific location for patients with tumor-infiltrating anterior mesorectum. The resection scope is 1 cm above the peritoneal reflection and down to 0.5 cm from the seminal vesicle (male) or 5 cm below the peritoneal reflection (female) to ensure the integrity of the anterior mesentery. After excision, the anterior lobe of the DVF is shaped in an inverted "U" from both sides to the inner side of the NVB. When invaded by a tumor, the fascia should be separated downward in front of it. If the condition is severe, a portion of the seminal vesicle (male) or the posterior vaginal wall (female) should be excised. After the separation of the anterior and posterior rectal spaces, the lateral rectal space should be separated from the anterosuperior side toward the posteroinferior side, and the sacred plane should be found to ensure complete mesorectum wrapping, which can prevent damage to the pelvic plexus or the NVB. Specifically, the membrane bridge is first incised in an arc 1 cm above the peritoneal reflection and directly to the anterior space of the DVF. A free space is observed in front of the thick anterior lobe of DVF under the magnifying effect of laparoscopy or robot, which is similar to the structure of "hairs of the angel". Then, it is facile to enter the anterior space of DVF through this space. Because of the dense anterior lobe of DVF, it is simple to maintain the integrity of the anterior lobe and mesentery of DVF. Furthermore, the 1 cm of peritoneum on the peritoneal reflection can be used for intraoperative retraction, which facilitates the exposure of the loose connective tissues in the anterior rectal space and the expansion of the surgical operation space and causes difficulty in fogging the laparoscopic mirror. In this way, it is extremely beneficial for pelvic floor operation in male patients with contracted pelvis. The hypogastric nerve, hypogastric nerve plexus, and subabdominal fascia are all covered by the first layer of fascia (DVF) and the anterior abdominal fascia. Importantly, the anterolateral side of this layer is the most key anatomical site. NVB can be found but is not always visible after the anterior lobe of DVF is transected. This phenomenon can be explained by the fact that NVB cannot be found when the incision line is located before the stratification of the anterior lobe of DVF, since NVB is covered by the middle layer of the anterior lobe of DVF after stratification; however, NVB is obviously exposed and has a sponge-like structure when the incision line is located after the stratification of the anterior lobe of DVF because its surface is not covered by membranous tissues. Accordingly, the NVB is not ensured to be undamaged if the surgical plane is selected between the first and second layers at the semi-prostate angle level. The third layer originates from the posterior bladder neck and then courses upward to attach to the second layer while crossing the upper surface of the bladder to form a common layer. This layer is separated by loose connective tissues from the lower bladder fascia and the upper peritoneum. Meanwhile, it receives some NVB branches from both sides, similar to the second layer. Some researchers consider that this layer is the third layer of DVF, not the bladder-related fascia, because it is completely isolated from the bladder that is covered by the adventitia. Additionally, this layer extends upward and connects to the second layer, which is considered one of the mentioned DVF complexes. Furthermore, at 2 and 10 o'clock directions, NVB specifies the location of the second and third layers with a highly complicated neural network, where there was no evident dissociative innervation,

thus enabling us to believe that this layer is one of the multi-layer DVF complexes. According to Lu *et al*[23], the surgery should be performed with an approach above the peritoneal reflection. Next, separation should be conducted in close proximity to the DVF during the surgery. The DVF should be severed near the bottom of the seminal vesicle for male patients and 5 cm below the peritoneal reflection for female patients. The separation is subsequently continued by entering the space between the fascia propria of the rectum and the DVF. This surgery not only maintains the integrity of the local fascia propria of the rectum during excision, but also protects the autonomic nerve and prevents seminal vesicle damage. This surgery method should be widely used in clinical practice since it not only is beneficial for reducing mesangial injury but also elevates the complete rate of anterior mesangial resection. Meanwhile, it is useful for preventing or avoiding bleeding and peripheral nerve injury during pelvic free surgery to understand the interaction between DVF and surrounding tissues. Finding and dissecting DVF and elaborating on the surgical approach and technology for the anterior rectal space provide essential surgical experience in addressing this challenging and critical issue.

Dissection anterior to the DVF is not recommended when the tumor does not invade the fascia propria of the rectum or DVF[24], since the NVB coursing from the tail of the seminal vesicle to the bladder, seminal vesicle, prostate, and urethra in males is easily damaged during this surgery, therefore resulting in the occurrence of postoperative urogenital dysfunction. DVF should be removed when the tumor is located in the anterior wall of the rectum or invades the fascia propria or DVF, the local tumor is at the late stage, or edema and fibrosis changes occur in the focus due to preoperative neoadjuvant chemoradiotherapy. A prior study[25] demonstrated that DVF was directly connected to the fascia propria anterior to the rectum, contributing to difficulty in its dissection. Hence, the anatomy should be conducted in front of the DVF during the surgery, and attention should be paid to NVB protection when it reaches the anterior side of the mesorectum. The author recommends that the region in front of the DVF and spaces of the seminal vesicle, the vas deferens, and the fascia propria of prostate should be dissected for males with tumors in the anterior rectal wall or a tumor at > T2 stage who receive preoperative neoadjuvant radiotherapy and chemotherapy. For female patients, the region in the front of the DVF and the space of the fascia of the posterior vaginal wall should be dissected. When it reaches the anterior side of the rectum, the DVF can be cut off and dissected along the fascia propria surface outside the mesentery of the anterior side of the rectum, preserving as much as possible the integrity and continuity of the anatomical plane and preventing fascia plane distortion due to insufficient or excessive traction tension.

CONTROVERSY ON DVF PRESERVATION

Patients are pursuing radical surgery with increasing concern for postoperative prognosis and quality of life as their requirements for postoperative quality of life increase[26]. Previous research[27] revealed that after laparoscopic radical resection for rectal cancer, approximately 70% of patients might develop dysuria, approximately 45%-55% experienced erectile dysfunction, and 40% suffered from ejaculatory dysfunction and that the above adverse outcomes were related to the damage to the rectum, abdominal cavity, and pelvic cavity during the surgery. It has been reported that intraoperative fascia preservation could substantially improve the quality of life of patients after surgery. DVF is a critical pelvic floor fascia that is positioned anterior to the rectum. DVF may be regarded as a part of the mesorectum in the classic radical resection for rectal cancer and must be entirely excised to assure the radical resection of tumors. Meanwhile, DVF has a complex anatomical structure, whose intraoperative preservation elevates the complexity of the surgery. Hence, DVF preservation during radical resection for rectal cancer is now disputed in the clinic. Abroad, some researchers[28] discovered that the excised DVF tissues had many nerve fibers, including NOS-positive nerve fibers associated with erectile function, which were distributed more broadly and not limited to the previously described NVB region. Therefore, even in the "inverted U-shaped" resection of DVF, NVB preservation is futile, as the efferent branch of inferior hypogastric plexus may be injured, then compromising postoperative urine and sexual functions, particularly erectile function[29]. A prior study[30] utilized intraoperative nerve stimulation to identify PANs and unraveled that after DVF excision, nerve stimulation cannot elicit active bladder contraction, objectively validating the intimate association between DVF and PAN. Li *et al*[31] conducted a retrospective comparison study on the issue of DVF preservation or not in laparoscopic radical resection for low rectal cancer. The use of DVF in laparoscopic radical resection of low rectal cancer not only minimizes the amount of intraoperative bleeding, but also promotes the postoperative recovery of urine and sexual functions in patients and improves their quality of life. In addition, the research by Fang *et al*[32] exhibited that compared to standardized TME surgery, iTME can successfully minimize the incidence of postoperative urinary and sexual disorders in male patients with low rectal cancer without affecting the short-term radical outcome.

CONCLUSION

Conclusively, DVF, an influential separating and barrier structure surrounding the rectum, is of paramount significance to the quality of life and the protection of PANs following surgery for rectal cancer. Previously, the PUF-01 multicenter prospective study was performed on the impact of partial and complete preservation of DVF on the postoperative sexual and urinary function of patients with rectal cancer[24], which unraveled that the complete preservation of DVF exerted a protective effect on postoperative urogenital function as compared to the partial resection of DVF during laparoscopic TME. Nevertheless, long-term follow-up data are lacking for postoperative urogenital function in this group of patients both at home and abroad, precluding a more precise and detailed dynamic evaluation. In China, a tentative agreement has been achieved on the surgical treatment of DVF. According to the China Expert Consensus of iTME[4], iTME surgery can deliver short-term overall survival rates comparable to those of traditional TME surgery for male patients with

middle and low rectal cancer at preoperative clinical stages of T1-4 (T1-2 for anterior wall tumor), N0-2, and M0 (7th editions of AJCC staging). According to this study, iTME can lower the incidence of postoperative micturition and sexual dysfunction in patients with rectum cancer at T1-4, N0-2, and M0 stages. However, existing evidence only supports individuals with tumors in the rectal anterior wall at T1-2, N0-2, and M0 stages. More importantly, PAN protection in radical resection for rectal cancer is a multi-step process that cannot be achieved by focusing only on a few important elements. As a result, further analysis of the entire pelvic structure is warranted to further optimize the membrane-guided PAN protection technology and maximize the benefits to patients from therapy.

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FOOTNOTES

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ORIGINAL ARTICLE

Basic Study

Effects of thrombopoietin pre-treatment on peri-liver transplantation thrombocytopenia in a mouse model of cirrhosis with hypersplenism

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Abstract

BACKGROUND

During cirrhosis, the liver is impaired and unable to synthesize and clear thrombopoietin properly. At the same time, the spleen assumes the function of hemofiltration and storage due to liver dysfunction, resulting in hypersplenism and excessive removal of platelets in the spleen, further reducing platelet count. When liver function is decompensated in cirrhotic patients, the decrease of thrombopoietin (TPO) synthesis is the main reason for the decrease of new platelet production. This change of TPO leads to thrombocytopenia and bleeding tendency in cirrhotic patients with hypersplenism.

AIM

To investigate the clinical efficacy of recombinant human TPO (rhTPO) in the treatment of perioperative thrombocytopenia during liver transplantation in cirrhotic mice with hypersplenism.

METHODS

C57BL/6J mice and TPO receptor-deficient mice were used to establish models of cirrhosis with hypersplenism. Subsequently, these mice underwent orthotopic liver transplantation (OLT). The mice in the experimental group were given rhTPO treatment for 3 consecutive days before surgery and 5 consecutive days after surgery, while the mice in the control group received the same dose of saline at the same frequency. Differences in liver function and platelet counts were determined between the experimental and control groups. Enzyme-linked immunosorbent assay was used to assess the expression of TPO and TPO receptor (c-Mpl) in the blood.

RESULTS

Preoperative administration of rhTPO significantly improved peri-OLT thrombocytopenia in mice with cirrhosis and hypersplenism. Blocking the expression of TPO receptors exacerbated peri-OLT thrombocytopenia. The concentration of

TPO decreased while the concentration of c-Mpl increased in compensation in the mouse model of cirrhosis with hypersplenism. TPO pre-treatment significantly increased the postoperative TPO concentration in mice, which in turn led to a decrease in the c-Mpl concentration. TPO pre-treatment also significantly enhanced the Janus kinase (Jak)/signal transducers and activators of transcription pathway protein expressions in bone marrow stem cells of the C57BL/6J mice. Moreover, the administration of TPO, both before and after surgery, regulated the levels of biochemical indicators, such as alanine aminotransferase, alkaline phosphatase, and aspartate aminotransferase in the C57BL/6J mice.

CONCLUSION

Pre-treatment with TPO not only exhibited therapeutic effects on perioperative thrombocytopenia in the mice with cirrhosis and hypersplenism, who underwent liver transplantation but also significantly enhanced the perioperative liver function.

Key Words: Thrombopoietin pre-treatment; Cirrhosis; Liver transplantation; Perioperative period; Platelet

Core Tip: Our research results confirm that thrombopoietin (TPO) can improve liver function after liver transplantation in mice by enhancing the effect of platelets. Pre-treatment with TPO not only exhibited therapeutic effects on perioperative thrombocytopenia in the mice with cirrhosis and hypersplenism, who underwent liver transplantation but also significantly enhanced the perioperative liver function.

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INTRODUCTION

Thrombocytopenia in cirrhosis is a rare condition with various causes including hypersplenism, reduced levels of thrombopoietin (TPO), presence of anti-platelet autoantibodies, suppression of bone marrow cells by hepatitis viruses, adverse reactions to excessive alcohol intake, liver dysfunction, and vitamin B12 and folic acid deficiencies. Of these, hypersplenism is the most common cause. However, for patients with cirrhosis in the decompensated stage, a decrease in TPO production by hepatocytes is the main cause for the reduced production of new platelets[1-3]. Most patients with cirrhosis and hypersplenism, who are candidates for orthotopic liver transplantation (OLT), are in the decompensated stage, with comorbidities, such as hepatitis or a long history of excessive alcohol consumption. As a result, these patients exhibit more pronounced hypersplenism and have a slower postoperative recovery compared to those with cirrhosis and hypersplenism alone. A study of patients with liver failure, before and after liver transplantation, found that all patients manifested prominent thrombocytopenia before transplantation, with serum levels so low that TPO was undetectable. In contrast, the serum TPO levels increased significantly 2 d after transplantation and reached their peaks at 4-6 d. At the same time, platelet counts began to rise and peaked at 14 d after transplantation. Furthermore, other cytokines affecting platelet production did not change significantly before and after transplantation[4,5]. These findings suggest that, in patients with liver failure, TPO plays a critical role in thrombocytopenia and in the restoration of platelet count after liver transplantation. Gollomp *et al*[6] found similar serum TPO levels before and after liver transplantation, as well as significantly lower TPO mRNA expressions in the liver tissues of patients with cirrhosis. Thrombocytopenia in patients with liver failure is challenging. Current research to improve the postoperative platelet counts of these patients and, thus, reduce the risk of bleeding and promote rapid recovery from hypersplenism is necessary.

MATERIALS AND METHODS

Study of the treatment efficacy of TPO for perioperative thrombocytopenia in mice undergoing liver transplantation for cirrhosis with hypersplenism

A mouse model of liver cirrhosis with hypersplenism was established by weighing the mice and injecting them intraperitoneally with carbon tetrachloride (CCl4, 1 mL/kg body weight) three times a week for 6 wk. At the end of the 6 wk, blood was collected from the orbital vein to determine the serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and the liver tissues were stained with hematoxylin and eosin (HE) to determine whether the model was successfully developed.

Groups: C57BL/6J mice were used to establish a model of cirrhosis with hypersplenism. These mice subsequently underwent OLT. The experimental group received recombinant human TPO (rhTPO) treatment for 3 consecutive days before surgery and 5 consecutive days after surgery, while the control group received saline instead at the same dose and frequency.

Sample collection: Blood samples were collected 1 d before and 5 d after surgery. Liver tissue samples and bone marrow mesenchymal stem cells were collected from euthanized experimental and control mice 5 d after surgery.

Assessed indicators: Changes in liver function [ALT, AST, and alkaline phosphatase (ALP) levels] were assessed by biochemical assays at different time points. Changes in the level of leukocytes, erythrocytes, platelets, *etc.* were detected by routine blood tests at different time points. Pathological liver changes were observed in the tissue sections at different time points. Serum TPO and c-Mpl levels were determined using enzyme-linked immunosorbent assay (ELISA). The expression of Jak/signal transducers and activators of transcription (STAT), in extracted mouse bone marrow mesenchymal stem cells, was detected with Western blotting.

Study on whether blocking the expression of TPO receptor can exacerbate perioperative thrombocytopenia

Groups: Mice with a silenced TPO receptor gene and C57BL/6J mice were used to establish the model of cirrhosis with hypersplenism. These mice then all underwent OLT. The experimental group received rhTPO treatment for 3 consecutive days before surgery and 5 consecutive days after surgery, while the control group received saline instead at the same dose and frequency.

Sample collection: Same as described above.

Assessed indicators: Same as described above.

Statistical analysis

SPSS, version 22.0 (IBM Corp., Armonk, NY, United States) was used for analysis. Normally distributed quantitative data were expressed as mean ± SD, and a *t*-test was used for comparison between the groups. The data with skewed distributions were expressed as M (range), and a Mann-Whitney *U* test was used for comparison between the groups. Count data were expressed as absolute numbers or percentages, and a χ^2 test or a Fisher's exact test was used for comparisons between the groups. Data with repeated measurements were analyzed using repeated-measures analysis of variance (ANOVA). $P < 0.05$ was considered statistically significant.

RESULTS

Study of the treatment efficacy of TPO for perioperative thrombocytopenia in mice undergoing liver transplantation for cirrhosis with hypersplenism

C57BL/6J mice were treated with CCl4 to establish a model of cirrhosis with hypersplenism. Subsequently, these mice underwent OLT. In the experimental group, rhTPO was administrated for 3 consecutive days before and 5 consecutive days after surgery, while in the control group, an equal amount of saline was administrated at the same frequency instead. Routine blood tests and liver function assessments of the experimental and control mice were performed 1 d before and 5 d after surgery to monitor the changes. The results showed that TPO pre-treatment significantly ameliorated erythropenia and thrombocytopenia during the perioperative period of liver transplantation in the experimental C57BL/6 mice compared to the control mice (Figure 1A and C). However, the leukocyte count was not affected by TPO pre-treatment (Figure 1B). Importantly, TPO pre-treatment significantly improved the perioperative liver function of these mice (Figure 1D-F). In contrast, TPO receptor-deficient mice responded poorly to TPO pre-treatment compared to C57BL/6J mice. As such, TPO pre-treatment failed to elevate the perioperative platelet counts in TPO receptor-deficient mice (Figure 2A and B).

ELISA to determine the differences in TPO and c-Mpl levels

ELISA was used to determine the differences in TPO and c-Mpl levels between the experimental and control groups, 1 d before and 5 d after surgery. Compared to the control group, the results from the experimental group showed that the TPO treatment significantly increased serum TPO after liver transplantation, which in turn, led to a decrease in the c-Mpl level (Figure 2C and D).

HE staining and differential analysis of protein expression after liver transplantation

HE staining showed that the mice in the experimental group which received TPO pre-treatment had significantly reduced inflammatory responses in the liver tissues compared to those in the control group (Figure 3). Considering that the Jak/STAT pathway plays an important role in the differentiation and maturation of megakaryocytes and the promotion of platelet production, we examined the differential expression of the Jak/STAT pathway proteins between the TPO receptor-deficient mice and the C57BL/6J mice. TPO pre-treatment significantly enhanced the expression of the Jak/STAT pathway proteins in the bone marrow stem cells of C57BL/6J mice compared to those of the TPO receptor-deficient mice (Figure 4).

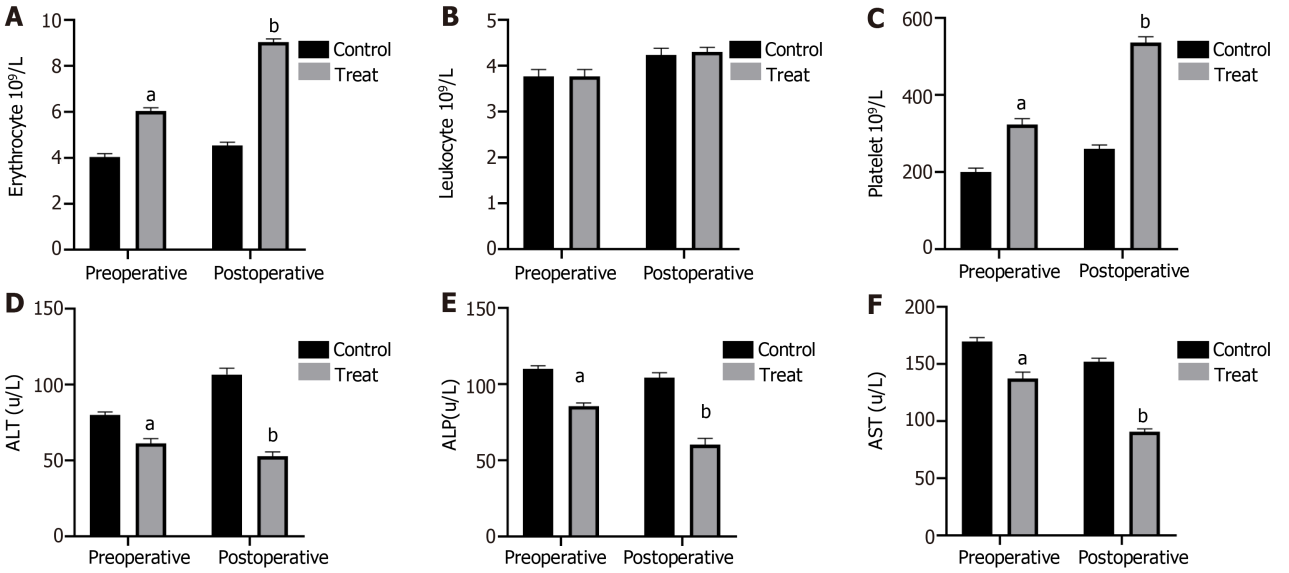

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Figure 1 Comparison of routine blood and biochemistry results between the experimental and control groups during the perioperative period of liver transplantation. The experimental group was treated with thrombopoietin, while the control group was treated with an equal amount of saline. [a]*P* < 0.05; [b]*P* < 0.01. ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase.

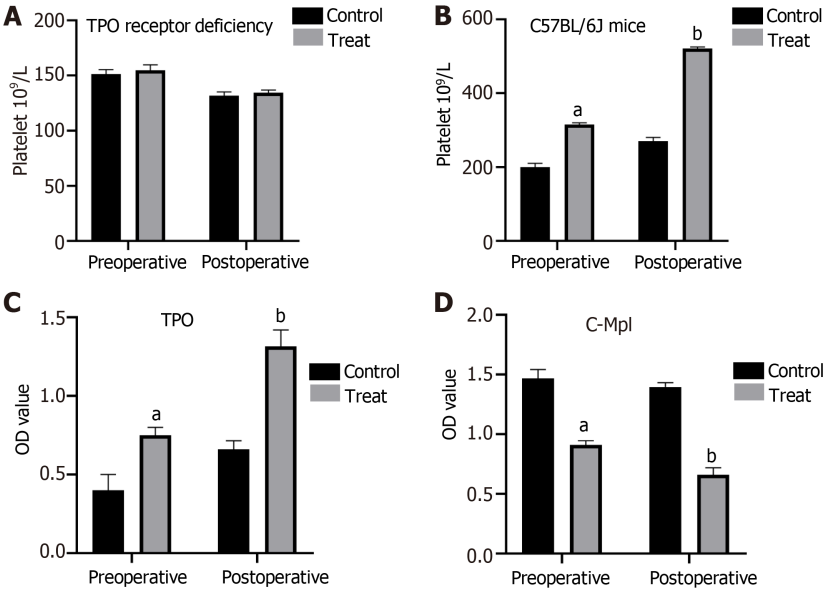

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Figure 2 Evaluation of the responsiveness to thrombopoietin pre-treatment and Differences in thrombopoietin and c-Mpl levels. A and B: Evaluation of the responsiveness to thrombopoietin pre-treatment in thrombopoietin receptor-deficient mice and C57B/6J mice during the perioperative period of liver transplantation; C and D: Differences in thrombopoietin and c-Mpl levels between the experimental and control groups during the perioperative period of liver transplantation determined by enzyme-linked immunosorbent assay. The experimental group was treated with thrombopoietin, while the control group was treated with an equal amount of saline. [a]*P* < 0.05; [b]*P* < 0.01. TPO: Thrombopoietin.

DISCUSSION

TPO is a glycoprotein with 332 amino acids produced mainly by hepatocytes and is an endogenous cytokine that stimulates the growth and differentiation of megakaryocytes. It has stimulative effects on megakaryopoiesis at all stages, including the proliferation of precursor cells and the development and maturation of polyploid megakaryocytes. Once TPO binds to its receptor, c-Mpl, it induces the homodimerization of c-Mpl, activating the family of JAK in signaling pathways, including Jak/STAT, P13K/Akt, Ras/MAPK, *etc.*, and the secretion of a series of signaling molecules to induce megakaryocyte differentiation and maturation and promote platelet production. The secretion of TPO is mainly influenced by the number of peripheral blood platelets, and TPO, in turn, acts to maintain a stable number of peripheral

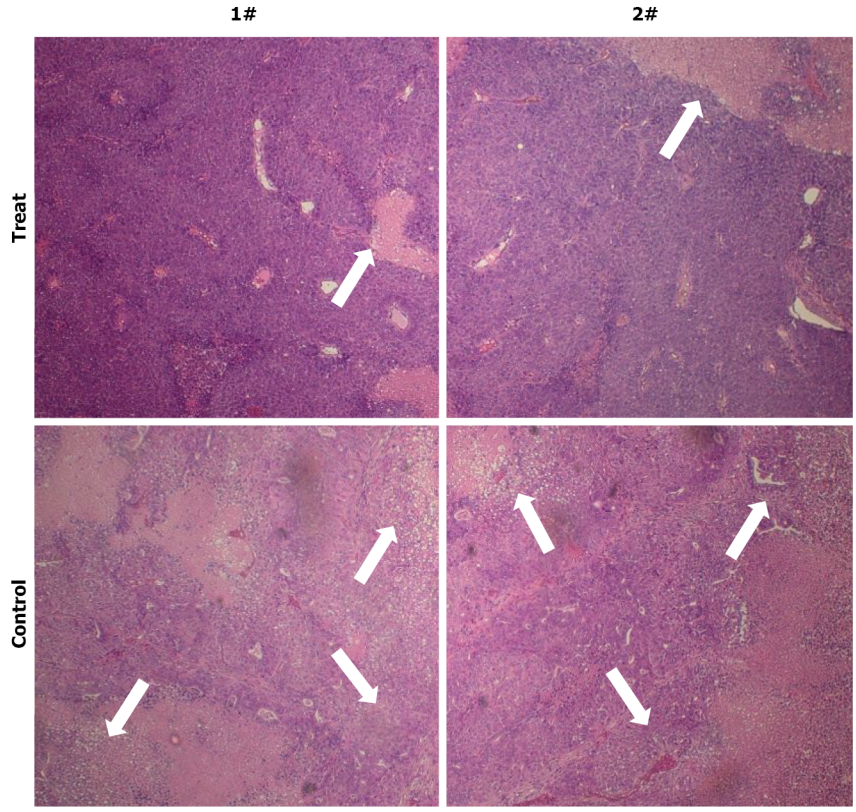

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Figure 3 Comparison of the HE-stained liver tissues between the experimental and control groups after liver transplantation. The experimental group was treated with thrombopoietin, while the control group was treated with an equal amount of saline. The arrows indicate the area of inflammatory necrosis.

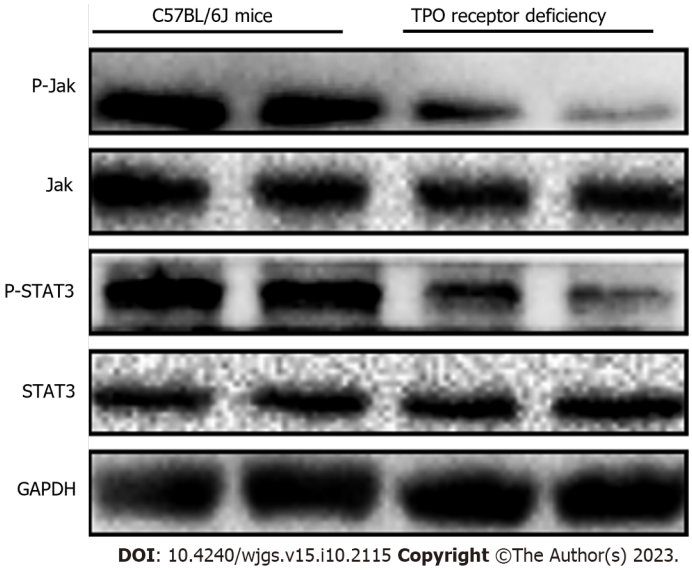

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Figure 4 Changes in the expression of Jak/STAT pathway proteins in the bone marrow stem cells of C57BL/6J mice and thrombopoietin receptor-deficient mice after thrombopoietin pre-treatment using Western blotting. TPO: Thrombopoietin; STAT: Signal transducers and activators of transcription.

blood platelets[7-10]. rhTPO is a purified full-length glycosylated TPO produced by Chinese hamster ovary cells that are modified using recombinant gene technology. It has the same amino acid sequence as TPO and is fully glycosylated with similar platelet-elevating pharmacological effects as endogenous TPO[11-13]. Most patients with cirrhosis and hypersplenism who require OLT are in a decompensated stage of cirrhosis, with comorbidities, such as hepatitis or a long history of excessive alcohol consumption. As such, thrombocytopenia tends to be more severe, and postoperative

recovery is usually slower in these patients than those with cirrhosis and hypersplenism alone. However, the therapeutic effects of rhTPO in these patients have not yet been elucidated.

Several studies have employed in-situ hybridization techniques to demonstrate that the liver is the primary organ expressing mRNA of TPO, despite the expression of TPO mRNA in other organs[14-16]. It is now confirmed that the main site of TPO production in the body is the liver. Under physiological conditions, TPO is cleared from the blood by binding to its receptors on the platelet surface. As the platelet count increases, TPO clearance also increases, resulting in a decreasing blood TPO level. Conversely, blood TPO level increases when the platelet count decreases[17,18]. There are two major contributors to thrombocytopenia in cirrhosis: Abnormal platelet distribution and a decreased production of hepatic TPO. Abnormal platelet distribution is related to the circuiting platelets being trapped in the spleen, and the degree of entrapment is positively associated with the size of the spleen. The decreased production of hepatic TPO is related to TPO production in organs, specifically 70% of TPO originates from the liver and only 30% originates from the kidneys and other organs. The indications for rhTPO during the per-OLT period in patients with cirrhosis and hypersplenism are as follows: (1) Patients with hypersplenism who have reduced circulating platelets before liver transplantation, leading to a high risk of intra- and postoperative bleeding. In this case, pre- and postoperative administration of rhTPO can appropriately raise the level of platelets to reduce the risk of surgical bleeding, with a long-lasting effect even after discontinuation as rhTPO has a long half-life; and (2) patients in the initial period following liver transplantation. During this critical time, the patient's liver function remains impaired, resulting in reduced TPO production. Moreover, hypersplenism is still present in these patients since the condition ameliorates very slowly. Therefore, these patients also have a high risk of postoperative bleeding. The continuous administration of rhTPO after surgery can promote platelet production, while promoting the release of functional circulating platelets to reduce the liver burden, promote rapid restoration of liver function, and lay a good foundation for hepatic TPO production. The restoration of liver function can also reduce portal pressure, promote rapid remission of hypersplenism, and reduce platelet phagocytosis, thus forming a virtuous circle.

The present study found that preoperative administration of rhTPO significantly improved peri-liver transplantation thrombocytopenia in mice with cirrhosis and hypersplenism. Blocking the expression of TPO receptors exacerbated peri-OLT thrombocytopenia. The concentration of TPO decreased, while the concentration of c-Mpl increased in compensation, in the mouse model of cirrhosis with hypersplenism. TPO pre-treatment significantly increased the postoperative TPO concentration in mice, which in turn, led to a decrease in the c-Mpl concentration. TPO pre-treatment significantly enhanced the expressions of proteins involved in the Jak/STAT pathway in the bone marrow stem cells of C57BL/6J mice, which is consistent with the results from other studies. Additionally, two animal studies have shown that TPO can promote liver regeneration and ameliorate liver fibrosis by promoting platelet production[19,20]. A clinical study has also shown that platelet transfusion can improve liver function in patients with chronic liver disease and cirrhosis. In the present study, we demonstrated that TPO can regulate the levels of the biochemical indicators, such as ALT, ALP, and AST in C57BL/6J mice, regardless of the timing of its administration (before or after surgery). Our results also validated that TPO can improve liver function in mice by enhancing the effects of platelets. However, there are still some limitations and deficiencies in this study. First, the study was limited to a mouse model, and the clinical effects of TPO on perioperative liver transplant patients need to be further explored in the future. In addition, the study found that TPO exerts pharmacological effects by activating the Jak/Stat3 pathway, and the specific molecular mechanisms in this pathway still need to be further demonstrated by basic experiments.

CONCLUSION

In conclusion, we found that preoperative prophylactic use of TPO has a therapeutic effect on perioperative thrombocytopenia in cirrhotic hyper splenic mice undergoing liver transplantation. In addition, TPO pretreatment can significantly improve the liver function of perioperative mice. TPO pretreatment also improved postoperative liver inflammation and reduced liver cell necrosis in mice.

ARTICLE HIGHLIGHTS

Research background

During cirrhosis, the liver undergoes significant impairment, leading to various complications, including thrombocytopenia and bleeding tendency. Thrombopoietin (TPO) is a hormone produced by the liver that plays a crucial role in regulating platelet production and clearance. However, in cirrhotic patients, the liver's ability to synthesize and clear TPO is compromised. The impaired liver function in cirrhosis results in reduced TPO synthesis. TPO is primarily produced in the liver sinusoidal endothelial cells, and when the liver is damaged, the production of TPO is significantly decreased. This reduction in TPO levels leads to a decrease in the production of new platelets in the bone marrow, contributing to thrombocytopenia.

Research motivation

It is important to manage thrombocytopenia and bleeding tendency in cirrhotic patients. Treatment options may include platelet transfusions, medications that stimulate platelet production (such as TPO receptor agonists), and interventions to address the underlying liver dysfunction. Close monitoring and collaboration with a healthcare provider are crucial in

managing these complications in cirrhotic patients.

Research objectives

To evaluate the clinical effectiveness of recombinant human TPO (rhTPO) in managing perioperative thrombocytopenia during liver transplantation in cirrhotic mice with hypersplenism. We aimed to assess whether rhTPO administration could effectively increase platelet count and reduce bleeding complications in this specific population.

Research methods

To achieve this objective, we conducted a controlled experiment using a cirrhotic mouse model with hypersplenism. The mice were divided into two groups: A treatment group receiving rhTPO and a control group receiving a placebo or standard care. We monitored the platelet counts of the mice before and after liver transplantation, as well as during the perioperative period.

Research results

The results of our study demonstrated that preoperative administration of rhTPO effectively improved perioperative thrombocytopenia in mice with cirrhosis and hypersplenism undergoing liver transplantation (OLT). This finding suggests that rhTPO may have potential clinical efficacy in managing thrombocytopenia in cirrhotic patients undergoing liver transplantation. Furthermore, we found that blocking the expression of TPO receptors exacerbated peri-OLT thrombocytopenia, indicating the importance of the TPO/c-Mpl pathway in platelet regulation during liver transplantation in cirrhotic mice with hypersplenism. In our study, we observed a decrease in TPO concentration in the mouse model of cirrhosis with hypersplenism, while the concentration of c-Mpl increased in compensation. However, pre-treatment with TPO significantly increased the postoperative TPO concentration in mice, leading to a decrease in the c-Mpl concentration. This suggests that TPO administration can regulate the TPO/c-Mpl pathway and potentially improve platelet production and function. Additionally, TPO pre-treatment significantly enhanced the protein expressions of the Janus kinase (Jak)/signal transducers and activators of transcription (STAT) pathway in bone marrow stem cells of the mice. The Jak/STAT pathway is involved in regulating various cellular processes, including cell proliferation and differentiation, and plays a role in platelet production. The enhancement of this pathway may contribute to the increased platelet production observed with TPO administration. Moreover, the administration of TPO, both before and after surgery, was found to regulate the levels of biochemical indicators, such as alanine aminotransferase (ALT), alkaline phosphatase (ALP), and aspartate aminotransferase (AST) in the mice. This suggests that TPO administration may have additional beneficial effects on liver function and overall liver health in cirrhotic mice undergoing liver transplantation.

Research conclusions

Pre-treatment with TPO not only exhibited therapeutic effects on perioperative thrombocytopenia in the mice with cirrhosis and hypersplenism, who underwent liver transplantation but also significantly enhanced the perioperative liver function.

Research perspectives

Overall, our study provides evidence supporting the clinical efficacy of rhTPO in managing perioperative thrombocytopenia during liver transplantation in cirrhotic mice with hypersplenism. These findings may have implications for the development of potential therapeutic strategies for managing thrombocytopenia in cirrhotic patients undergoing liver transplantation.

FOOTNOTES

Author contributions: Liu ZR, Cui ZL, and Tong W designed the research study; Liu ZR and Cui ZL performed the research; Liu ZR and Tong W contributed new reagents and analytic tools; Liu ZR and Cui ZL analyzed the data and wrote the manuscript; Zhang YM is responsible for reviewing the entire study; and all authors have read and approve the final manuscript.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Effect of low anterior resection syndrome on quality of life in colorectal cancer patients: A retrospective observational study

Dong-Ai Jin, Fang-Ping Gu, Tao-Li Meng, Xuan-Xuan Zhang

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Abstract

BACKGROUND

Low anterior resection syndrome (LARS) is a common complication of anus-preserving surgery in patients with colorectal cancer, which significantly affects patients' quality of life.

AIM

To determine the relationship between the incidence of LARS and patient quality of life after colorectal cancer surgery and to establish a LARS prediction model to allow perioperative precision nursing.

METHODS

We reviewed the data from patients who underwent elective radical resection for colorectal cancer at our institution from April 2013 to June 2020 and completed the LARS score questionnaire and the European Organization for Research and Treatment of Cancer Core Quality of Life and Colorectal Cancer Module questionnaires. According to the LARS score results, the patients were divided into no LARS, mild LARS, and severe LARS groups. The incidence of LARS and the effects of this condition on patient quality of life were determined. Univariate and multivariate analyses were performed to identify independent risk factors for the occurrence of LARS. Based on these factors, we established a risk prediction model for LARS and evaluated its performance.

RESULTS

Among the 223 patients included, 51 did not develop LARS and 171 had mild or severe LARS. The following quality of life indicators showed significant differences between patients without LARS and those with mild or severe LARS: Physical, role, emotional, and cognitive function, total health status, fatigue, pain,

shortness of breath, insomnia, constipation, and diarrhea. Tumor size, partial/total mesorectal excision, colostomy, preoperative radiotherapy, and neoadjuvant chemotherapy were identified to be independent risk factors for LARS. A LARS prediction model was successfully established, which demonstrated an accuracy of 0.808 for predicting the occurrence of LARS.

CONCLUSION
The quality of life of patients with LARS after colorectal cancer surgery is significantly reduced.

Key Words: Colorectal cancer; Low anterior resection syndrome; Precision nursing; Quality of life; Prediction model; Risk factors

Core Tip: Low anterior resection syndrome (LARS) is a common complication of anus-preserving surgery in patients with colorectal cancer. In this study, we found that LARS significantly affected patients' quality of life after colorectal cancer surgery, and that perioperative precision nursing could significantly reduce the incidence of LARS and improve patients' quality of life. Furthermore, we established a LARS prediction model, which showed excellent performance in predicting the occurrence of LARS after colorectal cancer surgery. This prediction model can enable implementation of perioperative precision nursing to improve the quality of life of patients with LARS.

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INTRODUCTION

Colorectal cancer is the third most common cancer worldwide[1], with a global incidence of 7.7 per 100000 population[2] and more than 1 million affected patients in the United States[3]. According to the National Cancer Institute's Surveillance, Epidemiology, and End Results program, improvements in living standards and changes in dietary habits correspond with an increase in the incidence of colorectal cancer in individuals aged 20-49 age by 51% since 1994[4,5]. In China, colorectal cancer is the fifth most common cancer, but its incidence is gradually increasing, with a significant increase observed in large cities in recent years[6,7].

Colorectal cancer treatment is based on a comprehensive multidisciplinary approach, and includes a variety of treatment methods, such as surgery, radiotherapy, chemotherapy, immunotherapy, and traditional Chinese medicine[8-11]. With the vigorous development of scientific research and the continuous exploration of approaches in clinical practice, the surgery-based multidisciplinary treatment strategy has played a significant role in improving the prognosis of patients with colorectal cancer[12,13].

With the continuous improvement of surgical techniques and equipment, the survival rates of patients with colorectal cancer have significantly improved[13,14]. According to the latest data from the American Cancer Society, the 5-year overall survival rate is 65%, with patients in local areas and hospitals having a better prognosis, with rates of up to 90% and 71%, respectively[15]. However, in patients with advanced colorectal cancer, the effect of surgical treatment is far from ideal. For these patients, current guidelines recommend the use of chemotherapy drugs, including 5-fluorouracil, oxaliplatin, and irinotecan[15].

Advancement in treatment methods has allowed colorectal cancer surgery to effectively improve patient symptoms in addition to providing good disease control and prolonging patient survival[16]. Retention of the anal canal, urinary function, and sexual function while ensuring radical resection has become the surgical objective. However, some patients develop low anterior resection syndrome (LARS) after anus-preserving surgery[17,18].

LARS is a subjective discomfort syndrome with common symptoms including incontinence, increased frequency and urgency of defecation, difficulty in emptying, and other symptoms, which brings great inconvenience to patients[9,19]. The incidence of LARS has been reported to range from 17.8% to 80.0%. Nonetheless, to date, there have been no population-based cohort studies to determine the incidence of LARS and its relationship with patient quality of life[20,21].

The accelerated development of rehabilitation surgery has shortened the overall length of hospital stay of patients with colorectal cancer[22]. However, a shorter hospitalization stay reduces the time for patients to acquire anal rehabilitation skills prior to being discharged from the hospital, which may lead to an increase in the incidence of LARS[23].

MATERIALS AND METHODS

Study design

This was a longitudinal observational retrospective cohort study with a hospital-based survey that included patients surgically treated for colorectal cancer. Postoperatively, patients were provided with the LARS score questionnaire, the third edition of the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30), and the Colorectal Cancer Module (EORTC QLQ-CR29) questionnaire[24]. To ensure patient compliance, each hospital assigned a responsible person to supervise and inspect the completion of the questionnaires. Researchers from the three hospitals met once a week to discuss the content of the study and the completion of the questionnaires.

Perioperative clinicopathological characteristics of patients and tumors were extracted from the medical records. Data were analyzed to determine the incidence of LARS and its effects on patient quality of life and to identify independent risk factors for the occurrence of LARS. Based on these factors, we established a risk prediction model for LARS and evaluated its performance.

Instrument with validity and reliability

LARS score: The LARS score questionnaire evaluates defecation frequency, occasional uncontrollable exhaust (flatulence), occasional anal leakage, stool properties, and urgency. Based on the findings of this questionnaire, patients were divided into three groups as follows: No LARS (0-20 points), mild LARS (21-29 points), and severe LARS (30-42 points).

EORTC QLQ-C30: The EORTC QLQ-C30 contains the following domains: Physical, role, emotional, and cognitive function, total health status, fatigue, nausea and vomiting, pain, shortness of breath, insomnia, loss of appetite, constipation, diarrhea, and economic difficulties. Body function was scored based on the ability of the patient to engage in strenuous activities and long- or short-distance walks outdoors, the necessity to stay in bed or a chair during the day, and the ability to eat, dress, bathe, or go to the toilet. Role function was scored based on restrictions in work and daily activities and hobby or leisure activities (physical strength). Emotional function was scored based on feelings of nervousness, worry, irritability, and depression. Cognitive function was scored based on the ability to concentrate and remember. Total health status was scored based on general health status and life quality, as assessed over one week. Fatigue was scored based on the requirement for rest and the presence of weakness and tiredness. The total QLQ-C30 score was obtained by summing the total percentile scores of each domain.

EORTC QLQ-CR29: The EORTC QLQ-CR29 contains the following domains: Urinary frequency, stool blood/mucus, body image, ostomy, male sexual function, impotence, female sexual function, pain, incontinence, urinary pain, abdominal pain, hip pain, abdominal distension, dry mouth, hair loss, taste abnormalities, anxiety, and obesity. The total QLQ-CR29 score was obtained by summing the total percentile scores of each domain.

Population

The study population included patients who underwent elective radical resection for colorectal cancer at our institution from April 2013 to June 2020 and completed the LARS score and the EORTC QLQ-C30 questionnaires.

The perioperative management and treatment of patients were in full compliance with current guidelines. All surgeries were performed by surgeons with more than 5 years of experience in performing primary surgery. Histopathological analysis was performed by the pathologists of our hospital.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Completed preoperative colonoscopy and postoperative pathological confirmation of colorectal cancer; (2) elective colorectal cancer surgery with definite indications and without contraindications; (3) age ≥ 18 years; and (4) ability to complete the questionnaires.

The exclusion criteria were as follows: (1) Palliative colorectal resection; (2) history of immune system disorders, uremia, or severe preoperative renal impairment; (3) concurrent other primary malignant tumors, except for gastric cancer; (4) emergency surgery due to ileus; and (5) incomplete or otherwise disqualified questionnaire data.

Data sources and collection

Relevant clinical, surgical, and pathological data were extracted from the patient medical records, which included age, sex, preoperative radiotherapy, neoadjuvant chemotherapy, tumor size, length, resection margin (cm), tumor-node-metastasis (TNM) stage, degree of differentiation (01/23), total/partial mesorectal excision (TME/PME), anal distance (cm), presence of stoma, lymphatic dissection, and surgery type (open or endoscopic).

Data analysis

For analyses, patients were divided into no-LARS and LARS groups based on the LARS score results. The LARS group included patients with mild and severe LARS. The above clinicopathological factors were compared between the groups. Continuous variables are expressed as the mean with standard deviation or median with interquartile range and were compared using Student's *t*-test or Mann-Whitney's *U* test, as appropriate. Categorical variables are expressed as frequencies with percentages and were compared using the Chi-square test.

Table 1 Association between low anterior resection syndrome symptoms and patient quality of life

	No LARS (*n* = 51)	LARS (*n* = 171)	*P* value
Physical function: High/low	36 (70.6%)/15 (29.4%)	87 (50.6%)/85 (49.4%)	0.008[1]
Role function: High/low	33 (64.7%)/18 (35.3%)	88 (51.5%)/84 (48.5%)	0.06
Emotional function: High/low	38 (74.5%)/13 (25.5%)	98 (56.9%)/74 (43.1%0	0.017[2]
Cognitive function: High/low	36 (70.6%)/15 (29.4%)	75 (43.8%)/97 (56.2%)	0.001[1]
Total health status: High/low	29 (56.9%)/22 (43.1%)	69 (40.3%)/103 (59.7%)	0.026[2]
Fatigue: High/low	33 (64.7%)/18 (35.3%)	86 (50%)/86 (50%)	0.045[2]
Nausea and vomiting: High/low	45 (88.2%)/6 (11.8%)	146 (84.9%)/26 (15.1%)	0.365
Pain: High/low	44 (86.3%)/7 (13.7%)	109 (63.4%)/63 (36.6%)	0.001[1]
Polypnea: High/low	46 (90.2%)/5 (9.8%)	129 (75.0%)/43 (25%)	0.013[2]
Sleeplessness: High/low	40 (78.4%)/11 (21.6%)	93 (54.1%)/79 (45.9%)	0.001[1]
Appetite loss: High/low	42 (82.3%)/9 (17.6%)	126 (73.3%)/46 (26.7%)	0.126
Constipation: High/low	35 (68.6%)/16 (31.4%)	71 (41.3%)/101 (58.7%)	0.001[1]
Diarrhea: High/low	41 (80.4%)/10 (19.6%)	77 (44.8%)/95 (57.2%)	0.001[1]
Financial difficulty: High/low	46 (90.2%)/5 (9.8%)	142 (82.5%)/30 (17.5%)	0.135

[1]$P \leq 0.001$.
[2]$P \leq 0.05$, statistically significant.
LARS: Low anterior resection syndrome.

The Chi-square and Fisher's exact tests were used for univariate analysis to identify factors associated with LARS. Multivariate logistic regression analysis was performed based on the univariate analysis results, and odds ratios and 95% confidence intervals were calculated. Least absolute shrinkage and selection operator (LASSO) regression was employed to select significant clinicopathological factors associated with LARS. Based on the selected independent risk factors, a visual prediction model of LARS risk and survival line chart were constructed.

IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, United States) was used for statistical analyses. Statistical significance was set at $P < 0.05$. All P values were two-tailed.

Ethical considerations

The study was approved by the Ethics Committee of our institution.

RESULTS

Patient characteristics

Of the 312 patients who underwent colorectal surgery during the study period, 19 were excluded for the following reasons: Seven due to preoperative metastasis to other sites and palliative surgical treatment, three due to preoperative diagnosis of severe renal failure, and nine due to discrepancy between the pre- and postoperative diagnosis. Therefore, a total of 293 patients received questionnaires, of whom 265 (90.4%) returned completed questionnaires. Among them, 42 patients who completed the questionnaires in less than 300 s were excluded. Finally, 223 (84.15%) patients with qualified questionnaires were included in the analysis.

There were 65 women (25.12%) and 158 men (74.88%), with an average age of 59.21 (range, 52-68) years. According to the LARS score results, 51 (22.86%) patients did not have LARS, 47 (121.07%) had mild LARS, and 125 (56.05%) had severe LARS.

Relationship between LARS and quality of life

Compared with those without LARS, patients with LARS had significantly lower scores for physical, emotional, and cognitive function and total health status and higher scores for fatigue, nausea and vomiting, pain, shortness of breath, insomnia, constipation, and diarrhea. The relationship between LARS and quality of life assessed using the EORTC QLQ-C30 and EORTC QLQ-CR29 questionnaires is shown in Tables 1 and 2, respectively. The scatterplot correlation analysis showed good consistency between the two quality of life assessment methods (Figure 1).

Clinicopathological factors associated with LARS

According to the findings of the LARS score assessment, 99 patients received low LARS scores and 124 received high

Table 2 Association between low anterior resection syndrome symptoms and quality of life in patients with colorectal cancer

	Without LARS (*n* = 51)	With LARS (*n* = 171)	*P* value
Frequent micturition: With/without	27 (52.3%)/24 (47.9%)	74 (43.0%)/98 (56.9%)	0.138
Blood in stool: With/without	41 (80/4%)/10 (19.6%)	106 (61.6%)/66 (38.4%)	0.009[1]
Body image: With/without	41 (80/4%)/10 (19.6%)	88 (51.2%)/84 (48.8%)	0.001[1]
Male sexual function: With/without	16 (44.4%)/20 (55.6%)	60 (53.6%)/52 (46.4%)	0.223
Impotence: With/without	21 (61.7%)/13 (38.3%)	52 (50%)/52 (50%)	0.160
Female sexual function: With/without	9 (81.8%)/2 (18.2%)	37 (80.4%)/9 (19.6%)	0.644
Pain: With/without	8 (88.8%)/1 (11.1%)	33 (78.6%)/9 (21.4%)	0.429
Uroclepsia: With/without	49 (96.1%)/2 (3.9%)	149 (86.6%)/23 (13.3%)	0.061
Odynuria: With/without	47 (92.1%)/4 (7.8%)	157 (91.3%)/15 (8.7%)	0.816
Stomachache: With/without	44 (86.3%)/7 (13.7%)	129 (75.0%)/43 (25.0%)	0.062
Pygalgia: With/without	48 (94.1%)/3 (5.9%)	128 (74.4%)/44 (25.6%)	0.001[1]
Ventosity: With/without	44 (86.3%)/7 (13.7%)	110 (63.9%)/62 (36.1%)	0.001[1]
Thirst: With/without	32 (19.6%)/19 (37.2%)	83 (48.3%)/89 (51.2%)	0.048[1]
Alopecia: With/without	47 (92.2%)/4 (7.8%)	118 (68.6%)/54 (31.4%)	0.001[1]
Allotriogeustia: With/without	46 (90.2%)/5 (9.8%)	114 (66.3%)/28 (33.8%)	0.180
Anxiety: With/without	29 (56.9%)/22 (43.1%)	54 (31.3%)/118 (68.6%)	0.001[1]
Obesity: With/without	35 (68.6%)/16 (31.3%)	97 (56.4%)/75 (43.6%)	0.08[1]

[1]P ≤ 0.001, statistically significant difference.
LARS: Low anterior resection syndrome.

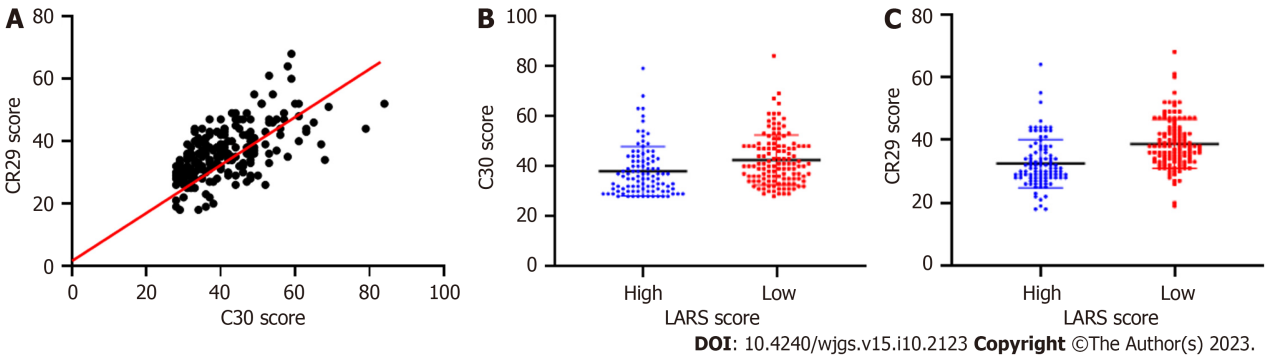

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Figure 1 Relationship between low anterior resection syndrome scores and postoperative quality of life. A: Scatterplot showing good consistency between the Quality of Life Questionnaire (QLQ)-C30 and QLQ-CR29 quality of life scores; B: Patients in the low low anterior resection syndrome (LARS) score group had lower QLQ-C30 scores, fewer symptoms affecting quality of life, and better quality of life ($P < 0.05$); C: Patients in the low LARS score group had lower QLQ-CR29 scores, fewer symptoms affecting quality of life, and better quality of life ($P < 0.05$). LARS: Low anterior resection syndrome.

scores. A comparison of clinicopathological factors between the groups showed that TME/PME, ostomy, preoperative radiotherapy, and neoadjuvant chemotherapy were significantly correlated with LARS scores ($P < 0.05$, Table 3).

Impact of perioperative precision nursing on postoperative quality of life

According to the perioperative nursing method and patient clinical course, patients were divided into precision and routine nursing groups. The two groups were compared based on the LARS, QLQ-C30, and QLQ-CR29 scores (Figure 2). Perioperative precision nursing was associated with lower LARS scores and higher QLQ-C30 and QLQ-CR29 scores ($P < 0.05$). These results indicate that perioperative precision nursing is of great significance for reducing the incidence of LARS and improving patient quality of life.

LARS prediction model

LASSO regression analysis showed that TME/PME, ostomy, preoperative radiotherapy, and neoadjuvant chemotherapy

Table 3 Low anterior resection syndrome is correlated with clinicopathological features of colorectal cancer patients

	Low LARS score (*n* = 99)	High LARS score (*n* = 124)	*P* value
Age (yr): < 59/≥ 60	49 (49.5%)/50 (50.5%)	62 (50.0%)/62 (50.0%)	0.524
Sex: Male/female	73 (73.4%)/26 (26.3%)	81 (65.3%)/43 (34.6%)	0.114
Tumor size (cm): < 4/≥ 4	44 (44.4%)/52 (55.6%)	69 (55.6%)/49 (44.4%)	0.044
Length (cm): < 12/≥ 12	25 (25.3%)/63 (74.7%)	25 (23.1%)/83 (76.8%)	0.249
Length of distal margin (cm): < 3/≥ 3	43 (52.4%)/39 (47.6%)	52 (57.1%)/39 (42.8%)	0.32
T: 0, 1/2, 3	10 (15.1%)/56 (84.8%)	13 (17.6%)61 (82.4%)	0.439
N: < 17/≥ 17	60 (61.8%)/37 (38.1%)	77 (63.1%)/45 (36.9%0	0.479
M: No/yes	86 (92.5%)/7 (7.5%)	86 (89.6%)/10 (10.4%)	0.331
Differentiated degree: 0, 1/2, 3	31 (31.9%)/66 (68.1%0	45 (37.8%)/74 (62.2%)	0.264
TME/PME	59 (62.1%)/39 (37.9%)	58 (47.5%)/64 (52.4%)	0.041
Anal distance: < 9/≥ 9(cm)	41 (41.8%)/57 (58.2%)	62 (51%)/60 (49%)	0.117
Fistulation: No/yes	53 (53.5%)/46 (46.5%)	50 (41.3%)/71 (58.7%)	0.005
Preoperation radiotherapy: No/yes	79 (81.4%)/18 (18.6%)	79 (64.7%)/43 (35.1%)	0.021[1]
Neoadjuvant chemotherapy: No/yes	84 (85.7%)/14 (24.3%)	84 (68.3%)/39 (31.7%)	0.007[2]

[1]$P \leq 0.05$.
[2]$P \leq 0.001$, statistically significant difference.
T: Tumor; N: Node; M: Metastasis; TME/PME: Total/partial mesorectal excision.

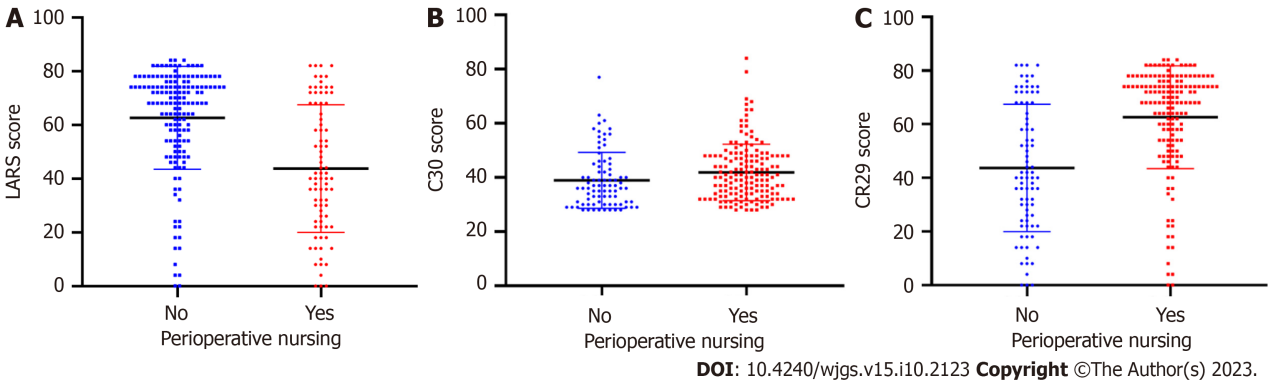

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Figure 2 Relationship between perioperative precision nursing and postoperative quality of life. A-C: Patients provided with perioperative precision nursing had (A) significantly lower low anterior resection syndrome scores (LARS) after surgery and a reduced probability of developing LARS ($P < 0.05$), (B) higher postoperative Quality of Life Questionnaire (QLQ)-C30 scores ($P < 0.05$), and (C) higher postoperative QLQ-CR29 scores ($P < 0.05$). LARS: Low anterior resection syndrome.

were independent risk factors for the occurrence of LARS after colorectal surgery ($P < 0.05$). These factors were used to establish a prediction model, which had an area under the receiver operating characteristic curve of 0.808 for predicting LARS (Figure 3).

DISCUSSION

Before the LARS score questionnaire was developed in 2012, most studies on postoperative long-term quality of life focused on the incontinence symptom of defecation dysfunction[25]. This research method formed the misunderstanding that "intestinal dysfunction recovers within 1 year after surgery and the function of long-term survival patients is acceptable"[11]. In this study, we found that LARS significantly affected patient quality of life after colorectal cancer surgery and that perioperative precision nursing has the potential to significantly reduce the incidence of LARS and improve patient quality of life. Furthermore, TME/PME, ostomy, preoperative radiotherapy, and neoadjuvant chemotherapy were identified as independent risk factors for LARS. Based on these clinicopathological factors, we

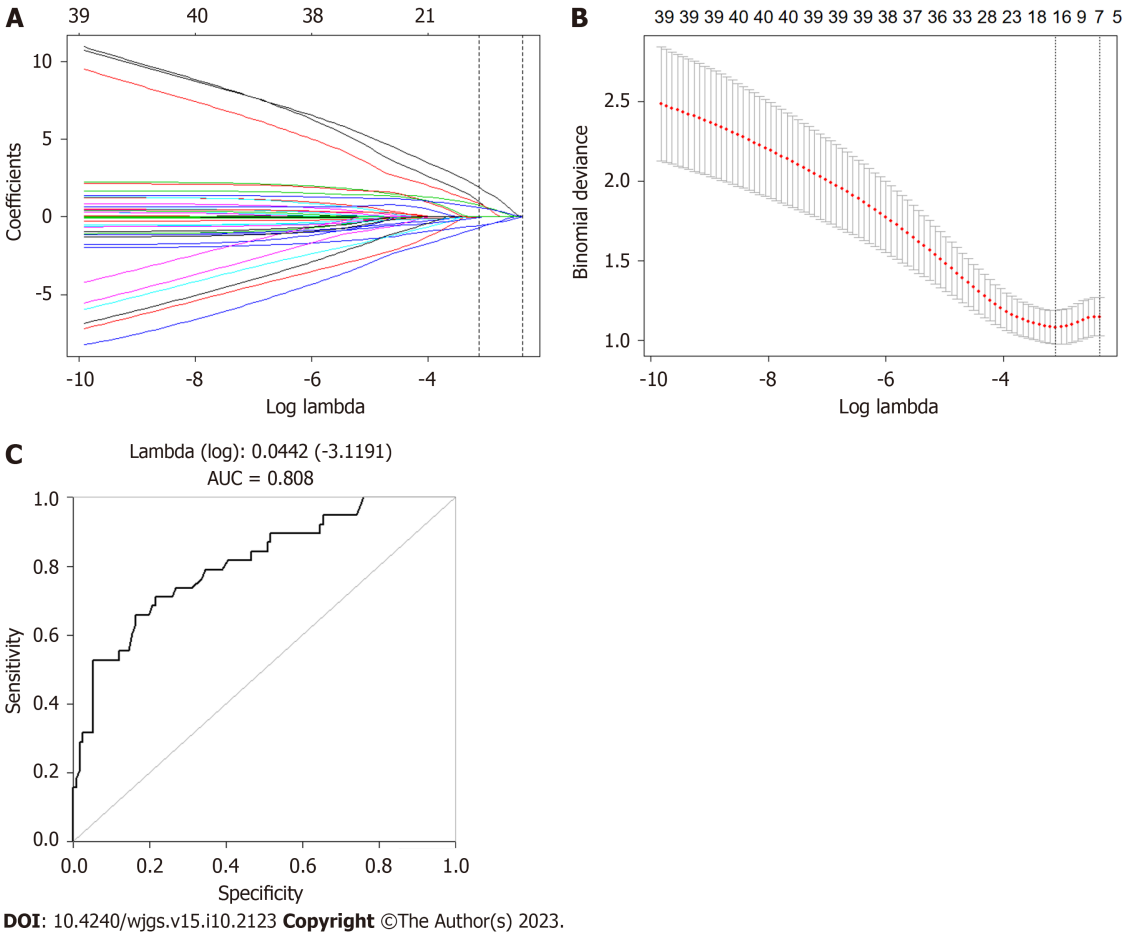

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Figure 3 Low anterior resection syndrome prediction model established by least absolute shrinkage and selection operator regression. A and B: Total/partial mesorectal excision, ostomy, preoperative radiotherapy, and neoadjuvant chemotherapy were identified as risk factors for low anterior resection syndrome (LARS) and were used to establish an LARS prediction model; C: The accuracy of the LARS prediction model reached over 80%. AUC: Area Under Curve.

established a LARS prediction model that showed excellent performance in predicting the occurrence of LARS after colorectal cancer surgery.

Surgical resection is the main method for treating colorectal cancer[26]. With the continuous updating of surgical techniques and equipment and the expanding knowledge on neoadjuvant chemoradiotherapy and colorectal cancer pathology and molecular pathology, postoperative survival rates continue to increase[27]. LARS is a common complication of anus-preserving surgery, for which a targeted and effective treatment is not available[25]. Currently, LARS treatment includes rehabilitation therapy and diet adjustment[18]. With the application of laparoscopic minimally invasive technology and the double-anastomosis technique[28], LARS has gradually become the most important treatment challenge in patients with middle and low rectal cancer[29]. LARS is more likely to occur in older patients than in other age groups due to their reduced pelvic floor bearing capacity[9].

Although most LARS symptoms disappear within 1 year after surgery, the occurrence greatly inconveniences patients. In this study, patients with LARS had a significantly poorer quality of life than those without, and the quality of life decreased with the aggravation of LARS symptoms. To assess patient quality of life, we used the EORTC QLQ-C30 and EORTC QLQ-CR29 questionnaires. Our analysis showed good consistency between the scores of these two questionnaires, confirming that both reflect the quality of life of patients well[30].

In the present study, we found that TME/PME, ostomy, preoperative radiotherapy, and neoadjuvant chemotherapy were independent risk factors for LARS. This is consistent with the results of a prior study that identified the anastomotic site-anal edge distance, anastomotic leakage, radiotherapy, neoadjuvant chemotherapy, TNM stage, and sex as risk factors for LARS after surgery for low rectal cancer[31]. Furthermore, we established a LARS risk prediction model, which had an accuracy of over 80%.

Most prior studies on LARS have focused on the causes and risk factors for LARS without exploring factors that may help reduce LARS incidence and severity[32]. In the current study, we found that personalized precision nursing during the perioperative period could help reduce LARS scores and improve patient quality of life. Therefore, perioperative precision nursing is an important protective factor for LARS. As personalized precision nursing is labor-intensive and requires substantial material resources, patients should undergo LARS risk assessment before surgery, and precision nursing should be applied according to the results, which can improve patient quality of life[33].

The findings of this study are of great significance for predicting the long-term functional prognosis of patients after anal preservation. If the patient has not received radiation and the anastomotic height is high, it is unlikely that severe

LARS will occur from a long-term survival perspective. If these patients have more severe LARS symptoms early after surgery, active treatment may result in a good functional prognosis[33].

There are still some limitations in this study. All patients included in this study retrospectively. According to the LARS risk prediction model established in this study, prospective perioperative nursing studies can be conducted, which will be the plan of further research[34].

CONCLUSION

The LARS risk prediction model established in this study can enable the implementation of perioperative precision nursing for high-risk patients after colorectal cancer surgery. This may result in reduced LARS incidence and severity, which is of great value for improving the quality of life and happiness index of patients undergoing colorectal cancer surgery.

ARTICLE HIGHLIGHTS

Research background

Low anterior resection syndrome (LARS) is a common complication of anus-preserving surgery for colorectal cancer, which seriously affects the daily life of patients.

Research motivation

In order to reduce the incidence and severity of LARS, while improving the quality of life of patients undergoing colorectal cancer surgery.

Research objectives

The purpose of this study was to investigate the relationship between LARS and patient quality of life in a large cohort of patients and to identify perioperative clinicopathological factors that can predict the occurrence of LARS.

Research methods

This was a longitudinal retrospective cohort study using a hospital-based survey. In this study, the LARS score questionnaire and the European Organization for Research and Treatment of Cancer Core Quality of Life and Colorectal Cancer module questionnaires were completed.

Research results

Multiple independent risk factors for LARS were identified in the study. The accuracy of the LARS prediction model established was 0.808.

Research conclusions

The LARS prediction model in this study can implement perioperative precision nursing and improve the quality of life of LARS patients.

Research perspectives

The LARS prediction model would enable the implementation of perioperative precision nursing interventions to improve patient quality of life.

FOOTNOTES

Author contributions: Jin DA conceptualized and designed the study; Gu FP collected the data; Meng TL analyzed the data; Zhang XX wrote the original draft.

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Institutional review board statement: The study was reviewed and approved by the Sir Run Run Shaw Hospital Medical Ethics Committee (No. 20210607-31).

Informed consent statement: This study was a retrospective study, and the process of data collection, data analysis, and paper writing did not disclose patients' private information, so no informed consent was signed.

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

Data sharing statement: No additional data are available.

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

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ORIGINAL ARTICLE

Retrospective Cohort Study

Stent fracture after transjugular intrahepatic portosystemic shunt placement using the bare metal stent/stent-graft combination technique

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Abstract

BACKGROUND

A transjugular intrahepatic portosystemic shunt (TIPS) is widely placed to treat portal hypertension. Because the Viatorr® stent (W. L. Gore and Associates, Flagstaff, AZ, United States) is not available in all hospitals in China, the bare metal stent (BMS)/stent-graft combination technique is still popular for TIPS construction. Stent fracture is a complication after TIPS placement using this technique, with limited available literature focusing on it.

AIM

To assess the incidence of stent fracture after TIPS placement using the BMS/stent-graft combination technique and to identify the risk factors for stent fracture. We proposed technique modifications to improve the clinical results of TIPS placement with the BMS/stent-graft combination technique.

METHODS

We retrospectively analyzed the computed tomography (CT) data of all patients with portal hypertension who underwent the TIPS procedure between June 2011 and December 2021 in a single center. Patients implanted with the BMS/stent graft and had follow-up imaging data available were included. We identified patients with stent fracture and analyzed their characteristics. Multivariable logistic regression was applied to identify the potential predictors of stent fracture.

RESULTS

Of the 68 included patients, stent fracture occurred in seven (10.3%) patients.

Based on CT images, the stent fractures were categorized into three types. Our study consisted of four (57.1%) type I fractures, one (14.3%) type II fracture, one (14.3%) type IIIa fracture, and one (14.3%) type IIIb fracture. After adjusting for covariates, multivariable logistic regression revealed that the risk factors for stent fracture were the implantation of a greater number of stents [adjusted odds ratio (aOR) = 22.2, 95% confidence interval (CI): 1.2-415.4, P = 0.038] and a larger proximal sagittal stent bending angle (aOR = 1.1, 95%CI: 1.0-1.3, P = 0.020).

CONCLUSION

Stent fracture occurred in approximately 10% of patients with portal hypertension who underwent TIPS with the BMS/stent-graft combination technique. The number of implanted stents and stent bending angle at the inferior vena cava end were predictors of stent fracture, which suggests that the incidence of stent fracture could potentially be reduced by procedural modifications.

Key Words: Portal hypertension; Transjugular intrahepatic portosystemic shunt; Stent fracture; Bare metal stent/stent-graft combination; Risk factor; Fracture types

Core Tip: The bare metal stent (BMS)/stent-graft combination technique for transjugular intrahepatic portosystemic shunt construction has an incidence of stent fractures of around 10%, which all occurred at the junction of BMS and the proximal end of the stent-graft. Fractures may be associated with the number of stents implanted and stent excessive bending. Hence, we recommend a greater overlap of the stent-graft with the BMS at the inferior vena cava (IVC) end of the shunt, and the selection of a position closer to the opening of the hepatic vein into the IVC as the starting puncture site to establish a shunt.

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INTRODUCTION

The transjugular intrahepatic portosystemic shunt (TIPS) effectively controls portal hypertension and is especially important in patients with gastrointestinal bleeding or refractory ascites[1]. In China, TIPSs are frequently constructed using the bare metal stent (BMS)/stent-graft combination technique, in which a BMS is used to establish access between the hepatic and portal veins (PVs), and a stent graft is used to cover the liver parenchyma[2,3]. A stent fracture is a rare complication after TIPS placement using the BMS/stent-graft combination technique[4-8]. In addition to TIPS dysfunction, stent fracture may cause severe consequences such as tricuspid regurgitation if the fractured stent is displaced into the heart chamber[8].

In the present study, we retrospectively examined the clinical data of patients who underwent TIPS placement with the BMS/stent-graft combination technique to assess the incidence and analyze the potential causes of stent fracture. Based on this information, we proposed technique modifications to improve the clinical results of TIPS placement with the BMS/stent-graft combination technique.

MATERIALS AND METHODS

Data sources and sample selection

The institutional review board of Peking University Third Hospital approved this retrospective study of data retrieved from electronic medical records. Ethical approval was granted by the Ethics Committee of Peking University Third Hospital, Beijing, China (No. M2022314). Patients who were admitted to Peking University Third Hospital between June 1, 2011 and December 31, 2021 and underwent TIPS placement with the BMS/stent-graft combination technique to treat complications of portal hypertension (*e.g.*, gastrointestinal bleeding, refractory ascites) were included. Patients with no available follow-up computed tomography (CT) images were excluded.

Preoperative evaluation of liver function

The modified Child-Pugh classification was used to evaluate preoperative liver function. Liver function was categorized as Child-Pugh class A (Child-Pugh score 5-6, well-compensated disease), Child-Pugh class B (Child-Pugh score 7-9 points, significant functional compromise), or Child-Pugh class C (Child-Pugh score 10-15 points, decompensated disease)[9].

Surgical procedures

TIPS procedures were usually performed under local anesthesia. General anesthesia was used for patients with heavy bleeding and unstable blood circulation. A transjugular approach was used for all TIPS procedures. The RUPS-100 puncture device (Cook, Bloomington, IN, United States) was used in all patients.

Indirect portography was achieved by superior mesenteric arteriography or splenography. An angiography catheter was then selectively inserted into the left hepatic artery and retained as an indirect indicator of the left PV, which was the target vessel for puncture. Once the PV was successfully punctured, a pigtail angiographic catheter was introduced into the superior mesenteric vein to obtain an outline of the PV anatomy. The pressures in the PV and inferior vena cava (IVC) were recorded.

A guidewire (0.035 inch, Amplatz Super Stiff, Cordis Corporation, Fremont, CA, United States) was introduced and retained in the superior mesenteric vein. A 5 mm × 6 cm balloon was placed in the shunt for dilation. The length of the parenchymal segment of the shunt was recorded.

A 10-F sheath was advanced into the main stem of the PV. A 4-F Cobra catheter was introduced into the gastric coronary vein to identify the variceal veins and embolize them with coils or tissue adhesive.

A BMS was positioned between the left PV and IVC. With the deployment of the BMS, the liver parenchymal segment of the shunt (the narrow segment of the stent) was clearly displayed for stent-graft deployment. The portosystemic gradient (PSG) was measured. If the PSG was higher than needed, the shunt was dilated with a larger diameter balloon (> 5 mm). A stent graft with a corresponding diameter (Fluency®, Bard International, Inc., NJ, United States) was then deployed to exactly cover the parenchymal section of the shunt. If the PSG was lower than needed, a smaller diameter stent graft (Fluency®) with the same length as the parenchymal section was deployed. The final PSG was then recorded.

Follow-up

After the TIPS procedure, patients were followed up in the outpatient department. The patients' symptoms, liver function, and shunt function were recorded. Color Doppler ultrasound and contrast-enhanced abdominal CT were used to evaluate the shunt blood flow dynamics and the status of the stents, especially the stent integrity. If ultrasound or CT revealed shunt dysfunction, digital subtraction angiography was performed, and the dysfunctional stent was corrected by shunt angioplasty and the implantation of another stent.

Evaluation of the in vivo configuration of the stents

For construction of the TIPS, stents were placed between the IVC and the PV. The shunts were situated in a three-dimensional space within the liver, usually in an irregular three-dimensional configuration, rather than a simple two-dimensional orientation. CT images were analyzed to examine the proximal IVC segment of the shunt stents and to measure the bending angle of the stent axis of the end segment and the middle segment in both the coronal and sagittal planes, subsequently referred to as angle 1 and angle 2, respectively (Figure 1).

Statistical analysis

Patient characteristics, such as sex, age, Child-Pugh classification, number of deployed stents, stent bending angle of the proximal segment (angle 1 and angle 2), and revision operation details, were evaluated. Patients with stent fracture detected on follow-up CT were classified as the stent fracture group, while those without stent fracture were classified as the stent integrity group. Differences between the stent integrity group and stent fracture group were analyzed using Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Adjusted odds ratios (aORs) were computed by multivariable logistic regression to evaluate the associations between stent fracture and patient characteristics. The model was adjusted for covariates with clinical relevance and those found to be significant in univariate analyses. Two-sided P values of < 0.05 were considered statistically significant. Analyses were conducted using STATA/MP 14.0 software.

RESULTS

Patient characteristics

From June 1, 2011 to December 31, 2021, 137 patients underwent the TIPS procedure in the Department of Interventional Radiology and Vascular Surgery of Peking University Third Hospital. Among these 137 patients, 69 patients were excluded because of a lack of available postoperative CT images (63 patients) or TIPS placement with a single stent graft (six patients). Therefore, a final total of 68 patients were included in the analysis. The patient characteristics are summarized in Table 1. The median follow-up was 421 d (range: 1-2878 d), and the cohort included 38 (55.9%) men. The mean ± SD patient age was 60.7 ± 9.9 years (range: 33-82 years). A total of 151 stents were implanted, with an average of 2.2 stents implanted in each patient (range: 2-4). Eleven patients underwent revision surgery due to shunt dysfunction (stenosis/occlusion), including two in the stent fracture group and nine in the stent integrity group. All patients who underwent reoperation were implanted with a self-expanding BMS to restore shunt function.

Univariate analysis of risk factors for stent fracture

The univariate Fisher's exact test showed no significant differences between the stent fracture group and the stent integrity group in sex, age (> 60 years or ≤ 60 years), Child-Pugh classification, number of stents deployed, reoperation, or PSG (all $P > 0.05$). There was a tendency for angle 1 to be larger in the stent fracture group than in the stent integrity

Table 1 Patient characteristics (%)

Characteristics	All		Integrity group		Fracture group		*P* value[a]
	No. patient		No. patient		No. patient		
Total	68	100.0	61	89.7	7	10.3	
Sex							
Male	38	55.9	34	89.5	4	10.5	0.633
Female	30	44.1	27	90.0	3	10.0	
Age (yr)							
≤ 60	32	47.1	29	90.6	3	9.4	0.567
> 60	36	52.9	32	88.9	4	11.1	
Child-Pugh classification							
A	22	32.4	18	32.4	4	20.0	0.444
B	34	50.0	32	50.0	2	5.9	
C	12	17.6	11	17.6	1	8.3	
Stent number							
2	55	80.9	51	92.7	4	7.3	0.095
3	11	16.2	9	81.8	2	18.2	
4	2	2.9	1	50.0	1	50.0	
Reoperation							
No	59	86.8	54	91.5	5	8.5	0.230
Yes	9	13.2	7	77.8	2	22.2	
Gradient							
Portosystemic gradient (median, IQR)			15.0 mmH_2O (12.0-16.0)		14.0 mmH_2O (13.5-15.0)		0.745
Stent angle							
Angle 1 (median, IQR)			1.0 (0-22.0)		20.0 (3.5-35.0)		0.151
Angle 2 (median, IQR)			15.5 (0-33.8)		39.5 (30.5-60.5)		0.009

[a]Differences between the stent integrity group and the stent fracture group were analyzed using the Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables.
IQR: Interquartile range.

group, but this difference was not statistically significant (1.0 *vs.* 20.0, $P = 0.151$). Angle 2 was significantly larger in the stent fracture group than in the stent integrity group (15.5 *vs.* 39.5, $P = 0.009$, Table 1).

Incidence, structural type, and location of stent fracture

Follow-up CT revealed stent fractures in seven of 68 (10.3%) patients. The characteristics and outcomes of patients with stent fracture are summarized in Table 2. All stent fractures were located on the IVC side of the BMS. The median interval from TIPS construction to the detection of stent fracture was 512 d (range: 141-1, 406 d).

Based on follow-up CT images, the stent fractures were categorized into three types (Figure 2). Type I was defined as a partial fracture of the stent struts. Type II was defined as an annular fracture of the stent struts, resulting in stent transection without structural displacement of the stent. Type III was defined as stent transection with displacement of the fractured stent. Type III stent fractures were further categorized as type IIIa fractures with a small amount of displacement so that the fractured stent was still located in the original vascular structure (*i.e.*, the hepatic vein or IVC) or type IIIb fractures with the fractured stent displaced out of the original vessel into adjacent structures (*i.e.*, the superior vena cava or cardiac chamber). In the present study cohort, there were four (57.1%) type I fractures, one (14.3%) type II fracture, one (14.3%) type IIIa fracture, and one (14.3%) type IIIb fracture. All stent fractures were located at the junction of the BMS and the stent graft in the direction of the IVC (Figure 3).

Multivariable analysis of risk factors for stent fracture

After adjusting for relevant covariates (*i.e.*, stent number, reoperation, and stent angle) in a multivariable logistic regression model, stent fractures were associated with the number of deployed stents [aOR = 22.2, 95% confidence

Table 2 Characteristics and clinical outcomes of patients with stent fracture after transjugular intrahepatic portosystemic shunt placement

Case	Age (yr)	Sex	Child-Pugh classification	Number of procedures	Fracture time (days after procedure)	Fracture type	Symptoms	Clinical outcome
1	60	Male	B	1	159	IIIb	None	Re-operation to implant a bare metal stent to connect the fractured stent
2	63	Female	A	1	512	I	Bleeding recurrence CT revealed shunt stenosis	Endoscopic hemostasis
3	49	Male	C	2	675	I	Bleeding recurrence CT revealed shunt stenosis	Re-operation using a bare metal stent to reconstruct the shunt
4	70	Female	A	1	175	I	None	Observation
5	79	Female	B	1	141	IIIa	None CT revealed shunt stenosis	Observation
6	51	Male	A	1	1752	I	None CT revealed shunt stenosis	Observation
7	62	Male	A	2	1406	II	None	Observation

CT: Computed tomography.

Table 3 Multivariable logistic regression of the risk factors for stent fracture

Characteristic	Adjusted odds ratio[a]	*P* value	95%CI
Stent number	22.2	0.038	1.2-415.4
Reoperation			
No	Reference		
Yes	0.3	0.562	0.0-13.8
Stent Angle			
Angle 1	0.9	0.191	0.8-1.3
Angle 2[b]	1.1	0.020	1.0-1.3

[a]Models were adjusted for covariates with clinical relevance (*i.e.*, stent number, reoperation and Angle 1) and those found to be significant in univariate analyses (*i.e.*, Angle 2).
[b]Bending angle of the axis of the end segment and the mid-segment of the stent in the sagittal plane.
CI: Confidence interval.

interval (CI): 1.2-415.4, $P = 0.038$] and the size of angle 2 (aOR = 1.1, 95%CI: 1.0-1.3, $P = 0.020$) (Table 3).

DISCUSSION

The goal of TIPS placement is to relieve portal hypertension by establishing an artificial shunt between the PV and the systemic circulation. Because the Viatorr® stent (W. L. Gore and Associates, Flagstaff, AZ, United States) is not available in all hospitals in China, the BMS/stent-graft combination technique is still popular for TIPS construction. The BMS/stent-graft combination technique was designed to preserve the shunted portal branch blood flow and hepatic venous flow by using a BMS; this combination technique results in a lower risk of venous thrombosis compared with the single stent-graft technique. The BMS/stent-graft combination technique also enables the shunt flow and portal pressure to be adjusted precisely owing to the variation in the caliber of the stents. Compared with the single stent-graft procedure, the BMS/stent-graft combination technique is advantageous in that it protects liver function and has similar stent patency and hepatic encephalopathy rates[2]. However, although rare, stent fractures after TIPS placement can occur, which could decrease the stent patency rate or even cause severe consequences due to displacement of the fractured stent.

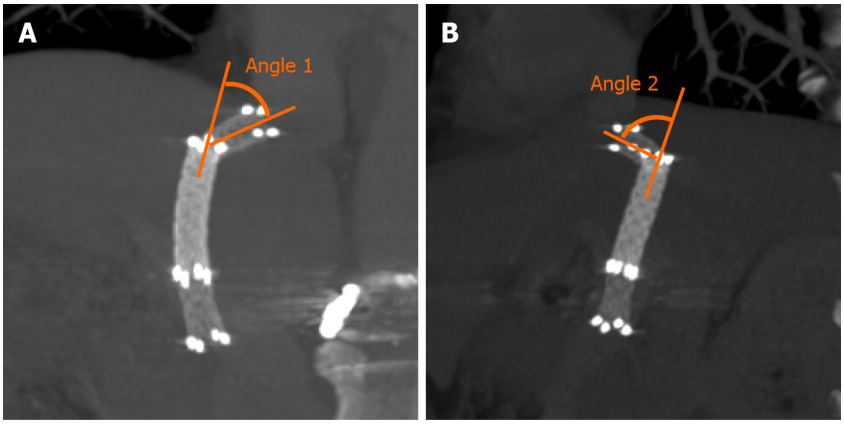

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Figure 1 Computed tomography images showing angle 1 and angle 2. A: The angle between the proximal end of the bare metal stent and the stent-graft is measured angle 1 in the coronal plane; B: Angle 2 in the sagittal plane.

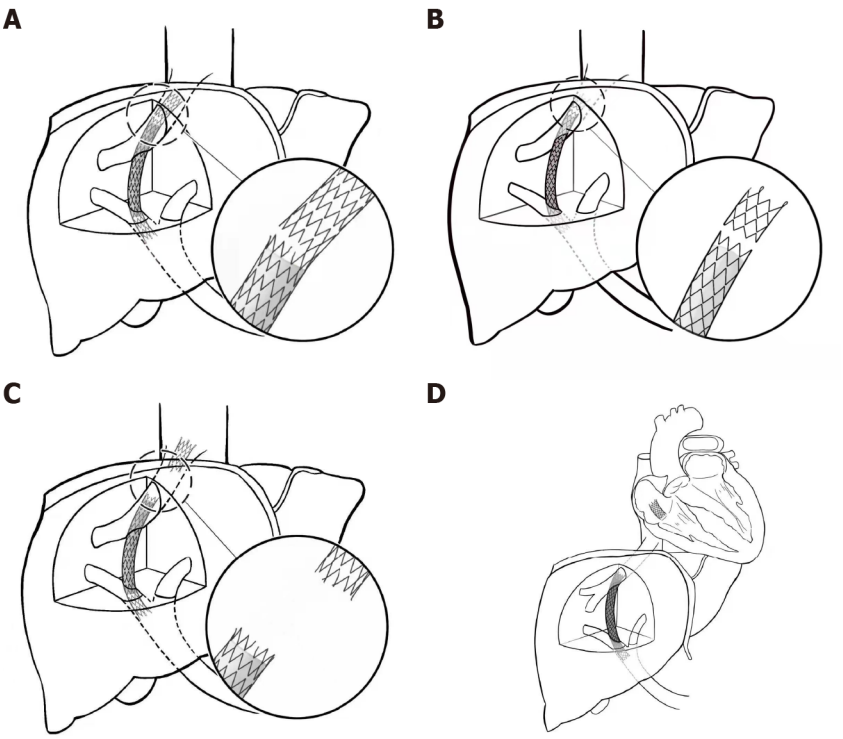

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Figure 2 Types of stent fracture after the transjugular intrahepatic portosystemic shunt procedure. A: Type I partial fractures of the stent struts; B: Type II annular fractures of the stent struts, but without displacement; C and D: Type III stent transection with fractured stent displacement (C, IIIa: Small displacement; D, IIIb: Displacement of the stents from the original vessels into adjacent structures).

Main findings and interpretation

To the best of our knowledge, this is the first study to investigate the potential reasons for stent fracture after the TIPS procedure. The incidence of stent fracture was 10.3% during a median follow-up of 421 d. Based on the imaging features, we proposed a classification system and categorized stent fractures into three types. In our case series, type I fractures (57.1%) were the most common, followed by type III fractures (14.3% type IIIa and 14.3% type IIIb) and type II fractures (14.3%). This suggests that stent fracture occurred abruptly rather than progressively. That is, partial or complete circular fracture of the stent struts may decrease the local stress on the stent, which may relieve the external force that promotes the further development of stent fracture.

The predictive factors of stent fracture were the number of implanted stents and the stent bending angle at the IVC end. For every additional stent placed, the risk of stent fracture increased by 740%; for every additional angle of 2, the risk of stent fracture increased by 10%.

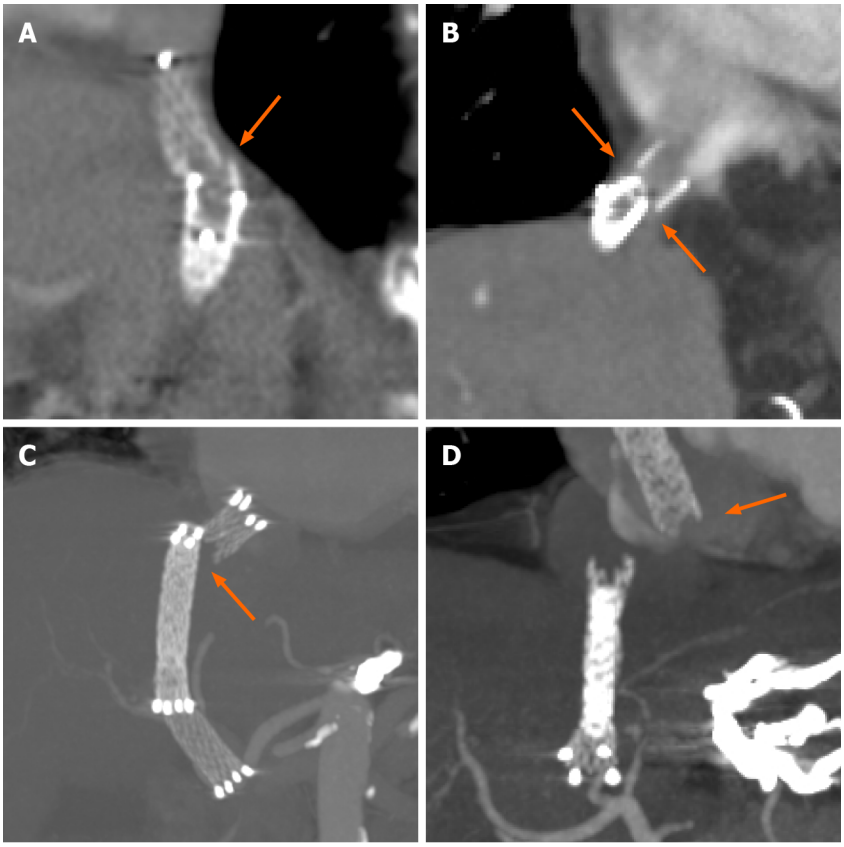

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Figure 3 Representative computed tomography images of the types of stent fracture after transjugular intrahepatic portosystemic shunt placement. The orange arrows show the position and displacement of stent fractures. A: Type I partial fracture of the stent struts; B: Type II annular fracture of the stent struts; C: Type IIIa fractured stent with minimal displacement and D: Type IIIb fractured stent displaced into the heart chamber.

Literature review and discussion

All stent fractures occurred at the IVC end at the junction of the stent graft and the BMS, and all fractured stents were BMSs. These findings are consistent with previously reported cases of stent fracture. The cause of stent fracture after the TIPS procedure was first reported in 2014 by Zabicki *et al*[4], who proposed that the main reason for stent fracture is an abnormal shunt shape caused by unique liver anatomy. Ding *et al*[5] reported that the fractured stents in their study did not have an excessive bending angle and speculated that stent fracture is caused by continuous tension generated at the proximal end of the overlapping part as a result of the motion at the junction of the trailing end of the stents. Komaki *et al*[6] suggested that stent fracture is related to the stent material and design. All the fractured stents reported in previous studies are open-loop self-expanding nickel-titanium alloy bare stents, which are the same as the fractured stents in our case series. We also found that the number of implanted stents and stent bending angle at the proximal end were predictors of stent fracture.

Suggested technical modifications to reduce the risk of stent fracture

Our results showed that the risk of stent fracture significantly increased as the number of implanted stents increased. This may be related to the impacts of respiratory and cardiac motions on the tension of the stent at the IVC end. When using the BMS/stent-graft combination technique, as the number of implanted stents increases, the stress distributed on the stent becomes much more uneven, and the junction of the combined stents is more likely to become a fulcrum. The resultant increased tension on the overlapping part may result in stent fracture. The Viatorr® stent graft was approved for use in China in 2015. However, as Viatorr® stent-grafts are not yet available in all hospitals in China, the BMS/stent-graft combination technique is still used in many Chinese medical centers. Compared with TIPS placement using the Viatorr® stent-graft, the greater number of implanted stents in TIPS placement using the BMS/stent-graft combination technique might result in an increased incidence of stent fractures because of the uneven distribution of stent stress. To reduce the risk of stent fracture, we proposed the following technical modifications for the BMS/stent-graft combination technique.

First, surgeons should adjust the overlapping strategy of the BMS/stent-graft combination technique. To avoid excessive local tension on the BMS, it should be fully covered by the stent graft at the IVC end of the shunt to ensure that stress is uniformly distributed on the stents. In addition, the overlapping stents can increase the longitudinal supporting force, which can decrease the bending angle of the IVC end of the stent and reduce its risk of fracture. If possible, the shunt should be established using a closed-loop stent, which may relieve the uneven stress distribution.

Second, TIPS construction should be performed using a more precise positioning approach, such as anterior-posterior and lateral angiography. This may help prevent the proximal end of the stent from protruding excessively into the IVC, thereby reducing the stress on the stent caused by respiratory and cardiac motions.

Third, as excessive bending of the proximal end of the stent may result in stent fracture, the starting puncture point in the hepatic vein should be as close as possible to the IVC. Finally, the development of stents with better conformability and appropriate structure may help to avoid stent fractures.

Limitations

This was a retrospective study of the clinical data of small sample of patients treated in one medical center. Large-scale prospective studies are needed to explore the exact mechanism and risk factors for stent fracture after TIPS placement using the BMS/stent-graft combination technique.

CONCLUSION

The widely used BMS/stent-graft combination technique for TIPS construction in China has an incidence of stent fractures of approximately 10%. All the stent fractures occurred at the junction of the BMS and the proximal end of the stent graft. Stent fractures may be associated with the number of stents implanted and excessive bending of the stent. To avoid stent fracture, we recommend a greater overlap of the stent graft with the BMS at the IVC end of the shunt and the selection of a position closer to the opening of the hepatic vein into the IVC as the starting puncture site to establish a shunt.

ARTICLE HIGHLIGHTS

Research background

Transjugular intrahepatic portosystemic shunt (TIPS) placement is widely used to treat portal hypertension. In China, TIPSs are frequently constructed using the bare metal stent (BMS)/stent-graft combination technique.

Research motivation

Stent fracture is a rare complication after TIPS placement using the BMS/stent-graft combination technique and stent fracture may cause severe consequences.

Research objectives

To assess the incidence of stent fracture after TIPS placement using the BMS/stent-graft combination technique and identify the risk factors for stent fracture.

Research methods

Retrospective cohort study.

Research results

Of the 68 included patients, stent fracture occurred in seven (10.3%) patients. The risk factors for stent fracture were the implantation of a greater number of stents [adjusted odds ratio (aOR) = 22.2, 95% confidence interval (CI): 1.2-415.4, P = 0.038] and a larger proximal sagittal stent bending angle (aOR = 1.1, 95%CI: 1.0-1.3, P = 0.020).

Research conclusions

We found three types of stent fracture occurred in 10.3% of the sample patients. The number of implanted stents and the stent bending angle at the inferior vena cava end were the independent risk factor of stent fracture.

Research perspectives

Our results suggested that the incidence of stent fracture could potentially be reduced by procedural modifications.

FOOTNOTES

Author contributions: Liu QJ and Wang CM conceptualized and designed the study; Liu QJ, Cao XF, and Pei Y collected data and carried out the initial analyses; Liu QJ drafted the initial manuscript; Li X, Dong GX, and Wang CM reviewed and revised the manuscript; Wang CM coordinated and supervised questionnaires collection, and critically reviewed the manuscript for important intellectual content; All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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ORIGINAL ARTICLE

Retrospective Study

Robotic natural orifice specimen extraction surgery I-type F method *vs* conventional robotic resection for lower rectal cancer

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Abstract

BACKGROUND

Robotic resection using the natural orifice specimen extraction surgery I-type F method (R-NOSES I-F) is a novel minimally invasive surgical strategy for the treatment of lower rectal cancer. However, the current literature on this method is limited to case reports, and further investigation into its safety and feasibility is warranted.

AIM

To evaluate the safety and feasibility of R-NOSES I-F for the treatment of low rectal cancer.

METHODS

From September 2018 to February 2022, 206 patients diagnosed with low rectal cancer at First Affiliated Hospital of Nanchang University were included in this retrospective analysis. Of these patients, 22 underwent R-NOSES I-F surgery (R-NOSES I-F group) and 76 underwent conventional robotic-assisted low rectal cancer resection (RLRC group). Clinicopathological data of all patients were collected and analyzed. Postoperative outcomes and prognoses were compared between the two groups. Statistical analysis was performed using SPSS software.

RESULTS

Patients in the R-NOSES I-F group had a significantly lower visual analog score for pain on postoperative day 1 (1.7 ± 0.7 *vs* 2.2 ± 0.6, $P = 0.003$) and shorter postoperative anal venting time (2.7 ± 0.6 *vs* 3.5 ± 0.7, $P < 0.001$) than those in the RLRC group. There were no significant differences between the two groups in terms of sex, age, body mass index, tumor size, TNM stage, operative time, intrao-

perative bleeding, postoperative complications, or inflammatory response ($P > 0.05$). Postoperative anal and urinary functions, as assessed by Wexner, low anterior resection syndrome, and International Prostate Symptom Scale scores, were similar in both groups ($P > 0.05$). Long-term follow-up revealed no significant differences in the rates of local recurrence and distant metastasis between the two groups ($P > 0.05$).

CONCLUSION

R-NOSES I-F is a safe and effective minimally invasive procedure for the treatment of lower rectal cancer. It improves pain relief, promotes gastrointestinal function recovery, and helps avoid incision-related complications.

Key Words: Robotic surgery; Natural orifice specimen extraction surgery; Lower rectal cancer; Robotic resection using the natural orifice specimen extraction surgery I-type F method

Core Tip: This retrospective study examined the efficacy and safety of a novel surgical procedure called robotic resection using the natural orifice specimen extraction surgery I-type F method (R-NOSES I-F) for lower rectal cancer. Through a comparison with robotic-assisted low rectal cancer resection, the study demonstrates that R-NOSES I-F is a safe and effective minimally invasive surgical approach for low rectal cancer. It offers several benefits, including decreased postoperative pain, improved gastrointestinal function recovery, reduced abdominal wall dysfunction, and avoidance of complications associated with abdominal wall incisions. Furthermore, R-NOSES I-F does not negatively impact anal and urinary functions and does not increase the risk of local recurrence or distant metastasis.

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INTRODUCTION

Colorectal cancer is a highly prevalent malignancy, ranking third in terms of incidence and second in terms of mortality worldwide in 2020[1]. The most recent cancer statistics in China indicate a significant increase in the incidence and mortality rates of colorectal cancer[2]; it ranks second in incidence and fifth in mortality rates in China[3,4]. Therefore, enhancing surgical techniques to improve the postoperative quality of life for patients with rectal cancer is crucial, especially for those with lower rectal cancer. In recent years, the combination of robotic surgery and natural orifice specimen extraction surgery (NOSES) has gained attention in the management of colorectal cancer[5-8].

The robotic surgical platform has a magnified 3D high-definition field of view, a flexible robotic arm capable of 540° free rotation in seven directions, a stable camera platform, and enhanced depth perception, mitigating the challenges of hand-eye coordination. These features enable surgeons to operate with greater precision within the limited space of the pelvic cavity[9]. Robotic-assisted total rectal mesenteric resection has played a pivotal role in the minimally invasive treatment of lower rectal cancer[10,11]. Therefore, robotic NOSES has garnered increasing attention as a surgical approach for the treatment of lower rectal cancer.

The introduction of the concept of NOSES has ushered in a new era of "no incision" in minimally invasive surgery[12]. Expert consensus on NOSES in colorectal neoplasms was initially published by the China NOSES Alliance in 2017[13], and was later updated and improved in 2019[14]. Additionally, an international consensus on NOSES for colorectal cancer has been published[15]. In 2022, China published the first expert consensus on robotic NOSES for colorectal neoplasm[16]. These guidelines have served to guide and standardize the development of robotic NOSES for lower rectal cancers.

Previous studies[5,7,8,17] have confirmed the safety and feasibility of robotic NOSES surgery as a minimally invasive procedure, enhancing surgical quality and expediting postoperative recovery. Robotic resection using the NOSES I-type F method (R-NOSES I-F) represents a novel approach characterized by intussusception to achieve transanal specimen eversion. This technique involves resecting the specimen and placing the anvil into the proximal bowel extra-abdominally [16]. However, existing studies related to this surgical approach are limited to case reports[18,19], with a lack of long-term follow-up results. Therefore, this study aimed to compare the postoperative outcomes of R-NOSES I-F with those of conventional robotic low rectal cancer resection (RLRC) through retrospective analysis, thereby evaluating the effectiveness and safety of R-NOSES I-F in the treatment of low rectal cancer.

MATERIALS AND METHODS

Patient information

In this retrospective analysis, we collected and analyzed clinicopathological data of patients diagnosed with rectal cancer at our hospital from September 2018 to February 2022. The following inclusion criteria were applied: (1) Pathologically confirmed rectal malignancy through preoperative assessment; (2) Tumor located 3–7 cm from the anal verge; (3) Age between 18 and 80 years; (4) Body mass index (BMI) ≤ 30 kg/m^2; and (5) Absence of distant metastasis. The exclusion criteria were as follows: (1) Patients who received preoperative neoadjuvant therapy; (2) TNM stage IV; (3) Requirement for multiorgan resection; (4) Presence of concomitant primary malignancies in other organs or multi-origin colorectal malignancies; (5) Emergency surgery due to acute intestinal obstruction, perforation, or bleeding; and (6) Major comorbidities such as coronary heart disease and cerebral infarction. According to the above criteria, patients who underwent R-NOSES I-F surgery were included in the R-NOSES I-F group, while patients who underwent RLRC surgery were included in the RLRC group. All patients provided informed consent before surgery. The study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University and conducted following the principles outlined in the Declaration of Helsinki.

Perioperative management

All patients underwent a comprehensive preoperative evaluation, including physical examination, blood tests for tumor markers, colonoscopy, pathological biopsy, chest computed tomography or radiography, abdominal computed tomography, and rectal magnetic resonance imaging. Bowel preparation was performed using 2 L of polyethylene glycol solution 1 d before surgery, and postoperative self-administered analgesia was employed. Postoperative pain was assessed using a visual analog scale (VAS) calibrated from 0 to 10, with 0 indicating no pain and 10 representing the most intense pain imaginable. Pain scores were recorded on postoperative days 1, 3, and 5. The postoperative inflammatory response was evaluated using global white blood cell and neutrophil counts (on postoperative days 1, 3, and 5), and body temperature (from postoperative days 1 to 5).

Surgical procedure

Following successful endotracheal intubation and general anesthesia, the patient was positioned in a lithotomy position with the head lowered and feet elevated between 15° and 30° and tilted to the right between 10° and 15°. The procedure was performed using a five-port approach with five trocar placements. The specific port locations were as follows: (1) Camera port C (12 mm), positioned 3-4 cm above the right side of the umbilicus; (2) Robotic operating port R1 (ultrasonic knife; 8 mm), located at one-third of the distance between the umbilicus and the right anterior superior iliac spine; (3) Robotic operating port R2 (bipolar electrocoagulation; 8 mm), placed 4–5 cm above the left side of the umbilicus; (4) Robotic operating port R3 (noninvasive grasping clamp; 8 mm), positioned 2 cm below the left anterior axillary line rib margin; and (5) Auxiliary port A (12 mm), medial to the right midclavicular line, corresponding to the position of the flat camera port (Figure 1). After establishing pneumoperitoneum, laparoscopic exploration was conducted to confirm the absence of tumor implantation and metastasis within the abdominal cavity and determine the precise location of the tumor.

The first incision was made below the sacral promontory, and dissection was carried out along Toldt's space. The inferior mesenteric arteries and veins were ligated at the level of the duodenum. The rectal mesentery was freed to expose the bilateral seminal vesicles (men) or the posterior vaginal wall (women). The left and right intestinal walls of the rectum were further exposed 2–3 cm below the lower edge of the tumor, and the pre-cut line was determined approximately 10 cm above the tumor. The sigmoid mesentery was dissected, and the intestinal canal was exposed.

For the R-NOSES I-F group, the specimen resection and digestive tract reconstruction were performed as follows (Figure 2 and Video 1): The anus was fully dilated to accommodate the passage of six fingers, and a sterile plastic protective sleeve was inserted through the anus, extending 5 cm above the tumor. The oval forceps was introduced through the protective sleeve to the pre-excision site of the bowel lumen, approximately 10 cm from the upper edge of the tumor, and, under robotic view, it was secured to the bowel lumen with sutures (Figure 2A); then, the pre-excision bowel and mesentery were pulled out of the anus (Figure 2B). The tumor location was determined, and the tumor was flushed with iodophor water. The bowel was incised by the site of the oval forceps fixation, and the pre-exposed bowel was identified and disconnected (Figure 2C); after placing the anvil, it was secured at the sigmoid colon break and returned to the abdominal cavity (Figure 2D). The rectum was transected under direct vision, approximately 0.5–2 cm above the lower edge of the tumor, depending on the distance of the tumor from the anal edge (Figure 2E). The specimen was removed, and the distal rectal section was returned to the abdominal cavity. The anus was disinfected with iodophor water, and a circular stapler was used to perform a sigmoid-rectal end-to-end anastomosis (Figure 2F).

Specimen resection and digestive tract reconstruction in the RLRC group involved the following steps: The rectum was transected at a distance of 0.5-2 cm distal to the tumor, using a linear cutting closure device under the robotic system. Subsequently, a 6 cm incision was made adjacent to the rectus abdominis muscle in the left lower abdomen. The incision was protected with a protective sleeve. The proximal rectum and sigmoid colon containing the tumor were exteriorized from the abdominal cavity, and the affected intestinal segment was excised. An anvil was inserted into the proximal colon, pneumoperitoneum was re-established, and sigmoid-rectal end-to-end anastomosis was performed transanally using an anastomotic clutch while visualized through direct laparoscopy.

After thorough rinsing of the abdominopelvic cavity with iodophor water and injection of iodophor saline through the anus to ensure no anastomotic leakage, certain postoperative measures were implemented. First, an anal tube was inserted through the anus. Second, a double-sleeve drainage tube was positioned on the left side of the anastomosis and

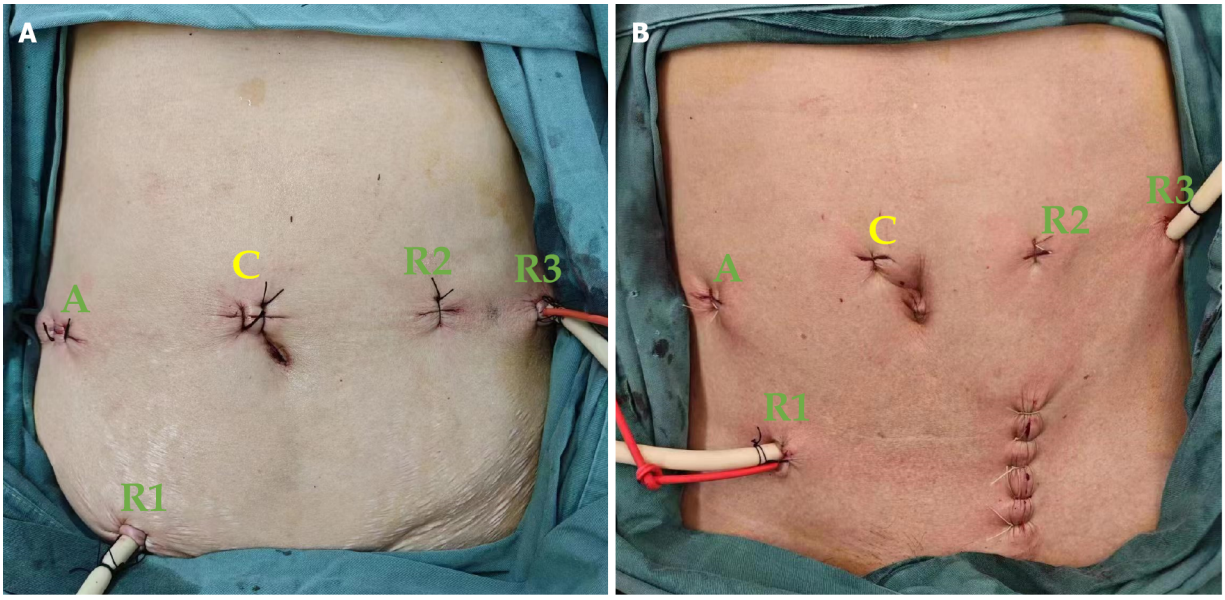

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Figure 1 Surgical incisions. A: Robotic resection using the natural orifice specimen extraction surgery I-type F method I-F surgical incisions; B: Robotic-assisted low rectal cancer resection surgical incisions. C: Camera port; R1: Robotic operating port; R2: Robotic operating port; R3: Robotic operating port; A: Auxiliary port.

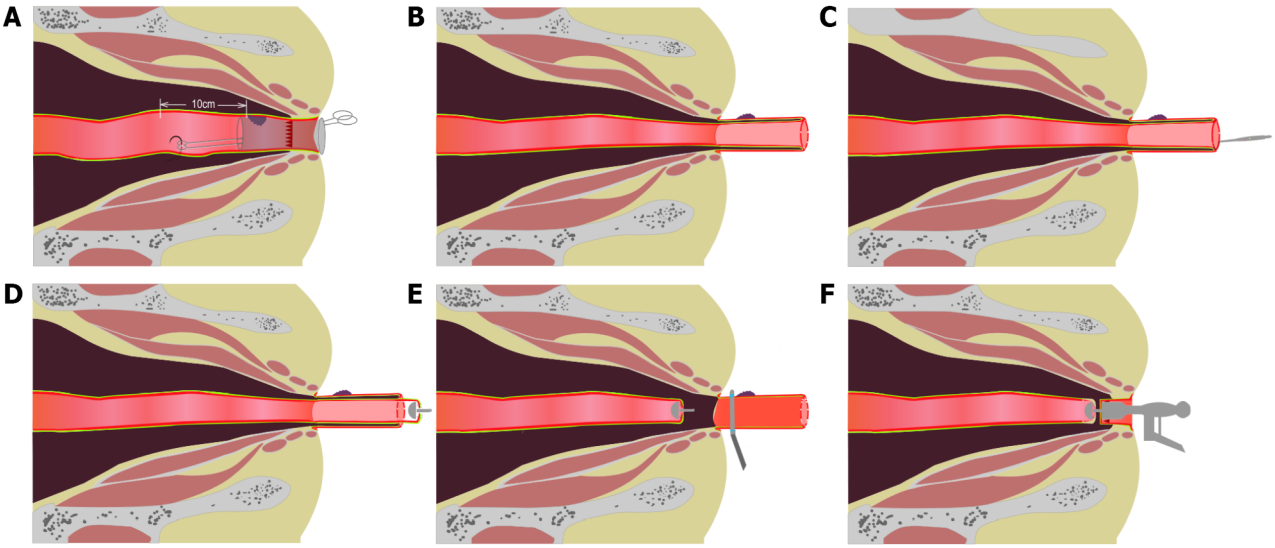

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Figure 2 Robotic resection using the natural orifice specimen extraction surgery I-type F specimen resection and digestive tract reconstruction. A: About 10 cm from the upper edge of the tumor, the oval forceps were fixed to the bowel lumen; B: Turn the pre-excised bowel out of the anus; C: The bowel was incised at the oval clamp fixation; D: The anvil was placed into the bowel lumen; E: The rectum was cut off at the lower edge of the tumor with a cutting closure; F: The circular stapling was placed into the rectum to complete the sigmoid-rectal end-to-end anastomosis.

drained through the presacral area. Finally, another drainage tube was placed on the right side of the anastomosis and drained through the trocar orifice on the right side of the abdomen. These steps were performed at the conclusion of the surgery.

Follow-up visits

Patients with postoperative pathological TNM stage I or II without risk factors did not receive chemotherapy, a few patients with stage II with risk factors underwent fluorouracil single-agent oral chemotherapy, and those with stage III underwent XELOX regimen chemotherapy. After the surgical procedure, patients were scheduled for outpatient clinic visits every 3 mo for a period of 2 years. Subsequently, the follow-up frequency was adjusted to every 6 mo. During each visit, patients underwent a comprehensive physical examination and tumor marker analysis. Additionally, chest and whole abdominal computed tomography scans were performed to monitor their condition. Regular communication with patients *via* WeChat or telephone was also maintained to ensure continuous follow-up. At 6 mo after surgery, the

postoperative anal function was evaluated using the low anterior resection syndrome (LARS) rating scale and Wexner Incontinence Score. The postoperative urinary function was assessed using the International Prostate Symptom Scale (IPSS). Owing to the impact of the novel coronavirus epidemic, some patients were followed up remotely through phone calls or WeChat. The final follow-up was conducted in June 2023.

Statistical analysis

All data analyses were performed using SPSS software (version 23.0; IBM, Armonk, NY, United States). Continuous variables were presented as mean ± SD and compared using the Mann-Whitney U test. Categorical variables were expressed as percentages and compared using the χ^2 test or Fisher's exact test, as appropriate. P values were two-tailed and differences were considered statistically significant at $P < 0.05$.

RESULTS

Clinical and pathological characteristics

A total of 22 patients were included in the R-NOSES I-F group and 76 in the RLRC group. The clinical and pathological characteristics of the patients are summarized in Table 1. No significant differences were observed between the two groups in terms of sex, age, BMI, tumor size, distance of the lower margin of the tumor from the anal verge, CEA level, or TNM stage of the tumor ($P > 0.05$).

Perioperative results

Perioperative results are summarized in Table 2. All procedures were performed using the da Vinci Surgical System (Da Vinci® Si System, Intuitive Surgical, Sunnyvale, CA, United States) and were performed by the same surgeon following the principles of total rectal mesenteric resection. None of the patients in the R-NOSES I-F or RLRC groups underwent open surgery. The operative time (173.0 ± 39.5 min *vs* 187.3 ± 50.9 min, $P = 0.389$) and intraoperative blood loss were comparable between the two groups (89.6 ± 47.9 mL *vs* 74.5 ± 62.8 mL, $P = 0.068$). No significant difference in the proportion of patients with a prophylactic stoma was observed between the two groups (31.8% *vs* 47.4%, $P = 0.196$). Regarding postoperative recovery, VAS scores on postoperative day 1 were significantly lower for patients in the R-NOSES I-F than for those in the RLRC group (1.7 ± 0.7 *vs* 2.2 ± 0.6, $P = 0.003$), and no significant difference in VAS scores on postoperative days 3 and 5 was observed ($P > 0.05$). The postoperative venting time was significantly shorter in the R-NOSES I-F group than in the RLRC group (2.7 ± 0.6 d *vs* 3.5 ± 0.7 d, $P < 0.001$). Regarding postoperative complications, three complications in the R-NOSES I-F group and 12 in the RLRC group occurred, with no significant difference between the two groups (13.6% *vs* 15.8%, $P = 0.632$). Regarding postoperative inflammation, no significant differences in global white blood cell and neutrophil counts were observed between the two groups on postoperative days 1, 3, and 5 ($P > 0.05$). Furthermore, no significant difference in the body temperature of the patients between postoperative days 1 and 5 was observed ($P > 0.05$).

Postoperative chemotherapy and follow-up results

As shown in Table 3, no significant difference in the proportion of patients receiving postoperative chemotherapy between the R-NOSES I-F and RLRC groups ($P = 0.995$) was observed. The Wexner, LARS, and IPSS scores in both groups were not significantly different ($P > 0.05$), indicating a similar degree of damage to the anal and urinary systems for both surgical procedures. Until the last follow-up in June 2023, the median follow-up time was 26 and 36 mo (range 16-57 mo) in the R-NOSES I-F and RLRC groups, respectively. No deaths were reported for the R-NOSES I-F group, while two were reported for the RLRC group. One local anastomotic recurrence occurred in the R-NOSES I-F group, while nine distant metastases occurred in the RLRC group (four liver metastases, three lung metastases, and two pelvic metastases). However, no significant difference between the two groups ($P = 0.291$) was observed.

DISCUSSION

Robotic technology combined with the NOSES concept has revolutionized minimally invasive surgeries by offering new possibilities. This retrospective cohort study represents the first published comparison between R-NOSES I-F and conventional laparoscopic RLRC. The study findings indicate that R-NOSES I-F is a safe and effective minimally invasive surgical technique for the treatment of lower rectal cancer.

In 2010, our center performed an improved laparoscopic transanal pull-through (ILTPT) technique for lower rectal cancer, which eliminated the need for auxiliary incisions in four patients with rectal cancer. This technique was the first of its kind on an international scale and the study represented the first investigation of laparoscopic R-NOSES I-F for lower rectal cancer. The results of this study demonstrated favorable short-term outcomes, with no instances of surgical site infections or complications in any of the cases. These findings provide substantial evidence that ILTPT is a safe and feasible approach for anus-preserving surgery in the treatment of lower rectal cancer[20]. Expert consensus[13] supports the notion that the anus serves as an ideal natural passage for extracting colorectal specimens, aligning with the requirements of minimally invasive surgery. Leveraging the clinical use of the Da Vinci robot, our center has also published a case report on R-NOSES I-F for low rectal cancer[18,19]. Although the above studies have shown good short-term results, they had the limitations of small sample sizes, lack of controlled trials, and lack of long-term follow-up

Table 1 Clinical and pathological features of the patient

Baseline characteristics	R-NOSES I-F (*n* = 22)	RLRC (*n* = 76)	*P* value
Age (year)	56.5 ± 8.9	59.5 ± 11.1	0.107
BMI (kg/m^2)	21.8 ± 2.5	22.6 ± 2.0	0.136
Gender			0.580
Male	8 (36.4)	45 (59.2)	
Female	14 (63.6)	31 (40.8)	
ASA score			0.552
I, II	5 (22.7)	11 (14.5)	
III	17 (77.3)	65 (85.5)	
Previous history of abdominal surgery	4 (18.2)	13 (17.1)	1.000
Maximum circumferential diameter of specimen (cm)			0.217
< 5	19 (86.4)	56 (73.7)	
≥ 5	3 (13.6)	20 (26.3)	
Tumour location from anal verge (cm)	4.3 ± 1.2	4.5 ± 0.9	0.278
Abnormal serum CEA (ng/mL)			0.700
≤ 5	16 (72.7)	52 (68.4)	
> 5	6 (27.3)	24 (31.6)	
Specimen length (cm)	11.4 ± 2.2	12.8 ± 3.1	0.068
Distal margin (cm)	1.1 ± 0.7	1.1 ± 0.8	0.737
Grade of differentiation			0.976
Well	3 (13.6)	12 (15.8)	
Moderate	16 (72.7)	52 (68.4)	
Poor	2 (9.1)	7 (9.2)	
Mucinous	1 (4.5)	5 (6.6)	
T stage			0.376
T0, Tis, T1	6 (27.3)	12 (15.8)	
T2	7 (31.8)	17 (22.4)	
T3	5 (22.7)	27 (35.5)	
T4	4 (18.2)	20 (26.3)	
N Stage			0.511
N0	14 (63.6)	46 (60.5)	
N1	7 (31.8)	20 (26.3)	
N2	1 (4.5)	10 (13.2)	
pTNM			0.110
0, I	12 (54.5)	23 (30.3)	
II	4 (18.2)	23 (30.3)	
III	6 (27.3)	30 (39.5)	
Number of lymph nodes harvested (*n*)	14.2 ± 7.3	13.7 ± 6.0	0.759
Nerve violation	9 (40.9)	30 (39.5)	0.904
Lymphovascular violation	7 (31.8)	17 (22.4)	0.364

R-NOSES I-F: Robotic resection using the natural orifice specimen extraction surgery I-type F method; RLRC: Robotic-assisted low rectal cancer resection;

BMI: Body mass index; ASA: American Society of Anesthesiologists; CEA: Carcinoembryonic antigen; TNM: Tumor node metastasis staging.

Table 2 Perioperative outcomes

Outcomes	R-NOSES I-F (*n* = 22)	RLRC (*n* = 76)	*P* value
Surgery time (min)	173.0 ± 39.5	187.3 ± 50.9	0.389
Intraoperative blood loss (mL)	89.6 ± 47.9	74.5 ± 62.8	0.068
Prophylactic stoma, *n* (%)	7 (31.8)	36 (47.4)	0.196
VAS score			
POD1	1.7 ± 0.7	2.2 ± 0.6	0.003
POD3	1.5 ± 0.6	1.6 ± 0.6	0.411
POD5	1.1 ± 0.6	1.2 ± 0.4	0.247
Time to pass flatus (d)	2.7 ± 0.6	3.5 ± 0.7	< 0.001
Postoperative hospital stay (d)	11.1 ± 5.2	9.9 ± 5.1	0.091
Hospitalization costs ($)	85098.7 ± 11067.9	82267.9 ± 14993.9	0.130
Postoperative complications, *n* (%)			0.632
Anastomosis Leakage, *n* (%)	2 (9.1)	2 (2.6)	
Pelvic hemorrhage	0	1 (1.3)	
Abdominal infection	0	1 (1.3)	
Ileus, *n* (%)	1 (4.5)	1 (1.3)	
Incision infection, *n* (%)	0	2 (2.6)	
Incisional hernia of the abdominal wall, *n* (%)	0	4 (5.3)	
Urinary retention	0	1 (1.3)	
White blood cell count (× 10^9/L)			
POD1	9.0 ± 2.8	9.4 ± 2.9	0.462
POD3	7.6 ± 2.2	8.5 ± 3.0	0.321
POD5	6.8 ± 2.1	8.1 ± 4.3	0.112
Neutrophil count (× 10^9/L)			
POD1	7.8 ± 2.6	8.1 ± 2.7	0.579
POD3	6.0 ± 2.0	6.6 ± 3.0	0.563
POD5	5.1 ± 2.0	5.9 ± 2.7	0.266
Body temperature (℃)			
POD1	36.9 ± 0.4	37.0 ± 0.4	0.600
POD2	37.1 ± 0.6	36.9 ± 0.4	0.057
POD3	37.0 ± 0.4	36.9 ± 0.4	0.295
POD4	36.8 ± 0.4	36.7 ± 0.4	0.300
POD5	36.9 ± 0.7	36.7 ± 0.5	0.166

R-NOSES I-F: Robotic resection using the natural orifice specimen extraction surgery I-type F method; RLRC: Robotic-assisted low rectal cancer resection; VAS: Visual analog scale; POD: Postoperative days.

results.

In this study, the R-NOSES I-F and RLRC groups had similar operative time (P = 0.389) and intraoperative blood loss (P = 0.068). However, the R-NOSES I-F group demonstrated significantly lower VAS scores on the first postoperative day (P = 0.003) and a significantly shorter postoperative anal venting time (P < 0.001) compared to those of the RLRC group. These findings are consistent with previous studies on laparoscopic NOSES[21,22]. Severe acute postoperative pain is

Table 3 Postoperative chemotherapy and follow-up results

Outcomes	R-NOSES I-F (*n* = 22)	RLRC (*n* = 76)	*P* value
Postoperative chemotherapy			0.995
XELOX	7 (31.8)	24 (31.6)	
Fluorouracil monotherapy	3 (13.6)	11 (14.5)	
Defecation and urination function scores			
Wexner	4.9 ± 2.6	5.2 ± 3.1	0.817
LARS	15.3 ± 9.1	12.8 ± 10.1	0.177
IPSS	3.7 ± 4.6	3.5 ± 2.9	0.255
Status at last follow-up			0.291
Local recurrence	1 (4.5)	0	
Liver metastasis	0	4 (5.3)	
Lung metastasis	0	3 (3.9)	
Pelvic metastasis	0	2 (2.6)	
Dead	0	2 (2.6)	

R-NOSES I-F: Robotic resection using the natural orifice specimen extraction surgery I-type F method; RLRC: Robotic-assisted low rectal cancer resection; Wexner: Wexner Incontinence Score; LARS: Low Anterior Resection Syndrome rating scale; IPSS: International Prostate Symptom Score.

reported as a risk factor for poor long-term prognosis[23]. Therefore, effective postoperative analgesia is crucial. By avoiding a long abdominal incision, patients in the R-NOSES I-F group experienced reduced postoperative abdominal pain, earlier mobilization, and faster recovery of gastrointestinal function, leading to a shorter postoperative anal venting time.

Regarding postoperative complications, our results revealed no significant difference in the incidence of complications between the R-NOSES I-F and RLRC groups (P = 0.632). The R-NOSES I-F group exhibited a 9.1% incidence of anastomotic leak, which is comparable to previous studies on robot-assisted rectal cancer resection (4.5%-12.1% incidence)[24-26]. Notably, the RLRC group experienced two cases of incisional infections and four incisional hernias, whereas no incisional complications occurred in the R-NOSES I-F group. A retrospective study conducted in China[27], involving 79 hospitals and including 718 patients treated with NOSES for colorectal tumors, has reported no complications associated with abdominal wall incisions. The R-NOSES I-F approach, which avoids abdominal wall incisions during transanal specimen retrieval, offers unique and minimally invasive advantages. It maximizes preservation of abdominal wall function, reduces postoperative pain, minimizes complications related to abdominal wall incisions, provides favorable cosmetic outcomes, and alleviates the psychological stress associated with surgical scars.

Inflammation is closely associated with the development, progression, and prognosis of cancer[28,29]. A growing array of evidence suggests that local and systemic inflammatory responses are important predictors of prognosis and recurrence in patients with colorectal cancer[30-32]. Previous animal experiments and clinical studies[22,33,34] have shown that transanal NOSES for colorectal cancer elicits a stronger systemic inflammatory response compared to conventional laparoscopic surgery. However, unlike previous studies, our study found that postoperative global white blood cell and neutrophil counts, and body temperature did not differ significantly between the patients in the two groups (P > 0.05). We conclude that the R-NOSES I-F group avoided the abdominal incision used to obtain the surgical specimen, thereby reducing surgical stress and decreasing the release of inflammatory mediators. Most importantly, the dissection and resection of specimens in the R-NOSES I-F group were performed entirely under direct *in vitro* vision, which shortens the time of intra-abdominal surgeries, avoids the potential risk of infection caused by dissecting the intestinal canal in the abdomen, minimizes the risk of contamination of the surgical area, and reduces the probability of intestinal bacteria entering the circulation. Additionally, the iodophor water used for irrigation before intestinal cutting and during the placement of the transanal circular stapler for digestive tract reconstruction ensured distal cleanliness. Consequently, in line with Efetov's findings[35], we believe that the R-NOSES I-F surgical approach does not exacerbate the postoperative inflammatory response.

The attainment of sterile and tumor-free standards in NOSES remains a substantial concern among surgeons. A recent multicenter study has shown that robotic NOSES had no adverse impact on the radical outcome of tumors[17]. Expert consensus[16] provides the following indications for R-NOSES I-F: (1) Appropriateness for low rectal cancer with the lower margin of the tumor located 2-5 cm from the dentate line; (2) Suitability for tumor invasion depth within T3; and (3) Applicability to tumors with a circumference of less than 5 cm. In our study, the R-NOSES I-F group included 81.8% of patients with a tumor infiltration depth within T3 and 86.4% of patients with a tumor circumference of < 5 cm. Adequate tumor size and proper bowel preparation facilitate conducive transanal specimen eversion. Moreover, the entire procedure was conducted following high standards. Before the specimen removal, a sterile protective sleeve was positioned, and the specimen underwent repeated rinsing with iodophor water before resection and reconstruction of the

digestive tract. Additionally, resection of the specimen in the R-NOSES I-F group was performed entirely under direct extracorporeal vision with sufficient operating space, which provided favorable conditions for a more precise judgment of the surgical margins and allowed us to preserve more of the distal rectum while ensuring complete resection of the tumor. Finally, the perirectal circumferential resection margins were negative in both groups. The mean number of lymph nodes cleared in the R-NOSES I-F group was no less than that in the RLRC group (14.2 ± 7.3 *vs* 13.7 ± 6.0, $P = 0.759$) and exceeded the recommended threshold of at least 12 lymph nodes cleared, as outlined by the College of American Pathologists. Thus, we conclude that the R-NOSES I-F surgical approach adheres to aseptic and tumor-free principles.

The development and promotion of new approaches should prioritize the patient postoperative quality of life and long-term survival rates. Performing TME in the lower rectum is challenging owing to pelvic limitations, which can result in nerve injury. However, the magnified high-definition 3D view provided by robotic technology, along with the flexible and stable robotic arm, can help prevent permanent nerve injury during surgery[36]. In our study, we did not observe statistically significant differences in LARS and Wexner scores between patients in the R-NOSES I-F and RLRC groups ($P > 0.05$). This result is consistent with the findings of Tang *et al*[37]. No significant difference in the IPSS between the two groups ($P = 0.207$) was observed. Therefore, we believe that the R-NOSES I-F procedure does not cause more damage to the anal sphincter or urinary system during transanal specimen retrieval than the RLRC procedure. Furthermore, we did not find any difference in the incidence of local recurrence or distant metastasis between the two groups over the long follow-up period ($P = 0.291$).

However, it is important to acknowledge the limitations and disadvantages of R-NOSES I-F: (1) The method involves using intussusception to remove the required intestinal segments externally, which requires moving the descending colon upward during the surgery, increasing the operational complexity; and (2) In our study, we utilized single-point suture fixation to secure the oval forceps to the intestinal wall in the proximal pre-excision section. This approach places considerable tension on the intestinal wall amount of and carries a risk of intestinal tears. In future endeavors, we plan to improve this technique by employing a metal rod with a large head end and a small tail end (resembling the shape of a mushroom) as a replacement for the oval forceps. This modified approach involves binding the neck of the metal rod to the colon wall under robotic vision and then extracting the specimen, substantially reducing tension during specimen retrieval, and thereby mitigating surgical complexity and associated complications.

Furthermore, our study had several limitations. First, it was a single-center retrospective study, potentially introducing selection bias in patient enrollment. Second, the sample size was small, and the follow-up period was insufficient for some patients. A prospective multicenter randomized trial with a larger sample size and longer follow-up period is necessary to evaluate the advantages of R-NOSES I-F in the treatment of lower rectal cancer.

CONCLUSION

In conclusion, our findings support that R-NOSES I-F is a safe and effective, minimally invasive surgical approach for the treatment of lower rectal cancers. This procedure to did not lead to an increased postoperative inflammatory response compared to RLRC. It offers several advantages, including reduced postoperative pain, enhanced recovery of gastrointestinal function, minimized abdominal wall dysfunction, avoidance of complications associated with abdominal wall incisions, favorable cosmetic outcomes, and comparable rates of local recurrence and distant metastasis over a long follow-up period.

ARTICLE HIGHLIGHTS

Research background

Robotic resection using the natural orifice specimen extraction surgery I-type F method (R-NOSES I-F) is a novel minimally invasive surgical strategy for the treatment of lower rectal cancer with robotic resection of rectal cancer and natural oral specimen extraction surgery. But its safety and feasibility are still worth exploring.

Research motivation

To evaluate the safety and feasibility of R-NOSES I-F for the treatment of lower rectal cancer by comparing R-NOSES I-F with traditional robotic lower rectal cancer resection. To provide a new minimally invasive surgical method for the treatment of lower rectal cancer.

Research objectives

To investigate the safety and feasibility of R-NOSES I-F surgery in the treatment of low rectal cancer.

Research methods

We used retrospective analysis to include 22 patients who underwent R-NOSES I-F surgery into the R-NOSES I-F group and 76 patients who underwent robotic low rectal cancer resection (RLRC) surgery into the RLRC group. The clinicopathological data of all enrolled patients were analyzed to compare the postoperative outcomes and prognosis of the two groups.

Research results

Compared with the RLRC group, the R-NOSES I-F group had a lower visual analog scale of pain on day 1 after surgery (1.7 ± 0.7 *vs* 2.2 ± 0.6, $P = 0.003$) and a shorter postoperative ventilation time (2.7 ± 0.6 *vs* 3.5 ± 0.7, $P < 0.001$). After long-term follow-up, there was no significant difference in local recurrence rate and distant metastasis rate between the two groups ($P > 0.05$).

Research conclusions

R-NOSES I-F is a safe and effective minimally invasive procedure for the treatment of lower rectal cancer, which has the advantages of relieving pain, promoting gastrointestinal function recovery, and avoiding incision complications.

Research perspectives

The incidence and mortality of rectal cancer are increasing significantly, and it is particularly important to improve the postoperative quality of life of rectal cancer patients, especially those with low-grade rectal cancer, through improved surgical methods. In recent years, the combination of robotic surgery and NOSES has become one of the hot spots in rectal cancer surgery. R-NOSES I-F has the advantages of reducing postoperative pain, promoting gastrointestinal function recovery, reducing abdominal wall dysfunction, and avoiding complications of abdominal wall incision, and has certain cosmetic effects. It is a safe and effective minimally invasive surgical modality for the treatment of low-lying rectal cancer.

FOOTNOTES

Author contributions: Tao F, Li TY and Duan JY designed the study and reviewed the data; Tao F and Xu CY performed the acquisition of clinical data; Tao F drafting of manuscript; Duan JY and Liu DN critical revision of manuscript; Luo X and He PH data analysis; Luo X figure and video production; All authors read and approved the final manuscript.

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Gene polymorphisms associated with sudden decreases in heart rate during extensive peritoneal lavage with distilled water after gastrectomy

Shuang Yao, Yan Yuan, Jun Zhang, Yang Yu, Guang-Hua Luo

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Abstract

BACKGROUND

Our previous study found that the telomerase-associated protein 1 (*TEP1*, rs938886 and rs1713449) and homo sapiens RecQ like helicase 5 (*RECQL5*, rs820196) single nucleotide polymorphisms (SNPs) were associated with changes in heart rate (HR) ≥ 30% during peritoneal lavage with distilled water after gastrectomy. This study established a single tube method for detecting these three SNPs using two-dimensional (2D) polymerase chain reaction (PCR), and investigated whether SNP-SNP and SNP-environment interactions increase the risk of high HR variability (HRV).

AIM

To investigate whether genotypes, genetic patterns, SNP-SNP and SNP-environment interactions were associated with HRV.

METHODS

2D PCR was used to establish a single-tube method to detect *TEP1* rs938886 and rs1713449 and *RECQL5* rs820196, and the results were compared with those of sanger sequencing. After adjusting for confounders such as age, sex, smoking, hypertension, and thyroid dysfunction, a nonconditional logistic regression model was used to assess the associations between the genotypes and the genetic patterns (codominant, dominant, overdominant, recessive, and additive) of the three SNPs and a risk ≥ 15% or ≥ 30% of a sudden drop in HR during postoperative peritoneal lavage in patients with gastric cancer. Gene-gene and gene-environment interactions were analyzed using generalized multifactor dimensionality reduction.

RESULTS

The coincidence rate between the 2D PCR and sequencing was 100%. When the HRV cutoff value was 15%, the patients with the *RECQL5* (rs820196) TC genotype had a higher risk of high HRV than those who had the TT genotype (odds ratio = 1.97; 95%CI: 1.05-3.70; P = 0.045). Under the codominant and overdominant models, the TC genotype of *RECQL5* (rs820196) was associated with a higher risk of HR decrease relative to the TT and TT + CC genotypes (P = 0.031 and 0.016, respectively). When the HRV cutoff value was 30%, patients carrying the GC-TC genotypes of rs938886 and rs820196 showed a higher HRV risk when compared with the GG–TT genotype carriers (P = 0.01). In the three-factor model of rs938886, rs820196, and rs1713449, patients carrying the GC-TC-CT genotype had a higher risk of HRV compared with the wild-type GG-TT-CC carriers (P = 0.01). For rs820196, nonsmokers with the TC genotype had a higher HRV risk compared with nonsmokers carrying the TT genotype (P = 0.04). When the HRV cutoff value was 15%, patients carrying the TT-TT and the TC-CT genotypes of rs820196 and rs1713449 showed a higher HRV risk when compared with TT-CC genotype carriers (P = 0.04 and 0.01, respectively). Patients carrying the GC-CT-TC genotypes of rs938886, rs1713449, and rs820196 showed a higher HRV risk compared with GG-CC-TT genotype carriers (P = 0.02). When the HRV cutoff value was 15%, the best-fitting models for the interactions between the SNPs and the environment were the rs820196-smoking (P = 0.022) and rs820196-hypertension (P = 0.043) models. Consistent with the results of the previous grouping, for rs820196, the TC genotype nonsmokers had a higher HRV risk compared with nonsmokers carrying the TT genotype (P = 0.01).

CONCLUSION

The polymorphism of the *RECQL5* and *TEP1* genes were associated with HRV during peritoneal lavage with distilled water after gastrectomy.

Key Words: Homo sapiens RecQ like helicase 5; Telomerase-associated protein 1; Polymorphism; Peritoneal lavage; Heart rate variability; Two-dimensional polymerase chain reaction

Core Tip: Our previous study found that peritoneal lavage with distilled water may cause a sudden decrease in heart rate (HR) in some patients during clinical gastrectomy, which was related to telomerase-associated protein 1 and homo sapiens RecQ like helicase 5 gene polymorphisms. Here, instead of Sanger sequencing, we developed a single-tube method using two-dimensional polymerase chain reaction to genotyping single nucleotide polymorphisms (SNPs) quickly and economically. We also investigated whether genotypes, genetic patterns and the interaction effects of SNP-SNP and SNP-environment were associated with a risk of high HR variability. This study helps clinicians to better assess the perioperative risk of patients undergoing gastrectomy.

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INTRODUCTION

Gastric cancer currently ranks fifth in incidence and fourth in mortality worldwide[1]. Peritoneal metastasis is the most frequent pattern of postoperative recurrence in patients with gastric cancer. In order to reduce abdominal metastasis and planting caused by surgery, distilled water or normal saline are normally used to wash the peritoneum after radical distal gastrectomy. The Chinese SEIPLUS trial reported that, for extensive intraoperative peritoneal lavage (EIPL), a new prophylactic strategy for the prevention of the peritoneal metastasis of locally advanced gastric cancer, the short-term postoperative complication rate following surgery alone (17%) was significantly higher than that following combined surgery and multiple warm physiological saline lavages (11.1%)[2]. However, they found that addition of EIPL with saline did not improve the 3-year survival rate of advanced gastric cancer patients compared with surgery alone[3]. A latest randomized study evaluated the efficacy and long-term outcome of advanced gastric cancer patients with EIPL[4]. It was found that EIPL can reduce the possibility of perioperative complications including ileus and abdominal abscess. The overall survival curve and recurrence-free survival curve were better in the EIPL group. A multicenter study found that EIPL with saline after surgery did not provide a survival benefit compared with surgery alone and should not be recommended for patients undergoing curative gastrectomy for gastric cancer[5]. Distilled water can induce osmotic lysis in cancer cells. Takemoto *et al*[6] demonstrated the cytocidal effects of distilled-water-induced hypotonic shock on colorectal cancer cells, which supported the use of peritoneal lavage with distilled water to remove and kill colorectal cells during surgery. Recently, a randomized trial was performed to assess the survival impact of extensive peritoneal lavage using distilled water or saline at high volumes after pancreatic resection for pancreatic ductal adenocarcinoma,

which suggested that lavage with distilled water or saline could become standard practice during surgery for pancreatic cancer if it proves to be beneficial to the long-term prognosis of the patient[7].

Our previous study found that peritoneal lavage with distilled water may have caused a sudden decrease in heart rate in some patients during clinical gastrectomy. To investigate whether gene polymorphisms are associated with high heart rate variability (HRV), we genotyped 194 patients who underwent distal gastrectomy and identified three single nucleotide polymorphisms (SNPs) (*TEP1* rs938886 and rs1713449 and *RECQL5* rs820196) associated with a risk of high HRV using whole-exome sequencing[8]. In this study, two-dimensional (2D) polymerase chain reaction (PCR) was used to establish a single-tube method to detect these three SNPs in 192 patients (two were excluded due to incomplete clinical data). Single-gene analysis may not be appropriate for the further study of complex traits because the main effect of a single locus may be too limited for observation. Therefore, SNP-SNP and SNP-environment interactions among the three variants from the two selected genes were tested using a generalized multifactor dimensionality reduction (GMDR) approach.

MATERIALS AND METHODS

Study Population

A total of 192 patients (137 males and 55 females) scheduled to undergo distal gastrectomy were enrolled. Patients were diagnosed according to clinical and pathological data, and those with a history of other cancers or arrhythmia were excluded. Participant demographic data (age, sex, hypertension, diabetes, thyroid dysfunction, and smoking status) were collected using a standard clinical information questionnaire. Evaluation of the genomic differences of these gastric cancer patients was conducted in a previous study[8]. Patients were divided into two groups according to the changes in HR (using 30% and 15% as cutoffs). Change in HR = (ultimate HR before lavage-HR after lavage)/HR before lavage × 100%. This study received ethical approval from the institutional review board of the Third Affiliated Hospital of Soochow University and was conducted in accordance with the Helsinki Declaration on human medical research.

DNA Extraction and SNP Genotyping

Standard techniques were adopted for the collection of venous blood samples from the participants. Whole blood was stored at -80 ℃ for subsequent SNP analysis. Genomic DNA was extracted using the TIANamp Blood DNA Kit (Tiangen Biotech, Beijing, China). According to the principles of 2D PCR and amplification-refractory mutation system PCR, the mutation sites of the *TEP1* (rs1713449), *TEP1* (rs938886), and *RECQL5* (rs820196) genes were designed at the 3' ends of the specific forward primers. The respective specific reverse primers were designed according to the DNA sequence using the PrimerPremier5.0 software, wherein the primer for *TEP1* (rs1713449) was designed according to the reverse complementary strand. Three fluorescein amidite tags and three hexachloro-fluorescein tags were used to label the wild-type and mutant forward primers (respectively) of *TEP1* (rs1713449), *TEP1* (rs938886), and *RECQL5* (rs820196). The sequences of the primers and probes are listed in Supplementary Table 1, which were synthesized by Sangon Biotech (Shanghai, China). The optimized 2D multiplex PCR system included 2 μL genomic DNA, 2.5 μL 10 × Immobuffer (Bioline, London, United Kingdom), 0.75 μL 25 mmol/L $MgCl_2$ (Bioline), 0.7 μL 10 mmol/L dNTPs (Takara Bio, Shiga, Japan), 0.5 μL 5 U/μL IMMOLASE DNA polymerase (Bioline), 0.4 μL each probe (10 μM), 0.1 μL each forward primer (10 μM; 0.2 μL for *TEP1* rs938886), 0.6 μL reverse primer (10 μM), and deionized water, to make a total volume of 25 μL. The PCRs were carried out with the following thermal cycling conditions: Initial denaturation of DNA at 95 ℃ for 10 min; amplification for five cycles at 95 ℃ for 20 s and 60 ℃ for 15 s; and 35 cycles at 95 ℃ for 20 s, 72 ℃ for 1 s, and 60 ℃ for 15 s. The fluorescence acquisition commenced with heating at 95 ℃ for 15 s and 30 ℃ for 4 min; the temperature was gradually increased from 30 ℃ to 70 ℃ with a ramp rate of 0.1 ℃/s, and the fluorescence signal was acquired continuously. The final step was cooling at 40 ℃ for 30 s. The results of 2D PCR were compared with sanger sequencing.

Statistical analysis

Statistical analyses were performed using SAS version 9.4 (Cary, NC, United States), and the nominal P value ≤ 0.05 was considered the significance threshold. Normally and non-normally distributed continuous variables were compared using student's t test and Mann–Whitney U test, respectively, and the variables were expressed as mean ± SD. The genotype and allelic frequency distributions of polymorphisms between two groups were compared using the χ^2 test and the Hardy–Weinberg equilibrium. Associations between polymorphisms and HR change were assessed by calculating odds ratios (ORs) with 95%CIs using logistic regression analysis adjusted for age, sex, hypertension, thyroid dysfunction, and smoking status. The pairwise linkage disequilibrium (LD) and frequency of haplotypes were calculated with Haploview 4.2. GMDR was used to analyze the SNP-SNP and SNP-environment interactions. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

We recruited 192 patients with gastric cancer. The basic characteristics are presented in Tables 1 and 2. The HRV cutoff values used were 30% and 15%. There were no significant differences in the baseline demography, smoking status, hypertension, diabetes, and thyroid dysfunction between the two groups ($P > 0.05$).

Table 1 Baseline and clinical parameters of patients with ≥ 30% *vs* < 30% heart rate variability, *n* (%)

Variable	HRV ≥ 30%	HRV < 30%	χ^2	*P* value
Sex			1.828	0.18
Female	9 (16.36)	46 (83.64)		
Male	13 (9.49)	124 (90.51)		
Age (yr)			0.098	0.75
< 60	5 (14.29)	30 (85.71)		
≥ 60	17 (10.83)	140 (89.17)		
Smoking status			0.592	0.44
No	20 (12.58)	139 (87.42)		
Yes	2 (6.06)	31 (93.94)		
Hypertension			0.213	0.64
No	13 (10.66)	109 (89.34)		
Yes	9 (12.86)	61 (87.14)		
Diabetes			0.299	0.58
No	19 (10.80)	157 (89.20)		
Yes	3 (18.75)	13 (81.25)		
Blood type			0.964	0.81
A	9 (12.33)	64 (87.67)		
AB	1 (5.00)	19 (95.00)		
B	5 (11.36)	39 (88.64)		
O	7 (12.73)	49 (87.27)		
Thyroid function			0.005	0.95
Normal	20 (11.70)	151 (88.30)		
Abnormal	2 (9.52)	19 (90.48)		

All *P* values are more than 0.05. HRV: Heart rate variability.

Genotyping by 2D PCR

Figure 1 shows the melting curves of six alleles of the three genes detected by 2D PCR. Six melting valleys were clearly identified (Figure 1A) and six different alleles were intuitively typed. The genotypes of *TEP1* (rs1713449), *TEP1* (rs938886), and *RECQL5* (rs820196) in 190 gastric cancer patients investigated by 2D PCR were completely consistent with those determined by sanger sequencing (the remaining two cases were not validated because of sample loss, Figure 1).

Genotypes and allele dissemination of SNPs

Genotypes and allele frequencies of *TEP1* (rs938886), *TEP1* (rs1713449) and *RECQL5* (rs820196) in patients with a 30% or 15% decrease in HR as the cutoff points were compared. When the patients were grouped according to the 30% decrease in HR cutoff, there were no significant differences in the distribution of heterozygous and homozygous mutant and wild-type genotypes (Table 3, $P > 0.05$). However, when the patients were grouped using the 15% decrease in HR cutoff, the distribution of the *RECQL5* (rs820196) genotype frequencies was significantly different between the two groups. For *RECQL5* (rs820196), compared with individuals with the TT genotype, patients with the TC genotype had a significantly increased risk of adverse HR decline, with an OR of 1.97 (95%CI: 1.05-3.70), which implies that *RECQL5* (rs820196) was associated with HRV in the allelic models (Table 4, $P < 0.05$).

Associations between SNPs and HRV risk under different inheritance model

We next applied five genetic models (codominant, dominant, overdominant, recessive, and additive) to further analyze the relationships between the three SNPs and HRV. No significant differences were found between the patients in the HRV ≥ 30% group and the control group for the studied SNPs in all the genetic models ($P > 0.05$, Table 5). However, when the patients were grouped according to the 15% HRV cutoff, *RECQL5* (rs820196) was associated with a higher risk of HR change in the codominant and overdominant models. In the codominant model, the TC genotype was associated with a higher risk relative to the TT genotype (OR = 2.0; 95%CI: 1.06-3.76; $P = 0.031$). In the overdominant model, the TC

Table 2 Baseline and clinical parameters of patients with ≥ 15% *vs* < 15% heart rate variability, *n* (%)

Variable	HRV ≥ 15%	HRV < 15%	χ^2	*P* value
Sex			0.015	0.90
Female	21 (38.18)	34 (61.82)		
Male	51 (37.23)	86 (62.77)		
Age (yr)			1.232	0.27
< 60	16 (45.71)	19 (54.29)		
≥ 60	56 (35.67)	101 (64.33)		
Smoking status			0.412	0.52
No	58 (36.48)	101 (63.52)		
Yes	14 (42.42)	19 (57.58)		
Hypertension			0.006	0.94
No	46 (37.70)	76 (62.30)		
Yes	26 (37.14)	44 (62.86)		
Diabetes			2.618	0.11
No	63 (35.80)	113 (64.20)		
Yes	9 (56.25)	7 (43.75)		
Blood type			1.803	0.61
A	27 (36.99)	46 (63.01)		
AB	5 (25.00)	15 (75.00)		
B	17 (38.64)	27 (61.36)		
O	23 (41.82)	32 (58.18)		
Thyroid function			0.289	0.59
Normal	63 (36.84)	108 (63.16)		
Abnormal	9 (42.86)	12 (57.14)		

All *P* values are more than 0.05. HRV: Heart rate variability.

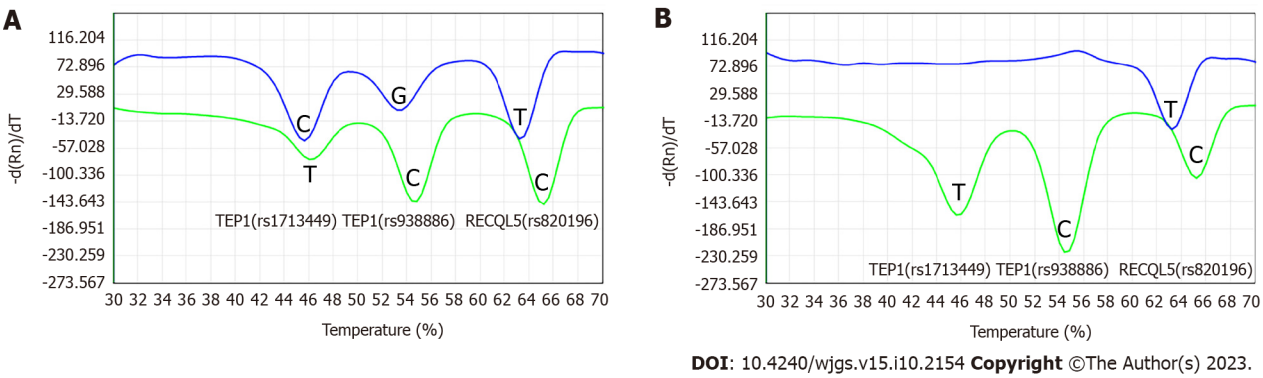

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Figure 1 Genotypes of telomerase-associated protein 1 (*TEP1*) (rs1713449), *TEP1* (rs938886), and recQ like helicase 5 (*RECQL5*) (rs820196) identified by two-dimensional polymerase chain reaction in a single tube. Subtype color indicates the type of reporter dye: Blue-fluorescein amidite; green-hexachloro-fluorescein. A: All three mutations identified were heterozygous; B: *TEP1* (rs1713449) and *TEP1* (rs938886) were homozygous for the TT and CC genotypes, respectively, and *RECQL5* (rs820196) was heterozygous for the TC genotype. *TEP1:* Telomerase-associated protein 1; *RECQL5:* RecQ like helicase 5.

Table 3 Comparison of genotype and allele dissemination of single nucleotide polymorphisms in patients with ≥ 30% *vs* < 30% heart rate variability, *n* (%)

SNP	HRV ≥ 30%	HRV < 30%	χ^2	*P* value	OR (95%CI)
TEP1 (rs938886)			1.30	0.52	
GG	9 (10.00)	81 (90.00)			1.00 (Reference)
GC	12 (14.12)	73 (85.88)			1.63 (0.63, 4.20)
CC	1 (5.88)	16 (94.12)			0.72 (0.081, 6.39)
			0.016	0.90	
G	30 (11.32)	235 (88.68)			1.00 (Reference)
C	14 (11.76)	105 (88.24)			1.16 (0.58, 2.31)
TEP1 (rs1713449)			1.54	0.46	
CC	9 (10.11)	80 (89.89)			1.00 (Reference)
CT	12 (14.29)	72 (85.71)			1.63 (0.63, 4.21)
TT	1 (5.26)	18 (94.74)			0.62 (0.071, 5.43)
			0.0001	0.99	
C	30 (11.45)	232 (88.55)			1.00 (Reference)
T	14 (11.48)	108 (88.52)			1.11 (0.56, 2.22)
RECQL5 (rs820196)			3.93	0.14	
TT	7 (8.05)	80 (91.95)			1.00 (Reference)
TC	14 (16.47)	71 (83.53)			2.39 (0.90, 6.33)
CC	1 (5.00)	19 (95.00)			0.65 (0.073, 5.72)
			0.33	0.57	
T	28 (10.81)	231 (89.19)			1.00 (Reference)
C	16 (12.80)	109 (87.20)			1.27 (0.66, 2.47)

All *P* values are more than 0.05. Logistic regression analyses adjusting for age, gender, smoking, hypertension, and thyroid function. Two covariates with missing values were dropped. SNP: Single nucleotide polymorphisms; *TEP1:* Telomerase-associated protein 1; HRV: Heart rate variability; OR: Odds ratio; CI: Confidence interval; *RECQL5:* RecQ like helicase 5.

genotype was associated with a higher risk relative to the TT and CC genotypes (OR = 2.10; 95%CI: 1.15-3.84; *P* = 0.016, Table 6).

LD and haplotype analysis

The results of the pairwise LD analysis of the two *TEP1* SNPs are presented in Figure 2. We detected a haplotype block with a strong LD between the rs938886 and rs1713449 SNPs. The D value was 1, indicating that these two SNPs tend to be co-inherited. The haplotype analysis indicated that, regardless of whether the patients were grouped according to the 30% or 15% HRV cutoff, the rs938886-C/rs1713449-T and rs938886-G/rs1713449-T haplotypes were not associated with HRV risk (Tables 7 and 8, *P* > 0.05).

SNP–SNP and SNP-environment interaction analysis

The GMDR approach was used to evaluate the effect of SNP-SNP interactions among the three *TEP1* and *RECQL5* SNPs. The results obtained from the GMDR analysis of the one-to three-locus models in the patients with HRV ≥ 30% are summarized in Table 9. The one-locus model of *RECQL5* rs820196 was the best model of SNP-SNP interaction, recording the highest cross-validation consistency (CVC) of 10/10 and a testing accuracy of 0.6127 (*P* value based on 1000 permutations, *P* = 0.032).

In order to obtain an OR with a 95%CI for the joint effects of SNP-SNP interactions on HRV, we also conducted interaction analyses of the GMDR models using logistic regression. After adjusting for the factors of age, gender, smoking, hypertension, and thyroid function by multivariate logistic regression analysis, the combination of the rs93886 and rs820196 SNPs (GC-TC) was correlated with a higher risk of decreased HR ≥ 30% (Figure 3A). One-to three-locus models in the patients with decreased HR ≥15% are showed in Figure 3B. Table 10 describes the results generated from the GMDR method for the two-way and three-way gene-gene interaction analyses using covariate adjustment. Compared with the wild-type, individuals with the GC-TC (rs93886 and rs820196, respectively) genotype and the GC-TC-CT (rs93886, rs820196, and rs1713449, respectively) genotype showed a significantly increased HRV risk (OR = 6.16 and 6.27

Table 4 Comparison of genotype and allele frequencies of single nucleotide polymorphisms in patients with ≥ 15% *vs* < 15% heart rate variability, *n* (%)

SNP	HRV ≥ 15%	HRV < 15%	χ^2	*P* value	OR (95%CI)
TEP1 (rs938886)			1.56	0.46	
GG	30 (33.33)	60 (66.67)			1.00 (Reference)
GC	34 (40.00)	51 (60.00)			1.34 (0.72, 2.52)
CC	8 (47.06)	9 (52.94)			1.74 (0.59, 5.15)
			1.50	0.22	
G	94 (35.47)	171 (64.53)			1.00 (Reference)
C	50 (42.02)	69 (57.98)			1.30 (0.83, 2.04)
TEP1 (rs1713449)			2.02	0.36	
CC	29 (32.58)	60 (67.42)			1.00 (Reference)
CT	34 (40.48)	50 (59.52)			1.42 (0.75, 2.67)
TT	9 (47.37)	10 (52.63)			1.85 (0.66, 5.21)
			2.00	0.16	
C	92 (35.11)	170 (64.89)			1.00 (Reference)
T	52 (42.62)	70 (57.38)			1.36 (0.87, 2.13)
RECQL5 (rs820196)			6.20	0.045	
TT	27 (31.03)	60 (68.97)			1.00 (Reference)
TC	40 (47.06)	45 (52.94)			1.97 (1.05, 3.70)[a]
CC	5 (25.00)	15 (75.00)			0.69 (0.22, 2.13)
			0.49	0.48	
T	94 (36.29)	165 (63.71)			1.00 (Reference)
C	50 (40.00)	75 (60.00)			1.15 (0.74, 1.78)

[a]*P* < 0.05 *vs* TT.

Logistic regression analyses adjusting for age, gender, smoking, hypertension, and thyroid function. Two covariates with missing values were dropped. SNP: Single nucleotide polymorphism; *TEP1:* Telomerase-associated protein 1; HRV: Heart rate variability; OR: Odds ratio; CI: Confidence interval; *RECQL5*: RecQ like helicase 5.

with *P* = 0.01).

Table 11 describes the results generated with the GMDR method for the SNP-environment interaction analysis using covariate adjustment. The rs820196-smoking two-factor model was found to exhibit a statistically significant association with HRV ≥ 30% (*P* = 0.045) (Figure 4).

After adjusting for age, gender, hypertension, and thyroid function, logistics regression showed that the nonsmokers with the rs820196 TC genotype had a significantly higher risk of HRV than the nonsmokers with the TT genotype (*P* = 0.04, Table 12).

The results obtained from the GMDR analysis of the one-to three-locus models in the patients with HRV ≥ 15% are summarized in Table 13. The one-locus model of *RECQL5* rs820196 was the best model of SNP-SNP interaction, recording the highest CVC of 10/10 and a testing accuracy of 0.5920 (*P* = 0.039).

Table 14 summarizes the results obtained from the GMDR analysis for the two- to three-loci models of gene–gene interactions. Compared with the TT-CC (rs820196-rs1713449) genotype, the TT-TT and TC-CT genotypes were associated with a higher risk of HRV ≥ 15% (*P* = 0.04 and 0.01, respectively). Compared with the GG-CC-TT (rs938886-rs1713449-rs820196) genotype, the GC-CT-TC genotype showed a significantly increased HRV risk (*P* = 0.02).

Table 15 and Figure 5 describe the results generated with the GMDR method for the SNP-environment interaction analysis using covariate adjustment. The rs820196-smoking and rs820196-hypertension two-factor models were found to exhibit a statistically significant association with HRV ≥ 15% (*P* < 0.05).

After adjusting for age, gender, and thyroid function, logistics regression showed that the nonsmokers with the rs820196 TC genotype had a significantly higher risk of HRV ≥ 15% than the nonsmokers with the TT genotype (*P* = 0.01, Table 16).

Table 5 Association of telomerase-associated protein 1 and RecQ like helicase 5 polymorphisms with heart rate variability ≥ 30% under different inheritance models

Inheritance model	*TEP1* (rs938886)		*TEP1* (rs1713449)		*RECQL5* (rs820196)	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Codominant						
Aa *vs* AA	1.67 (0.64, 4.31)	0.293	1.67 (0.65, 4.34)	0.289	2.35 (0.88, 6.24)	0.087
aa *vs* AA	0.62 (0.068, 5.70)	0.675	0.54 (0.060, 4.84)	0.582	0.58 (0.065, 5.21)	0.628
Dominant (Aa + aa *vs* AA)	1.49 (0.59, 3.76)	0.403	1.46 (0.58, 3.68)	0.429	2.02 (0.78, 5.25)	0.151
Overdominant (Aa *vs* AA + aa)	1.69 (0.68, 4.24)	0.261	1.74 (0.69, 4.35)	0.238	2.54 (0.99, 6.49)	0.051
Recessive (aa *vs* Aa + AA)	0.56 (0.067, 4.64)	0.590	0.48 (0.059, 3.92)	0.494	0.41 (0.050, 3.27)	0.396
Additive (AA *vs* Aa *vs* aa)	1.18 (0.57, 2.42)	0.657	1.12 (0.55, 2.27)	0.752	1.28 (0.65, 2.51)	0.472

All *P* values are more than 0.05. Logistic regression analyses adjusting for age, gender, smoking, hypertension, and thyroid function. A: Major allele; a: Minor allele; *TEP1:* Telomerase-associated protein 1; OR: Odds ratio; CI: Confidence interval; *RECQL5:* RecQ like helicase 5.

Table 6 Association of telomerase-associated protein 1 and RecQ like helicase 5 polymorphisms with heart rate variability ≥ 15% under different inheritance models

Inheritance model	*TEP1* (rs938886)		*TEP1* (rs1713449)		*RECQL5* (rs820196)	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Codominant						
Aa *vs* AA	1.36 (0.72, 2.55)	0.341	1.43 (0.76, 2.69)	0.271	2.00 (1.06, 3.76)	0.031[a]
aa *vs* AA	1.31 (0.75, 2.29)	0.345	1.34 (0.79, 2.28)	0.279	0.82 (0.46, 1.45)	0.492
Dominant (Aa + aa *vs* AA)	1.40 (0.77, 2.56)	0.273	1.49 (0.81, 2.72)	0.196	1.64 (0.90, 2.98)	0.109
Overdominant (Aa *vs* AA + aa)	1.23 (0.67, 2.23)	0.506	1.27 (0.70, 2.31)	0.441	2.10 (1.15, 3.84)	0.016[b]
Recessive (aa *vs* Aa + AA)	1.50 (0.53, 4.25)	0.442	1.56 (0.58, 4.16)	0.378	0.50 (0.17, 1.46)	0.202
Additive (AA *vs* Aa *vs* aa)	1.33 (0.83, 2.12)	0.233	1.38 (0.88, 2.18)	0.166	1.15 (0.74, 1.80)	0.537

[a]$P < 0.05$ *vs* TT.

[b]$P < 0.05$ *vs* TT + CC.

Logistic regression analyses adjusting for age, gender, smoking, hypertension, and thyroid function. A: Major allele; a: Minor allele; *TEP1:* Telomerase-associated protein 1; OR: Odds ratio; CI: Confidence interval; *RECQL5:* RecQ like helicase 5.

DISCUSSION

RECQL5 protein is involved in the regulation of transcription elongation, the DNA damage response and DNA replication[9,10]. Mutations in RECQ helicases are associated with the genetic disorders bloom syndrome, werner syndrome, and Rothmund-Thomson syndrome, which are characterized by chromosomal instability, premature aging, and a predisposition to cancer[11-13]. *RECQL5*-knockout mice are more likely to develop cancer, and human cells deficient in *RECQL5* display chromosomal instability and elevated sister chromatid exchange events, similar to cells deficient in any of the other RECQ helicases[14]. According to a recent study, *RECQL5* promotes metastasis and resistance to cisplatin in non-small cell lung cancer[15]. A large case-control study suggests that *RECQL5* is a new moderate-risk breast cancer gene[16]. *RECQL5* protein overexpression in breast cancer is strongly correlated with poor prognosis and survival, and with therapeutic resistance. A small molecule targeting *RECQL5* was able to preferentially kill *RECQL5*-expressing breast cancers and led to the efficient sensitization of cisplatin-resistant breast cancers[17]. Philip *et al*[18] identified *RECQL5* as a novel pharmacological target for expanding Poly (ADPRibose) Polymerase inhibitor based treatment horizon for homologous recombination-proficient cancers. Low *RECQL5* expression indicates poor prognosis in gastric carcinoma and is an independent prognostic factor[19]. To date, no study has shown that *RECQL5* is associated with arrhythmias, although a variant in chromodomain helicase DNA-binding protein 4 associated with childhood idiopathic epilepsy with sinus arrhythmia has been reported[20]. Given the cardinal role of the *RECQL5* protein in genome stability[21], one might speculate that DNA disrepair caused by *RECQL5* mutations is the probable cause of myocardial apoptosis and arrhythmia. Further investigations are required to determine the risk of sudden cardiogenic arrhythmia caused by *RECQL5* mutations.

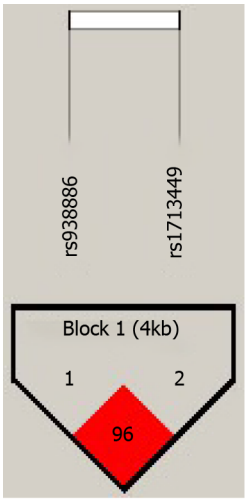

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Figure 2 Haplotype block map for candidate single nucleotide polymorphisms in the telomerase-associated protein 1 gene. Two single nucleotide polymorphisms in the haplotype map (rs938886 and rs1713449) were in significant linkage disequilibrium (LD). A standard color frame was used to illustrate the LD pattern.

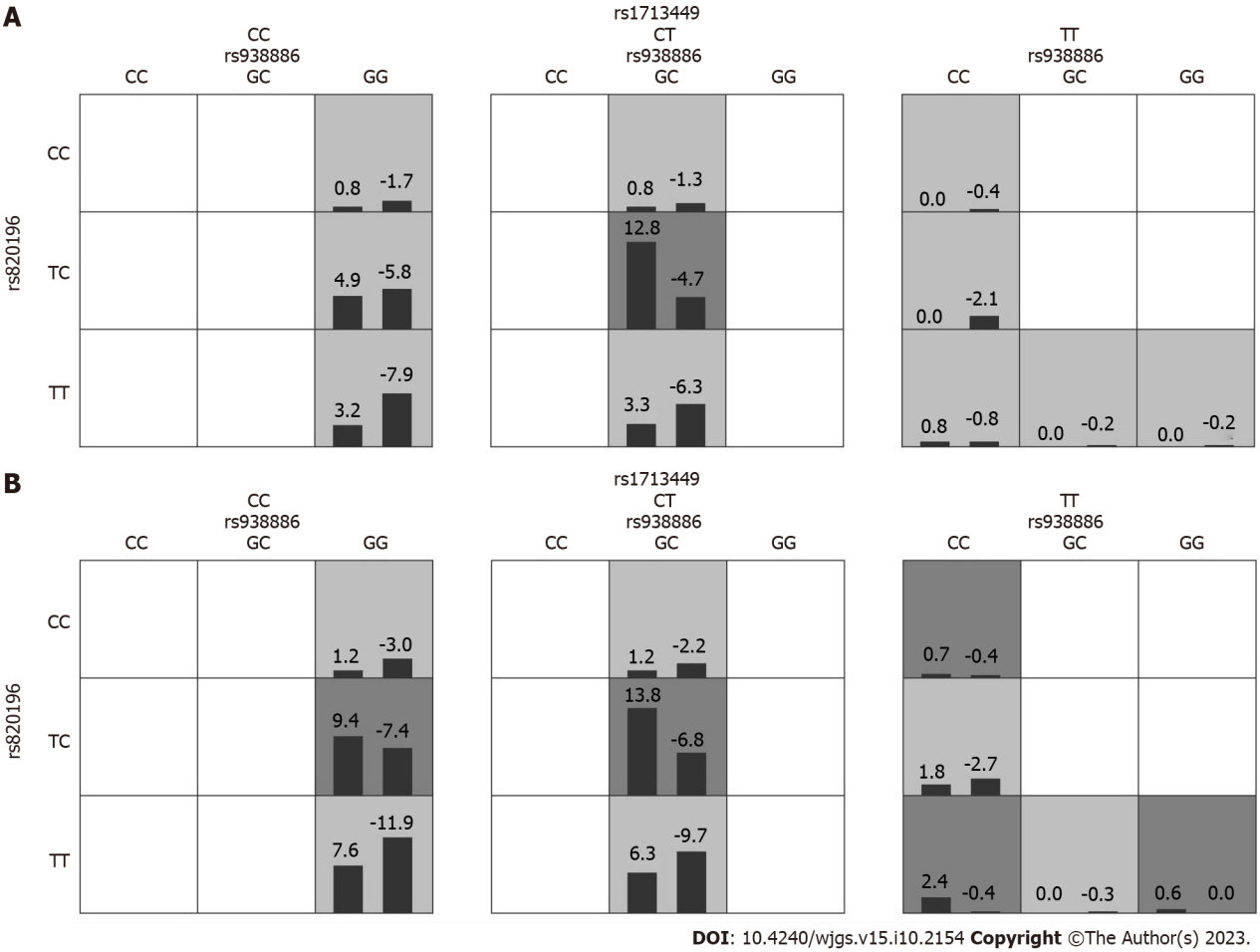

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Figure 3 Single nucleotide polymorphism-single nucleotide polymorphism interaction of three loci. A: heart rate variability (HRV) cutoff value = 30%; B: HRV cutoff value = 15%. For each multifactor cell, the score of patients with HRV ≥ 30% or 15% is displayed on the left bar and the score of patients with HRV < 30% or 15% is displayed on the right bar. The high-risk interaction genotype was assigned as 1 and the low-risk interaction genotype was assigned as 0 in the multivariable logistic regression analyses. Dark gray cells indicate high-risk combinations, and light gray cells indicate low-risk combinations.

Table 7 Association of telomerase-associated protein 1 haplotypes with heart rate variability risk using a 30% heart rate variability cutoff

TEP1 (rs938886)	*TEP1* (rs1713449)	Frequency	HRV ≥ 30% (*n* = 22)	HRV < 30% (*n* = 170)	OR (95%CI)	*P* value
G	C	0.682	30 (11.45)	232 (88.55)	1.00 (Reference)	-
C	T	0.310	14 (11.76)	105 (88.24)	1.15 (0.58, 2.28)	0.70
G	T	0.008	0 (00.00)	3 (100.00)	-	-

All *P* values are more than 0.05. Logistic regression analyses adjusting for age, gender, smoking, hypertension, and thyroid function. *TEP1:* Telomerase-associated protein 1; HRV: Heart rate variability; OR: Odds ratio; CI: Confidence interval.

Table 8 Association of telomerase-associated protein 1 haplotypes with heart rate variability risk using a 15% heart rate variability cutoff

TEP1 (rs938886)	*TEP1* (rs1713449)	Frequency	HRV ≥ 15% (*n* = 72)	HRV < 15% (*n* = 120)	OR (95%CI)	*P* value
G	C	0.682	92 (35.11)	170 (64.89)	1.00 (Reference)	-
C	T	0.310	50 (42.02)	69 (57.98)	1.33 (0.85-2.08)	0.22
G	T	0.008	2 (66.67)	1 (33.33)	4.13 (0.37, 46.59)	0.25

All *P* values are more than 0.05. Logistic regression analyses adjusting for age, gender, smoking, hypertension, and thyroid function. *TEP1:* Telomerase-associated protein 1; HRV: Heart rate variability; OR: Odds ratio; CI: Confidence interval.

Table 9 Best single nucleotide polymorphism-single nucleotide polymorphism interaction models identified by generalized multifactor dimensionality reduction with covariable adjustment (heart rate variability cutoff value = 30%)

Best model	Training balanced accuracy	Testing balanced accuracy	Cross-validation consistency	*P* value
rs820196	0.6116	0.6127	10/10	0.032[a]
rs938886, rs820196	0.6495	0.5782	10/10	0.151
rs938886, rs820196, rs1713449	0.6495	0.5753	10/10	0.168

[a]*P* < 0.05 means the one-locus model of RecQ like helicase 5 rs820196 is the best model for predicting heart rate variability risk.
Logistic regression analyses adjusting for age, gender, smoking, hypertension, and thyroid function.

Table 10 Association analysis of the interaction between different genotypes of single nucleotide polymorphism loci and a risk of heart rate variability cutoff value ≥ 30%

SNP genotypes			HRV ≥ 30% (*n* = 22)	HRV < 30% (*n* = 170)	OR (95%CI)	*P* value
rs938886 rs820196						
GG	TT		3 (6.67)	42 (93.33)	1.00 (Reference)	-
GG	TC		5 (14.29)	30 (85.71)	2.91 (0.63, 13.55)	0.17
GG	CC		1 (10.00)	9 (90.00)	2.19 (0.19, 25.37)	0.53
GC	TT		3 (8.11)	34 (91.89)	1.65 (0.31, 8.74)	0.56
GC	TC		9 (22.50)	31 (77.50)	6.16 (1.53, 24.83)	0.01[a]
CC	TT		1 (20.00)	4 (80.00)	5.84 (0.46, 74.57)	0.17
Others			0 (0.00)	20 (100.00)	-	-
rs938886 rs820196 rs1713449						
GG	TT	CC	3 (6.82)	41 (93.18)	1.00 (Reference)	-

GG	TC	CC	5 (14.29)	30 (85.71)	2.97 (0.64, 13.79)	0.17
GG	CC	CC	1 (10.00)	9 (90.00)	2.23 (0.19, 25.87)	0.52
GC	TT	CT	3 (8.33)	33 (91.67)	1.73 (0.33, 9.18)	0.52
GC	TC	CT	9 (22.50)	31 (77.50)	6.27 (1.56, 25.28)	0.01[b]
CC	TT	TT	1 (20.00)	4 (80.00)	5.94 (0.47, 75.98)	0.17
Others			0 (0.00)	22 (100.00)	-	-

[a]*P* < 0.05 *vs* GG-TT.
[b]*P* < 0.05 *vs* GG-TT-CC.
Logistic regression analyses adjusting for age, gender, smoking, hypertension, and thyroid function. SNP: Single nucleotide polymorphism; HRV: Heart rate variability; OR: Odds ratio; CI: Confidence interval.

Table 11 Single nucleotide polymorphism-smoking, single nucleotide polymorphism -hypertension, and single nucleotide polymorphism-thyroid function interaction models in patients with heart rate variability ≥ 30% evaluated with the generalized multifactor dimensionality reduction approach

Best model	Training balanced accuracy	Testing balanced accuracy	CVC	*P* value
SNP-smoking interaction[1]				
Smoking	0.5265	0.5135	10/10	0.263
rs820196-smoking	0.6281	0.6021	10/10	0.045[a]
rs938886-rs820196-smoking	0.6703	0.5947	8/10	0.099
SNP-hypertension interaction[2]				
Hypertension	0.5292	0.3308	10/10	0.800
rs820196-hypertension	0.6117	0.5648	10/10	0.190
rs820196-rs1713449-hypertension	0.6996	0.5063	8/10	0.426
SNP-thyroid function interaction[3]				
Thyroid function	0.5123	0.4980	10/10	0.194
rs820196-thyroid function	0.6263	0.5895	10/10	0.104
rs938886-rs820196-thyroid function	0.6665	0.5727	8/10	0.153

[a]*P* < 0.05 means rs820196-smoking two-factor model associated with HRV ≥ 30%.
[1]Adjusted for age, gender, hypertension, and thyroid function.
[2]Adjusted for age, gender, smoking, and thyroid function.
[3]Adjusted for age, gender, smoking, and hypertension.
SNP: Single nucleotide polymorphism; CVC: Cross-validation consistency.

Table 12 Analysis of interaction between rs820196 genotype and smoking in patients with heart rate variability ≥ 30% and < 30%

Smoking	rs820196 genotype	HRV ≥ 30% (*n* = 22)	HRV < 30% (*n* = 170)	OR (95%CI)	*P* value
No	TT	6 (7.89)	70 (92.11)	1.00 (Reference)	-
Yes	TT	1 (9.09)	10 (90.91)	1.47 (0.15, 14.27)	0.74
No	TC	13 (19.70)	53 (80.30)	2.91 (1.03, 8.20)	0.04[a]
Yes	TC	1 (5.26)	18 (94.74)	0.80 (0.088, 7.36)	0.85
No	CC	1 (5.88)	16 (94.12)	0.81 (0.089, 7.35)	0.85
Other		0 (0.00)	3 (100.00)	-	-

[a]*P* < 0.05 *vs* nonsmokers with the rs820196 TT.
Logistic regression analyses adjusting for age, gender, hypertension, and thyroid function. HRV: Heart rate variability; OR: Odds ratio; CI: Confidence

interval.

Table 13 Best single nucleotide polymorphism-single nucleotide polymorphism interaction models identified by generalized multifactor dimensionality reduction with covariable adjustment (heart rate variability cutoff value = 15%)

Best model	Training balanced accuracy	Testing balanced accuracy	CVC	*P* value
rs820196	0.5885	0.5920	10/10	0.039[a]
rs820196, rs1713449	0.6301	0.5798	9/10	0.052
rs938886, rs820196, rs1713449	0.6335	0.5885	10/10	0.066

[a]*P* < 0.05 means the one-locus model of RecQ like helicase 5 rs820196 is the best model for predicting heart rate variability risk.
Adjusted for age, gender, hypertension, smoking, and thyroid function. CVC: Cross-validation consistency.

Table 14 Association analysis of interactions between different genotypes of single nucleotide polymorphism loci and risk of heart rate variability ≥ 15%

SNPs genotypes			HRV ≥ 15% (*n* = 72)	HRV < 15% (*n* = 120)	OR (95%CI)	*P* value
rs820196 rs1713449						
TT	CC		12 (27.27)	32 (72.73)	1.00 (Reference)	-
TT	CT		10 (27.78)	26 (72.22)	1.03 (0.38, 2.79)	0.95
TT	TT		5 (71.43)	2 (28.57)	6.87(1.15, 41.09)	0.04[a]
TC	CC		15 (42.86)	20 (57.14)	2.07 (0.79, 5.45)	0.14
TC	CT		22 (55.00)	18 (45.00)	3.26 (1.30, 8.20)	0.01[b]
TC	TT		3 (30.00)	7 (70.00)	1.06 (0.22, 5.06)	0.94
CC	CC		2 (20.00)	8 (80.00)	0.56 (0.098, 3.21)	0.52
CC	CT		2 (25.00)	6 (75.00)	0.87 (0.15, 5.11)	0.88
CC	TT		1 (50.00)	1 (50.00)	2.90 (0.17, 50.84)	0.47
rs938886 rs1713449 rs820196						
GG	CC	TT	12 (27.27)	32 (72.73)	1.00 (Reference)	
GG	CC	TC	15 (42.86)	20 (57.14)	1.87 (0.74, 4.77)	0.19
GG	CC	CC	2 (20.00)	8 (80.00)	0.51 (0.09, 2.87)	0.45
GC	CT	TT	10 (27.78)	26 (72.22)	0.93 (0.36, 2.44)	0.89
GC	CT	TC	22 (55.00)	18 (45.00)	2.96 (1.21, 7.22)	0.02[c]
GC	CT	CC	2 (25.00)	6 (75.00)	0.79 (0.14, 4.57)	0.79
CC	TT	TT	4 (80.00)	1 (20.00)	9.71 (0.97, 96.94)	0.05
CC	TT	TC	3 (30.00)	7 (70.00)	0.98 (0.21, 4.63)	0.98
Others			2 (50.0)	2 (50.0)	-	-

[a]*P* < 0.05 *vs* TT-CC.
[b]*P* < 0.05 *vs* *TT-CC*.
[c]*P* < 0.05 *vs* GG-CC-TT. Logistic regression analyses adjusting for age, gender, smoking, hypertension, and thyroid function.
SNPs: Single nucleotide polymorphisms; HRV: Heart rate variability; OR: Odds ratio; CI: Confidence interval.

Table 15 Single nucleotide polymorphism-smoking, single nucleotide polymorphism-hypertension and SNP-thyroid function interaction models in patients with heart rate variability ≥ 15% evaluated with the generalized multifactor dimensionality reduction approach

Best model	Training balanced accuracy	Testing balanced accuracy	CVC	*P* value

SNP-smoking interaction[1]				
Smoking	0.5191	0.5171	10/10	0.349
rs820196-smoking	0.6148	0.5954	10/10	0.022[a]
rs820196-rs1713449-smoking	0.6510	0.5764	9/10	0.065
SNP-hypertension interaction[2]				
Hypertension	0.5156	0.3564	10/10	0.995
rs820196-hypertension	0.5885	0.5920	10/10	0.043[b]
rs820196-rs1713449-hypertension	0.6434	0.5343	9/10	0.219
SNP-thyroid function interaction[3]				
Thyroid function	0.5126	0.5113	10/10	0.381
rs820196-thyroid function	0.5888	0.5814	10/10	0.065
rs820196-rs1713449-thyroid function	0.6411	0.5706	9/10	0.075

[a]$P < 0.05$ means rs820196-smoking two-factor model associated with Heart rate variability (HRV) ≥ 15%.
[b]$P < 0.05$ means rs820196-hypertension two-factor model associated with HRV ≥ 15%.
[1]Adjusted for age, gender, hypertension, and thyroid function.
[2]Adjusted for age, gender, smoking, and thyroid function.
[3]Adjusted for age, gender, smoking, and hypertension.
SNP: Single nucleotide polymorphism; CVC: Cross-validation consistency.

Table 16 Analysis of interaction between rs820196 genotype and smoking and hypertension in patients with heart rate variability ≥ 15% and < 15%

Environment	rs820196 genotype	HRV ≥ 15% (*n* = 72)	HRV < 15% (*n* = 120)	OR (95%CI)	*P* value
Smoking					
No	TT	22 (28.95)	54 (71.05)	1.00 (Reference)	-
Yes	TT	5 (45.45)	6 (54.55)	2.12 (0.57, 7.95)	0.26
No	TC	33 (50.00)	33 (50.00)	2.53 (1.26, 5.08)	0.01[a]
Yes	TC	7 (36.84)	12 (63.16)	1.43 (0.48, 4.22)	0.52
No	CC	3 (17.65)	14 (82.35)	0.48 (0.12, 1.89)	0.30
Yes	CC	2 (66.67)	1 (33.33)	4.68 (0.39, 56.33)	0.22
Hypertension					
No	TT	18 (32.73)	37 (67.27)	1.00 (Reference)	-
Yes	TT	9 (28.13)	23 (71.88)	0.77 (0.28, 2.11)	0.62
No	TC	25 (46.30)	29 (53.70)	1.75 (0.80, 3.82)	0.16
Yes	TC	15 (48.39)	16 (51.61)	1.90 (0.75, 4.78)	0.18
No	CC	3 (23.08)	10 (76.92)	0.58 (0.14, 2.42)	0.45
Yes	CC	2 (28.57)	5 (71.43)	0.72 (0.12, 4.26)	0.72

[a]$P < 0.05$ *vs* nonsmokers with the rs820196 TT.
Logistic regression analyses adjusting for age, gender, and thyroid function. HRV: Heart rate variability; OR: Odds ratio; CI: Confidence interval.

In this study, patients with gastric cancer were divided into two groups according to two different cutoffs for HRV: 30% and 15%. There were no significant differences in gender, age, smoking history, hypertension, diabetes, blood type, and thyroid function between the two groups regardless of the cutoff used, indicating that these factors had no effect on HRV. The distribution of the *RECQL5* (rs820196) genotype frequency in patients with HRV ≥ 15% differed from that in the control group. The relationships between these SNPs and HRV risk were evaluated by the inheritance models. Under the co-dominant and overdominant models, the TC genotype was associated with a higher risk of HR decrease relative to the TT and TT + CC genotypes.

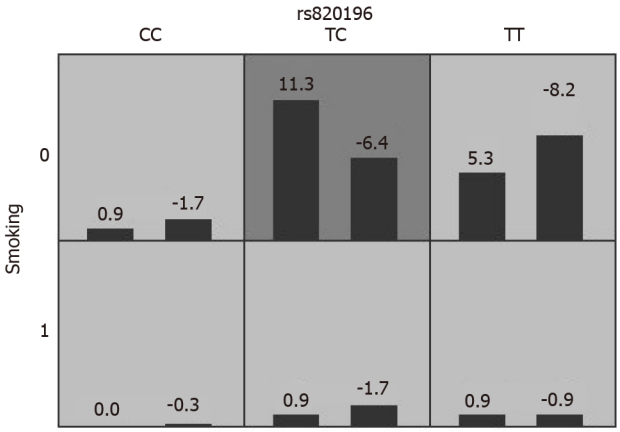

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Figure 4 Interaction between rs820196 and smoking in patients grouped by the 30% heart rate variability cutoff. For each multifactor cell, the score of patients with heart rate variability (HRV) ≥ 30% is displayed on the left bar and the score of patients with HRV < 30% is displayed on the right bar. The high-risk interaction genotype was assigned as one and the low-risk interaction genotype was assigned as zero in the multivariable logistic regression analyses. Dark gray cells indicate high-risk combinations and light gray cells indicate low-risk combinations. No smoking = 0; smoking = 1.

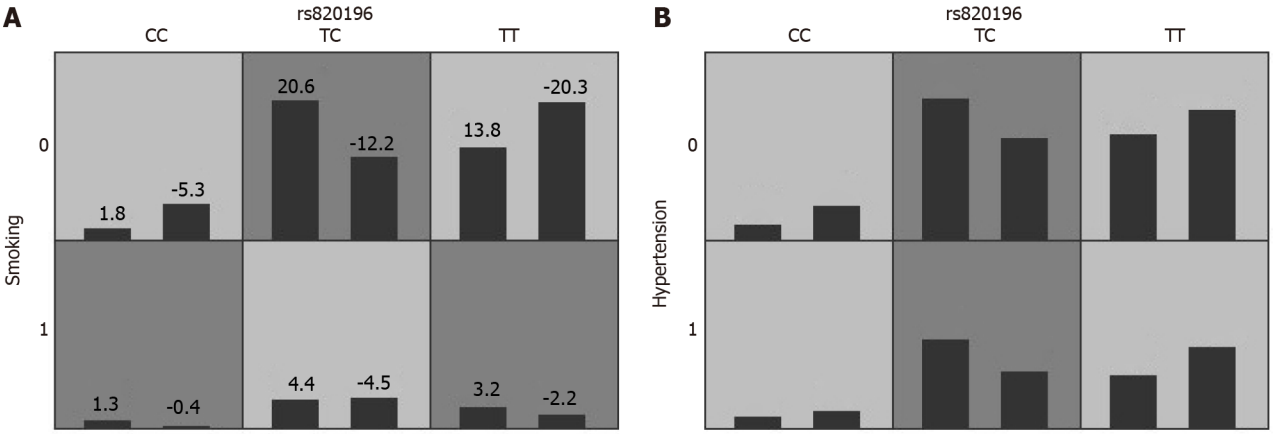

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Figure 5 Interaction between rs820196 and smoking and hypertension in patients grouped by the 15% heart rate variability cutoff. A: Rs820196-smoking interaction. No smoking = 0; smoking = 1; B: Rs820196-hypertension interaction. No hypertension = 0; hypertension = 1. For each multifactor cell, the score of patients with heart rate variability (HRV) ≥ 15% is displayed on the left bar and the score of patients with HRV < 15% is displayed on the right bar. The high-risk interaction genotype was assigned as 1 and the low-risk interaction genotype was assigned as 0 in multivariable logistic regression analyses. Dark gray cells indicate high-risk combinations, and light gray cells indicate low-risk combinations.

TEP1 is a component of the telomerase ribonucleoprotein complex, and is responsible for catalyzing the addition of new synthetic telomere sequences to chromosome ends[22]. Genetic variations in telomere-associated pathway genes might affect telomere length and chromosomal stability, and subsequently disease susceptibility. In this study, the LD analysis showed that *TEP1* rs938886 and *TEP1* rs1713449 had a strong linkage relationship. Unexpectedly, there were no differences among the three haplotypes ($P > 0.05$).

GMDR is a novel and powerful statistical tool for detecting and modeling epistasis. It is a non-parametric and model-free alternative to logistic regression for detecting and characterizing non-linear interactions among discrete genetic and environmental attributes[23]. It is mainly used to detect gene-gene and gene-environment interactions underlying complex traits in epidemiological and genetic research. In this study, after adjusting for a multitude of covariates, we found that the best one-factor model was rs820196, whether the HRV cutoff was 30% or 15%. Logistic regression analysis was performed for better risk assessment. When the HRV cutoff value was 30%, there was a significant gene–gene interaction between rs938886 and rs820196. The subjects carrying the GC-TC genotypes of rs938886 and rs820196 showed a higher HRV risk when compared with the GG-TT genotype carriers. In the three-factor model of rs938886, rs820196, and rs1713449, the patients carrying the GC-TC-CT genotype had a higher risk of HRV compared with the GG-TT-CC wild-type genotype. We also found a potential gene-environment interaction between rs820196 and smoking, such that the nonsmokers carrying the TC genotype of rs820196 had a higher HRV risk compared with the nonsmokers carrying the TT genotype. When the HRV cutoff was 15%, patients carrying the TT-TT and TC-CT genotypes of rs820196 and rs1713449 showed a higher HRV risk when compared with the TT-CC genotype carriers. Patients carrying the GC-CT-TC genotypes of rs938886, rs1713449, and rs820196 showed a higher HRV risk when compared with the GG-CC-TT genotype carriers.

When the HRV cutoff was 15%, the best-fitting models for SNP-environment interactions were rs820196-smoking and rs820196-hypertension. Consistent with the results of the previous grouping, the nonsmokers carrying the TC genotype of rs820196 had a higher HRV risk compared with the nonsmokers carrying the TT genotype.

Although several positive associations were observed, some limitations of this study should be considered. First, the sample size was small, with only 192 patients being enrolled. Second, all the participants were recruited from the same hospital; hence, inherent selection bias was unavoidable. Third, was the prognosis of patients with high HRV poorer than that of those with low HRV? Did the patients with high HRV ever have arrhythmias in daily life? These questions need to be investigated. Given these limitations, further studies with larger sample sizes and more comprehensive clinical information will be required to confirm our findings.

This study on *RECQL5* and *TEP1* genetic polymorphisms may help uncover the underlying mechanisms of arrhythmia phenotypic variation. The 2D PCR used in this study helped to screen the three SNP loci more quickly and economically. In the future, when performing tumor resection and peritoneal lavage with distilled water, we suggest anesthesiologists assess the risk of sudden HR drop based on the genetic polymorphisms of *RECQL5* (rs820196) and *TEP1* (rs938886 and rs1713449), and medical history. If patients are at high risk and the baseline HR is < 40 beats/min, vasopressors such as norepinephrine, epinephrine, dopamine, and phenylephrine will be recommended before surgery. During the perioperative period, all patients are routinely monitored for arterial blood pressure by electrocardiography. An anesthetic machine is used to support breathing and monitor end-expiratory carbon dioxide partial pressure. Once the HR decreases by 30% or < 40 beats/min after lavage, vasopressors should be used immediately. If cardiac arrest occurs, cardiac compression should be performed immediately, so that the heartbeat pause time is strictly limited to 1 min. Extensive peritoneal lavage with warm distilled water is widely used in surgery for breast cancer, lung cancer and gastrointestinal cancer. The purpose of this study was to screen high-risk groups through the SNP detection of high-risk genes, and focus on improving safety during the perioperative period.

CONCLUSION

In conclusion, our results showed, for the first time, that polymorphisms of the *RECQL5* and *TEP1* genes were associated with sudden decreases in HR during abdominal lavage in patients with gastric cancer. Nonsmokers carrying the TC genotype of rs820196 and the GC-CT-TC genotype carriers of rs938886, rs1713449 and rs820196 were found to have a higher HRV risk.

ARTICLE HIGHLIGHTS

Research background

Peritoneal lavage with distilled water to kill residual tumor cells is a routine procedure in gastrectomy, but this procedure often causes a sudden decrease in heart rate (HR) in some patients.

Research motivation

To investigate whether there are differences in genetic background between patients with discordant HR changes and help clinicians to better assess the perioperative risk of patients undergoing gastrectomy.

Research objectives

To investigate whether genotypes, genetic patterns, single nucleotide polymorphism (SNP)-SNP and SNP-environment interactions were associated with high heart rate variability (HRV).

Research methods

A total of 192 patients who underwent distal gastrectomy were divided into two groups according to changes in HR (using 30% and 15% as cutoffs). Two-dimensional polymerase chain reaction was used to establish a single-tube method to detect telomerase-associated protein 1 (*TEP1*) rs938886 and rs1713449 and RecQ like helicase 5 (*RECQL5*) rs820196. Genotypes, genetic patterns and the interaction of SNP-SNP and SNP-environment were analyzed by non-conditional logistic regression model and generalized multifactor dimensionality reduction.

Research results

The polymorphism of the *RECQL5* gene (rs820196) was associated with a sudden decrease in HR during abdominal lavage in patients with gastric cancer. Rs820196-smoking and rs820196-hypertension were associated with HRV ≥ 15%. Nonsmokers carrying the TC genotype of rs820196 and patients carrying the GC-CT-TC genotype of rs938886, rs1713449 and rs820196 had higher HRV risk.

Research conclusions

The polymorphisms of *RECQL5* (TC genotype of rs820196) and *TEP1* (GC-CT genotype of rs938886 and rs1713449) genes were associated with HRV.

Research perspectives

HRV risk assessment in patients who are about to undergo peritoneal lavage is helpful for perioperative safety. This cost-effective SNP screening method can be extended to other patients undergoing tumor resection (such as breast cancer, lung cancer and other gastrointestinal cancer) and multicenter studies.

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FOOTNOTES

Author contributions: Luo GH designed the research study; Yao S and Yuan Y wrote the manuscript; Yao S, Zhang J and Yu Y performed the experiments and analyzed the data; All authors have read and approved the final manuscript.

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

Informed consent statement: As the study used anonymous and pre-existing data, the requirement for the informed consent from patients was waived.

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

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ORIGINAL ARTICLE

Retrospective Study

Analgesic effect of ultrasound-guided bilateral transversus abdominis plane block in laparoscopic gastric cancer

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Abstract

BACKGROUND

Postoperative complications are important factors affecting the survival time and quality of life of patients undergoing radical gastrectomy.

AIM

To investigate and compare the anesthetic effects of intravenous general anesthesia combined with epidural anesthesia or ultrasound-guided bilateral transversus abdominal plane block (TAPB) in gastric cancer patients undergoing laparoscopic radical gastrectomy.

METHODS

The clinical data of 85 patients who underwent laparoscopic radical gastrectomy in our hospital from December 2020 to January 2023 were retrospectively collected and divided into a TAPB group (n = 45) and epidural anesthesia group (n = 40) according to the different anesthesia and analgesia programs used. The TAPB group received general anesthesia combined with TAPB, and the epidural anesthesia group received general anesthesia combined with epidural anesthesia. The pain status, cognitive status, intestinal barrier indicators, recovery quality, and incidence of complications were compared between the two groups.

RESULTS

Compared with the epidural anesthesia group, the TAPB group's visual analog scale scores were significantly lower 6 h, 12 h, 24 h and 48 h after surgery (P < 0.05). The incidence of postoperative cognitive dysfunction (POCD) in the TAPB group was significantly lower than that in the epidural anesthesia group, and the Mini-mental State Examination score 24 h after surgery was significantly higher in the TAPB group than the epidural anesthesia group (P < 0.05). The levels of diamine oxidase and plasma D-lactate were significantly lower in the TAPB group than the epidural anesthesia group 24 h after surgery (P < 0.05). The agitation score and the incidence of agitation during recovery were significantly lower in

the TAPB group than epidural anesthesia group ($P < 0.05$). The total incidence of postoperative complications in the TAPB group was 4.44%, significantly lower than the 20.00% in the epidural anesthesia group ($P < 0.05$).

CONCLUSION

Compared with epidural anesthesia combined with general anesthesia, TAPB combined with general anesthesia had a good analgesic effect in laparoscopic radical gastrectomy and can further reduce the incidence of POCD and postoperative complications, improve the levels of intestinal barrier indicators, and improve postoperative recovery quality.

Key Words: Laparoscopic radical gastrectomy; Ultrasound-guided bilateral transversus abdominal plane block; Cognitive impairment; Intestinal barrier function

Core Tip: As an important part of surgical treatment, anesthesia significantly impacts the incidence of postoperative complications. In this study, the anesthetic effects of intravenous general anesthesia combined with epidural anesthesia or ultrasound-guided bilateral transversus abdominal plane block (TAPB) in patients with laparoscopic gastric cancer were compared. The results showed that, compared with epidural anesthesia combined with general anesthesia, TAPB combined with general anesthesia had better analgesic effects in laparoscopic gastric cancer surgery and could further reduce the incidence of postoperative cognitive dysfunction and postoperative complications, improve the levels of intestinal barrier index, and improve the quality of postoperative recovery.

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INTRODUCTION

Gastric cancer is the fifth most common malignant tumor in the world. According to incomplete statistics[1], the incidence of gastric diseases in China increases as the average population age increases. As the early symptoms of gastric cancer are not specific, it is mostly clinically diagnosed in the middle and late stages, and surgery is the main method of clinical treatment. Compared with traditional open surgery, laparoscopic radical gastrectomy causes less surgical trauma to patients and has a clearer intraoperative field of vision, which helps operators to perform more detailed lymph node dissection. Therefore, laparoscopic radical gastrectomy has become a standard surgical method for the treatment of some early and advanced gastric cancer patients[2]. Previous studies have shown that[3] postoperative complications are important factors affecting the survival time and quality of life of patients undergoing radical gastrectomy. Furthermore, anesthesia, as an important part of surgical treatment, significantly impacts the incidence of postoperative complications. In recent years, general anesthesia combined with epidural anesthesia has been applied in laparoscopic surgery with good analgesic effects[4], effectively reducing the need for single opioid drugs. Ultrasound-guided bilateral transversus abdominal plane block (TAPB) provides analgesic effects by injecting a local anesthetic into the plane between the internal oblique and transversal abdominal muscles under the guidance of ultrasound, thus blocking sensory nerves that pass through this plane. With the advantages of fast onset and a good analgesic effect, TAPB has been widely used for auxiliary anesthesia and postoperative analgesia in patients undergoing abdominal surgery[5,6]. At present, there are few relevant literature reports comparing the application effects of epidural anesthesia and TAPB in laparoscopic radical gastrectomy. This study mainly analyzed and compared the effects of epidural anesthesia and TAPB on postoperative cognitive dysfunction (POCD), intestinal barrier function, and postoperative recovery quality in gastric cancer patients undergoing laparoscopic radical gastrectomy to provide a reference for the clinical selection of appropriate anesthesia programs.

MATERIALS AND METHODS

Clinical data

A retrospective study was conducted on the clinical data of 85 patients who underwent laparoscopic radical gastrectomy in our hospital from December 2020 to January 2023. Inclusion criteria: Patients undergoing elective laparoscopic radical gastrectomy, patients aged 18-65 years old, patients with grade I to II according to the American Society of Anesthesiologists (ASA), patients with a body mass index (BMI) of 18-24 kg/m^2, patients undergoing primary surgery, patients who received TAPB or epidural anesthesia, and patients with complete clinical data. Exclusion criteria: A history of

analgesic drug abuse, history of abnormal blood coagulation and chronic pain, infection at the puncture site, peripheral neuropathy, and incomplete clinical data. Eighty-five patients were divided into the TAPB group (n = 45) and epidural anesthesia group (n = 40) according to the different anesthesia and analgesia programs they received.

Anesthesia methods

All patients were forbidden to drink and eat for 8 h before surgery, and no drugs were used before the operation. Noninvasive blood pressure, electrocardiogram, oxygen saturation, and double-frequency index (BIS) were monitored after entering the operation room. Peripheral venous access was opened, and radial artery puncture and right internal jugular vein puncture and catheterization were conducted under local anesthesia.

Anesthesia methods for patients in the epidural anesthesia group were as follows: Before general anesthesia induction, the anesthesiologist conducted an epidural puncture and catheterization between T8 and T9 of the patients and adopted the posterior median approach. The oblique angle of the puncture needle was placed longitudinally parallel to the dural fibers, and the needle was slowly advanced. Advancement of the puncture needle was stopped when there was a characteristic resistance change when passing through the ligamentum flavum and dura mater. After cerebrospinal fluid was seen to flow out smoothly, excluding the possibility that the catheter entered the spinal canal and simultaneously verifying the location of the anesthesia plane and epidural catheter, 5 mL of 2% lidocaine was injected; then 4-6 mL of 1% ropivacaine was injected. Anesthesia induction was performed when the patient's vital signs were stable. The anesthesia induction method was as follows: 0.3-0.4 μg/kg sufentanil, 2 mg/kg propofol, 0.6 mg/kg rocuronium, and 0.5 μg/kg dextrometomidine were used for anesthesia induction, and tracheal intubation was performed after successful induction. For anesthesia maintenance, 4-10 mg/kg/h propofol was used for target-controlled infusion, and the BIS was maintained between 40 and 60. During the surgery, 1% ropivacaine (4-6 mL/h) was administered through an epidural catheter according to the patient's condition, and 0.1 mg/kg/h cisatracurium was intermittently administered to maintain the neuromuscular block. After pneumoperitoneum was stopped, the use of muscle relaxants was stopped, and the tracheal intubation was removed after reaching the indication for extubation. A patient-controlled intravenous analgesia (PCIA) pump was used after surgery. The drug formula for the injection was 100 μg sufentanil, 4.48 mg tropisetron, and sodium chloride diluted to 100 mL. The parameters were set to 2 mL/h, a single compression dose of 2 mL, and a locking time of 20 min.

The following anesthesia method for patients in the TAPB group was applied. Before general anesthesia induction, the anesthesiologist placed the ultrasonic probe vertically on the anterior axillary line between the patient's iliac crest and costal margin, and identified the structures of the external oblique, internal oblique, transversal, and peritoneum of the abdomen. Using in-plane technology, a 20G puncture needle was placed in the middle of the transversus abdominis muscle and the internal oblique muscle of the abdomen. After no blood or air bubbles were extracted, 1 mL of sodium chloride was injected using water separation technology to prove that the needle tip was located at the transversus abdominal plane. Then 0.375% ropivacaine and 0.75 μg/kg dexmedetomidine were injected at a uniform rate, using 20 mL on each side. Anesthesia induction was performed after the block was completed. The methods of anesthesia induction and maintenance were the same as those of the epidural anesthesia group.

Observation indicators

(1) The general data of the two groups were compared; (2) The visual analog scale (VAS) was used to evaluate the degree of pain felt 6 h, 12 h, 24 h, and 48 h after surgery, with the score ranging from 0 to 10 points. The higher the score, the more severe the pain; (3) The occurrence of POCD 24 h and 72 h after surgery was recorded and compared between the two groups. The Mini-mental State Examination (MMSE) was used to evaluate the cognitive status of the two groups before and after surgery. A score of < 27 points indicated cognitive impairment, and the higher the score, the better the cognitive function; (4) Intestinal barrier function indexes, including diamine oxidase (DAO) and plasma D-lactate (D-LA), for the two groups were compared before and 24 h after surgery; (5) The agitation score and the incidence of agitation of the two groups during the recovery period were recorded and compared. An agitation score of 1 point indicated an inability to wake up, 2 points indicated excessive sedation, 3 points indicated sedation, 4 points indicated sedation and cooperation, 5 points indicated agitation with stimulation, 6 points indicated agitation without stimulation, 7 points indicated severe agitation, and 5 to 7 points indicated agitation during the awakening period; and (6) Postoperative complications were compared between the two groups.

Statistical analysis

The data obtained were analyzed and processed by SPSS23.0 software. Measurement data conforming to a normal distribution were expressed as the mean ± SD and were compared by t test. Count data were expressed as cases or percentages, and the chi-square test was used for comparison. $P < 0.05$ was considered to be statistically significant.

RESULTS

Comparison of general data between two groups

There were no statistically significant differences in sex, age, BMI, ASA grade, operation time, or intraoperative bleeding between the two groups ($P > 0.05$), as shown in Table 1.

Table 1 Comparison of general data between two groups

Group	Gender (male/female)	Age (yr, mean ± SD)	BMI (kg/m², mean ± SD)	ASA grade (I/II)	Operation time (min, mean ± SD)	Intraoperative bleeding (mL, mean ± SD)	Sufentanil consumption (μg, mean ± SD)
TAPB group (n = 45)	25/20	59.56 ± 6.82	23.08 ± 0.58	23/22	148.52 ± 22.63	135.81 ± 22.56	25.36 ± 4.88
Epidural anesthesia group (n = 40)	23/17	59.08 ± 6.94	22.84 ± 0.65	21/19	150.97 ± 20.51	136.44 ± 22.79	27.12 ± 4.15
Statistical value	0.033	0.321	1.799	0.017	0.521	0.128	1.779
P value	0.857	0.749	0.076	0.898	0.604	0.899	0.079

BMI: Body mass index; ASA: American Society of Anesthesiologists; SD: Standard deviation; TAPB: Transversus abdominal plane block.

Comparison of VAS scores between two groups

Compared with the epidural anesthesia group, TAPB group patients' VAS scores were significantly lower 6 h, 12 h, 24 h, and 48 h after surgery ($P < 0.05$), as shown in Table 2.

Comparison of cognitive function between two groups

There was no statistically significant difference in MMSE scores between the two groups before surgery ($P > 0.05$). The incidence of POCD in the TAPB group was significantly lower than that in the epidural anesthesia group, and the MMSE score was significantly higher in the TAPB group than the epidural anesthesia group 24 h after surgery ($P < 0.05$), as shown in Table 3.

Comparison of intestinal barrier function indicators between two groups

There were no statistically significant differences in the preoperative DAO or D-LA levels of the two groups ($P > 0.05$). The DAO and D-LA levels 24 h after surgery in the TAPB group were significantly lower than those in the epidural anesthesia group ($P < 0.05$), as shown in Table 4.

Comparison of postoperative recovery quality between two groups

The agitation score of the TAPB group was significantly lower than that of the epidural anesthesia group, and the incidence of agitation in the TAPB group was significantly lower than that of the epidural anesthesia group during the recovery period ($P < 0.05$), as shown in Table 5.

Comparison of postoperative complication rates between two groups

The total incidence of postoperative complications in the TAPB group was 4.44%, significantly lower than the 20.00% recorded in the epidural anesthesia group ($P < 0.05$), as shown in Table 6.

DISCUSSION

With the promotion and application of the concept of enhanced recovery after surgery in clinical practice in recent years, methods to reduce the incidence of complications, shorten the length of the hospital stay, and accelerate the recovery of patients after laparoscopic gastric cancer surgery have gradually become hot spots and the focus of clinical attention[7]. More and more anesthesia guidelines recommend the use of multi-mode analgesia programs in laparoscopic surgery. Multi-mode analgesia programs prevent the introduction of pain stimuli from various sources by using analgesic techniques and drugs with different mechanisms to block the transmission of pain signals and improve the postoperative recovery of patients[8,9]. Although PCIA can rapidly control breakthrough pain through impact doses in laparoscopic surgery, the opioids used tend to cause adverse reactions such as nausea, vomiting, and respiratory depression[10], which are not conducive to the postoperative recovery of patients and can affect the length of the patients' hospital stay. Therefore, it is of great significance to patient recovery and comfort to optimize anesthesia and analgesia programs.

Epidural anesthesia combined with general anesthesia is a commonly used anesthesia and analgesia program for abdominal surgery. However, studies have revealed[11] that epidural anesthesia has a failure rate of about 7%. It is also difficult to implement and requires a high level of clinical experience and operational skill in anesthesiologists. In recent years, the application of ultrasound technology in the clinical work of anesthesiology departments has been increasing, which promotes the clinical application of TAPB to a certain extent. Ultrasound-assisted visual operation makes TAPB a simple, safe, and effective local nerve block technique. Most studies[12,13] have shown that TAPB has a good blocking effect in abdominal surgery and can effectively reduce postoperative pain, reduce the dosage of analgesic drugs needed, and reduce inflammation. In a comparison of the anesthetic effects of TAPB and epidural anesthesia in laparoscopic radical gastrectomy, the VAS scores of patients in the TAPB group 6 h, 12 h, 24 h, and 48 h after surgery were significantly lower that lose in the epidural anesthesia group ($P < 0.05$), indicating that TAPB could further relieve the

Table 2 Comparison of visual analog scale scores between two groups (points, mean ± SD)

Group	6 h after surgery	12 h after surgery	24 h after surgery	48 h after surgery
TAPB group (n = 45)	2.53 ± 0.44	2.31 ± 0.39	2.01 ± 0.31	1.32 ± 0.29
Epidural anesthesia group (n = 40)	2.78 ± 0.39	2.69 ± 0.45	2.55 ± 0.37	1.92 ± 0.36
t value	2.757	4.171	7.319	8.501
P value	0.007	< 0.001	< 0.001	< 0.001

SD: Standard deviation; TAPB: Transversus abdominal plane block.

Table 3 Comparison of cognitive function between two groups

Group	Incidence of POCD, n (%)	MMSE score	
		Before surgery	24 h after surgery
TAPB group (n = 45)	2 (4.44)	27.94 ± 0.78	25.63 ± 1.25
Epidural anesthesia group (n = 40)	9 (22.50)	27.82 ± 0.84	24.45 ± 2.97
Statistical value	6.128	0.683	2.435
P value	0.013	0.497	0.017

TAPB: Transversus abdominal plane block; POCD: Postoperative cognitive dysfunction; MMSE: Mini-mental State Examination.

Table 4 Comparison of intestinal barrier function indicators between two groups (mg/L, mean ± SD)

Group	DAO		D-LA	
	Before surgery	24 h after surgery	Before surgery	24 h after surgery
TAPB group (n = 45)	4.64 ± 0.85	3.17 ± 0.72	5.28 ± 0.67	4.21 ± 0.44
Epidural anesthesia group (n = 40)	4.52 ± 0.91	3.85 ± 0.64	5.09 ± 0.78	4.63 ± 0.32
t value	0.628	4.578	1.208	4.978
P value	0.531	< 0.001	0.230	< 0.001

SD: Standard deviation; TAPB: Transversus abdominal plane block; DAO: Diamine oxidase; D-LA: D-lactate.

Table 5 Comparison of postoperative recovery quality between two groups

Group	Agitation score	Incidence of agitation during the recovery period, n (%)
TAPB group (n = 45)	4.21 ± 0.85	0 (0.00)
Epidural anesthesia group (n = 40)	5.08 ± 0.66	5 (12.50)
Statistical value	5.222	5.977
P value	< 0.001	0.015

TAPB: Transversus abdominal plane block.

postoperative pain of patients with gastric cancer. The reason for this is speculated to be because TAPB alleviates peripheral and central pain sensitization by inhibiting nociceptive stimuli such as skin incision and separation, helping to relieve pain. In addition, the 0.375% ropivacaine selected in this study can effectively guarantee the effectiveness and safety of TAPB in ultrasound-guided bilateral TAPB and meet the needs of analgesic plane.

POCD is one of the most common complications in patients who have undergone laparoscopic gastric cancer surgery and is related to many factors, such as age, underlying disease, surgical and anesthesia methods, and surgical time. Anesthetic drugs can act on multiple targets in the brain, thereby affecting brain function, and the choice of drug is an important factor leading to postoperative POCD in patients[14]. MMSE is a commonly used scale for evaluating cognitive

Table 6 Comparison of postoperative complication rates between two groups

Group	Nausea and vomiting (cases)	Respiratory depression (cases)	Hypotension (cases)	Total incidence rate (%)
TAPB group (n = 45)	2	0	0	4.44
Epidural anesthesia group (n = 40)	5	0	3	20.00
χ^2 value				4.936
P value				0.026

TAPB: Transversus abdominal plane block.

function in clinical practice. The results of this study showed that the incidence of POCD in the TAPB group was significantly lower than that in the epidural anesthesia group, and the MMSE score 24 h after surgery was significantly higher in the TAPB group than the epidural anesthesia group ($P < 0.05$). The results indicated that, compared with epidural anesthesia, TAPB improved the cognitive function of patients. It was speculated that TAPB allows anesthesiologists to observe the diffusion of anesthetic drugs and the degree of anesthesia through ultrasonic visualization, properly control the dosage of anesthetic drugs, effectively reduce the degree of damage to the nervous system, and thus reduce the incidence of postoperative POCD.

In the results of this study, the levels of DAO and D-LA in the TAPB group were significantly lower than those in the epidural anesthesia group 24 h after surgery ($P < 0.05$), indicating that compared to epidural anesthesia, TAPB can help improve the postoperative intestinal barrier index levels of patients and promote intestinal peristalsis. A possible reason for this may be that opioid drugs inhibit gastrointestinal function by activating the u and k receptors distributed in the gastrointestinal tract. Previous studies[15,16] have found evidence that opioids can lead to intestinal peristalsis disorders and even constipation. TAPB reduces the need to use opioids during the perioperative period; alleviates the adverse symptoms caused by opioids, such as nausea, vomiting, and decreased intestinal motility; promotes intestinal peristalsis; and improves the levels of intestinal barrier indicators in patients[17]. In addition, this study showed that the agitation score, the incidence of agitation during recovery, and the total incidence of postoperative complications were significantly lower in the TAPB group than the epidural anesthesia group ($P < 0.05$), further confirming the benefits of TAPB in improving the postoperative recovery quality of patients and reducing incidences of postoperative complications.

CONCLUSION

In summary, compared to the scheme of epidural anesthesia combined with general anesthesia, TAPB combined with general anesthesia has a good analgesic effect in laparoscopic gastric cancer surgery. It can reduce the incidence of POCD and postoperative complications, improve the level of intestinal barrier indicators, and improve postoperative recovery quality, and thus is worthy of clinical promotion and application. There were some limitations in this study. As it was a single-center retrospective study, there was no blank control group. It is hoped that the sample size can be further expanded in the future to analyze the effect of ultrasound-guided bilateral transversus abdominis plane block on the expected prognosis of patients with laparoscopic gastric cancer.

ARTICLE HIGHLIGHTS

Research background

Postoperative complications are important factors affecting the survival time and quality of life of patients undergoing radical gastrectomy. Choosing an ideal anesthesia and analgesia program is of great significance for ensuring good surgical effect and reducing the incidence of postoperative complications. Although patient-controlled intravenous analgesia (PCIA) can control the outbreak of pain in time, opioids can easily cause adverse reactions such as nausea, vomiting, and respiratory depression. Epidural anesthesia combined with general anesthesia is commonly used in abdominal surgery, and ultrasound-guided transversus abdominal plane block (TAPB) is also effective in reducing postoperative pain and reducing the amount of analgesic drugs required. At present, there are few reports on the application of these two schemes in radical gastrectomy.

Research motivation

PCIA has been the most frequently used analgesic regimen in laparoscopic surgery in the past. Although it can control the outbreak of pain in time through the impact dose, the opioids used can easily cause adverse reactions, such as nausea, vomiting, and respiratory depression, which are not conducive to the postoperative rehabilitation of patients. It is thus necessary to optimize the anesthesia and analgesia program. By comparing the effects of epidural anesthesia and TAPB

on the incidence of postoperative cognitive dysfunction (POCD), intestinal barrier function, and postoperative recovery quality in patients with laparoscopic gastric cancer, we can gather data that should be helpful when choosing the most suitable anesthesia and analgesia scheme for clinical practice.

Research objectives

The main goal was to select a more appropriate surgical anesthesia/analgesia program for patients with gastric cancer. Multimodal analgesia can prevent the introduction of pain stimulation from many sources and thereby block the transmission of pain signals and improve postoperative rehabilitation. By comparing the effects of epidural anesthesia and TAPB on postoperative recovery quality and complications in patients with laparoscopic gastric cancer, we may find ways to reduce the need to apply opioids during perioperative period and accelerate postoperative rehabilitation.

Research methods

This was a retrospective study in which differences in postoperative pain, cognitive function, intestinal barrier function index, and incidences of agitation were observed between an epidural anesthesia group and an ultrasound-guided bilateral transversus abdominis plane block group. Cognitive dysfunction is one of the most common complications in patients undergoing laparoscopic gastric cancer surgery, and intestinal barrier function is an important indicator affecting postoperative intestinal peristalsis and recovery speed. By observing these indicators, we can obtain good reference data for future research.

Research results

Compared with patients in the epidural anesthesia group, patients in the ultrasound-guided TAPB group had less postoperative pain; significantly lower incidences of cognitive dysfunction, emergence agitation, and postoperative complications; and greater improvements in intestinal barrier function. The differences in the above indicators were statistically significant. However, the effects of the two anesthesia methods on the intraoperative vital signs of patients need to be further explored.

Research conclusions

In contrast to previous studies, this study used retrospective analysis to explore and compare the effects of epidural anesthesia and TAPB on cognitive dysfunction, intestinal barrier function, and postoperative recovery quality in patients with laparoscopic gastric cancer. It was concluded that, compared with epidural anesthesia combined with general anesthesia, TAPB combined with general anesthesia had a good analgesic effect in laparoscopic gastric cancer surgery patients. TAPB combined with general anesthesia helped to reduce the incidence of postoperative cognitive dysfunction, and the emergence agitation and concurrent tension, and had a good effect on improving the quality of postoperative recovery.

Research perspectives

Because this study was a retrospective analysis, the effects of the two anesthesia/analgesia regimens on the vital signs of a large sample of patients with gastric cancer needs to be analyzed in a prospective study.

FOOTNOTES

Author contributions: Wang YY initiated the project and designed the experiment, wrote the original manuscript, performed postoperative follow-up, and recorded data; Fu HJ conducted a number of collations, conducted clinical data collection and statistical analysis, and revised the paper; both authors have read and approved the final manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of Shaanxi Provincial People's Hospital, and the Ethics Committee also agreed to waive the requirement for informed consent.

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ORIGINAL ARTICLE

Retrospective Study

Effects of an Omaha System-based follow-up regimen on self-care and quality of life in gastrointestinal surgery patients

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Abstract

BACKGROUND

Currently, a variety of new nursing methods and routine nursing have been widely used in the nursing of gastrointestinal surgery patients.

AIM

To investigate the effect of follow-up protocol based on the Omaha System on self-care ability and quality of life of gastrointestinal surgery patients.

METHODS

A total of 128 patients with inflammatory bowel disease in gastrointestinal surgery in gastrointestinal surgery from March 2019 to August 2021 were divided into A (n = 64) and B (n = 64) groups according to different nursing methods. The group A received a follow-up program Omaha System-based intervention of the group B, whereas the group B received the routine nursing intervention. Medical Coping Modes Questionnaire, Crohn's and Colitis Knowledge Score (CCKNOW), inflammatory bowel disease questionnaire (IBDQ), Exercise of Self-nursing Agency Scale (ESCA), The Modified Mayo Endoscopic Score, and Beliefs about Medicine Questionnaire (BMQ) were compared between the two groups.

RESULTS

Following the intervention, the group A were facing score significantly increased

than group B, while the avoidance and yield scores dropped below of group B (all $P < 0.05$); in group A, the level of health knowledge, personal care abilities, self-perception, self-awareness score and ESCA total score were more outstanding than group B (all $P < 0.05$); in group A the frequency of defecation, hematochezia, endoscopic performance, the total evaluation score by physicians and the disease activity were lower than group B (all $P < 0.05$); in the group A, the total scores of knowledge in general, diet, drug, and complication and CCKNOW were higher than group B (all $P < 0.05$); in group A, the necessity of taking medicine, score of medicine concern and over-all score of BMQ were more significant than group B (all $P < 0.05$); at last in the group A, the scores of systemic and intestinal symptoms, social and emotional function, and IBDQ in the group A were higher than group B (all $P < 0.05$).

CONCLUSION

For gastrointestinal surgery patients, the Omaha System-based sequel protocol can improve disease awareness and intervention compliance, help them to face the disease positively, reduce disease activity, and improve patients' self-nursing ability and quality of life.

Key Words: Gastrointestinal surgery; Omaha System; Follow-up protocol; Disease activity; Intervention compliance; Inflammatory bowel disease questionnaire

Core Tip: The Omaha System was applied in the follow-up of gastrointestinal surgery patients in this study, and the previous follow-up care of gastrointestinal surgery was integrated and re-innovated. The purpose of this study was to compare the nursing effect of conventional gastrointestinal surgery care and the follow-up plan based on the Omaha System on gastrointestinal surgery patients. The follow-up program based on Omaha System has a good nursing effect on gastrointestinal surgery patients.

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INTRODUCTION

The primary cause of inflammatory bowel disease (IBD) is still unknown. It is believed that the damage of intestinal epithelial mucosa cells is an essential pathophysiological basis of IBD. Normal intestinal mucosa constitutes the intestinal barrier of patients, and intestinal mucosal epithelial cells, intestinal flora, and mucus are in a relatively stable state[1]. IBD is a long-course disease that requires prolonged intervention due to easy recurrence and needs long-term nursing. However, most patients receive intervention and nursing in a passive manner, lack awareness of participation, and lack self-nursing after discharge, leading to repeated illness after discharge[2]. Previous studies have suggested that continuous care used to consolidate the therapeutic effect of IBD patients can improve patients' awareness of the disease, stimulate their self-initiative, enable patients to actively participate in the disease, develop and ensure their self-management and quality of life, and reduce the recurrence rate and economic burden[3]. Omaha System is a standardized nursing language system established by the American Nursing Association, and it evaluates the nursing degree through comprehensive evaluation, effective intervention, and corresponding effect evaluation[4]. This nursing model has been widely used in inpatient, community, and continuing care, but its application in IBD is still in the exploration stage. In order to serve as a guide for establishing a nursing intervention program for IBD, this study sought to investigate the impact of an Omaha System-based follow-up program on the disease activity, intervention compliance, and life quality of patients.

MATERIALS AND METHODS

Clinical data

Data of 128 patients with IBD in gastrointestinal surgery from March 2019 to August 2021 were retrospectively analyzed, and they were divided into group A and group B according to different nursing methods, with 64 cases in group A and 64 cases in group B.

Inclusion criteria

Patients matched the diagnostic standards of IBD in the *Consensus Opinion on the Diagnosis and intervention of Inflammatory Bowel Disease in gastrointestinal surgery* (2018, Beijing)[5]; all patients underwent surgical intervention; and patients signed the consent form.

Exclusion criteria

Patients with chronic heart, liver, and kidney function; patients with lingual function and intellectual impairment; patients with ischemic colitis, infectious colitis, and other colonic diseases; patients with intestinal cancer and obstructive diseases; and patients with incomplete clinical case data.

Methods

The lecture discussed patients' health knowledge of inflammatory enteritis during hospitalization and answered the questions on the spot. Propaganda posters were posted in the department, and medication guidance was given to the patients when hospitalized. The patients were instructed to follow the doctor's prescription in taking medicine, recognize adverse drug reactions, and ask for return visits regularly.

Group A was given a follow-up intervention based on the Omaha System on the basis of routine intervention for a total of three months. As the framework of nursing practice, Omaha System consists of three parts: Problem classification system, intervention system, and effect evaluation.

Problem classification system: Based on the patient's clinical symptoms, signs, and basic personal situation, the related nursing problems were put forward from the physiology, psychology, health behavior, and ecological perspectives of the Omaha System. The nursing problems were described and ranked in the priority order by evaluating the patients' coping styles, disease awareness, and self-nursing ability using corresponding scales. The nursing problems include low awareness of the disease, high psychological pressure, and poor living habits.

Health education, guidance, and consultation: Scientific knowledge lectures on inflammatory diseases were organized regularly every week, and on-site guidance and explanation were provided for patients' problems. A patient association, an example, or a mutual aid group can be established. The patient with outstanding comprehensive quality was selected as the group leader, showing strong self-management ability, outgoing personality, sense of responsibility, and communication ability. The purpose was to assist the nursing staff of the transitional care group in managing IBD patients. Tencent's official account of inflammatory diseases in our department was established. Patients used the scale in the official account to conduct self-assessment, and targeted intervention was given based on the evaluation results of patients. *The Handbook of Out-of-Hospital Self-nursing for IBD Patients* was issued (compiled by members of the transitional care team based on clinical nursing experience and literature, approved by physicians). This manual included knowledge of IBD disease, dietary advice, behavioral contraindications, common symptoms during the recovery period, intervention plans in case of particular accidents, and other matters needing attention. Health registration forms were issued, which were registered by the nursing staff while the patient was in the hospital. After discharge, the record of the diet, exercise, medication, adverse reactions, self-feeling, and other symptoms of patients were performed by patients themselves. WeChat groups and QQ groups for doctor-patient interaction were created. Each patient or his or her family members were ensured in the group when discharged. Their real names were marked to facilitate follow-up disease communication, doubts answering, supervision and guidance. Each patient was informed of the department's hotline. WeChat official account to ensure that each patient records and follows, as well as the push cycle and content arrangement of the WeChat official account (regular push at 13:00 on Mondays, Wednesdays, and Fridays, mainly with pictures and texts, supplemented by videos, and the pushed content included disease knowledge, self-nursing knowledge, and health knowledge).

Operating procedures: (1) Medication guide: Based on the registration form of the patient during hospitalization and the recovery status of the patient, the relevant knowledge of medication was popularized to the patient and his family members, and the adverse reactions and symptoms of the drug were informed, the time and dosage of medication were told to the patient, and the dosage of medication was ensured; (2) Diet nursing: The nursing staff emphasized the importance of dietary care to the patients and their families. Eating foods rich in cellulose, protein, easy to digest, and high calories and prohibiting functional stimulant foods are suggested. If the patients suffer from food intake obstruction, it is suggested that the patients should be hospitalized for a follow-up visit. The intravenous injection of nutrients was taken to reduce the burden on the digestive system, and the patients and their families were guided to write diet diaries; (3) Abdominal pain nursing: Analgesic methods were explained to the patient based on the location, degree, and changes of abdominal pain. Antispasmodic drugs were given according to the patient's situation, and the dosage of drugs was reminded for the patient; (4) Diarrhea care: Patients with mild diarrhea should strengthen perianal cleaning and nursing, keep the bed dry and smooth to avoid infection, and monitor the occurrence of diarrhea. It is also essential to monitor the number of diarrheas, stool color, bleeding, blood stool care, and severe IBD patients with gastrointestinal pus and blood symptoms should seek intervention immediately; (5) Daily life: Patients were instructed to work and rest regularly and to take low-intensity physical exercises, such as walking and playing Tai Chi; (6) Self-nursing ability: Patients were guided to measure the changes in body temperature and weight regularly every day to identify related symptoms and complications, such as severe abdominal pain and stool bleeding, which were needed to seek medical attention in time; and (7) Follow-up frequency: Home follow-up was conducted once a week after discharge < 1 mo and once every 2 wk after discharge 1-3 mo. The primary objective of the sequel was to diagnose the effect on patients, understand medication compliance, diet, exercise, and psychological changes, answer complex problems encountered during the nursing process

on-site, and correct bad behavior, emphasizing the importance of persistent nursing.

Case management: Achievable goals were made, and corresponding nursing measures were executed based on the ability of patients and caregivers to promote rehabilitation. For example, establishing self-health management, record daily habits, abdominal pain, diarrhea and possible symptoms and signs, guide patients to self-supervision, actively participate in disease management, and improve patients' self-care awareness and self-health management ability. Patient's family members can also be invited to participate, urge patients to get rid of bad habits, encourage patients to exercise actively, and promote collaborative management of family members.

Nursing evaluation: The coping style, disease awareness, quality of life, self-nursing ability, disease activity, and compliance of patients after the intervention were evaluated.

Data collection

Medical Coping Modes Questionnaire (MCMQ)[6], Crohn's and Colitis Knowledge Score (CCKNOW)[7], Inflammatory bowel disease in gastrointestinal surgery questionnaire (IBDQ)[8], Exercise of Self-nursing Agency Scale (ESCA)[9], The Modified Mayo Endoscopic Score[10], and Beliefs about Medicine Questionnaire (BMQ)[11] date were collected and analyzed of the two groups. MCMQ mainly included three dimensions: Facing (8 objects, 0-32 points), avoidance (7 objects, 0-28 points) and surrender (5 objects, 0-20 points). CCKNOW was used to evaluate patients' disease awareness before and after the intervention. It mainly included general knowledge (11 questions), diet knowledge (2 questions), drug knowledge (6 questions), and complications knowledge (5 questions). The score ranged from 0 to 23 (the 14th and 15th questions applied to Crohn's disease and respective ulcerative colitis). The score was positively proportional to the awareness of the disease. IBDQ mainly included four aspects: Systemic symptoms, intestinal symptoms, social function, and emotional function, and each aspect included seven items. Each item ranges from 1-8 points, with an overall score of 28 to 224. ESCA mainly included four aspects, including the level of health knowledge, personal care-abilities, self-perception, and self-awareness score, totaling 43 items. The range of a single object starts from 1 to 4 points, and overall the score ranges between 43-172 points. Modified Mayo scoring system included four aspects: Frequency of defecation, frequency of bloody stool, endoscopic performance, and the overall evaluation of doctors. Single objects range from 0-3 points; overall, the score range was 0-12. The score of the disease was positively correlated with the severity of the disease. BMQ were used to assess patients' medication beliefs. This scale mainly included two dimensions: Medication necessity (5 items) and medication concern (5 items). A single item from 1 to 5 points, and the range of scores was 10-50 points. The score was directly proportional to the more substantial the medication belief.

Statistical analysis

Data descriptive statistics were analyzed using SPSS (version 22.0). The scoring data were measured as a percentage (%) and then compared between groups using a χ^2 test. The categorical variables were represented as mean ± SD after the normality test, and then the data of both groups were compared using the independent sample *t*-test. The paired sample of the *t*-test was used to compare differences within the groups. GraphPad Prism-5 was used for representing the data in graphs keeping the significance level at $P < 0.05$.

RESULTS

Comparison of general information between the two groups

The study showed no significant differences in the general data between these two groups (all $P < 0.05$, Table 1).

Comparison of MCMQ scores before and after the intervention

As before, the intervention showed no significant differences in confronting, avoidance, and surrender scores between both groups (all $P < 0.05$). After an intervention, it showed that the group A scored higher in confronting but lower in avoidance and surrender scores than the group B (all $P < 0.05$, Figure 1A). The confronting score of the group A was more significant than the group B, and the avoidance and surrender scores were lower than the group B (all $P < 0.05$, Table 2, Figure 1A).

Comparison of ESCA scores before and after the intervention

Before the intervention, showed no significance in the differences in individual scores and total scores on the ESCA scale between both groups (all $P > 0.05$). After the intervention, the level of health knowledge, self-nursing skills, self-concept, self-responsibility score, and ESCA total scores of the group A were more significant than the group B (all $P < 0.05$, Table 3, Figure 1B).

Comparison of disease activity before and after the intervention

Before the intervention showed no significant differences in the score of disease activity and total scores between the two groups (all $P > 0.05$), after the intervention, the hematochezia, endoscopic manifestations, overall physician evaluation score, and total score of disease activity in the group A were lower than in the group B (all $P < 0.05$, Table 4, Figure 1C).

Table 1 Comparison of general information between the two groups (*n*)

Group	Group A (*n* = 64)	Group B (*n* = 64)	χ^2/t	*P* value
Gender				
Male	38	35	0.287	0.592
Female	26	29		
Age	43.11 ± 4.77	41.80 ± 4.48	1.605	0.111
Course of disease	1.25 ± 0.25	1.18 ± 0.25	1.392	0.166
Degree of education				
Junior high school and below	19	21	0.145	0.703
High school and above	45	43		
Disease type				
Ulcerative colitis	56	59	0.771	0.380
Crohn's disease	8	5		
Family history of digestive disorders	7	5	0.368	0.544

Table 2 Comparison of Medical Coping Modes Questionnaire scores before and after the intervention (mean ± SD, points)

Group	Group A (*n* = 64)	Group B (*n* = 64)	*t* value	*P* value
Confront points				
Before intervention	19.44 ± 2.65	18.66 ± 3.11	1.528	0.129
After intervention	25.98 ± 4.23[a]	24.19 ± 3.11[a]	2.741	0.007
Debarb points				
Before intervention	20.64 ± 4.70	20.94 ± 3.97	0.386	0.700
After intervention	13.00 ± 2.15[a]	15.44 ± 2.54[a]	5.859	< 0.001
Surrender points				
Before intervention	12.28 ± 2.51	12.84 ± 2.08	1.381	0.170
After intervention	7.28 ± 1.34[a]	9.02 ± 1.46[a]	6.994	< 0.001

[a]$P < 0.05$, compared with the same group before intervention.

Comparison of CCKNOW scores before and after the intervention

No significant difference was existed between the individual score and total score of the CCKNOW scale (all $P > 0.05$). After the intervention, the score of general knowledge, drug knowledge, complication knowledge, and total CCKNOW score in the group A was more significant than in the group B (all $P < 0.05$, Table 5, Figure 1D).

Comparison of intervention compliance between two groups

Before the intervention, no significant differences were observed in individual scores and total score of BMQ between the two groups (all $P > 0.05$). After the intervention, the scores of medication necessity, medication concern, and BMQ total score in the group A were more significant than in the group B (all $P < 0.05$, Table 6, Figure 1E).

Comparison of IBDQ scores between two groups before and after intervention

Showed no significant differences in individual scores and total scores of IBDQ between both groups (all $P > 0.05$). After the intervention, the scores of systemic symptoms, intestinal symptoms, social function, emotional function, and IBDQ total score in the group A were more significant than in the group B (all $P < 0.05$, Table 7, Figure 1F).

DISCUSSION

IBD is a known idiopathic inflammatory disease of the intestinal tract. Its onset sites are primarily concentrated in the ileum and rectum, and patients often manifest abdominal pain, diarrhea, and tenesmus. Some patients are also accom-

Table 3 Comparison of Exercise of Self-nursing Agency scores before and after the intervention (mean ± SD, points)

Group	Group A (*n* = 64)	Group B (*n* = 64)	*t* value	*P* value
Health knowledge points				
Before intervention	35.13 ± 4.68	35.75 ± 3.56	0.851	0.396
After intervention	53.33 ± 4.07[a]	49.81 ± 4.23[a]	4.786	< 0.001
Self care skills points				
Before intervention	19.39 ± 2.00	19.66 ± 2.04	0.744	0.458
After intervention	37.97 ± 2.77[a]	36.45 ± 2.44[a]	3.286	0.001
Self-concept points				
Before intervention	16.14 ± 2.84	15.72 ± 2.78	0.849	0.398
After intervention	25.47 ± 2.43[a]	22.75 ± 2.30[a]	6.507	< 0.001
Self-responsibility points				
Before intervention	13.33 ± 2.64	13.30 ± 2.65	0.067	0.947
After intervention	17.22 ± 2.00[a]	14.98 ± 2.83[a]	5.154	< 0.001
Total ESCA points				
Before intervention	83.98 ± 6.22	84.42 ± 6.26	0.397	0.692
After intervention	133.98 ± 5.56[a]	124.00 ± 5.56[a]	10.153	< 0.001

[a]*P* < 0.05, compared with the same group before intervention.
ESCA: Exercise of Self-nursing Agency.

Table 4 Comparison of disease activity before and after the intervention (mean ± SD, points)

Group	Group A (*n* = 64)	Group B (*n* = 64)	*t* value	*P* value
Defecation time				
Before intervention	1.48 ± 0.50	1.55 ± 0.50	0.703	0.483
After intervention	0.63 ± 0.49[a]	0.78 ± 0.42[a]	1.948	0.054
Hematochezia				
Before intervention	1.89 ± 0.31	1.86 ± 0.35	0.531	0.596
After intervention	0.52 ± 0.50[a]	0.94 ± 0.24[a]	6.030	< 0.001
Endoscopic performance				
Before intervention	1.77 ± 0.46	1.70 ± 0.46	0.766	0.445
After intervention	0.77 ± 0.43[a]	0.97 ± 0.18[a]	3.521	< 0.001
Overall physician evaluation				
Before intervention	1.50 ± 0.50	1.55 ± 0.50	0.527	0.599
After intervention	0.27 ± 0.45[a]	0.89 ± 0.31[a]	9.173	< 0.001
Total disease activity score				
Before intervention	6.72 ± 0.93	6.88 ± 0.83	1.003	0.318
After intervention	2.17 ± 0.83[a]	3.58 ± 0.66[a]	10.618	< 0.001

[a]*P* < 0.05, compared with the same group before intervention.

Table 5 Comparison of Crohn's and Colitis Knowledge scores before and after the intervention (mean ± SD, points)

Group	Group A (*n* = 64)	Group B (*n* = 64)	*t* value	*P* value
General knowledge score				
Before intervention	5.03 ± 1.18	5.23 ± 1.15	0.985	0.326
After intervention	8.00 ± 0.84[a]	6.55 ± 0.85[a]	9.734	< 0.001
Diet knowledge score				
Before intervention	0.91 ± 0.29	0.98 ± 0.13	1.958	0.054
After intervention	1.14 ± 0.35[a]	1.09 ± 0.29[a]	0.820	0.414
Drug knowledge score				
Before intervention	3.13 ± 0.33	3.14 ± 0.35	0.258	0.796
After intervention	4.78 ± 0.58[a]	4.48 ± 0.53[a]	3.022	0.003
Complication knowledge score				
Before intervention	3.02 ± 0.13	3.06 ± 0.24	1.368	0.175
After intervention	4.31 ± 0.50[a]	4.02 ± 0.42[a]	3.646	< 0.001
Total CCKNOW scores				
Before intervention	12.08 ± 1.25	12.42 ± 1.29	1.527	0.129
After intervention	18.23 ± 1.21[a]	16.14 ± 1.07[a]	10.406	< 0.001

[a]*P* < 0.05, compared with the same group before intervention.
CCKNOW: Crohn's and Colitis Knowledge.

Table 6 Comparison of intervention compliance between two groups (mean ± SD, points)

Group	Group A (*n* = 64)	Group B (*n* = 64)	*t* value	*P* value
Medication necessity score				
Before intervention	15.05 ± 2.90	15.50 ± 1.76	1.069	0.288
After intervention	20.80 ± 2.30[a]	18.94 ± 2.39[a]	4.481	< 0.001
Medication care score				
Before intervention	15.53 ± 2.49	14.95 ± 2.41	1.336	0.184
After intervention	21.66 ± 2.35[a]	20.00 ± 2.08[a]	4.222	< 0.001
Total BMQ scores				
Before intervention	30.58 ± 3.42	30.45 ± 3.14	0.215	0.830
After intervention	42.45 ± 3.22[a]	38.94 ± 3.15[a]	6.241	< 0.001

[a]*P* < 0.05, compared with the same group before intervention.
BMQ: Beliefs about Medicine Questionnaire.

panied by symptoms such as fever and anemia. This disease is characterized by prolonged course and easy relapse, with the tendency of carcinogenesis being one of the modern refractory diseases. The psychological burden of patients is heavy, which can affect their personal quality of life[12]. Relevant studies have pointed out that improving patients' cognition of disease can indirectly improve their quality of life[13]. The follow-up program based on the Omaha System can formulate targeted interventions based on patients' conditions and help patients and their families quickly improve their understanding of the disease[14]. The present study showed that the CCKNOW score of the group A was more significant than the group B, confronting score was greater than the group B. The avoidance and surrender scores were lower than the group B, suggesting that the follow-up program Omaha System based on the intervention could improve disease awareness and change the cognitive mode of the disease in patients with IBD. This is mainly due to the establishment of the patient association, the use of a health handbook, and the conduction of lectures during the intervention of the program, which strengthened the understanding of the disease patients, making them face the disease with a positive attitude. Furthermore, the present study showed that the application of Omaha System-based follow-up protocol in the clinical intervention of IBD patients could improve their intervention compliance, mainly related to

Table 7 Comparison of inflammatory bowel disease questionnaire scores between two groups before and after intervention (mean ± SD, points)

Group	Group A (*n* = 64)	Group B (*n* = 64)	*t* value	*P* value
Systemic symptom score				
Before intervention	35.13 ± 3.45	35.23 ± 2.91	0.194	0.847
After intervention	48.75 ± 4.86[a]	42.78 ± 4.70[a]	7.069	< 0.001
Intestinal symptoms score				
Before intervention	28.48 ± 4.69	29.17 ± 5.28	0.778	0.438
After intervention	43.05 ± 4.55[a]	40.61 ± 3.49[a]	3.399	0.001
Social function score				
Before intervention	31.92 ± 2.70	32.78 ± 3.07	1.680	0.096
After intervention	46.27 ± 4.97[a]	40.66 ± 4.85[a]	6.463	< 0.001
Affective function score				
Before intervention	29.89 ± 2.59	30.38 ± 2.09	1.163	0.247
After intervention	42.55 ± 2.96[a]	39.55 ± 3.32[a]	5.397	< 0.001
Total IBDQ scores				
Before intervention	125.42 ± 6.72	127.78 ± 6.88	1.962	0.052
After intervention	180.61 ± 8.77[a]	164.44 ± 8.62[a]	10.523	< 0.001

[a]*P* < 0.05, compared with the same group before intervention.
IBDQ: Inflammatory bowel disease questionnaire.

improving their disease awareness. In addition, this study also gave patients detailed medication guidance, so that they understand the knowledge of drug use, adverse reactions and symptoms, medication time and dosage, to ensure that patients take drugs correctly. A number of follow-up visits were conducted to urge patients to take drugs on time to improve intervention compliance.

When IBD patients are in the active stage of disease, their abdominal pain, diarrhea, and gastrointestinal bleeding are more severe and frequent, which has a significant impact on their life, work and social life, and they are more likely to be affected by negative emotions, namely anxiety and depression[13]. Hence, it is necessary to strengthen nursing care for IBD patients in the active stage, strictly monitor patients' vital signs, strengthen pain management, and give psychological support to encourage patients to express their own needs and ideas. Studies have shown that improving coping strategies positively impacts the survival of IBD patients. Cognitive behavioral therapy to improve coping styles can develop the quality of life of IBD children and even lessen their disease activity[15,16]. This study found that after intervention, the scores of defecation, hematochezia, endoscopy, overall evaluation of physicians and total score of disease activity in the group A were lower than those in the group B, indicating that the follow-up plan of IBD patients based on Omaha could reduce disease activity. This is mainly related to the strict diet guidance, exercise nursing, and medication guidance for patients in this study. Abdominal pain is the most common symptom in the active stage of the disease. In this study, nursing staff took precautionary measures to relieve abdominal pain that helped the patients to improve their quality of life and further expand the intervention effect of this nursing mode in IBD.

Self-nursing ability is a kind of ability developed by patients in coping with chronic diseases, including symptom control, intervention monitoring, behavior and emotion regulation, and lifestyle change[17]. Relevant reports indicate that good self-nursing ability can positively affect health outcomes and reduce medical costs[18,19]. Patients with a high level of self-nursing ability can safeguard and enhance their health through their behaviors, monitor and manage signs and symptoms of their diseases, and minimize the impact of diseases on their social functions, emotions, and interpersonal relationships[20,21]. This study also found that after intervention, the level of health knowledge, self-nursing skills, self-concept, self-responsibility score and ESCA total score of the group A were higher than those of the group B, indicating that the follow-up project intervention of IBD patients based on Omaha System can improve the self-care ability of patients. This is due to the fact that medical staff instruct patients to take regular changes in body temperature and weight every day, identify whether there are related symptoms and complications, and inform them of their coping plans during nursing intervention, so as to improve patients' understanding of the disease and improve their self-care ability.

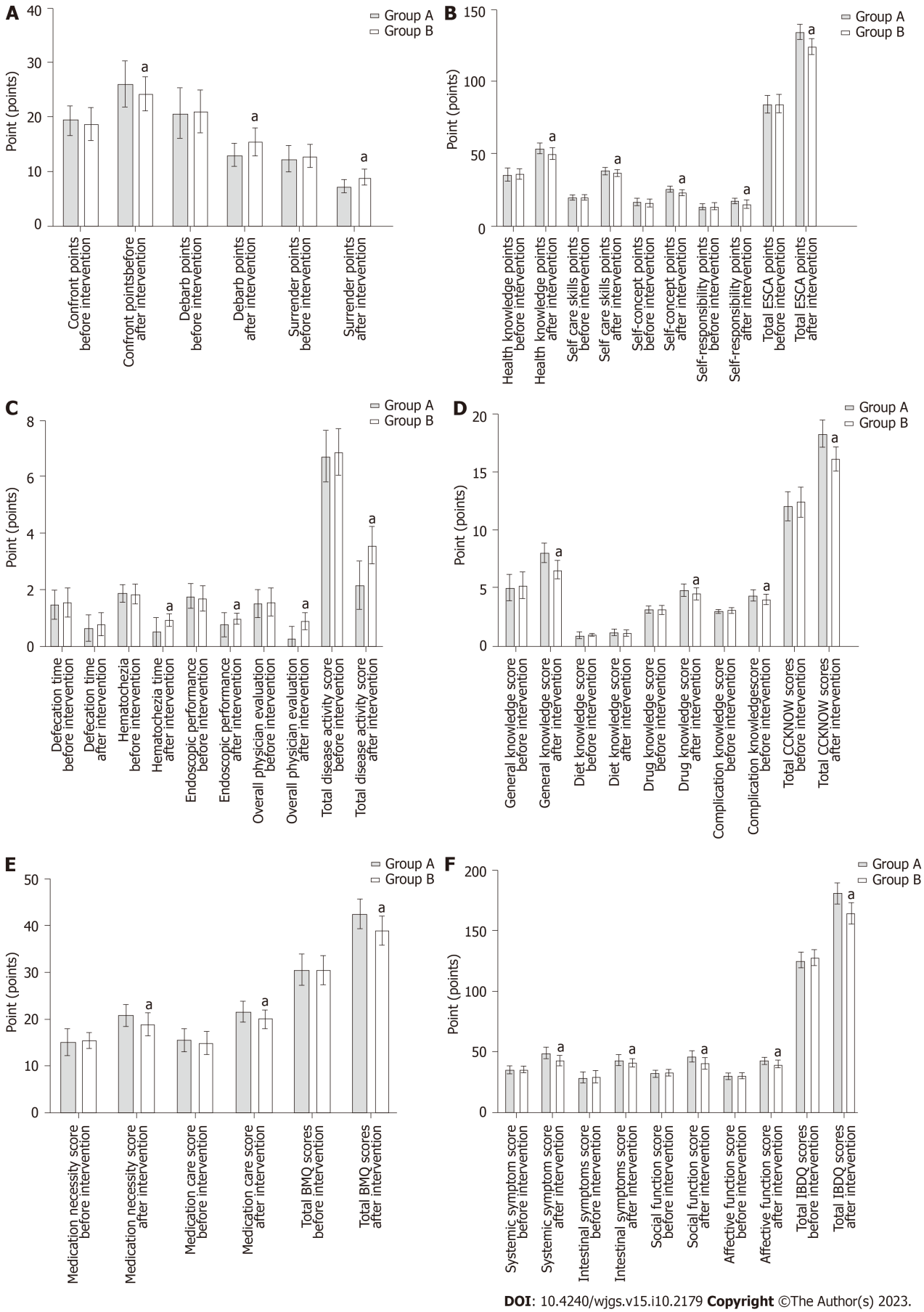

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Figure 1 Comparison of different methods among both groups before and after the intervention (points). A: Medical Coping Modes Questionnaire scores; B: Exercise of Self-nursing Agency scores; C: Disease activity; D: Crohn's and Colitis Knowledge scores; E: Intervention compliance; F:

Inflammatory bowel disease questionnaire scores. [a]$P < 0.05$, comparison with the group A. ESCA: Exercise of Self-nursing Agency; CCKNOW: Crohn's and Colitis Knowledge; BMQ: Beliefs about Medicine Questionnaire; IBDQ: Inflammatory bowel disease questionnaire.

CONCLUSION

The follow-up program intervention based on Omaha System for IBD patients in gastrointestinal surgery can improve patients' disease awareness and intervention compliance, make them face the disease positively, reduce disease activity, and develop their self-nursing ability and quality of life. The limitation of this study is that it is a regressive study with a small sample size, and the results may be biased. It is expected that a large sample and prospective study will further verify the effectiveness of the follow-up protocol based on the Omaha System.

ARTICLE HIGHLIGHTS

Research background

Postoperative follow-up nursing of gastrointestinal surgery patients can effectively improve the quality of life of patients. Currently, a variety of new nursing methods and routine nursing have been widely used in the nursing of gastrointestinal surgery patients. The purpose of this study is to explore a more effective nursing plan for postoperative follow-up nursing of gastrointestinal surgery patients.

Research motivation

The main content of this study is postoperative follow-up care for gastrointestinal surgery patients. Currently, more effective follow-up care plans are needed to improve the prognosis of gastrointestinal surgery patients. The significance of this study is to affirm the effectiveness of new nursing methods for gastrointestinal surgery patients, encourage clinical teams to continue to explore better nursing methods for gastrointestinal surgery patients, and promote continuous improvement and innovation of nursing plans.

Research objectives

The main objective of this study was to compare the nursing effects of different nursing methods, observe the advantages of the follow-up program based on the Omaha System in the follow-up care of intestinal surgery patients, confirm that the follow-up program based on the Omaha System can effectively improve the disease awareness, treatment compliance, self-care ability and quality of life of gastrointestinal surgery patients, and prove that the nursing method has a good nursing effect. It provides a new reference for postoperative follow-up nursing of gastrointestinal surgery patients.

Research methods

In this study, data of patients with inflammatory bowel disease in gastrointestinal surgery were retrospectively analyzed and grouped according to nursing methods. Then, independent sample t test, paired sample t test and χ^2 test were used to conduct statistical analysis on the general information, disease coping style, disease awareness, quality of life, self-care ability, disease activity and compliance of the two groups of patients. The characteristics of retrospective study are that it is easier to obtain case data by exploring the causes through the results.

Research results

The follow-up program based on the Omaha system has a remarkable nursing effect, with better improvements in patients' disease coping style, disease awareness, quality of life, self-care ability, disease activity and compliance, providing a new nursing method for postoperative follow-up care of gastrointestinal surgery patients, and further prospective exploration is needed to further explore the effectiveness of inflammation modification nursing method.

Research conclusions

The postoperative coping style of gastrointestinal surgery patients can affect their prognosis and quality of life, so clinical nursing should pay attention to improving the coping style of patients and strengthening the psychological nursing management. The follow-up plan based on the Omaha System has a good nursing effect, and the best nursing plan should be given priority in clinic.

Research perspectives

Follow-up care based on the Omaha System can improve the objective indicators of gastrointestinal surgery patients, while the impact of subjective indicators on patients such as postoperative recovery and complications needs to be further explored.

FOOTNOTES

Author contributions: Li YD initiated the project and designed the experiment; Qu N conducted clinical data collection; Yang J, Lv CY performed postoperative follow-up and recorded data; Tang Y conducted a number of collation and statistical analysis; Li P wrote the original and revised the paper; all authors reviewed and approved the paper; and all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Optimizing surgical outcomes for elderly gallstone patients with a high body mass index using enhanced recovery after surgery protocol

Yue-Xia Gu, Xin-Yu Wang, Yang Chen, Jun-Xiu Shao, Shen-Xian Ni, Xiu-Mei Zhang, Si-Yu Shao, Yu Zhang, Wen-Jing Hu, Ying-Ying Ma, Meng-Yao Liu, Hua Yu

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Abstract

BACKGROUND

Rehabilitation of elderly patients with a high body mass index (BMI) after cholecystectomy carries risks and requires the adoption of effective perioperative management strategies. The enhanced recovery after surgery (ERAS) protocol is a comprehensive treatment approach that facilitates early patient recovery and reduces postoperative complications.

AIM

To compare the effectiveness of traditional perioperative management methods with the ERAS protocol in elderly patients with gallbladder stones and a high BMI.

METHODS

This retrospective cohort study examined data from 198 elderly patients with a high BMI who underwent cholecystectomy at the Shanghai Fourth People's Hospital from August 2019 to August 2022. Among them, 99 patients were managed using the traditional perioperative care approach (non-ERAS protocol), while the remaining 99 patients were managed using the ERAS protocol. Relevant indicator data were collected for patients preoperatively, intraoperatively, and postoperatively, and surgical outcomes were compared between the two groups.

RESULTS

The comparison results between the two groups of patients in terms of age, sex, BMI, underlying diseases, surgical type, and preoperative hospital stay showed no statistically significant differences. However, the ERAS group had a significantly shorter preoperative fasting time than the non-ERAS group (4.0 ± 0.9 h *vs* 7.6 ± 0.9 h). Regarding intraoperative indicators, there were no significant differences between the two groups of patients. However, in terms of postoperative recovery, the ERAS protocol group exhibited significant advantages over the non-ERAS group, including a shorter hospital stay, lower postoperative pain scores and postoperative hunger scores, and higher satisfaction levels. The readmission rate was lower in the ERAS protocol group than in the non-ERAS group (3.0% *vs* 8.1%), although the difference was not significant. Furthermore, there were significant differences between the two groups in terms of postoperative nausea and vomiting severity, postoperative abdominal distention at 24 h, and daily life ability scores.

CONCLUSION

The findings of this study demonstrate that the ERAS protocol confers significant advantages in postoperative outcomes following cholecystectomy, including reduced readmission rates, decreased postoperative nausea and vomiting, alleviated abdominal distension, and enhanced functional capacity. While the protocol may not exhibit significant improvement in early postoperative symptoms, it does exhibit advantages in long-term postoperative symptoms and recovery. These findings underscore the importance of implementing the ERAS protocol in the postoperative management of cholecystectomy patients, as it contributes to improving patients' recovery and quality of life while reducing health care resource utilization.

Key Words: Enhanced recovery after surgery protocol; Cholecystectomy; Rehospitalization rate; Postoperative nausea and vomiting; Degree of abdominal distension; Daily living ability

Core Tip: This study compared the effectiveness of the enhanced recovery after surgery (ERAS) protocol with traditional perioperative management methods in elderly patients with gallbladder stones and a high body mass index. The results showed that the ERAS protocol demonstrated significant advantages in postoperative outcomes, including reduced readmission rates, improved postoperative nausea and vomiting, alleviated abdominal distension, and enhanced daily living ability. However, the protocol may not exhibit significant improvement in early postoperative symptoms but demonstrates advantages in long-term symptoms and recovery. Implementing the ERAS protocol in the postoperative management of cholecystectomy patients can contribute to improved recovery and quality of life while reducing health care resource utilization.

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INTRODUCTION

Due to the increasingly ageing population, there are a growing number of patients with a high body mass index (BMI) and gallstones, which are two factors that pose risks for surgical treatment. To mitigate these risks, enhanced recovery after surgery (ERAS) has been widely implemented in clinical practice for gallbladder surgery. The ERAS protocol emphasizes comprehensive perioperative management, including preoperative preparation, intraoperative management, and postoperative recovery, thus aiming to reduce surgical risks, shorten hospital stays, and improve rehabilitation outcomes[1-4]. Although the effectiveness of the ERAS protocol has been demonstrated in young and healthy patients, its application and effectiveness in elderly patients with a high BMI and gallstones warrant further investigation.

Patients with a high BMI have more prominent surgical risks, such as longer surgical duration, larger incisions, greater blood loss, and prolonged postoperative hospital stays[5,6]. Therefore, the implementation of an ERAS protocol to optimize the surgical treatment of elderly patients with gallbladder stones and a high BMI holds significant clinical significance.

Previous studies have demonstrated the widespread utilization and effectiveness of ERAS protocols in the management of gallbladder surgical procedures[7,8]. However, the majority of these investigations have predominantly focused on young and healthy patient populations, and there is a lack of specialized research concerning elderly patients with a high BMI and gallstone pathology[9,10]. In this retrospective analysis, we collected pertinent clinical data from elderly patients with a high BMI who underwent cholecystectomy at the Fourth People's Hospital of Shanghai from

August 2019 to August 2022. By comparing the surgical outcomes between the ERAS protocol group and the conventional non-ERAS protocol group, we aimed to provide a comprehensive understanding of the application of ERAS protocols in the surgical treatment of elderly patients with a high BMI and gallstone pathology.

MATERIALS AND METHODS

Subject selection

This study employed a retrospective research design and included a total of 198 elderly patients with a high BMI who underwent cholecystectomy at the Fourth People's Hospital of Shanghai from August 2019 to August 2022. Among them, 99 patients were managed with the traditional non-ERAS protocol for perioperative care, while the remaining 99 patients were managed with the ERAS protocol. We specifically chose elderly patients with a high BMI because this population carries certain risks related to postoperative recovery and is more sensitive to factors related to perioperative management. This study obtained approval from the institutional ethics committee and adhered to relevant ethical principles and privacy protection measures (No. 2019047). All participating patients provided informed consent and agreed to the use of their data for research analysis.

Inclusion criteria

The inclusion criteria were as follows: (1) Nonurgent patients scheduled for gallbladder removal; (2) age ≥ 65 years, regardless of sex; (3) no contraindications for biliary surgery or general anaesthesia; (4) absence of significant gallbladder enlargement or gallbladder discharge on ultrasound or magnetic resonance imaging; (5) no concomitant choledocholithiasis or other conditions requiring surgical intervention, no acute or chronic gastrointestinal obstruction, and no symptoms of delayed gastric emptying; (6) willingness of the patient to undergo gallbladder removal; (7) absence of significant mental or psychological disorders, hearing impairment, or language barriers, ability to communicate normally during treatment, possessing independent legal capacity, and ability to express oneself clearly; and (8) agreement from the patient to receive ERAS treatment.

Evaluation indicators and scales

Elderly patients with a high BMI typically refer to patients aged 65 years and above with a BMI equal to or greater than 28 kg/m^2. Baseline comorbidities refer to preexisting or existing chronic conditions such as hypertension and diabetes. The Hunger score is an indicator used to assess the degree of hunger among patients during the perioperative period. It is generally rated on a scale of 0-2, where 0 indicates no hunger at all, 1 indicates mild hunger that is tolerable, and 2 indicates intolerable hunger or hypoglycaemia requiring intravenous fluid therapy[11]. The postoperative nausea and vomiting (PONV) score is a quantification tool used to assess the severity of PONV[12]. It is scored as follows: 0 points indicate no nausea or vomiting; 1 point indicates mild nausea or vomiting, with patients reporting mild nausea [Visual Analogue Scale (VAS) score < 3 cm] or one episode of vomiting or short-duration (less than 10 min) persistent nausea that resolves without antiemetic medication; and 2 points indicate moderate nausea or vomiting, with patients experiencing 1-2 episodes of vomiting or nausea with a VAS score > 3 cm due to endogenous stimuli, requiring one dose of antiemetic medication for relief. The abdominal distension score is an indicator used to assess the sensation of abdominal bloating in patients and is often used in postoperative or other relevant conditions[13,14]. It is typically described using a scoring system ranging from 0-2 to indicate the degree of abdominal distension. A score of 0 points indicates no abdominal distension, 1 point indicates mild abdominal distension that is tolerable, and 2 points indicate intolerable abdominal distension. The Barthel Index is a scale used to assess activities of daily living[15]. The VAS is also a commonly used pain assessment method, and in this study, the VAS was used to evaluate patients' pain levels. The satisfaction score is a method used to assess patients' satisfaction with medical care or treatment processes[16]. It is typically represented using a numerical range to indicate the degree of satisfaction, with 100 points representing the highest level of satisfaction.

Introduction to the ERAS protocol

The ERAS protocol is a comprehensive treatment approach aimed at promoting early recovery and reducing postoperative complications through strategies such as minimally invasive surgery, thorough preoperative preparation, early postoperative nutritional support, and early rehabilitation training. Specifically, the ERAS protocol encompasses various aspects, including preoperative preparation, anaesthesia, surgical techniques, postoperative pain management, and early nutritional support, among others, providing patients with high-quality perioperative care in a multidimensional manner. The specific protocol flow is detailed in Figure 1.

Data collection

We collected relevant data on preoperative, intraoperative, and postoperative indicators of the patients by reviewing their medical records, surgical records, and follow-up records. Preoperative indicators included age, sex, underlying medical conditions, BMI, and preoperative fasting score at 1 h. Intraoperative indicators included surgical duration, incision length, and blood loss. Postoperative indicators included the incidence of complications, length of hospital stay, pain score at 24 h, fasting score at 6 h postoperatively, satisfaction level, readmission rate, degree of nausea and vomiting at 6 and 24 h postoperatively, degree of abdominal distension at 6 and 24 h postoperatively, and daily living ability score at 24 h postoperatively. These indicators reflected the surgical risk and postoperative recovery of the patients.

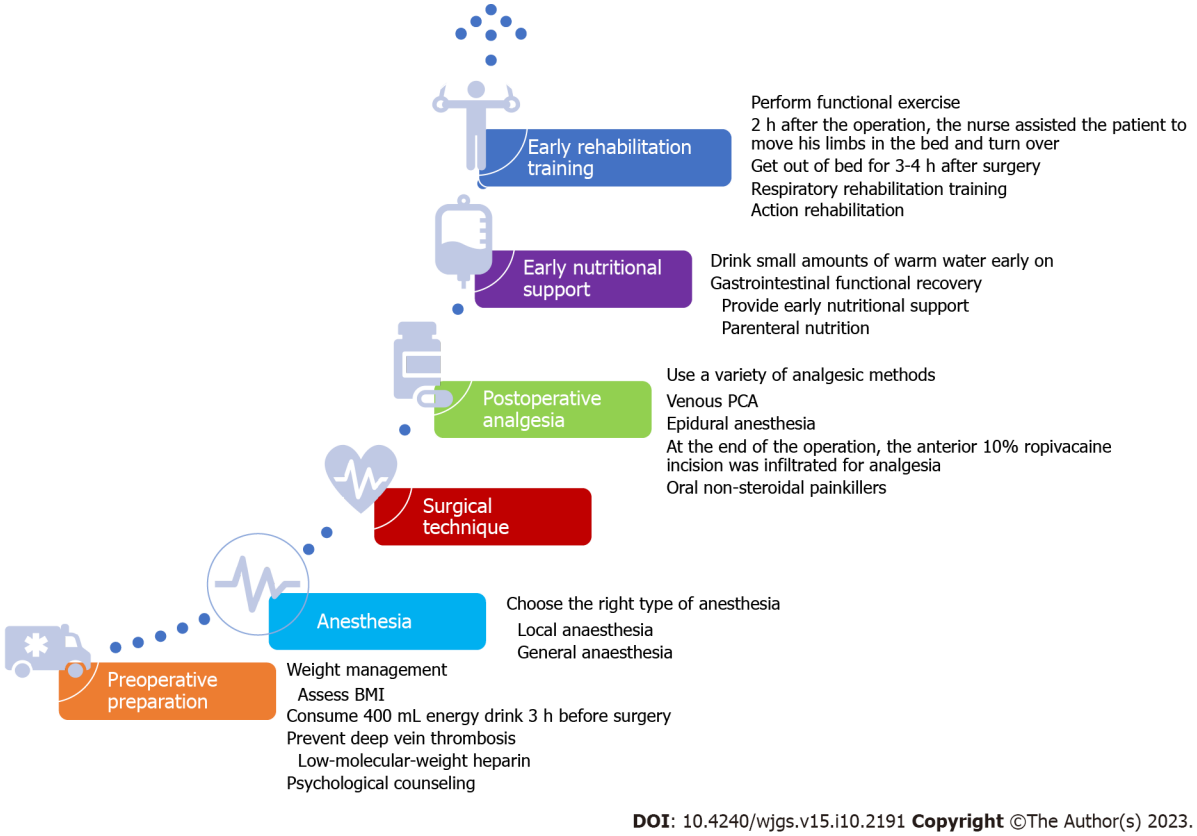

Figure 1 Flowchart of the enhanced recovery after surgery protocol. BMI: Body mass index; PCA: Patient controlled analgesia.

Statistical analysis

Data analyses were performed using SPSS 23.0 software (IBM, 2015, United States). Normality tests were conducted for all continuous variables in this study. Normally distributed variables are reported as the mean ± SD and were compared using independent sample *t* tests. Nonnormally distributed variables are reported as medians (25^{th}-75^{th} percentile). Categorical data were analysed using Pearson's chi-square test. A *P*-value of < 0.05 was considered statistically significant.

RESULTS

Participant characteristics

A total of 198 elderly patients with a high BMI were included in this study, with 99 patients in the traditional non-ERAS protocol group and another 99 patients in the ERAS protocol group. The basic characteristics of the two groups, including age, sex, BMI, preoperative hunger score, and other variables, are presented in Table 1. There were no significant differences between the two groups in terms of age, sex, BMI, underlying diseases, surgical type, and preoperative hospital stay ($P > 0.05$). However, there was a significant difference in preoperative fasting time between the two groups, with an average fasting time of 4.0 ± 0.9 h in the ERAS group compared to 7.6 ± 0.9 h in the non-ERAS group ($P < 0.001$).

Surgical process and postoperative recovery

The comparison of surgical process variables, including operative time, incision length, blood loss, number of drainage tubes, extubation time, postoperative complications, and pain score at 6 h postoperatively, showed no statistically significant differences between the two groups. However, the ERAS protocol group demonstrated significantly better postoperative recovery than the non-ERAS protocol group. The length of hospital stay (4.62 ± 1.01 *vs* 5.51 ± 1.15), pain score at 24 h postoperatively (3.43 ± 1.19 *vs* 4.43 ± 1.21), hunger score, and satisfaction at 6 h postoperatively (98.42 ± 1.13 *vs* 93.72 ± 2.76) were all significantly better in the ERAS protocol group (Table 2).

Rehospitalization rate and postoperative nausea, vomiting, bloating, and activities of daily living

The aim of this study was to compare the differences in hospital readmission rates and postoperative nausea, vomiting, bloating, and activities of daily living scores between the ERAS group and the non-ERAS group. The results showed that the hospital readmission rate was lower in the ERAS protocol group than in the non-ERAS protocol group (3.0% *vs* 8.1%, $P > 0.05$), but the difference did not reach statistical significance. Significant differences were observed between the two groups in terms of PONV at 24 h, bloating at 24 h, and activities of daily living scores. However, there was no statistically

Table 1 Comparison of baseline characteristics of study participants

Characteristic	ERAS group (*n* = 99)	Non-ERAS group (*n* = 99)	*P* value
Age (yr), mean ± SD	69.5 ± 3.6	69.4 ± 3.0	0.746
Gender, male, *n* (%)	49 (49.5)	46 (46.5)	0.670
BMI (kg/m²), mean ± SD	29.3 ± 1.2	29.1 ± 1.4	0.276
Underlying diseases, *n* (%)	20 (20.2)	25 (25.3)	0.386
Surgical procedure (laparoscopic/open)	85/14	83/16	0.692
Preoperative hunger score, *n* (%)			0.052
0	41 (41.4)	25 (25.3)	
1	49 (49.5)	61 (61.6)	
2	9 (9.1)	13 (13.1)	
Preoperative hospitalization time (d)	2.4 ± 0.9	2.3 ± 0.8	0.223
Preoperative fasting time (h)	4.0 ± 0.9	7.6 ± 0.9	< 0.001

SD: Standard deviation; BMI: Body mass index; ERAS: Enhanced recovery after surgery.

Table 2 Comparison of surgical process indexes and postoperative recovery

Characteristic	ERAS group (*n* = 99)	Non-ERAS group (*n* = 99)	*P* value
Surgical duration (min)	81.27 ± 23.17	82.97 ± 24.13	0.614
The incision length (cm)	10.33 ± 2.84	10.46 ± 2.81	0.744
Blood loss (mL)	93.52 ± 28.64	93.68 ± 24.39	0.966
No. of drainage tubes, *n* (%)			0.754
0	37 (37.4)	32 (32.3)	
1	30 (30.3)	33 (33.3)	
2	32 (32.3)	34 (34.3)	
Extubation time (h)	39.72 ± 18.00	40.96 ± 18.61	0.634
Postoperative complication rate, *n* (%)	5 (5.1)	10 (13.1)	0.048
Length of hospital stay (d)	4.62 ± 1.01	5.51 ± 1.15	< 0.001
Postoperative pain score at 6 h	1.96 ± 1.11	2.21 ± 0.82	0.07
Postoperative pain score at 24 h	3.43 ± 1.19	4.43 ± 1.21	< 0.001
Postoperative 6-h hunger score			< 0.001
0	45	32	
1	51	35	
2	3	32	
Satisfaction (%)	98.42 ± 1.13	93.72 ± 2.76	< 0.001

ERAS: Enhanced recovery after surgery.

significant difference between the two groups in terms of PONV at 6 h and bloating (Table 3). Taking all the results into consideration, the ERAS protocol group demonstrated a significant advantage in terms of rehospitalization rate, with a reduced rehospitalization rate compared to the non-ERAS protocol group. These findings suggest that the ERAS protocol may effectively reduce the rehospitalization rate in patients undergoing cholecystectomy. There may not be significant improvements in early postoperative symptoms, but the protocol may have advantages in terms of long-term symptoms and recovery. These findings emphasize the importance of the ERAS protocol in postcholecystectomy care, as it helps improve patients' recovery and quality of life while reducing health care resource utilization. In addition, rehospitalization rates were not statistically associated with surgical complications or patient comorbidities.

Table 3 Comparison of rehospitalization rate and postoperative scores for nausea and vomiting, abdominal distention, and activities of daily living, *n* (%)

Characteristic	ERAS group (*n* = 99)	Non-ERAS group (*n* = 99)	*P* value
Rehospitalization rate	3 (3.0)	8 (8.1)	0.12
PONV at 6 h			0.322
0	43 (43.4)	49 (49.5)	
1	40 (40.4)	30 (30.3)	
2	16 (16.2)	20 (20.2)	
PONV at 24 h			0.005
0	39 (39.4)	32 (32.3)	
1	50 (50.5)	39 (39.4)	
2	10 (10.1)	28 (28.3)	
Postoperative bloating score at 6 h			0.178
0	40 (40.4)	53 (53.5)	
1	52 (52.5)	41 (41.4)	
2	7 (7.1)	5 (5.1)	
Postoperative bloating score at 24 h			0.006
0	47 (47.5)	34 (34.3)	
1	38 (38.4)	32 (32.3)	
2	14 (14.1)	33 (33.4)	
ADL score	85.75 ± 5.83	83.87 ± 6.72	0.037

RAS: Enhanced recovery after surgery; PONV: Postoperative nausea and vomiting score; ADL: Activities of daily living.

DISCUSSION

In recent years, with the increasing population of elderly individuals and patients with a higher BMI, perioperative management for this specific population has become particularly important[17-19]. The aim of this study was to compare the differences in surgical outcomes between traditional perioperative management methods and the ERAS protocol in elderly patients with a high BMI and gallbladder stones. Through a retrospective study design, we included a total of 199 elderly patients with a high BMI for comparative analysis.

Our research findings indicate that there were no significant differences between the two groups in terms of age, sex, BMI, underlying diseases, surgical type, and preoperative hospital stay, indicating comparability between the two groups at baseline. However, the ERAS protocol group had a significantly shorter preoperative fasting time than the non-ERAS group, which aligns with the characteristic of the ERAS protocol to reduce unnecessary fasting time and alleviate preoperative hunger sensation in patients[20-22].

In terms of intraoperative indicators, there were no significant differences between the two patient groups, indicating that the ERAS protocol did not have a significant impact on the surgical procedure itself. However, in terms of postoperative recovery, the ERAS protocol group showed significant advantages over the non-ERAS protocol group. Patients in the ERAS protocol group exhibited superior outcomes in terms of hospital stay duration, postoperative pain scores, postoperative hunger scores, and satisfaction levels compared to patients in the non-ERAS protocol group. These findings suggest that the ERAS protocol can facilitate early patient recovery, alleviate postoperative pain and hunger, and improve patient satisfaction[10,23-26].

The readmission rate is one of the important indicators for evaluating surgical treatment outcomes. Our study found that the readmission rate in the ERAS protocol group was lower than that in the non-ERAS protocol group. Although there was no significant difference, this result still demonstrates the potential advantage of the ERAS protocol in reducing readmission rates. Additionally, significant differences were observed between the two groups in terms of PONV, bloating, and daily living ability scores. This indicates the clear advantages of the ERAS protocol in reducing postoperative complications and promoting patient recovery[19,27,28].

Although the ERAS group showed a lower readmission rate, the small sample size might lead to a limited ability to observe significant differences in the statistical analysis. Second, while the ERAS group received a series of optimized postoperative care measures, the non-ERAS group might have also received certain effective nursing interventions, resulting in a lack of significant differences in readmission rates. Last, there might be potential confounding factors that influence readmission rates in addition to ERAS interventions, such as patients' underlying diseases, postoperative

rehabilitation support, and adherence to medical instructions. These factors might differ between the two groups, affecting readmission rates without being statistically significant.

Based on the aforementioned results, this study demonstrates significant advantages of implementing the ERAS protocol following cholecystectomy. The application of the ERAS protocol is associated with a reduction in readmission rates, improvement in postoperative nausea, vomiting, and abdominal distention, and enhancement of patients' daily life functionality. While there may not be a significant improvement in early postoperative symptoms, it exhibits advantages in terms of improvement of long-term symptoms and recovery[29-31]. These findings emphasize the importance of the ERAS protocol in postcholecystectomy care, as it contributes to the improvement of patients' rehabilitation and quality of life while reducing the utilization of health care resources[28].

Although this study has yielded some meaningful results, there are still some limitations that need to be acknowledged. First, the study design employed in this research is retrospective, which might have introduced selection bias and information bias. Further prospective randomized controlled trials would provide stronger evidence. Second, this study is limited to the experience of a single medical centre, and the results may not be widely applicable. Multicentre studies with larger sample sizes would better assess the effectiveness of the ERAS protocol in elderly patients with a high BMI and gallstones. Additionally, this study did not include long-term follow-up data, thus limiting the evaluation of the long-term effects and survival rates associated with the ERAS protocol.

In future studies, we recommend incorporating a broader range of clinical indicators and postoperative follow-up data to further evaluate the application of the ERAS protocol in the surgical treatment of elderly patients with gallbladder stones and a high BMI. Additionally, comparative research with other treatment approaches should be considered to further substantiate the advantages and scope of the ERAS protocol.

CONCLUSION

The findings of this study demonstrate that the adoption of the ERAS protocol in elderly patients with a high BMI who are undergoing cholecystectomy provides significant advantages over traditional perioperative management methods. The ERAS protocol is associated with reduced readmission rates, improved PONV symptoms, alleviated abdominal distension, and enhanced functional capacity in these patients. Although there may not be significant improvement in early postoperative symptoms, the ERAS protocol exhibits advantages in terms of long-term postoperative symptoms and recovery. These findings underscore the importance of implementing the ERAS protocol in the postoperative management of cholecystectomy patients, as it contributes to improving patients' recovery and quality of life while reducing health care resource utilization.

ARTICLE HIGHLIGHTS

Research background

The rehabilitation of elderly patients with a high body mass index (BMI) after cholecystectomy poses risks and requires effective perioperative management strategies. The enhanced recovery after surgery (ERAS) protocol is a comprehensive treatment approach that promotes early patient recovery and reduces postoperative complications.

Research motivation

The aim of this study was to compare the effectiveness of traditional perioperative management methods with the ERAS protocol in elderly patients with gallbladder stones and a high BMI.

Research objectives

The study aimed to assess and compare the outcomes of elderly patients with a high BMI undergoing cholecystectomy using the ERAS protocol and traditional perioperative care, focusing on various indicators, including fasting time, surgical outcomes, hospital stay, pain scores, satisfaction levels, readmission rates, postoperative symptoms, and functional capacity.

Research methods

A retrospective cohort study design was employed, involving 198 elderly patients with a high BMI who underwent cholecystectomy. The patients were divided into two groups: One managed using traditional perioperative care (non-ERAS protocol) and the other managed using the ERAS protocol. Data on relevant indicators were collected preoperatively, intraoperatively, and postoperatively, and a comparison of surgical outcomes was conducted.

Research results

The comparison results showed no statistically significant differences between the two groups in terms of age, sex, BMI, underlying diseases, surgical type, and preoperative hospital stay. However, the ERAS group had a significantly shorter preoperative fasting time. In terms of postoperative recovery, the ERAS protocol group exhibited significant advantages over the non-ERAS group, including shorter hospital stay, lower postoperative pain scores, hunger scores, and higher satisfaction levels. The readmission rate was also significantly lower in the ERAS protocol group. Furthermore, there

were significant differences in postoperative nausea and vomiting (PONV) severity, postoperative abdominal distention at 24 h, and daily life ability scores between the two groups.

Research conclusions

The study findings demonstrate that the ERAS protocol provides significant benefits in postoperative outcomes following cholecystectomy. It reduces readmission rates, improves PONV, alleviates abdominal distension, and enhances patients' functional capacity. Although the ERAS protocol may not show significant improvement in early postoperative symptoms, it exhibits advantages in long-term postoperative symptoms and recovery. Implementing the ERAS protocol in postoperative management is crucial for improving patients' recovery and quality of life while reducing health care resource utilization.

Research perspectives

The results highlight the importance of incorporating the ERAS protocol in the postoperative management of cholecystectomy patients. Further research can explore the long-term effects of the ERAS protocol on patient outcomes and assess its applicability in other surgical procedures or patient populations.

FOOTNOTES

Author contributions: Gu YX and Wang XY contributed equally in analysis of the data and writing of the manuscript; Yu H designed the study; Chen Y, Shao JX, Ni SX, Zhang XM, Shao SY, Zhang Y, Hu WJ, Ma YY, and Liu MY collected the data and corrected the paper; all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Establishment and application of three predictive models of anastomotic leakage after rectal cancer sphincter-preserving surgery

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Abstract

BACKGROUND

Anastomotic leakage (AL) occurs frequently after sphincter-preserving surgery for rectal cancer and has a significant mortality rate. There are many factors that influence the incidence of AL, and each patient's unique circumstances add to this diversity. The early identification and prediction of AL after sphincter-preserving surgery are of great significance for the application of clinically targeted preventive measures. Developing an AL predictive model coincides with the aim of personalised healthcare, enhances clinical management techniques, and advances the medical industry along a more precise and intelligent path.

AIM

To develop nomogram, decision tree, and random forest prediction models for AL following sphincter-preserving surgery for rectal cancer and to evaluate the predictive efficacy of the three models.

METHODS

The clinical information of 497 patients with rectal cancer who underwent sphincter-preserving surgery at Jincheng People's Hospital of Shanxi Province between January 2017 and September 2022 was analyzed in this study. Patients were divided into two groups: AL and no AL. Using univariate and multivariate analyses, we identified factors influencing postoperative AL. These factors were used to establish nomogram, decision tree, and random forest models. The sensitivity, specificity, recall, accuracy, and area under the receiver operating characteristic curve (AUC) were compared between the three models.

RESULTS
AL occurred in 10.26% of the 497 patients with rectal cancer. The nomogram model had an AUC of 0.922, sensitivity of 0.745, specificity of 0.966, accuracy of 0.936, recall of 0.987, and accuracy of 0.946. The above indices in the decision tree model were 0.919, 0.833, 0.862, 0.951, 0.994, and 0.955, respectively and in the random forest model were 1.000, 1.000, 1.000, 0.951, 0.994, and 0.955, respectively. The DeLong test revealed that the AUC value of the decision-tree model was lower than that of the random forest model ($P < 0.05$).

CONCLUSION
The random forest model may be used to identify patients at high risk of AL after sphincter-preserving surgery for rectal cancer owing to its strong predictive effect and stability.

Key Words: Cancer of rectum; Anastomotic leakage; Nomogram; Decision tree; Random forest

Core Tip: Anastomotic leakage (AL) is a very dangerous complication of rectal cancer surgery, which not only increases the recurrence rate of the tumor but also lowers the quality of life of affected patients. We examined the clinical data of 497 patients with rectal cancer to determine variables that influence AL. We established nomogram, decision tree, and random forest models to identify a prediction model tool for forecasting AL after rectal cancer surgery.

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INTRODUCTION

According to the most recent data from 2020, colorectal cancer has become the third most common cancer worldwide. In China, colorectal cancer has the third highest incidence and fatality rate among all malignancies. Cases of rectal cancer account for 39% of total colorectal cancer cases, making it a serious public health issue in China[1,2]. Radical surgery remains the first choice of treatment for rectal cancer, both for primary and secondary tumors[3]. With advances in medical technology, the prognosis of patients undergoing rectal cancer surgery has significantly improved, and the sphincter preservation rate has also continuously improved[4].

Nevertheless, anastomotic leakage (AL) remains the most common complication following sphincter-preserving surgery for rectal cancer. The perioperative mortality of patients with AL is as high as 18.6%, and these patients are more likely to experience other complications[5,6]. The early identification and prediction of AL after sphincter-preserving surgery are of great significance for the application of clinically targeted preventive measures. At present, a logistic regression analysis of the factors influencing AL in clinical practice is performed[7,8]; however, it cannot intuitively show the importance of each factor to the outcome. Therefore, this study developed nomogram, decision tree, and random forest models for predicting AL following rectal cancer sphincter-preserving surgery. The predictive power of the models were evaluated to identify a tool that would enable the identification of high-risk patients.

MATERIALS AND METHODS

Patient characteristics

For this retrospective analysis, we collected clinical data from 497 patients with rectal cancer who underwent sphincter-preserving surgery at Jincheng People's Hospital of Shanxi Province between January 2017 and September 2022. The inclusion criteria were: Rectal cancer diagnosed by colonoscopy or anal biopsy; tumor within 12 cm of the anal margin; age ≥ 18 years old; and complete clinical data. The exclusion criteria were: Extensive tumor metastasis or the presence of other malignant tumors; a history of rectal surgery, anal stenosis or anal fistula; and conversion to laparotomy. The patients were divided into two groups, those with AL and those without (no AL). The study was approved by the Jincheng People's Hospital of Shanxi Province (JCPH.No20230407001) and written informed consent was obtained from all study participants or their legal guardians.

Study variables

The following variables were analyzed: Sex, age, body mass index, diabetes mellitus, hypertension, smoking history, neoadjuvant treatment, hemoglobin level, albumin (Alb) level, tumor size, tumor-node-metastasis stage, American Society of Anesthesiologists score, tumor location, surgical approach, operative time, and blood loss.

Definition of AL

The diagnosis of AL was based on clinical manifestations (pain, persistent body temperature of > 38 °C, peritonitis, watery fecal matter, food residue in fecal matter, or pus in the drainage fluid), laboratory tests (elevated white blood cell count and neutrophil percentage), and imaging findings (computed tomography following an enema with a liquid, gas, or water-soluble contrast agent)[9].

Statistical analysis

Statistical analyses were performed using SPSS for Windows version 26.0 (IBM Corp., Armonk, NY, United States). All continuous variable data are presented as mean ± SD, and student's *t*-tests were used to compare differences. Data from discrete variables are presented as numbers and percentages, and the χ^2 test was used to assess differences between groups. Variables associated with AL were identified using univariate and multivariate logistic regression analyses.

The prediction models were constructed using the R software, and the data were randomly divided between a training set and a verification set in a 7:3 ratio. The nomogram was created using the 'rms' package, the decision tree with the 'rpart' package, and the random forest using the 'random Forest' package. The model with the best predictive effect was selected by comparing the sensitivity, specificity, accuracy, recall rate, precision rate, and area under the receiver operating characteristic curve (AUC). AUCs were compared using the DeLong test. The statistical significance level was set at $P < 0.05$.

RESULTS

Patient characteristics

There were 271 men and 226 women among the 497 patients. The incidence of AL was 10.26% (51/497). Patients in the AL group had a mean age of 60.98 ± 10.83 years. The no AL group included 446 patients with a mean age of 59.27 ± 10.76 years.

Univariate analysis

Univariate analysis revealed statistically significant differences between the AL and no AL groups for the following variables: Sex, diabetes mellitus, smoking history, neoadjuvant treatment, Alb level, tumor size, and tumor location (Table 1).

Influencing factors of AL

Whether the patient had AL after surgery (not occurring = 0, occurring = 1) was used as the dependent variable, and the statistically significant factors identified by univariate analysis and shown in Table 1 (sex, diabetes mellitus, smoking history, neoadjuvant treatment, Alb level, tumor size, and tumor location) were used as independent variables. Table 2 lists the assignments of the indicators. A multivariate logistic regression analysis revealed sex [odds ratio (OR) = 3.656, 95% confidence interval (CI): 1.538-8.264, $P = 0.003$), diabetes mellitus (OR = 5.669, 95%CI: 2.455-13.092, $P < 0.001$), Alb level (OR = 0.898, 95%CI: 0.846-0.953, $P < 0.001$), tumor size (OR = 2.604, 95%CI: 1.840-3.684, $P < 0.001$), and tumor location (OR = 0.272, 95%CI: 0.180-0.413, $P < 0.001$) as factors that influence AL in patients with rectal cancer following sphincter-preserving surgery (Table 3).

Nomogram model

According to the results presented in Table 3, five variables (sex, diabetes mellitus, Alb level, tumor size, and tumor location) were used to construct a nomogram model for predicting AL after sphincter-preserving surgery for rectal cancer (Figure 1).

Decision tree model

A decision tree prediction model for AL after sphincter-preserving surgery for rectal cancer was also constructed, and four explanatory variables were screened: Tumor location, tumor size, Alb level, and sex. The results of the model showed that tumor location was the first-level factor influencing AL in patients with rectal cancer after sphincter-preserving surgery. The incidence of AL was 100% in patients with a distance of the tumor from the anal verge < 2.7 cm, and 78% in male patients with tumor location < 6.3 cm, Alb level < 41 g/L, and tumor size ≥ 5.1 cm (Figure 2).

Random forest model

According to the change in the overall prediction accuracy of the best model, the variables affecting AL in patients with rectal cancer after sphincter-preserving surgery were tumor location, tumor size, diabetes mellitus, sex, and Alb level (Figure 3).

Evaluation of the prediction efficacy of the three models

In the training dataset, the overall performance of the random forest model in predicting AL after sphincter-preserving surgery for rectal cancer was comparable to that of the decision tree model. The AUC of the random forest model was significantly higher than that of the decision tree model ($Z = -2.836$, $P = 0.004$) (Table 4 and Figure 4). In the validation dataset, the overall effectiveness of the three models was equivalent (Table 5 and Figure 5).

Table 1 Single factor analysis of anastomotic leakage, *n* (%)

Patient characteristics	AL (*n* = 51)	No AL (*n* = 446)	t/χ^2	*P* value
Sex			6.921	0.009
Male	33 (64.71)	244 (54.71)		
Female	18 (35.29)	202 (45.29)		
Age, year (mean ± SD)	60.98 ± 10.83	59.27 ± 10.76	1.073	0.284
BMI, kg/m² (mean ± SD)	22.30 ± 2.91	21.45 ± 3.06	1.896	0.058
Diabetes mellitus			14.164	< 0.001
No	21 (41.18)	302 (67.71)		
Yes	30 (58.82)	144 (32.29)		
Hypertension			0.232	0.630
No	16 (31.37)	155 (34.75)		
Yes	35 (68.63)	291 (65.25)		
Smoking history			6.970	0.008
No	14 (27.45)	209 (46.86)		
Yes	37 (72.55)	237 (53.14)		
Neoadjuvant treatment			7.973	0.005
No	16 (31.37)	233 (52.24)		
Yes	35 (68.63)	213 (47.76)		
Hb, g/L (mean ± SD)	135.60 ± 10.46	136.75 ± 10.41	0.746	0.456
Alb, g/L (mean ± SD)	33.23 ± 6.59	37.13 ± 7.25	3.664	< 0.001
Tumor size, cm (mean ± SD)	4.73 ± 1.22	3.42 ± 1.26	7.009	< 0.001
Tumor location, cm (mean ± SD)	4.32 ± 1.28	6.13 ± 1.30	9.378	< 0.001
TNM stage			0.010	0.995
I	32 (62.75)	281 (63.00)		
II	12 (23.53)	106 (23.77)		
III	7 (13.72)	59 (13.23)		
ASA score			0.289	0.866
I	34 (66.67)	282 (63.23)		
II	12 (23.53)	111 (24.89)		
III	5 (9.80)	53 (11.88)		
Surgical approach			1.676	0.195
Open	13 (25.49)	154 (34.53)		
Laparoscopic	38 (74.51)	292 (65.47)		
Operation time, min (mean ± SD)	182.19 ± 6.25	181.87 ± 5.79	0.378	0.705
Blood loss, mL (mean ± SD)	230.45 ± 17.62	232.74 ± 20.58	0.761	0.447

AL: Anastomotic leakage; Alb: Albumin; ASA: American Society of Anesthesiologists; BMI: Body mass index; Hb: Hemoglobin; TNM: Tumor-node-metastasis.

DISCUSSION

Rectal carcinoma is a prevalent cancer of the digestive system. Currently, the treatment of this disease is mainly surgical [10]. AL is one of the most common and dangerous complications associated with rectal cancer surgery. According to studies, the incidence of AL after rectal cancer surgery ranges from 2.6% to 19.0%[11]. AL not only affects recovery from surgery, but also leads to a variety of complications, such as intra-abdominal abscesses, diffuse peritonitis, and sepsis,

Table 2 Assignment of each factor

Factor	Assignment
Sex	Female = 0, male = 1
Diabetes mellitus	No = 0, yes = 1
Smoking history	No = 0, yes = 1
Neoadjuvant treatment	No = 0, yes = 1
Albumin level	Enter the original value
Tumor size	Enter the original value
Tumor location	Enter the original value

Table 3 Analysis of influencing factors of anastomotic leakage

Factor	β	SE	Wald χ^2	*P* value	OR (95%CI)
Sex	1.271	0.429	8.778	0.003	3.656 (1.538-8.264)
Diabetes mellitus	1.735	0.427	16.504	< 0.001	5.669 (2.455-13.092)
Smoking history	1.758	0.967	3.309	0.069	5.801 (0.873-38.572)
Neoadjuvant treatment	-0.947	0.940	1.015	0.314	0.388 (0.062-2.448)
Albumin level	-0.108	0.030	12.627	< 0.001	0.898 (0.846-0.953)
Tumor size	0.957	0.177	29.204	< 0.001	2.604 (1.840-3.684)
Tumor location	-1.300	0.212	37.699	< 0.001	0.272 (0.180-0.413)

CI: Confidence interval; OR: Odds ratio.

Table 4 Prediction efficiency of the three model training sets

Model	Sensitivity	Specificity	Accuracy	Recall	Precision	AUC (95%CI)
Nomogram	0.745	0.966	0.936	0.987	0.946	0.922 (0.883-0.961)
Decision tree	0.833	0.862	0.951	0.994	0.955	0.919 (0.863-0.975)
Random forest	1.000	1.000	0.951	0.994	0.955	1.000 (1.000-1.000)

AUC: Area under the receiver operating characteristic curve; CI: Confidence interval.

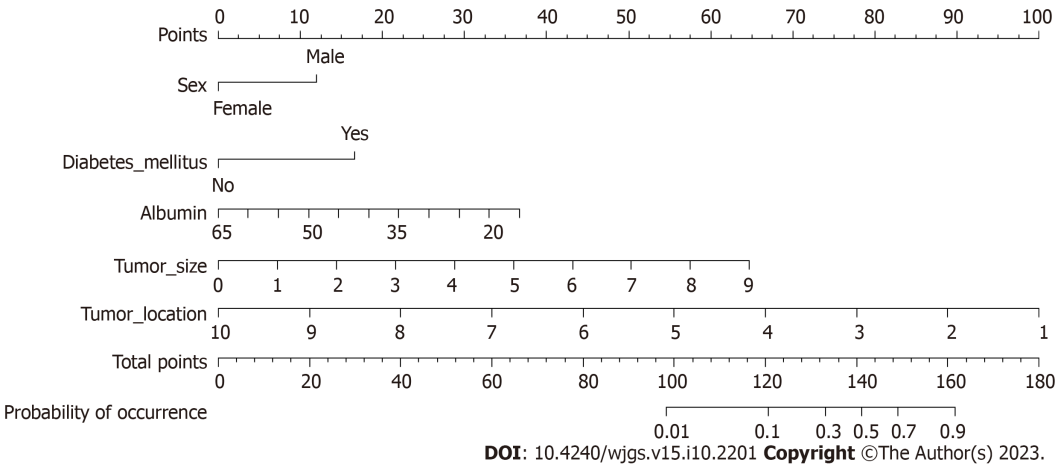
Table 5 Prediction efficiency of the three model validation sets

Model	Sensitivity	Specificity	Accuracy	Recall	Precision	AUC (95%CI)
Nomogram	0.867	0.909	0.927	1.000	0.921	0.950 (0.908-0.992)
Decision tree	0.836	0.864	0.951	0.994	0.955	0.882 (0.797-0.968)
Random forest	0.984	0.727	0.893	1.000	0.889	0.934 (0.883-0.985)

AUC: Area under the receiver operating characteristic curve; CI: Confidence interval.

and can even cause tumor recurrence. In severe cases, secondary surgery is required, which worsens patient survival rates[12]. Therefore, it is critical to identify the factors that influence the development of AL in patients with rectal cancer after sphincter-preserving surgery and provide targeted interventions to reduce its occurrence.

The incidence of postoperative AL was analyzed in 497 patients with rectal cancer admitted to our hospital. A total of 51 patients developed postoperative AL, representing an incidence of 10.26%. This is similar to the incidence of AL reported by Degiuli *et al*[13] in 5398 patients with rectal cancer (10.2%), but lower than that reported by Peltrini *et al*[14] in 367 patients with rectal cancer (17.4%). These differences may be related to factors such as inclusion criteria and different



DOI: 10.4240/wjgs.v15.i10.2201

Figure 1 Nomogram for predicting anastomotic leakage following rectal cancer surgery.

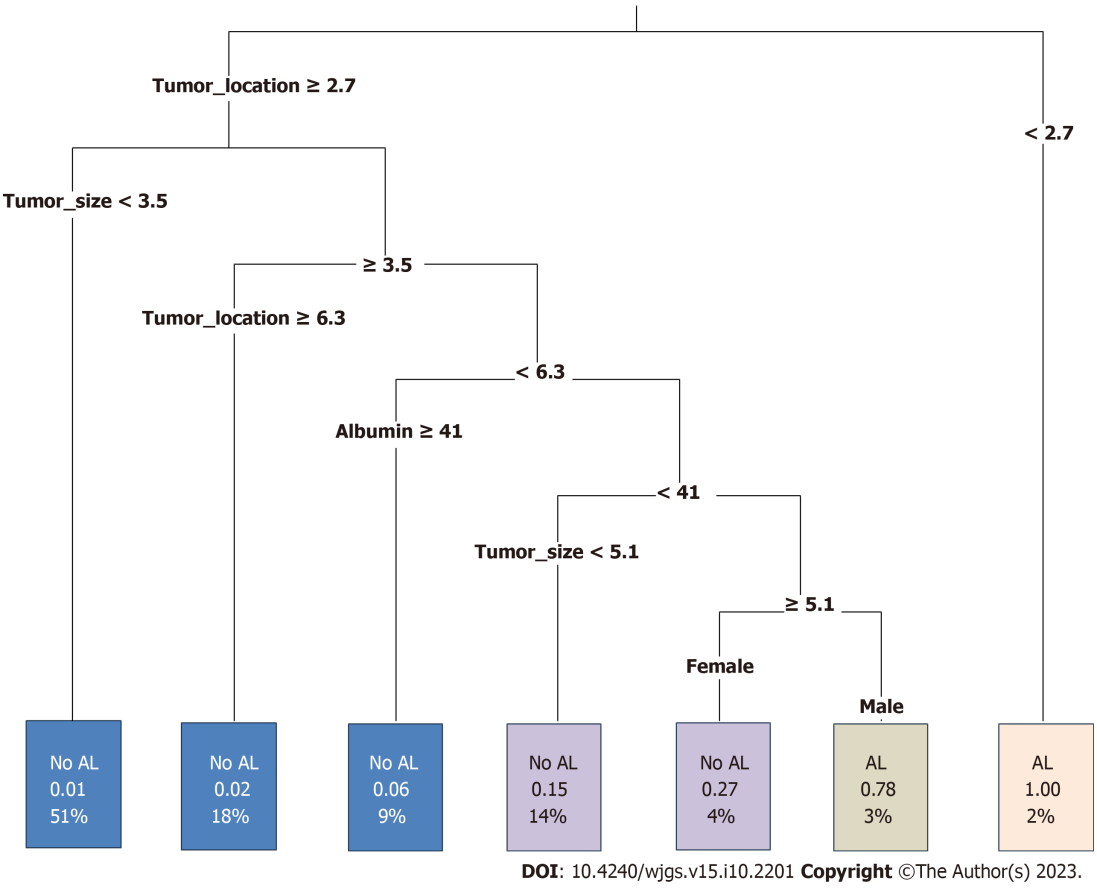


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Figure 2 Decision tree for predicting anastomotic leakage following rectal cancer surgery. AL: Anastomotic leakage.

populations. AL after sphincter-preserving surgery for rectal cancer results from multiple factors, including patient characteristics, tumor status, and operation-related factors. The results of this study showed that sex, diabetes mellitus, Alb level, tumor size, and tumor location influence AL.

According to this study, males were 3.656 times more likely to have postoperative AL than women, which is consistent with the results of most studies[15,16]. As the male pelvis is narrow, the visual field is not fully exposed during the operation, making surgery more challenging; this may cause the rectal stump to retract and cause secondary injury[17].

Penna *et al*[18] confirmed that diabetes mellitus is an independent risk factor for AL after transanal total mesorectal excision. Additionally, this study reported that individuals with diabetes had an AL risk 5.669 times greater than that of non-diabetic patients. Diabetes mellitus can affect the anastomotic blood supply as uncontrolled hyperglycemia leads to vascular damage, reduced blood flow, and cellular accumulation of toxic glucose-derived metabolites, resulting in a significant decrease in anastomotic healing and the ability to fight infection[19].

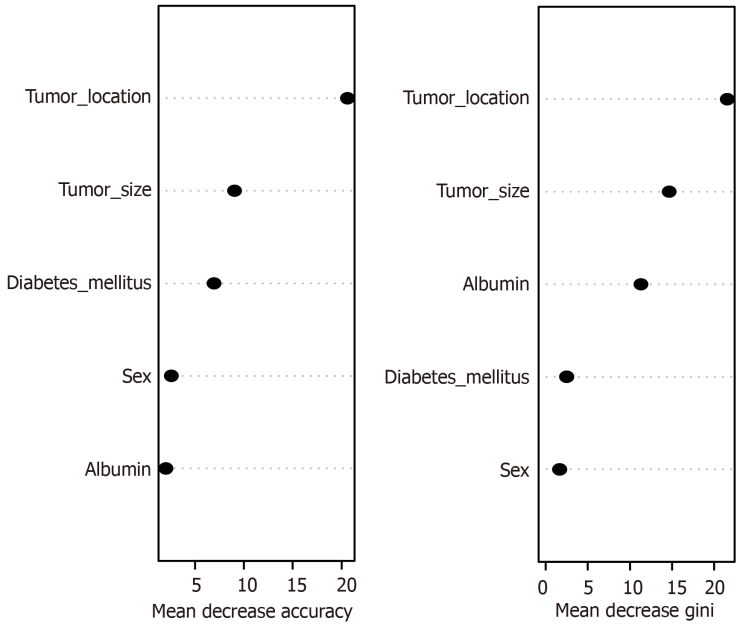

Figure 3 Importance of variables in the random forest model.

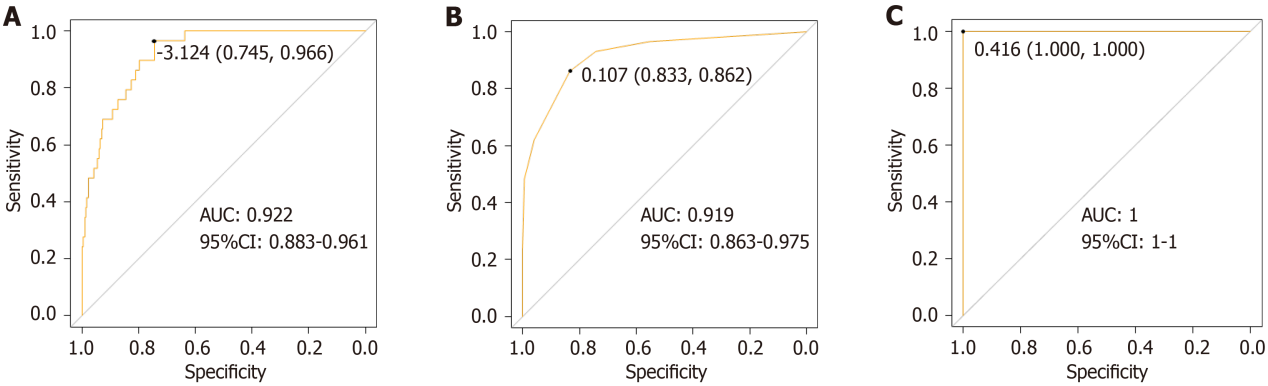

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Figure 4 Receiver operating characteristic curves of the three models in the training set. A: Nomogram; B: Decision tree; C: Random forest. AUC: Area under the receiver operating characteristic curve; CI: Confidence interval.

According to the findings of this study, which are consistent with those of Shimura *et al*[20], there is a direct association between preoperative Alb levels and the risk of developing postoperative AL. This may be due to a low perioperative nutritional status leading to reduced immune function and a greater risk of infection and the spread of infection[21]. Yasui *et al*[22] found that patients with tumor sizes ≥ 4 cm were more likely to develop AL. This study also found that the probability of postoperative AL increases with tumor size. As more tissue has to be removed during surgery, more damage occurs and the chance of developing AL subsequently increases[23].

Both domestically and internationally, there is consensus on the impact of tumor location on AL following low anterior resection of rectal cancer; that is, the closer the tumor is to the anal margin, the higher the risk of AL[24-26]. The same conclusion was reached in the present study. This may be because the closer the tumor is to the anus, the larger the wound during resection. In addition, intraoperative electrocoagulation damage to the tissue and blood vessels causes exudation and bleeding, which reduces the blood supply to the anastomosis and increases the risk of postoperative AL [27].

Currently, there is no consensus regarding whether neoadjuvant therapy increases the incidence of AL. Arezzo *et al*[12] analyzed the effects of short- and long-term radiotherapy on AL and showed that the risk of postoperative AL significantly increased in patients receiving short-term radiotherapy. However, Chang *et al*[28] found no difference in the incidence of AL between patients with rectal cancer who underwent chemoradiotherapy before surgery, and those who did not. The present study also found that neoadjuvant therapy had no effect on AL occurrence.

With the development of computer software and artificial intelligence, machine learning has become a new direction for medical research. Studies have used machine learning models to predict the risk of anti-tuberculosis drug-induced liver injury in inpatients with tuberculosis[29], and machine learning can also predict the risk of essential hypertension [30]. In this study, five indicators with statistically significant differences in the multivariate analysis were used to

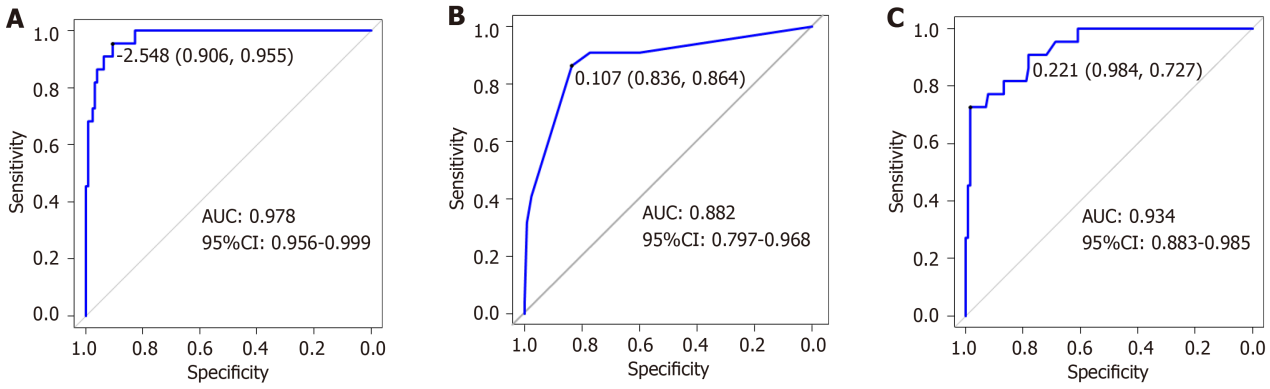

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Figure 5 Receiver operating characteristic curves of the three models in the validation set. A: Nomogram; B: Decision tree; C: Random forest. AUC: Area under the receiver operating characteristic curve; CI: Confidence interval.

establish three prediction models of AL after sphincter-preserving surgery for rectal cancer using machine learning algorithms. In the training dataset, the sensitivity, specificity, accuracy, recall rate, and precision rate of the nomogram were lower than those of the random forest and decision tree models, and the prediction efficacy of the random forest model was better than that of the decision tree. But the sensitivity, specificity, and AUC of the random forest model reached 1, indicating that the random forest model may have overfitting or the generalization effect may be poor due to insufficient data in the training set. In the validation dataset, the three models exhibited similar prediction performances. Although the random forest model has better predictive performance, it also has some disadvantages. As a result, in practice, each of the three prediction models has benefits and limitations, and the most appropriate method should be chosen based on the situation.

As this was a single-center retrospective study, it has several limitations. The representativeness of single-center research is limited, and there may be some bias owing to time constraints. This study did not analyze additional risk factors for AL after sphincter-preserving surgery for rectal cancer, and the constructed model may have been overfitted. Future research will use a larger and more comprehensive sample set and multicenter studies to verify and build a more complete prediction model.

CONCLUSION

Overall, AL is a serious complication of rectal cancer surgery, with a high incidence rate. In this study, nomogram, random forest, and decision tree prediction models of AL after sphincter-preserving surgery for rectal cancer were established using machine learning algorithms. The random forest model was found to have excellent predictive effect and stability, and might serve as a reference for the clinical identification of high-risk groups for AL following sphincter-preserving surgery for rectal cancer.

ARTICLE HIGHLIGHTS

Research background

With advances in medical technology, the success rate of sphincter-preserving surgery in patients with rectal cancer is increasing. However, anastomotic leakage (AL) remains a devastating complication.

Research motivation

AL significantly lowers patients' quality of life. This study examines the elements that influence AL and establishes models to help doctors predict whether patients will develop AL, allowing the timely adoption of preventive measures.

Research objectives

This study aimed to identify the characteristics that influence AL and utilize these factors to build a prediction model for AL after sphincter-preserving surgery for rectal cancer.

Research methods

The clinical data of patients with rectal cancer who underwent sphincter-preserving surgery at our institution in the past five years were examined to analyze the factors influencing AL; nomogram, decision tree, and random forest prediction models were established; and the predictive efficacy of the three models was compared.

Research results

The factors influencing AL after sphincter-preserving surgery for rectal cancer were sex, diabetes mellitus, albumin level, tumor size, and tumor location. To predict the probability of postoperative AL, we constructed nomogram, decision tree, and random forest models.

Research conclusions

This study compared the predictive efficacy of the three prediction models. The random forest model performed the best and may be a useful alternative tool for predicting patients at a high risk of AL.

Research perspectives

Future research will include larger and more comprehensive cohorts across multiple centers, and build a more complete prediction model.

FOOTNOTES

Author contributions: Li HY designed the study and wrote the manuscript; Wu SF designed the study and reviewed the manuscript; Zhou JT, Wang YN, and Zhang N provided clinical advice.

Institutional review board statement: The study was reviewed and approved by the Jincheng People's Hospital of Shanxi Province (JCPH.No20230407001).

Informed consent statement: All study participants or their legal guardians provided written informed consent for personal and medical data collection before study enrolment.

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

Data sharing statement: Dataset available from the corresponding author at wushaofen3322@163.com.

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ORIGINAL ARTICLE

Retrospective Study

Identification of multiple risk factors for colorectal cancer relapse after laparoscopic radical resection

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Abstract

BACKGROUND

Colorectal cancer (CRC) is a common life-threatening disease that often requires surgical intervention, such as laparoscopic radical resection. However, despite successful surgeries, some patients experience disease relapse. Identifying the risk factors for CRC relapse can help guide clinical interventions and improve patient outcomes.

AIM

To determine the risk factors that may lead to CRC relapse after laparoscopic radical resection.

METHODS

We performed a retrospective analysis using the baseline data of 140 patients with CRC admitted to our hospital between January 2018 and January 2020. All included participants were followed up until death or for 3 years. The baseline data and laboratory indicators were compared between the patients who experienced relapse and those who did not experienced relapse.

RESULTS

Among the 140 patients with CRC, 30 experienced relapse within 3 years after laparoscopic radical resection and 110 did not experience relapse. The relapse group had a higher frequency of rectal tumors with low differentiation and

lymphatic vessel invasion than that of the non-relapse group. The expression of serum markers and the prognostic nutritional index were lower, whereas the neutrophil-to-lymphocyte ratio, expression of cytokeratin 19 fragment antigen 21-1, vascular endothelial growth factor, and Chitinase-3-like protein 1 were significantly higher in the relapse group than those in the non-relapse group. The groups did not differ significantly based on other parameters. Logistic regression analysis revealed that all the above significantly altered factors were independent risk factors for CRC relapse.

CONCLUSION
We identified multiple risk factors for CRC relapse following surgery, which can be considered for the clinical monitoring of patients to reduce disease recurrence and improve patient survival.

Key Words: Colorectal cancer; Laparoscopic surgery; Relapse; Risk factors

Core Tip: This study aimed to identify the risk factors for colorectal cancer (CRC) relapse after laparoscopic radical resection by comparing the baseline data and laboratory indicators of 140 patients with CRC, of whom 30 patients experienced relapse within 3 years. Rectal tumors with low differentiation and lymphatic vessel invasion were associated with higher relapse rates. Lower $CD4^+/CD8^+$ ratio, immunoglobulins (Ig) IgA, IgG, IgM, albumin-globulin ratio, and prognostic nutritional index and higher neutrophils to lymphocytes ratio, cytokeratin 19 fragment antigen 21-1, vascular endothelial growth factor, and Chitinase-3-like protein 1 were also identified as independent risk factors for CRC relapse following surgery. These findings suggested that monitoring these factors could reduce the risk of disease recurrence and improve patient outcomes.

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INTRODUCTION

Colorectal cancer (CRC) is a prevalent digestive tract cancer associated with lifestyle and living conditions. The lack of specific symptoms at the early stage of the disease leads to a low early detection rate. Thus, many patients are diagnosed at an advanced stage, and their prognoses are often unsatisfactory[1,2]. Treatments for CRC have progressed rapidly, and the overall principle is to adopt surgical intervention supplemented by comprehensive standardized treatments, such as radiotherapy and targeted therapy. Endoscopic technology has gradually replaced traditional laparotomy and is the first choice and main intervention for the treatment of CRC[3,4]. Although patients with CRC receive timely consolidation treatment with adjuvant therapies, such as chemoradiotherapy and molecular targeted therapy after surgery, the risk of postoperative relapse remains high, leading to a high mortality rate[5,6]. Approximately 30% of patients with CRC who have undergone laparoscopic radical surgery show a risk of metastasis or relapse after surgery, and the 5-year survival rate of such patients is only approximately 19%. Liver metastasis presents a major clinical challenge. Therefore, exploring the factors that may lead to postoperative relapse is necessary to enhance the vigilance of patients at high risk of relapse and guide more appropriate clinical interventions, ultimately reducing the risk of postoperative relapse and enhancing patient prognosis[7,8]. A search for clinical literature related to the exploration of factors that may affect relapse after laparoscopic radical resection in patients with CRC revealed varying factors, such as patient age, tumor stage, and tumor size, with no firm consensus[9-11]. Therefore, in this study, we compared and analyzed the baseline data of included participants to identify the influencing factors that may lead to relapse in patients with CRC after laparoscopic radical resection to guide future interventions and reduce the risk of relapse in patients with CRC after surgery.

MATERIALS AND METHODS

Participants

Baseline data were collected from 140 patients (80 male and 60 female) with CRC admitted to Peking University Shenzhen Hospital between January 2018 and January 2020. The inclusion criteria were as follows: (1) Patients with CRC who met the diagnostic requirements of the "Clinical Guideline for Diagnosis and Treatment of Tumor"[12] and were confirmed using biopsy; (2) those who underwent successful laparoscopic radical resection; and (3) those with baseline data and complete laboratory test results.

The exclusion criteria were as follows: (1) Patients with other cancerous lesions; (2) those with metastasis diagnosed before or during the surgery; (3) those who received targeted therapy, chemoradiotherapy, and other adjuvant treatments before the surgery; (4) those with reduced compliance due to psychological disorders; and (5) presence of acute or chronic diseases, such as impaired liver and kidney function, pulmonary, cardiovascular, cerebrovascular, and hematological diseases, or coagulation disorders, intestinal diseases including intestinal obstruction and intestinal perforation, and acute and chronic infections or active inflammation that may affect the prognosis of the patient.

Methods

We retrospectively analyzed the baseline data of the enrolled patient cohort.

Diagnostic criteria for relapse

The diagnostic criteria included patients followed up effectively until death or up to 3 years (until January 31, 2023). Relapse was determined as the detection of pathological lesions similar to the primary lesions regrowing around the sites of the primary lesion, intestinal anastomosis, peri-intestinal tissue, mesentery, and lymph node regions through clinical imaging (B-scan ultrasonography, abdominal radiography, computed tomography) and further confirmation by tissue biopsy for patients suspected of relapse.

Baseline data collection

The following baseline data were collected: Sex; age (≥ 60 years); tumor node metastasis (TNM)[13] stage (stage I–II, stage III–IV); degree of differentiation (with reference to the Edmondson-Stener classification of tumor pathological grade[14] (stage I: Highly differentiated carcinoma, stage II: Moderately differentiated carcinoma; stage III and IV: Poorly differentiated carcinoma); maximum tumor diameter (≥ 5 cm); location of the lesion (rectum, left/right hemicolon); lymphovascular invasion (present, absent); pathological type (glandular cancer, mucinous adenocarcinoma, Indian cell carcinoma); depth of invasion (T1 + T2, T3 + T4); serum tumor and immune indicators including lymphocytes ($CD4^+$/$CD8^+$), immunoglobulins (Ig) IgA, IgG, IgM, neutrophils to lymphocytes ratio (NLR), albumin-globulin ratio (AGR), cytokeratin 19 fragment antigen 21-1 (CYFRA 21-1), vascular endothelial growth factor (VEGF), prognostic nutritional index (PNI), and the inflammatory biomarker Chitinase-3-like protein 1 (YKL-40).

Detection of serum indicators

Fasting peripheral blood was collected in anticoagulation tubes and used for the following assays: Absolute neutrophil count and absolute lymphocyte count (ALC) using the XE-2100 blood cell analyzer (SYSMEX Corporation, Japan; NLR = PLT/ALC); enzyme-linked immunosorbent assay detection of immunoglobulins, VEGF and YKL-40, Huamei, and Zhenke Biotechnology, China, respectively); total serum protein and albumin detection by an auto chemistry analyzer (BK-400, Jinan Olebo Electronic Commerce, China; globulin = total protein-albumin, AGR = albumin/globulin); CYFRA 21-1 detection by electrochemical luminescence; PNI determination by calculating the albumin concentration and lymphocyte counts using the AU680 automatic biochemical analyzer [Beckman Coulter, United States; PNI = albumin (mg/L) + 5 × lymphocyte counts (× 10^9/L)].

Statistical analysis

Data analysis was conducted using SPSS 25.0 software. The Shapiro-Wilk test was used to determine the normality of the measurement data. Measurement data conforming to a normal distribution were expressed as mean ± SD. The independent sample *t*-test was used for inter-group comparison; count data were presented as *n* (%) and analyzed using the χ^2 test was used. Logistic regression analysis was used to analyze the risk factors for relapse in patients with CRC after laparoscopic radical resection, maintaining an inspection level of $\alpha = 0.05$.

RESULTS

Relapse status of patients after radical resection of CRC

Among the 140 patients with CRC included in the study, 30 experienced relapse within 3 years after laparoscopic radical resection, whereas 110 did not experience relapse, resulting in the relapse rate being 21.43% (30/140) and non-relapse rate being 78.57% (110/140). We analyzed baseline data of the relapsed and non-relapsed groups.

Comparison of baseline data between the two groups

The relapse and non-relapse groups were comparable in terms of their baseline characteristics. However, significant differences between the two groups were observed in the degree of tumor differentiation, lesion location, lymphatic vessel invasion, and several serum indicators. Most patients in the relapse group exhibited rectal tumors characterized by low differentiation and lymphatic vessel invasion. However, patients in the non-relapse group predominantly presented tumors in the left/right hemicolon, with higher differentiation and lack of lymphatic invasion (Table 1). The $CD4^+$/$CD8^+$ ratio and levels of IgG, IgA, IgM, AGR, and PNI were lower, whereas the expression of NLR, CYFRA21-1, VEGF, and YKL-40 was higher in the relapse group than those in the non-relapse group, and the differences were statistically significant ($P < 0.05$).

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

Criteria	Relapse group (*n* = 30)	Non-relapse group (*n* = 110)	Statistical values (χ^2/t)	*P* value
Gender				
Male	20 (66.67)	60 (54.55)	0.414	0.234
Female	10 (33.33)	50 (45.45)		
Age (year)				
≥ 60	18 (60.00)	70 (63.64)	0.134	0.715
< 60	12 (40.00)	40 (36.36)		
TNM stage				
I-II	15 (50.00)	65 (59.09)	0.796	0.372
III-IV	15 (50.00)	45 (40.91)		
Differentiation				
Low	25 (83.33)	23 (20.91)	40.768	< 0.001
Medium/high	5 (16.67)	87 (79.09)		
Tumor maximum diameter (cm)				
≥ 5	20 (66.67)	65 (59.09)	0.567	0.451
> 5	10 (33.33)	45 (40.91)		
Lesion location				
Rectum	24 (80.00)	25 (22.73)	33.986	< 0.001
left/right hemicolon	6 (20.00)	85 (77.27)		
Lymphatic vascular invasion				
Present	22 (73.33)	20 (18.18)	34.141	< 0.001
Absent	8 (26.67)	90 (81.82)		
Postoperative adjuvant therapy				
Not done or incomplete	15 (50.00)	60 (54.55)	$\chi^2 = 0.196$	0.658
Complete	15 (50.00)	50 (45.45)		
Pathological type				
Glandular cancer	10 (33.33)	30 (27.27)	0.951	0.622
Mucinous adenocarcinoma	8 (26.67)	25 (22.73)		
Indian cell carcinoma	12 (40.00)	55 (50.00)		
Infiltration depth				
T1 + T2	18 (60.00)	70 (63.64)	0.134	0.715
T3 + T4	12 (40.00)	40 (36.36)		
Immune indicators				
$CD4^+/CD8^+$	1.02 ± 0.26	1.48 ± 0.38	6.236	< 0.001
IgG (g/L)	4.14 ± 0.60	5.72 ± 0.94	8.722	< 0.001
IgA (g/L)	0.50 ± 0.08	0.69 ± 0.14	7.111	< 0.001
IgM (g/L)	0.68 ± 0.22	0.95 ± 0.32	4.344	< 0.001
NLR	4.18 ± 0.95	3.42 ± 0.55	5.636	< 0.001
AGR	1.60 ± 0.40	1.98 ± 0.36	0.003	< 0.001
Tumor indicators				
CYFRA21-1 (ng/mL)	4.78 ± 0.52	3.25 ± 0.35	13.369	< 0.001

VEGF (ng/L)	190.12 ± 50.25	140.12 ± 42.25	4.171	< 0.001
PNI	40.75 ± 2.02	43.21 ± 2.18	4.534	< 0.001
YKL-40 (ng/mL)	104.25 ± 20.52	78.95 ± 15.25	5.420	< 0.001

TNM: Tumor node metastasis; Ig: Immunoglobulins; NLR: Neutrophils to lymphocytes ratio; AGR: Albumin-globulin ratio; CYFRA21-1: Cytokeratin 19 fragment antigen 21-1; VEGF: Vascular endothelial growth factor; PNI: Prognostic nutritional index; YKL-40: Inflammatory biomarker Chitinase-3-like protein 1.

Logistic regression analysis of relapse after laparoscopic radical resection of CRC

To determine whether the factors that were significantly different between patients in the relapse and non-relapse groups were significant risk factors for relapse after laparoscopic radical resection, we performed logistic regression analysis with relapse after surgery being treated as the dependent variable (1 = relapse, 0 = non-relapse) and indicators with significant differences from Table 1 as the independent variables (Table 2 presents the assignment). The results demonstrated that the degree of differentiation (low differentiation); location of the lesion (rectum); lymphatic vessel invasion (present); low expression of serum $CD4^+/CD8^+$, IgG, IgA, IgM, AGR, and PNI; and high expression of serum NLR, CYFRA21-1, VEGF, and YKL-40 were independent risk factors for relapse in patients with CRC after laparoscopic radical surgery (OR > 1, $P < 0.05$; Table 3).

DISCUSSION

Laparoscopic radical resection can significantly improve overall patient outcomes and reduce the impact of open surgery on immune function. However, the risk of relapse remains high in patients with CRC after radical resection. Our present study supports this conclusion, as our results are consistent with the observed relapse rate of 21.43% observed in a cohort of 140 patients. The results negatively impact patients' quality of life and overall survival rate. Therefore, for patients with CRC, early detection of relapse after surgery and exploration of the risk factors that may lead to relapse are particularly crucial for guiding further treatment, prolonging survival time, and improving the quality of life[15,16].

This study demonstrated that patients with rectal tumors with a low degree of differentiation and lymphatic vessel invasion were at higher risk of postsurgical relapse than that of patients with more differentiated tumors located within the colon and without lymphatic vessel invasion. Other immune/tumor-related risk factors for relapse included lower expression of $CD4^+/CD8^+$, IgG, IgA, IgM, AGR, and PNI and higher expression of NLR, CYFRA21-1, VEGF, and YKL-40. Logistic regression analysis indicated that all variables were independent risk factors for CRC relapse after laparoscopic radical resection.

The complex rectal lymphatic drainage system may be a possible reason for the higher relapse rate in patients with rectal tumors. The absence of a serosa in the lower rectal cancer tube may allow lesions to easily adhere to the surrounding tissues, increasing the difficulty of complete surgical removal and the risk of postoperative relapse[17]. The degree of tissue differentiation has a significant effect on the biological behavior of tumors. A lower degree of differentiation indicates that the tumor tissue has strong regenerative ability; a fast growth rate due to rapid cell division and proliferation; and high migration and invasiveness into surrounding tissues, lymphatic vessels, and capillaries, contributing to a high probability of postoperative relapse[18,19].

As an important immune organ, the lymph node is the switch that activates the immune response in the body. Because of the abundant lymphatic and blood vessels in the mesorectum, cancer cells can easily invade these circulatory systems, forming circulating tumor cells that are resistant to apoptosis and attacks from the immune system and many other environmental factors, eventually invading new tissues to form metastases, thereby increasing the relapse rate of patients after surgery[20,21]. The body's immune function is essential for monitoring and inhibiting tumor progression, and T cells and their subsets are particularly associated with the progression of malignant diseases. $CD8^+$ T cells can directly act as effector cells to kill tumor cells, whereas $CD4^+$ T cells mainly inhibit inflammatory factors, secrete specific cytokines to assist other immune cells, regulate the body's immune function against tumors, and increase the body's immune tolerance to achieve antitumor immunity. Thus, changes in the $CD8^+/CD4^+$ ratio directly affect the ability of the body to resist tumor cells[22-24]. Regulatory T cells contribute to the immune escape mechanisms of cancer lesions. When the $CD4^+/CD8^+$ ratio is high, many regulatory T cells infiltrate the tumor and elicit a significant immunosuppressive effect contributing to tumor occurrence, progression, and metastasis. When the $CD4^+/CD8^+$ ratio is increased for various reasons, it indicates that the immune function is in an inhibitory state with decreased immunity and increased tolerance, and the antitumor immune response is also damaged, leading to the proliferation and progression of cancerous lesions and a directly increase in the risk of postoperative relapse. When a patient experiences relapse after surgery, many soluble immunosuppressive factors are produced during tumor regeneration and progression. These hinder the maturation of $CD4^+$ cells, inhibit the immune system, and promote disease progression. This vicious cycle leads to poor patient prognosis[25-27]. Immunoglobulins, such as IgG, IgA, and IgM, are important immune system components. They mainly activate the complement system by specifically binding to antigens, accelerating cell lysis, and enhancing antibody regulation to achieve antitumor immune effects. Abnormal immunoglobulin expression is a manifestation of impaired humoral immune function. Decreased IgG, IgA, and IgM expression indicates decreased mucosal defense and weakened complement-mediated phagocytosis. Thus, the reduced phagocytic removal of cancer cells potentially

Table 2 Assignment of the main independent variables

Independent variable	Variable type	Assignment condition
Degree of differentiation	Dichotomous	1 = low differentiation, 0 = medium and high differentiation
Lesion location	Dichotomous	1 = rectum, 0 = left and right hemicolon
Lymphatic vascular invasion	Dichotomous	1 = presence, 0 = absence
$CD4^+/CD8^+$	Continuous	-
IgG	Continuous	-
IgA	Continuous	-
IgM	Continuous	-
AGR	Continuous	-
NLR	Continuous	-
CYFRA21-1	Continuous	-
VEGF	Continuous	-
PNI	Continuous	-
YKL-40	Continuous	-

TNM: Tumor node metastasis; Ig: Immunoglobulins; NLR: Neutrophils to lymphocytes ratio; AGR: Albumin-globulin ratio; CYFRA21-1: Cytokeratin 19 fragment antigen 21-1; VEGF: Vascular endothelial growth factor; PNI: Prognostic nutritional index; YKL-40: Inflammatory biomarker Chitinase-3-like protein 1.

Table 3 Logistic regression analysis of variables affecting colorectal cancer relapse after laparoscopic radical resection

Correlative factor	β	Standard error	Wald	*P* value	Odds ratio	95%CI
Degree of differentiation	2.940	0.543	29.300	< 0.001	18.913	6.523-54.835
Lesion location	2.610	0.510	26.192	< 0.001	13.600	5.005-36.953
Lymphatic vascular invasion	2.516	0.481	27.330	< 0.001	12.375	4.819-31.780
$CD4^+/CD8^+$	3.794	0.810	21.936	< 0.001	44.438	9.083-217.423
IgG	2.770	0.537	26.597	< 0.001	15.955	5.568-45.712
IgA	3.438	0.721	14.386	< 0.001	32.975	8.889-642.800
IgM	3.292	0.846	15.145	< 0.001	26.883	5.123-141.065
AGR	2.728	0.675	16.332	< 0.001	15.305	4.076-57.474
NLR	1.567	0.355	19.491	< 0.001	4.792	2.390-9.608
CYFRA21-1	8.672	2.245	14.921	< 0.001	5838.165	71.654-475674.916
VEGF	0.024	0.005	19.752	< 0.001	1.025	1.014-1.036
PNI	0.531	0.117	20.459	< 0.001	1.700	1.351-2.140
YKL-40	0.081	0.016	26.151	< 0.001	1.084	1.051-1.119

TNM: Tumor node metastasis; Ig: Immunoglobulins; NLR: Neutrophils to lymphocytes ratio; AGR: Albumin-globulin ratio; CYFRA21-1: Cytokeratin 19 fragment antigen 21-1; VEGF: Vascular endothelial growth factor; PNI: Prognostic nutritional index; YKL-40: Inflammatory biomarker Chitinase-3-like protein 1.

increases the risk of postoperative relapse in patients[28-30].

The AGR and NLR are markers of inflammation that indicate systemic inflammatory response and immunosuppressive function of the body. Inflammatory responses are triggered when the body is infected or exposed to other stimuli. However, unregulated inflammation can cause significant damage to the body, and a chronic inflammatory state impedes immune infiltration and increases angiogenesis, providing an ideal environment for the growth and reproduction of cancer cells and promoting the generation and spread of cancerous lesions. Relapsing tumors aggravate the inflammatory response in the body and form a negative feedback loop that increases the risk of postoperative relapse in patients[31-33].

In addition to the AGR, a combination of albumin and lymphocyte count readouts in the form of PNI may be a useful marker in cancer biology. Lymphocytes are important components of the immune system and are involved in protein recovery and nutrient transport; therefore, PNI can highlight the nutritional status of an individual. Reduced PNI values indicate decreased lymphocyte counts and albumin levels, along with possible inflammation and malnutrition in the body. This can lead to treatment intolerance and a decline in antitumor immune function, increasing cancer cell proliferation and the risk of postoperative relapse[34-36].

The protein antigen CYFRA21-1 is mainly present in the lymph nodes, bone marrow, and epithelium of healthy individuals. When cells become cancerous, proteases are activated, and normal colorectal epithelial tissues are damaged. When cells die, the activated protease accelerates the dissolution rate, a large amount of CYFRA21-1 is released into the blood, and the expression of CYFRA21-1 in serum is increased. Thus, high expression of CYFRA21-1 indicates extensive cell death or damage. We should be aware of the reinvasion of cancer lesions, which indicates that patients have a high risk of relapse[37-39].

Many vascular stimulatory factors can stimulate cancer cells to release many angiogenic factors that promote angiogenesis within tumors. VEGF has a strong induction effect that can accelerate tumor abnormalities and rapid growth. High levels of serum VEGF can promote the abnormal proliferation of tumor cells, accelerate the transformation of cancer cells into solid tumors, stimulate their migration and invasion into surrounding tissues and organs, destroy normal colorectal epithelial tissues and cells, accelerate neoangiogenesis, change the microenvironment, and increase the chance of relapse[40-42].

YKL-40 is a secretory glycoprotein mainly produced by chondrocytes, neutrophils, and other cells under the influence of inflammation. YKL-40 has many biological functions and signals through multiple pathways involved in angiogenesis, cell proliferation and differentiation, and immune and inflammatory responses. High YKL-40 expression may accelerate colorectal epithelial-mesenchymal transition (EMT) by upregulating vimentin and N-cadherin and downregulating E-cadherin. Because EMT is an important process for tumor migration and invasion, increased YKL-40 expression may increase the risk of relapse in patients with CRC after radical surgery[43,44].

CONCLUSION

In this study, we highlighted several risk factors associated with relapse in patients with CRC after surgery, which will enable the adoption of targeted interventions in clinical practice based on the combination of risk factors present. These factors can serve as monitoring strategies for identifying high-risk patients and detecting early disease recurrence. Direct interventions to reduce abnormal expression of these serum indicators may also reduce the risk of relapse after radical surgery. However, owing to the retrospective nature of this study and the limited sampling within a single center, the reproducibility and generalizability of our conclusions requires validation through further exploration. In addition, the results of this study revealed that the TNM stage is not a risk factor for postoperative recurrence in patients with CRC, which is inconsistent with the findings of Ma *et al*[45]. However, this study did not elaborate on the reasons for these inconsistent results. Further research is needed to determine the impact of the TNM stage on postoperative recurrence in patients with CRC.

In conclusion, we identified many risk factors for CRC relapse following laparoscopic radical resection, including tumors located in the rectum with low differentiation and lymphatic vessel invasion; low serum expression of $CD4^+$/$CD8^+$, IgG, IgA, IgM, AGR, and PNI; and high serum expression of NLR, CYFRA21-1, VEGF, and YKL-40. Monitoring these risk factors will help enhance vigilance regarding the risk of CRC relapse after laparoscopic radical surgery.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) is a prevalent and life-threatening disease that often necessitates surgical intervention, such as laparoscopic radical resection. However, despite successful surgical procedures, a subset of patients experiences relapse. The identification of risk factors associated with CRC relapse is crucial for guiding clinical interventions and enhancing patient outcomes. This study aimed to conduct a comparative analysis of baseline data and laboratory indicators in CRC patients to determine the risk factors contributing to relapse following laparoscopic radical resection. A retrospective analysis was performed on 140 CRC patients, of which 30 experienced relapse within three years after surgery. The study revealed that tumors located in the rectum with low differentiation and lymphatic vessel invasion were associated with higher relapse rates. Additionally, specific serum markers, including $CD4^+/CD8^+$ ratio, immunoglobulins (Ig) IgA, IgG, IgM, albumin-globulin ratio (AGR), neutrophils to lymphocytes ratio (NLR), cytokeratin 19 fragment antigen 21-1 (CYFRA 21-1), vascular endothelial growth factor (VEGF), and the inflammatory biomarker Chitinase-3-like protein 1 (YKL-40), were identified as independent risk factors for CRC relapse. These findings underscore the importance of monitoring these factors to reduce the risk of disease recurrence and improve patient outcomes.

Research motivation

CRC is a significant health burden with the potential for relapse even after successful surgical intervention. The identification of risk factors associated with CRC relapse is crucial to guide clinical interventions and enhance patient outcomes. This study aimed to analyze the baseline data and laboratory indicators of CRC patients who underwent

laparoscopic radical resection, with the objective of determining the risk factors contributing to relapse. The findings highlighted several key factors, including tumor location, differentiation, lymphatic vessel invasion, as well as serum markers such as $CD4^+/CD8^+$ ratio, IgG, IgA, IgM, AGR, NLR, CYFRA21-1, VEGF, and YKL-40. Understanding these risk factors can aid in identifying high-risk patients and implementing proactive measures for monitoring and intervention, ultimately reducing the risk of relapse and improving the long-term survival prospects for CRC patients.

Research objectives

This study aimed to compare baseline data and laboratory indicators of CRC patients who underwent laparoscopic radical resection to identify risk factors associated with CRC relapse. The objectives were to determine the differences in tumor characteristics, analyze serum markers, assess statistical significance, identify independent risk factors using logistic regression, and provide insights for clinical monitoring and interventions to reduce relapse risk and improve patient outcomes.

Research methods

This study utilized a retrospective analysis of baseline data from 140 CRC patients admitted to the hospital between January 2018 and January 2020. The included subjects were followed up until death or a maximum of three years. Comparative analysis was conducted to compare the baseline data and laboratory indicators between patients who experienced relapse and those who did not. Tumor characteristics, including location, differentiation, and lymphatic vessel invasion, were assessed. Serum markers, such as $CD4^+/CD8^+$ ratio, IgG, IgA, IgM, AGR, NLR, CYFRA21-1, VEGF, and YKL-40, were measured and compared between the relapse and non-relapse groups. Statistical analyses were performed to determine the significance of the observed differences. Logistic regression was employed to identify independent risk factors associated with CRC relapse after laparoscopic radical surgery. The research methods aimed to provide valuable insights into the identification and monitoring of risk factors for disease recurrence and improving patient survival outcomes.

Research results

Out of the 140 CRC patients included in the study, 30 cases (21.43%) experienced relapse within three years after laparoscopic radical resection, while 110 patients (78.57%) did not relapse. The relapse group exhibited a higher frequency of tumors located in the rectum with low differentiation and lymphatic vessel invasion compared to the non-relapse group. Significant differences were observed in the levels of several serum markers. The relapse group showed lower expressions of $CD4^+/CD8^+$ ratio, IgG, IgA, IgM, AGR, and PNI. Conversely, the relapse group had higher levels of NLR, CYFRA21-1, VEGF, and YKL-40. Logistic regression analysis confirmed that all these altered factors were independent risk factors for CRC relapse following laparoscopic radical surgery, with odds ratios greater than 1 and statistically significant values ($P < 0.05$). These findings emphasize the importance of monitoring these factors for reducing disease recurrence and improving patient survival outcomes.

Research conclusions

Based on our comparative analysis of baseline data and laboratory indicators in CRC patients who underwent laparoscopic radical resection, we have identified several important conclusions. Firstly, tumors located in the rectum with low differentiation and lymphatic vessel invasion are associated with a higher risk of relapse after surgery. Additionally, lower levels of $CD4^+/CD8^+$ ratio, IgG, IgA, IgM, AGR, and PNI, along with higher levels of NLR, CYFRA21-1, VEGF, and YKL-40, serve as independent risk factors for CRC relapse following surgery. These findings highlight the significance of monitoring these factors to guide clinical interventions and reduce the risk of disease recurrence. By focusing on these risk factors, healthcare professionals can enhance patient surveillance and develop strategies to improve survival outcomes in CRC patients undergoing laparoscopic radical resection.

Research perspectives

The identification of multiple risk factors for CRC relapse following laparoscopic radical surgery provides valuable insights into improving patient outcomes. Moving forward, prospective studies should focus on validating these findings in larger patient populations and diverse healthcare settings. Further investigations can explore the molecular mechanisms underlying the identified risk factors to gain a deeper understanding of their roles in disease recurrence. Additionally, the development of predictive models incorporating these risk factors could aid in personalized treatment strategies and postoperative surveillance. Long-term follow-up studies are warranted to assess the impact of monitoring these factors on long-term survival and quality of life in CRC patients. Furthermore, intervention studies targeting modifiable risk factors may offer potential avenues for reducing disease relapse rates. Overall, continued research efforts in this field will contribute to optimizing clinical management and ultimately enhancing the prognosis of CRC patients undergoing laparoscopic radical resection.

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ORIGINAL ARTICLE

Retrospective Study

Examining the impact of early enteral nutritional support on postoperative recovery in patients undergoing surgical treatment for gastrointestinal neoplasms

Zhi Chen, Bo Hong, Jiang-Juan He, Qian-Qian Ye, Qiao-Yi Hu

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Abstract

BACKGROUND

Patients with gastrointestinal tumors often suffer from poor nutritional status during treatment. Surgery is the main treatment for these patients, but the long postoperative recovery period is often accompanied by digestive and absorption dysfunction, leading to further deterioration of the nutritional status. Early enteral nutrition support is hypothesized to be helpful in improving this situation, but the exact effects have yet to be studied in depth.

AIM

To observe the effect of early enteral nutritional support on postoperative recovery in patients with surgically treated gastrointestinal tract tumors, with the expectation that by improving the nutritional status of patients, the recovery process would be accelerated and the incidence of complications would be reduced, thus improving the quality of life.

METHODS

A retrospective analysis of 121 patients with gastrointestinal tract tumors treated in our hospital from January 2020 to January 2023 was performed. Fifty-three of these patients received complete parenteral nutrition support as the control group

for this study. The other 68 patients received early enteral nutritional support as the observation group of this study. The clinical indicators comparing the two groups included time to fever, time to recovery of postoperative bowel function, time to postoperative exhaustion, and length of hospital stay. The changes in immune function and nutritional indexes in the two groups were compared. Furthermore, we utilized the SF-36 scale to compare the changes in the quality of life between the two groups of patients. Finally, the occurrence of postoperative complications between the two patient groups was also compared.

RESULTS

The postoperative fever time, postoperative bowel function recovery time, postoperative exhaustion time, and hospitalization time were all higher in the control group than in the observation group ($P < 0.05$). The levels of CD3+, CD4+, immunoglobulin (Ig) A, IgM, and IgG in the observation group were significantly higher than those in the control group at 1 d and 7 d postoperatively, while CD8+ was lower than in the control group ($P < 0.05$). Total protein, albumin, prealbumin, and transferrin levels were significantly higher in the observation group than in the control group at 7 d postoperatively ($P < 0.05$). The SF-36 scores of patients in the observation group were significantly higher than those in the control group ($P < 0.0001$). The overall incidence of adverse reactions after the intervention was significantly lower in the control group than in the observation group ($P = 0.021$).

CONCLUSION

We found that patients with gastrointestinal tumors are nutritionally vulnerable, and early enteral nutrition support programs can improve the nutritional status of patients and speed up postoperative recovery. This program can not only improve the immune function of the patient and protect the intestinal function, but it can also help to improve the quality of life of the patient. However, this program will increase the incidence of complications in patients. Caution should be taken when adopting early enteral nutrition support measures for patients with gastric cancer. The patient's condition and physical condition should be comprehensively evaluated and closely monitored to prevent possible complications.

Key Words: Early enteral nutrition support; Surgical treatment; Gastrointestinal tumor; Postoperative recovery; Immune function

Core Tip: This study demonstrated the critical role of early enteral nutritional support in the postoperative recovery of patients undergoing surgery for gastrointestinal tract tumors. This strategy not only helped to improve patient nutritional status, accelerate postoperative recovery, and reduce the incidence of complications but also improved patient quality of life by enhancing immune function and protecting intestinal function. Early enteral nutritional support becomes an important component of postsurgical care for gastrointestinal tumors and helps to improve the overall outcome of patients.

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INTRODUCTION

The continuous development of medical technology has significantly improved the effectiveness of prevention and treatment of many diseases[1]. Nonetheless, the comprehensive fight against cancer remains an unfinished task that seriously threatens the lives and health of patients[2]. According to the Global Cancer Statistics 2020 report[3], colorectal and gastric cancers ranked third and fifth in global cancer incidence and second and fourth in mortality, respectively. Gastrointestinal tract tumors, especially gastric and colorectal cancers, are commonly seen in people over 50 years of age and are among the common diseases in the malignancy category[4]. These two types of cancers often have no obvious specific clinical manifestations in their early stages, resulting in most patients not receiving timely and effective interventions[5]. As the cancer progresses, the demand for nutrients by the cancerous cells increases and the location occupied by the tumor affects the normal absorption function of the intestine, leading to depletion of the body's nutrient reserves and destruction of immune function[6]. For elderly patients with gastric and colorectal cancer, their nutritional status and immune function are often substantially reduced by the effects of cancer, while the stress response of the body triggered by surgery may further exacerbate this situation[7]. Therefore, it is particularly important to implement postoperative clinical nutritional support measures for this specific population.

Parenteral nutrition is widely used in clinical practice by a wide range of physicians to provide effective nutritional supplementation for patients with impaired postoperative gastrointestinal function[8]. It has demonstrated remarkable

efficacy in energy supplementation and maintenance of water-electrolyte balance in patients in the perioperative period [9]. However, as its application has expanded, medical professionals have identified progressive shortcomings after in-depth studies and comparisons[10]. Long-term reliance on parenteral nutrition after gastrointestinal surgery may go against the normal physiology of the gut, resulting in reduced basic activity of the gastrointestinal mucosa, impaired absorption and secretion, and disturbance of the balance of the intestinal flora[11,12]. These effects disrupt the normal microecological environment of the gut, raising the risk of infectious complications, and further delaying the patient's postoperative recovery.

Conventional wisdom tends to suggest that early feeding after gastrointestinal surgery may increase the patient's risk of abdominal pain, bloating, nausea, and vomiting as well as complications such as anastomotic fistula and abdominal infection and that patients are usually allowed to eat after gastrointestinal function has been restored[13]. However, with the in-depth study of early enteral nutrition support modalities after gastrointestinal surgery, some studies have pointed out that providing enteral nutrition support early to patients after radical gastric cancer surgery can promote the absorption and secretion function of the gastrointestinal tract and shorten the length of hospital stay of patients[14]. Moreover, compared with parenteral nutrition support, enteral nutrition support early after gastric cancer surgery does not increase the incidence of postoperative complications[15]. Early postoperative feeding is more in line with the normal physiological needs of the body and has a stimulating effect on the digestive and secretory functions of the gastrointestinal tract, which is conducive to the recovery of the gastrointestinal mucosa, promotes the absorption of nutrients, and reduces postoperative adverse reactions. However, there are insufficient studies on whether early enteral nutritional support has an impact on the postoperative recovery of patients with gastrointestinal tumors.

In the present study, we analyzed the effect of early enteral nutritional support on postoperative recovery in patients with surgically treated gastrointestinal tract tumors and provided reference for clinical gastrointestinal tract tumor nutritional supplementation protocols.

MATERIALS AND METHODS

Ethical statement

This study was conducted with the approval of Xiangshan First People's Hospital Medical and Health Group Medical Ethics Committee, ethical approval number: 2023-(k)-41.

Clinical data

We conducted a retrospective analysis of 121 patients with gastrointestinal tract tumors treated at our hospital from January 2020 to January 2023. Fifty-three of these patients received complete parenteral nutrition support as the control group for this study. The other 68 patients received early enteral nutritional support as the observation group of this study.

Inclusion and exclusion criteria

Inclusion criteria: Patients with diagnosed gastric and colorectal cancer; patients having undergone radical tumor resection or partial gastrointestinal resection; patients over 60 years of age; patients with a clear state of consciousness and normal communication skills; and patients having complete clinical information.

Exclusion criteria: presence of severe psychological or psychiatric illness; presence of other types of malignancy; insufficiency of vital organs such as the heart, liver, and kidneys; and comorbidities at other sites.

Support program

Control group: Complete parenteral nutrition support was used in the control group. After central venous cannulation, prepared nutritional solutions such as sodium chloride injection and compounded amino acids were administered *via* intravenous drip starting 20 h after surgery. The indwelling gastric tube was removed after the patient's gastrointestinal function was restored.

Observation group: The observation group received early enteral nutritional support. A nasojejunal tube and a gastrointestinal decompression tube were left in place during the operation. The jejunal tube was placed under direct vision along a guide wire into the jejunal output collaterals, while the end of the gastric tube was placed into the stomach. Twenty hours after surgery, warm saline was dripped through the enteral tube, and a slow drip of enteral nutrition mix was administered. The temperature of the nutrient solution should be kept at 37 to 40 C. After the anus has begun to pass, remove the gastric tube and start a small amount of liquid food by mouth, while reducing the amount of nutrient solution injected through the jejunal tube. Once the patient was able to eat normal liquid food, the nutrition tube was removed. The nursing staff used positive and optimistic words to encourage the patient during daily rounds, identified any negative emotions in time, and provided targeted psychological counselling to help the patient build up confidence in overcoming the disease.

Indicator testing

Immune function: Venous blood was collected on an empty stomach before surgery and 1 d and 7 d after surgery, and peripheral blood T cell subset (CD3+, CD4+, and CD8+) activity was measured by flow cytometry. Immunoglobulins (Igs) [IgA, IgM, and IgG] were measured by enzyme-linked immunoassay.

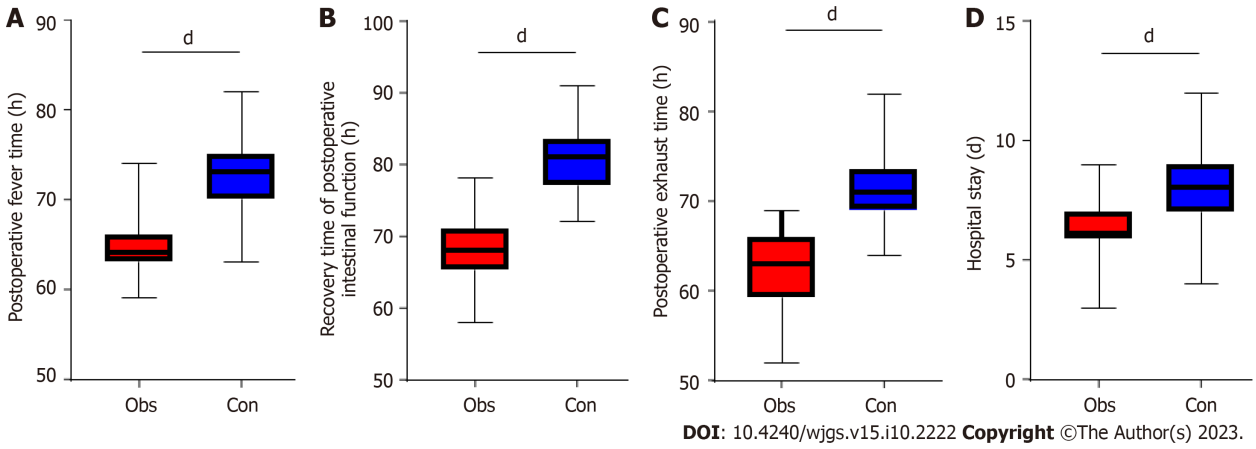

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Figure 1 Comparison of patient postoperative clinical indicators. A: Comparison of the time to postoperative fever after surgery; B: Comparison of patient postoperative bowel function recovery time; C: Comparison of patient postoperative time to exhaustion; D: Comparison of patient length of stay in hospital. $^{d}P < 0.0001$. Con: Control group (received complete parenteral nutritional support); Obs: Observation group (received early enteral nutritional support).

Nutritional parameters: Venous blood was collected before surgery and 1 d and 7 d after surgery on an empty stomach. Total protein (TP) and albumin (ALB) were measured by the bicuculline method, prealbumin (PAB) was measured by the immunoturbidimetric method, and transferrin (Tf) was measured by the immunoscattering turbidimetric method.

Observation indexes

Main observation indexes: The clinical indexes of the two groups including time to fever, time to recover intestinal function after surgery, time to postoperative exhaustion, and length of hospital stay were compared. The changes in immune function and nutritional indicators between the two groups were also compared.

Secondary observation indexes: The clinical data and postoperative complications of the two groups of patients were compared. Using the SF-36 scale[16], the changes in quality of life of patients in the two groups was compared.

Statistical analysis

The data collected in this study were statistically analyzed using the SPSS 26.0 software package, and GraphPad Prism 9 was used to plot the pictures of this data. The count data were expressed in % using the χ^2 test as well as the Fisher test. The measurement data were expressed using the mean ± SD. The preoperative and postoperative comparisons between the same groups were made using the paired t test, and independent samples t test was used for comparison between two groups. Statistical differences were indicated when $P < 0.05$.

RESULTS

Comparison of general clinical information

A comparison of the clinical data between the two groups revealed that there was no statistical difference in age, sex, body mass index, tumor location, degree of tumor differentiation, history of diabetes mellitus, hypertension, smoking, and alcohol abuse between the control group and the observation group ($P > 0.05$; Table 1).

Comparison of clinical indicators

In this study we also compared the clinical indicators of the two groups of patients after treatment. Our results found that the time to postoperative fever, time to recovery of postoperative bowel function, time to postoperative evacuation, and time to hospitalization were all higher in the control group than in the observation group ($P < 0.001$; Figure 1).

Comparison of immune function

In this study, we compared the immune function of the two groups of patients. We found that there was no difference in CD3+, CD4+, CD8+, IgA, IgM, and IgG between the two groups of patients before surgery ($P > 0.05$). In both groups, there was a decrease in CD3+, CD4+, IgA, IgM, and IgG and an increase in CD8+ at 1 d postoperatively compared to the preoperative period ($P < 0.05$; Figures 2 and 3). However, further comparison revealed that CD3+, CD4+, IgA, IgM, and IgG levels were significantly higher in the observation group than in the control group at 1 d postoperatively, while CD8+ was lower than in the control group ($P < 0.05$; Figures 2 and 3). At the 7th postoperative day, CD3+, CD4+, IgA, IgM, and IgG levels increased in both groups, while CD8+ decreased in both groups ($P < 0.05$; Figures 2 and 3). In addition, the levels of CD3+, CD4+, IgA, IgM, and IgG in the observation group were significantly higher than those in the control group at 7 d postoperatively compared with those at 1 d, while CD8+ was lower than that in the control group ($P < 0.05$;

Table 1 Comparison of the general clinical data of the two group

Characteristic	Observation group, *n* = 53	Control group, *n* = 68	*P* value
Age in yr			
≥ 65	30	44	0.369
< 65	23	24	
Sex			
Male	25	37	0.444
Female	28	31	
BMI in kg/m^2			
≥ 25	13	14	0.511
< 25	40	54	
Tumor location			
Stomach	24	37	0.275
Colorectal	29	31	
Tumor differentiation			
Low	20	31	0.438
Medium, high	33	37	
Diabetes mellitus			
Yes	6	12	0.363
No	47	56	
Hypertension			
Yes	10	17	0.432
No	43	51	
Smoking			
Yes	27	37	0.584
No	27	31	
Alcohol			
Yes	4	3	0.500
No	49	65	

BMI: Body mass index.

Figures 2 and 3). Further comparison revealed that the CD3+, CD4+, IgA, IgM, and IgG levels in the observation group were significantly higher than those in the control group at 7 d postoperatively, while CD8+ was lower than that in the control group ($P < 0.05$; Figures 2 and 3).

Comparison of nutritional function

In this study we compared the nutritional function of the two groups of patients. Our comparison revealed no difference in preoperative TP, ALB, PAB, and Tf between the two groups ($P > 0.05$). TP, ALB, PAB, and Tf decreased in both groups at 1 d postoperatively compared to preoperatively ($P < 0.05$; Figure 4). However, further comparison revealed that TP, ALB, PAB, and Tf levels were significantly higher in the observation group than in the control group at 1 d postoperatively ($P < 0.05$; Figure 4). At the 7th postoperative day, TP, ALB, PAB, and Tf were all increased in both groups ($P < 0.05$; Figure 4). The TP, ALB, PAB, and Tf levels in the observation group were significantly higher than those in the control group at day 7 compared to day 1, while CD8+ was lower than that in the control group ($P < 0.05$; Figure 4). Further comparison revealed that TP, ALB, PAB,, and Tf levels in the observation group were significantly higher than those in the control group at 7 d postoperatively ($P < 0.05$; Figure 4).

Comparison of quality of life

The quality of life was assessed between the two groups of patients before surgery and before discharge. The results

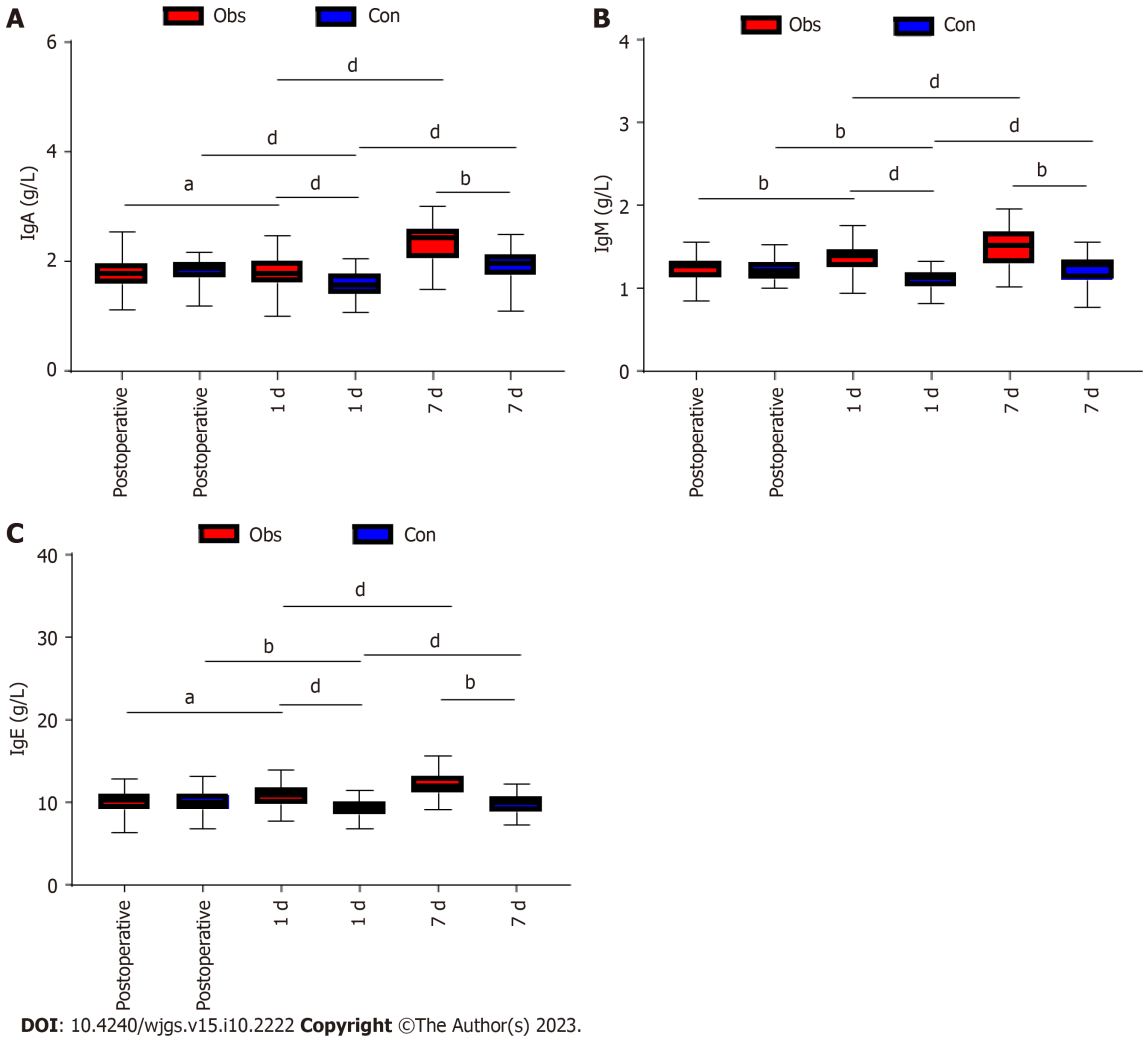

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Figure 2 Comparison of immunoglobulin indicators between the two groups of patients. A: Comparison of the changes in immunoglobulin (Ig) A before surgery and 1 d and 7 d after surgery; B: Comparison of IgM changes before surgery and 1 d and 7 d after surgery between the two groups; C: Comparison of IgG changes before surgery and 1 d and 7 d after surgery between the two groups of patients. $^{a}P < 0.05$; $^{b}P < 0.01$; $^{d}P < 0.0001$. Con: Control group (received complete parenteral nutritional support); Obs: Observation group (received early enteral nutritional support).

showed that there was no difference in the preoperative SF-36 scores between the two groups ($P > 0.05$), and the SF-36 scores of patients in both groups increased significantly after the intervention compared with those before the intervention ($P < 0.0001$). The SF-36 score was significantly higher in the observation group than in the control group before discharge ($P < 0.0001$; Figure 5).

Adverse reaction statistics

Statistics on adverse reactions after treatment in both groups showed that the overall incidence of adverse reactions after intervention was significantly lower in the control group than in the observation group ($P = 0.021$; Table 2).

DISCUSSION

The nutritional management of patients with gastrointestinal tract tumors remains a difficult issue globally. Studies have shown that these patients are at very high nutritional risk and that patients suffer from concomitant malnutrition[17]. The stomach and intestines are important components of the digestive system. They play an important role in the digestion and absorption of nutrients, and tumor invasion can severely interfere with these normal digestive and absorption functions[18]. Surgery is the main treatment modality, but it is also associated with significant surgical trauma, long recovery times, and the absence of parts of the gastrointestinal tract[19]. These problems, together with the metabolic disorders caused by the tumor, can affect the nutritional status of the patient.

Patient digestive and metabolic capacity is reduced as a result of the disease, and they eat less, which in turn leads to a decrease in immune function[20]. This immunosuppression is more likely to occur in postsurgical patients due to their inability to eat normally[21]. Therefore, it is crucial to provide professional nutritional support after surgery for patients with gastrointestinal tumors, not only to improve the safety of surgery but also to speed up the recovery of the disease. In

Table 2 Adverse reaction statistics

Groups	Gastrointestinal symptoms	Incisional infection	Anastomotic leak	Incidence
Observation group, n = 53	4	3	2	9
Control group, n = 68	1	1	1	3
χ^2				5.267
P value				0.021

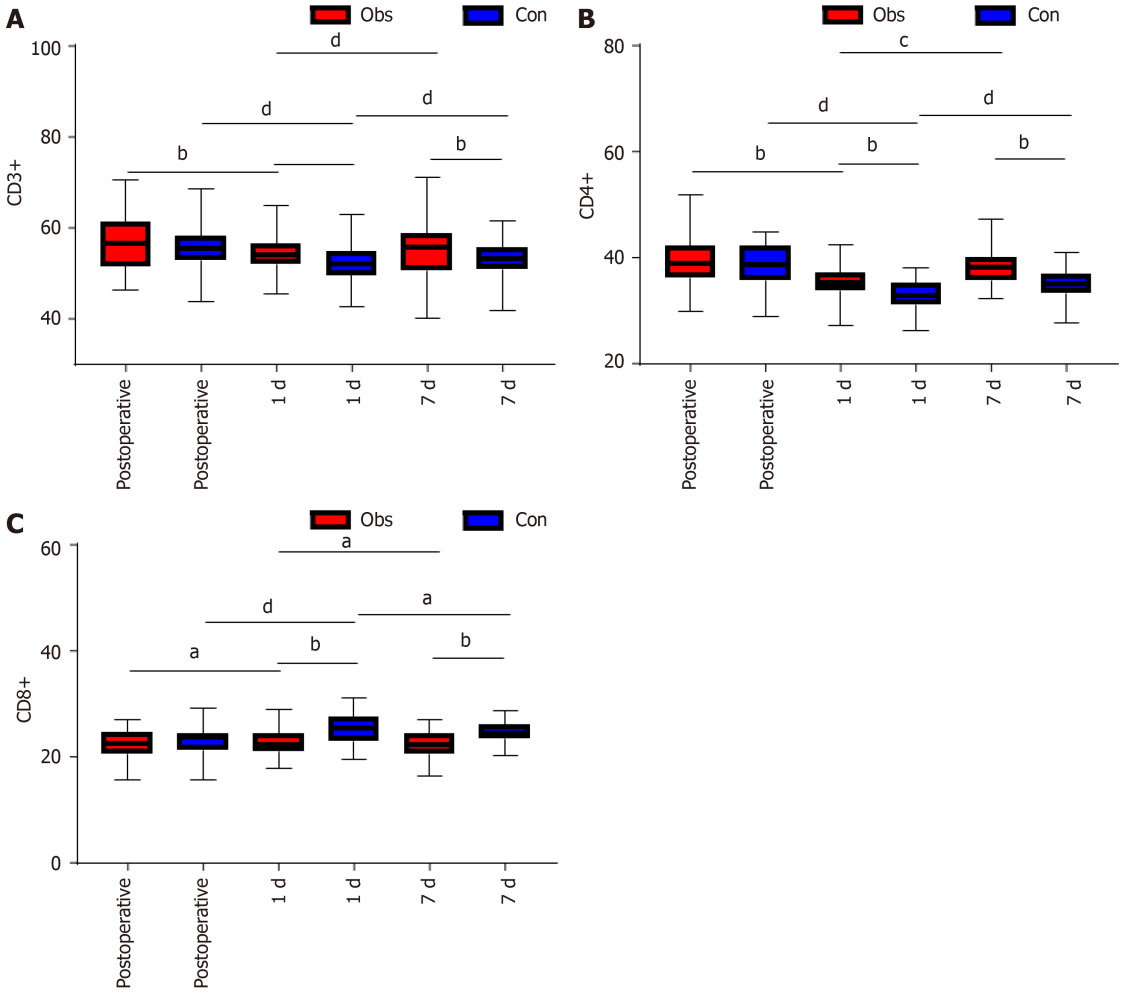

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Figure 3 Comparison of peripheral blood T lymphocyte subpopulation indicators between the two groups of patients. A: Comparison of CD3 changes before surgery and 1 d and 7 d after surgery between the two groups; B: Comparison of CD4 changes before surgery and 1 d and 7 d after surgery between the two groups; C: Comparison of the changes in CD8 before surgery and 1 d and 7 d after surgery between the two groups of patients. $^{a}P < 0.05$; $^{b}P < 0.01$; $^{c}P < 0.001$; $^{d}P < 0.0001$. Con: Control group (received complete parenteral nutritional support); Obs: Observation group (received early enteral nutritional support).

this study, we found that patients in the observation group who received the early enteral nutrition support protocol had significantly lower postoperative fever time, postoperative bowel function recovery time, postoperative exhaustion time, and hospital stay than the control group who did not receive the protocol. But, the overall incidence of postoperative complications was significantly lower in the control group than in the observation group.

These findings suggest that early enteral nutrition support programs can accelerate disease recovery. This finding is in line with the meta-analysis by Li *et al*[22], which found that patients with gastric cancer combined with diabetes were more effective in maintaining glycemic stability after early enteral nutrition intervention compared to those receiving total parenteral nutrition intervention, resulting in better outcomes. Another study conducted by Yan *et al*[23] also pointed out that early enteral nutritional support after surgery for patients with gastrointestinal tract tumors significantly reduced the incidence of postoperative complications and shortened the length of hospital stay. However, our study found that the early enteral nutrition program increased the incidence of postoperative complications in patients with gastric cancer. The reason for this may be related to the risk of early enteral nutrition and the patient's condition. Specifically, early enteral nutrition may cause excessive enteral nutrition and increase gastrointestinal symptoms such as

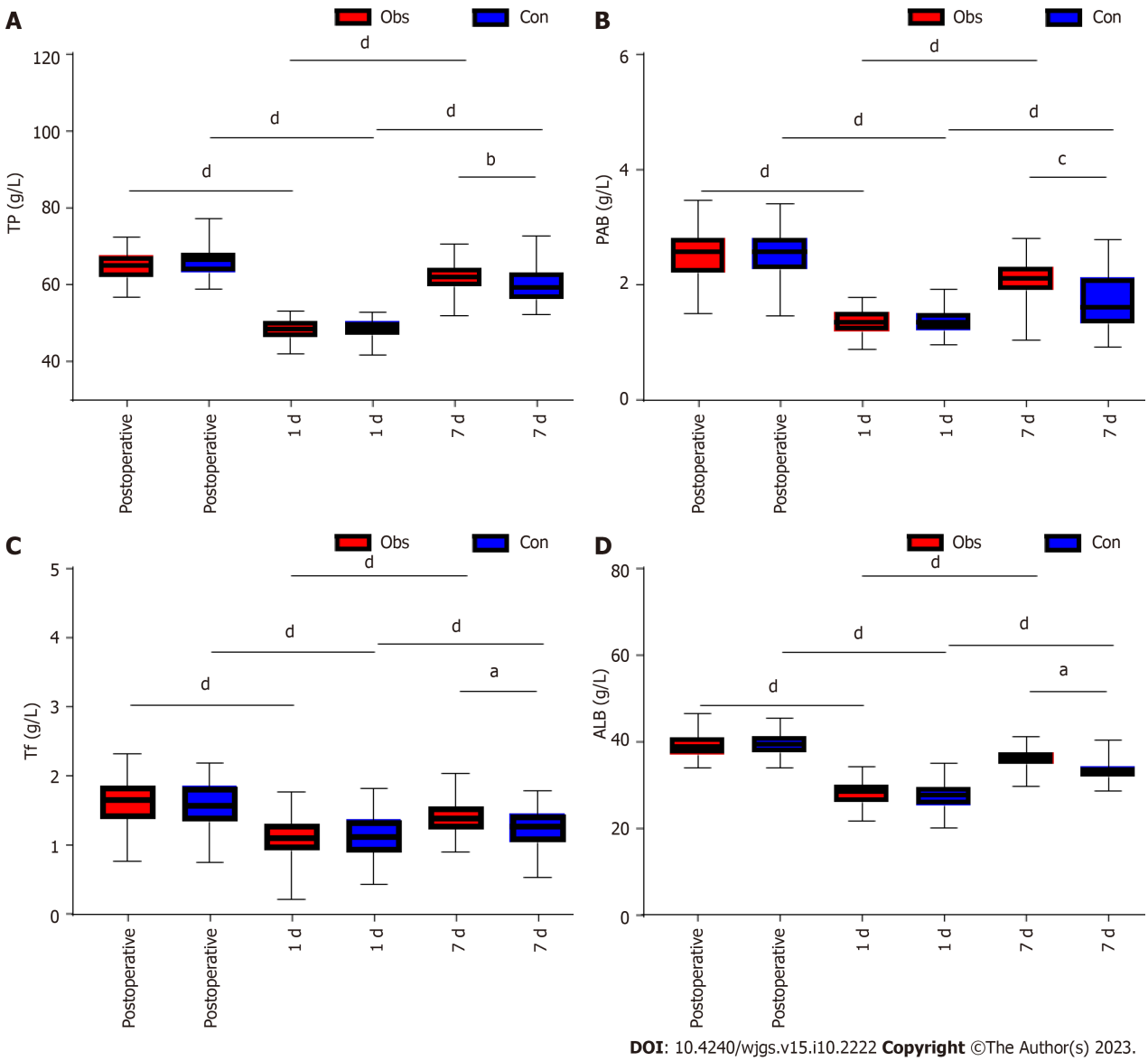

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Figure 4 Comparison of nutritional function indicators between the two groups of patients. A: Comparison of the changes in total protein before surgery and 1 d and 7 d after surgery between the two groups; B: Comparison of the changes in prealbumin before surgery and 1 d and 7 d after surgery between the two groups; C: Comparison of the changes in transferrin (Tf) before surgery and 1 d and 7 d after surgery in the two groups; D: Comparison of the changes in albumin before surgery and 1 d and 7 d after surgery in the two groups. $^{a}P < 0.05$; $^{b}P < 0.01$; $^{c}P < 0.001$; $^{d}P < 0.0001$. Con: Control group (received complete parenteral nutritional support); Obs: Observation group (received early enteral nutritional support).

diarrhea; at the same time, early enteral nutrition also carries risk of complications such as infection, bleeding and intestinal obstruction. In addition, considering the large surgical wound produced by gastric cancer treatment, early enteral nutrition may increase the probability of serious complications such as anastomotic leakage. As for the patients themselves, all were of advanced age, a factor that increases the risk of various postoperative complications. Therefore, the results of this study suggest that early enteral nutritional support measures for gastric cancer patients should be applied with caution, and each patient's condition and physical status should be comprehensively assessed, while close monitoring should be performed to prevent complications or promptly address any that may arise.

We believe that early enteral nutrition support protocol is effective because it helps the synthesis of visceral proteins, thus shortening the recovery time of postoperative bowel function and postoperative fever. In addition, early enteral nutrition can reduce the damage to the intestinal mucosa and is more in line with the physiological state of the body, thus reducing the impact on the circulatory system and decreasing the time of postoperative exhaustion. This effect not only helps to reduce the length of the patient's hospital stay but also reduces the cost of treatment to a certain extent.

The immune system plays a vital role in the body. However, in serious diseases such as gastrointestinal tumors, the function of the immune system may be compromised[24]. For example, treatment modalities such as surgery, chemotherapy, or radiotherapy may lead to a reduction in immune cells, which may affect immune function[25]. In such cases, enteral nutritional support can play an important role. In the current study, we found that patients in the observation group had significantly higher levels of CD3+, CD4+, IgA, IgM, and IgG and lower levels of CD8+ than the control group at postoperative day 1 and day 7, suggesting that early enteral nutritional support can maintain the

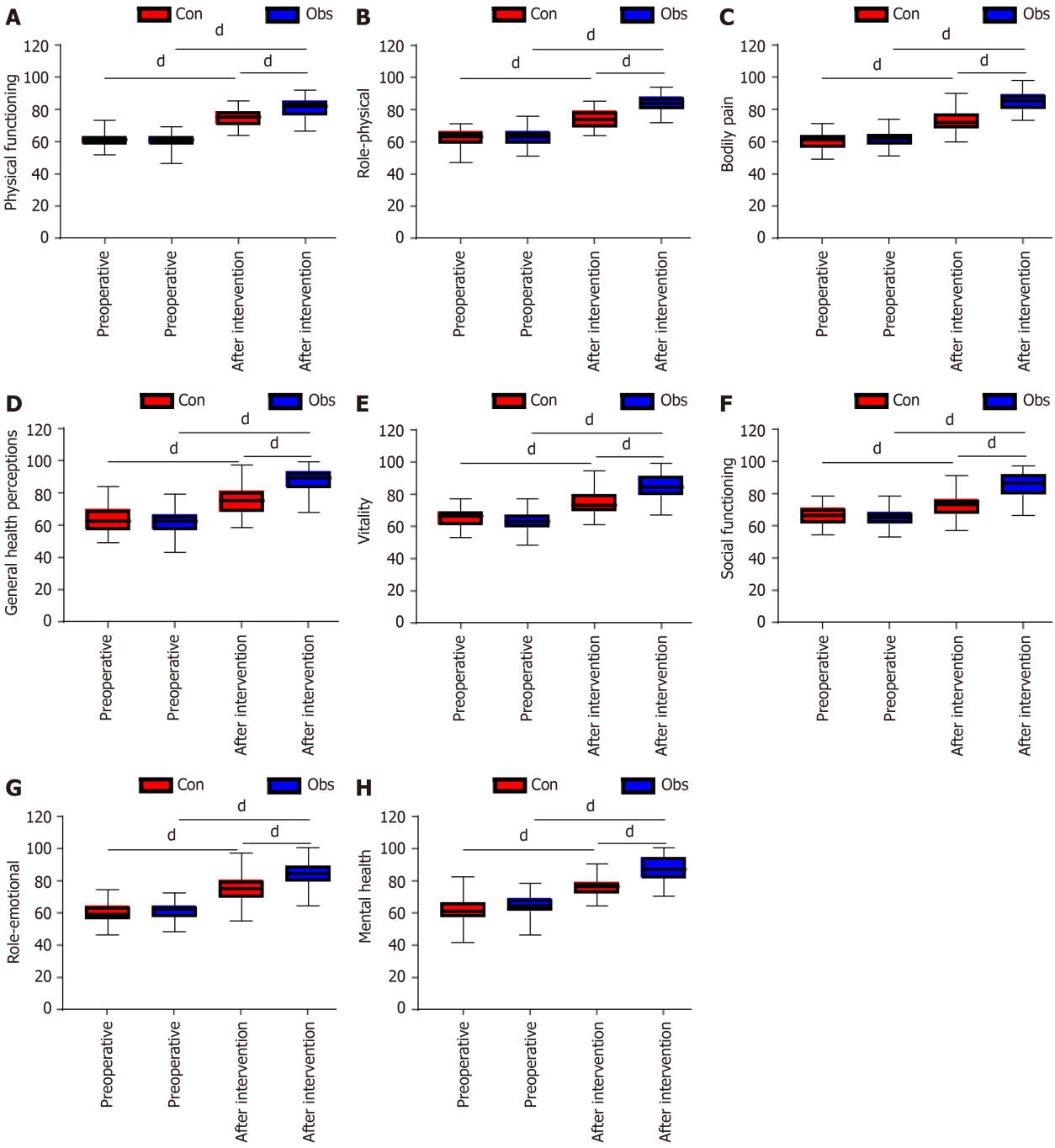

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Figure 5 Comparison of patient quality of life scores before and after the intervention. A: Physical functioning scores before and after the intervention; B: Role-physical scores before and after intervention; C: Bodily pain scores before and after intervention; D: General health perceptions scores before and after the intervention; E: Vitality scores before and after the intervention; F: Social functioning scores before and after the intervention; G: Role-emotional scores before and after the intervention; H: Mental health scores before and after the intervention. $^{d}P < 0.0001$. Con: Control group (received complete parenteral nutritional support); Obs: Observation group (received early enteral nutritional support).

stability of immune function in patients.

Previously, in a study by Wang *et al*[26], early enteral nutritional support was found to improve immune function in patients after radical chemotherapy gastric cancer to reduce the occurrence of postoperative complications. This is largely consistent with our study. We hypothesize this is due to the immune system requiring high amounts of energy and nutrients, including protein, fat, carbohydrates, vitamins, and minerals, to function properly. Early enteral nutritional support ensures that patients receive these essential nutrients to maintain and enhance the function of the immune system. Early enteral nutritional support can protect the function of the intestinal tract from damage caused by tumor treatment (*e.g.*, surgery, chemotherapy) and maintain the immune function of the intestinal tract. Early enteral nutritional support can speed up postoperative recovery and reduce surgical complications, such as infection and delayed wound healing.

At the end of the study we analyzed the nutritional function and quality of life of patients in both groups. In our results, TP, ALB, PAB, and Tf levels in the observation group were not different from those in the control group before and 1 d after the intervention, but at 7 d after the intervention TP, ALB, PAB and Tf were higher than those in the control group. These results suggested that early enteral nutrition support can improve nutritional function and enhance quality of life. This is because early enteral nutrition support, in line with the natural physiological characteristics of human diet, is beneficial to the growth of intestinal mucosal cells and maintains the integrity of the intestinal mucosal barrier, thus ensuring the normal intake of nutrients[27-29]. The application of this nutritional support strategy can rapidly provide patients with the necessary nutrients to effectively improve their nutritional status, enhance their body protein content, and improve their negative nitrogen balance. Effective psychological care by nursing staff also plays an important role, which helps to improve the emotional state of patients, their confidence in treatment, and their resistance to the disease. This holistic approach to care, which includes nutritional and psychological support, provides strong support for the patient's full recovery.

In this study, we determined the value of early enteral nutritional support in patients with gastrointestinal tumors, but there are still limitations to this study. First, we did not obtain long-term prognostic data in this study, and more experimental data are needed to verify whether early enteral nutrition support has an effect on patient prognosis. Second, this study is a single-center retrospective study, and the sample size was small. Therefore, more data are needed to support whether it is representative. Finally, we anticipate that more clinical studies will be conducted in subsequent studies to refine our findings.

CONCLUSION

We found that patients with gastrointestinal tumors are nutritionally vulnerable, and early enteral nutrition support programs can improve the nutritional status of patients and speed up postoperative recovery. This program can not only improve the immune function of the patient and protect the intestinal function but also help to improve the quality of life of the patient. However, this program will increase the incidence of complications in patients. Caution should be taken when adopting early enteral nutrition support measures for patients with gastric cancer. Each patient's condition and physical status should be comprehensively evaluated and closely monitored with the aim of preventing the possible complications.

ARTICLE HIGHLIGHTS

Research background

Patients with gastrointestinal tumors often suffer from malnutrition, and surgical treatment may further affect nutrient absorption and metabolism. In this context, nutritional interventions to improve patients' postoperative recovery and quality of life become critical. Early enteral nutrition support as a form of nutritional management can theoretically help to improve the nutritional status of patients and accelerate recovery, but its actual effectiveness needs to be supported by clinical evidence.

Research motivation

The postoperative nutritional management of patients with gastrointestinal tumors remains a global challenge that has a significant impact on patient recovery and overall prognosis. Our motivation was to investigate the impact of early enteral nutritional support on postoperative recovery in patients with gastrointestinal tract tumors.

Research objectives

The main objective of this study was to evaluate the use of early enteral nutrition support in patients undergoing surgery for gastrointestinal tract tumors and to determine how it improves postoperative complications, enhances quality of life, promotes immune function, and improves nutritional status.

Research methods

In a retrospective study, we compared patients who received early enteral nutrition support with those who did not, examining the incidence of postoperative complications, time to recovery, nutritional parameters, and quality of life.

Research results

The results showed that early enteral nutrition support significantly improved recovery time and nutritional status, increased the incidence of postoperative complications, and improved quality of life.

Research conclusions

We concluded that early enteral nutrition support plays a key role in the postoperative recovery of patients with surgically treated gastrointestinal tract tumors, suggesting that the importance of early enteral nutrition support in the postoperative management of these patients should not be overlooked.

Research perspectives

Further research is needed to examine the impact of early enteral nutrition support on the long-term prognosis of patients with gastrointestinal tumors and its potential application in a broader clinical context. We look forward to future clinical studies that will provide more data and insight into this area.

FOOTNOTES

Author contributions: Chen Z and Hong B contributed equally to this work; Chen Z, Hong B, He JJ, Ye QQ, and Hu QY designed the research study; Chen Z, Hong B, and He JJ performed the research, analyzed the data, and wrote the manuscript; Ye QQ and Hu QY contributed new reagents and analytic tools; All authors have read and approved the final manuscript.

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Institutional review board statement: The study was conducted with the approval of the Ethics Committee of the Medical and Healthcare Group of the First People's Hospital of Xiangshan County, with the ethical approval number: 2023-(k)-41.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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

Data sharing statement: The data collected for this study are available from the corresponding author.

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ORIGINAL ARTICLE

Retrospective Study

Predicting lymph node metastasis in colorectal cancer: An analysis of influencing factors to develop a risk model

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Abstract

BACKGROUND

Colorectal cancer (CRC) is a significant global health issue, and lymph node metastasis (LNM) is a crucial prognostic factor. Accurate prediction of LNM is essential for developing individualized treatment strategies for patients with CRC. However, the prediction of LNM is challenging and depends on various factors such as tumor histology, clinicopathological features, and molecular characteristics. The most reliable method to detect LNM is the histopathological examination of surgically resected specimens; however, this method is invasive, time-consuming, and subject to sampling errors and interobserver variability.

AIM

To analyze influencing factors and develop and validate a risk prediction model for LNM in CRC based on a large patient queue.

METHODS

This study retrospectively analyzed 300 patients who underwent CRC surgery at two Peking University Shenzhen hospitals between January and December 2021. A deep learning approach was used to extract features potentially associated with LNM from primary tumor histological images while a logistic regression model was employed to predict LNM in CRC using machine-learning-derived features and clinicopathological variables as predictors.

RESULTS

The prediction model constructed for LNM in CRC was based on a logistic regression framework that incorporated machine learning-extracted features and

clinicopathological variables. The model achieved high accuracy (0.86), sensitivity (0.81), specificity (0.87), positive predictive value (0.66), negative predictive value (0.94), area under the curve for the receiver operating characteristic (0.91), and a low Brier score (0.10). The model showed good agreement between the observed and predicted probabilities of LNM across a range of risk thresholds, indicating good calibration and clinical utility.

CONCLUSION

The present study successfully developed and validated a potent and effective risk-prediction model for LNM in patients with CRC. This model utilizes machine-learning-derived features extracted from primary tumor histology and clinicopathological variables, demonstrating superior performance and clinical applicability compared to existing models. The study provides new insights into the potential of deep learning to extract valuable information from tumor histology, in turn, improving the prediction of LNM in CRC and facilitate risk stratification and decision-making in clinical practice.

Key Words: Colorectal cancer; Lymph node metastasis; Machine learning; Risk prediction model; Clinicopathological factors; Individualized treatment strategies

Core Tip: This study developed a robust risk prediction model for lymph node metastasis (LNM) in colorectal cancer (CRC) using machine learning and clinicopathological factors. The model achieved high accuracy, sensitivity, and specificity, demonstrating its superior performance compared to existing models. By leveraging deep learning to extract information from tumor histology, the model improves LNM prediction, facilitating individualized treatment strategies and clinical decision-making in CRC.

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INTRODUCTION

Colorectal cancer (CRC) is a significant global health issue, and lymph node metastasis (LNM) is a crucial prognostic factor in CRC patients. Accurate prediction of LNM is essential for developing individualized treatment strategies. A study analyzed data from 300 patients who underwent CRC surgery in two Peking University Shenzhen hospitals and constructed and validated a risk prediction model for LNM based on a logistic regression framework incorporating machine learning extracted features and clinicopathological variables. The model achieved high accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the receiver operating characteristic (ROC) curve (AUROC) in the validation set and demonstrated good calibration and clinical utility. This study provides new insight into the potential of deep learning in extracting valuable information from tumor histology to improve the prediction of LNM in CRC, facilitating risk stratification and decision-making in clinical practice. CRC has emerged as the dominant form of cancer worldwide and plays a substantial role in the mortality associated with cancer [1]. LNM is a crucial prognostic factor and determinant of the treatment strategy for CRC[2]. Patients with LNM have significantly worse survival outcomes than those without LNM and require more aggressive treatment modalities, such as adjuvant chemotherapy or radiotherapy[3]. Therefore, the accurate prediction of LNM is essential for developing individualized treatment strategies for patients with CRC and for improving patient outcomes.

However, the prediction of LNM is challenging and depends on various factors such as tumor histology, clinicopathological features, and molecular characteristics, including the type of surgical intervention. For instance, studies have indicated that old age and male sex are associated with a higher risk of LNM[4]. Notably, tumors in the right colon exhibit an elevated risk of LNM compared with those in the left colon[5]. Additionally, larger and poorly differentiated tumors are more likely to metastasize to lymph nodes[6]. Research indicates that the extent of lymph node dissection during surgery may influence the likelihood of detecting LNM[7]. Moreover, neoadjuvant therapy can potentially influence lymph node status during surgical procedures[8]. Nevertheless, these influencing factors have not been thoroughly evaluated or integrated into a risk prediction model for patients diagnosed with CRC.

The most reliable method to detect LNM is histopathological examination of surgically resected specimens[9]. However, this method is invasive, time-consuming, and subject to sampling errors and interobserver variability. Moreover, some patients may undergo unnecessary surgery or overtreatment owing to false-positive or false-negative results[10]. Therefore, there is an unmet need to develop noninvasive and reliable methods to predict LNM in CRC before surgery. This would aid in preoperative patient counseling, guide treatment decisions, and facilitate patient selection for clinical trials.

Several studies have attempted to identify the risk factors or biomarkers for LNM in CRC using conventional statistical methods or machine learning techniques[11-13]. However, most of these studies had limitations, such as small sample size, single-center design, lack of external validation, and low predictive performance[14-16]. Moreover, most of these studies have singularly focused on either tumor histology or clinicopathological factors, while ignoring the potential synergistic effects of combining multiple sources of information[17,18].

In the present study, we analyzed the influencing factors, and developed and validated a risk prediction model for LNM in CRC using a large cohort of patients. Relevant attributes were extracted from the histology of primary tumors and clinicopathological data using machine learning. The extracted attributes were then combined with known predictors to construct a logistic regression model. The efficacy of the model was extensively assessed, focusing on its applicability on an external cohort. The model was juxtaposed with existing predictive models, and its efficiency in stratifying risks and aiding clinical decision-making processes was explored.

MATERIALS AND METHODS

Study population and data collection

This study retrospectively analyzed 300 patients who underwent CRC surgery at Peking University Shenzhen Hospital between January and December 2021. The eligibility criteria for the study was as follows: Histopathologically confirmed diagnosis of adenocarcinoma of the colon or rectum, diagnosis of stage I-III disease as per the 8th edition of the American Joint Committee on Cancer staging system, availability of primary tumor histology slides and clinicopathological data, and no prior history of neoadjuvant therapy, synchronous or metachronous malignancy, or hereditary CRC syndrome. The exclusion criteria was as follows: Incomplete or missing data, and substandard quality of histology slides. Finally, 258 participants were included in this study. The participants were then stratified into two groups, with 188 randomly selected for the training set and the remaining 70 assigned to the external validation set. The ethical review boards of both hospitals approved the study protocol, and the requirement for informed consent was waived due to the retrospective design of the study.

Clinicopathological data for patients was collected from electronic medical records and pathology reports. Data included age, gender, tumor location, tumor size, tumor differentiation, depth of tumor invasion, lymphovascular invasion, perineural invasion, tumor budding, and lymph node status. Primary tumor histology slides were retrieved from the pathology archives and scanned using a digital slide scanner (Aperio AT2, Leica Biosystems, Wetzlar, Germany). The scanned images were stored on a secure server and accessed using Image Viewer software (Aperio ImageScope, Leica Biosystems).

Feature extraction from primary tumor histology

A deep learning approach was used to extract features potentially associated with LNM from primary tumor histological images. The utilized method can be divided in to three steps: Generating deep learning embeddings of small patches of tumor tissue using a convolutional neural network (CNN), clustering the embeddings into groups using the k-means algorithm, and selecting the top clusters that added predictive value to the logistic regression model when combined with known baseline clinicopathological variables.

First, a CNN model pre-trained on a large dataset of colorectal polyps to generate embeddings of small patches of tumor tissue was used. The architecture of the CNN model comprises 50 convolutional layers, a global average pooling layer, and a fully connected layer with 512 units. It categorized colorectal polyps into four distinct classes. The output of the model served as the embedding vector for each patch. This model was teste using the training set and subsequently, validated using both the training and external validation sets. From each histological image, patches of 224 × 224 pixels were extracted at 20 × magnification, utilizing a sliding window approach with a stride of 112 pixels. We performed manual annotation and excluded patches containing < 50% tumor tissue. Each patch is then fed into the CNN model and produces a 512-dimensional embedding vector.

Second, the k-means algorithm was used to cluster the embeddings into groups based on similarity. Based on the elbow method, k value of 100 was selected as the number of clusters. Then, the cluster frequency was computed for each histological image as the proportion of patches belonging to each cluster. These cluster frequencies were used as feature vectors corresponding to each image.

Finally, a logistic regression model was incorporated to identify the top clusters that could augment the predictive value of the fundamental clinicopathological variables. LNM was the outcome variable in our analysis and six fundamental clinicopathological variables (age, gender, tumor location, tumor size, tumor differentiation, and tumor invasion depth) served as primary predictors. Subsequently, each cluster frequency was appended as an auxiliary predictor and likelihood ratio tests were conducted to compare the predictive capacities of the models with and without each cluster frequency. By ordering the clusters based on their P value, the top ten clusters with $P < 0.05$ were selected. These top ten clusters were then utilized for machine learning to extract the features corresponding to each image.

Construction and validation of risk prediction model

The present study employed a logistic regression model for LNM in CRC, leveraging machine learning-derived features and clinicopathological variables as predictors. LNM was utilized as the outcome variable and 10 predictors *i.e.*, age, gender, tumor position, size, differentiation, depth of invasion, lymphovascular invasion, perineural invasion, tumor budding, and frequency of the top ten clusters, were used. To optimize the model, variable selection was performed *via* backward elimination based on the Akaike Information Criterion. The developed model was then evaluated using a

training cohort and validated using both training and external validation cohorts.

Model performance was evaluated using various metrics including accuracy, sensitivity, specificity, PPV, NPV, AUROC, area under the precision-recall curve (AUPRC), calibration plot, decision curve analysis, net reclassification improvement (NRI), integrated discrimination improvement (IDI), and Brier scores. We compared our model with three existing models for LNM prediction in CRC: Kikuchi's model that uses four clinicopathological variables (tumor size > 3 cm, depth of submucosal invasion > 1 m, positive lymphatic invasion, and positive venous invasion), Ueno's model that uses five clinicopathological variables (depth of submucosal invasion > 1000 μm, positive lymphatic invasion, positive venous invasion, high budding grade, and poor differentiation grade), and Krogue's model that uses six clinicopathological variables (age > 65 years, male gender, right-sided tumor location, tumor size > 4 cm, depth of submucosal invasion > 1000 μm, and poor differentiation grade) and machine learning extracted features from primary tumor histology[19-21].

Statistical analysis

Statistical analysis was performed using R software version 4.0.3. Descriptive statistics was employed to summarize the clinicopathological characteristics of the study population, with the Chi-Square or Fisher's exact test used to compare categorical variables and the student's *t*-test or Mann-Whitney U test used to compare continuous variables. Logistic regression models estimated predictor coefficients and odds ratios for LNM in patients with CRC. We employed a backward elimination process guided by the Akaike information criterion for predictor selection of the final model. Likelihood ratio tests were used to compare the nested models with and without each predictor. The discriminatory abilities of the models were assessed using ROC and precision-recall curves. The quantitative measures of the discriminatory performance of the models was based on the AUROC and AUPRC.

Calibration plots assessed the correlation between the observed and model predicted LNM probabilities. Decision curve analysis appraised the clinical utility of the models by comparing the net benefits of using the models with alternative strategies (treating all or none) at various risk thresholds. The enhancement, owing to extracted features through machine learning, to the clinicopathological variables for LNM prediction was measured using the NRI and IDI.

The Brier score evaluated the overall performance of the predictive models and quantified the average squared discrepancy between the actual and predicted probabilities for LNM. Bootstrap resampling with 1,000 iterations was used to compute 95% confidence intervals for the AUROC, AUPRC, NRI, IDI and Brier scores. Statistical significance was set at a threshold of $P < 0.05$ for statistical significance in all evaluations.

RESULTS

Clinicopathological characteristics of the study population

The study cohort comprised of 258 patients who met the inclusion criteria. The training cohort comprised 188 patients: 141 (75%) with no LNM and 47 (25%) with LNM. The external validation cohort included 70 patients: 52 (74.3%) without LNM and 18 (25.7%) with LNM, as shown in Figure 1. Table 1 shows the clinicopathological characteristics of these patients, with all *P* value greater than 0.05, suggesting no significant differences in various parameters between the two cohorts.

Extraction of features from primary tumor histology

In our study, a CNN model was employed that was pretrained on an extensive dataset of colorectal polyps to derive 512-dimensional embeddings for each tumor tissue patch. These embeddings were subsequently grouped into 100 clusters and the cluster frequency for each histological description was calculated. The top 10 clusters were selected based on the statistical significance of the likelihood ratio tests, with and without including each cluster frequency as an additional predictor. Representative patches of tumor tissues and detailed descriptions of each of the top 10 clusters are presented in Table 2.

Construction and validation of risk prediction model

The prediction model for LNM in CRC was based on a logistic regression framework incorporating machine learning-extracted features and clinicopathological variables. Backward elimination based on the Akaike Information Criterion led to the selection of 10 significant predictors: Age, tumor location, tumor size, tumor differentiation, tumor invasion depth, lymphovascular invasion, perineural invasion, tumor budding, cluster frequency of cluster 1, and cluster frequency of cluster 2.

Therefore, the resulting logistic regression model integrates these 10 predictors and can be represented by the following mathematical formula: LogP/1-p = −4.32 + 0.02 × age - 0.65 × left colon - 1.04 × rectum + 0.17 × tumor size -0.48 × tumor differentiation + 1.32 × T1 + 2.12 × T2 + 3.45 × T3 + 4.67 × T4a + 5.89 × T4b + 1.23 × lymphovascular invasion + 1.01 × perineural invasion + 0.87 × tumor budding + 0.05 × cluster frequency of cluster 1 - 0.04 × cluster frequency of cluster 2. (P is the probability of LNM in CRC, and Tis is the depth of tumor invasion. Right colon is the reference for tumor location). Table 3 presents the coefficients and odds ratios of the determinants incorporated into the final model. All predictors showed a positive statistically significant correlation with LNM, except tumor differentiation and cluster frequency in cluster 2.

Table 1 Clinicopathological characteristics of the study population (%)

Variable	Training set (*n* = 188)	Validation set (*n* = 70)	*P* value
Age (yr)			0.86
mean ± SD	60.4 ± 13.1	60.6 ± 13.5	
Median (range)	61 (18-95)	61 (20-93)	
Sex			0.91
Male	112 (59.6)	42 (60)	
Female	76 (40.4)	28 (40)	
Tumor location			0.97
Right colon	60 (31.9)	22 (31.4)	
Left colon	60 (31.9)	23 (32.9)	
Rectum	68 (36.2)	25 (35.7)	
Tumor size (cm)			0.83
mean ± SD	4.2 ± 2.1	4.2 ± 2.0	
Median (range)	4 (1-15)	4 (1-12)	
Tumor differentiation			0.99
Well/moderate	162 (86.2)	60 (85.7)	
Poor/undifferentiated/others[1]	26 (13.8)	10 (14.3)	
Tumor invasion depth			0.98
Tis	3 (1.6)	1 (1.4)	
T1	14(7.4)	5(7.1)	
T2	32 (17)	11 (15.7)	
T3	121 (64.4)	45 (64.3)	
T4a	15 (8)	6 (8.6)	
T4b	3 (1.6)	2 (2.9)	
Lymphovascular invasion			0.95
Negative	147 (78)	55 (78.6)	
Positive	41 (21.7)	15 (21.4)	
Indeterminate[2]	N/A	N/A	
Perineural invasion			0.96
Negative	168 (89.4)	63 (90)	
Positive	20 (10.3)	7 (10)	
Indeterminate	N/A	N/A	
Tumor budding			0.09
Absent[3]	121 (64.3)	38 (54.3)	
Low	44 (23.7)	19 (27.1)	
High	23 (12)	13 (18.6)	
LNM status			0.90
Negative	141 (74.9)	52 (74.3)	
Positive	47 (25.1)	18 (25.7)	

[1]Others included mucinous, signet-ring cell, neuroendocrine differentiation, medullary carcinoma, mixed adenoneuroendocrine carcinoma, micropapillary carcinoma, and serrated adenocarcinoma.
[2]Indeterminate means that the presence or absence of lymphovascular invasion or perineural invasion cannot be determined.

[3]Absent: No tumor budding; Low: ≤ 10 tumor buds per high-power field; High: > 10 tumor buds per high-power field.
LNM: Lymph node metastasis; N/A: Not applicable; Tis: Carcinoma in situ; T1: Tumor invades submucosa; T2: Tumor invades muscularis propria; T3: Tumor invades through muscularis propria into pericolorectal tissues; T4a: Tumor penetrates to the surface of the visceral peritoneum; T4b: Tumor directly invades or is adherent to other organs or structures.

Table 2 Representative patches of tumor tissue for each of the top 10 clusters

Cluster	Description
1	Poorly differentiated tumor cells with a high nuclear-cytoplasmic ratio, irregular glandular formation, and sparse stroma
2	Well-differentiated tumor cells with low nuclear-cytoplasmic ratio, regular glandular formation, and abundant stroma
3	Tumor cells with moderate differentiation, moderate nuclear-cytoplasmic ratio, and moderate stroma
4	Tumor cells with signet-ring cell differentiation, high nuclear-cytoplasmic ratio, and mucin production
5	Tumor cells with neuroendocrine differentiation, high nuclear-cytoplasmic ratio, and rosette-like structures
6	Tumor cells with serrated adenocarcinoma differentiation, low nuclear-cytoplasmic ratio, and serrated glandular formation
7	Tumor cells with mucinous differentiation, low nuclear-cytoplasmic ratio, and abundant extracellular mucin
8	Tumor cells with medullary carcinoma differentiation, high nuclear-cytoplasmic ratio, and solid growth pattern
9	Tumor cells with micropapillary carcinoma differentiation, high nuclear-cytoplasmic ratio, and papillary projections
10	Tumor cells with mixed adenoneuroendocrine carcinoma differentiation, high nuclear-cytoplasmic ratio, and dual expression of neuroendocrine and epithelial markers

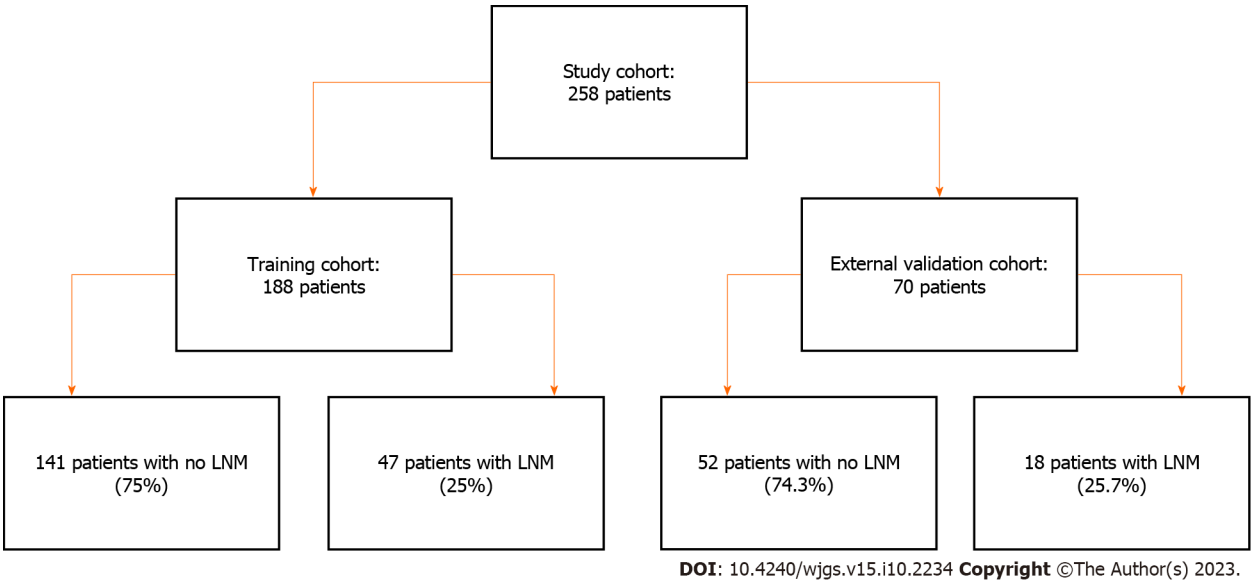

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Figure 1 Flowchart of study cohort division. LNM: Lymph node metastasis.

Performance of the risk prediction model

To evaluate the effectiveness of the risk-prediction model, a comparative analysis was conducted with existing models for LNM prediction in CRC using a range of performance metrics. As shown in Table 4, these metrics included the accuracy, sensitivity, specificity, PPV, NPV, AUROC, AUPRC, NRI, IDI, and Brier score. The model achieved high accuracy (0.86), sensitivity (0.81), specificity (0.87), PPV (0.66), NPV (0.94), AUROC (0.91), AUPRC (0.77), NRI (0.28), and IDI (0.11) and a low Brier score (0.10) in the validation set. Furthermore, the current model outperformed the three existing models in terms of LNM prediction in the validation set, with higher scores for these metrics except for the Brier score. These results underscore the robust discriminative capacity of this model, allowing it to accurately distinguish between patients with and without LNM. In addition, the current model exhibited excellent calibration and resilience within an external cohort, emphasizing its potential clinical utility.

Calibration and decision curve analysis of the risk prediction model

The calibration and decision curve analysis of the predicted probabilities of LNM between our risk prediction model and

Table 3 Coefficients and odds ratios of the predictors in the final model

Predictor	Coefficient	Odds ratio	*P* value
Age (yr)	0.02	1.02	0.01[a]
Tumor location			< 0.001[b]
Right colon	Reference	Reference	
Left colon	-0.65	0.52	
Rectum	-1.04	0.35	
Tumor size	0.17	1.19	< 0.001[a]
Tumor differentiation	-0.48	0.62	0.02[a]
Tumor invasion depth			< 0.001[b]
Tis	Reference	Reference	
T1	1.32	3.74	
T2	2.12	8.34	
T3	3.45	31.49	
T4a	4.67	106.71	
T4b	5.89	361.23	
Lymphovascular invasion	1.23	3.42	< 0.001[a]
Perineural invasion	1.01	2.75	< 0.001[a]
Tumor budding	0.87	2.38	< 0.001[a]
Frequency of cluster 1	0.05	1.05	< 0.001[a]
Frequency of cluster 2	-0.04	0.96	0[c]
Frequency of cluster 3	0.03	1.03	0.02[a]
Frequency of cluster 4	-0.02	0.98	0.04[a]
Frequency of cluster 5	0.04	1.04	0.01[a]
Frequency of cluster 6	-0.03	0.97	0.03[a]
Frequency of cluster 7	0.02	1.02	0.05[a]
Frequency of cluster 8	-0.01	0.99	0.06[c]
Frequency of cluster 9	0.01	1.01	0.07[c]
Frequency of cluster 10	-0.01	0.99	0[c]

[a]$P < 0.05$, statistically significant.
[b]$P < 0.001$, highly statistically significant.
[c]$P > 0.05$, not statistically significant.

Table 4 Performance of the risk prediction model and the existing models in the validation set

Model	NRI	IDI	Brier score
Our model	0.28	0.11	0.10
Kikuchi's model	-0.04	-0.03	0.17
Ueno's model	-0.01	-0.01	0.15
Krogue's model	0.12	0.05	0.12

NRI: Net reclassification improvement; IDI: Integrated discrimination improvement.

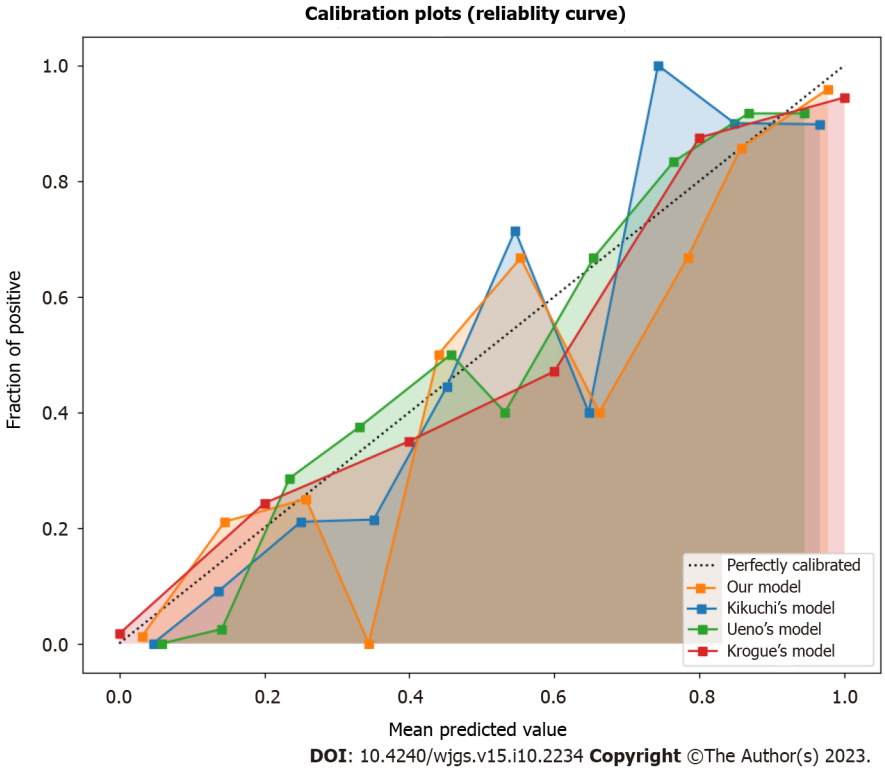

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Figure 2 Calibration plots of the risk prediction model and the existing models in the validation set.

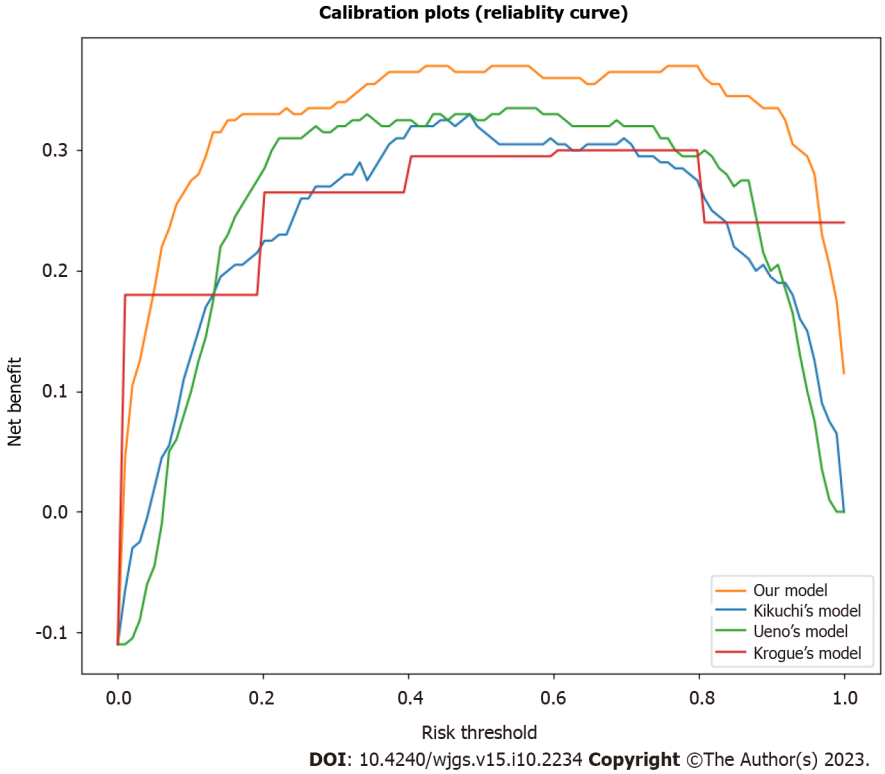

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Figure 3 Decision curve analysis of the risk prediction model and the existing models in the validation set.

existing models in the validation set was assessed, as shown in Figures 2 and 3. The current model demonstrated good agreement between the observed and predicted probabilities of LNM across a range of risk thresholds, with a higher net benefit across a wide range of risk thresholds, indicating good calibration and clinical utility. However, the existing models showed some deviation from the ideal line with a lower net benefit, especially at low and high-risk thresholds, indicating poor calibration and clinical utility.

Risk stratification and treatment guidance of the risk prediction model

The risk prediction model devised in this study facilitated the classification of patients into various risk strata based on the calculated probability of LNM: Low (< 10%), intermediate (10%-30%), and high-risk (> 30%). As shown in Table 5, of the 70 CRC patients, 27 (38.6%) were classified as low-risk, 26 (37.1%) as intermediate-risk, and 17 (24.3%) as high-risk. Among the 18 cases of LNM, 1 (5.6%) was classified as low-risk, 6 (33.3%) as intermediate-risk, and 11 (61.1%) as high-risk. Appropriate therapeutic strategies should be judiciously selected in accordance with the assessment of LNM risk in patients with CRC.

DISCUSSION

In the present study, we constructed and validated a risk-prediction model for LNM in CRC based on a large cohort of patients. For this purpose, machine learning techniques were used to extract features from primary tumor histology and clinicopathological data and combine them with established predictors to build a logistic regression model. The features extracted from machine learning provided additional predictive value for LNM in CRC, thereby improving the accuracy and discriminating capacity of the logistic regression model. Additionally, the model demonstrated good calibration and robustness in the validation set. Furthermore, the model can effectively stratify patients into different risk groups and guide the selection of appropriate treatment options.

To avoid the toxicity of over-therapeutic procedures in patients classified as low risk by the current model, curative treatment measures, such as endoscopic resection or local excision that eliminate the need for lymphadenectomy or adjuvant therapy, are recommended. For patients presenting with intermediate-risk T1 CRC, the recommendation is surgical resection accompanied by lymphadenectomy as curative treatment, with the decision for adjuvant therapy contingent on other prognostic factors. In contrast, patients with high-risk T1 CRC are recommended to be administered neoadjuvant therapy followed by surgical resection with lymphadenectomy for significantly minimizing the risk of recurrence.

Previous studies have shown that tumor histology contains rich information that reflects the biological behavior and molecular characteristics of tumor cells[22-24]. However, conventional histopathological evaluations are subjective, qualitative, and limited by human perception. Deep learning is a powerful tool that automatically learns complex and high-dimensional patterns from images and generates quantitative and objective features[25,26]. The current study used a pre-trained CNN model to generate the quantitative features of tumor histology. The top cluster frequencies were identified and added to the logistic regression model to enhance their predictive value when combined with baseline clinicopathological variables. These selected histological features may reflect the aggressiveness and invasiveness of the tumor cells and their interaction with the microenvironment, which may influence their ability to metastasize to the lymph nodes.

In this study, we opted for logistic regression as the optimum modeling method, driven by its simplicity, interpretability, and extensive usage in clinical practice[27,28]. To avoid the risks of overfitting and multicollinearity, backward elimination, based on the Akaike information criterion for the variable selection, was employed. The current model's ten predictors align with previous research that identified risk factors for LNM in CRC[29,30]. Furthermore, we discovered two clusters that were significantly associated with LNM, in line with the current understanding of disease stages based on tumor biological behavior. The positively correlated cluster 1 (characterized by poorly differentiated tumor cells with a high nuclear-cytoplasmic ratio, irregular glandular formation, and sparse stroma) represented a more malignant phenotype of tumor cells. In contrast, the negatively correlated cluster 2 (characterized by well-differentiated tumor cells with a low nuclear-cytoplasmic ratio, regular glandular formation, and abundant stroma) represents a more benign phenotype of tumor cells that are less likely to metastasize to the lymph nodes.

CONCLUSION

The present study provides valuable insights into the determinants of LNM in patients with CRC and presents an innovative risk prediction model; however, it has certain limitations. First, the retrospective design of the study may have contributed to selection bias. Second, we could not include potentially relevant risk factors, such as genetic and lifestyle influences, because of data unavailability. Third, model validation was performed exclusively within an independent cohort from the same institution, underscoring the need for future studies to validate the model across diverse populations and within a prospective framework. Finally, the limited size of the validation cohort could potentially affect the reliability of the validation findings. Despite these constraints, our model exhibited high efficacy and adeptness in distinguishing between patients with and without LNM, in addition to displaying sound calibration and robustness within an external cohort. This study forms a strong foundation for future efforts to develop and refine predictive models for LNM in patients with CRC.

In conclusion, a potent and effective risk-prediction model for LNM in patients with CRC was successfully developed and validated. The model utilized machine learning-derived features extracted from primary tumor histology and clinicopathological variables and demonstrated superior performance and clinical applicability compared to existing models. The study provided new insights into the potential of deep learning to extract valuable information from tumor histology, which can improve the prediction of LNM in CRC and facilitate risk stratification and decision-making in clinical practice. Further investigations are crucial to affirm the utility of the present model within larger and more

Table 5 Distribution of patients and lymph node metastasis in each risk group in the validation set (%)

Risk group	Predicted probability of LNM	Number of patients	Number of LNMs
Low risk	< 10	27 (38.6)	1 (5.6)
Intermediate risk	10-30	26 (37.1)	6 (33.3)
High risk	> 30	17 (24.3)	11 (61.1)

LNM: Lymph node metastasis.

heterogeneous cohorts and to probe the biological and molecular mechanisms underlying the features extracted using machine learning.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) is a significant global health issue, and accurate prediction of lymph node metastasis (LNM) is crucial for individualized treatment strategies. However, predicting LNM is challenging due to various factors and limitations in the histopathological examination method. This study aimed to develop a risk prediction model for LNM in CRC by incorporating machine learning and clinicopathological factors. The model demonstrated high accuracy, sensitivity, and specificity, providing valuable insights into the potential of deep learning in improving LNM prediction and guiding clinical decision-making for CRC patients.

Research motivation

Accurate prediction of LNM in CRC is crucial for improving patient outcomes and developing personalized treatment strategies. However, existing methods are invasive, time-consuming, and prone to errors. This study aimed to address these limitations by developing a risk prediction model using machine learning and clinicopathological factors. The motivation was to provide a more accurate and efficient approach for predicting LNM in CRC, enabling clinicians to make informed decisions regarding treatment and facilitating improved patient care.

Research objectives

The main objectives of this study were to analyze the factors influencing LNM in CRC, and to develop and validate a risk prediction model for LNM based on a large patient cohort. The study aimed to utilize machine learning techniques and clinicopathological factors to construct an accurate prediction model that outperforms existing models. The goal was to improve the prediction of LNM in CRC, enabling personalized treatment strategies and enhancing clinical decision-making. Additionally, the study sought to explore the potential of deep learning in extracting valuable information from tumor histology for improved risk stratification.

Research methods

In this study, a retrospective analysis was conducted on 300 patients who underwent CRC surgery at two Peking University Shenzhen hospitals between January and December 2021. The main approach involved the development of a risk prediction model for LNM in CRC. A deep learning method was utilized to extract features from primary tumor histological images that could be associated with LNM. Additionally, a logistic regression model was used, incorporating these machine-learning-derived features along with clinicopathological variables, as predictors for LNM in CRC. The performance of the prediction model was evaluated based on accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), receiver operating characteristic (ROC), and Brier score to assess calibration and clinical utility.

Research results

The developed risk prediction model for LNM in CRC achieved excellent performance. The model demonstrated high accuracy (0.86), sensitivity (0.81), specificity (0.87), PPV (0.66), NPV (0.94), and area under the curve for the ROC (0.91). Additionally, it exhibited a low Brier score of 0.10. The observed and predicted probabilities of LNM showed strong agreement across various risk thresholds, indicating reliable calibration and clinical utility. These findings highlight the effectiveness and clinical applicability of the model, which utilizes machine-learning-derived features from primary tumor histology and clinicopathological variables.

Research conclusions

The study successfully developed and validated a powerful risk prediction model for LNM in CRC. The model, incorporating machine-learning-derived features from primary tumor histology and clinicopathological variables, displayed superior performance and clinical applicability compared to existing models. By leveraging deep learning

techniques, valuable information was extracted from tumor histology, leading to improved LNM prediction. This development has significant implications for individualized treatment strategies and clinical decision-making in CRC, enabling better risk stratification. The findings highlight the potential of machine learning and deep learning in enhancing LNM prediction and improving patient outcomes in CRC management.

Research perspectives

The successful development and validation of a potent risk prediction model for LNM in CRC opens up promising research avenues. Further exploration can focus on refining the model by incorporating additional molecular characteristics and genetic data to enhance its predictive accuracy. Additionally, prospective studies can be conducted to validate the model's performance in larger and diverse patient populations. Furthermore, the integration of real-time image analysis techniques and artificial intelligence algorithms can streamline the prediction process, enabling faster and more accurate LNM assessment. These advancements have the potential to revolutionize clinical practice and optimize treatment strategies for CRC patients.

FOOTNOTES

Author contributions: Lei YP, Lv GQ proposed the concept of this study; Song QZ collected the data; Liu S and Lv GQ contributed to formal analysis; Xie JY and Lei YP conducted the survey; Song QZ and Liu S contributed to these methods; Lei YP and Song QZ guided the research; Lei YP, Lv GQ validated the results of the study; Song QZ contributed to the visualization of the study; Lei YP Song QZ and Lv GQ reviewed and edited the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Novel prognostic score based on the preoperative total bilirubin-albumin ratio and fibrinogen-albumin ratio in ampullary adenocarcinoma

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Abstract

BACKGROUND

The preoperative total bilirubin-albumin ratio (TBAR) and fibrinogen-albumin ratio (FAR) have been proven to be valuable prognostic factors in various cancers.

AIM

To detect the prognostic value of TBAR and FAR in ampullary adenocarcinoma (AC) patients who underwent curative pancreaticoduodenectomy.

METHODS

AC patients who underwent curative pancreaticoduodenectomy in the National Cancer Center of China between 1998 and 2020 were retrospectively reviewed. The prognostic cutoff values of TBAR and FAR were determined through the best survival separation model. Then, a novel prognostic score combining TBAR and FAR was calculated and validated through the logistic regression analysis and Cox regression analysis.

RESULTS

A total of 188 AC patients were enrolled in the current study. The best cutoff values of TBAR and FAR for predicting overall survival were 1.7943 and 0.1329, respectively. AC patients were divided into a TBAR-low group (score = 0) *vs* a TBAR-high group (score = 1) and a FAR-low group (score = 0) *vs* a FAR-high group (score = 1). The total score was calculated as a novel prognostic factor. Multivariable logistic regression analysis revealed that a high score was an independent protective factor for recurrence [score = 1 *vs* score = 0: Odds ratio

(OR) = 0.517, *P* = 0.046; score = 2 *vs* score = 0 OR = 0.236, *P* = 0.038]. In addition, multivariable survival analysis also demonstrated that a high score was an independent protective factor in AC patients (score = 2 *vs* score = 0: Hazard ratio = 0.230, *P* = 0.046).

CONCLUSION
A novel prognostic score based on preoperative TBAR and FAR has been demonstrated to have good predictive power in AC patients who underwent curative pancreaticoduodenectomy. However, more studies with larger samples are needed to validate this conclusion.

Key Words: Ampullary adenocarcinoma; Total bilirubin-albumin ratio; Fibrinogen-albumin ratio; Recurrence; Overall survival

Core Tip: Considering that effective prognostic predictors are still lacking for ampullary carcinoma, we conducted a retrospective study to elucidate the prognostic value of total bilirubin-albumin ratio (TBAR) and fibrinogen-albumin ratio (FAR) in ampullary adenocarcinoma (AC) patients who underwent curative pancreaticoduodenectomy. We found that the novel prognostic score based on the preoperative TBAR and FAR was an independent predictor for tumor recurrence and an independent protective factor for overall survival in AC patients who underwent curative pancreaticoduodenectomy.

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INTRODUCTION

Ampullary adenocarcinoma (AC) is an uncommon malignant digestive adenocarcinoma and accounts for approximately 0.2% of all digestive malignancies[1]. Radical surgery is the only potential curative treatment for AC patients[2]. It has been reported that the 5-year survival rate of AC patients after surgery is 45%, and postoperative recurrence and metastasis are the main factors affecting the prognosis of AC patients[1,3]. Unfortunately, effective prognostic predictors are still lacking, especially perioperative peripheral blood biomarkers.

Preoperative total bilirubin (TB) is a critical biomarker for the diagnosis of biliary obstruction and is present at the first diagnosis for the majority of AC patients. In addition, preoperative albumin has been widely used for defining immune and nutritional statuses[4]. Recently, several studies have proven that the preoperative fibrinogen-albumin ratio (FAR) is a significant prognostic biomarker in multiple tumor types, including lung cancer[5], hepatocellular carcinoma[6], colorectal cancer[7], gastric cancer[8], bladder cancer[9], and rectal cancer[10]. However, whether the relationship of preoperative TB, fibrinogen, and albumin could be used as prognostic factors is still debated. Therefore, in the current study, we aimed to explore the relationship among the preoperative TB-albumin ratio (TBAR), FAR, and long-term prognosis in AC patients based on a high-volume retrospective cohort in the National Cancer Center of China.

MATERIALS AND METHODS

Patients

AC patients who received curative surgery at the National Cancer Center of China between 1998 and 2020 were retrospectively reviewed. The main inclusion criteria were as follows: (1) Patients who were pathologically confirmed as having AC; (2) patients who received pancreaticoduodenectomy; and (3) patients with negative surgical margins. The main exclusion criteria were as follows: (1) Patients who died within one month after surgery; (2) patients who were lost to follow-up; (3) patients whose critical clinical information was missing; and (4) patients for whom preoperative TBAR and FAR were unavailable. As this was a retrospective cohort study, ethical exemption and informed consent exemption were obtained from the Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

Calculation of preoperative TBAR and FAR

The TBAR was calculated as preoperative TB (μmol/L) divided by preoperative albumin (g/L). The FAR was calculated as preoperative fibrinogen (g/L) divided by preoperative albumin (g/L).

Follow-up

The postoperative follow-up was performed through telephone review, clinic visits, and the death registration system. The last follow-up time was December 2021. None of the patients was lost to follow-up. The median follow-up time was 36 mo.

Statistical analysis

All categorical variables are expressed as frequencies (percentages), and continuous variables are expressed as medians (interquartile ranges). The χ^2 test or Fisher's exact test was used for comparison of categorical variable groups, and the Mann-Whitney *U* test was used for comparison of continuous variable groups. The cutoff values of TBAR and FAR were calculated by the best survival separation model through the "Survival" and "Survminer" packages in R software (version 4.0.3). The corresponding *P* value and hazard ratio (HR) were calculated one by one with each TBAR and FAR value as the cutoff value by setting a cycle. When the *P* value was the smallest, the cutoff TBAR and FAR values were the best survival separation cutoff values. The correlations between preoperative carbohydrate antigen 199 (CA199), carcinoembryonic antigen (CEA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), TBAR, and FAR were conducted by Spearman analysis. Univariable and multivariable Cox regression analyses were performed to validate the independent prognostic factors. Variables with $P < 0.1$ in the univariable survival analysis were included in the multivariable survival analysis. The results in the present study are described as HRs, 95% confidence intervals (CIs), and *P* values. A *P* value less than 0.05 was considered statistically significant. All statistical analyses were performed using R software (version 4.0.3).

RESULTS

Baseline characteristics

In total, 188 AC patients were enrolled in the study, with an overall male:female ratio of 1.47. Overall, nearly a quarter of patients had lymph node metastasis. Since all patients underwent open pancreaticoduodenectomy and the surgical trauma was relatively large, nearly half of the patients received intraoperative blood transfusion. In addition, a total of 54 patients (28.72%) received postoperative adjuvant therapy. The detailed baseline clinicopathologic characteristics of AC patients in the current study are illustrated in Table 1.

Cutoff values of TBAR and FAR

The cutoff values of TBAR and FAR were calculated through the best survival separation model. In the current study, the cutoff value of TBAR was 1.7943, while the cutoff value of FAR was 0.1329 (Figure 1). Furthermore, we conducted correlations between preoperative CA199, CEA, ALT, AST, TBAR, and FAR. The results demonstrated that FAR was significantly correlated with preoperative AST, ALT, and CA199, while TBAR was signi-ficantly correlated with preoperative AST, ALT, CEA, and CA199 (Figure 2, Supplementary Tables 1 and 2).

Total score combining the TBAR and FAR

In the current study, we defined TBAR-low and FAR-low as score 0 and TBAR-high and FAR-high as score 1. Directly after, we calculated the total score and classified all the patients into the score-0 group, score-1 group, and score-2 group. By comparing the baseline clinicopathologic data, we found that there were no significant differences among the three groups in tumor stage, tumor differentiation degree, tumor size, CA199 level, CEA level, or postoperative adjuvant therapy (Table 1).

Survival analysis

The 1-year, 3-year, and 5-year overall survival (OS) rates were 91.3%, 63.6%, and 41.7%, respectively. According to the univariable survival analysis, the TBAR-high group, FAR-high group, and score-high group had better prognoses (Figure 3). In the multivariable logistic regression analysis, score 1 [odds ratio (OR) = 0.517; 95%CI: 0.270-0.988; $P = 0.046$) and score 2 (OR = 0.236; 95%CI: 0.060-0.922; $P = 0.038$] were independent protective factors for tumor recurrence (Table 2). However, in the multivariable survival analysis, a high score was not an independent factor for recurrence-free survival (RFS) ($P > 0.05$) (Supplementary Table 3). Furthermore, we conducted multivariable OS analysis and found that only the score-2 group was an independent protective factor for OS (HR = 0.230; 95%CI: 0.054-0.972; $P = 0.046$) (Table 3).

DISCUSSION

Most previous studies separately analyzed the prognostic value of preoperative TB, fibrinogen, and albumin for solid tumors, and the results from different cohorts are still controversial. After inclusion of these predictors, we found that TBAR combined with the FAR was an independent predictor for tumor recurrence and an independent protective factor for OS in AC patients. These peripheral blood biomarkers could be used as prognostic factors and are novel, reliable, economic, and easily accessible biomarkers for advanced AC.

The hemostatic system can regulate angiogenesis in various ways. Fibrinogen is an extracellular matrix protein composed of three polypeptide chains with fibrinogen alpha, beta, and gamma. Recent studies have shown that the FAR

Table 1 Comparing the baseline characteristics of different score groups in ampullary adenocarcinoma

Variables	Total (*n* = 188)	Score-0 (*n* = 88)	Score-1 (*n* = 84)	Score-2 (*n* = 16)	*P* value
Gender, *n* (%)					0.166
Male	112 (59.574)	58 (65.909)	47 (55.952)	7 (43.750)	
Female	76 (40.426)	30 (34.091)	37 (44.048)	9 (56.250)	
Age, median (IQR)	58 (50, 64)	58 (51, 64)	59 (50, 66)	53 (45, 64)	0.449
Differentiation, *n* (%)					0.052
Poor	73 (38.830)	34 (38.636)	36 (42.857)	3 (18.750)	
Moderate	70 (37.234)	38 (43.182)	27 (32.143)	5 (31.250)	
Well	45 (23.936)	16 (18.182)	21 (25.000)	8 (50.000)	
Tumor size, *n* (%)					0.479
≤ 2 cm	94 (50.000)	43 (48.864)	45 (53.571)	6 (37.500)	
> 2 cm	94 (50.000)	45 (51.136)	39 (46.429)	10 (62.500)	
AST (U/L), median (IQR)	57 (35, 112)	72 (48, 126)	50 (23, 94)	30 (20, 72)	< 0.001
ALT (U/L), median (IQR)	87 (36, 150)	105 (66, 186)	54 (29, 117)	45 (18, 70)	< 0.001
CEA (ng/mL), median (IQR)	2.75 (1.88, 3.81)	3.06 (1.85, 4.48)	2.58 (1.92, 3.78)	2.24 (1.94, 2.97)	0.193
CA199 (U/mL), median (IQR)	55.80 (18.83, 184.30)	60.84 (27.41, 162.30)	55.80 (13.57, 191.40)	35.46 (20.32, 72.94)	0.444
Perioperative transfusion, *n* (%)					0.226
No	96 (51.064)	45 (51.136)	46 (54.762)	5 (31.250)	
Yes	92 (48.936)	43 (48.864)	38 (45.238)	11 (68.750)	
T stage, *n* (%)					0.088
I	36 (19.149)	10 (11.364)	21 (25.000)	5 (31.250)	
II	57 (30.319)	28 (31.818)	23 (27.381)	6 (37.500)	
III	95 (50.532)	50 (56.818)	40 (47.619)	5 (31.250)	
Examined lymph nodes, median (IQR)	11 (7, 18)	12 (8, 18)	11 (6, 19)	9 (4, 10)	0.044
Examined lymph node, *n* (%)					0.035
< 12	107 (56.915)	47 (53.409)	46 (54.762)	14 (87.500)	
≥ 12	81 (43.085)	41 (46.591)	38 (45.238)	2 (12.500)	
Lymph node metastasis, *n* (%)					0.402
No	140 (74.468)	63 (71.591)	63 (75.000)	14 (87.500)	
Yes	48 (25.532)	25 (28.409)	21 (25.000)	2 (12.500)	
TNM stage, *n* (%)					None
I	82 (43.617)	32 (36.364)	40 (47.619)	10 (62.500)	
II	76 (40.426)	37 (42.045)	33 (39.286)	6 (37.500)	
III	30 (15.957)	19 (21.591)	11 (13.095)	0 (0.000)	
Vessel invasion, *n* (%)					None
No	141 (75.000)	57 (64.773)	68 (80.952)	16 (100.000)	
Yes	47 (25.000)	31 (35.227)	16 (19.048)	0 (0.000)	
Postoperative complications, *n* (%)					0.353
No	110 (58.511)	49 (55.682)	49 (58.333)	12 (75.000)	
Yes	78 (41.489)	39 (44.318)	35 (41.667)	4 (25.000)	
Adjuvant treatment, *n* (%)					0.235

No	134 (71.277)	59 (67.045)	61 (72.619)	14 (87.500)	
Yes	54 (28.723)	29 (32.955)	23 (27.381)	2 (12.500)	
Fibrinogen (g/L), median (IQR)	3.68 (3.12, 4.22)	3.71 (3.20, 4.02)	3.74 (3.15, 4.42)	3.06 (2.67, 3.96)	0.153
Albumin (g/L), median (IQR)	37.10 (31.40, 41.20)	39.00 (35.40, 41.40)	35.70 (27.60, 41.70)	4.13 (3.82, 4.47)	< 0.001
Total bilirubin (μmol/L), median (IQR)	38.70 (12.82, 173.60)	161.90 (63.10, 228.80)	15.31 (8.96, 24.58)	1.32 (0.75, 1.99)	< 0.001
FAR, median (IQR)	0.106 (0.086, 0.150)	0.095 (0.086, 0.109)	0.134 (0.084, 0.195)	0.687 (0.174, 0.764)	< 0.001
TBAR, median (IQR)	0.538 (0.205, 2.325)	0.266 (0.162, 0.580)	1.807 (0.386, 3.303)	3.694 (2.742, 5.027)	< 0.001

IQR: Interquartile range; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen 199; TNM: Tumor-node-metastasis; FAR: Fibrinogen-albumin ratio; TBAR: Total bilirubin-albumin ratio.

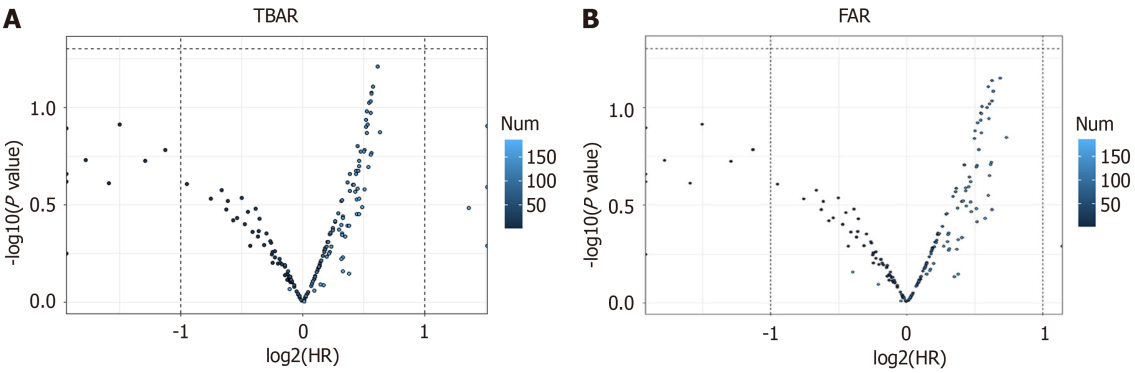

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Figure 1 Volcano plot showing the cutoff values of total bilirubin-albumin ratio and fibrinogen-albumin ratio through the best survival separation model. A: Total bilirubin-albumin ratio; B: Fibrinogen-albumin ratio.

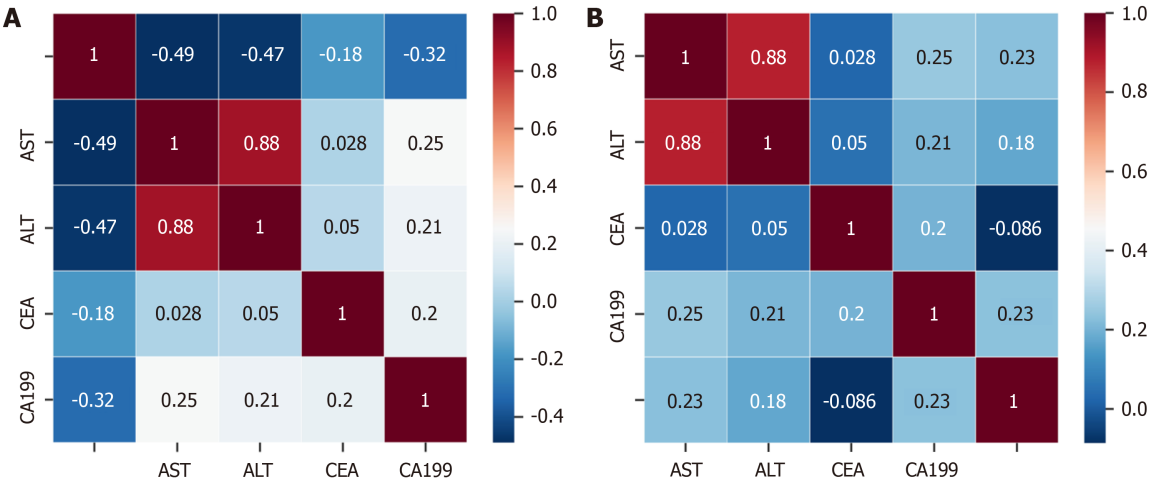

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Figure 2 Spearman correlations between preoperative carbohydrate antigen 199, carcinoembryonic antigen, alanine aminotransferase, aspartate aminotransferase, total bilirubin-albumin ratio and fibrinogen-albumin ratio. A: Total bilirubin-albumin ratio; B: Fibrinogen-albumin ratio. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen 199.

is associated with prognosis in several solid malignancies, including pancreatic neuroendocrine neoplasms[11] and gastrointestinal stromal tumors[12]. FAR is considered a feasible and predictive biomarker for prognosis in patients. In addition, Zhang and Xiao[13] revealed that the FAR was significantly associated with deeper tumor invasion and increased regional lymph node involvement. However, Zhao *et al*[14] showed that fibrinogen-derived fibrinostatin has antiangiogenic activity by inhibiting endothelial cell proliferation, adhesion, migration and tubule formation. By inducing apoptosis and inhibiting epithelial-mesenchymal transition, alpha may suppress lung adenocarcinoma cell growth and

Table 2 Univariate and multivariate logistic analysis of independent factors predicting the tumor recurrence

Variables	Univariable analysis			Multivariable analysis		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Gender						
Male		Reference				
Female	1.176	0.656-2.110	0.586			
Age						
< 60		Reference				
≥ 60	0.747	0.414-1.347	0.332			
Differentiation						
Poor		Reference				
Moderate	1.150	0.596-2.216	0.677			
Well	0.599	0.279-1.286	0.189			
Tumor size						
≤ 2 cm		Reference				
> 2 cm	0.879	0.496-1.561	0.661			
Perioperative transfusion						
No		Reference				
Yes	0.619	0.347-1.103	0.104			
Operation time						
≤ 3 h						
> 3 h and ≤ 6 h						
> 6 h						
T stage						
I		Reference			Reference	
II	1.197	0.506-2.833	0.683	0.815	0.321-2.064	0.665
III	2.051	0.930-4.521	0.075	0.743	0.132-4.184	0.736
Examined lymph nodes						
< 12		Reference				
≥ 12	1.359	0.761-2.427	0.300			
Lymph node metastasis						
No		Reference			Reference	
Yes	2.735	1.384-5.406	0.004	1.224	0.425-3.524	0.707
TNM stage						
I		Reference			Reference	
II	1.560	0.823-2.956	0.173	1.574	0.289-8.574	0.600
III	6.005	2.300-15.676	< 0.001	4.149	0.491-35.043	0.191
Vessel invasion						
No		Reference			Reference	
Yes	2.601	1.313-5.151	0.006	1.353	0.616-2.970	0.451
Postoperative complications						
No		Reference				
Yes	0.696	0.387-1.250	0.225			

Adjuvant treatment						
No		Reference				
Yes	1.689	0.893-3.192	0.107			
CEA	1.071	0.978-1.172	0.139			
CA199	1.000	1.000-1.000	0.824			
TBAR	0.988	0.895-1.090	0.807			
FAR	0.504	0.182-1.393	0.186			
Score						
0		Reference			Reference	
1	0.469	0.255-0.863	0.015	0.517	0.270-0.988	0.046
2	0.167	0.045-0.630	0.008	0.236	0.060-0.922	0.038

CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen 199; TNM: Tumor-node-metastasis; FAR: Fibrinogen-albumin ratio; TBAR: Total bilirubin-albumin ratio; OR: Odds ratio; CI: Confidence interval.

metastasis[15]. Nevertheless, the specific mechanism of the relationship between the FAR and prognosis still needs to be investigated further.

Bilirubin is one of the routine biochemical testing items, which originates primarily from circulating hemoglobin and is the most important product of hemoglobin decomposition. It has antioxidant properties and can protect cells against oxidative stress as an endogenous antioxidant[16]. Sun *et al*[17] found that decreases in serum bilirubin levels are associated with poorer prognoses in some types of cancer through antioxidant activity. Another study also revealed that high serum bilirubin was related to low cancer mortality[18]. However, Feng *et al*[19] demonstrated that baseline bilirubin and serum proteins were not associated with the prognosis of advanced pancreatic cancer. Instead, a Japanese study indicated that a low albumin-bilirubin (ALBI) grade is related to better OS and RFS in esophageal cancer patients[20]. AC will directly affect the biliary tract, and the presence of jaundice can predict malignant ampullary strictures[21]; thus, their disease may be diagnosed at an earlier stage.

Albumin is a secretory protein produced only by functional hepatocytes, and it reflects the chronic nutritional state, which is commonly used for nutritional status assessment. The nutritional state of cancer patients was associated with unfavorable outcomes in malignant tumor patients. Our score is a composite indicator containing representative results of biochemical analysis, which can reflect the nutritional and inflammatory status, liver function and tumor effect. FAR in conjunction with TBAR has the potential to assist clinicians in the stratification of patients. Nevertheless, further investigation is still needed for the application of the novel score in clinical practice.

The traditional Child-Pugh grade used to assess liver function faces several inherent limitations. Therefore, Johnson *et al*[22] developed a simple model based on albumin and bilirubin levels alone, the ALBI grade, which can stratify patients into three risk categories and objectively prognosticate survival. A meta-analysis demonstrated that high pretreatment ALBI is closely associated with poor prognosis in hepatocellular cancer[23]. The ALBI grade also showed improved discriminatory ability in pancreatic cancer[24] and colorectal cancer[25]. Our new score adds the blood coagulation index and broadens the use of AC. In addition, the score is easily calculated compared with the ALBI grade and increases versatility and usefulness.

High scores were independent factors for RFS in the univariable survival analysis but not in the multivariable analysis. Although there were some differences in RFS, these were not statistically significant. Furthermore, we conducted multivariable OS analysis and found that only the score-2 group was an independent protective factor for OS. Such conflicting results might be related to several factors. First, patients with higher scores might be more likely to detect recurrence earlier and receive more aggressive treatment as a result. Consequently, this might not significantly affect RFS but could emerge as an independent prognostic factor for OS. Second, the number of patients in the score-high groups was relatively small, and it might be challenging to detect statistically significant differences in RFS. Third, the inclusion of other prognostic factors in the model might have resulted in multicollinearity or confounding effects, which could attenuate the initial observed relationship between the score-high groups and RFS. These results emphasize the need for further research, potentially involving larger patient cohorts to comprehensively understand the underlying mechanisms and relationships between the scoring system and different survival outcomes.

During tumor growth, tumor markers are produced and released into the blood circulation, which can be used for the diagnosis and monitoring of tumors. However, sensitive tumor markers are still lacking for predicting survival and treatment outcomes in AC[26]. In recent years, liquid biopsies have been increasingly emphasized. Circulating tumor DNA (ctDNA) derived from tumors is being used in analyzing prognosis and tumor burden in some solid tumors. Patel *et al*[27] found that higher levels of total ctDNA were an independent prognostic factor for worse survival for patients with advanced pancreatic ductal adenocarcinoma. However, this new technique can be limited by the small amounts of circulating biomarkers, and not everyone has detectable ctDNA levels[28]. To date, liquid biopsy is a complement to tissue biopsy, and more research studies are needed for the improvement of clinical applications. They are not considered to be perfect predictors for the above reasons. Therefore, our new scoring system contained three common indicators and

Table 3 Univariable and multivariable Cox regression analysis of overall survival time in ampullary adenocarcinoma

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Gender						
Male		Reference				
Female	1.080	0.711-1.639	0.719			
Age						
< 60		Reference				
≥ 60	1.198	0.788-1.822	0.398			
Differentiation						
Poor		Reference			Reference	
Moderate	0.873	0.548-1.391	0.568	0.981	0.600-10603	0.938
Well	0.596	0.344-1.034	0.066	0.979	0.501-1.911	0.949
Tumor size						
≤ 2 cm		Reference				
> 2 cm	1.139	0.756-1.716	0.534			
Perioperative transfusion						
No		Reference				
Yes	0.861	0.570-1.298	0.474			
T stage						
I		Reference			Reference	
II	0.927	0.485-1.769	0.817	0.792	0.375-1.672	0.541
III	2.128	1.211-3.741	0.009	1.731	0.474-6.322	0.407
Examined lymph nodes						
< 12		Reference				
≥ 12	1.344	0.881-2.051	0.171			
Lymph node metastasis						
No		Reference			Reference	
Yes	2.203	1.407-3.447	0.001	1.704	0.851-3.412	0.132
TNM stage						
I		Reference			Reference	
II	1.965	1.230-3.137	0.005	0.886	0.272-2.888	0.841
III	3.030	1.711-5.368	< 0.001	0.918	0.208-4.057	0.910
Vessel invasion						
No		Reference				
Yes	1.410	0.885-2.248	0.148			
Postoperative complications						
No		Reference				
Yes	1.343	0.886-2.035	0.164			
Adjuvant treatment						
No		Reference				
Yes	0.946	0.590-1.514	0.816			
CEA	1.001	0.999-1.004	0.359			

CA199	1.000	1.000-1.000	0.585			
TBAR	0.966	0.880-1.061	0.470			
FAR	0.748	0.359-1.558	0.438			
Score						
0		Reference			Reference	
1	0.787	0.518-1.196	0.262	0.890	0.577-1.373	0.599
2	0.176	0.043-0.726	0.016	0.230	0.054-0.972	0.046

CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen 199; TNM: Tumor-node-metastasis; FAR: Fibrinogen-albumin ratio; TBAR: Total bilirubin-albumin ratio; HR: Hazard ratio; CI: Confidence interval.

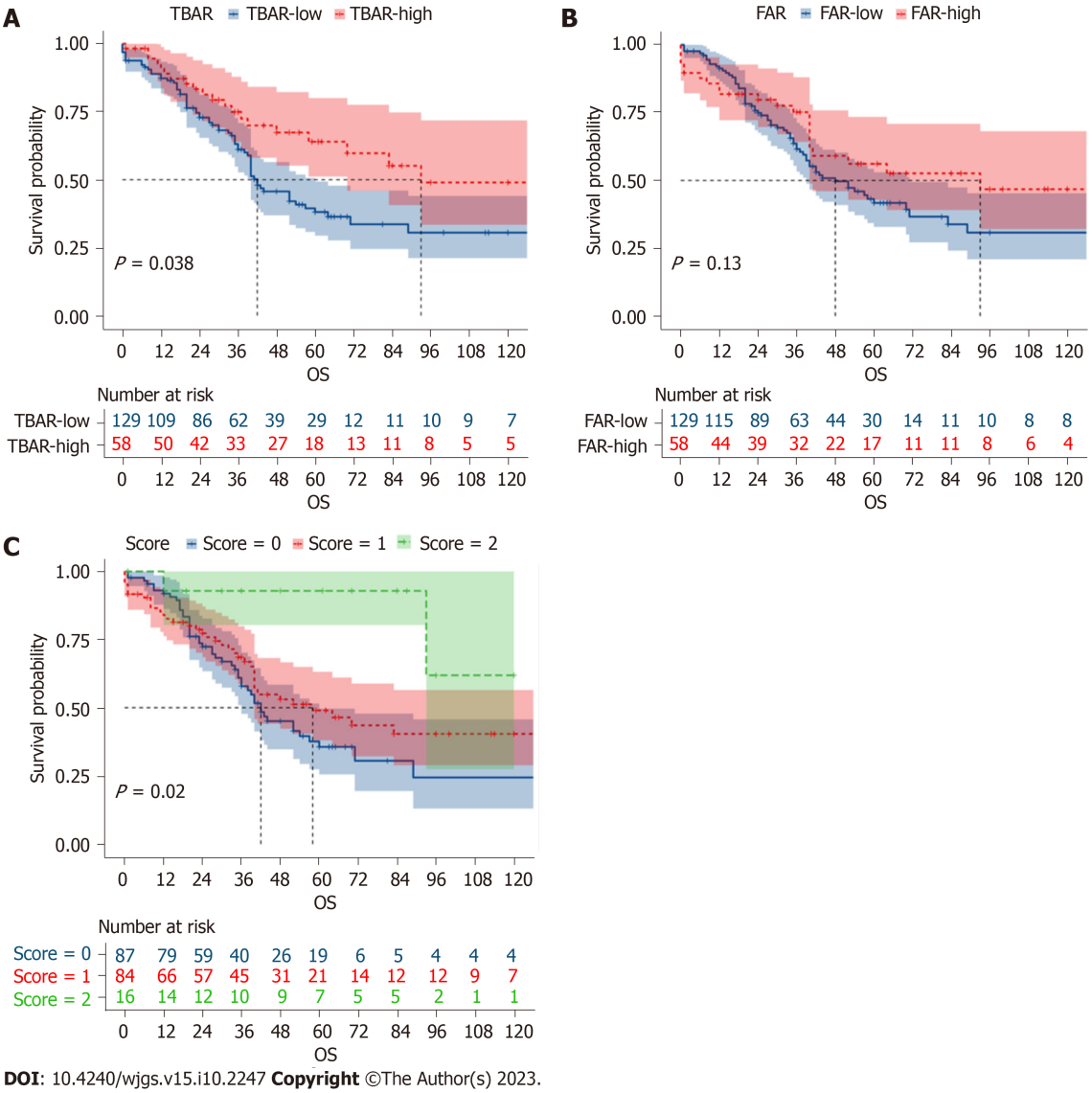

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Figure 3 Comparing the Kaplan-Meier survival curves of different groups divided by total bilirubin-albumin ratio, fibrinogen-albumin ratio and total score. A: Total bilirubin-albumin ratio; B: Fibrinogen-albumin ratio; C: Total score. TBAR: Total bilirubin-albumin ratio; FAR: Fibrinogen-albumin ratio; OS: Overall survival.

showed great predictive power in AC patients who underwent curative pancreaticoduodenectomy. The novel score is expected to become a new biomarker for identifying poor prognosis in patients with AC.

There were limitations to this study. First, this was a single-center retrospective study with a relatively small sample, and multicentric prospective studies with large samples are needed in the future. Second, we did not perform a cohort verification of the results, and external validation is needed. Third, we did not investigate whether the postoperative

peripheral blood biomarkers could be used as prognostic factors and analyzed the dynamic changes in the three indicators. Future research can evaluate the impact of these changes in great depth.

CONCLUSION

The novel prognostic score based on the preoperative TBAR and FAR was an independent predictor for tumor recurrence and an independent protective factor for OS in AC patients who underwent curative pancreaticoduodenectomy. However, more studies with larger samples are needed to validate this conclusion.

ARTICLE HIGHLIGHTS

Research background

Whether the relationship of preoperative total bilirubin, fibrinogen, and albumin could be used as prognostic factors is still debated.

Research motivation

The present study attempted to explore the prognostic value of total bilirubin-albumin ratio (TBAR) and fibrinogen-albumin ratio (FAR) in ampullary adenocarcinoma (AC) patients who underwent curative pancreaticoduodenectomy.

Research objectives

This study aimed to investigate whether there was an association between the novel prognostic score and poor oncologic outcomes in ampullary carcinoma.

Research methods

The clinicopathological data of ampullary carcinoma patients who underwent surgery from January 1998 to January 2020 were analyzed. Then, a novel prognostic score combining TBAR and FAR was calculated and validated through logistic regression analysis and Cox regression analysis.

Research results

Multivariable logistic regression analysis revealed that a high score was an independent protective factor for recurrence. In addition, multivariable survival analysis also demonstrated that a high score was an independent protective factor in AC patients.

Research conclusions

We found that the novel prognostic score based on the preoperative TBAR and FAR has good predictive power in AC patients who underwent curative pancreaticoduodenectomy.

Research perspectives

There are several limitations in this retrospective study, and more studies with larger samples are needed to validate this conclusion.

FOOTNOTES

Author contributions: Zhang XJ and Fei H contributed equally to this work; Guo CG and Zhao DB designed the research study, they are the corresponding authors of this paper; Fei H and Zhang XJ analyzed the data; all authors wrote the manuscript; and all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Analysis of textbook outcomes for ampullary carcinoma patients following pancreaticoduodenectomy

Xiao-Jie Zhang, He Fei, Chun-Guang Guo, Chong-Yuan Sun, Ze-Feng Li, Zheng Li, Ying-Tai Chen, Xu Che, Dong-Bing Zhao

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Abstract

BACKGROUND

Textbook outcomes (TOs) have been used to assess the quality of surgical treatment for many digestive tumours but not ampullary carcinoma (AC).

AIM

To discuss the factors associated with achieving a TO and further explore the prognostic value of a TO for AC patients undergoing curative pancreaticoduodenectomy (PD).

METHODS

Patients who underwent PD at the China National Cancer Center between 1998 and 2020 were identified. A TO was defined by R0 resection, examination of ≥ 12 Lymph nodes, no prolonged hospitalization, no intensive care unit treatment, no postoperative complications, and no 30-day readmission or mortality. Cox regression analysis was used to identify the prognostic value of a TO for overall survival (OS) and recurrence-free survival (RFS). Logistic regression was used to identify predictors of a TO. The rate of a TO and of each indicator were compared in patients who underwent surgery before and after 2010.

RESULTS

Ultimately, only 24.3% of 272 AC patients achieved a TO. A TO was indepen-

dently associated with improved OS [hazard ratio (HR): 0.443, 95% confidence interval (95%CI): 0.276-0.711, P = 0.001] and RFS (HR: 0.379, 95%CI: 0.228-0.629, P < 0.001) in the Cox regression analysis. Factors independently associated with a TO included a year of surgery between 2010 and 2020 (OR: 4.549, 95%CI: 2.064-10.028, P < 0.001) and N1 stage disease (OR: 2.251, 95%CI: 1.023-4.954, P = 0.044). In addition, the TO rate was significantly higher in patients who underwent surgery after 2010 (P < 0.001) than in those who underwent surgery before 2010.

CONCLUSION

Only approximately a quarter (24.3%) of AC patients achieved a TO following PD. A TO was independently related to favourable oncological outcomes in AC and should be considered as an outcome measure for the quality of surgery. Further multicentre research is warranted to better elucidate its impact.

Key Words: Ampullary carcinoma; Textbook outcomes; Pancreaticoduodenectomy; Prognosis

Core Tip: Surgery has improved substantially with advances in surgical techniques, however we still lack an effective measure to evaluate the quality of surgery in ampullary carcinoma. As a composite metric, textbook outcome (TO) concluded the strengths of all indicators based on important short-term outcomes, which was more reliable and comprehensive than single outcome measure. Pancreaticoduodenectomy was still quite complicated and required a broad judgement to monitor and compare the quality of procedures. TO should be considered as an outcome measurement for the quality of surgery, our study will be helpful in completely and effectively evaluating the overall quality of surgical care, and even in the hospital administration.

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INTRODUCTION

Ampullary carcinoma (AC) is a rare tumour constituting only 0.6%–0.8% of all digestive system malignancies[1], and the incidence of AC has increased over the last 2 decades[2]. Pancreaticoduodenectomy (PD) is one of the standard treatment strategies for curative purposes. The prognosis of AC patients is better than that of patients with other peri ACs[3], with a nearly 50% resection rate[4]. Surgery has improved substantially with advances in surgical techniques; however, there is still a lack an effective measure to evaluate the quality of surgery. Sun *et al*[5] found inflammatory index can be regarded as a more useful prognostic index and Gonzalez *et al*[3] established a nomogram to predict disease-specific survival; however, these method did not have intuitive indicators. Recently, textbook outcomes (TOs) have emerged and been applied in evaluating treatments for many tumours. To our knowledge, no previous study has explored the clinical value of a TO in AC patients.

The concept of the TO was first proposed by Kolfschoten *et al*[6] to investigate hospital variation in the Netherlands as a composite quality metric that encompassed several indicators of quality. Generally, individual quality metrics such as mortality and complications are applied to evaluate the quality of surgery[7,8]; however, these single indicators may lack practicality in reflecting the overall prognosis. As a composite metric, the TO represents the strength of all indicators based on important short-term outcomes and is thus more reliable and comprehensive than a single outcome measure[9,10]. Since the concept of the TO emerged in surgery for colon cancer, it has been defined for the treatment of many other tumours, such as gastroesophageal cancer and intrahepatic cholangiocarcinoma[9,11]. The definition of a TO follows the all-or-none principle[12] because partially favourable outcomes are not perfect postoperative outcomes.

Previous studies have successfully proven that a TO is associated with improved long-term survival in pancreatic adenocarcinoma patients who undergo PD[13-15], as well as for patients in other surgical fields[6,16,17]. Milbank considered PD to require a broad judgement to monitor and compare the quality of procedures[18]. Based on the above situation, the aims of this study were to propose a TO definition for AC patients and characterize the impact of a TO on survival. In addition, we assessed the factors associated with achieving a TO.

MATERIALS AND METHODS

Data source and study population

Patients who underwent surgery for AC between 1998 and 2020 in the China National Cancer Center were selected for analysis. Inclusion criteria: (1) Pathologically proved as AC; and (2) Patients were submitted to radical surgery. Patients

with missing data necessary to define TO were excluded: R0 resection (n = 4), lymph nodes examined (n = 9), hospitalization (n = 8) intensive care unit (ICU) treatment (n = 6), postoperative complications (n = 10), tumor differentiation (n = 4). A total of 41 patients were excluded from analysis and 272 AC patients were included.

TO

TO represents optimal oncologic care after PD for AC as a single composite measure. TO was achieved if the following indicators are fulfilled: The surgical margin was negative (R0 resection), ≥ 12 Lymph nodes examined (American Joint Committee on Cancer, eighth edition)[19], no prolonged hospitalization (< 75th percentile)[6,20], no ICU treatment, no postoperative complications, no 30-day readmission or mortality[13], hospitalization was defined as day of operation to day of discharge.

Statistical analysis

we counted the number of patients each of the indicator and calculated the cumulative proportion. The collected data was presented as frequencies and proportions, and was compared between the groups with and without TO using the Chi-square test. Cox regression analysis was used to identify if TO was an independent prognostic factor for overall survival (OS) and recurrence-free survival (RFS). Multivariable logistic regression was performed to determine the relationship between baseline characteristics and TO, factors with P < 0.2 in univariate analysis were included in the multivariate analysis, and odds ratios (OR) or hazard ratios (HR) and their 95% confidence intervals (95%CI) were reported. Survival curves of OS and RFS were plotted using the Kaplan–Meier method to determine the effect of TO on survival. We divided the patients into two groups by the year of surgery before and after 2010 to see the TO rate trend.

Follow-up was mainly conducted by telephone and though outpatient rechecks, other information was obtained by medical records and population death register information system. All data were analyzed with SPSS software (version 21; SPSS Inc., Chicago, IL, United States). Kaplan–Meier survival analyses were performed in R software (Version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria). P value < 0.05 was considered statistically significant.

RESULTS

TO and survival

A total of 272 AC patients met the inclusion criteria. A TO was observed in 66 (24.3%) patients. Among the indicators used to define a TO, R0 resection (99.6%), no 30-day readmission or mortality (93.0%) and no ICU treatment (90.1%) were achieved easily, while Examination of ≥ 12 Lymph nodes (58.5%) and no postoperative complications (48.9%) were not achieved as easily. The data for the 6 TO indicators and the cumulative proportions are shown in Figure 1.

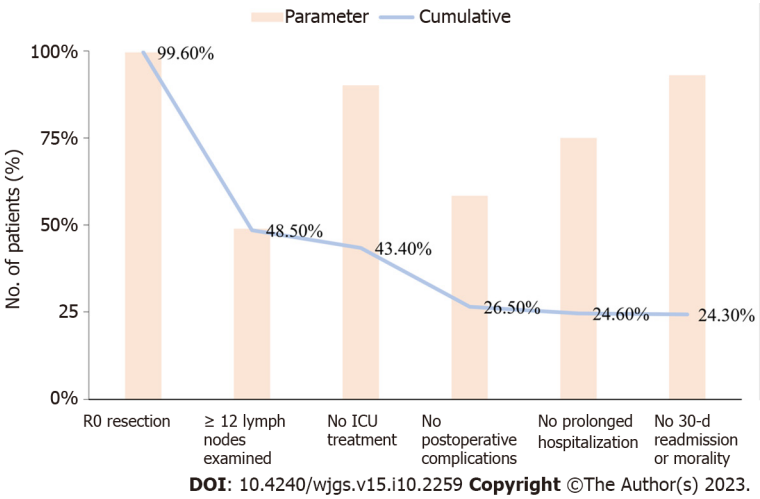

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Figure 1 Textbook Outcome percentages (parameter and cumulative) after pancreatoduodenectomy.

Cohort characteristics

Patients were divided into a TO group (66 patients, 24.3%) and a non-TO group (206 patients, 75.7%). There were significant differences in the year of surgery, N stage, TNM stage and lymphovascular invasion (P < 0.05) between the two groups and no significant differences in sex, age, operation time, blood transfusion, tumour size, differentiation, CA199, T stage or adjuvant treatment (P > 0.05). Baseline characteristics for the TO and non-TO groups are presented in Table 1.

Table 1 Baseline characteristics for patients with or without a Textbook Outcome after pancreatoduodenectomy

Characteristic	Textbook outcome		No textbook outcome		*P* value
	n = 66	Percentage	*n* = 206	Percentage	
Year of surgery					< 0.001
1998-2010	15	22.7%	117	56.8%	
2011-2020	51	77.3%	89	43.2%	
Sex					0.634
Male	40	60.6%	118	57.3%	
Female	26	39.4%	88	42.7%	
Age (yr)					0.618
≤ 60	42	63.6%	124	60.2%	
> 60	24	36.4%	82	39.8%	
Operation time (h)					0.622
≤ 6	45	68.2%	147	71.4%	
> 6	21	31.8%	59	28.3%	
Blood transfusion					0.328
No	35	53.0%	95	46.1%	
Yes	31	47.0%	111	53.9%	
Tumor size (cm)					0.155
≤ 2.0	27	40.9%	105	51.0%	
> 2.0	39	59.1%	101	49.0%	
Differentiation					0.369
Well	10	15.2%	47	22.8%	
Moderate	29	43.9%	88	42.7%	
Poor	27	40.9%	71	34.5%	
CA199					0.941
0-40	23	34.8%	74	35.9%	
> 40	37	56.1%	111	53.9%	
unknown	6	9.1%	21	10.2%	
N stage					0.038
N0	39	59.1%	154	74.8%	
N1	23	34.8%	41	19.9%	
N2	4	6.1%	11	5.3%	
T stage					0.585
T1	9	13.6%	33	16.0%	
T2	26	39.4%	67	32.5%	
T3	31	47.0%	106	51.5%	
TNM stage					0.034
I	29	43.9%	93	45.1%	
II	10	15.2%	58	28.2%	
III	27	40.9%	55	26.7%	
Lymphovascular invasion					0.001
No	40	60.6%	166	80.6%	

Yes	26	39.4%	40	19.4%	
Adjuvant treatment					0.223
No	15	22.7%	31	15.0%	
Yes	16	24.2%	43	20.9%	
Unknown	35	53%	132	64.1%	

Survival analysis

On Kaplan-Meier survival analysis, a TO was associated with better OS and RFS (all $P < 0.05$) in AC (Figure 2). The median survival and median recurrence-free survival in the non-TO group were 48 and 42 mo, respectively, whereas the median survival was not reached in the TO group. The Kaplan–Meier survival curve is shown in Figure 2.

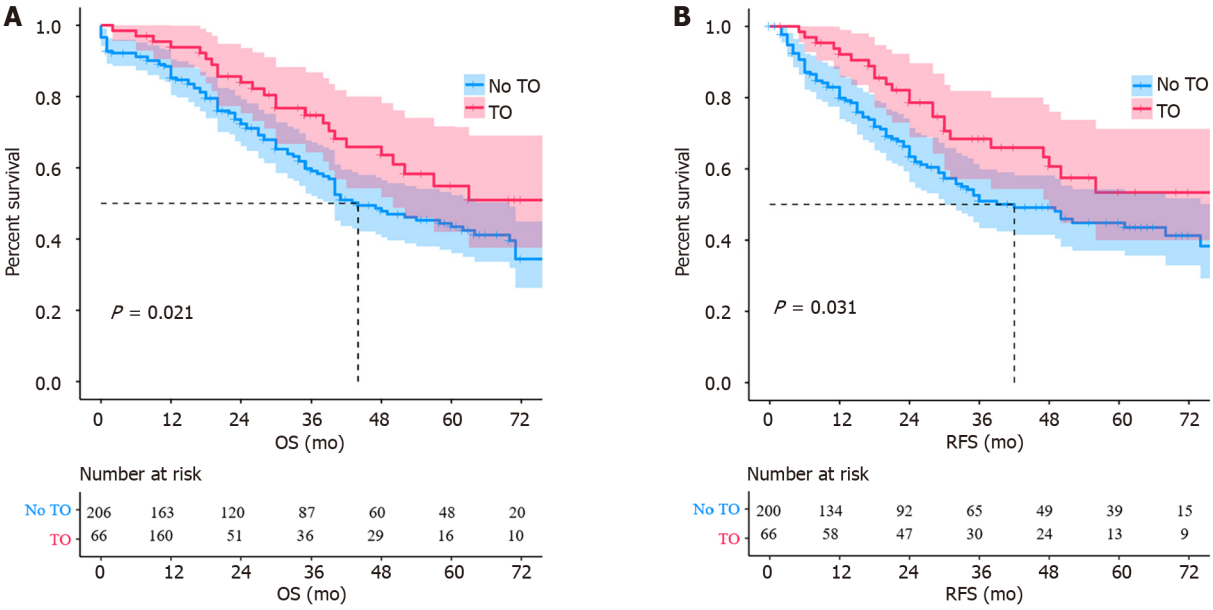

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Figure 2 The Kaplan–Meier survival curves stratified by achievement of textbook outcome for ampullary carcinoma patients after pancreaticoduodenectomy. A: Overall survival curve; B: Recurrence free survival curve. ICU: Intensive care unit; OS: Overall survival; RFS: Recurrence free survival; TO: Textbook outcomes.

Cox regression analysis showed that a TO was related to improved OS (HR: 0.443, 95%CI: 0.276-0.711, $P = 0.001$) and RFS (HR: 0.379, 95%CI: 0.228-0.629, $P < 0.001$) and that N1 stage disease (HR: 1.872, 95%CI: 1.178-2.977, $P = 0.008$) was an independent risk factor for OS. Regarding RFS, preoperative CA 199 Level > 40 (HR: 1.601, 95%CI: 1.025-2.501, $P = 0.038$), N1 stage disease (HR: 1.675, 95%CI: 1.006-2.789, $P = 0.047$) and lymphovascular invasion (HR: 1.892, 95%CI: 1.161-3.081, $P = 0.010$) were all independent risk factors. The detailed data are depicted in Tables 2 and 3.

TO-associated factors

Logistic regression revealed that a year of surgery between 2010 and 2020 (OR: 4.549, 95%CI: 2.064-10.028, $P < 0.001$) and N1 stage disease (HR: 2.251, 95%CI: 1.023-4.954, $P = 0.044$) were independently associated with lower odds of a TO. The results of the univariable and multivariable logistic regression analyses are shown in Table 4.

Time-related trends

Fifteen (132, 11.4%) patients treated before 2010 and 52 (140, 36.4%) patients treated after 2010 achieved a TO. The TO rate significantly increased after 2010 ($P < 0.001$), mainly due to improvements in lymphadenectomy ($P < 0.001$) and 30-day readmission or mortality ($P = 0.030$). The detailed data are depicted in Table 5.

DISCUSSION

TOs are composite measures that represent ideal outcomes and have been used to assess the quality of surgical treatment for many digestive tumours. To our knowledge, this is the first study to define and examine a TO in the evaluation of

Table 2 Univariable and multivariable Cox regression analyses of clinicopathological factors for overall survival

Characteristic	Univariable analysis		Multivariable analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Textbook outcome				
No	Reference		Reference	
Yes	0.598 (0.383-0.934)	0.024	0.443 (0.276-0.711)	0.001
Year of surgery				
1998-2010	Reference			
2011-2020	1.095 (0.767-1.562)	0.619		
Sex				
Male	Reference			
Female	0.914 (0.641-1.303)	0.619		
Age (yr)				
≤ 60	Reference			
> 60	1.254 (0.875-1.797)	0.218		
Operation time (h)				
≤ 6	Reference			
> 6	1.259 (0.861-1.839)	0.235		
Blood transfusion				
No	Reference			
yes	0.998 (0.702-1.417)	0.990		
Tumor size (cm)				
≤ 2.0	Reference		Reference	
> 2.0	1.396 (0.985-1.978)	0.061	1.327 (0.919-1.917)	0.131
Differentiation				
Poor	Reference		Reference	
Moderate	1.077 (0.730-1.588)	0.709	1.243 (0.830-1.863)	0.291
Well	0.644 (0.389-1.065)	0.086	1.026 (0.563-1.868)	0.934
CA199				
0-40	Reference		Reference	
> 40	1.495 (1.010-2.213)	0.045	1.339 (0.885-2.026)	0.168
Unknown	1.393 (0.741-2.619)	0.303	2.022 (1.025-3.990)	0.042
N stage				
N0	Reference		Reference	
N1	1.939 (1.303-2.886)	0.001	1.872 (1.178-2.977)	0.008
N2	2.077 (1.002-4.305)	0.049	1.850 (0.856-4.002)	0.118
T stage				
T1	Reference		Reference	
T2	1.092 (0.616-1.936)	0.764	0.824 (0.441-1.542)	0.546
T3	2.230 (1.309-3.799)	0.003	1.469 (0.771-2.799)	0.243
Lymphovascular invasion				
No	Reference		Reference	
Yes	1.528 (1.026-2.275)	0.037	1.252 (0.797-1.966)	0.330

Adjuvant treatment		
No	Reference	
Yes	1.082 (0.624-1.876)	0.780
Unknown	0.886 (0.548-1.431)	0.620

95%CI: 95% Confidence interval; HR: Hazard ratio.

Table 3 Univariable and multivariable Cox regression analyses of clinicopathological factors for recurrence free survival

Characteristic	Univariable analysis		Multivariable analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Textbook outcome				
No	Reference		Reference	
Yes	0.607 (0.382-0.963)	0.034	0.379 (0.228-0.629)	< 0.001
Year of surgery				
1998-2010	Reference			
2011-2020	1.030 (0.703-1.509)	0.879		
Sex				
Male	Reference			
Female	1.009 (0.685-1.485)	0.965		
Age (yr)				
≤ 60	Reference			
> 60	0.972 (0.652-1.449)	0.891		
Operation time (h)				
≤ 6	Reference			
> 6	1.051 (0.689-1.603)	0.818		
Blood transfusion				
No	Reference			
Yes	0.932 (0.638-1.363)	0.717		
Tumor size (cm)				
≤ 2.0	Reference		Reference	
> 2.0	1.540 (1.051-2.257)	0.027	1.365 (0.909-2.048)	0.133
Differentiation				
Poor	Reference		Reference	
Moderate	1.112 (0.730-1.693)	0.622	1.472 (0.946-2.290)	0.086
Well	0.546 (0.307-0.974)	0.040	1.002 (0.508-1.976)	0.997
CA199				
0-40	Reference			
> 40	1.751 (1.145-2.677)	0.010	1.601 (1.025-2.501)	0.038
Unknown	1.225 (0.584-2.568)	0.591	1.646 (0.746-3.634)	0.217
N stage				
N0	Reference		Reference	
N1	1.801 (1.170-2.771)	0.008	1.675 (1.006-2.789)	0.047
N2	2.563 (1.173-5.604)	0.018	1.807 (0.833-4.138)	0.162

T stage				
T1	Reference		Reference	
T2	1.152 (0.613-2.166)	0.661	0.885 (0.446-1.754)	0.726
T3	2.488 (1.387-4.463)	0.002	1.419 (0.709-2.842)	0.323
Lymphovascular invasion				
No	Reference		Reference	
Yes	2.002 (1.321-3.033)	0.001	1.892 (1.161-3.081)	0.010
Adjuvant treatment				
No	Reference			
Yes	1.271 (0.730-2.215)	0.397		
Unknown	0.671 (0.405-1.112)	0.122		

95%CI: 95% Confidence interval; HR: Hazard ratio.

outcomes in AC patients undergoing PD. We performed a hospital-based retrospective study of 272 patients undergoing curative surgery and found that only 24.3% achieved a TO. In addition, we found that a TO was independently associated with improved OS and RFS. The current study is important because it is the first to demonstrate that a TO is a potentially significant composite indicator for evaluating the quality of surgical treatment for AC.

Improving the quality of care remains a topic of interest for patients and physicians. As far back as 20 years ago, the Society for Thoracic Surgeons started a clinical audit to monitor their results[21]. Recently, TOs have become increasingly accessible for use in assessing the quality of surgical care as combinations of universal variables[17]. Prior studies have typically used isolated parameters to measure quality, such as prolonged hospitalization, morbidity, mortality and readmission[7,22,23]. However, the limitations of these individual metrics were gradually revealed with the progression of research, and they cannot reflect the quality of care completely[14,24,25]. On the other hand, hospitals might perform well in terms of one indicator and worse in terms of another[6,7]. Combining these isolated parameters to build a multidimensional metric might be a more accurate method for measuring quality[26]. As such, TOs are more reliable and comprehensive than single outcome measures, and the use of TOs might address different domains of surgical quality[27-29]. Of note, the all-or-none principle[12] could more accurately reflect desirable patient outcomes and align with ideal patient experiences. From this perspective, a TO is a much more patient-centred metric.

A TO directly reflects the short-term outcomes of rapid recovery and early discharge. However, assessment of long-term outcomes is equally important. Several studies have examined the relationship between a TO and survival among cancer patients. Kulshrestha *et al*[30] found that 37.2% of oesophageal cancer patients achieved a TO, which appeared to be associated with improved OS [Ed1]. Aquina *et al*[31] indicated that achieving a TO was related to better OS in the treatment of all eight kinds of cancer in the National Cancer Database. Consistently, similar results were found for PD in the treatment of pancreatic neuroendocrine tumours[32] and pancreatic adenocarcinoma[13-15,33]. Furthermore, we found that achieving a TO was independently associated with improved OS (HR: 0.443, 95%CI: 0.276-0.711, $P = 0.001$) and RFS (HR: 0.379, 95%CI: 0.228-0.629, $P < 0.001$). As such, achieving a TO is very significant, and these studies demonstrate the necessity and importance of improving surgical techniques and the quality of clinical care[34,35]. To this end, a TO is a reliable and valuable metric and should be applied in more clinical research.

Only approximately a quarter (24.3%) of patients achieved a TO in our research, meaning that adverse events occurred in a sizable fraction of patients. Previous studies on the achievement of a TO have shown large variations, with an average of 49% in colon cancer[6], 25.5% in intrahepatic cholangiocarcinoma[8], 32.1% in gastric cancer and 29.7% in oesophageal cancer patients[15]. Merath *et al*[36] found that TO rates varied from 11.1% to 69.6% after pancreatic surgery among hospitals. Aquina and associates[31] showed that the TO rate of pancreatic cancer patients was the lowest at 25% among that of all cancer patients. Similarly, only 16.8% of patients achieved a TO in the study by Sweigert and his colleagues[13]. In the present study, the achievement of a TO was mainly hampered by examination of ≥ 12 Lymph nodes (58.5%) and no postoperative complications (48.9%). The major hampering indicators in other studies include R0 resection [31], no prolonged hospital stay[36], and receipt of adjuvant chemotherapy within 12 wk[13,15], which showed considerable variation. As mentioned above, the wide variation among different hospitals further supports the superiority of TOs. Factors independently associated with a TO included a year of surgery between 2010 and 2020 (OR: 4.549, 95%CI: 2.064-10.028, $P < 0.001$) and N1 stage disease (OR: 2.251, 95%CI: 1.023-4.954, $P = 0.044$). Similar results were also found in pancreatic adenocarcinoma patients[13], which was mainly attributed to advancements in surgical techniques and the increasing number of examined lymph nodes. The proportion of AC patients with a TO remained low even at a large medical centre such as ours, which indicates great potential for improvement. Overall, a TO could be applied to guide quality improvement as a reliable metric[31].

Due to the observation of increasing trends in TO rates over the years ($P < 0.05$), we divided the patients into two groups by the year of surgery before and after 2010 and compared the trends of every indicator over time. Of note, the improvement in the TO rate was mainly attributed to the reduction in postoperative complications and increase in adequate lymphadenectomy, which indicated that there were significant advances in surgical techniques over time.

Table 4 Univariable and multivariable logistic regression analyses of factors associated with textbook outcome

Characteristic	Univariable analysis		Multivariable analysis	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Year of surgery				
1998-2010	Reference		Reference	
2011-2020	4.470 (2.361-8.462)	< 0.001	4.549 (2.064-10.028)	< 0.001
Sex				
Male	Reference			
Female	0.872 (0.495-1.535)	0.634		
Age (yr)				
≤ 60	Reference			
> 60	0.864 (0.487-1.534)	0.618		
Operation time (h)				
≤ 6	Reference			
> 6	1.163 (0.638-2.118)	0.622		
Transfusion				
No	Reference			
Yes	0.758 (0.435-1.321)	0.328		
Tumor size (cm)				
≤ 2.0	Reference		Reference	
> 2.0	1.502 (0.856-2.633)	0.156	1.728 (0.924-3.231)	0.087
Differentiation				
Poor	Reference		Reference	
Moderate	0.867 (0.471-1.595)	0.646	1.194 (0.597-2.390)	0.616
Well	0.559 (0.248-1.262)	0.162	1.007 (0.360-2.812)	0.990
CA199				
0-40	Reference			
> 40	1.072 (0.590-1.950)	0.819		
Unknown	0.919 (0.331-2.551)	0.872		
N stage				
N0	Reference		Reference	
N1	2.215 (1.192-4.117)	0.012	2.251 (1.023-4.954)	0.044
N2	1.436 (0.434-4.754)	0.554	1.236 (0.314-4.864)	0.762
T stage				
T1	Reference		Reference	
T2	1.423 (0.599-3.380)	0.424	1.205 (0.455-3.191)	0.707
T3	1.072 (0.464-2.481)	0.870	0.449 (0.150-1.341)	0.151
Lymphovascular invasion				
No	Reference		Reference	
Yes	2.697 (1.477-4.927)	0.001	1.483 (0.688-3.199)	0.315
Adjuvant treatment				
No	Reference		Reference	
Yes	0.769 (0.331-1.785)	0.541	1.144 (0.450-2.912)	0.777

Unknown	0.548 (0.267-1.126)	0.102	1.459 (0.629-3.387)	0.379

95%CI: 95% Confidence interval; OR: Odds ratio.

Table 5 Trends over years for individual textbook outcome parameters after controlling clinicopathological factors by logistic regression analyses

Characteristic	OR (95%CI)	*P* value
R0 resection	-	-
≥ 12 lymph nodes examined	14.620 (5.323-40.156)	< 0.001
No ICU treatment	0.255 (0.052-1.258)	0.093
No postoperative complications	3.375 (1.268-8.984)	0.015
No prolonged hospitalization	2.057 (0.738-5.734)	0.168
No 30-d readmission or mortality	6.399 (0.496-82.620)	0.155

95%CI: 95% Confidence interval; ICU: Intensive care unit; OR: Odds ratio.

However, Hyer *et al*[37] found that the improvement was mainly driven by a decline in mortality and prolonged hospital stay. Perioperative management should be further strengthened to better improve the quality of surgery.

There are several limitations to this study. First, the current study was a retrospective review of data from a large single centre, which might introduce the risk of selection bias. Second, our study had some missing data, such as estimated blood loss and details regarding adjuvant treatment. In addition, only a few patients underwent minimally invasive surgery, a subgroup analysis was not conducted. These factors could limit the generalizability of the study results. Third, no patients with T4 stage disease were included in this study due to the combined effects of the inclusion and exclusion criteria; therefore, the TO rate is possibly lower than described. Fourth, the TO definition was based on previous studies and is still in the early phase of development. Some indicators, such as patient satisfaction, social vulnerability[38] and hospital volume[39], which have been shown to affect the chances of achieving a TO, were not evaluated. There is an urgent need for a standard definition for a TO in AC patients who undergo PD.

CONCLUSION

In conclusion, only approximately a quarter (24.3%) of patients achieved TO in AC patients following PD and achieving TO was independently related to favorable oncological outcomes in AC. This study demonstrated that TO was a simple and reliable composite measure of ideal outcomes following PD which could completely and effectively evaluate the overall quality of surgical care. Further multicenter research is warranted to better elucidate its impact.

ARTICLE HIGHLIGHTS

Research background

Textbook outcome (TO) is a composite measure that represents the ideal outcome and has been used to assess the quality of surgical treatment in many digestive tumors.

Research motivation

Lack of an effective measure to evaluate the quality of surgery for ampullary carcinoma (AC).

Research objectives

This study aimed to investigate the impact of TO on survival for AC patients following pancreaticoduodenectomy and the factors associated with achieving TO.

Research methods

We defined the concept of TO in ampullary carcinoma and cox regression analysis was used to identify if TO was an independent prognostic factor for overall survival and recurrence free survival.

Research results

Only approximately a quarter (24.3%) of patients achieved TO and TO was independently related to favorable oncological outcomes in AC.

Research conclusions

TO was a simple and reliable composite measure of ideal outcomes following pancreaticoduodenectomy.

Research perspectives

Further multicenter research is warranted to better elucidate the impact of TO.

FOOTNOTES

Author contributions: Zhang XJ, Fei H and Guo CG contributed equally to this work; Chen YT, Che X and Zhao DB designed the research study, they are the corresponding authors of this paper; Fei H and Zhang XJ analyzed the data; Sun CY, Li Z and Li ZF collected the data; All author wrote the manuscript; All authors have read and approve the final manuscript.

Institutional review board statement: Ethical review and approval were not required for this study in accordance with the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

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

Conflict-of-interest statement: None of the authors have conflicts of interest related to the manuscript.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Retrospective Study

Endoscopic retrograde cholangiopancreatography for diagnosing and treating pediatric biliary and pancreatic diseases

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Abstract

BACKGROUND

This study evaluated the safety and effectiveness of endoscopic retrograde cholangiopancreatography (ERCP) in pediatric patients with biliary and pancreatic diseases. A retrospective analysis was conducted on 57 ERCP procedures performed in 41 children, primarily for treating pancreatic diseases. The overall success rate was 91.2%, with no major complications observed. Post-ERCP pancreatitis (PEP) occurred in 8.8% of cases. Follow-up examinations over one year showed no recurrence of biliary or pancreatic diseases. Notably, endoscopic treatment led to a significant increase in body mass index (BMI). These findings demonstrate the valuable role of ERCP in managing such conditions.

AIM

To evaluate the safety and efficacy of ERCP for the management of biliary and pancreatic diseases in pediatric patients.

METHODS

We conducted a retrospective analysis of data from children aged 1-18 years who underwent ERCP for biliary and pancreatic diseases at Beijing Children's Hospital between January 2021 and December 2022. The collected data included procedure time, endoscopic treatment, success rate, and postoperative complications.

RESULTS

Forty-one children underwent 57 ERCP procedures, including 14 with biliary duct disease and 27 with pancreatic disease. The mean age of the patients was 7.48 ±

3.48 years. Biliary duct-related treatments were performed 18 times, and pancreatic disease treatments were performed 39 times. ERCP was primarily used to treat pediatric pancreatic diseases [68.4% (39/57) of the procedures]. The overall success rate was 91.2% (52/57 patients). PEP was noted in five patients (8.8%, 5/57), and no instances of bleeding, perforation, or cholangitis were observed. The patients were followed up for over one year, and no recurrence of biliary or pancreatic diseases was detected. Importantly, BMI significantly increased after endoscopic treatment compared to that before treatment (P = 0.001).

CONCLUSION

The high success rate and lack of major complications support the valuable role of ERCP in the management of pediatric biliary and pancreatic diseases in the pediatric population.

Key Words: Pediatric; Endoscopic retrograde cholangiopancreatography; Choledocholithiasis; Chronic pancreatitis; Pancreatic ducts; Postoperative complications

Core Tip: We evaluated the safety and efficacy of endoscopic retrograde cholangiopancreatography (ERCP) in pediatric patients with biliary and pancreatic diseases. In total, 57 ERCP procedures were performed in 41 children, primarily for the treatment of pancreatic diseases. The overall success rate was 91.2% with no instances of bleeding, perforation, or cholangitis. Post-ERCP pancreatitis occurred in 8.8% of the cases. The patients were followed up for over one year, and no recurrence of biliary or pancreatic diseases was detected. Importantly, endoscopic treatment significantly increased body mass index. These findings highlighted the valuable role of ERCP in managing these conditions.

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INTRODUCTION

The study indicated that endoscopic retrograde cholangiopancreatography (ERCP) may be a safe and effective diagnostic and therapeutic approach for pediatric biliary and pancreatic diseases. The spectrum of the disease which was the indication of the ERCP of the adult is different from the children. The disease of the children was mainly the pancreatic disease, rather than the biliary tract disease. This also made the ERCP surgery more difficult in children. However, further prospective studies are required to determine the efficacy and safety of ERCP in pediatric patients.

MATERIALS AND METHODS

The majority of ERCP experience in pediatric patients is gained by treating adult patients[1,2]. Research on this technique in specialized pediatric hospitals is scarce. In this retrospective study, we shared our experience of performing ERCP in pediatric patients at specialized pediatric hospitals in China. The endoscopic procedures were performed by skilled pediatricians who closely monitored the patients throughout the procedure. We performed ERCP 18 and 39 times in patients with biliary duct and pancreatic diseases, respectively, and achieved an overall success rate of 91.2% (52/57 patients). Remarkably, we found no severe postoperative complications or instances of biliary or pancreatic disease recurrence during the 1-year follow-up period. Furthermore, the improvement in body mass index (BMI) after the procedure indicated the effectiveness of ERCP in treating biliary and pancreatic diseases.

In this study, ERCP was performed 57 times in a cohort of 41 children with a mean age of 7.48 ± 0.48 years. The current study suggested no strict age limitation for children undergoing ERCP[3]. Weng *et al*[4] reported that ERCP is safe for infants aged 6 mo to 1 year.

The success of ERCP in pediatric patients is affected by several factors, such as age, type of biliary or pancreatic disease, instrument and accessory selection, and depth of anesthesia. Various challenges arise due to the limited tolerance, low cooperation, and delicate digestive tracts of children; therefore, ERCP requires skilled operators and specialized instruments. In addition, in pediatric patients, procedures are performed under anesthesia[5]. In this study, general anesthesia was administered to all the children because of their underlying conditions and poor general health. Anesthesiologists from our hospital assisted with the entire procedure to ensure smooth completion and operational safety. Some studies have suggested that pediatric duodenoscopy using a duodenoscope with a smaller diameter should be the preferred option for children weighing less than 10 kg, while larger duodenoscopes designed for adults can be used for children weighing > 10 kg[6]. In our study, the success rate of the procedure was 91.2%, which is slightly lower

than the previously reported rate of 98.3%[7], and can be attributed to the limited number of enrolled patients and the diversity of pancreatic diseases. Furthermore, the success rate of intubation is lower in pancreatic diseases than in biliary diseases[7].

Post-ERCP pancreatitis (PEP) is a common complication that occurs in approximately 3%-14.7% of ERCP cases[8-10]. PEP is associated with intrapancreatic procedures, such as difficult nipple intubation, pre-cut sphincterotomy, pancreatic duct sphincterotomy, contrast agent injection into the pancreatic duct, and balloon dilation of the bile duct[11,12]. A retrospective study involving 313 pediatric patients reported that pancreatic duct injection, papilla, and pancreatic duct sphincterotomy were risk factors for PEP, whereas a history of chronic PEP was a protective factor against PEP[13,14]. In the present study, the incidence of PEP was 8.7% (5/57). Other children exhibited increased amylase levels; however, these levels were within three times the normal ranges. This can be attributed to the impaired function of the pancreatic cells in chronic PEP. The protective effects of chronic PEP against PEP are associated with pancreatic atrophy and decreased enzyme activity[15].

This study had several limitations. This was a single-center study with a relatively small cohort and a short follow-up period. Therefore, the results may be subject to bias due to the limited number of patients. Furthermore, this study has inherent limitations since it was a retrospective study.

RESULTS

General information

A total of 41 children, comprising 17 boys and 24 girls, with biliary or pancreatic disease were enrolled in the study. The mean age was 7.48 ± 3.48 years. A total of 57 ERCP were performed. Among the 14 patients with biliary disease, there were six who had bile duct stones, three with abnormal pancreaticobiliary confluence, two with biliary stricture, and three with biliary fistula (Table 1). The biliary stones comprised sediment-like stones (8 patients) and hard lump stones (one patient). Endoscopic treatments for biliary disease included biliary stent placement (eight procedures), biliary stone extraction (nine procedures), biliary balloon dilation (two procedures), and biliary duct sphincterotomy (two procedures).

A total of 27 children exhibited pancreatic disease, including 16 with chronic PEP, one with a pseudocyst resulting from acute PEP, four with pancreatic fistula associated with systemic lupus erythematosus (SLE) and acute lymphoblastic leukemia (ALL), two with pancreatic fistula resulting from the procedure, and one with pancreatic duct stricture resulting from ulcerative colitis (UC) (Table 2). Endoscopic treatments for pancreatic disease included pancreatic stent placement (39 procedures), pancreatic stone extraction (23 procedures), and pancreatic duct sphincterotomy (six procedures). Some cases of the ERCP are shown in Figure 1.

The success rate and the related disease

Eighteen procedures were performed for biliary disease and 39 for pancreatic disease. The overall success rate was 91.2% (52/57 patients). The success rate was 94.4% in the patients with biliary disease (17/18). Two patients underwent multiple bile stone procedures, including one with an abnormal pancreaticobiliary confluence. One patient required three procedures because of the presence of a bile fistula, which resulted from an abdominal surgery that was performed to change the stent. The only unsuccessful case involved a bile duct stricture resulting from duodenal surgery.

Two patients underwent four procedures for pancreatic disease, including those for pancreatic fistulas and pseudocysts resulting from SLE and chronic PEP with *CFTR* mutation. In total, nine patients underwent two procedures, including those for chronic PEP (three cases), pancreatic fistula and pseudocyst resulting from SLE (one case), and ALL (one case). The success rate was 89.7% (35/39 patients). There were four cases of unsuccessful procedures, including those for pancreatic pleural fistula resulting from chronic PEP (two cases), pancreatic duct stricture resulting from UC (one case), and pancreatic fistula resulting from trauma (one case). The success rates of the biliary and pancreatic procedures were not significantly different ($P > 0.05$).

The complication of ERCP

The procedure-associated complications included PEP, hemorrhage, perforation, and infection. In total, five cases of PEP (8.87%, 5/57) without hemorrhage, perforation, or infection were present. Approximately 30 patients experienced postoperative hyperamylasemia that was successfully treated symptomatically. The complication rates among patients with biliary and pancreatic diseases were 5.56% (1/18) and 10.2% (4/39), respectively, with no significant difference ($P > 0.05$). Among the five children with postoperative PEP, one had bile duct stricture resulting from duodenal surgery, one had pancreatic pleural fistula, one had chronic abdominal pain that did not improve significantly after pancreatic duct stent placement, one had recurrent episodes of chronic PEP resulting from pancreatic pleural fistula, pancreatic head pancreatic duct stenosis, and failed ERCP intubation, and one had pancreatic fistula due to ALL.

Follow-up data

Five children were followed up for more than one year. Stent replacement was performed 2-4 times at an interval of 3 to 12 mo. Data on disease recurrence, weight, and height were collected, and no disease recurrence was observed among children who underwent successful procedures. Furthermore, the mean preoperative BMI (13.2 ± 1.13) kg/m^2 significantly differed from the postoperative BMI (15.3 ± 1.32) kg/m^2 ($P = 0.001$).

Table 1 The biliary disease and the endoscopic retrograde cholangiopancreatography treatment

Disease site	Patients (*n* = 14)	ERCP treatment (*n* = 18)
Bile duct stone	6	7
Abnormal pancreaticobiliary confluence	3	4
Biliary stricture caused by the surgery of the abdominal or digestive tract	2	2
Biliary fistula caused by the abdominal surgery	3	5
Surgery performed through ERCP		
Biliary duct sphincterotomy	2	
Biliary balloon dilation	2	
Biliary stones' extraction	9	
Biliary stent placement	8	

ERCP: Endoscopic retrograde cholangiopancreatography.

Table 2 The pancreas disease and the endoscopic retrograde cholangiopancreatography treatment

Disease site	Patients (*n* = 27)	ERCP treatment (*n* = 39)
Chronic pancreatitis	16	22
Pancreas divisum	7	10
Gene mutation	9	12
Pseudocyst caused by acute pancreatitis	1	1
Pancreatic fistula and pseudocyst caused by the SLE (3 cases) and ALL (1 case)	4	10
Pancreatic fistula caused by the trauma	3	3
Pancreatic fistula caused by the abdominal surgery	2	2
Pancreatic duct stricture caused by UC	1	1
Surgery performed through ERCP		
Pancreas duct sphincterotomy	6	
Pancreas stones extraction	23	
Pancreas stent placement	39	

ERCP: Endoscopic retrograde cholangiopancreatography; SLE: Systemic lupus erythematosus; ALL: Acute lymphoblastic leukemia; UC: Ulcerative colitis.

DISCUSSION

Study design and patients

Data from children who underwent ERCP for biliary and pancreatic diseases at the Beijing Children's Hospital between January 2021 and December 2022 were retrospectively analyzed. The inclusion criteria were as follows: (1) Children aged 1-18 years and weighing > 10 kg; and (2) Confirmed diagnosis of biliary and pancreatic diseases using ultrasound, computed tomography (CT), or magnetic resonance cholangiopancreatography (MRCP).

This study was approved by the Ethics Committee of Beijing Children's Hospital, and the requirement for informed consent from the patients was waived owing to the retrospective nature of the study. All procedures followed the ethical standards outlined in the Declaration of Helsinki, as revised in Brazil in 2013.

ERCP procedure

Before the procedure, the patients fasted for 6 h and received active rehydration support. Preoperative assessments included routine blood examinations, biochemical tests, coagulation profiles, abdominal ultrasound, CT, or MRCP. Based on these results, the patients were preliminarily diagnosed with bile duct and/or pancreatic disease.

ERCP was performed using equipment from Olympus, Japan, including a T-JF260 electronic duodenoscope, radiography catheter, guidewire, incision knife, stone basket support, and balloon (Cook Company and Boston Company). General anesthesia with tracheal intubation was administered to all children. For procedures lasting > 1 h,

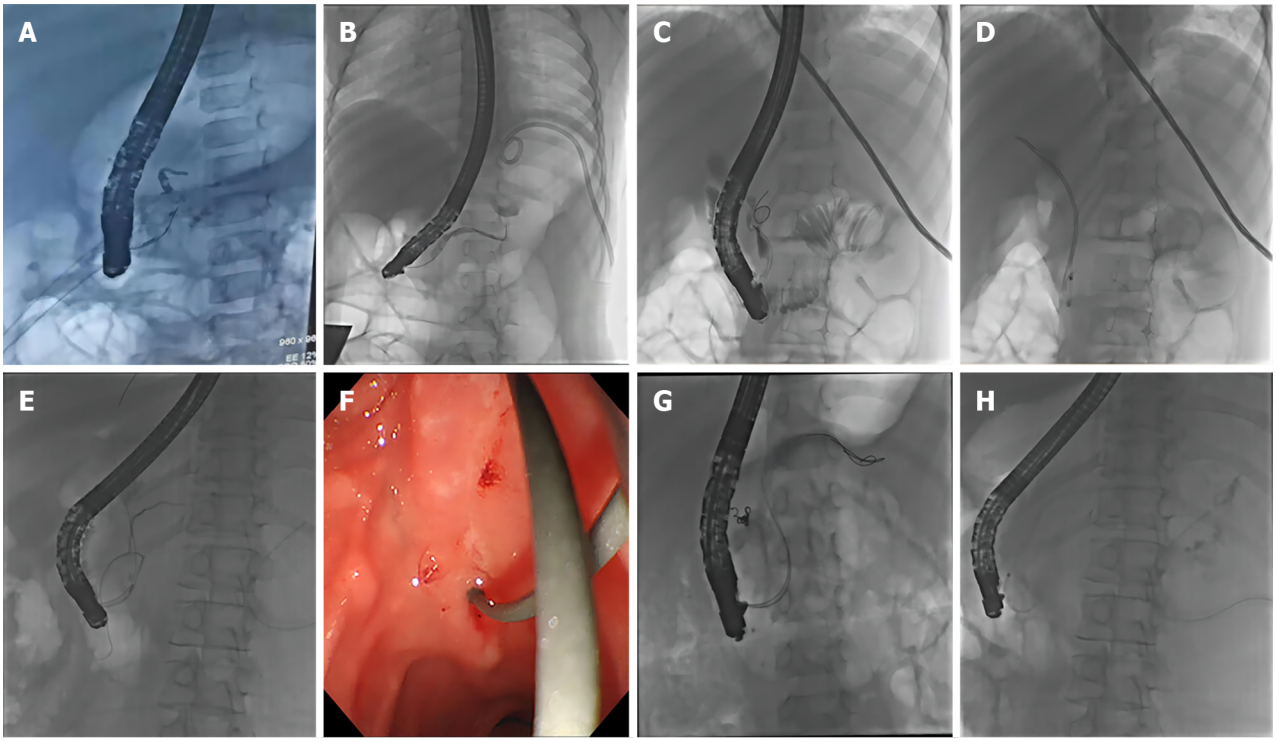

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Figure 1 Intraoperative findings during endoscopic retrograde cholangiopancreatography. A: Case 1 involved a pancreatic fistula following retroperitoneal neuroblastoma surgery, who was treated with a 5Fr stent placement; B: Case 11 presented with a pancreatic pleural fistula; C and D: In Case 12, acute necrotizing pancreatitis (PEP) and abnormal pancreaticobiliary confluence were recorded. The patient received a bile duct stent (7Fr-7 cm) and a pancreatic duct stent (5Fr-7 cm) placement; E: Case 9 had chronic PEP complicated by gastrointestinal bleeding. Accordingly, interventional embolization was performed, and the pancreatic fistula was treated with the placement of 5Fr-9 cm and 5Fr-7 cm stents; F-H: Case 2 experienced spontaneous nipple intubation, which resulted in the penetration of the guide wire from the accessory nipple. Pseudocysts subsequently developed from the distal end of the pancreatic duct after this procedure.

indwelling catheterization was performed, considering the patient's age and preoperative condition. Anesthesiologists continuously monitored heart rate, respiratory rate, and pulse oxygen saturation throughout the procedure.

Experienced endoscopists performed all endoscopic procedures using routine adult duodenoscopy. Various interventions have been performed after successful selective intubation, including endoscopic sphincterotomy, pancreatic duct sphincterotomy, nipple-balloon dilatation, net basket/balloon lithotomy, endoscopic nasobiliary drainage, endoscopic nasopancreatic drainage, endoscopic retrograde biliary drainage, and endoscopic retrograde pancreatic drainage. Radiation protection measures have been implemented to safeguard the thyroid, thymus, breasts, and reproductive systems. Pressure ulcer prevention nursing care was provided.

Following ERCP, all patients were hospitalized for observation of potential post-ERCP complications. At 3 and 24 h after the procedure, serum amylase levels were evaluated to monitor dynamic changes. Complications including PEP, bleeding, perforation, and cholangitis were defined based on the literature[16].

Data collection

Patient demographics, preoperative symptoms, ERCP completion, consumable data, postoperative complications, and follow-up data were extracted from the FUTang Updating medical REcords Database. Detailed information regarding the data cleaning process has been reported previously[17].

Statistical analysis

Data were analyzed using SPSS version 20.0 software. Normally distributed continuous data were presented as mean ± SD deviation and were compared using the *t*-test. The success rate of the procedure and the incidence of complications in the biliary and pancreatic regions were calculated using the chi-square test. Statistical significance was set at $P < 0.05$.

CONCLUSION

ERCP is a widely used procedure that combines radiography and upper gastrointestinal (GI) endoscopy to diagnose and treat disorders affecting the bile and pancreatic ducts in adults. Over time, it has evolved from a diagnostic tool to a predominantly therapeutic intervention and is considered a technically demanding and high-risk procedure for GI endoscopy[18]. Recent advances in duodenoscopic design and techniques have extended the application of ERCP to the diagnosis and treatment of biliary and pancreatic diseases in pediatric patients[19]. However, concerns remain regarding

the effectiveness, safety, and qualifications of pediatric ERCP examiners.

Recent retrospective studies have revealed that ERCP has comparable efficacy and safety profiles in infants, children, and adolescents. For example, a study by Asenov *et al*[20] in 2019 reported that patients aged 6-17 years underwent ERCP between 1994 and 2014 and concluded that ERCP is valuable for diagnosing and treating pancreaticobiliary disorders in the pediatric population. Similarly, a two-center retrospective study by Mercier *et al*[21] in 2022 evaluated ERCP outcomes in children aged ≤ 15 years over the past three years, reporting excellent success and safety outcomes when performed by experienced endoscopists. A Portuguese study reported similar conclusions after evaluating the outcomes of children aged < 18 years who were admitted to a tertiary referral hospital between January 1994 and June 2022[20]. Keil *et al*[3] conducted 856 ERCP procedures in 626 pediatric patients with biliopancreatic disorders at University Hospital Motol, Prague between January 1999 and January 2018, with 59% of the procedures being therapeutic and 41% diagnostic. Studies have also revealed comparable outcomes between adults and children, although with varying success rates[22]. However, limited research has focused on the use of this technology in specialized pediatric hospitals. Therefore, this retrospective study aimed to assess the safety and efficacy of ERCP in the diagnosis and treatment of biliary and pancreatic diseases in the pediatric population.

ARTICLE HIGHLIGHTS

Research background

The research findings provide important perspectives for future research on endoscopic retrograde cholangiopancreatography (ERCP) in pediatric patients with biliary and pancreatic diseases. Areas of focus include conducting long-term follow-up studies to assess durability and recurrence rates, comparative studies to compare ERCP with other treatments, investigating risk factors for post-ERCP pancreatitis (PEP), assessing the impact on quality of life, and conducting cost-effectiveness analyses. By addressing these research perspectives, further advancements can be made in optimizing the use of ERCP, improving outcomes, and guiding clinical decision-making in managing pediatric biliary and pancreatic diseases.

Research motivation

This study demonstrates that ERCP is both safe and effective for managing biliary and pancreatic diseases in pediatric patients. Among the 57 ERCP procedures performed in 41 children, a high success rate of 91.2% was achieved, with no major complications observed such as bleeding, perforation, or cholangitis. PEP occurred in 8.8% of cases, indicating a potential risk associated with the procedure. However, over a follow-up period of one year, no recurrences of biliary or pancreatic diseases were detected. Importantly, endoscopic treatment led to a significant increase in body mass index (BMI), highlighting its positive impact on nutritional status in pediatric patients. These findings support the valuable role of ERCP in effectively managing pediatric biliary and pancreatic diseases, thereby providing important insights for clinical practice and decision-making.

Research objectives

The research findings from this study evaluating ERCP in pediatric patients with biliary and pancreatic diseases indicate its safety and effectiveness. Among the 57 ERCP procedures performed in 41 children, the overall success rate was 91.2% with no major complications observed. PEP occurred in 8.8% of cases. Over a one-year follow-up period, there were no recurrences of biliary or pancreatic diseases. Notably, endoscopic treatment resulted in a significant increase in BMI, highlighting its potential positive impact on nutritional status. These results affirm the valuable role of ERCP in managing pediatric biliary and pancreatic diseases, emphasizing its efficacy and favorable outcomes in this patient population.

Research methods

In this study, a retrospective analysis was conducted to evaluate the safety and effectiveness of ERCP in pediatric patients with biliary and pancreatic diseases. Data from 41 children who underwent 57 ERCP procedures at Beijing Children's Hospital were analyzed. The study assessed the success rate of ERCP procedures, occurrence of major complications, incidence of PEP, recurrence of biliary or pancreatic diseases during follow-up, and changes in BMI. The findings revealed a high overall success rate of 91.2% with no major complications observed. PEP occurred in 8.8% of cases. Follow-up examinations over one year showed no disease recurrence. Notably, endoscopic treatment led to a significant increase in BMI.

Research results

The main objectives of this study were to evaluate the safety and efficacy of ERCP in pediatric patients with biliary and pancreatic diseases. These objectives included assessing the success rate of ERCP procedures, determining the occurrence of major complications, investigating PEP incidence, monitoring disease recurrence during follow-up examinations, exploring the impact on BMI, and evaluating the overall effectiveness of ERCP as a management strategy. By addressing these objectives, the study aimed to provide valuable insights into the role of ERCP in managing pediatric biliary and pancreatic diseases, contributing to improved patient care and treatment outcomes.

Research conclusions

The management of biliary and pancreatic diseases in pediatric patients presents unique challenges, and there is a lack of research on the effectiveness of ERCP specifically in this population. Therefore, this study aimed to evaluate the safety and efficacy of ERCP in pediatric patients with these conditions. Through a retrospective analysis of ERCP procedures performed at Beijing Children's Hospital, important insights were gained regarding the success rate, postoperative complications, and long-term outcomes of ERCP in this patient group. These findings provide valuable groundwork for further research and optimization of treatment strategies for pediatric biliary and pancreatic diseases, enhancing the care provided to this vulnerable population.

Research perspectives

This study assessed the safety and effectiveness of ERCP in pediatric patients with biliary and pancreatic diseases. A total of 57 ERCP procedures were performed on 41 children, primarily targeting pancreatic diseases. The overall success rate was 91.2%, with no occurrences of bleeding, perforation, or cholangitis. PEP affected 8.8% of cases. Follow-up examinations spanning one year revealed no recurrence of biliary or pancreatic diseases. Notably, endoscopic treatment led to a significant increase in BMI. These findings underscore the valuable role of ERCP in managing such conditions.

FOOTNOTES

Author contributions: Qin XM, Wu J, Yu FH proposed the concept of this study; Wu J and Liu ZM made contributions to data collection; Lv CK and Yu FH contributed to formal analysis; Qin XM, Liu ZM, Wu J, Yu FH participated in the study; Wu J contributed to the methods; Qin XM, Liu ZM, Wu J guided the research; Wu J and Qin XM validated the effectiveness of this study; Yu FH and Qin XM contributed to the visualization of this study; Qin XM and Wu J drafted the first draft; Yu FH, Liu ZM, Lv CK jointly reviewed and edited the manuscript.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Beijing Children's Hospital Affiliated to Capital Medical University of the National Children's Medical Center.

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

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

Data sharing statement: No additional data are available.

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SYSTEMATIC REVIEWS

Systematic review of diagnostic tools for peritoneal metastasis in gastric cancer-staging laparoscopy and its alternatives

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Abstract

BACKGROUND

Gastric cancer is one of the leading causes of cancer burden and mortality, often resulting in peritoneal metastasis in advanced stages with negative survival outcomes. Staging laparoscopy has become standard practice for suspected cases before a definitive gastrectomy or palliation. This systematic review aims to compare the efficacy of other diagnostic modalities instead of staging laparoscopy as the alternatives are able to reduce cost and invasive staging procedures. Recently, a radiomic model based on computed tomography and positron emission tomography (PET) has also emerged as another method to predict peritoneal metastasis.

AIM

To determine if the efficacy of computed tomography, magnetic resonance imaging and PET is comparable with staging laparoscopy.

METHODS

Articles comparing computed tomography, PET, magnetic resonance imaging, and radiomic models based on computed tomography and PET to staging laparoscopies were filtered out from the Cochrane Library, EMBASE, PubMed, Web of Science, and *Reference Citations Analysis* (https://www.referencecitationanalysis.com/). In the search for studies comparing computed tomography (CT) to staging laparoscopy, five retrospective studies and three prospective studies were found. Similarly, five retrospective studies and two prospective studies were also included for papers comparing CT to PET scans. Only one retrospective study and one prospective study were found to be suitable for papers comparing CT to magnetic resonance imaging scans.

RESULTS

Staging laparoscopy outperformed computed tomography in all measured aspects, namely sensitivity, specificity, positive predictive value and negative predictive value. Magnetic resonance imaging and PET produced mixed results, with the former shown to be only marginally better than computed tomography. CT performed slightly better than PET in most measured domains, except in specificity and true negative rates. We speculate that this may be due to the limited F-fluorodeoxyglucose uptake in small peritoneal metastases and in linitis plastica. Radiomic modelling, in its current state, shows promise as an alternative for predicting peritoneal metastases. With further research, deep learning and radiomic modelling can be refined and potentially applied as a preoperative diagnostic tool to reduce the need for invasive staging laparoscopy.

CONCLUSION

Staging laparoscopy was superior in all measured aspects. However, associated risks and costs must be considered. Refinements in radiomic modelling are necessary to establish it as a reliable screening technique.

Key Words: Gastric cancer; Peritoneal metastases; Computed tomography; Positron emission tomography; Magnetic resonance imaging; Staging laparoscopy

Core Tip: This systematic review aimed to compare the efficacy of staging laparoscopy against computed tomography (CT) scanning in the diagnosis of peritoneal metastases, where staging laparoscopy was found to be unequivocally superior. We then proceeded to investigate the efficacy of CT scans against positron emission tomography (PET) and magnetic resonance imaging (MRI) scans. CT scans were marginally better than PET scans but were slightly inferior to MRI scans based on the measured domains. Radiomic modelling has also been shown to have the potential to become a promising alternative for predicting peritoneal metastases with further research.

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INTRODUCTION

Gastric cancer is the fifth most common malignancy worldwide, the most common malignancy in many South-Central Asian countries and the fourth most common cause of cancer-related deaths, according to GLOBOCAN 2020 data[1]. Peritoneal carcinomatosis is the most common[2-4] type of metastasis secondary to gastric cancer, and its presence is associated with a higher risk of mortality, disease progression and poorer survival rates[4-6]. Currently, computed tomography (CT) scans and staging laparoscopy are the two most commonly utilised modalities for detecting peritoneal metastases[7,8]. This is attributed to CT scans having high rates of sensitivity and specificity, short scanning time, as compared to other imaging modalities such as positron emission tomography (PET) and magnetic resonance imaging (MRI)[9-11]. This review aims to investigate the efficacy of multi-imaging modalities in detecting peritoneal metastasis prior to management planning and during surveillance to detect disease recurrence.

The identification of peritoneal carcinomatosis is difficult as its presentation is commonly asymptomatic and hence, discovered late[12]. The detection of peritoneal metastasis on CT is dependent on visualising unique features such as ascites, omental caking and peritoneal thickening[13], but smaller deposits (< 5 mm) such as peritoneal nodules may be missed on imaging[14]. To rule out peritoneal metastasis prior to oncological gastrectomy, staging laparoscopy is commonly performed, especially in advanced gastric cancer patients. In this systematic review, we aim to investigate current evidence to determine if CT scans can yield comparable detection rates of peritoneal metastasis secondary to gastric cancer, with the goal of reducing the routine practice of staging laparoscopy.

PET and MRI scans are valuable non-invasive imaging techniques that are often used as alternatives to CT scans. PET scans detect cancer dissemination by mapping radioactive tracers, usually F-fluorodeoxyglucose (FDG)[15]. They are frequently used in oncological staging in primaries such as lymphoma and lung cancer[16], due to the high metabolic rate of these malignancies, which tend to have increased uptake of the tracers[15]. However, it is important to note that PET scans may not be as suitable for malignancies with low avidity for FDG, and infective or inflammatory sites may be mistaken for malignancies[17]. Since up to 90% of primary gastric malignancies have significant FDG uptake visible on PET[18], excluding patients with tumours of low FDG avid signet ring cells histology[19], we intend to find out if PET scans can be a useful modality in the diagnosis of peritoneal metastases.

As for MRI scans, its main advantage lies in its superior sensitivity, which provides better soft tissue definition, particularly when coupled with non-radioactive contrast[20]. Disadvantages to using MRI include its inability to be used in

patients with magnetic implants, allergy to gadolinium, its high cost, longer scanning duration and high rate of motion artifacts[21-23]. Hence, we also evaluated the efficacy of PET and MRI scans as an alternative to CT scans in the detection of peritoneal metastasis secondary to gastric cancer. Although other forms of diagnostic modalities, such as ultrasound scanning, have been considered, it has proven to be inferior in sensitivity and specificity for the detection of peritoneal metastases. This has been attributed to the acoustic impedance of gas and fat, which decreases visualisation through bowel, omentum, mesentery and adipose tissues[7,24]. Endoscopic ultrasound has shown to be a valuable tool in predicting the T stage of tumours and local invasion. However, its efficacy in detecting distant peritoneal metastasis remains limited. Recent animal studies conducted in 2022 have shown promising results in imaging and scoring peritoneal metastasis, but this is still in the trial phase and requires further validation.

The use of PET/MRI scans have also gained attention in recent years as it has shown better detection of peritoneal metastasis secondary to primary abdominopelvic malignancies compared to PET/CT. A recent systematic review demonstrated that PET/MRI scans exhibited better sensitivity for detecting peritoneal metastasis in gastric cancer than PET/CT scans. However, this systematic review was limited to five papers, each assessing a small cohort of 10-15 patients, thereby making it difficult to draw definitive conclusions regarding the efficacy of peritoneal metastasis detection until further studies are conducted.

In recent years, there has been a growing interest in the use of big data and artificial intelligence, to develop radiomic models that can accurately predict peritoneal metastasis based on preoperative CT and PET scans[25]. These models may also have the potential to prognosticate and estimate recurrence rates based on deep learning of retrospective cohorts [26]. As such, we have also included radiomic analysis in our search strategy in order to see the latest development in the diagnosis of peritoneal metastases.

In this paper, we investigate whether there are non-invasive alternatives that can provide comparable accuracy to the current standard of peritoneal metastases detection, staging laparoscopy. This is an important question, as staging laparoscopy is an invasive procedure that carries risks for patients. Identifying non-invasive alternatives that are equally effective would represent a significant advance in the field of peritoneal metastases detection and could improve patients' management and safety outcomes.

MATERIALS AND METHODS

Search strategy

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The Cochrane Library, EMBASE, PubMed, Web of Science libraries and *Reference Citations Analysis* (https://www.referencecitationanalysis.com/) were searched using the following search terms: Stomach neoplasms, gastric cancer, peritoneal neoplasms, peritoneal metastasis, peritoneal carcinomatosis, laparoscopy, CT, PET, and MRI. The respective search terms are detailed in the appendix as Supplementary Tables 1 and 2. After reviewing the references in the reports and articles for CT and staging laparoscopy, no additional relevant studies were identified.

Studies were considered in the review if they met the inclusion criteria: (1) Prospective or retrospective comparative papers; (2) Diagnosis of peritoneal metastases secondary to gastric cancer; and (3) Compared CT against PET or MRI or staging laparoscopy.

Studies were excluded if the following were met: (1) Articles were not in English; (2) Articles were case reports, guidelines, letters, non-comparative studies, protocols; or meta-analyses; (3) Patients were already diagnosed with metastatic disease; (4) Diagnostic modality used was none of laparoscopy, CT, PET nor MRI; and (5) Comparison was not made for peritoneal metastases.

Quality assessment

The risk of bias was assessed as low, moderate, or high based on the Newcastle-Ottawa scale (NOS)[27] for non-randomised studies based on cohort selection, comparability, and outcomes. All 17 studies were determined to be of low risk of bias as they all scored a seven on the NOS. Two points were lost as the studies did not standardise the age and sex of the cohort involved, and some subjects were lost to follow-up in the study by Burbidge *et al*[28], while the other nine had no clear description of follow-up rates.

Data collection: The following data were extracted from the included studies: (1) Patient demographics; (2) Tumour characteristics; (3) The specific type of diagnostic modality used; and (4) Statistical outcomes in the detection of peritoneal carcinomatosis.

RESULTS

CT vs staging laparoscopy

Figure 1 shows the flow chart for the article selection process. Eight relevant articles for CT and staging laparoscopy were identified and included for review. Search details are reflected in Supplementary Table 1.

A total of five retrospective studies and three prospective studies were included. A summary of the patient demographics (Table 1), tumour characteristics and type of CT used (Table 2) and outcome parameters (Table 3) are included below.

Table 1 Patient demographics

Ref.	Total number of patients	Mean age in years (range)	Gender ratio (M:F)
Burbidge *et al*[28], 2013	220	69 (41-96)	136:84
Li *et al*[29], 2020	385	-	-
Davies *et al*[30], 1997	105	69 (33-92)	68:37
Kim *et al*[31], 2009	498	59.6 (27-89)	332:166
Stell *et al*[32], 1996	103	65 (33-91)	68:35
Asencio *et al*[58], 1997	71	65.8 (47-81)	43:27
Fujimura *et al*[59], 2002	39	(26-80)	17:22
Leeman *et al*[60], 2017	74	67.6 (29-84)	54:20

Table 2 Tumour characteristics and computed tomography modality used

Ref.	Primary tumour location	Tumour histology	CT modality
Burbidge *et al*[28], 2013	-	Adenocarcinoma (220, 100%)	Multidetector CT with gastric staging protocol
Li *et al*[29], 2020	-	-	Unenhanced, two-phase dynamic enhanced CT
Davies *et al*[30], 1997	-	Adenocarcinoma (105, 100%)	Philips Tomoscan SR 7000 scanner (120 Kvp and 225-300 mAs), contrast enhanced spiral CT
Kim *et al*[31], 2009	-	Intestinal (162, 32.5%) Diffuse (336, 67.5%)	16-detector row (n = 427) or 64-detector row (n = 71) scanners
Stell *et al*[32], 1996	Proximal third (60, 58.3%) Body (24, 23.3%) Antrum (10, 9.7%) Body and antrum (6, 5.8%) Fundus (2, 1.9%) Linitis plastica (1, 1%)	Adenocarcinoma (103, 100%)	Contrast-enhanced CT using a GE model 9800 Hilight whole-body scanner (GEC, Milwaukee, Wisconsin, United States)
Asencio *et al*[58], 1997	Upper third (12, 17%) Middle third (21, 30%) Lower third (19, 27%)	Adenocarcinoma (71, 100%)	Dynamic contrast-enhanced CT
Fujimura *et al*[59], 2002	Japanese classification of gastric carcinoma type 1 (1, 2.6%); type 2 (4, 10.3%); type 3 (14, 35.9%); type 4 (20, 51.3%)	Differentiated (16, 41%) Undifferentiated (23, 59%)	CT
Leeman *et al*[60], 2017	Proximal (7, 9.5%) Body (23, 31.1%) Distal (10, 13.5%) Linitis plastica (6, 8.1%)	Adenocarcinoma (74, 100%)	Toshiba Aquilion 16 (16 slice), Siemens Somatom Sensation 16 (16 slice), Toshiba Aquilion Multi (4 slice)

CT: Computed tomography.

A total of 1495 patients with synchronous peritoneal metastases were included in the studies. Excluding the participants from Li *et al*[29] as the gender proportion was not provided, 718 (64.7%) were male and 391 (35.2%) were female. The age distributions of the participants are also described in Table 1.

The details of the distribution and histological subtypes of the tumours are listed in Table 2, along with the type of CT scanner used. The findings of the study indicate that the source of the primary tumour does not exhibit any discernible pattern, although the histological subtype of lesion typically presents as an adenocarcinoma. The anatomical distribution of the primary lesion was not listed by Burbidge *et al*[28], Davies *et al*[30], Kim *et al*[31] and Li *et al*[29] Histological

Table 3 Statistical results of computed tomography and staging laparoscopy

Ref.	Sensitivity		Specificity		Positive predictive value		Negative predictive value	
	CT	Staging laparoscopy	CT	Staging laparoscopy	CT	Staging laparoscopy	CT	Staging laparoscopy
Burbidge *et al*[28], 2013	25%	-	99%	-	83%	-	82%	-
Li *et al*[29], 2020	87.5%	-	76.4%	-	31.8%	-	-	-
Davies *et al*[30], 1997	71%	-	93%	-	67%	-	94%	-
Kim *et al*[31], 2009	28.3%	-	98.9%	-	-	-	-	-
Asencio *et al*[58], 1997	0%	88.9%	-	100%	-	100%	-	95.5%
Fujimura *et al*[59], 2002	38%	86%	100%	100%	67%	92%	-	-
Leeman *et al*[60], 2017	58.8%	94.1%	89.6%	100%	66.7%	100%	86%	98%
					False positives		**False negatives**	
Stell *et al*[32], 1996	8%	69%	100%	100%	0%	0%	12%	4%

CT: Computed tomography.

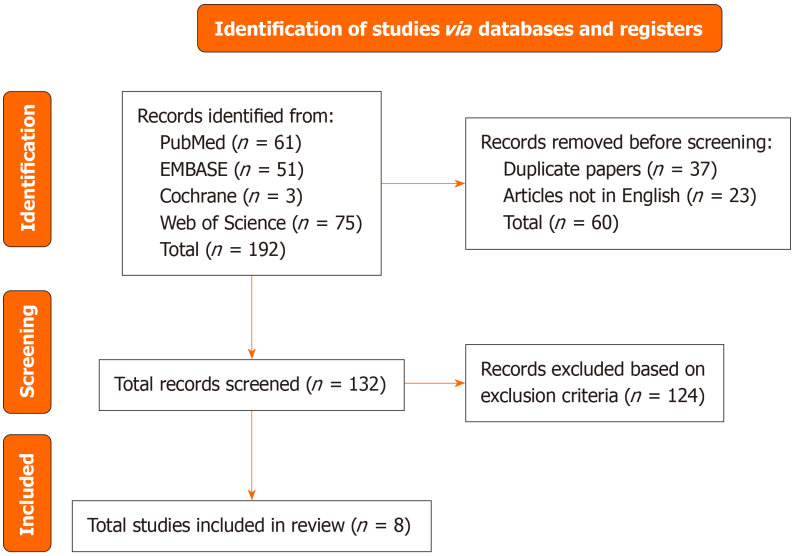

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Figure 1 Flowchart for the selection of articles comparing computed tomography to staging laparoscopy in this systematic review.

subtypes were not mentioned by Li *et al*[29].

Among the studies that compared the sensitivities of both CT and laparoscopy, staging laparoscopy consistently yielded better results at an average of 58.3%. Staging laparoscopy also demonstrated an average of 3.5% better specificity compared to CT in all studies that compared the two. Similarly, staging laparoscopy exhibited better positive and negative predictive values, with an average improvement of 29.2% and 12% respectively. Stell *et al*[32] reported false positive and false negative rates instead, in which staging laparoscopy had less or equal numbers of incorrect reporting. This study did not note any false positives, and CT reported an average of 8% more false negatives. In the papers by Burbidge *et al*[28], Davies *et al*[30], Kim *et al*[31] and Li *et al*[29], statistics for staging laparoscopy were not provided as laparoscopy was used to confirm the provisional diagnosis derived from CT scanning.

CT vs PET or MRI

Following this discovery, we proceeded to evaluate whether PET or MRI scans are accurate enough to be used as alternatives to CT scans for the purpose of minimising the need for invasiveness of staging laparoscopy, while simultaneously maintaining high detection rates.

Figures 2 and 3 show the flow chart for the article selection process. Seven relevant articles comparing CT to PET and two articles comparing CT to MRI were identified and included for review. Search details are reflected in Supple-

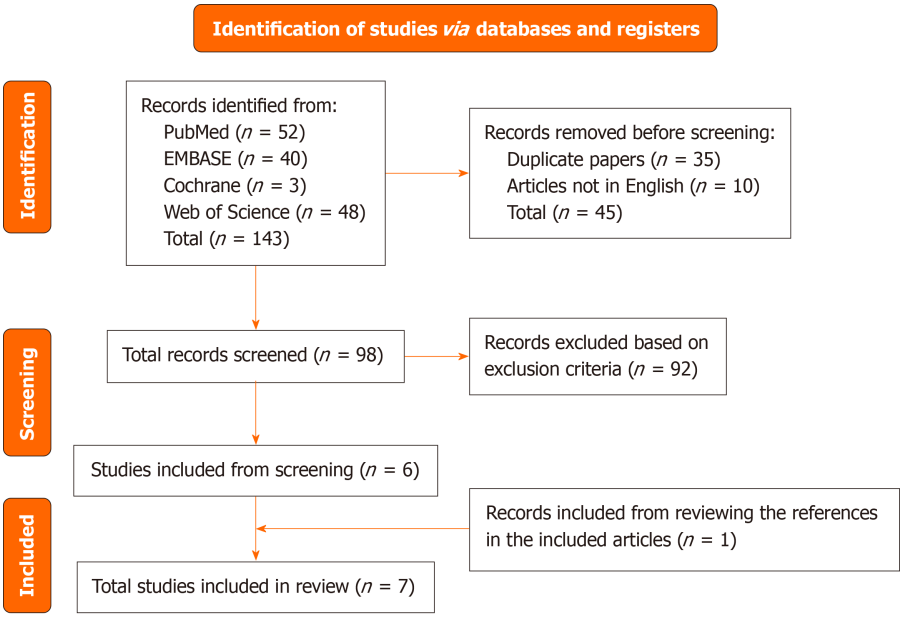

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Figure 2 Flowchart for the selection of articles comparing computed tomography to positron emission tomography in this systematic review.

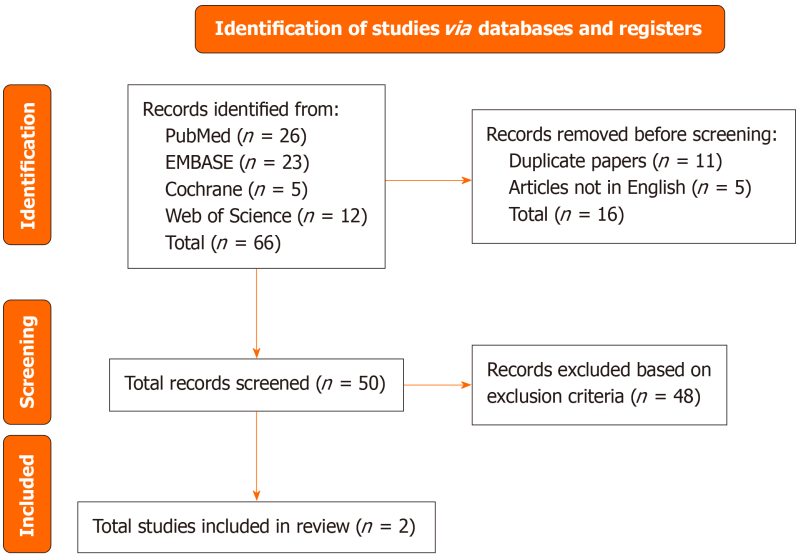

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Figure 3 Flowchart for the selection of articles comparing computed tomography to magnetic resonance imaging in this systematic review.

mentary Table 2.

A total of five retrospective studies and two prospective studies were included for CT *vs* PET scans. One retrospective and one prospective study were included for CT *vs* MRI scans. A summary of the patient demographics (Table 4), tumour characteristics and type of CT used (Table 5), and outcome parameters (Tables 6 and 7) are included below. Following the review of the references in the reports and articles available, the study by Sim *et al*[33] was also included.

A total of 474 and 94 patients with metachronous peritoneal metastases identified by CT or PET and CT or MRI respectively were included in the studies. A total of 288 (60.8%) were male and 186 (39.2%) were female in the CT *vs* PET group. In the CT *vs* MRI group, 42 (44.7%) patients were male and 52 (55.3%) were female. The age distributions of the participants are also described in Table 4.

The origin of the primary tumour in these two populations also does not seem to exhibit a discernable pattern but among the studies that have reported histology, the histological subtype of the lesion is typically an adenocarcinoma. The details of the distribution and histological subtypes of the tumours are listed in Table 5, along with the type of CT, PET or MRI scanner used. The studies by Turlakow *et al*[34] and Lin *et al*[35] did not specify the histology of gastric cancer in their patients.

Table 4 Patient demographics

Modality	Ref.	Total number of patients	Mean age in years (range)	Gender ratio (M:F)
PET	Lim *et al*[11], 2006	17	51.4 (32-74)	12:5
	Sim *et al*[33], 2009	52	62 (median) (33-80)	43:9
	Turlakow *et al*[34], 2003	88	54 (28-84)	50:38
	Perlaza *et al*[36], 2018	50	65.7 ± 12.1	30:20
	Kim *et al*[37], 2017	60	60.6 (29-80)	16:44
	Chen *et al*[38], 2005	68	54.8 (28-81)	49:19
	Kim *et al*[39], 2011	139	61.5 ± 11.6	88:51
MRI	Lin *et al*[35], 2021	62 (11 gastric)	56 ± 12 (54 ± 13 in gastric)	20:42 (6:5 in gastric)
	De Vuysere *et al*[40], 2021	32	(29-85)	22:10

PET: Positron emission tomography; MRI: Magnetic resonance imaging.

The sensitivity of CT seems to be superior to PET in all studies except in Perlaza *et al*[36] and Turlakow *et al*[34]. Conversely, the specificity of PET is superior to CT in every study except in Kim *et al*[37], where both had 100% specificity. This parameter was not measured by Turlakow *et al*[34]. Positive predictive value (PPV) was only calculated by Kim *et al*[37], Sim *et al*[33] and Turlakow *et al*[34] where CT slightly outperformed PET by an average of 3.1%. Negative predictive value (NPV) was only reported by Kim *et al*[37] where CT was better than PET by 10%. The accuracy of CT was also marginally greater than or equal to PET in the studies by Chen *et al*[38], Kim *et al*[39], Kim *et al*[37] and Lim *et al*[11] by an average of 2.875%. True positive, true negative, false positive, false negative values were only reported by Lim *et al*[11], where CT was better at picking up true positive cases (13 *vs* 6) and had lower false negative rates (4 *vs* 11). PET was better than CT at picking up true negative cases (87 *vs* 94) and had lower false positive rates (8 *vs* 1).

The values obtained by Lin *et al*[35] were the calculated average value between the two types of CT and MRI scanners used. The decimal values in Lin *et al*[35] were converted to percentages in the calculation of average scores.

The sensitivity of MRI was superior to CT in both papers by an average of 38.1%. Conversely, CT had better or equal specificity than MRI by an average of 6%. In the study by De Vuysere *et al*[40], PPV was equally high at 100% but MRI had much greater NPV at 68.7% better. MRI also had better accuracy by an average of 33.75%. Precision was only reported by Lin *et al*[35], where CT was 8.3% better. Iodinated contrast (Telebrix, Xenetix, Omnipaque) were used in both studies, and T2-weighted, diffusion-weighted images were obtained.

Radiomic modelling is a cutting-edge technique that employs artificial intelligence and a quantitative approach to augment medical imaging data, thereby improving diagnostic accuracy. The use of radiomic analysis and deep learning is gaining traction in the diagnosis of peritoneal metastases, with several preliminary papers demonstrating its potential. However, there is currently a lack of comparative studies that evaluate the efficacy of radiomic models. In the study by Jiang *et al*[14], the performance of radiomics was significantly better than conventional clinicopathological factors [Area under the curve (AUC) range, 0.51-0.63]. It also had value as an independent predictor of occult peritoneal metastases. In a separate paper by Jiang *et al*[41], radiomic modelling was able to predict peritoneal recurrence (AUC: 0.857, 0.856 and 0.843) and disease-free survival independently in all three cohorts stated (C-index 0.654, 0.668 and 0.610). The paper by Huang *et al*[26] affirms this possibility as radiomic modelling has been demonstrated to be an independent predictor of peritoneal metastases, with AUC values of 0.751, 0.802 and 0.745. Xue *et al*[42] have reported promising performance with the radiomic model, achieving an AUC of 0.90 in the training cohort and 0.88 in the validation cohort respectively. Ultimately, radiomic modelling is still in a developmental phase, requiring the multidisciplinary coordination of physicians, computers and data scientists in order to interpret the imaging data and analysis.

DISCUSSION

The mean age of participants falls between 58 to 69 years, which is in line with the peak age where gastric cancer and peritoneal metastasis are reported[2,43]. Most of the participants in the studies were male, except in those by Fujimura *et al*[59], Kim *et al*[37] and Lin *et al*[35], which is converse to current literature. In the 2021 systematic review by Rijken *et al*[44], peritoneal metastases were noted more frequently in females. Tan *et al*[45] also reported similar findings in their retrospective review[45].

Although the location of the primary tumour in the studies included did not show any distinct distribution pattern, most of the lesions arise from non-cardia areas, which corresponds to literature by Rijken *et al*[44] and Sanjeevaiah *et al*[46] It is frequently reported that signet ring cell or diffuse type tumours have a greater risk of peritoneal metastases but the majority of cases seen in the studies are adenocarcinomas[44,47,48]. This may be attributed to the vast majority of gastric cancers being adenocarcinomas or intestinal types[49,50].

Table 5 Tumour characteristics and computed tomography, positron emission tomography or magnetic resonance imaging modality used

Modality	Ref.	Tumour histology	Specific scanner used	
			CT	PET/MRI
PET	Lim *et al*[11], 2006	Moderate differentiation (*n* = 2) Mixed type of moderate and poor differentiation (*n* = 2) Signet cell differentiation (*n* = 4) Poor differentiation (*n* = 9)	Single-section spiral CT, HiSpeed CT/I or multi-detector CT scanning fourdetector row, LightSpeed Plus	GE advance PET scanner or Philips Allegro PET system
	Sim *et al*[33], 2009	Adenocarcinoma (*n* = 47) Signet ring cell (*n* = 4) Unknown (*n* = 1)	Not mentioned	PET/CT system, Philips Gemini, DA best
	Turlakow *et al* [34], 2003	Gastric (*n* = 48) Ovarian (*n* = 13) Adrenocortical (*n* = 6) Mesothelioma (*n* = 21)	Not mentioned	PET
	Perlaza *et al*[36], 2018	Well-differentiated (*n* = 4) Moderately differentiated (*n* = 20) Poorly differentiated (*n* = 26)	Somatom sensation 64	Hybrid PET/CT biograph mCT 64S
	Kim *et al*[37], 2017	Adenocarcinoma (*n* = 51) Signet ring cell carcinoma (*n* = 5) Mucinous carcinoma (*n* = 4)	16 or 64-detector row CT scanner, LightSpeed 16 or LightSpeed VCT	Discovery ST PET/CT system
	Chen *et al*[38], 2005	Adenocarcinoma (*n* = 13) Undifferentiated adenocarcinoma (*n* = 55)	Somatom Plus-S or Tomoscan 310 or LightSpeed Plus	GE Advance
	Kim *et al*[39], 2011	Adenocarcinoma (*n* = 117) Signet ring cell carcinoma (*n* = 19) Mucinous adenocarcinoma (*n* = 1) Others (*n* = 2)	Multi-detector row CT scanners, Somatom Volume Zoom	Cyclotron RDS-111
MRI	Lin *et al*[35], 2021	Appendiceal (*n* = 6) Colon (*n* = 25) Ovarian (*n* = 20) Gastric (*n* = 11)	Somatom sensation 64, Aquilion 64 or Aquilion ONE	MRI
	De Vuysere *et al* [40], 2021	Adenocarcinoma (*n* = 9) Adenocarcinoma with signet ring cell differentiation (*n* = 9)	Somatom Force	Aera 1.5 T scanner

CT: Computed tomography; PET: Positron emission tomography; MRI: Magnetic resonance imaging.

The use of staging laparoscopy has demonstrated superior or comparable results to CT scans in all domains of measurement, namely sensitivity, specificity, PPV, NPV, false negative and false positive rates. These findings are consistent with current research indicating that staging laparoscopy more accurately reflects the actual M stage of patients, leading to a significant reduction in unnecessary laparotomies[51]. A systematic review by Giger *et al*[51] suggested the number of diagnostic laparotomies performed can be lowered by up to 63% by performing staging laparotomy prior.

However, the risks of staging laparoscopy were not properly assessed in the studies. The most significant risk appeared to be port-site metastasis as seen in the five cases reported by Shoup *et al*[52], one case by McCulloch *et al*[53] and one case by Davies *et al*[54] Despite these findings, all three papers suggest that the value of diagnostic laparoscopy far outweighs the risks, and such occurrences are rare and unlikely.

Table 6 Statistical results of computed tomography and positron emission tomography

Ref.	Sensitivity		Specificity		Positive predictive value		Negative predictive value		Accuracy		True positive/true negative		False positive/false negative	
	CT	PET	CT	PET	CT	PET	CT	PET	CT	PET	CT	PET	CT	PET
Lim *et al*[11], 2006	96.5%	35.3%	91.6%	98.9%	-	-	-	-	89.3%	89.3%	13/87	6/94	8/4	1/11
Sim *et al*[33], 2009	86.6%	46.6%	91.9%	94.2%	82.3%	80%	-	-	-	-	-	-	-	-
Turlakow *et al* [34], 2003	43%	57%	-	-	100%	93%	-	-	-	-	-	-	-	-
Perlaza *et al* [36], 2018	64%	68%	93%	100%	-	-	-	-	-	-	-	-	-	-
Kim *et al*[37], 2017	96%	50%	100%	100%	100%	100%	99%	89%	99%	90%	-	-	-	-
Chen *et al*[38], 2005	80%	30%	91%	98%	-	-	-	-	89%	88%	-	-	-	-
Kim *et al*[39], 2011	63.6%	18.2%	97.7%	100%	-	-	-	-	95%	93.5%	-	-	-	-

CT: Computed tomography; PET: Positron emission tomography.

Table 7 Statistical results of computed tomography and magnetic resonance imaging

Ref.	Sensitivity		Specificity		Positive predictive value		Negative predictive value		Accuracy		Precision	
	CT	MRI	CT	MRI	CT	MRI	CT	MRI	CT	MRI	CT	MRI
Lin *et al*[35], 2021	41.4%	69.0%	93.9%	81.9%	-	-	-	-	69.4%	75.8%	85.7%	77.4%
De Vuysere *et al*[40], 2021	51.4%	100%	100%	100%	100%	100%	31.3%	100%	38.9%	100%	-	-

CT: Computed tomography; MRI: Magnetic resonance imaging.

The results from comparing between CT and PET scans were not as clear cut. CT scans performed marginally better than PET scans in most aspects, namely sensitivity, PPV, NPV, accuracy, and the detection of true positive cases with lower false negative rates. However, PET scans offered slightly better specificity and greater identification of true negative cases with lower false positive rates. These findings are consistent with the study by Dromain *et al*[55], which found that PET scans did not perform as well as CT scans in detecting peritoneal metastases in gastrointestinal malignancies. The limited FDG uptake due to the small (< 2 mm) and even microscopic size of peritoneal metastasis could be a contributing factor to this discrepancy[55].

MRI scans had outperformed or performed equally well to CT scans in all areas of comparison except when comparing specificity and precision, where CT scans were superior. This includes sensitivity, PPV, NPV and accuracy. Similar results were also reported by Low *et al*[22], where MRI scans were found to be more successful than CT scans in detecting peritoneal metastasis in all cases of low, moderate and large tumour burden. However, it should be noted that the significant downsides of using MRI scans include the high cost and time necessary for the procedure, along with the motion artefacts that can compromise image quality.

The use of PET/MRI has become increasingly prevalent and has demonstrated its effectiveness in detecting peritoneal metastasis. The degree of peritoneal involvement is a crucial factor in determining the resectability and prognosis of the tumor. However, the detection rate of 18-fluorothymine-FDG in peritoneal metastasis is often poor due to its low level of FDG uptake, leading to potential underestimation of the degree of involvement. In a recent study by Wang *et al*[3,9], [68Ga]Ga-FAPI-04 PET MRI/CT was found to be 100% sensitive in detecting peritoneal metastasis in gastric cancer. This success may be attributed to the fibrotic reaction of tumor cells invading the peritoneum, and the targeting of fibroblast activating protein (FAP) by FAPI. By improving the detection rate of peritoneal metastasis, clinicians can more accurately assess disease involvement and evaluate treatment response.

In the same vein, recent advances in PET radiotracers have shown promise in addressing the limitations of imaging FDG non-avid tumours, such as early stage, diffuse type, and mucinous tumours. Some examples of novel PET radiotracers that have shown potential in this regard include 18-fluorothymine, FAPI, and DOTA-FAPI PET. Further research is needed to fully understand the potential of these radiotracers, but early results are encouraging.

The use of radiomic modelling has also emerged as a potential tool for diagnosing peritoneal metastasis with the aid of CT and PET scanning, as shown by the papers by Jiang *et al*[14,41], Huang *et al*[26], and Xue *et al*[42]. Chen *et al*[25] also

reported encouraging results in their preliminary evaluation of radiomics in the use of non-invasive peritoneal metastases diagnosis by studying three types (R_IU model for iodine uptake images, R_MIX model for mixed images, R_comb model for the combined radiomics model) of radiomics models in dual-energy CT scanning. The retrospective paper by Kim *et al* [56] has further shown the possibility of using texture analysis and entropy in CT scans to detect occult peritoneal metastases. When the cut-off value for entropy was applied, the sensitivity and specificity were found to be 80% and 90% respectively. With further research, deep learning and radiomic modelling can be refined and potentially applied as a preoperative diagnostic modality, thereby reducing the need for invasive staging laparoscopy.

Limitations

The lack of homogeneity in the methodology of studies included in the review is a key concern that could have contributed to some disparity as different types of data were reported. For instance, while the paper by Stell *et al*[32] reported false negative and false positive rates, other papers reported PPV and NPV instead. Additionally, papers by Burbidge *et al*[28], Davies *et al*[30], Kim *et al*[31] and Li *et al*[29], did not report the statistical values representing staging laparoscopies, as they utilized laparoscopy to confirm the preoperative diagnosis made by CT scans, basing the statistical values reported for CT scans on laparoscopy. This implied that staging laparoscopy was assumed to have maximum accuracy and remained the standard of care prior to definitive gastrectomy based on features such as poorly differentiated adenocarcinoma on histology, linitis plastica, large sized type 3, or equivocal CT findings for peritoneal dissemination[57]. However, it is important to acknowledge that heterogeneity among studies is a common occurrence, particularly when papers are produced by various institutions that adhere to different reporting guidelines and compare different methods of diagnostic tools.

The type of CT, PET and MRI scanners used also varied from study to study. With different types of scanners used, the cut of the images obtained will also vary, potentially affecting the accuracy. The quality of images obtained will also vary, which could result in inconsistencies in the level of human error when reading the scans.

Similarly, the staging laparoscopy procedures were performed by different surgeons with differing levels of competency and proficiency with the laparoscope. This difference in ability could have altered the accuracy rates yielded as well. However, considering that many of the statistics obtained from the papers are 100%, the margin of error in this aspect appears to be limited.

Included reviews comparing MRI and CT scans were only limited to two studies by Lin *et al*[35] and De Vuysere *et al* [40], reducing the quality of analysis obtained due to a small sample size. Some of the statistics obtained were non-overlapping, which impacted the data analysis, resulting in a less robust comparison. Additionally, the study by Lin *et al* [35] was not specific for gastric cancer. This is a clear indication for further studies specifically comparing MRI and CT scans in the detection of peritoneal metastases secondary to gastric cancer. Several studies evaluating the use of PET/MRI in detecting peritoneal metastasis in gastric cancer have been conducted, but due to the nascent nature of these studies, the use of PET/MRI may not be currently available for patients.

There were no studies comparing radiomic modelling to the conventional diagnostic modalities available at the time of the search. Hence, essential analysis of quantitative values could not be carried out and the efficacy of radiomic modelling cannot be fully assessed. Due to its high potential based on preliminary investigations, more research is necessary to provide patients with a possible non-invasive alternative to staging laparoscopy in the diagnosis of peritoneal metastases.

CONCLUSION

Overall, staging laparoscopy outperformed CT scans in every measured aspect. These findings indicate that staging laparoscopy is statistically the superior modality for the diagnosis of peritoneal metastases in patients with gastric cancer or to rule out peritoneal metastases in other patients. It is important to note, however, that staging laparoscopies are still considered an invasive surgical procedure where general anaesthesia is necessary and multiple surgeons are involved. This would implicate the risks of anaesthesia, infection, and require more time and resources, and as a result, cost per patient may increase.

As such, non-invasive imaging remains invaluable in the work-up of gastric cancer patients. Among the commonly available scanning modalities, MRI scans have demonstrated superior performance in detecting peritoneal metastases compared to CT scans, which in turn showed slightly better results than PET scans. Hence, there is potential in these scanning modalities to provide patients with a non-invasive yet accurate alternative to staging laparoscopy, especially with the addition of alternate radiotracers such as FAPI and Flurothyrmine. However, further research is imperative to enhance the sensitivity and specificity of these techniques in the diagnosis of peritoneal carcinomatosis, such that they may soon be comparable to staging laparoscopies. In the same vein, more research in radiomic modelling is pivotal in achieving the same goal, as it has shown great promise in attaining a comparable, non-invasive alternative to staging laparoscopies.

ARTICLE HIGHLIGHTS

Research background

Staging laparoscopy is currently the gold standard for diagnosing peritoneal metastasis in gastric cancer patients. However, this procedure comes with risks of general anaesthesia and surgery which are of importance in elderly and frail

patients, the demographic most affected by gastric cancer. Hence, we sought to evaluate non-invasive alternatives to staging laparoscopy with comparable accuracy.

Research motivation

Staging laparoscopy remains the gold standard for diagnosing peritoneal metastasis in gastric cancer patients, which comes with risks of general anaesthesia and surgery. Many non-invasive diagnostic modalities are available in the current day and age, hence, we sought to evaluate non-invasive alternatives to staging laparoscopy that may provide us with comparable accuracy. With further research in this field, along with newer developments such as radiomic modelling and new radiotracers, there is great potential for developing such a diagnostic tool with comparable or even greater accuracy than staging laparoscopy.

Research objectives

We sought to determine if computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) could be a potential non-invasive yet accurate alternative to staging laparoscopy.

Research methods

Data from relevant studies that reported patients with peritoneal metastasis secondary to gastric cancer diagnosed by non-invasive scans were extracted and presented according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Significant data such as sensitivity, specificity, negative and positive predictive values were analysed and compared between diagnostic modalities in our systematic review.

Research results

Our findings suggested that staging laparoscopy still delivered the best results in terms of sensitivity, specificity, negative and positive predictive values when compared to CT scans in diagnosing peritoneal metastasis in advanced gastric cancer. MRI had generally outperformed CT scans which had in turn, generally performed better than PET scans. Despite this, the difference in performance between all the diagnostic modalities are marginal, suggesting that there is great potential for the development of the ideal diagnostic tool capable of providing us with the same or even better accuracy than staging laparoscopy, while remaining non-invasive. With additional tools such as radiomic modelling and new radiotracers, the development of such a diagnostic modality may be possible sooner than expected.

Research conclusions

Although staging laparoscopy remains superior to other non-invasive diagnostic modalities in the detection of peritoneal metastasis in advanced gastric cancer, the potential for developing a comparable or even better diagnostic tool is great. This may be achieved with new technologies such as radiomic modelling and new radiotracers, on top of the already advanced capabilities of CT, MRI and PET scans. With further research, this breakthrough may be possible sooner than expected.

Research perspectives

Given the rapid and enthusiastic development of new technologies in diagnostic tools, the development of a highly sensitive and specific non-invasive alternative to staging laparoscopy in peritoneal metastasis detection is highly likely with further research. On top of the already cutting edge diagnostic modalities, additional improvements and developments may bring us closer than ever to this goal.

FOOTNOTES

Author contributions: Ho SYA took part in screening the included studies, performed data extraction, analysed and interpreted the results, and prepared the manuscript; Tay KV led the study conception and design, took part in screening the included studies, and contributed in manuscript revision; All authors reviewed the results and approved the final version of the manuscript.

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SYSTEMATIC REVIEWS

Prediction of lymph node metastasis in early esophageal cancer

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Abstract

BACKGROUND

Given the poor prognosis of patients with lymph node metastasis, estimating the lymph node status in patients with early esophageal cancer is crucial. Indicators that could be used to predict lymph node metastasis in early esophageal cancer have been reported in many recent studies, but no recent studies have included a review of this subject.

AIM

To review indicators predicting lymph node metastasis in early esophageal squamous cell carcinoma (ESCC) and early esophageal adenocarcinoma (EAC).

METHODS

We searched PubMed with "[early esophageal cancer (Title/Abstract)] and [lymph node (Title/Abstract)]" or "[early esophageal carcinoma (Title/Abstract)] and [lymph node (Title/Abstract)]" or "[superficial esophageal cancer (Title/Abstract)] and [lymph node (Title/Abstract)]." A total of 29 studies were eligible for analysis.

RESULTS

Preoperative imaging (size), serum markers (microRNA-218), postoperative pathology and immunohistochemical analysis (depth of invasion, tumor size, differentiation grade, lymphovascular invasion, neural invasion, expression of PIM-1 < 30%) were predictive factors for lymph node metastasis in both early ESCC and EAC. Serum markers (thymidine kinase 1 ≥ 3.38 pmol/L; cytokeratin 19 fragment antigen 21-1 > 3.30 ng/mL; stathmin-1) and postoperative pathology and immunohistochemical analysis (overexpression of cortactin, mixed-lineage

leukaemia 2, and stanniocalcin-1) were predictive for lymph node metastasis in early ESCC. Transcription of CD69, myeloid differentiation protein 88 and toll-like receptor 4 and low expression of olfactomedin 4 were predictive of lymph node metastasis in early EAC. A total of 6 comprehensive models for early ESCC, including logistic regression model, nomogram, and artificial neural network (ANN), were reviewed. The areas under the receiver operating characteristic curve of these models reached 0.789-0.938, and the ANN performed best. As all these models relied on postoperative pathology, further models focusing on serum markers, imaging and immunohistochemical indicators are still needed.

CONCLUSION

Various factors were predictive of lymph node metastasis in early esophageal cancer, and present comprehensive models predicting lymph node metastasis in early ESCC mainly relied on postoperative pathology. Further studies focusing on serum markers, imaging and immunohistochemical indicators are still in need.

Key Words: Early esophageal cancer; Esophageal squamous cell carcinoma; Esophageal adenocarcinoma; Lymph node metastasis; Systematic review

Core Tip: In this study, we reviewed factors predicting lymph node metastasis in early esophageal squamous cell carcinoma (ESCC) and early esophageal adenocarcinoma (EAC). Imaging (size), serum microRNA-218, postoperative pathology and immunohistochemical analysis (depth, size, differentiation grade, lymphovascular invasion, neural invasion, PIM-1) were predictive for both ESCC and EAC. Serum markers (thymidine kinase 1; cytokeratin 19 fragment antigen 21-1; stathmin-1) and overexpression of cortactin, mixed-lineage leukaemia 2, and stanniocalcin-1 were predictive for ESCC. Transcription of CD69, myeloid differentiation protein 88 and toll-like receptor 4 and low expression of olfactomedin 4 were predictive for EAC. Six comprehensive models for ESCC were reviewed, and the areas under the curve reached 0.789-0.938.

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INTRODUCTION

Esophageal cancer was the seventh most commonly diagnosed cancer and the sixth leading cause of cancer death worldwide in 2018[1]. Squamous cell carcinoma (SCC) (85%) was the most common histological type, followed by adenocarcinoma (14%)[2]. Esophageal SCC (ESCC) and esophageal adenocarcinoma (EAC) differ greatly in tumor location and biological behaviour[3]. ESCC mainly occurs in the proximal two-thirds of the esophagus, while EAC mainly occurs in the distal third of the esophagus and the gastroesophageal junction. Alcohol and tobacco are risk factors for ESCC, and Barrett's esophagus is correlated with EAC[4]. Early detection and treatment improve the prognosis[5,6]. According to the 8th edition of the Cancer Staging Manual for Esophagus and Esophagogastric Junctions developed by the American Joint Committee on Cancer and the Union for International Cancer Control, early esophageal cancer includes high-grade dysplasia or tumor in situ (Tis) and tumors limited to the mucosa (T1a) or submucosa (SM) (T1b), regardless of lymph node status[7]. As the risk of lymph node metastasis varied greatly due to the depth of invasion, Japanese investigators subclassified mucosal and SM esophageal cancer into 6 types (M1, limited to the epithelial layer; M2, invading the lamina propria; M3, invading into but not through the muscularis mucosa; SM1, penetrating the upper one-third of the SM; SM2, penetrating the middle one-third of the SM; SM3, penetrating the deepest one-third of the SM)[8,9]. Regarding the therapeutic strategy for early esophageal cancer, endoscopic resection is appropriate due to its fewer complications and similar survival compared with esophagectomy[10,11]. However, the incidence of lymph node metastasis in patients with newly diagnosed early esophageal cancer was reported as 20%-27%[12-14]. As lymph node involvement is related to poor prognosis[15], the lymph node status must be assessed when designing the therapeutic strategy, especially before surgery. To our knowledge, many recent studies have yielded reports of indicators that could predict lymph node metastasis in early esophageal cancer, but there has been no study in which this subject has been reviewed from the perspective of recent findings. Therefore, this study was designed to review predictive indicators for lymph node metastasis in patients with newly diagnosed early esophageal cancer.

MATERIALS AND METHODS

We searched PubMed with "[early esophageal cancer (Title/Abstract)] and [lymph node (Title/Abstract)]" or "[early

esophageal carcinoma (Title/Abstract)] and [lymph node (Title/Abstract)]" or "[superficial esophageal cancer (Title/Abstract)] and [lymph node (Title/Abstract)]." The last sought date of each resource was May 1, 2023. All studies were reviewed in detail, and only articles focusing on lymph node metastasis in T1 esophageal cancer were included. Case reports, reviews, systematic reviews, meta-analyses and articles without available full texts in English were excluded. Finally, a total of 29 studies were eligible for analysis, and all relevant factors are discussed below (Table 1).

RESULTS

Imaging

The assessment of lymph node metastasis using computed tomography (CT) was mainly based on size. Intrathoracic and abdominal nodes larger than 10 mm in the short axis were generally suspected as lymph node metastasis, compared with supraclavicular nodes greater than 5 mm and retrocrural nodes greater than 6 mm[16]. This method might miss metastasis within normal-sized lymph nodes and misdiagnose inflammation within enlarged lymph nodes, given its sensitivity of 57% and specificity of 83%[17]. Moreover, these criteria were inappropriate for detecting lymph node metastasis in patients with early esophageal cancer [sensitivity of 1/18 (5%) and specificity of 25/31 (80%)][18]. Betancourt *et al*[18] considered lymph nodes adjacent to the primary tumor as positive for malignancy when they were round or ovoid with a mean size (short axis + long axis/2) > 5 mm or not adjacent when the mean size was > 7 mm. The sensitivity, specificity, and accuracy were 61% (11/18), 45% (14/31), and 51% (25/49), respectively[18].

Endoscopic ultrasonography was used to assess regional lymph node metastasis. The criteria were as follows: (1) Size greater than 10 mm; (2) a round shape; (3) sharply demarcated borders; and (4) hypoechoic structure[19]. Catalano *et al* [19] reported an accuracy of 100% if all four criteria were met, but other studies showed an accuracy of 66%-75%[20,21]. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) improved the sensitivity (14/22, 63% *vs* 28/30, 93%; $P < 0.05$) and accuracy (23/33, 70% *vs* 29/31, 93%; $P < 0.05$) of detecting nonperitumoral lymph node metastasis[22]. However, EUS-FNA must not traverse the malignancy to avoid tumor seeding from the primary site and false-positive results, which might decrease the sensitivity. With EUS-FNA, Betancourt *et al*[18] reported that 32.7%(16/49) of patients with positive lymph node metastasis were inappropriately designated as cN0.

Positron emission tomography and CT (PET/CT) are commonly used for tumor, node, and metastasis staging of malignancy. ^{18}F-Fluorodeoxyglucose is the most commonly used contrast agent and is a radiolabelled glucose analogue mainly concentrated in tissues with high glucose consumption, such as malignant tissues[23]. However, the assessment of regional lymph node status might be affected by the signal uptake from the adjacent tumor. Cuellar *et al*[24] enrolled 79 patients with early esophageal cancer and performed N-staging using PET/CT. All 3 patients positive on PET/CT were negative on biopsy, and all 13 patients positive on biopsy were falsely negative on PET/CT. The sensitivity and positive predictive values were both 0%. Therefore, PET/CT might be inappropriate for the routine assessment of lymph node status in patients with early esophageal cancer.

Serum markers

Jiang *et al*[25] reported that patients with esophageal cancer (96 ESCC/10 EAC) with lymph node metastasis had a much lower concentration of serum microRNA-218 (0.64 ± 0.44 *vs* 0.33 ± 0.30, $P < 0.05$) than those with no lymph node metastasis. However, this study enrolled patients with esophageal cancer in both Tis-T1 (19.8%, 21/106) and T2-3 stages (80.2%, 85/106)[25]. Yang *et al*[26] also reported that microRNA-218 expression was lower in early esophageal cancer than in normal esophageal tissue. MicroRNA-218 might act as a suppressive miRNA in esophageal cancer, but the mechanism needs further clarification.

A high level of serum thymidine kinase 1 (TK1) (≥ 3.38 pmol/L) was more common in patients with lymph node metastasis of ESCC than in those without (21/29, 72.4% *vs* 21/51, 41.2%, $P < 0.05$)[27]. This study included patients with ESCC in both T1 stage and T2-4 stages, and no subgroup analysis was available. A high level of serum cytokeratin 19 fragment antigen 21-1 (CYFRA21-1) (> 3.30 ng/mL) was also more common in patients with lymph node metastasis of ESCC than in those without (9/15, 60% *vs* 5/42, 11.9%, $\chi^2 = 11.33$, $P = 0.001$)[28]. The levels of serum SCC antigen and carcinoembryonic antigen between patients with and without lymph node metastasis differed insignificantly. This study enrolled patients with ESCC in both Tis-T1 stage ($n = 24$) and T2 stage ($n = 33$)[28]. Further explorations are needed to investigate the correlations between the levels of serum TK1 and CYFRA21-1 and lymph node metastasis of early ESCC.

Stathmin-1 (STMN1) is a microtube regulatory protein that prevents the polymerization of tubulin heterodimers, destabilizing the microtubule cytoskeleton[29]. STMN1 was overexpressed in ESCC tissues[30], and serum STMN1 levels were significantly higher in patients with early ESCC than in healthy controls ($P < 0.001$)[29]. Patients with lymph node metastasis of early ESCC also had higher serum STMN1 levels than those not ($P < 0.01$)[29]. STMN1 might promote tumor cell metastasis by activating the integrin alpha5-focal adhesion kinase-extracellular signal-regulated kinase[31].

Postoperative pathology and immunohistochemical analysis

SM invasion was relevant to a higher risk of lymph node metastasis (SM 22.6%-45.5% *vs* mucosa 0%-7.9%; $P < 0.05$), reflecting common knowledge to most researchers[32-35]. Some studies showed that early esophageal cancer with SM2/3 invasion had a much higher rate of lymph node metastasis than the same with SM1 invasion (SM2/3 17/35, 48.6% *vs* SM1 3/36, 8.3%; $P < 0.05$)[33]. Other studies showed that early esophageal cancer with SM3 invasion had a much higher rate of lymph node metastasis than those with SM1/2 invasion (SM3 45.1%-55.6% *vs* SM1/2 8.7%-16.1%; $P < 0.05$)[34,36]. We believe that the risk of lymph node metastasis increased with increasing invasion depth. This might be related to the abundant lymphatic drainage of the SM and the direct connections of the SM to the central lymphatic channels[37].

Table 1 Predictive factors of lymph node metastasis in early esophageal cancer

Category		ESCC	EAC
Imaging	CT	The intrathoracic and abdominal nodes larger than 10 mm in the short axis, supraclavicular nodes greater than 5 mm and retrocrural nodes greater than 6 mm	
	EUS	Regional lymph node metastasis: (1) Size greater than 10 mm, (2) a round shape, (3) sharply demarcated borders, and (4) hypoechoic structure	
Serum markers		TK1 ≥ 3.38 pmol/L; CYFRA21-1 > 3.30 ng/mL; stathmin-1	NA
		MicroRNA-218	
Postoperative pathology and immunohistochemical analysis		Depth of invasion; tumor size; histological differentiation grade; angiolymphatic invasion; neural invasion; expression of PIM-1	
		Overexpression of cortactin; the protein levels of mixed-lineage leukaemia 2; the expression of stanniocalcin-1	Transcriptions of CD69, MYD88 and TLR4; low expression of olfactomedin 4

ESCC: Esophageal squamous cell carcinoma; EAC: Esophageal adenocarcinoma; CT: Computed tomography; EUS: Endoscopic ultrasonography; TK1: Thymidine kinase 1; CYFRA21-1: Cytokeratin 19 fragment antigen 21-1; NA: Not available; TLR4: Toll-like receptor 4; MYD88: Myeloid differentiation protein 88.

Preoperative narrow band imaging and magnifying endoscopy contributed to the assessment of the invasion depth of early esophageal cancer. This therapeutic strategy has been widely adopted: esophageal cancer with a preoperative diagnosis of invasion into SM1 is first resected endoscopically, and the decision regarding subsequent surgery is informed by the depth of invasion and vascular invasion[38].

Tumor size was also relevant, but the cutoff value varied in different studies. Chen *et al*[39] reported that tumor size ≥ 1.85 cm was a risk factor (98/327, 30% *vs* 35/406, 8.6%; $P < 0.05$), and Zheng *et al*[40] suggested that patients with tumor size > 1.5 cm had a higher risk of lymph node metastasis (49/242, 20.2% *vs* 17/239, 7.1%; $P < 0.05$). Other cutoff values, such as 2.0 and 1.75 cm, were also reported to be significant in univariate and multivariate analyses[41,42]. The increase in tumor size was correlated with a higher risk of lymph node metastasis ($P < 0.05$)[32,36]. The values of incidence of lymph node metastasis in patients with tumor sizes ≤ 10, 11-20, 21-30, and ≥ 31 mm were 0% (0/26), 17.1% (6/35), 15% (3/20), and 33.3% (3/9) ($P < 0.05$), respectively[43]. Therefore, we might consider tumor size as a predictive factor. However, the cutoff-value selection should involve consideration of other confounding factors, and comprehensive modelling might be appropriate.

The histological differentiation grade was also related. Patients with moderately (G2) and poorly (G3) differentiated early ESCC had a higher risk of lymph node metastasis than those with high differentiation (G1) (19/89, 21.3% *vs* 2/39, 5.1%; $P < 0.05$)[32]. Patients with poorly differentiated and undifferentiated (G0) early esophageal cancer (67 ESCC/31 EAC) had a higher risk of lymph node metastasis than those with high and moderate differentiation (12/34, 35.3% *vs* 8/64, 12.5%; $P < 0.05$)[33]. Similarly, Chen *et al*[39] reported that patients with poorly differentiated early ESCC had a higher risk of lymph node metastasis than those with high and moderate differentiation (77/226, 34.1% *vs* 56/507, 11%; $P < 0.05$). This might be related to the highly progressive capacity of poorly differentiated and undifferentiated tumors[15].

Several studies showed that lymphovascular invasion (LVI) was related to a higher risk of lymph node metastasis (44.4%-60% *vs* 0-18.1%, $P < 0.05$), which might be the first step towards regional lymph node metastasis[32,33,36]. Ancona *et al*[33] revealed that neural invasion was also relevant to a higher risk of lymph node metastasis (8/14, 57.1% *vs* 12/84, 14.3%, $P < 0.05$). The sensitivity and specificity were 40% and 92%, respectively[33].

High expression of the proto-oncogene PIM-1 was detected in ESCC with lymph node metastasis[44], and PIM-1 siRNA inhibited the proliferation of ESCC cells and induced apoptosis[45]. Upregulation of PIM-1 was also found in gastric glands correlated with the lymph node metastasis of gastric cancer[46]. Plum *et al*[47] explored whether the expression of PIM-1 was associated with lymph node involvement in early esophageal cancer (28 ESCC/39 EAC). The expression of PIM-1 was insignificantly different between ESCC and EAC, and low-grade expression of PIM-1 (< 30%) was correlated with lymph node metastasis (low-grade 10/16, 62.5% *vs*. high-grade 16/51, 31.4%; $P < 0.05$)[47].

Kotsafti *et al*[48] analysed the tumor immune microenvironment in therapy-naïve EAC. The infiltration of $CD8^+$ $CD28^+$ T cells was lower in both tumoral and peritumoral mucosa for patients with lymph node metastasis. The transcription levels of CD69, myeloid differentiation protein 88 (MYD88) and toll-like receptor 4 (TLR4) were lower in the tumoral specimens from patients with lymph node metastasis. The areas under the receiver operating characteristic curve (AUROC) of CD69, MYD88 and TLR4 mRNA expression were 0.76 [95% confidence interval (CI): 0.47-0.93], 0.80 (95%CI: 0.52-0.95), and 0.80 (95%CI: 0.52-0.95), respectively ($P < 0.05$). In the peritumoral healthy mucosa, the levels of MYD88, TLR4, and CD69 mRNA levels were correlated with CD80 mRNA levels (Rho = 0.65, 0.47 and 0.82, respectively) ($P < 0.05$). In the external cohort (seven matched tumor and adjacent normal tissue samples), the expression levels of CD8A, CD8B and TBX21 were lower in the peritumoral mucosa for patients with lymph node involvement ($P = 0.05$). CD80 mRNA levels were correlated with CD38 mRNA (Rho = 0.85, $P = 0.03$) and CD69 mRNA (Rho = 0.77, $P = 0.05$) levels, confirming the possible role of CD80 in the pathway activating CD8 T cells. Moreover, the infiltration of CD8 T cells and M1 macrophages was also lower in patients with lymph node metastasis in the external cohort.

Olfactomedin 4 (OLFM4), formerly named hGC-1 or GW112, a secreted glycoprotein, could mediate cell adhesion by interacting with extracellular matrix proteins such as cadherins and lectins[49]. OLFM4-positive cells were found in Barrett's esophagus, mainly confined to the base of metaplastic glands[50]. Low expression (< 30%) of OLFM4 was associated with nodal metastases in advanced EAC [odds ratio (OR) 2.7; 95%CI: 1.16-6.41; $P = 0.022$] but insignificantly in early EAC (OR 2.1; 95%CI: 0.46-9.84; $P = 0.338$)[51]. In this study, the sample size of early EAC ($n = 44$) was relatively small, and OLFM4 expression in early and advanced EAC with lymph node metastasis differed insignificantly ($P = 0.844$) [51]. Further exploration analysing the correlation between the expression of OLFM4 and lymph node metastasis in early EAC is still needed.

Lu *et al*[52] analysed the genome-wide gene expression profile of 10 primary ESCCs and their adjacent normal esophageal tissues. The overexpression of cortactin (CTTN) (dark brown staining in > 50% of normal or malignant esophageal squamous cells completely obscuring the cytoplasm) was associated with lymph node metastasis (N_0 54/109, 49.5% *vs* N_1 72/98, 80.9%; $P < 0.05$) and pathological stage (I + IIA 58/113, 51.3% *vs* IIB + III 68/85, 80.0%; $P < 0.05$). However, this study enrolled patients with ESCC in stages I-III, and no subgroup analysis was performed. The relationship between the overexpression of CTTN and lymph node metastasis of early ESCC needs further exploration.

Li *et al*[53] compared the positive staining of mixed-lineage leukaemia 2 (MLL2), also known as KMT2D, in 25 pairs of early ESCC (with and without lymph node metastasis). The MLL2 levels were much higher in tumors with lymph node metastasis ($P < 0.001$). In vitro, silencing MLL2 expression resulted in decreased migration of esophageal squamous carcinoma cells. Moreover, the expression of stanniocalcin-1 (STC1) was also higher in tumors with lymph node metastasis, which could be decreased with MLL2 siRNA treatment. Further investigations indicated that MLL2 was recruited to the STC1 promoter by p65 (RelA) and activated the expression of STC1[53].

Predictive models

Although a large number of factors were correlated, it was still difficult to assess the risk of lymph node metastasis with a single indicator. Several comprehensive models have been built to predict the risk of lymph node metastasis in early ESCC (Table 2).

In 2016, Jia *et al*[43] built a logistic regression model using the depth of invasion and lymphovascular metastasis: $p = e^x/(1 + e^x)$, and $x = -5.469 + 0.839 \times$ depth of invasion (M1 labelled 1; M2 labelled 2; M3 labelled 3; SM1 labelled 4, SM2 labelled 5, and SM3 labelled 6) $+ 1.992 \times$ lymphovascular metastasis (negative 0, positive 1). The AUROC was 0.858 (95%CI: 0.757-0.959). However, the cutoff value and the calibration of this model were not reported.

In 2018, Zheng *et al*[40] built a nomogram using depth of tumor invasion, grade of differentiation, tumor size, and LVI (Figure 1). The Harrell's concordance index (C-index) was 0.790 (95%CI: 0.717-0.864) and 0.789 (95%CI: 0.709-0.869) in the training and validation sets, respectively. The corresponding cutoff values were 0.142 and 0.224 in the training and validation cohorts, respectively. The *P* values in the Hosmer-Lemeshow test of the derivation and validation cohorts were 0.966 and 0.754, respectively.

In 2019, Zhou *et al*[42] built a logistic regression model using tumor size, tumor grade, depth of invasion, and presence of angiolymphatic invasion: $\hat{y} = 1/[1 + \exp(-x\beta)]$, $x\beta = -4.339 + 1.211 \times$ tumor size (≤ 1.75 cm labelled 0, > 1.75 cm labelled 1) $+ 1.078 \times$ tumor grade (G1 labelled 0, G2/3 labelled 1) $+ 1.036 \times$ depth of invasion (M1-3 labelled 0, SM1-3 labelled 1) $+ 2.661 \times$ angiolymphatic invasion (absent labelled 0, present labelled 1). The AUROCs in the training and validation sets were 0.80 (95%CI: 0.737-0.862) and 0.814 (95%CI: 0.724-0.905), respectively. The predicted value ranged from 3.33% to 86.67%, and the optimal cutoff value of the estimated risk was 20%. Meanwhile, they built a nomogram to predict the risk of lymph node metastasis (Figure 2), with an AUROC of 0.80 (95%CI: 0.739-0.856) in the training cohort and 0.814 (95%CI: 0.725-0.900) in the validation cohort. Whether the Hosmer-Lemeshow test was performed and whether the *P* was > 0.05 were not reported.

In 2020, Chen *et al*[39] built another logistic regression model with a previous history of alcohol consumption, tumourtumor size, SM invasion, histologic grade, LVI, and preoperative CT result: $\hat{y} = 1/(1 + e^{-z})$, $z = -5.213 + 2.061 \times$ invasion depth (M1/M2/M3 labelled 0, SM1/SM2 or deeper labelled 1) $+ 3.216 \times$ LVI (negative labelled 0, positive labelled 1) $+ 0.956 \times$ histologic grade (G1 and G2 labelled 0, G3 labelled 1) $+ 1.107 \times$ CT results (negative labelled 0, positive labelled 1) $+ 0.594 \times$ alcohol consumption (no labelled 0, yes labelled 1) $+ 1.327 \times$ tumor size (< 1.85 cm labelled 0, ≥ 1.85 cm labelled 1) (Table 1). The optimal cutoff value of *z* was 3.735. The total AUROC and accuracy of the training, validation and test cohorts were 0.868 (95%CI: 0.837-0.900) and 74.49% (95%CI: 71.17-77.61), respectively. They further built an artificial neural network (ANN) model using these factors (Figure 3), with a much higher total AUROC of 0.915 (95%CI: 0.887-0.943) and a much higher total accuracy of 90.72% (95%CI: 88.39-92.72%) ($P < 0.05$).

DISCUSSION

Esophageal cancer is a malignancy with high morbidity and mortality. Endoscopic resection was applied to patients with early esophageal cancer owing to its lower trauma and fewer complications. However, lymph node metastasis is not rare and is often treated with additional surgery. In this study, we reviewed predictive indicators of lymph node metastasis in patients with early esophageal cancer, especially as observed in recent findings about serum markers, immunohistochemical indicators and comprehensive models. Preoperative imaging (size), serum markers (microRNA-218, TK1, CYFRA21-1, STMN1), postoperative pathology and immunohistochemical analysis (depth of invasion, tumor size, differentiation grade, angiolymphatic invasion, and neural invasion; PIM-1 expression < 30%; transcription of CD69, MYD88 and TLR4; low expression of OLFM 4; overexpression of CTTN, MLL 2, and STC1) were related. The sensitivity and specificity of a single criterion were relatively low, and comprehensive models, including the logistic regression model,

Table 2 Models predicting lymph node metastasis in early esophageal squamous cell carcinoma

Number	Ref.	Year	Factors	Category	Training set		Validation set	
					Cutoff value	C-index (95%CI)	Cutoff value	C-index (95%CI)
1	Jia *et al* [43]	2016	Depth of invasion and lymphovascular metastasis	Logistic regression model	NA	0.858 (0.757-0.959)	NA	NA
2	Zhou *et al* [42]	2019	Dumor size, tumor grade, depth of invasion, and angiolymphatic invasion	Logistic regression model	20%	0.80 (0.737-0.862)	20%	0.814 (0.724-0.905)
3				Nomogram	NA	0.80 (0.739-0.856)	NA	0.814 (0.725-0.900)
4	Zheng *et al*[40]	2018	Depth of tumor invasion, grade of differentiation, tumor size, and lymphovascular invasion	Nomogram	0.142	0.790 (0.717-0.864)	0.224	0.789 (0.709-0.869)
5	Chen *et al* [39]	2020	Tumor size, histologic grade, invasion depth, lymphovascular invasion, CT-results, and alcohol taking	Logistic regression model	3.735	0.857 (NA)	3.735	0.881 (NA)
6				artificial neural network	NA	0.904 (NA)	NA	0.938 (NA)

C-index: Harrell's concordance index; CI: Confidence interval; NA: Not available; CT: Computed tomography.

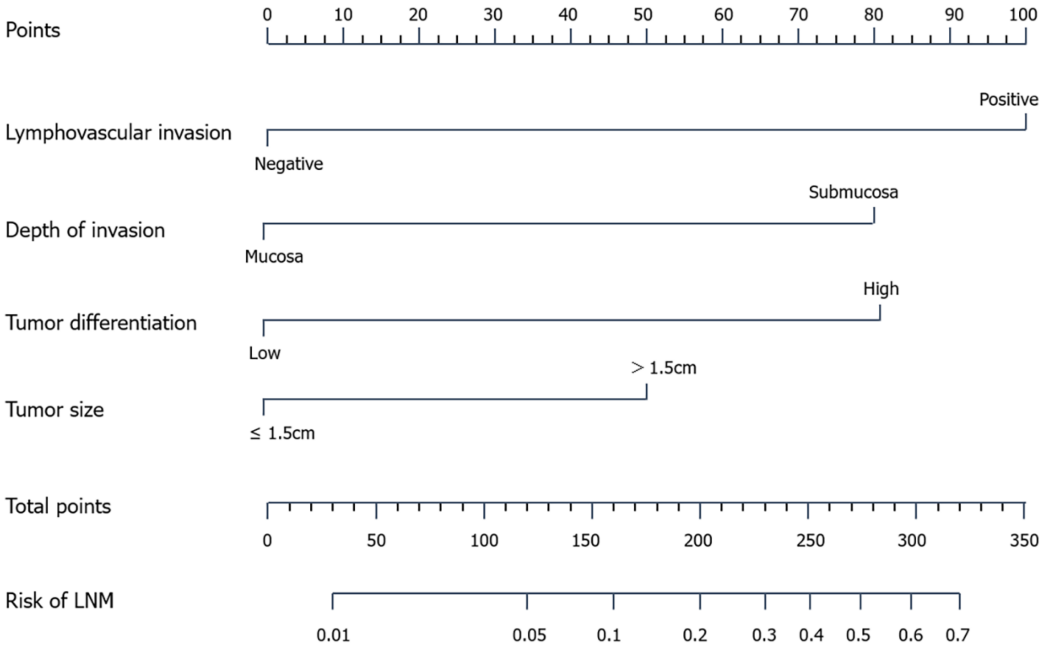

Figure 1 Nomogram predicting the risk of lymph node metastasis in patients with early esophageal cancer. Harrell's concordance index was 0.790 [95% confidence interval (CI): 0.717-0.864] and 0.789 (95%CI: 0.709-0.869) in the training and validation sets, respectively. The corresponding cutoff values were 0.142 and 0.224. The *P* value in the Hosmer-Lemeshow test of the derivation and validation cohorts were both > 0.05. LNM: Lymph node metastasis. Citation: Zheng H, Tang H, Wang H, Fang Y, Shen Y, Feng M, Xu S, Fan H, Ge D, Wang Q, Tan L. Nomogram to predict lymph node metastasis in patients with early oesophageal squamous cell carcinoma. *Br J Surg* 2018; 105: 1464-1470. Copyright ©The Author(s) 2018. Published by BJS Society Ltd[40].

nomogram, and ANN, performed much better. This helped clinical decision-making regarding whether endoscopic resection or radical surgery was appropriate and whether additional radical surgery was needed in patients with initial endoscopic resection. In this study, we mainly reviewed studies from PubMed, possibly missing some meaningful reports from other databases. In addition, all these comprehensive models relied on postoperative pathology. The present therapeutic strategy involves suggested initial endoscopic resection before subsequent surgery based on the depth of invasion and vascular invasion in patients with a preoperative diagnosis of SM1 invasion. If we could predict the lymph node status preoperatively, those with lymph node metastasis would not have to undergo endoscopic resection before radical surgery. Therefore, further studies using preoperative indicators such as imaging and serum markers are needed to predict lymph node status in patients with early esophageal cancer.

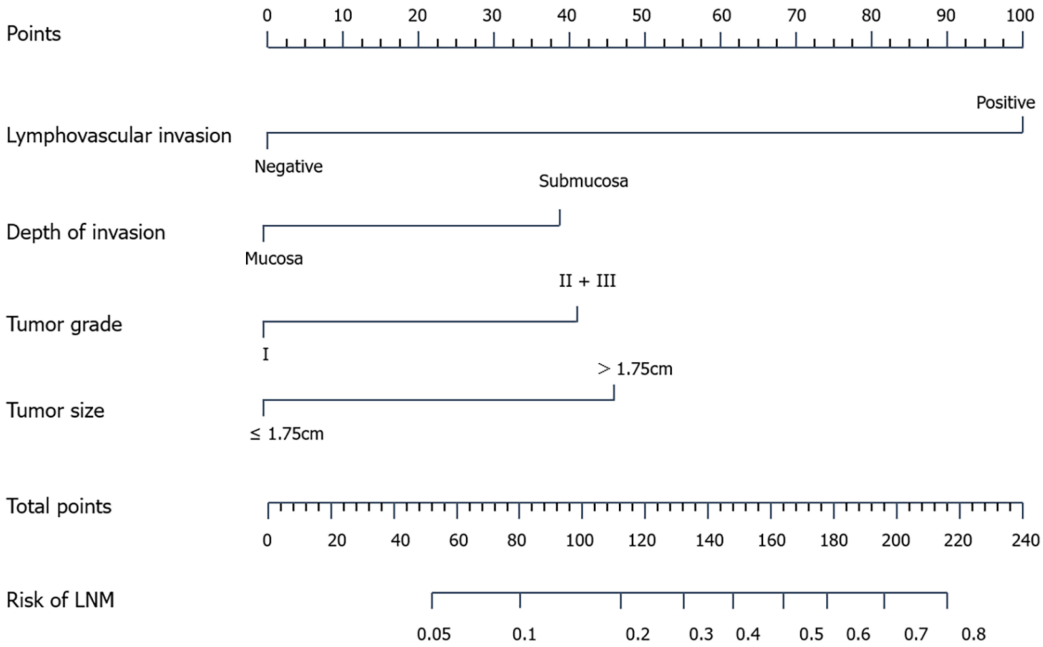

Figure 2 Nomogram predicting the risk of lymph node metastasis in patients with early esophageal cancer. The area under the curve was 0.80 [95% confidence interval (CI): 0.739-0.856] in the training cohort and 0.814 (95%CI, 0.725-0.900) in the validation cohort. The optimal cutoff value was 20%. Tumor grade I: High differentiation; Tumor grade II + III: moderate differentiation and poor differentiation. LNM: Lymph node metastasis. Citation: Zhou Y, Du J, Wang Y, Li H, Ping G, Luo J, Chen L, Zhang S, Wang W. Prediction of lymph node metastatic status in superficial esophageal squamous cell carcinoma using an assessment model combining clinical characteristics and pathologic results: A retrospective cohort study. *Int J Surg* 2019; 66: 53-61. Copyright ©The Author(s) 2019. Published by IJS Publishing Group Ltd[42].

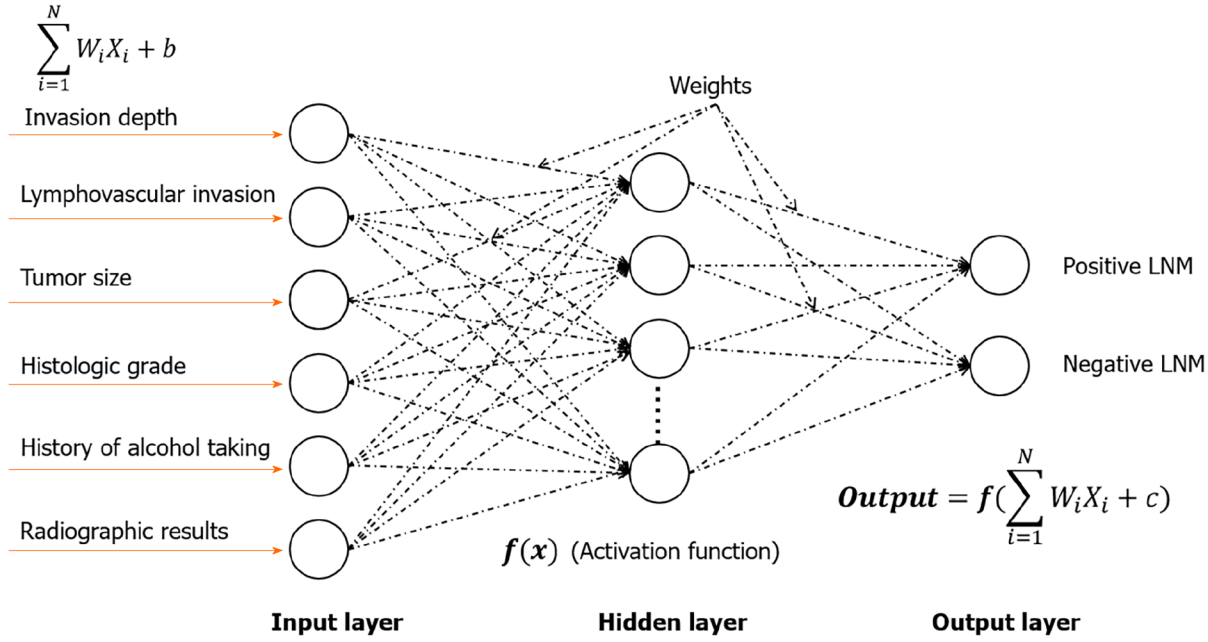

Figure 3 Artificial neural network model predicting the risk of lymph node metastasis in patients with early esophageal cancer. The hidden layer consisted of 20 neurons. The optimal performance was at epoch 6 with a mean squared error of 0.0432. The total area under the curve and accuracy of the training, validation and test cohorts were 0.915 [95% confidence interval (CI): 0.887-0.943] and 90.72% (95%CI: 88.39-92.72%) ($P < 0.05$), respectively. LNM: Lymph node metastasis. Citation: Chen H, Zhou X, Tang X, Li S, Zhang G. Prediction of Lymph Node Metastasis in Superficial Esophageal Cancer Using a Pattern Recognition Neural Network. *Cancer Manag Res* 2020; 12: 12249-12258. Copyright ©The Author(s) 2020. Published by Dove Medical Press[39].

CONCLUSION

Various factors, including preoperative imaging, serum markers, preoperative pathology and immunohistochemical indicators, were predictive of lymph node metastasis in early ESCC and EAC. Several comprehensive models predicting lymph node metastasis in early ESCC performed well, but these models relied on postoperative pathology. Further studies focusing on serum markers, imaging and immunohistochemical indicators are still needed.

ARTICLE HIGHLIGHTS

Research background

Given the poor prognosis of patients with lymph node metastasis, estimating the lymph node status in patients with early esophageal cancer is crucial. Indicators that could be used to predict lymph node metastasis in early esophageal cancer have been reported in many recent studies, but no recent studies have included a review of this subject.

Research motivation

This study aimed to review indicators predicting lymph node metastasis in early esophageal cancer.

Research objectives

This study was designed to review indicators predicting lymph node metastasis in early esophageal squamous cell carcinoma (ESCC) and early esophageal adenocarcinoma (EAC).

Research methods

We searched PubMed with "[early esophageal cancer (Title/Abstract) and (lymph node (Title/Abstract)]" or "[early esophageal carcinoma (Title/Abstract)] and [lymph node (Title/Abstract)]" or "[superficial esophageal cancer (Title/Abstract)] and [lymph node (Title/Abstract)]." All studies were reviewed in detail, and a total of 29 studies were eligible for analysis.

Research results

Preoperative imaging, serum microRNA-218, depth of invasion, tumor size, differentiation grade, lymphovascular invasion, neural invasion, expression of PIM-1 < 30% were predictive factors for lymph node metastasis in both early ESCC and EAC. Serum thymidine kinase 1 ≥ 3.38 pmol/L, cytokeratin 19 fragment antigen 21-1 > 3.30 ng/mL, stanniocalcin-1 and overexpression of cortactin, mixed-lineage leukaemia 2, stathmin-1 were predictive for lymph node metastasis in early ESCC. Transcription of CD69, myeloid differentiation protein 88, toll-like receptor 4 and low expression of olfactomedin 4 were predictive of lymph node metastasis in early EAC. A total of 6 comprehensive models for early ESCC were reviewed. The areas under the receiver operating characteristic curve reached 0.789-0.938.

Research conclusions

Various factors were predictive of lymph node metastasis in early ESCC and EAC. Several comprehensive models performed well, but these models relied on postoperative pathology. Further studies focusing on serum markers, imaging and immunohistochemical indicators are still in need.

Research perspectives

Further studies focusing on serum markers, imaging and immunohistochemical indicators are still needed.

FOOTNOTES

Author contributions: YiBi RH conceived this study; Li Y drafted the article; Wang JX provided critical revision of this article; All authors approved the final version.

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SYSTEMATIC REVIEWS

Hepatobiliary tuberculosis in the developing world

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Abstract

BACKGROUND

Hepatobiliary tuberculosis is a challenging disease that poses diagnostic difficulties due to its resemblance to other etiologies. Delayed diagnosis may lead to inadequate treatment, thus necessitating an urgent need for accurate diagnosis and appropriate management.

AIM

To systematically review case reports on hepatobiliary tuberculosis, focusing on symptomatology, diagnostic procedures, management, and outcomes to provide patient safety and ensure an uneventful recovery.

METHODS

A systematic search was conducted on PubMed from 1992 to 2022, using keywords such as hepatobiliary, liver, tuberculosis cholangitis, cholangiopathy, and mycobacterium. Only case reports or case series in English were included in the study, and research papers published as abstracts were excluded. The search yielded a total of 132 cases, which were further narrowed down to 17 case studies, consisting of 24 cases of hepatobiliary tuberculosis.

RESULTS

The 10 most common symptoms observed in these cases were fever, abdominal pain, weight loss, jaundice, anorexia, generalized weakness, pruritus, chills, fatigue, and chest pains. Objective findings in these cases included hepatomegaly, hepatic nodules, elevated liver enzymes, and elevated bilirubin. Computed tomography scan and ultrasound of the abdomen were the most useful diagnostic tools reported. Histologic demonstration of *Mycobacterium tuberculosis* confirmed the cases of hepatobiliary tuberculosis. Treatment regimens commonly used included Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol. Out of the 24 cases, 18 presented improvements while 4 had completely recovered.

CONCLUSION

Hepatobiliary tuberculosis is a disease that requires accurate diagnosis and appropriate management to avoid complications.

Key Words: Tuberculosis; Hepatic/diagnosis; Cholangitis; Sclerosing/complications; Ultrasonography; Interventional/methods; Biopsy; Needle/utilization; Treatment Outcome

Core Tip: Hepatobiliary tuberculosis presents diagnostic challenges due to its similarity to other conditions, emphasizing the need for timely and accurate diagnosis. This systematic review of 24 cases highlights the common symptoms, diagnostic procedures, and treatment outcomes. Fever, abdominal pain, weight loss, and jaundice were the most frequent symptoms observed. Computed tomography scan and ultrasound were effective diagnostic tools, while histologic confirmation confirmed the presence of *Mycobacterium tuberculosis*. Treatment with Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol showed positive outcomes in the majority of cases. This study underscores the importance of precise diagnosis and appropriate management to ensure successful recovery and patient safety.

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INTRODUCTION

Tuberculosis (TB) is an airborne disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*), commonly known as tubercle bacilli. The transmission of TB occurs through the air rather than surface contact. The Center for Disease Control [1] has identified several factors that increase the likelihood of transmission, including the susceptibility of the exposed individual, infectiousness of individuals with TB disease, environmental conditions affecting the concentration of *Mycobacterium tuberculosis* (*M. tuberculosis*), and the proximity, frequency, and duration of exposure.

Once infection takes place, tubercle bacilli are engulfed by macrophages and can spread through lymphatic channels or the bloodstream, triggering a systemic response. This dissemination allows the bacilli to reach various parts of the body, including the brain, larynx, lymph nodes, lungs, spine, bones, kidneys, and liver, resulting in miliary tuberculosis or disseminated TB.

Upon reaching the target organ, macrophages surround the bacilli, forming a barrier known as a granuloma, which contains and controls the infection. This controlled granuloma is termed latent tuberculosis infection and is neither infectious nor contagious. If the immune system fails to contain the tubercle bacilli, they multiply rapidly, leading to active TB disease.

This paper focuses specifically on the spread of *M. tuberculosis* into the liver in the context of hepatobiliary tuberculosis. Disseminated tuberculosis often affects the liver as the bacillus travels through hematogenous spread. Early diagnosis and appropriate treatment of hepatobiliary TB are crucial for preventing complications and ensuring patient safety.

Hepatobiliary TB has a high prevalence, particularly in developing countries during the late 1980s and early 1990s[2]. Certain racial and ethnic groups experience higher TB case rates due to factors such as being born in countries with a high TB prevalence, human immunodeficiency virus (HIV) infection, low socioeconomic status, and exposure to TB in high-risk settings[2]. Non-United States-born individuals contribute to approximately 70% of TB cases in the United States[2]. Populations at increased risk of latent TB infection or TB disease include those experiencing homelessness, limited access to medical care, low-income populations, and individuals engaged in substance abuse[2].

The prognosis of TB infection is influenced by various factors, including hepatobiliary or miliary TB, steroid therapy, age less than 20 years, cachexia, HIV, liver cirrhosis, and liver failure[3,4]. Liver TB is a common presentation in patients who die from tuberculous disease, accounting for 50%-80% of cases[4]. Untreated miliary tuberculosis carries a nearly 100% mortality rate[5]. However, timely access to critical care intervention, anti-tuberculous therapy, and possibly corticosteroid use may reduce the occurrence of severe complications and mortality. Biochemistry data can aid in predicting clinical outcomes, emphasizing the importance of early treatment to prevent disease spread and reduce mortality[5].

According to the World Health Organization (WHO) (2022), undernutrition is the leading cause of the global count of 1.9 million new cases of TB disease. The WHO South-East Asian Region has the highest number of new cases at 43%, followed by the African Region with 25%. Eight countries, including India, China, Indonesia, Philippines, Pakistan, Nigeria, Bangladesh, and South Africa, account for two-thirds of TB cases[6]. Treatment failure and drug resistance pose significant challenges, particularly with multi-drug resistant tuberculosis (MDR-TB), which is a public health crisis and security threat. The majority of affected individuals reside in the aforementioned eight countries, where efforts to eradicate the disease are challenging. Without proper treatment, 45% of the TB-infected population in these countries will succumb to the disease[6].

The discrepancy in TB treatment outcomes between developed and developing countries is striking, with a mortality rate of 2% in developed countries compared to 45% in underdeveloped countries. It is crucial to address this disparity in order to reduce the risk of mortality. Closing this gap would provide individuals in developing countries with firsthand

experience of the acute presentation of tuberculous disease and enable them to gain important insights into the existing treatment modalities for TB.

Hepatobiliary tuberculosis is a rare manifestation of miliary tuberculosis, typically originating from *M. tuberculosis* infection in the lungs or gastrointestinal tract[7]. The presentation of this form of TB is nonspecific, and there is a lack of imaging studies that can raise a high index of suspicion. Although multiple cases of miliary tuberculosis have been reported in Western journals, its prevalence is endemic and often underreported in developing countries like the Philippines. Early initiation of appropriate anti-tuberculous treatment is associated with a favorable prognosis for this disease, emphasizing the importance of timely therapy.

The Philippines ranks third in terms of TB prevalence, following South Africa and Lesotho, according to the WHO[8]. With approximately one million Filipinos diagnosed with active TB disease, urgent action is required. The WHO aims to eliminate TB by 2030, making the situation in the Philippines a focal point as the country continues to report active cases and daily loss of lives due to this highly curable disease. The neglect of TB in children, which is difficult to diagnose and treat, along with the intertwining challenges of malnutrition and tuberculosis, further emphasizes the need for concerted efforts to improve the health and quality of life of Filipinos.

Despite being curable and preventable, in 2020, the burden of TB was concentrated in certain countries, with 86% of new cases occurring in these high-burden countries. The top eight countries in terms of TB burden include India, China, Indonesia, Philippines, Pakistan, Nigeria, Bangladesh, and South Africa. Among these countries, MDR-TB poses a significant public health crisis and health security threat, as only one in three individuals with MDR-TB seek treatment. Insufficient funding for health programs, not limited to tuberculosis, in low- and middle-income countries remains a major obstacle in combating this global issue.

MDR-TB arises from inadequate and ineffective treatment in low-income countries, leading to drug resistance and posing a threat to tuberculosis control efforts. Patient resistance and emotional struggles, including anger and denial, can hinder treatment adherence. Special considerations are needed for individuals with HIV and those receiving antiretroviral therapy due to potential drug interactions and the need to modulate immune responses to overcome drug resistance in these populations[9].

A study conducted in the Philippines from 2011 to 2015 focused on disseminated TB and found that patients with miliary TB were typically young and without comorbidities. Long latency periods and non-pulmonary symptoms were observed before diagnosis. Co-infection with HIV, liver cirrhosis, and alcoholism were identified as predisposing conditions. Hepatobiliary tuberculosis was present in 0.2% of the studied population, with confirmation achieved through various diagnostic methods. Bacteriologic confirmation of extrapulmonary TB, particularly in the liver, remains challenging due to limited access to resources like computed tomography (CT) scans in the Philippines[10].

The incidence of TB increases progressively with age, particularly among the elderly. Reactivation of dormant lesions is the most common cause of tuberculosis in this age group, likely due to age-related changes in the immune system. Diagnosis of active TB in the elderly can be challenging due to nonspecific and subtle symptoms. Poor tolerance to anti-TB drugs and reduced treatment adherence in the elderly can lead to treatment failure and the development of MDR-TB. In regions heavily affected by the TB epidemic, infectivity in the elderly peaks at 65 years of age, with men being the most affected[11].

A study conducted by Wu *et al*[12] reported common clinical complaints in patients with tuberculosis, including mild fever, right upper quadrant pain, hepatomegaly, weakness, and night sweats. Serum analysis revealed increased alkaline phosphatase (ALP) levels and normal transaminase levels, indicating liver involvement. Imaging techniques such as ultrasound, CT scan, and magnetic resonance imaging (MRI) were used to confirm the diagnosis of hepatobiliary TB, showing features such as multiple lesions of varying density on CT scan and specific characteristics on MRI[12,13].

In a retrospective study of 320 TB cases, suspected hepatobiliary tuberculosis was identified through abnormal liver function tests and imaging findings. Among the patients, 68 showed hepatobiliary involvement, and 40 were diagnosed with hepatobiliary tuberculosis. Common symptoms included fever, weight loss, jaundice, hepatomegaly, and splenomegaly. Elevated levels of bilirubin, alanine aminotransferase, aspartate aminotransferase (AST), and ALP were documented, supporting the importance of early diagnosis and management based on laboratory findings[14].

Yu and Sheng[15] published a paper discussing a case of liver tuberculosis presenting as fever of unknown origin. Initially, ultrasound and CT scan did not provide significant findings, but positron emission tomography (PET)/CT scan showed diffuse increased metabolic activity with focal areas of increased activity, aiding in the identification of a site for biopsy and a correct diagnosis. This case highlights the importance of considering liver tuberculosis as a potential cause in cases of fever of unknown origin, especially when other laboratory analyses show non-specific slight elevation of liver enzymes. This approach to diagnosis opens up new possibilities for identifying the correct biopsy site in such cases[15].

A systematic review of Indian literature examined the delays in TB diagnosis and treatment, focusing on symptom onset, diagnostic delays, and treatment delays. The review revealed a median treatment delay of 55.3 d, with 48% of patients initially consulting private physicians and an average of 2.7 consultations before receiving TB treatment. The study highlighted the urgent need for new strategies to reduce diagnostic and treatment delays by establishing a first-contact healthcare provider system to address patients' health needs promptly[16].

In another study by Singh *et al*[14], laboratory findings in patients with hepatobiliary tuberculosis (HBTB) were investigated. The study found elevated levels of bilirubin, alanine transaminase (ALT), AST, and ALP in cases of hepatic, biliary, and HBTB. Jaundice was frequently observed in biliary tuberculosis, while hepatomegaly was more common in hepatic TB cases. The study emphasized the importance of considering both clinical features and laboratory findings to effectively evaluate hepatobiliary tuberculosis.

This paper aims to address the management of hepatobiliary tuberculosis and ensure patient safety and successful recovery. By identifying common symptoms, healthcare providers can promptly request additional laboratory and ancillary procedures to detect hepatobiliary or miliary tuberculosis as early as possible. The goal of this paper is to

provide recommendations for expediting the treatment of tuberculosis patients.

MATERIALS AND METHODS

This study followed the PRISMA guidelines[17] and aimed to summarize previously reported cases of hepatobiliary tuberculosis. The systematic review followed five steps: Framing the question, identifying relevant work, assessing study quality, summarizing the evidence, and interpreting the findings[18]. The search terms used were: ("tuberculosis" OR "mycobacterium") AND ("cholangiopathy" OR "cholangitis" OR "hepatobiliary"). The search was conducted on March 21, 2022. Multiple resources were searched for case reports without language restrictions. Clinical presentation, diagnostic modalities, interventions, treatment, and outcomes were recorded for analysis. Study quality was assessed based on selection criteria, including histopathologic confirmation and clearly stated outcomes. Tabulation of study characteristics facilitated comparisons. The focus of this paper is on the diagnosis, management, and outcomes of hepatobiliary tuberculosis, including medical and surgical approaches. Miliary tuberculosis studies were also included.

Data sources

A wide range of medical and scientific databases were searched from 1992 to 2022 to identify studies and case reports on hepatobiliary tuberculosis. The search was conducted in libraries including PubMed/MEDLINE using keywords related to hepatobiliary tuberculosis. No restrictions were placed on publication dates within the specified range, and language preferences were not considered during the initial publication of the papers.

Inclusion criteria and outcomes

Case reports or case series published between 1992 and 2022 were eligible for selection. In cases of duplication, the most recent studies were chosen for analysis. Abstracts and incomplete papers were excluded, as well as studies published in languages other than English. Each retrieved study was screened based on the title and abstract to ensure that it contained full-text case reports with complete details for data extraction. Preference was given to studies that provided comprehensive information, and availability of adequate follow-up data for transcription was also considered.

Study selection and data extraction

During the study selection and data extraction process, relevant papers were identified based on the titles and abstracts. Full-length papers meeting the eligibility criteria were then identified. A standardized form was used to extract data from the selected studies, including information on the characteristics of the subjects, clinical presentation, diagnostic tests, anti-tubercular drugs used, and outcomes. Any discrepancies in the study selection were resolved.

Clinical presentation and diagnostic modalities

The clinical presentation of the selected case reports was carefully examined, considering the duration of symptoms, associated subjective complaints, laboratory and ancillary procedures performed, the diagnosis, and the outcome. While not all reports included recorded values for certain laboratory parameters, such as AST, ALT, ALP, and bilirubin, the available data were retained for further analysis. The clinical diagnosis at the time of consultation was an important factor in data collection. In cases where two diagnoses were present, with hepatobiliary tuberculosis being an incidental finding, both diagnoses were included.

The diagnostic modalities employed in each case leading to the primary diagnosis were retrieved and summarized in a table for comparison and analysis. The detection of acid-fast bacilli through culture was a significant aspect of this study. The sample specimens could be obtained from various body cavities, tissues, or bodily fluids, not necessarily limited to the liver. Clinical findings were cross-referenced with other available data.

Medical management and outcomes

The medical management approaches for hepatobiliary tuberculosis were itemized and documented based on each case. Surgical interventions were also noted. The outcomes resulting from the management strategies were categorized as improved, recovered, or deceased.

Quality assessment

The collected materials were carefully assessed to ensure their credibility and reliability. The primary focus was on selecting peer-reviewed papers, but if a paper was not peer-reviewed, its credibility was evaluated based on several factors. These factors included the depth of information coverage, objectivity, identification of biases, currency of the information, authority from reputable and unbiased organizations, and the purpose of the paper. This step was crucial for establishing the trustworthiness of the overall summary and generating reliable inferences. Only high-quality studies that were considered credible and unbiased were included in the analysis. Papers that received a low score in the quality assessment were still included in the study selection, but inferences were avoided when drawing conclusions from these papers[18,19].

Statistical analysis

Descriptive statistics, such as the mean, standard deviation (SD), frequency, and median, were used to characterize the data. These measures provided a concise summary of the key features of the collected information.

Narrative synthesis

A narrative synthesis approach was employed to merge and synthesize the gathered information. This synthesis focused on addressing the diagnostic challenges associated with hepatobiliary/miliary tuberculosis as reported in the selected journals. The findings from the different case reports were interpreted with caution, taking into consideration the demographics of the research subjects and identifying the most common presentations of hepatobiliary tuberculosis.

RESULTS

Using the designated search strategy, a total of 132 references were initially identified. Among them, 17 duplicates were excluded. After carefully analyzing the titles and abstracts, an additional 77 references were deemed unrelated to the topic and excluded. Finally, 21 references were excluded based on specific criteria, as shown in the flow chart below. The remaining 38 references, consisting of case reports and case series, were included in the analysis. A comprehensive summary of the collected data can be found in Table 1, while Table 2 provides an overview of the gathered data. The quality analysis of the included papers is presented in Table 3.

Characteristics of the included cases

The cases mentioned in the included references originated from various countries, including Taiwan, Japan, India, Turkey, Ireland, China, Sénégal, Thailand, Portugal, United Kingdom, and the USA. The reported cases were distributed as follows: Taiwan (37.50%), Japan (12.50%), India (8.33%), Turkey (8.33%), Ireland (8.33%), China (8.33%), Sénégal (4.17%), Thailand (4.17%), Portugal (4.17%), United Kingdom (4.17%), and the United States (4.17%). A total of 24 patients were included in the analysis, with 15 (62.50%) being male and a mean age of 64.22 years (ranging from 14 to 80 years old). All patients were diagnosed with hepatobiliary tuberculosis, and in 14 cases, the diagnosis was confirmed through histopathology.

Clinical presentation of hepatobiliary tuberculosis

The most common clinical presentations of hepatobiliary tuberculosis were fever and abdominal pain, accounting for 37.50% of the cases. Other common symptoms included weight loss (29.17%), jaundice (25%), anorexia (16.67%), generalized weakness (16.67%), and non-specific symptoms such as chills associated with fever. In two cases, generalized weakness and fatigue were reported. One asymptomatic patient was incidentally diagnosed with miliary tuberculosis through routine ultrasound examination. These non-specific symptoms were correlated with objective findings. Miliary tuberculosis can manifest in various organs of the human body, leading to symptoms such as neurologic symptoms, chest pains, vomiting, dark urine, pale stools, groin swelling, cough, diarrhea, and upper gastrointestinal bleeding.

Clinical findings

Among the patients included in the study, 37.50% exhibited hepatomegaly and/or hepatic nodules. Liver enzyme and bilirubin levels were evaluated in 4 cases, leading to further diagnostic investigations such as ultrasound and CT scan. Other symptoms observed in the 24 cases included pleural effusion, splenomegaly, duodenal abnormality, and spontaneous bacterial peritonitis. The population also presented with comorbidities, including pulmonary tuberculosis in 4 out of 24 cases, gastric cancer, systemic lupus erythematosus, hypertension, type II diabetes mellitus, and chronic obstructive pulmonary disease (COPD).

Delays in management

A delay in seeking treatment despite the onset of symptoms was observed in 5 patients, with an average delay of 2 mo. One case report described a patient with a history of fever for 2 and a half years before seeking medical care. These delays highlight the need to address healthcare-seeking behaviors and improve early detection to ensure timely treatment and better outcomes. Prolonged delays can lead to a more difficult and protracted treatment course. Surgical intervention was required for one patient.

Medical management

All reported cases received medical management. The majority of cases (95.83%) were treated with a combination of Rifampicin and Ethambutol. Isoniazid was administered to 91.67% of the cases, while Pyrazinamide was prescribed to 87.50% of the patients. Levofloxacin was given to 12.50% of the population. Among the cases, 16.67% (4 cases) fully recovered, and 58.33% (14 cases) showed improvement from their initial condition. Four patients (16.67%) died, including two who succumbed to septic shock due to late diagnosis, one with stage 4 carcinoma on top of miliary tuberculosis, and another with acute biliary episode concomitant with liver failure. Two of the deceased patients were above 60 years old, while the other two were in their late 30s and early 50s and died due to septic shock. Mortality in this study was directly associated with delayed diagnosis and did not appear to be correlated with the age of the patient. The treatment approach for tuberculosis followed the guidelines set by the WHO, with different drugs administered on different days (daily or with skip days). The combination known as RIPE (Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol) was commonly used for tuberculosis treatment. The duration of medication varied based on the severity of the disease.

Table 1 PRISMA-P search strategy

Item	Description	
Identification	Record identified through database search (n = 132)	Sources: PubMed (n = 132)
Screening	Records after duplicates were removed (n = 115)	
	Records screened (n = 115)	Records excluded (n = 77)
Eligibility	Full-text articles assessed for eligibility (n = 38)	Full-text articles excluded (n = 21); full text not found = 8; not hepatobiliary tuberculosis = 10; not a case report = 20; and individual patient data not available = 3
Included	Studies included in qualitative synthesis (n = 17)	
	Studies included in quantitative synthesis (meta-analysis; n = 17)	

DISCUSSION

This systematic review focuses on the clinical presentation, diagnostic modalities, treatment, and outcomes of patients with hepatobiliary or miliary tuberculosis from different countries. Hepatobiliary tuberculosis presents challenges in diagnosis, particularly in developing countries where diagnostic tools may be limited[20]. Miliary tuberculosis primarily affects elderly individuals, the urban poor, and immunocompromised patients, and it is believed to spread *via* hematogenous dissemination through the hepatic artery. Some studies suggest that hepatobiliary tuberculosis is present in all cases of miliary tuberculosis, with or without pulmonary involvement[21,22].

The patients included in the published cases of hepatobiliary tuberculosis ranged in age from 14 to 80 years old, with a female-to-male ratio of 3:5. TB remains a significant health problem in the Kingdom of Saudi Arabia, and the study identified non-Saudi countries with a high incidence of both pulmonary and extrapulmonary tuberculosis[23]. The incidence of tuberculosis varies between males and females, and a subject's predisposition to the disease is influenced by the country of origin where tuberculosis is endemic.

Most patients with hepatobiliary tuberculosis presented with non-specific symptoms such as fever, abdominal pain, jaundice, weight loss, fever with chills, anorexia, generalized weakness, and pruritus. Jaundice and pruritus are particularly suspicious of liver involvement. These findings are consistent with a previous study on hepatobiliary and pancreatic tuberculosis, which reported abdominal pain as the most common symptom, followed by jaundice, fever, anorexia, and weight loss[24].

Malnutrition is a major contributor to tuberculosis in developing nations. Therefore, obtaining accurate weight and height measurements to determine ideal body weight for each reported case may be important. This information could provide insights into the nutritional needs of patients with hepatobiliary tuberculosis. Anorexia, loss of appetite, and generalized body weakness can exacerbate malnutrition and hinder recovery.

Hepatobiliary ultrasound or CT scans revealed hepatomegaly and hepatic nodules in the majority of the subjects (8 out of 23), indicating the presence of hepatobiliary tuberculosis. Clinical and laboratory findings in patients with hepatobiliary tuberculosis have shown an increased incidence of *M. tuberculosis* in extrapulmonary locations, particularly among immunosuppressed individuals and young children. Diagnosis of hepatobiliary tuberculosis can be confirmed by elevated levels of bilirubin, ALT, AST, and ALP. Percutaneous transhepatic cholangiography can serve as a confirmatory test for visualized liver masses[14,25].

Tuberculosis cases are more prevalent among young people aged 10-24 years, with an estimated 1.78 million cases since 2012, accounting for 17% of all new tuberculosis cases globally. In 2019, the second and third highest incidence of tuberculosis cases was observed in the population over 65 years old. It is hypothesized that tuberculosis in the elderly may result from reactivation of latent infections from their youth or newly acquired infections due to their vulnerability. These findings may explain the higher prevalence of miliary and hepatobiliary tuberculosis in the population with a mean age of 64.22 years, as comorbidities, such as hypertension, and other variables may render the elderly population immunocompromised[26-28].

While CT scans or ultrasounds can detect the presence of liver masses, they cannot differentiate between hepatoma and hepatobiliary tuberculosis[29]. Liver biopsy is considered the gold standard for diagnosing hepatobiliary tuberculosis. A CT-guided fine needle aspiration biopsy can reveal caseating granulomas with lymphocytes, multinucleate giant cells, and epithelioid cells, which are compatible with tuberculosis. This method can rule out hepatocellular carcinoma. Computed tomography scan imaging of confirmed cases shows multiple lesions with varying densities, representing different pathological stages of hepatic tuberculosis, such as tuberculous granuloma, liquefaction necrosis, fibrosis, and calcification. A clinicopathologic analysis of 86 cases in Turkey identified the infectious etiology of liver granulomas caused by tuberculosis, characterized by necrotizing, palisading granulomas. Out of the 10 cases tested, only one stained positive with acid-fast bacilli, while the others showed positivity through PCR. Tissue analysis is essential for accurately diagnosing tuberculous infections and differentiating them from other causes of liver disease, such as primary biliary cirrhosis, tumors, and sarcoidosis[30].

Table 2 Summary of systematically reviewed clinical cases of hepatobiliary/miliary tuberculosis

Ref.	Country	Age (year)	Sex	Clinical presentation	Diagnostic modalities	Treatment	Outcome	Quality assessment
Patel *et al* [44], 2016	India	14	Female	Persistent, intermittent fever associated with chills, abdominal pain, anorexia for 1 mo; neurological symptoms	Ultrasound of abdomen with portosplenic doppler; CT scan of the abdomen; bacterial culture of liver abscess; TB-PCR; mycobacterium growth indicator tube culture; MRI of the brain	Dexamethaxone for meningitis; rifampicin, Isoniazid, pyrazinamide ethambutol	Neurological symptoms regressed; significant improvement	High
Sahin *et al* [45], 2014	Turkey			Elevated liver enzymes	Liver biopsy CT scan of the abdomen	Not specified	Not specified	Low
Diallo *et al* [46], 2016	Dakar, Sénégal	48	Female	Cholestatic jaundice, right upper quadrant pain, fever (38.5 °C) and weak general condition, weight loss of 15 kg in 2 mo; on physical examination there was jaundice, fever, abdomen was soft, tenderness at the RUQ with hepatomegaly	Abdominal ultrasound; thoracoabdominal CT scan; liver biopsy	Rifampicin, isoniazid, pyrazinamide ethambutol; levofloxacin (included in the triple therapy for 10 d)	Good evolution: Clinical improvement, normalization of liver function tests	High
Ozin *et al* [47], 2010	Turkey	43	Female	Initially complained of malaise and itching, with elevate liver enzymes and bilirubin; diagnosis: Hepatobiliary tuberculosis	Hepatobiliary tree and pancrease ultrasound; ERCP; liver biopsy	Rifampicin, isoniazid, pyrazinamide ethambutol	Liver function tests were improved	High
Jain *et al* [48], 2017	India	50	Male	Jaundice since 10 d associated with significant loss of weight & appetite; diagnosis: Hepatobiliary tuberculosis	Liver ultrasound; CT scan of the abdomen; MRCP; and liver hepatectomy	Rifampicin, isoniazid, pyrazinamide ethambutol	Responded well	High
Chang *et al* [49], 2018	Taiwan	80	Male	Smear-positive, culture confirmed pulmonary TB, fever and chills after 1 wk of treatment; abdominal pain; diagnosed with cholecystolithiasis	Abdominal ultrasound; sputum AFB	Laparoscopic cholecystectomy; rifampicin, isoniazid, pyrazinamide ethambutol	ABE were not noted	High
Chang *et al* [49], 2018	Taiwan	50	Male	A male patient in his 50 s with comorbid, medically controlled DM and COPD was diagnosed with pulmonary TB based on a histology report of a transbronchial lung biopsy and a mycobacterial; culture of bronchial washing sample; diagnosed with acute cholecystitis	Abdominal ultrasound; CT scan of the abdomen	Rifampicin, isoniazid, pyrazinamide ethambutol	Improved	High
Chang *et al* [49], 2018	Taiwan	50	Male	Hypertension and COPD, irregular medical control, diagnosed with smear-positive, culture-confirmed pulmonary TB. Two weeks prior to the commencement of standard anti-TB treatment, he had pneumonia with respiratory failure and septic shock; multiple cholelithiasis was noted with dilated intrahepatic duct; treatment was halted	Hepatobiliary tree and pancrease ultrasound	Rifampicin, isoniazid, pyrazinamide ethambutol	Died of refractory septic shock	High

Chang *et al* [49], 2018	Taiwan	20	Male	Fever, chest pains, left pleural effusionIm-pression: Intermittent biliary obstruction due to a passing of stone	Sputum-AFB	Rifampicin, isoniazid, pyrazi-namide ethambutol	Improved	High
Yamashita *et al*[50], 2014	Japan	48	Female	Past history of systemic lupus erythematosus developed autoimmune hepatitis, fever; diagnosis: Miliary tuberculosis	CT scan of the abdomen; liver biopsy	Isoniazid, rifampicin, ethambutol, pyrazinamide; subsequently changed to levofloxacin, ethambutol and streptomycin	Recovered liver function improved and no inflam-matory reaction	Moderate
Yamane *et al* [51], 2010	Japan	47	Male	Incidental finding of an abnormality in the duodenum during endoscopy; no subjective symptoms; diagnosis: Tubercular papillitis of vater	Esophagogastroduodenoscopy; colonoscopy	Rifampicin, isoniazid, pyrazi-namide ethambutol	Improvement of the duodenal lesion and colonic lesion	High
Ratanarapee *et al*[52], 1991	Thailand	38	Male	2-mo history of painless obstructive jaundice; cachectic and deeply icteric, with a normal temperature and an impalpable liver; diagnosis: Tuberculosis of the common bile duct	Ultrasound of the hepatibiliary tree	Rifampicin, isoniazid, ethambutol	Good health	High
Tewari *et al* [53], 2009	Japan	70	Female	Episodes of mild upper abdominal pain and vomiting of 3 mo; mild jaundice for 2 mo that subsided on its own; diagnosis: Tubercular ampullary papillitis	Ultrasound of the abdomen; CT scan of abdomen; EGD; ERCP; excision of the ampulla, with biopsy	Rifampicin, isoniazid, pyrazi-namide ethambutol	Improved	High
Li *et al*[54], 2015	China	39	Female	10-d history of fatigue, anorexia, and jaundice. She had no abdominal pain or fever; diagnosis: Pelvic and Salpinx tuberculosis with secondary fulminant hepatic failure	CT scan of abdomen	Rifampicin, isoniazid, pyrazi-namide ethambutol	Died as a consequence of ischemic cholangitis and pulmonary infection	High
Hickey *et al* [35], 1999	Ireland	50	Male	Pyrexia of unknown origin which was ongoing for 2.5 yr with multiple previous hospital admissions; diagnosis: Splenic tuberculosis	Ultrasound of the abdomen; abdominal CT scan	Rifampicin, isoniazid, pyrazi-namide ethambutol	Well for over 6 yr	High
Hickey *et al* [35], 1999	Ireland	70	Male	6-wk history of progressive jaundice, severe pruritus, dark; urine, pale stools, and weight loss, with groin swelling	Percutaneous transhepatic cholangiography; biopsy of groin swelling	Rifampicin, isoniazid, pyrazi-namide ethambutol	No recurrence for 5 yr	High
Gaspar *et al* [55], 2018	Portugal	35	Male	Fatigue, fever, weight loss, cough, abdominal pain, diarrhea, pruritus, hepato-megaly; diagnosis: Hepatic granuloma	CT scan of the abdomenliver biopsy	Rifampicin, isoniazid, pyrazi-namide ethambutol	Discharged from the hospital	Mod
Musumba *et al*[56], 2013	United Kingdom	47	Male	5-d history of intermittent fever, rigors and night sweats; post cadaveric renal transplant 1 mo prior, and receives immunosuppressive therapy; diagnosis:	Whole body positron emission tomography/computed tomography; liver biopsy	Rifampicin, isoniazid, pyrazi-namide ethambutol	Good clinical response	High

				Miliary tuberculosis				
Poplin *et al* [57], 2020	United States	52	Male	1 mo PTC, hospitalized for culture-negative spontaneous bacterial peritonitis, liver disease was incidentally found; recurrent fever; diagnosis: Miliary TB; end-stage liver disease	Liver biopsy; CT scan of abdomen	Rifampicin, ethambutol, levofloxacin, amikacin 3 times weekly	Died due to ABE	High
Huang *et al* [21], 2003	Taiwan	47	Male	Epigastric pain; CT scan solitary liver nodule 13.5 cm tumor left lobe	Lobectomy, anti-TB Meds	Rifampicin, isoniazid, pyrazinamide ethambutol	Improved	High
Huang *et al* [21], 2003	Taiwan	57	Male	Malaise, weight loss; CT scan; solitary liver nodule 5.0 cm tumor at the left lobe	Wedge resection, anti-tb meds	Rifampicin, isoniazid, pyrazinamide ethambutol	Improved	High
Huang *et al* [21], 2003	Taiwan	63	Male	Managed for gastric cancer; CT scan; solitary liver nodule 2.0 cm at segment IV	Wedge biopsy		Expired	High
Huang *et al* [21], 2003	Taiwan	67	Female	Managed for gastric cancer; CT scan MULTIPLE small liver nodules at both lobes	Biopsy, refused treatment	Rifampicin, isoniazid, pyrazinamide ethambutol	Dropped out of management	High
Huang *et al* [21], 2003	Taiwan	71	Female	Epigastric pain with upper gastrointestinal tract bleeding; CT scan; solitary liver nodule 12.0 cm at the left lobe; nodular density at the right lower lung field on chest X-ray	Left hepatectomy; anti-tb meds	Rifampicin, isoniazid, pyrazinamide ethambutol	Improved	High
Zhang *et al* [29], 2014	China	30	Male	Weight loss, poor appetite, body weakness, abdominal distention, chest congestion	CT scan; FNAB	Rifampicin, isoniazid, pyrazinamide ethambutol	Improved	High

TB: Tuberculosis; COPD: Chronic obstructive pulmonary disease; FNAB: Fine needle aspiration biopsy; RUQ: Right upper quadrant; MRCP: Magnetic resonance cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatography; CT: Computed tomography; MRI: Magnetic resonance imaging; PCR: Polymerase chain reaction; ABE: Acute biliary events.

Hepatobiliary ultrasound or CT scans can detect hepatomegaly and hepatic nodules, indicating hepatobiliary tuberculosis. Tuberculosis cases are more common among young people and the elderly, with the latter group potentially experiencing reactivation of latent infections or acquiring new infections due to vulnerability. Liver biopsy is crucial for confirming hepatobiliary tuberculosis and distinguishing it from other liver diseases.

Abdominal ultrasound is a readily available and cost-effective diagnostic tool that raises suspicion of hepatobiliary tuberculosis compared to malignancy[31]. Chen *et al*[31] conducted a study exploring different imaging modalities and highlighted the challenges in diagnosing tuberculous liver. They observed hyperechoic mass-like lesions on ultrasound, and these findings were confirmed by ultrasound-guided percutaneous needle biopsy. Ultrasound is commonly used as the initial modality for screening liver parenchymal lesions, but its findings can be vague and require additional percutaneous aspiration or tissue sampling for confirmation[31]. The combination of ultrasound and contrast-enhanced CT can enhance the specificity of sonographic findings[32]. However, it is worth noting that ultrasound detected a lower number of hepatobiliary lesions caused by hepatobiliary tuberculosis compared to CT scan, making CT scan the preferred imaging modality[32].

Liver biopsy played a significant role, accounting for 58.33% of cases in this study. Biopsies were obtained through hepatectomy, CT scan, or ultrasound-guided percutaneous biopsy, enabling the identification of tuberculoma for histopathological examination[14].

In this study, 12.5% of subjects were diagnosed with *M. tuberculosis* using endoscopic retrograde cholangiopancreatography (ERCP). Saluja *et al*[24] reported attempting ERCP in five patients, where bile was aspirated through the hilar stricture. One patient demonstrated acid-fast bacilli during bile cytology. Only four patients were diagnosed perioperatively, while the remaining cases were diagnosed using various diagnostic modalities over a two-decade analysis of hepatobiliary and pancreatic tuberculosis[24].

The diagnosis of hepatobiliary tuberculosis relies on multiple diagnostic modalities, as no single radiologic approach can secure an accurate diagnosis. The gold standard remains the detection of acid-fast bacilli through the polymerase

Table 3 Quality assessment of included cases of hepatobiliary and miliary tuberculosis

Ref.	Case number	Selection	Ascertainment		Causality				Reporting	Quality assessment
		Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	
		Did the patient(s) represent the whole case(s) of the medical center?	Was the exposure adequately ascertained?	Was the outcome adequately acertained?	Were other alternative causes that may explain the observation ruled out?	Was there a response to the specific treatment for tuberculosis?	Was there a histological confirmation of the diagnosis?	Was follow-up long enough for outcomes to occur?	Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?	
Patel *et al* [44], 2016	1	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Patel *et al* [44], 2016	1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Sahin *et al* [45], 2014	35	Yes	Yes	Yes	Yes	No	Yes	No	No	Low
Diallo *et al* [46], 2016	1	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Ozin *et al* [47], 2010	1	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	High
Jain *et al* [48], 2017	1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Chang *et al* [49], 2018	4	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Yamashita *et al*[50], 2014	1	No	Yes	Yes	No	Yes	Yes	Yes	No	Low
Yamane *et al* [51], 2010	1	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	High
Ratanarapee *et al*[52], 1991	1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Tewari *et al* [53], 2009	1	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	High
Li *et al*[54], 2015	1	No	Yes	Yes	Yes	Yes	Yes	Yes	No	High
Hickey *et al* [35], 1999	2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Gaspar *et al* [55], 2018	12	Yes	No	Yes	Yes	No	Yes	No	Yes	Mod
Musumba *et al*[56], 2013	1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Poplin *et al* [57], 2020	1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Huang *et al* [21], 2003	5	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	High
Zhang *et al* [29], 2014	1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High

chain reaction for *M. tuberculosis* or a positive enzyme-linked immunosorbent spot (ELISpot) assay for tuberculosis diagnosis (T-SPOT TB) test[29]. The T-SPOT TB, a commercially available test, is a single visit blood test that utilizes T cells to reduce assay variability and maximize sensitivity in detecting tuberculosis[29].

All subjects included in this study received anti-tubercular therapy. The majority of cases (87.50%) underwent the standard 7-mo rifampicin, isoniazid, pyrazinamide, and ethambutol (RIPE) regimen[33]. Treatment regimens for tuberculous infection vary based on individual characteristics and drug resistance profiles. In addition to the RIPE regimen, a 4-mo Rifapentine-moxifloxacin TB Treatment Regimen and a 9-mo RIPE TB Treatment Regimen are recommended for specific patient populations[33].

Abdominal ultrasound serves as an initial screening tool for hepatobiliary tuberculosis, but CT scan remains the preferred imaging modality. Liver biopsy is crucial for histopathological confirmation. Various diagnostic modalities contribute to accurate diagnosis, and the gold standard involves detecting acid-fast bacilli through molecular techniques or a positive T-SPOT TB test. Treatment regimens are tailored based on individual factors and include different combinations of anti-tubercular drugs.

In this case report, 75% of the subjects showed improvement and recovery with the indicated treatment regimen. A portion of the subjects, 16.67%, unfortunately, died due to associated immunodeficiency and other end-stage diseases during the tuberculosis diagnosis, while 4.17% dropped out of the study and were lost to follow-up. The positive outcomes of recovery and improvement can be attributed to the recommended treatment for tuberculosis.

Hepatobiliary tuberculosis poses a diagnostic challenge that was addressed by the papers in this review. Among the patients, all except one who was initially managed as a case of gastric cancer with a liver mass, which was thought to be liver metastases, died. Three of the deceased patients died of shock; one was non-compliant with medications despite receiving treatment for hepatobiliary tuberculosis, one healthy female died due to fulminant liver failure resulting from widespread tuberculosis infection, and the last patient died of end-stage liver disease due to delays in diagnosis. However, the remaining 24 subjects showed recovery, improvement, and good clinical response.

The common finding in the four deceased cases was the presence of a chronic illness, either unrelated or caused by tuberculosis itself. The delay in management led to liver failure in three cases, while the other death occurred during a wedge resection procedure for gastric cancer. Early diagnosis and management, particularly through CT scan-guided biopsy during the early stage of the disease, could have potentially prevented these deaths.

This systematic review of hepatobiliary tuberculosis highlights the symptoms observed in cases of hepatobiliary tuberculosis, the diagnostic approaches employed in the included case reports, and the management strategies for diagnosed cases. Symptoms such as fever, abdominal pain, weight loss, anorexia, generalized weakness, along with jaundice and pruritus, should raise suspicion of liver involvement. The disease can spread hematologically, originating from a pulmonary tuberculosis diagnosis and affecting extrapulmonary sites.

The majority of the cases presented in the systematic review showed positive outcomes, which can be attributed to different diagnostic modalities and the high index of suspicion among clinicians. The most commonly used diagnostic modalities included CT scan of the abdomen, liver biopsy, and abdominal ultrasound, among others.

The study revealed that Taiwan, Japan, India, Turkey, China, and Ireland reported the highest number of cases. However, this does not imply that these countries are the only ones affected by tuberculosis. It highlights the underreporting of tuberculosis cases and the existence of other endemic countries, including the Philippines, South Africa, and Lesotho, which have limited journal publications. Case reports from these countries can provide valuable insights to others with limited exposure to tubercular cases[34].

The present medical management recommended by the CDC should be continued to ensure patient safety and desirable outcomes[6]. Rifampicin, isoniazid, pyrazinamide, and ethambutol are the mainstay treatment for tuberculosis, displaying promising results with improvement and recovery rates close to 100%[9].

Hepatobiliary tuberculosis is difficult to diagnose, and delays in treatment due to delayed diagnosis can facilitate infection transmission, worsen the disease, and potentially lead to death[35,36]. The therapeutic approaches developed since 1944 and their continuous evolution serve as tools to combat the tuberculosis endemic through early detection, a high index of suspicion, and treatment compliance[37].

In hepatobiliary tuberculosis, the infection primarily affects the liver and/or the biliary system, whereas soft tissue tuberculosis refers to tuberculosis infection in the soft tissues of the body, such as muscles, tendons, and ligaments[38]. Tuberculosis treatment may lead to side effects such as gastrointestinal symptoms, liver toxicity, skin rashes, peripheral neuropathy, and visual disturbances, but regular monitoring and prompt reporting of any unusual symptoms are essential for successful management. Some current relevant differentials for hepatobiliary tuberculosis are post-COVID-19 cholangiopathy[39,40], hemophagocytic lymphohistiocytosis[41,42] and cytomegalovirus infection[43].

CONCLUSION

In conclusion, this study recommends a systematic approach for managing hepatobiliary tuberculosis and miliary tuberculosis, with the aim of eradicating all forms of tuberculosis and initiating therapy at the earliest possible time. Key indicators for suspicion of hepatobiliary TB include fever, abdominal pain, weight loss, anorexia, and generalized weakness, particularly in the presence of jaundice or pruritus. Ultrasound is a recommended initial imaging modality due to its affordability and accessibility, followed by a CT scan if ultrasound results are inconclusive. Liver biopsy is crucial in differentiating hepatobiliary TB from hepatoma and should be performed for patients with suspicious lesions. Routine liver enzyme and bilirubin tests can aid in early detection of hepatobiliary TB. Case reports and Mantoux tuberculin skin testing are essential for monitoring and treating pulmonary tuberculosis in high-risk populations. These recommend-

ations are derived from a comprehensive analysis of case reports and are applicable to various forms of tuberculosis. Timely treatment initiation may be based on clinical suspicion rather than awaiting confirmatory test results. Overall, a high index of suspicion and bedside procedures for obtaining tissue diagnosis are vital in managing tuberculosis.

ARTICLE HIGHLIGHTS

Research background

Tuberculosis (TB) is a highly contagious airborne disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*), and its transmission occurs through the air. The Center for Disease Control has identified several factors affecting TB transmission, including the susceptibility of exposed individuals, infectiousness of TB patients, environmental conditions, and proximity and duration of exposure. Once infected, tubercle bacilli can spread throughout the body, leading to various manifestations, including hepatobiliary tuberculosis (TB affecting the liver and biliary system). Early diagnosis and appropriate treatment of hepatobiliary TB are crucial for preventing complications and ensuring patient safety. Hepatobiliary TB has a significant prevalence, especially in developing countries, and specific populations are at increased risk, such as non-US-born individuals and those with HIV infection, low socioeconomic status, or exposure to TB in high-risk settings.

Research motivation

The main focus of this study is to investigate the spread of *M. tuberculosis* into the liver, specifically in the context of hepatobiliary TB. Early diagnosis and appropriate management are essential to prevent severe complications and reduce mortality rates associated with TB infection. Addressing the discrepancies in TB treatment outcomes between developed and developing countries is crucial to improving global health and reducing mortality risks, particularly for individuals in low-income countries. Moreover, the high prevalence of TB in certain regions and the challenges posed by multi-drug-resistant TB necessitate urgent action and innovative approaches to combat this public health crisis. By examining hepatobiliary TB in the Philippines and understanding the unique challenges faced in the region, this study aims to contribute to TB control efforts and improve patient outcomes.

Research objectives

The main objectives of this study include identifying common symptoms and laboratory findings associated with hepatobiliary TB to facilitate early detection and diagnosis. By understanding the clinical features and laboratory data, healthcare providers can promptly initiate appropriate diagnostic procedures to confirm hepatobiliary or miliary tuberculosis. The study aims to provide recommendations for expediting TB treatment and improving patient safety and recovery rates. Additionally, the research seeks to shed light on the challenges of TB diagnosis and treatment delays, particularly in developing countries, and identify potential strategies to reduce such delays and enhance patient care. By analyzing liver function test results and imaging findings, the study intends to enhance the evaluation of hepatobiliary TB, leading to more effective management strategies. Through these objectives, the research strives to contribute to the overall efforts to eliminate TB by 2030, as outlined by the World Health Organization.

Research methods

This study conducted a systematic review following PRISMA guidelines to summarize cases of hepatobiliary tuberculosis (HBTB). The research question was framed, and relevant studies were identified using specified search terms without language restrictions. Clinical presentation, diagnostic modalities, interventions, treatment, and outcomes were recorded from selected case reports published between 1992 and 2022. The study quality was assessed based on selection criteria, including histopathologic confirmation and clear outcomes. Data were extracted using a standardized form, and discrepancies in study selection were resolved. The clinical presentation, diagnostic modalities, and acid-fast bacilli detection were analyzed. Medical and surgical management approaches were documented, and outcomes were categorized as improved, recovered, or deceased. The collected materials were carefully assessed for credibility and reliability, focusing on peer-reviewed papers. Descriptive statistics were used to characterize the data, and a narrative synthesis approach was employed to interpret the findings and address diagnostic challenges related to hepatobiliary/miliary tuberculosis.

Research results

The systematic review of 38 case reports and case series on HBTB revealed important findings. Clinical presentation commonly included fever and abdominal pain (37.50%), along with weight loss (29.17%), jaundice (25.00%), and anorexia (16.67%). Hepatomegaly and/or hepatic nodules were observed in 37.50% of the cases, with liver enzyme and bilirubin levels playing a role in further diagnostic investigations. Comorbidities such as pulmonary tuberculosis, gastric cancer, and systemic lupus erythematosus were identified in the patient population. Delays in seeking treatment were observed in five patients, underscoring the importance of early detection and timely intervention. Surgical intervention was required for one patient. Medical management was the primary treatment approach for HBTB, with a combination of Rifampicin, Ethambutol, Isoniazid, and Pyrazinamide being commonly used. The majority of patients (58.33%) showed improvement, 16.67% fully recovered, and 16.67% succumbed to the disease, with delayed diagnosis and septic shock being contributing factors to mortality. The study contributes valuable insights into the clinical presentation, management, and outcomes of HBTB, emphasizing the significance of timely interventions to improve patient prognosis. Further research is needed to address the challenges associated with delayed diagnosis and management to reduce

morbidity and mortality rates in HBTB cases.

Research conclusions

This systematic review contributes to the understanding of hepatobiliary tuberculosis by highlighting its clinical presentation and diagnostic challenges, particularly in developing countries with limited resources. It sheds light on the association between miliary tuberculosis and hepatobiliary tuberculosis, with or without pulmonary involvement. The study emphasizes the importance of early detection and timely intervention to improve patient outcomes. The research proposes a systematic approach for managing hepatobiliary tuberculosis and miliary tuberculosis. It recommends using ultrasound as an initial screening tool, followed by computed tomography scan if needed, for detecting hepatomegaly and hepatic nodules. Liver biopsy is crucial in confirming hepatobiliary tuberculosis and distinguishing it from other liver diseases. The study emphasizes the use of a high index of suspicion and bedside procedures for obtaining tissue diagnosis.

Research perspectives

The direction of future research should focus on addressing the challenges in diagnosing hepatobiliary tuberculosis, especially in countries with a high incidence of tuberculosis. Improving diagnostic tools and methods in resource-limited settings is crucial to facilitate early detection and timely treatment. Additionally, further studies should explore the association between miliary tuberculosis and hepatobiliary tuberculosis to better understand the disease's pathogenesis and clinical manifestations. Research efforts should also aim to identify risk factors associated with delayed diagnosis and management, leading to better strategies for reducing morbidity and mortality rates. Furthermore, investigating the efficacy and safety of different treatment regimens for hepatobiliary tuberculosis will help optimize therapeutic approaches and improve patient outcomes. Collaborative efforts among researchers and healthcare providers are essential in eradicating tuberculosis and implementing effective management protocols worldwide.

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FOOTNOTES

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META-ANALYSIS

Timing of surgical operation for patients with intra-abdominal infection: A systematic review and meta-analysis

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Abstract

BACKGROUND

Intra-abdominal infections (IAIs) is the most common type of surgical infection, with high associated morbidity and mortality rates. In recent years, due to the use of antibiotics, various drug-resistant bacteria have emerged, making the treatment of abdominal infections more challenging. Early surgical exploration can reduce the mortality of patients with abdominal infection and the occurrence of complications. However, available evidence regarding the optimal timing of IAI surgery is still weak. In study, we compared the effects of operation time on patients with abdominal cavity infection and tried to confirm the best timing of surgery.

AIM

To assess the efficacy of early *vs* delayed surgical exploration in the treatment of IAI, in terms of overall mortality.

METHODS

A systematic literature search was performed using PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Ovid, and ScienceDirect. The systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-analyses method. Based on the timing of the surgical operation, we divided the literature into two groups: Early surgery and delayed surgery. For the early and delayed surgery groups, the intervention was performed with and after 12 h of the initial surgical intervention, respectively. The main outcome measure was the mortality rate. The literature search was performed from May 5 to 20, 2021. We also searched the World Health Organization International Clinical Trials Registry Platform search portal and ClinicalTrials.gov on May 20, 2021, for ongoing trials. This study was registered with the International Prospective Register of Systematic Reviews.

RESULTS
We identified nine eligible trial comparisons. Early surgical exploration of patients with IAIs (performed within 12 h) has significantly reduced the mortality and complications of patients, improved the survival rate, and shortened the hospital stay.

CONCLUSION
Early surgical exploration within 12 h may be more effective for the treatment of IAIs relative to a delayed operation.

Key Words: Intra-abdominal infection; Surgical exploration; Timing; Infection; Surgical operation; Systematic review; Meta-analysis

Core Tip: The available evidence regarding the optimal timing of intra-abdominal infection surgery is still limited. In a systematic review and meta-analysis of the cohort study, we compared the effects of operation time on patients with abdominal cavity infection and aimed to confirm the best timing of surgery.

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INTRODUCTION

Intra-abdominal infections (IAIs) include any infection of the internal organs in the abdominal cavity (including the peritoneum) as well as infectious diseases caused by pathogens invading the host's abdominal cavity, retroperitoneal cavity, or internal organs of the abdominal cavity and causing obvious damage[1,2]. An IAI is usually a mixed infection of a variety of intestinal microbes. The pathogenic bacteria are mainly intestinal flora and primarily Escherichia coli[3,4]. An IAI is the most common type of surgical infection, with high associated morbidity and mortality rates. The mortality rate can be as high as 23%-38%[5-7]. The mortality rate associated with severe IAIs is even higher, representing the second most common cause of sepsis in critically ill patients[8].

In recent years, due to the use of antibiotics, various drug-resistant bacteria have emerged, making the treatment of abdominal infections more challenging. The cornerstone of IAI management is timely and adequate control of the source of anatomical infection[8,9]. Regarding the control of the source of infection, each guide mentions that treatment first requires surgical control of the source of infection. Guidelines recommend initiating source control as soon as possible in cases of well-defined IAIs[10]. In 2017, the Surgical Infection Society issued a guideline recommending that the source of infection be controlled within 24 h after an IAI diagnosis[11]. If the initial source of infection control is delayed 24 h after the diagnosis is clear, the case fatality rate will increase significantly[1,11,12]. Some authors agree that reopening should be performed within 48 h after the initial operation[13]. However, the exact time has not yet been clearly determined[10,14,15].

An operation can reverse the multiorgan failure of some patients with intra-abdominal sepsis after surgery and reduce their mortality rate[16]. Although the mechanism is not fully understood, early surgical exploration can reduce the mortality of patients with abdominal infection and the occurrence of complications[13,17]. However, available evidence regarding the optimal timing of IAI surgery is still weak. In abdominal infections, clinical studies on the timing of surgery tend to have small sample sizes and be of relatively low levels of quality. In a systematic review and meta-analysis of the cohort study, we compared the effects of operation time on patients with abdominal cavity infection and tried to confirm the best timing of surgery.

MATERIALS AND METHODS

Literature search

PRISMA statement guidelines were followed for conducting and reporting meta-analysis data[18-20]. The PICOS scheme was followed for reporting inclusion criteria. A systematic literature search was performed independently by two of the authors (Shurui Song and Yangyang Liu) using PubMed, EMBASE, Cochrane Central Register of Controlled Trials, *via* Ovid, *Reference Citation Analysis* (https://www.referencecitationanalysis.com/) database and ScienceDirect. The search was limited to studies on humans and to articles reported in the English language. No restriction was set for type of publication, date, or publication status. This study has been registered with the International Prospective Register of

Systematic Reviews (no. CRD42021255402). PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Ovid, and ScienceDirect were systematically searched. The complete search used for PubMed was as follows: ((((((((((((intraabdominal infections[MeSH Terms]) OR intraabdominal infection*[Title/Abstract]) OR intra-abdominal infection*[Title/Abstract]) OR intra-abdominal infection*[Title/Abstract]) OR appendicitis[Title/Abstract]) OR diverticulitis[Title/Abstract]) OR peritonitis[Title/Abstract]) OR typhlitis[Title/Abstract]) OR peritonitis tuberculous[Title/Abstract]) OR subphrenic abscess[Title/Abstract]) OR abdominal sepsis[Title/Abstract]) OR intraabdominal sepsis[Title/Abstract]) OR intra-abdominal sepsis[Title/Abstract]) AND ((((((((((((surgery[MeSH Terms]) OR operative therapy[Title/Abstract]) OR invasive procedure*[Title/Abstract]) OR operative procedure*[Title/Abstract]) OR operation*[Title/Abstract]) OR perioperative procedure*[Title/Abstract]) OR intraoperative procedure*[Title/Abstract]) OR perioperative procedure*[Title/Abstract]) OR preoperative procedure*[Title/Abstract]) OR Surgical Procedure*[Title/Abstract]) OR Operative Surgical Procedure* [Title/Abstract]) OR Surgical Procedure[Title/Abstract]) OR Operative Surgical[Title/Abstract] OR laparoscopy[Title/Abstract]) OR laparotomy [Title/Abstract]) AND ((((((((((((((((time) OR Operative Times) OR Time, Operative) OR Times, Operative) OR Time Length of Surgery) OR Surgery Time Length) OR Surgery Time Lengths) OR Length of Operative Time) OR Operative Time Length) OR Operative Time Lengths) OR Time Length, Operative) OR Time Lengths, Operative) OR Surgical Time) OR Surgical Times) OR Time, Surgical) OR Times, Surgical)) AND ((((((((((((time) OR Time-to-Treatments) OR Time to Treatment) OR Time to Treatments) OR Door-to-Treatment Time) OR Door to Treatment Time) OR Delayed Treatment) OR Delayed Treatments) OR Treatment, Delayed) OR Treatment Delay) OR Delay, Treatment) OR Treatment Delays)). The search was performed from May 5 to 20, 2021. No language restrictions were applied.

Study selection

The same two authors independently screened the titles and abstracts of the primary studies that were identified in the electronic search. Duplicate studies were excluded. The inclusion criteria were: (1) Human subjects; (2) inclusion of mean values with standard deviation values of related indices of information ratios; and (3) a clear indication that the study subjects have symptoms of abdominal infections or diseases mentioned in the guidelines.

The exclusion criteria were: (1) Case reports, reviews, comments, protocols, meeting abstracts, and meta-analyses; (2) studies of other interventions; and (3) studies where it was impossible to retrieve or calculate data of interest or without full-text versions available.

The Cohen kappa statistic was used to quantify the agreement between the investigators.

Data extraction

The same two authors extracted the following main data (Tables 1 and 2): (1) First author, year of publication and study type; (2) number and characteristics of patients of both early surgical exploration and delayed operation groups; and (3) treatment outcomes, including mortality rate, length of hospital stay, survival rate, and the occurrence of procedure-related complications. All relevant texts, tables and figures were reviewed for data extraction; whenever further information was required, the corresponding authors of the papers were contacted by e-mail. Discrepancies between the two reviewers were resolved by consensus discussion.

Risk of bias

The Newcastle-Ottawa Scale was used for retrospective studies to assess quality. Funnel plots were constructed to assess the risk of publication bias across series for all outcome measures.

Statistical analysis

Review Manager version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used for primary data analyses. Data were presented using odds ratios (ORs) for categorical outcomes and mean differences (MDs) for continuous outcomes, with 95%CIs calculated for all estimates; in the random-effects model, $P < 0.05$ was considered to be statistically significant. Interstudy heterogeneity was evaluated using Cochran's Q statistic and quantified using the I^2 statistic; a value greater than 50%[21] indicated substantial heterogeneity, and statistical significance was indicated by $P < 0.10$. The source of heterogeneity was explored using sensitivity and subgroup analyses. Publication bias was assessed by a visual inspection of funnel plots.

RESULTS

Study selection

The literature search returned a total of 62646 records, of which 35 articles underwent full-text review and nine were finally included in our meta-analysis (Table 1)[22-30]. The details of the study selection process are presented as a literature search flow diagram (Figure 1). The nine studies included a total of 3373 patients who had acute diverticulitis, gastrointestinal perforation, appendicitis complicated by abdominal cavity infection manifestations, and/or bacterial inflammation in the abdominal cavity caused by other hollow organs. All nine selected studies were observational studies, with seven being retrospective cohort studies and two being prospective cohort studies; all nine included studies were full-text articles published in journals, meeting the inclusion criteria. Participants in the included studies were adults from seven countries (China, South Korea, India, the United States, Italy, Germany, and Japan). The six retrospective cohort studies reported follow-up periods ranging from 1 year to 9 years in length, and the three

Table 1 Characteristics of included studies

Ref.	Design	Sample size, *n*	Age in year	Sex, male/female	Start of time calculation	Primary end-point(s)	Follow-up time
Elramah *et al* [24]	RC	523	61	-	Admission time	Mortality rate; Cure rate	9 year
Giraudo *et al* [23]	RC	746	28.8	343/380	Admission time	Complications rate; Mortality rate	6 year
Lee *et al*[25]	RC	1076	35.2 ± 17.1	612/464	Time of symptom onset	Cure rate; Complications rate	3 year
Maroju *et al*[28]	PC	114	28.3	86/28	Time of symptom onset	Length of hospital stay	1 year
Kim *et al*[29]	RC	192	33.6 ± 19.5	99/93	Time of symptom onset	Complications rate; Length of hospital stay	1 year
Saar *et al*[30]	PC	270	35.4 ± 14.8	136/130	Time of symptom onset	Cure rate	1 year
Rause *et al*[22]	RC	197	68	51%/49%	Admission time	Mortality rate	8 year
Azuhata *et al* [26]	PC	154	66.5 ± 13.9	88/66	Admission time	Survival rate	4 year
Wen and Tang [27]	RC	101	56.26 ± 15.7	65/36	Admission time	Mortality rate; Length of hospital stay	3.5 year

PC: Prospective cohort; RC: Randomized controlled.

prospective cohort studies[26,28,30] had follow-up periods ranging from 1 year to 4 years in length.

Quality assessment

Based on the Newcastle-Ottawa scale, all included observational studies were of high quality (Table 2) but did not indicate whether or not they had received funding.

Primary outcome measure

Figure 2A shows the difference in mortality rate between the early surgical exploration group and the control group. The risk of mortality rate in the early surgical exploration group was significantly lower than in the control group (OR: 0.29; 95%CI: 0.11-0.78; P = 0.01), with no evidence of significant heterogeneity (I^2 = 27%; P = 0.25). According to Rausei *et al* [22], for patients having severe IAIs, the mortality rate increased linearly for each 6-hour delay in the timing of surgery. Notably, most patients in the 6-12 h delayed group had the highest prognostic scores.

Length of hospital stay

Figure 2B shows that patients in the early surgical exploration group had significantly shorter hospital stays (SMD: -1.85 d; 95%CI: -3.21 to -0.49 d; P = 0.008), with evidence of high heterogeneity (I^2 = 98%, P < 0.00001). A systematic removal of individual studies can change the results or account for the findings (SMD: -0.48 d; 95%CI: -0.66 to -0.30 d; P < 0.00001), with no evidence of significant heterogeneity (I^2 = 0%; P = 0.64) (Figure 2C). The reason for removal is because the time standard for inclusion in this study was from the onset of symptoms to the beginning of surgery.

Survival rate

Figure 2D shows the difference in the survival rate between the early surgical exploration within the 6 h group and the control group. The risk of survival rate in the early surgical exploration group was significantly higher than that in the control group (OR: 4.31; 95%CI: 2.27-8.18; P < 0.00001), with evidence of moderate heterogeneity (I^2 = 45%; P = 0.12). Azuhata *et al*[26] found that for patients with gastrointestinal perforation combined with septic shock, the survival rate decreased with delay in the operation start time, and the survival rate of patients who waited for more than 6 h was 0%.

Occurrence of procedure-related complications

Figure 2E shows the differences in the occurrence of procedure-related complications between the early surgical exploration group and the control group. The risk of occurrence of procedure-related complications in the early surgical exploration group was significantly lower than that in the control group (OR: 0.33; 95%CI: 0.20-0.54; P < 0.0001), with no evidence of significant heterogeneity (I^2 = 5%; P = 0.35).

Subgroup outcome

Figure 2F shows that patients in the surgery within 12 h group had significantly shorter hospital stays than those of patients in the surgery after 24 h group (SMD: -0.21 d; 95%CI: -0.43 to -0.01 d; P = 0.06), with no evidence of significant

Table 2 Results of quality assessment using the Newcastle-Ottawa Scale for case-control studies

Ref.	Selection				Comparability	Exposure			Quality score
	Adequate definition of cases	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Elramah *et al*[24]	[1]	[1]	-	[1]	[1]	[1]	[1]	[1]	7
Giraudo *et al*[23]	[1]	[1]	-	[1]	[1]	[1]	[1]	[1]	7
Lee *et al* [25]	[1]	[1]	-	[1]	[1]	[1]	[1]	[1]	7
Maroju *et al*[28]	[1]	[1]	-	[1]	[1]	[1]	[1]	[1]	7
Kim *et al* [29]	[1]	[1]	-	[1]	[1]	[1]	[1]	[1]	7
Saar *et al* [30]	[1]	[1]	-	-	[2]	[1]	[1]	[1]	7
Rause *et al*[22]	[1]	[1]	-	-	[1]	[1]	[1]	[1]	6
Azuhata *et al*[26]	[1]	[1]	-	[1]	[2]	[1]	[1]	[1]	8
Wen and Tang [27]	[1]	[1]	-	[1]	[2]	[1]	[1]	[1]	8

[1]Indicates that the inclusion study met the relevant criteria and represents a score of 1.
[2]Indicates that the inclusion study met the relevant criteria and represents a score of 2.

heterogeneity (I^2 = 0%; P = 0.47). Patients in the surgery within 12 h group had significantly shorter hospital stays than those of patients in the surgery within 12-24 h group [SMD: -0.06 d (95%CI: -0.25 to -0.36 d; P = 0.71)], with evidence of medium heterogeneity (I^2 = 50%; P = 0.16). Patients in the surgery within 12-24 h group had significantly shorter hospital stays than those of patients in the surgery after 24 h group [SMD: -0.38 d (95%CI: -0.58 to -0.19; P = 0.0001)], with no evidence of significant heterogeneity (I^2 = 0%; P = 0.79). A systematic removal of individual studies did not change the results.

Publication bias

A sensitivity analysis of the included observational studies was performed by excluding the abstracts with no available published full-text versions and the studies with the highest risk of bias; however, this did not affect the findings. Publication bias was evaluated by funnel plot analysis (Figure 3). Figure 3A shows a funnel plot of hospital stay length; when a system of individual studies was removed, the funnel chart indicated that there was no asymmetry (Figure 3B). In addition, funnel plots of the survival rate (Figure 3C) and length of hospital stay by surgical timing subgroup (Figure 3D) are presented and similarly suggested no asymmetry. Publication bias was not assessed for other components as there were less than four trial comparisons available.

DISCUSSION

Abdominal infection is the most common surgical infection[14,15]. IAI is a common postoperative complication after surgery, causing pain and suffering to patients. In addition, this complication has been associated with negative economic impact including increased morbidity, extended postoperative hospital stay, readmission, sepsis, and death[31]. Concerning the role of the surgical technique (*i.e.* open *vs* laparoscopic approach) on IAI, studies have shown that the technique of surgery does not appear to affect the incidence of IAI[32]. In the current research, the optimal duration of postoperative IAI in the treatment of critically ill patients is unclear[33]. In addition, our data show that, compared with delayed surgery, early surgical exploration reduces mortality and may reduce both hospital stay length and adverse events. In fact, the timing of infection control is critical for patients with IAIs, but the definition of 'early' control in the

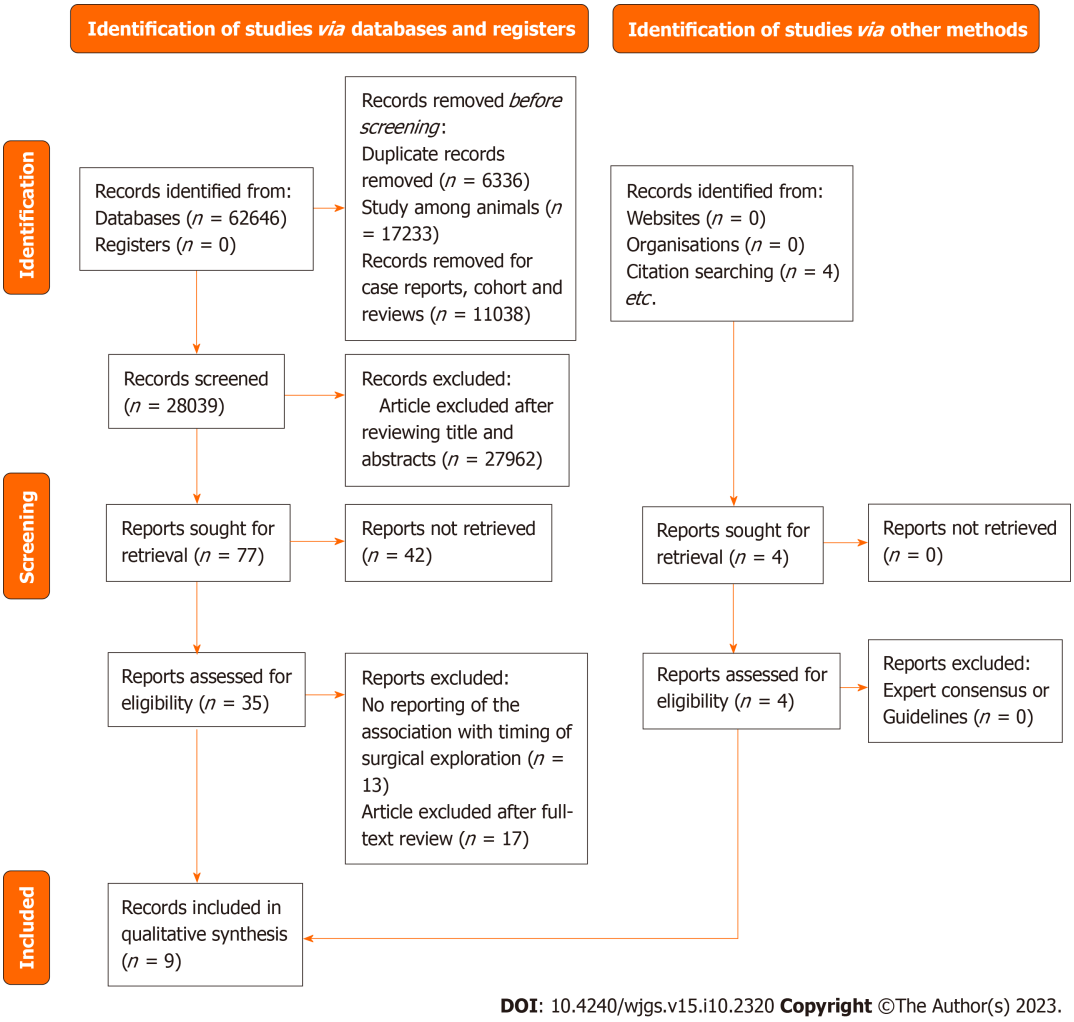

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Figure 1 Literature search flow diagram.

literature varies.

In recent years, scholars have performed a series of studies on the timing of surgery and offered their own opinions. Our results suggest that early surgery within 6 h can improve the survival rate of patients, which is consistent with the results of previous studies[22,27]. According to Rausei's observations[22], for every 6 h of delay in source control, the mortality rate will directly increase, and the rate of abdominal wound closure will also decrease. Azuhata's analysis[26] also supports that the target time for a good prognosis may be within 6 h after admission. When the start of surgery was delayed, the survival rate was decreased, and the survival rate for those treated after more than 6 h was 0%. However, this extreme result may be because their study only included a small group of patients and was an observational study conducted at a single institution.

Some studies have suggested that surgery performed within 12 h has a critical effect on reducing mortality and complications. The research by Lee *et al*[25] is biased toward performing surgery within 18 h, which will reduce the incidence of complications. Under certain conditions, surgery can be performed earlier, which will not adversely affect the outcome of the operation. A study by Saar *et al*[30] indicated that delaying surgery for 12 h will gradually increase the number of complications per comprehensive complication index and will also significantly lengthen the operation time and the hospital stay. Colson *et al*[34] also offered similar results. Patients who undergo surgery more than 12 h after the onset of their symptoms have a greater incidence of perforation. Interestingly, a study[35] found that early surgery within 6 h increased the abdominal closure rate but also the length of hospital stay. This may be due to insufficient preparations made for early surgery and longer inter-hospital observation and nursing times after surgery. In addition, for patients with abdominal cavity infections, the emergency may occur at night. At this time, a shortage of doctors and incomplete inspection may render preoperative preparations incomplete. Therefore, premature intervention can lead to a series of adverse effects not seen in concert with adequate preparation for surgery. "Most sepsis patients require surgical treatment and an emergency procedure, that is carried out when the patient's condition is severe and rapidly worsening. Furthermore, there is often multiorgan damage and a combination of chronic diseases. As a result, anesthesiologists should exercise caution when choosing anesthetics, and the optimization of anesthesia strategies is necessary. However, not all patients with IAIs develop sepsis, and not all patients with sepsis are also infected in the abdominal cavity". "In summary, for patients with non-emergency conditions, as well as those with obvious contraindications to surgery, it is beneficial to delay surgery, complete the relevant investigations, or optimize the anaesthetic protocol".

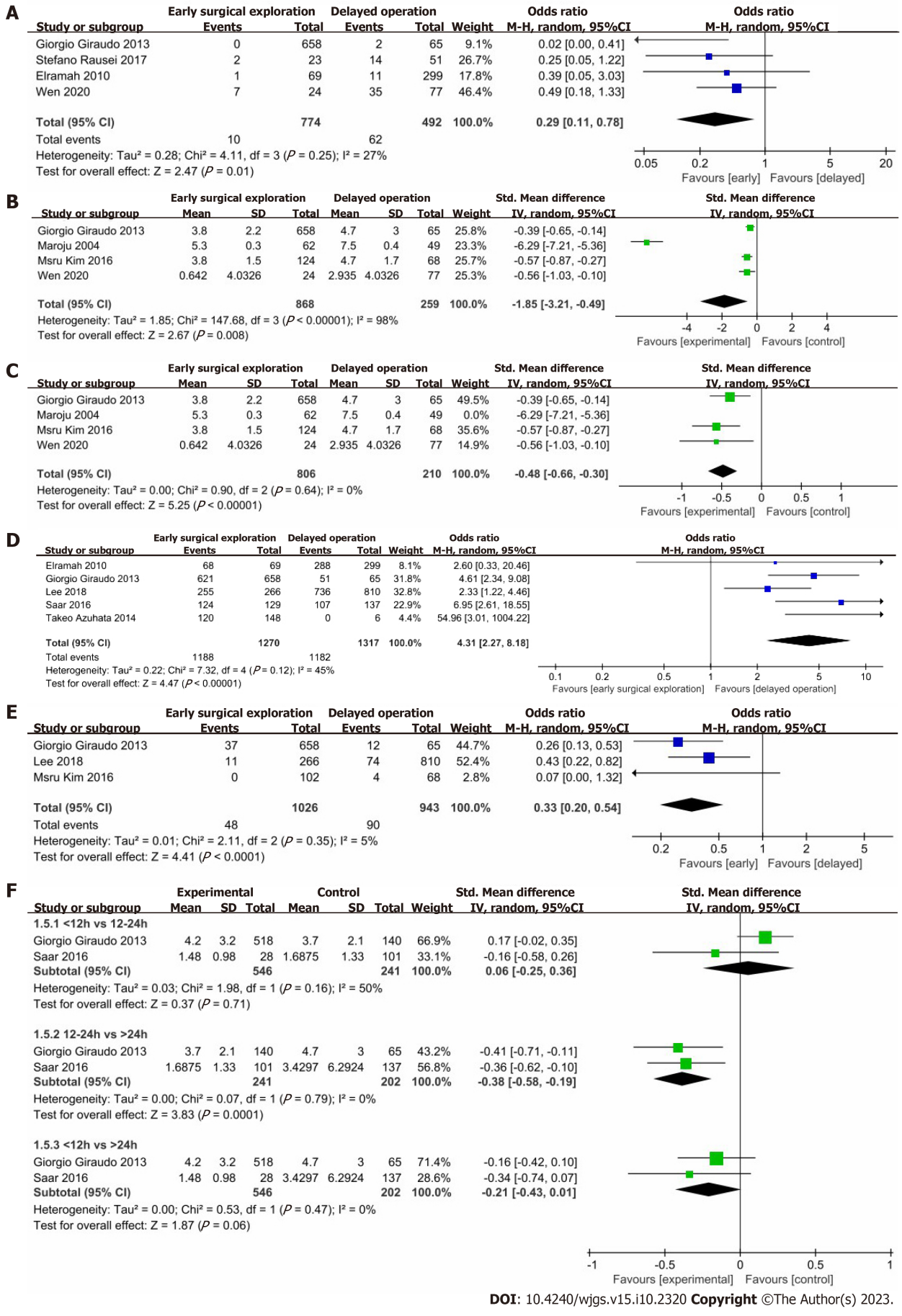

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Figure 2 Forest plot. A: Mortality rate; B: Length of hospital stay; C: Length of hospital stay with a systematic removal; D: Cure rate; E: Occurrence of procedure-

related complications rate; F: Length of hospital stay of subgroup. Early surgical exploration: < 12 h. CI: Confidence interval; SD: Standard deviation.

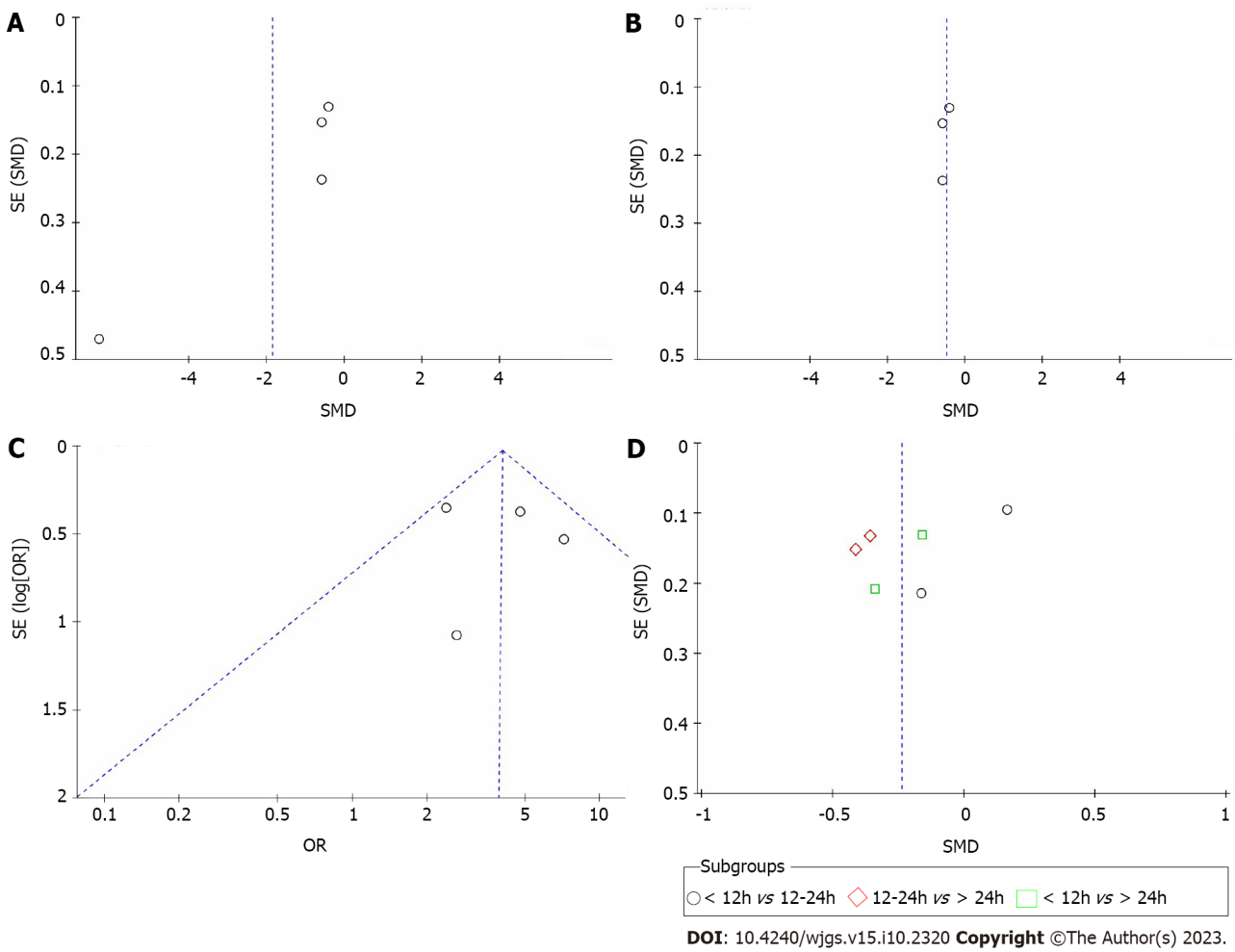

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Figure 3 Funnel plot. A: Length of hospital stay; B: Length of hospital stay with a systematic removal; C: Cure rate; D: Length of hospital stay of subgroup. OR: Odds ratio.

The results of our subgroup analysis showed that early surgical exploration (within 12 h) can shorten the hospital stay. When the operation is delayed, the abdominal cavity infection may be aggravated and thus become more difficult to control effectively. This may be mainly because early surgery can not only remove abdominal necrosis on time but can also further control the source of infection through surgical exploration. Moreover, compared with delayed treatment, the incidence of adverse events in early surgery is lower, which may also be related to this.

In short, most of the included studies were observational, with high-quality evidence and a moderate risk of bias. The conclusions of this study are limited by the heterogeneity between the included trials, our inability to know the study blinding status, the starting point of the operation time, and the difference in treatment standards. First, each country and hospital has a different standard for the definition of patients with abdominal cavity infection. So, the standards are not uniform.

In addition, different countries have varying indications for surgical intervention. Whether all patients need surgical intervention and whether surgical intervention is directly performed after diagnosis are controversial, which may lead to potential deviations between studies.

Furthermore, there is no uniform standard for calculating the start time of surgery. Some hospitals start the calculation based on the time of admission[23,26,27], while some hospitals start the calculation based on the time at which the patient shows symptoms[22,29]. Subjective factors such as time calculation will also affect the research results. In our research, for studies that did not indicate the starting point of time, we uniformly defined such as the time from the point of admission to the beginning of the operation.

Overall, due to a lack of research on the timing of abdominal infection surgery at home and abroad and the varying standards of observation methods between studies, we included fewer research projects, and the quality of the data obtained is not very high, which renders our results not universally applicable.

Our study results do support that, for patients with IAI, surgical intervention should be carried out within 12 h as much as possible, or even preferably within 6 h if possible. Although each doctor attempts to avoid delays in surgery, early surgery requires accurate judgment and precise surgical skills, which places greater demands on doctors. Moreover, it is necessary to improve preoperative preparations, closely monitor the vital signs of patients, and cooperate with each department involved in the procedure. Because studies spanned long periods and had differences in IAI and the data available from the included studies were limited, we did not analyze the time of surgical intervention for IAIs caused by various means. Attempting full preparation before surgery with a series of related inspections can help to carry out the procedure early.

CONCLUSION

Although further high-quality randomized controlled trials are still needed to determine the optimal surgical exploration time, our findings clearly show that in IAI patients, early surgical exploration within 12 h or even 6 h can reduce the mortality rate and adverse events, shorten the hospital stay, and improve the survival rate.

ARTICLE HIGHLIGHTS

Research background

Intra-abdominal infections (IAIs) is the most common type of surgical infection, with high associated morbidity and mortality rates. In recent years, due to the use of antibiotics, various drug-resistant bacteria have emerged, making the treatment of abdominal infections more challenging. Early surgical exploration can reduce the mortality of patients with abdominal infection and the occurrence of complications. However, available evidence regarding the optimal timing of IAI surgery is still weak.

Research motivation

We compared the effects of operation time on patients with abdominal cavity infection and tried to confirm the best timing of surgery.

Research objectives

This study aimed to assess the efficacy of early *vs* delayed surgical exploration in the treatment of IAI, in terms of overall mortality.

Research methods

A systematic literature search was performed using PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Ovid, and ScienceDirect. The systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-analyses method. Based on the timing of the surgical operation, we divided the literature into two groups: early surgery and delayed surgery. For the early and delayed surgery groups, the intervention was performed with and after 12 h of the initial surgical intervention, respectively. The main outcome measure was the mortality rate. The literature search was performed from May 5 to 20, 2021. We also searched the World Health Organization International Clinical Trials Registry Platform search portal and ClinicalTrials.gov on May 20, 2021, for ongoing trials. This study was registered with the International Prospective Register of Systematic Reviews.

Research results

We identified nine eligible trial comparisons. Early surgical exploration of patients with IAIs (performed within 12 h) has significantly reduced the mortality and complications of patients, improved the survival rate, and shortened the hospital stay.

Research conclusions

Early surgical exploration within 12 h may be more effective for the treatment of IAIs relative to a delayed operation.

Research perspectives

In this study, we developed a strict and reasonable study design, literature search strategy and screening and quality evaluation, selected appropriate statistical analysis methods, and analyzed the results' scientificity and sensitivity.

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FOOTNOTES

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META-ANALYSIS

Bariatric surgery reduces colorectal cancer incidence in obese individuals: Systematic review and meta-analysis

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Abstract

BACKGROUND

Colorectal cancer ranks third in global cancer prevalence and stands as the second leading cause of cancer-related mortalities. With obesity recognized as a pivotal risk factor for colorectal cancer, the potential protective role of bariatric surgery, especially laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy, has garnered attention.

AIM

To investigate the Roux-en-Y gastric bypass (RYGB) *vs* sleeve gastrectomy (SG) effect on colorectal cancer incidence in obese individuals.

METHODS

A systematic review and meta-analysis of the literature was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Seventeen studies with a total of 12497322 patients were included. The primary outcome was the relative risk (RR) of developing colorectal cancer in obese patients who underwent weight loss surgery compared to those who did not. Secondary outcomes included determining the RR for colon and rectal cancer separately and subgroup analyses by gender and type of weight loss surgery.

RESULTS

The meta-analysis revealed a 54% reduction in colorectal cancer risk in morbidly obese patients who underwent bariatric surgery compared to those who did not. A significant 46% reduction in colorectal cancer risk was observed among female patients. However, no significant differences were found in the meta-analysis for various types of bariatric surgery, such as SG and RYGB.

CONCLUSION

This meta-analysis reveals weight loss surgery, regardless of type, reduces colorectal cancer risk, especially in women, as indicated by RR and hazard ratio

assessments. Further validation is essential.

Key Words: Obesity; Weight loss surgery; Colorectal cancer; Meta-analysis; Risk reduction

Core Tip: This comprehensive meta-analysis evaluates the impact of bariatric surgery on colorectal cancer (CRC) risk using 17 studies with over 12 million patients. Results show a 54% reduction in CRC risk after surgery, with women experiencing a 46% decrease. Interestingly, the type of bariatric surgery, whether Sleeve Gastrectomy or Roux-en-Y Gastric Bypass, did not influence this risk reduction. Bariatric procedures underscore a pivotal role in managing CRC risk in the obese. The study highlights the surgery's protective effect, especially for women, and the need for further research on potential confounding factors.

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INTRODUCTION

Obesity is a multifaceted disease influenced by genetic, behavioral, socioeconomic, and environmental factors. These factors contribute to an elevated risk of morbidity and mortality from several debilitating conditions. Obesity increases the risk of a wide range of chronic diseases, from diabetes and dyslipidemia to mental health conditions. It has a significant impact on the risk of stroke, cardiovascular disease, certain cancers, and osteoarthritis. Worldwide, the rising prevalence of obesity presents substantial challenges to both chronic disease prevention and health promotion[1]. Given its global impact, the World Health Organization (WHO) defines obesity in Western populations as a body mass index (BMI) of ≥ 30 kg/m², while a BMI of ≥ 25 kg/m² is considered overweight. In the United States, 64.5% of adults are categorized as overweight and 30.5% as obese[2]. Data indicates that, relative to individuals with a normal BMI range (18.5-24.9 kg/m²), the mortality rate from various causes is markedly higher among the obese population, with cardiovascular diseases as the leading cause[3]. Although the overall BMI of Asian populations is lower than that of Western populations, Asians tend to exhibit central obesity. Thus, using a BMI ≥ 30 kg/m² as the threshold for diagnosing obesity in Asian populations may underestimate the risks associated with obesity, leading the WHO expert committee to define a BMI ≥ 25 kg/m² as the threshold for obesity in Asian populations[4]. Female obesity rates are generally higher than male rates, and there are gender differences in body fat distribution[5].

Previous reviews have indicated that, compared to individuals with normal weight, obesity increases the risk of developing colorectal cancer by 7% to 60%, with some studies suggesting a stronger association between obesity and colon cancer than rectal cancer[6]. According to research by Moghaddam *et al*[7], there is a direct and independent relationship between obesity and colorectal cancer. For every 2 kg/m² increase in BMI, the risk of colorectal cancer increases by 7%. A 2 cm increase in waist circumference is associated with a 4% increase in colorectal cancer risk. The association between obesity and colorectal cancer accounts for approximately 20% of the total risk. The risk for men is 1.41 (95%CI: 1.3-1.54), and for women, it is 1.08 (95%CI: 0.98-1.18) (P heterogeneity < 0.001). It is estimated that 6% of all cancer diagnoses in 2007 (4% for men and 7% for women) can be attributed to obesity. Obesity is not only a major risk factor for diabetes but also for most cancers. For a long time, it has been believed that obesity is associated with an increased risk of esophageal, colon, pancreatic, postmenopausal breast, endometrial, and kidney cancers[8].

Weight loss surgery can reduce the incidence of obesity-related tumors, particularly in female patients. An Australian study with over 65000 patients and a follow-up of up to 15 years found that the risk of colorectal cancer in male obese patients decreased by nearly 50% after weight loss surgery. Numerous clinical studies have confirmed that the reduction of insulin levels after weight loss surgery can reduce the risk of developing colorectal tumors[9].

Common weight loss surgeries include laparoscopic sleeve gastrectomy (LSG), Roux-en-Y laparoscopic gastric bypass (LRYGB), laparoscopic adjustable gastric banding, and other novel procedures. RYGB, originally proposed by Wittgrove *et al*[10], alters the digestive tracts pathway to reduce absorption and is a complex, high-risk procedure with numerous postoperative complications, involving the alteration of gastrointestinal anatomy. RYGB is more complex and has more complications than LSG, but for patients with type 2 diabetes mellitus unresponsive to medical treatment, RYGB is the preferred option. RYGB is also the gold standard for revision surgery in patients with postoperative weight regain or complications, such as high gastric leaks and severe reflux esophagitis. LRYGB is safe and effective in treating obesity and type 2 diabetes, and there is a correlation between BMI, blood glucose levels, and quality of life before and after surgery [11,12].

Due to its significant effects on weight loss and metabolic improvement, LSG has gained widespread application in the field of bariatric surgery. This surgical procedure is known for its simplicity, reduced surgical risks, and lower incidence of postoperative complications. LSG has remarkable weight loss and metabolic improvement effects.

The findings from these studies prompt an essential inquiry: Is the incidence of colorectal cancer lower in obese patients who undergo weight loss surgeries like LRYGB and LSG compared to those who opt against such procedures? Furthermore, do gender differences play a significant role in this issue, and are there any differences when choosing between RYGB and sleeve gastrectomy (SG) procedures? This meta-analysis seeks to discern the influence of weight loss surgeries on the colorectal cancer risk among obese individuals. Earlier meta-analytic studies have documented a decreased cancer risk following weight loss surgery. However, those studies encompassed research with considerable variances in follow-up durations and lacked specific analyses to address this bias. Therefore, our research objective is to conduct a new meta-analysis to elucidate the specific impact of weight loss surgery on the risk of colorectal cancer in obese patients.

MATERIALS AND METHODS

We conducted a systematic review of the literature following the guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Assessing the Methodological Quality of Systematic Reviews (AMSTAR)[13] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) recommendations. This study does not require ethical approval or informed consent, as all data were retrieved from published literature. The search, eligibility assessment, data extraction, and quality evaluation were independently performed by four researchers. Any disagreements were resolved through discussion, with consensus required among the four researchers.

Search strategy

We searched PubMed, Embase, Web of Science, and Cochrane Library up to April 30, 2023, without imposing any time restrictions. We specifically adapted vocabulary and syntax for each database. We used computerized searches of the PubMed database with the following keywords: Obesity, obesity and cancer, colorectal cancer, weight loss surgery, gastric bypass, and sleeve gastrectomy. We did not impose any language restrictions. We also manually screened the reference lists of relevant articles to identify other potential records. In our search strategy, we included studies and previous reviews on the topic, screening their references according to the selection criteria to find more related studies.

Selection criteria

In adherence to PRISMA guidelines, we employed the Population, Intervention, Comparison, Outcome, and Study design framework to determine study eligibility: Population (P): Adult individuals (≥ 18 years old) diagnosed with morbid obesity, followed up for at least three years to investigate the incidence of colorectal cancer. Intervention (I): Weight loss surgery. Comparison (C): Simple observation or any behavioral or pharmacological treatment. Outcome (O): Risk of developing colorectal cancer during the follow-up period. Study design (S): Retrospective and prospective comparative studies with at least ten patients in each group.

Exclusion criteria

Studies were excluded if they did not involve a comparison of colorectal cancer risk between obese patients who underwent or did not undergo weight loss surgery, did not provide specific indicators or metrics for evaluating colorectal cancer risk, the full text was not accessible, or the study was not in English.

Systematic review process

In the first step, 1399 articles were identified through literature searches. Duplicate entries found across different databases were removed using Mendeley reference software (Mendeley Ltd., London, United Kingdom). Then, the titles and abstracts of 713 records were screened using a filtering table created to guide study selection.

Quality assessment

We assessed the quality of the included studies using the Newcastle-Ottawa Scale (NOS)[14]. This scale consists of three domains: selection, comparability, and outcome/exposure, with a maximum score of 9 points. Two evaluators assessed the following nine NOS sections: Representativeness of the exposed cohort, selection of the non-exposed cohort (selection bias); ascertainment of exposure, demonstration of the outcome, comparability of cohorts (comparability bias); assessment of the outcome, sufficient follow-up time, adequacy of cohort follow-up (outcome bias). Scores of 0-3, 4-6, and 7-9 represent low, medium, and high study quality, respectively.

Data extraction and assessment of included studies

A computerized electronic spreadsheet (Microsoft Excel 2021; Microsoft Corporation, Redmond, Washington, United Kingdom) was used to collect information regarding study design and methods, participant demographics and baseline characteristics, obesity treatment details, colorectal cancer outbreak risk, and survival.

Primary and secondary endpoints

The primary outcome was expressed as the relative risk (RR) of developing colorectal cancer in obese patients who underwent weight loss surgery compared to those who did not. In the same subset, secondary outcomes included determining the RR for colon cancer and rectal cancer separately. Additionally, subgroup analyses were performed, considering the RR of colorectal cancer (CRC) for males and females separately, and depending on the type of weight loss

surgery performed (LSG *vs* RYGB). Finally, we determined the hazard ratio (HR) for developing colorectal cancer in obese individuals who underwent or did not undergo weight loss surgery.

Statistical analysis

We assessed study heterogeneity using chi-square statistics and quantified it with the I^2 statistic. An I^2 value of 0% suggests no observed heterogeneity, whereas an I^2 value greater than 50% points to significant heterogeneity, while an I^2 value > 50% indicates significant heterogeneity. We standardized the relative risk in each article and combined them using a random-effects model. We conducted sensitivity analyses to assess the robustness of our findings and to pinpoint any individual studies that might influence the overall effect size. This analysis involved sequentially removing each study from the meta-analysis and recalculating the overall effect size, checking whether the point estimate of the overall effect remained within the 95% confidence interval of the initial combined effect. Publication bias was examined using funnel plot symmetry and Egger's test in meta-analyses with ten or more eligible articles. If the funnel plot appeared asymmetrical, we evaluated if the assumption of unpublished negative studies, attributable to publication bias, had a significant impact on the effect estimate. In all statistical tests, two-sided P values < 0.05 were considered statistically significant. We used STATA version 17 (StataCorp, College Station, TX, United States) to analyze the data from randomized controlled trials that met our inclusion criteria.

RESULTS

As depicted in Figure 1, our quantitative and qualitative analyses encompassed 17 studies[15-31]. A total of 12497322 patients were analyzed in the meta-analysis (Table 1).

Colorectal cancer

Preliminary results were sourced from 17 studies[15-31]. The risk of developing colorectal cancer during the follow-up period was reduced by 54% (RR: 0.46, 95%CI: 0.32-0.67, P < 0.01, I^2 = 97.8%) in morbidly obese patients who underwent bariatric surgery (BS) (Figure 2). Due to the high degree of heterogeneity, a sensitivity analysis was performed (Figure 3). Four studies[22,23,26,31] were identified as primarily responsible for this heterogeneity, but their exclusion did not consistently reduce the heterogeneity; the advantage remained prominent for obese individuals with a history of BS (RR: 0.57, 95%CI: 0.47-0.69, P = 0.0001, I^2 =75%). Only three studies separately reported data on colon and rectal cancer[15,23,30]; for colon cancer, the meta-analysis showed a trend favoring BS patients, though not significant (RR: 0.75, 95%CI: 0.46-1.21, P = 0.2444, I^2 = 89%). Similarly, considering rectal cancer, there was no apparent trend in favor of BS patients (RR: 0.74, 95%CI: 0.4-1.39, P = 0.3523, I^2 = 87%).

Subgroup analysis

We identified five studies from the literature[16,19,21,23,30] that reported CRC incidence exclusively in males across both the BS and non-surgical groups. Meta-analysis showed a trend toward a reduced risk of CRC in males with a history of BS, although not significant (RR: 0.74, 95%CI: 0.43-1.28, P = 0.2798, I^2 = 96%). We found a significant reduction in CRC risk (46%) in females with a history of BS (RR: 0.54, 95%CI: 0.37-0.79, P = 0.0014, I^2 = 90%). We noted six studies[16,19,21,23,28,30] that detailed female-specific cancer incidence. Regarding the type of weight loss surgery, SG and RYGB were the most common. The meta-analysis of binary outcomes from 4 studies[16,19,27,31] showed no difference in CRC risk for patients with a history of SG or RYGB (RR: 1.02, 95%CI: 0.71-1.45, P = 0.8708, I^2 = 43%). Only three studies[16,27,31] reported data following laparoscopic adjustable gastric banding, and thus this technique was not included in the meta-analysis.

Meta-Analysis of HR

We focused on articles that reported HR estimates for CRC development in obese individuals, irrespective of their history of undergoing BS[16,17,23,26,27,29,30]. Although there was a trend favoring the BS group (HR: 0.88, 95%CI: 0.69-1.12, P = 0.2974, I^2 = 77%), the meta-analysis of HR did not find significant estimates favoring either the BS or non-surgical groups. However, after sensitivity analysis and exclusion of the study by Mackenzie *et al*[27], a significant reduction of 25% in HR was observed for obese patients with a history of BS (HR: 0.75, 95%CI: 0.68-0.82, P = 0.005, I^2 = 70.4%) (Figure 4).

Results of quality assessment

Using the NOS, we evaluated the methodological quality of each randomized controlled trial. Overall, 1 study scored 7 points, 15 studies scored 8 points, and 1 study scored 9 points. No studies were blinded, and there was no evidence of concealed allocation. No apparent funding bias was found in any of the studies. We found no studies with incomplete outcome data, premature stopping bias, or imbalances at baseline. The risks of bias and corresponding ratios are summarized in Table 2.

Results of publication bias

The funnel plot constructed from the observed studies showed symmetry, and no significant publication bias was detected in the funnel plot (Figure 5).

Table 1 Detailed characteristics of the study included in the research

Ref.	Country	Bariatric surgery[1]		Control[2]		Follow-up	Risk estimate (95%CI)[3]
		Total	Events	Total	Events		
Adams *et al*[17], 2009	United States	6596	25 (0.004)	9442	52 (0.006)	12.3	HR: 0.7 (0.43-1.15)
Christou *et al*[20], 2008	Canada	1035	2 (0.002)	5746	35 (0.006)	5	RR: 0.32 (0.076-1.313)
McCawley *et al*[28], 2009	United States	1482	1 (0.0007)	3495	11 (0.003)	-	
Derogar *et al*[21], 2013	Sweden	15095	70 (0.005)	62016	373 (0.006)	10	
Aravani *et al*[19], 2018	United States	39747	43 (0.001)	962860	3237 (0.003)	3	
Mackenzie *et al*[27], 2018	Sweden/United States	8794	16 (0.002)	8794	35 (0.004)	4.6	HR: 2.19 (1.21-3.96)[a]
Khalid *et al*[24], 2022	United States	19272	66 (0.003)	9636	55 (0.006)	5	
Kwak *et al*[23], 2019	United States	2231	5 (0.002)	2231	6 (0.002)	7.8	
Schauer *et al*[29], 2019	United States	22198	105 (0.005)	66427	533 (0.008)	3.5	HR: 0.59 (0.36-0.97)[a]
Tao *et al*[15], 2020	Denmark/Sweden/Norway/Finland/Iceland	49931	155 (0.003)	492427	3158 (0.006)	3.1	
Bailly *et al*[16], 2020	France	74131	423 (0.006)	971217	12629 (0.013)	5.7	HR: 0.68 (0.6-0.77)[a]
Tsui *et al*[31], 2020	United States	71000	340 (0.005)	323197	1334 (0.004)	-	
Taube *et al*[30], 2021	Sweden	2006	58 (0.03)	2038	67 (0.03)	22.2	HR: 0.89 (0.62-1.28)
Aminian *et al*[18], 2022	United States	5053	16 (0.003)	25265	86 (0.003)	6.1	
Desai *et al*[22], 2022	United States	279145	19 (0.0001)	7398104	32276 (0.004)	-	
Hussan *et al*[23], 2022	United States	88630	88 (0.001)	327734	325 (0.001)	3	HR: 1.02 (0.76-1.37)
Lazzati *et al*[26], 2022	France	288604	329 (0.0001)	851743	4434 (0.005)	5.7	HR: 0.93 (0.79-1.08)

[1]The crude incidence rate data depicts the occurrence of colorectal cancer over the follow-up duration, denoted as *n* (%).
[2]Risk estimation evaluates the likelihood of colorectal cancer onset in obese individuals undergoing bariatric surgery therapy relative to those without such intervention.
[3]HR: hazard ratio.
[a]$P < 0.05$.

DISCUSSION

Colorectal cancer is the third most common cancer worldwide and the second leading cause of cancer-related deaths. By 2020, approximately 1.9 million new cases and around 935000 deaths were related to colorectal cancer[32]. Obesity is a well-established risk factor for colorectal cancer. For every 5 kg/m² increase in BMI, the risk of colorectal cancer due to obesity rises by 24% in men and 9% in women. Additionally, obesity is linked to a 47% heightened risk of colorectal adenoma, implying its potential role in the initial stages of colorectal cancer progression. Postoperative risk of CRC is anticipated to decrease following BS, a procedure recognized for its ability to reduce inflammatory markers, mitigate genomic damage, and enhance anti-tumor response[33]. With sustained weight loss and alleviation or improvement of obesity-related comorbidities, BS is considered the most effective method for treating morbid obesity and its associated medical issues.

In this study, we conducted a meta-analysis of 17 studies, encompassing 12497322 patients. Our findings highlight that morbidly obese patient who underwent BS experienced a 54% reduction in CRC risk throughout the follow-up duration. Due to high heterogeneity, a sensitivity analysis was performed. Although no significant differences were found in the subgroup analysis of colon and rectal cancers, a 46% reduction in CRC risk was observed among female patients. However, no significant differences were found in the meta-analysis for various types of bariatric surgery, such as SG and RYGB. Lastly, a meta-analysis of articles reporting HR estimates for colorectal cancer in obese patients showed a significant 25% reduction in HR for those with a history of BS after sensitivity analysis.

Table 2 The quality assessment according to Newcastle-Ottawa Scale of each cohort study

Ref.	Selection				Comparability	Outcome			Total score
	Representativeness of the exposed cohort	Selection of the non - exposed cohort	Ascertainment of exposure	Demonstration that outcome	Comparability of cohorts	Assessment of outcome	Was follow-up long enough	Adequacy of follow up of cohorts	
Christou *et al*[20], 2008		★	★	★	★★	★	★	★	8
Adams *et al*[17], 2009	★	★	★	★	★★	★	★	★	9
McCawley *et al*[28], 2009	★	★	★	★	★	★	★	★	8
Derogar *et al*[21], 2013	★	★	★	★	★	★	★	★	8
Aravani *et al*[19], 2018	★	★	★	★	★★	★		★	8
Mackenzie *et al*[27], 2018		★	★	★	★	★	★	★	7
Kwak *et al* [25], 2019	★	★	★	★★	★	★	★		8
Schauer *et al*[29], 2019	★	★	★	★	★	★	★	★	8
Bailly *et al* [16], 2020	★	★	★	★	★	★	★	★	8
Tao *et al* [15], 2020	★	★	★	★	★★	★		★	8
Tsui *et al* [31], 2020	★	★	★	★	★	★	★	★	8
Taube *et al* [30], 2021	★	★	★	★	★	★	★	★	8
Aminian *et al*[18], 2022	★	★	★	★	★★	★		★	8
Desai *et al* [22], 2022	★	★	★	★★	★	★	★		8
Hussan *et al*[23], 2022	★	★	★	★	★	★	★	★	8
Khalid *et al*[24], 2022		★	★	★	★★	★	★	★	8
Lazzati *et al*[26], 2022	★	★	★	★	★★	★		★	8

The results of this study demonstrate that bariatric surgery has a significant impact on reducing the risk of colorectal cancer in morbidly obese patients. This aligns with earlier research, underscoring the risk-mitigating effect of bariatric surgery on colorectal cancer in those with obesity. Regarding gender disparities, our study pinpointed a marked decrease in CRC risk in female patients' post-bariatric surgery, potentially stemming from the varying impacts of obesity on colorectal cancer risk between the sexes. Renehan *et al*[34] found that for every 5 kg/m² increase in BMI, the risk of obesity-related colorectal cancer increased by 24% in men and 9% in women. This suggests that female patients might derive greater benefits from bariatric surgery. Regarding the types of bariatric surgery, no significant differences were found between SG and RYGB in reducing the risk of colorectal cancer. This may suggest that both procedures have similar effects on reducing the risk of colorectal cancer in obese patients. In sum, our findings reinforce the beneficial role of bariatric surgery in curtailing the risk of colorectal cancer for morbidly obese individuals, particularly emphasizing its pronounced impact on females. This finding may help clinicians develop more personalized treatment strategies to reduce the risk of colorectal cancer in obese patients. Nonetheless, subsequent studies should delve deeper into the enduring effects of varied bariatric surgical methods and investigate other potential determinants.

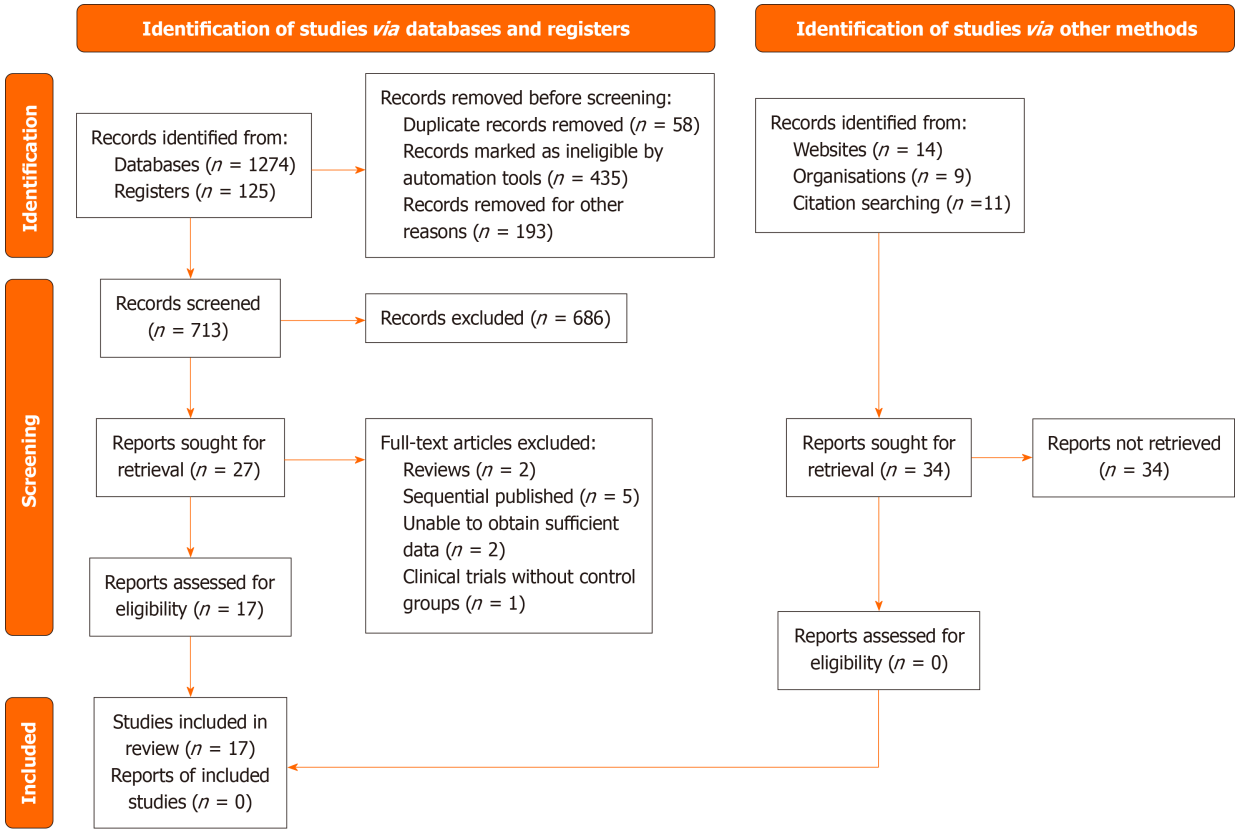

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Figure 1 The PRISMA flowchart illustrates the comprehensive review process.

By elucidating the role of bariatric surgery in reducing the risk of colorectal cancer in morbidly obese patients, this study emphasizes the importance of proactive intervention for obese individuals. Firstly, this research reveals the positive impact of bariatric surgery on reducing the risk of colorectal cancer in obese patients, particularly among female patients. This robustly advocates for the formulation of tailored treatment strategies that cater to individual genders. Secondly, the study found that SG and RYGB have similar effects on reducing the risk of colorectal cancer. This finding helps clinicians make more informed decisions when selecting the most suitable bariatric surgery for obese patients.

Lastly, the results of this study hold significant implications for clinicians and patients. Grasping the influence of bariatric surgery on colorectal cancer risk enables doctors and patients to judiciously evaluate the risks and benefits during treatment planning, facilitating tailored medical interventions for obese patients. This study's findings are pivotal in deciphering risk management for obese patients prone to colorectal cancer, bolstering both the efficacy and personalization of clinical treatments. Subsequent studies should delve deeper into the enduring impacts of varied bariatric surgeries and explore other potential determinants affecting colorectal cancer risk among obese patients.

Data from Hussan *et al*[23] indicates that men have an increased risk of colorectal cancer following weight loss surgery compared to women. In female patients, the risk of CRC decreased following RYGB compared to the control group, but not following SG. Our study found a significant 46% reduction in colorectal cancer risk among female patients, but the incidence rate was not associated with either RYGB or SG weight loss surgery. Bustamante-Lopez *et al*[35] specifically analyzed the impact of bariatric surgery on early-onset colorectal neoplasia, concluding no significant impact of bariatric surgery on Early-Onset Colorectal Cancer risk. In contrast, our study provided a broader perspective, revealing a significant 54% reduction in colorectal cancer risk among morbidly obese patients undergoing bariatric surgery, especially highlighting a 46% risk reduction in females. Research highlighted in Pararas *et al*[36] suggests that type 2 diabetes is a component of metabolic syndrome in morbidly obese patients and is an independent prognostic factor associated with increased colorectal cancer risk. The varying degrees of metabolic improvement and alleviation of type 2 diabetes may be the underlying cause for the differences in colorectal cancer risk among different weight loss surgery types. SG outperformed RYGB in warding off colorectal cancer, suggesting that malabsorptive surgeries exert a gentler effect, which might lead to unfavorable alterations in the colonic and rectal microenvironments. Tao *et al*[15] suggests that alterations in the gut microbiota may play a key role in the initiation and progression of colorectal cancer. It is worth noting that the gut microbiota in RYGB patients shares similarities with that of cancer patients, but our study found no association between RYGB or SG weight loss surgery and the incidence rate.

Recently, Davey *et al*[37] unveiled evidence pointing to a diminished CRC risk following bariatric surgery among obese subjects. Our research aligns with these findings but further expands upon them. We drew from a comprehensive dataset sourced from 17 studies, involving a significant sample size of 12497322 patients. This expansive dataset furnishes a comprehensive perspective on the interplay between bariatric surgery and CRC. Unlike Davey *et al*[37], who solely employed odds ratios, our study incorporates both RR and HR metrics, enhancing the depth of our risk assessment.

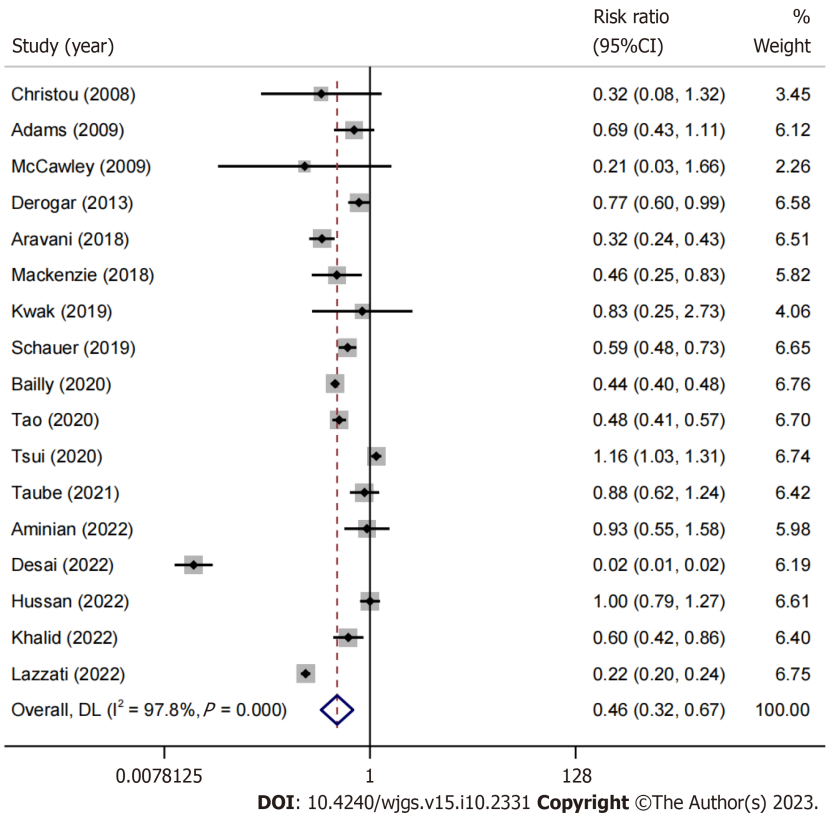

Figure 2 A forest plot contrasting the incidence of colorectal cancer in obese individuals who underwent or did not undergo bariatric surgery.

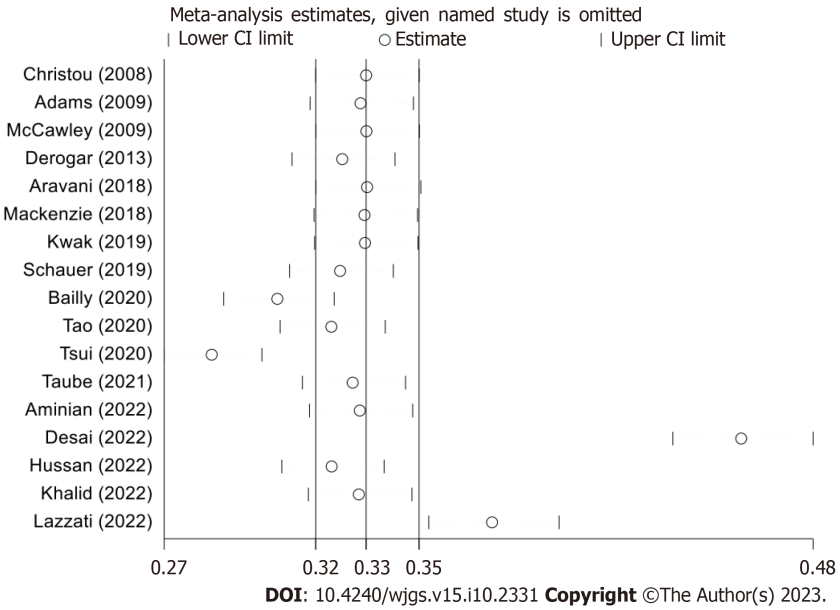

Figure 3 Meta-analysis Estimates (Omitting Named Study).

Additionally, where Davey *et al*[37] focused predominantly on RYGB and SG surgeries, we identified a generalized protective effect of diverse bariatric procedures against CRC. Importantly, our analysis indicates a 46% reduction in CRC risk among female patients, hinting at potential gender-specific mechanisms. Building on the foundational work of Wilson *et al*[38], we delved deeper into the intricacies of the CRC-obesity relationship and the protective role of bariatric interventions. We recognized a significant 46% decrease in CRC risk in females, an aspect less emphasized in previous literature. From a methodological standpoint, our adherence to PRISMA, AMSTAR, and MOOSE standards vouched for the accuracy and reproducibility of our study. In comparison to Pararas *et al*[36], our extensive sample provides further support for the protective association between bariatric surgery and CRC. Our study illuminates the 46% CRC risk

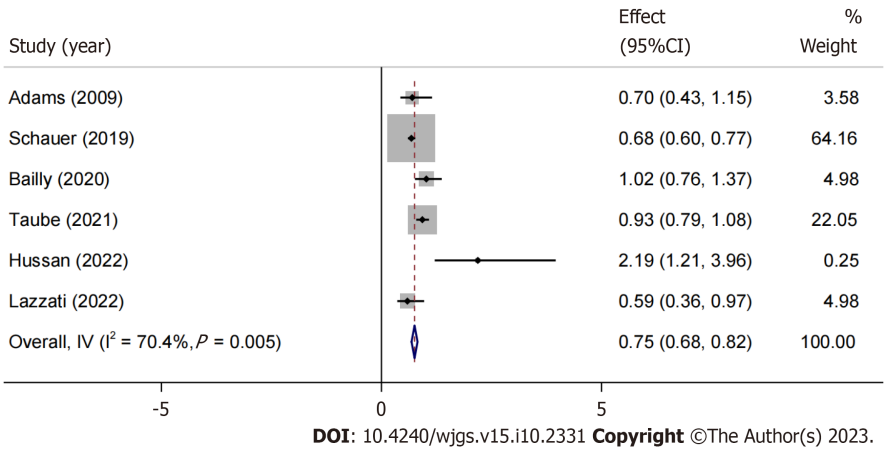

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Figure 4 After sensitivity analysis, an hazard ratio meta-analysis forest plot is created.

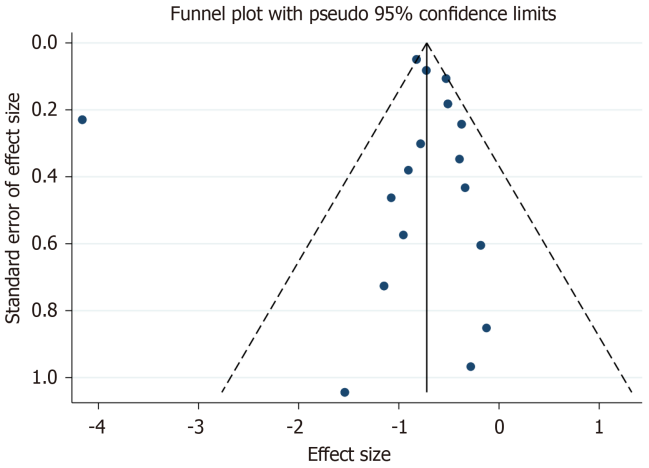

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Figure 5 Funnel plot with pseudo 95% confidence limit.

reduction in females, a perspective not central to Pararas *et al*'s research[36]. Chierici *et al*'s contributions were foundational in our inquiry[39]. We shed light on the global prevalence of CRC in relation to obesity. Our conclusions, backed by our vast sample, distinguish between the risks associated with colon and rectal cancer and underscore the pronounced 46% risk reduction in female patients.

Research by heavy-c2 underscores obesity as a risk factor for colorectal cancer. While some investigations hint at an escalated risk of colorectal cancer post weight loss surgery, the link remains neither significant nor robust. Our study involved 1.2 million participants and employed a population-based cohort research method, studying morbidly obese patients who underwent weight loss surgery in Denmark, Finland, Iceland, Norway, and Sweden between 1980 and 2015. The outcomes failed to offer compelling evidence linking weight loss surgery to a notable increase in rectal cancer risk. This could be attributed to limited sample size, inconsistent data, among other potential reasons. Our findings show that the risk of colorectal cancer significantly decreased during the follow-up period for morbidly obese patients who underwent weight loss surgery. Notably, three of the studies in our analysis exhibited abbreviated follow-up durations. This insinuates a potential limitation in these studies regarding insights into the protracted risk of colorectal cancer. Nevertheless, they provide crucial data regarding immediate risks, which contribute substantially to the overall effect estimate. The aforementioned studies with shorter follow-up durations might introduce some degree of bias. This could slightly overestimate or underestimate the risk of colorectal cancer. However, our sensitivity analysis revealed that omitting these three studies did not result in a significant change in the overall effect size.

Treatments for obesity include lifestyle changes (nutrition education, behavioral counseling, physical exercise), medications, and weight loss surgery for severe obesity. Weight loss surgery is evidenced to markedly trim down enduring weight among severely obese individuals, simultaneously diminishing mortality rates. When studying the relationship between weight loss surgery and cancer incidence, it is challenging to separate the effects of surgery from the multiple associated changes. It is essential to consider that weight loss surgery is more commonly performed in younger individuals, while cancer is more frequently observed in older individuals[40]. Our investigation might not have sufficiently addressed the age distribution variances, potentially affecting our final conclusions. Our study may not have fully considered the time-varying analysis, meaning that the cancer risk in obese patients may change over time during

the follow-up period. Our chief focus was on gauging the impact of weight loss surgery on colorectal cancer risk, sidelining other treatment modalities like lifestyle alterations and medications. Such treatments could influence the colorectal cancer risk and warrant exploration in subsequent studies. Our investigation might not have comprehensively catered to every confounding element, including dietary habits, genetic factors, and environmental influences. These factors may also influence colorectal cancer risk and warrant more detailed consideration in future studies. Chronic inflammation stemming from a compromised barrier can disturb the balance between beneficial and deleterious bacteria in the GI tract, amplifying the likelihood of CRC and T2D onset. Surgery stands as a frontline treatment approach for both primary and metastatic colorectal cancer, whereas probiotics aren't recognized as a viable treatment alternative[41].

CONCLUSION

Weight loss surgery stands validated in its efficacy to curtail weight, mitigate obesity-associated complications, and lower cancer occurrence rates. This meta-analysis confirms the protective effect of weight loss surgery on colorectal cancer through the assessment of RR and HR, particularly in women. Moreover, this assessment was independent of the type of surgery performed. Further research is needed to confirm these findings.

ARTICLE HIGHLIGHTS

Research background

Obesity, with varying global definitions due to body fat disparities between Western and Asian populations, elevates colorectal cancer risk by 7% to 60%. Weight loss surgeries, especially Roux-en-Y laparoscopic gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG), reduce this risk. Our meta-analysis addresses the varying post-surgery outcomes and research gaps from prior studies.

Research motivation

LRYGB and LSG surgeries exhibit potential impacts on colorectal cancer, but current studies show inconsistencies. Our research aims to bridge these gaps, informing clinical choices, shaping policies, and directing future investigations.

Research objectives

To quantitatively analyze the link between obesity and colorectal cancer, assess the impact of LRYGB and LSG surgeries, discern gender-specific risks, and refine methodological approaches in meta-analyses.

Research methods

We conducted a comprehensive search on PubMed, Embase, Web of Science, and Cochrane Library using terms including "obesity," "colorectal cancer," "gastric bypass," and "sleeve gastrectomy." We then assessed the retrieved articles based on the PRISMA-guided the Population, Intervention, Comparison, Outcome, and Study design framework: Population (adults with morbid obesity), Intervention (weight loss surgery), Comparison (observation or other treatments), Outcome (risk of colorectal cancer), and Study design (comparative studies with minimum ten patients/group).

Research results

Analyzing 17 studies with over 12 million patients, we found that bariatric surgery (BS) patients had a 54% reduced colorectal cancer risk. Subgroup insights showed a 46% risk reduction in females post-BS, while male trends were inconclusive. Specific surgical methods like sleeve gastrectomy and RYGB didn't show differential benefits. Rigorous hazard ratio and Newcastle-Ottawa Scale assessments validated our findings, with no detected publication bias. However, distinct outcomes for colon and rectal cancer remained unresolved.

Research conclusions

Bariatric surgery notably lowers colorectal cancer risk, especially in females, irrespective of the surgical type. Our expansive meta-analysis, adhering to rigorous standards, offers a nuanced insight into this relationship.

Research perspectives

Future studies should unravel the mechanisms behind bariatric surgery's protective effect, explore gut microbiota's role, compare surgery types, assess long-term impacts, and consider confounding factors.

FOOTNOTES

Author contributions: Liu YN and Gu JF contributed to the conception of the study; Zhang J and Liu YN contributed significantly to literature search, data extraction, quality assessment, data analyses and manuscript preparation; Xing DY contributed improving the article for language and style and protocol preparation; Gu JF helped perform the analysis with constructive discussions; Wang GQ

revised the manuscript and approved the final version.

Conflict-of-interest statement: The authors Ying-Ning Liu, Jing-Feng Gu, Jian Zhang, Dong-Yang Xing and Gui-Qi Wang all declare that there are no conflicts of interest related to this study.

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

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CASE REPORT

Postpolypectomy syndrome without abdominal pain led to sepsis/septic shock and gastrointestinal bleeding: A case report

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Abstract

BACKGROUND

Postpolypectomy syndrome (PPS) is a rare postoperative complication of colonic polypectomy. It presents with abdominal pain and fever accompanied by coagulopathy and elevated inflammatory markers. Its prognosis is usually good, and it only requires outpatient treatment or observation in a general ward. How-ever, it can be life-threatening.

CASE SUMMARY

The patient was a 58-year-old man who underwent two colonic polypectomies, each resulting in life-threatening sepsis, septic shock, and coagulopathy. Each of the notable manifestations was a rapid drop in blood pressure, an increase in heart rate, loss of consciousness, and heavy sweating, accompanied by shortness of breath and decreased oxygen in the finger pulse. Based on the criteria of organ dysfunction due to infection, we diagnosed him with sepsis. The patient also experienced severe gastrointestinal bleeding after the second operation. Curiously, he did not complain of any abdominal pain throughout the course of the illness. He had significantly elevated concentrations of inflammatory markers and coagulopathy. Except for the absence of abdominal pain, his fever, significant coagulopathy, and elevated inflammatory marker concentrations were all consistent with PPS. Abdominal computed tomography and superior mesenteric artery computed tomography angiography showed no free air or vascular damage. Thus, the diagnosis of colon perforation was not considered. The final blood culture results indicated *Moraxella osloensis*. The patient was transferred to the intensive care unit and quickly improved after fluid resuscitation, antibiotic treatment, oxygen therapy, and blood transfusion.

CONCLUSION

PPS may induce dysregulation of the systemic inflammatory response, which can

lead to sepsis or septic shock, even in the absence of abdominal pain.

Key Words: Postpolypectomy syndrome; Abdominal pain; Sepsis; Gastrointestinal bleeding; Case report

Core Tip: Postpolypectomy syndrome (PPS) is a rare postoperative complication of colonic polypectomy. The prognosis is usually good, and it is characterized by abdominal pain, fever, inflammatory markers, and abnormal coagulation. We report a 58-year-old man who developed life-threatening sepsis or septic shock and gastrointestinal bleeding after colonic polypectomy. Except for the absence of abdominal pain, the patient presented with characteristic PPS symptoms of fever, significant coagulation abnormalities, and elevated inflammatory markers. Final blood culture indicated *Moraxella osloensis*. This case implies that abdominal pain is not a necessary symptom of PPS, and PPS without abdominal pain may progress to life-threatening sepsis and bleeding.

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INTRODUCTION

Postpolypectomy syndrome (PPS) is a rare postoperative complication that occurs several days after colonic polypectomy [1,2]. Patients with PPS may pathologically develop serosal inflammation and coagulopathy because of a transmural burn and focal peritonitis following electrocoagulation of a portion of the bowel wall during polypectomy[3]. Patients with PPS may present with a sudden increase in heart rate (HR), fever, abdominal or lumbosacral pain, and abdominal distention, which makes it similar to bowel perforation, but no perforation occurs. Patients also have significantly elevated concentrations of inflammatory markers and coagulopathy[4]. Despite the good prognosis of most patients, a few patients require admission to the intensive care unit (ICU) because of severe hemodynamic instability. Sepsis is a life-threatening organ dysfunction syndrome because of a disordered immune response after host infection. Septic shock is classified as a subtype of sepsis, defined as the need for a vasopressor to maintain mean arterial pressure (MAP) ≥ 65 mmHg despite adequate volume resuscitation, with serum lactate levels > 2 mmol/L (18 mg/dL) (Sepsis-3 definitions)[5]. We present a unique case of PPS that had no abdominal pain but presented with typical manifestations of sepsis and septic shock with gastrointestinal bleeding. This report was written following the CARE reporting checklist.

CASE PRESENTATION

Chief complaints

A 58-year-old man was admitted to the department of gastrointestinal surgery of our hospital on November 15, 2021 (day 1) for fecal occult blood that had lasted for > 2 mo.

History of present illness

The patient underwent partial endoscopic mucosal resection (EMR) and electrocoagulation electro resection and cold resection for polyps in the cecum and colon under intravenous anesthesia at 16:30 h on November 17, 2021 (day 3). Several broad-based or pedicled polyps with diameters of 0.5-2.0 cm were observed in the cecum, ascending colon, transverse colon, descending colon, and sigmoid colon during the surgery. We removed these polyps by EMR, cold resection, and electrocoagulation and electro resection (Figure 1A and B).

While performing electrocoagulation of the sigmoid polyps, the patient suddenly developed shock, dyspnea, and sweating, and his BP decreased to 79/44 mmHg (MAP 55.67 mmHg), oxygen saturation (SpO_2) decreased to 77%, and HR increased to 133 beats/min at 17:10 h. After aggressive treatment in the ICU, the patient was first referred back to the Department of gastrointestinal surgery on November 18, 2021 (day 4) with stable vital signs and normal coagulation function.

The patient underwent colonoscopy-guided polypectomy under intravenous anesthesia at 16:40 h on November 23, 2021 (day 9). During the colonoscopy, several ulcerative foci scattered in the transverse colon and descending colon, as well as the wound of the first surgery, were observed (Figure 1C). Three 0.8-1.2 cm polyps scattered in the descending colon and sigmoid colon were removed by EMR (Figure 1D), and the wound surface was closed with titanium clips. On awakening from anesthesia after surgery at 17:20 h, his BP suddenly decreased to 76/42 mmHg (MAP 53.33 mmHg), HR increased to 133 beats/min, SpO_2 dropped to 90%, and he had mental irritability.

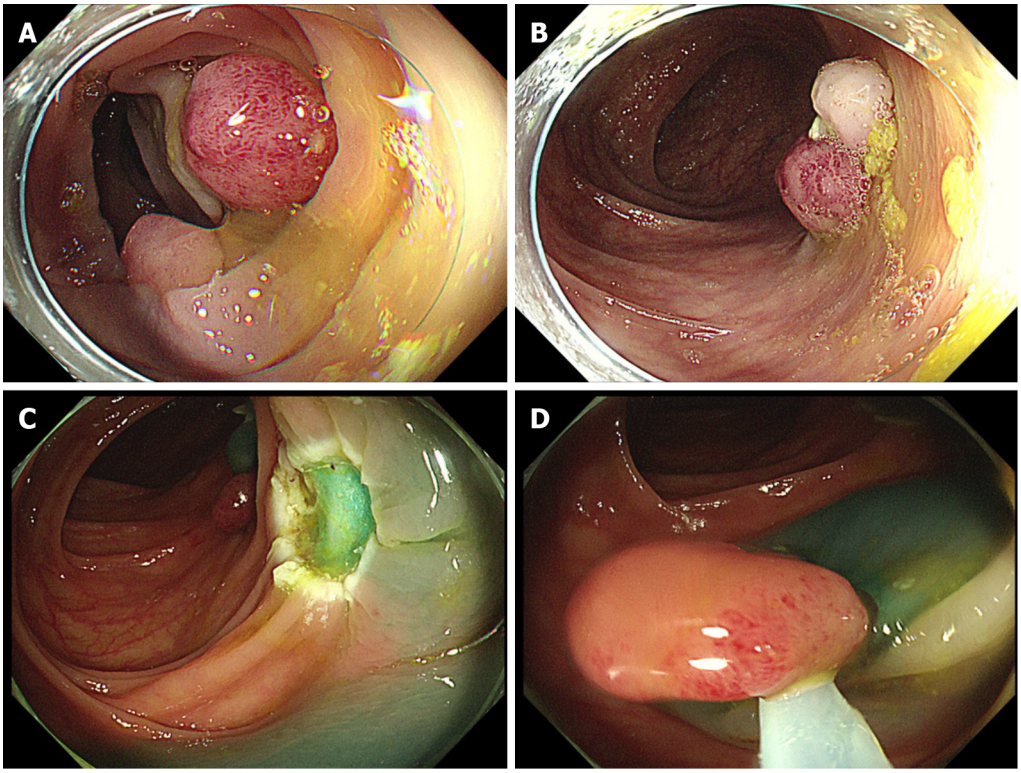

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Figure 1 Clinical findings during colonoscopy. A and B: The first colonoscopy (day 3) showed multiple broad-based or pedicled polyps with diameters ranging from 0.5 to 2.0 cm in the cecum, ascending colon, transverse colon, descending colon, and sigmoid colon; C: The second colonoscopy (day 9) showed multiple ulcerations in the transverse colon and descending colon, which were wounds from the first surgery; D: On the second colonoscopy (day 9), three polyps (0.8-1.2 cm) scattered in the descending and sigmoid colons were removed by endoscopic mucosal resection.

History of past illness

He underwent a gastrectomy in 2002 due to gastric ulcers. In September 2021, he received surgical treatment for oral cancer. In September 2020, he was hospitalized in another hospital for oral cancer, and his fecal occult tests were positive. On September 3, 2020, he underwent painless colonoscopy, and several polyps were found in the colon. No adverse events occurred.

Personal and family history

The patient denied any family genetic history.

Physical examination

Vital signs and physical examination changed rapidly with the disease; refer to the "History of present illness" and "TREATMENT" sections for details.

Laboratory examinations

November 17, 2021 (day 3): Blood gas analysis showed pH 7.33 (normal range: 7.35-7.45), partial pressure of carbon dioxide ($PaCO_2$) 37 mmHg (normal range: 35-45mmHg), partial pressure of oxygen (PaO_2) 211 mmHg (normal range: 60-100mmHg), lactate levels 4.8 mmol/L (normal range: 0.5-1.6 mmol/L), bicarbonate radical concentration 19.5 mmol/L (normal range: 22-26 mmol/L), base excess (BE) 5.8 mmol/L (normal range: -3-3 mmol/L), and potassium ion concentration 2.9 mmol/L (normal range: 3.5-5.0 mmol/L). The PaO_2/FiO_2 was 221 mmHg (normal range: > 300 mmHg). Blood routine results showed a white blood cell (WBC) count 3.29 × 10^9/L (normal range: 3.50 × 10^9-9.50 × 10^9/L), neutrophil percentage 87.8% (normal range: 40%-75%), and platelet count 142 × 10^{12}/L (normal range: 125 × 10^{12}-350 × 10^{12}/L). The concentrations of the infection-related markers were elevated: procalcitonin (PCT) concentration was 1.66 ng/mL (normal range: 0-0.05 ng/mL) and interleukin-6 (IL-6) concentration was > 5000 pg/mL (normal range: 0-7.0 pg/mL). The severe coagulopathy was characterized by a prothrombin time (PT) 36.2 s (normal range: 11.5-14.5 s), international normalized ratio (INR) 3.6 (normal range: 0.8-1.2), prothrombin activity (PTA) 21% (normal range: 80-120%), activated partial thromboplastin time (APTT) 69.1 s (normal range: 28-45 s), fibrinogen concentration < 0.6 g/L (normal range: 2.0-4.0 g/L), fibrin degradation product (FDP) concentration > 360 μg/mL (normal range: 0-5.0 μg/mL), D-dimer concentration > 40 μg/mL (normal range: 0-0.55 μg/mL), and antithrombin (AT) III level 69% normal range: 75%-125%). Blood culture was negative. We found no significant differences in the other laboratory results.

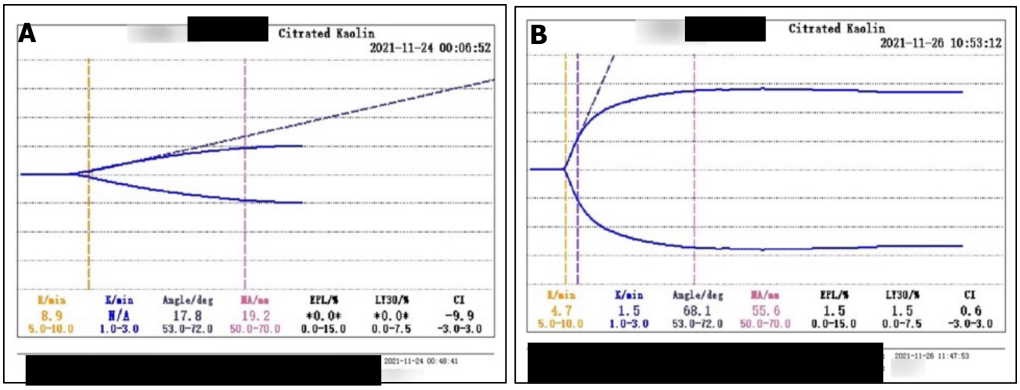

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Figure 2 Thrombelastogram. A: On day 9, the comprehensive coagulation index was -9.9, fibrinogen function α-angle (deg) was 17.8, K-time exceeded the upper limit, and maximum amplitude representing platelet function was 19.2 mm, showing severe coagulation dysfunction; B: On day 9, the indicators returned to normal.

November 23, 2021 (day 9): Blood gas analysis showed pH 7.23, $PaCO_2$ 33 mmHg, PaO_2 149 mmHg, lactate level 7.1 mmol/L, bicarbonate radical concentration 13.8 mmol/L, BE -12.7 mmol/L, and potassium ion concentration 6.5 mmol/L. PaO_2/FiO_2 was 186 mmHg. He also had leukocytosis, elevated concentrations of infection markers, and coagulopathy. His WBC count was 12.38 × 10^9/L, neutrophil percentage was 86.4%, hemoglobin concentration was 84 g/L, platelet count was 192 × 10^{12}/L, PCT concentration was 1.26 ng/mL, and IL-6 concentration was > 5000 pg/mL. The patient progressed to a depletion hypo-coagulable state. His PT was 36.5 s, INR 3.64, PTA 20%, APTT 62 s, fibrinogen concentration < 0.6 g/L, FDP concentrations > 360 μg/ mL, D-dimer concentration > 40 μg/mL, and AT III 65%. Thromboelastography showed a comprehensive coagulation index of -9.9, fibrinogen function α-angle (deg) of 17.8 and K-time exceeding the upper limit, and maximum amplitude (MA) representing the platelet function of 19.2 mm (Figure 2A).

November 25, 2021 (day 11): WBC count was 20.46 × 10^9/L, hemoglobin concentration 62 g/L, PCT concentration 5.72 ng/mL, and platelet count and coagulation function were normal (Figure 2B).

Imaging examinations

November 25, 2021 (day 11): Abdominal computed tomography (CT) and superior mesenteric artery CT angiography showed no intestinal perforation or lumbar lesion (Figure 3), and no vascular damage was observed.

FINAL DIAGNOSIS

November 17, 2021 (day 3)

According to the Sepsis-3 definition, organ dysfunction can be identified as an acute change in total sequential organ failure assessment (SOFA) score 2 points consequent to the infection. The baseline SOFA score can be assumed to be 0 in patients not known to have preexisting organ dysfunction. The patient had a SOFA score of 4 (Respiration 2, Coagulation 1, Cardiovascular 1), combined with an elevated PCT indicating infection, and was therefore diagnosed with sepsis. Based on previous similar cases, we concluded that this patient was consistent with the diagnosis of PPS with sepsis and septic shock.

November 23, 2021 (day 9)

The SOFA score was 5 (Respiration 3, Cardiovascular 2), and elevated PCT and IL-6 indicated infection. It is considered that infection may be associated with endoscopic colonic surgery. Vasoactive drugs are still required to maintain blood pressure after adequate fluid resuscitation. This patient met the diagnostic criteria for septic shock with Sepsis-3.

Blood culture results released on 29 November (samples sent on 23 November) indicated *Moraxella osloensis* (*M. osloensis*). Based on previous similar cases, we concluded that this patient was consistent with the diagnosis of PSS and had sepsis and septic shock.

TREATMENT

November 17, 2021 (day 3)

We discontinued the surgery immediately and gave high-flow oxygen for respiratory support (FiO_2 100%, flow 50 L/min). After fluid resuscitation and oxygen treatment, SpO_2 recovered to 98%. However, the patient was still in shock with no return of consciousness with a BP of 70/45 mmHg (MAP 53.33 mmHg) and HR of 122 beats/min and was transferred

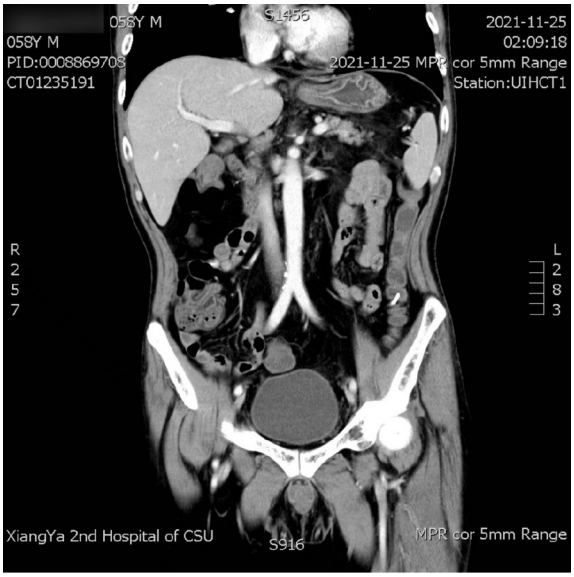

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Figure 3 Abdominal computed tomography and superior mesenteric artery computed tomography angiography. It showed no obvious intestinal perforation or lumbar lesion.

to the ICU at 17:44 h. Fluid resuscitation and volume assessments were performed. At 18:00 h, the patient regained consciousness with no complaints of abdominal pain or abdominal distension. His BP recovered to 115/66 mmHg without administration of vasoactive drugs, and his HR was 115 beats/min, respiratory rate (RR) was 25 breaths/min, SpO_2 was 95% (nasal catheter, 3L/min), and temperature was 38.9 °C. Cefoxitin (2.0 g Q12H for 1 d) was administered intravenously and plasma transfusion and fluid resuscitation were performed immediately.

November 23, 2021 (day 9)

We gave high-flow oxygen for respiratory support (FiO_2 80%, flow 50 L/min). We initially suspected anaphylactic shock and immediately administered antiallergic therapy and fluid resuscitation. At 17:42 h, the patient regained consciousness, but the shock, fever (39 °C), and chills persisted. We transferred him to the ICU at 18:00 h. Even with adequate fluid resuscitation, vasoactive drugs are still required to maintain MAP > 65 mmHg. As before, the patient had no abdominal pain. In addition to these tests, we also performed blood culture.

Antiallergic treatment did not improve the condition of the patient. At 22:00 h, the patient released 200 mL of dark red bloody stools. We administered cefoxitin (2.0 g Q12H for 3 d) intravenously and infused plasma, cryoprecipitate, and red blood cells during fluid resuscitation. His vital signs were stable and gastrointestinal bleeding ceased on November 25, 2021 (day 11).

OUTCOME AND FOLLOW-UP

The patient was discharged on November 26, 2021 (day 12). He said that he would not have polypectomy in the future and thanked us for our timely rescue. The clinical course is summarized in Figure 4.

DISCUSSION

This is a report of a unique case of a patient diagnosed with PPS without abdominal pain. He developed life-threatening sepsis and septic shock and gastrointestinal bleeding. He experienced the above conditions twice and improved rapidly after active antibiotic treatment, fluid resuscitation, and blood transfusion in the ICU.

PPS is a rare complication after colonic polypectomy, with an incidence of approximately 0.14%-2.9%[6,7]. It has also been reported after small bowel polypectomy[8]. PPS can present with local abdominal pain, abdominal muscle tension, rebound pain, and local peritonitis. Some patients also develop fever and leukocytosis within 6 h to 5 d after surgery[9,10]. Organ failure and sepsis are rarely reported[2,3]. The etiology is transmural inflammation, localized peritonitis, and coagulopathy caused by electrical coagulation that burns the local intestinal wall. For colonic polypectomy, PPS occurs when the current passes through the mucosa into the muscularis propria and serosa layer without perforation[11].

Hypertension, large lesions (> 2 cm), and in the ascending colon or cecum, and non-polypoid lesions are independent risk factors for PPS. Hypertension can increase the risk of PPS by three times[7,9,12]. Larger polyps require high amounts of energy and longer duration of electrocoagulation, as well as ligation of more normal mucosa[13]. A meta-analysis showed that the prophylactic use of antibiotics reduces the risk of PPS[14].

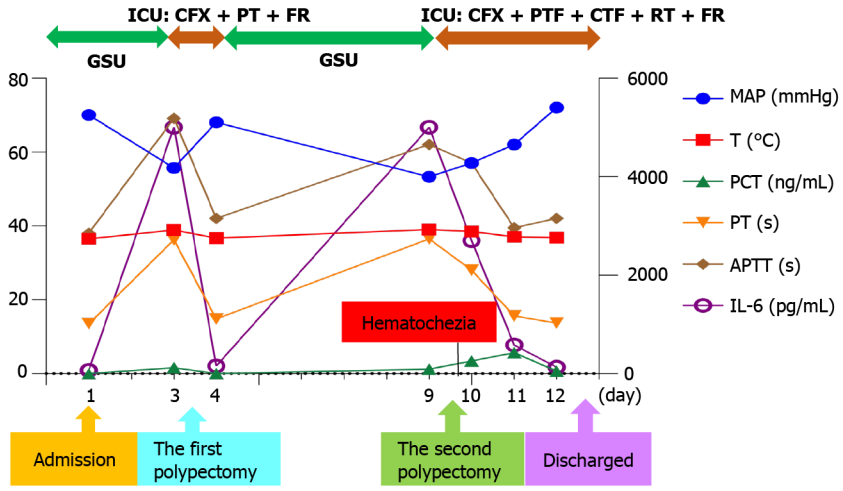

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Figure 4 Clinical course with laboratory results and treatment. GSU: Gastrointestinal surgery unit; ICU: Intensive care unit; CFX: Cefoxitin; PTF: Plasma transfusion; FR: Fluid resuscitation; CTF: Coprecipitation transfusion; RT: Red cells transfusion; MAP: Mean arterial pressure; T: Daily maximum body temperature; PCT: Procalcitonin; PT: Prothrombin time; APTT: Activated partial thromboplastin time; IL-6: Interleukin 6.

PPS shows several features on CT, including severe wall thickening and heterogeneous enhancement patterns, wall defects filled with fluid, surrounding fat infiltration, and the absence of extraluminal air. In addition, colonic segments are usually longer and thicker for PPS than for colon perforations on CT[6]. Patients with perforated colons can have different presentations depending on the location of the lesion. The perforation of a colon segment in the abdominal cavity, such as the mesentery, sigmoid colon, and cecum, is more likely to lead to free air and fluid in the abdominal cavity, while perforations of the ascending colon, descending colon, and rectum are more likely to lead to extraperitoneal air and fluid[9].

The prognosis of PPS is good[7]. Patients usually have pain, fever, and other mild abdominal inflammation symptoms, which disappear within 2-5 d, and they only require outpatient or ordinary infusion and symptomatic treatment. Antibiotic use for Gram-negative and anaerobic pathogens depends on the overall status of the patient[1,7,9,10]. There are few reports that full-thickness burns in patients may progress to delayed perforation and require emergency surgical exploration[12].

There were three noteworthy features of this case. First, shock occurred quickly during or after polypectomy. There were significant leukocytosis, elevated concentrations of inflammatory markers, and coagulopathy. In previous reports, PPS occurred at least 6 h after polypectomy[10]. Secondly, there was no abdominal pain during the course of the disease, which is different from previous reports[1,9,10,12]. Third, systemic inflammation was more severe than local inflammation. CT on the day 3 after the second polypectomy did not show extraluminal air or intestinal wall edema. However, the significantly higher concentrations of inflammatory markers, leukocytosis, shock, and SOFA score indicated a systemic inflammatory response. This case report, however, has one limitation. We did not perform abdominal CT immediately on the day of shock. The condition of the patient was critical, and he needed immediate rescue and could not leave the ICU for a CT scan.

We analyzed the causes of sepsis and septic shock in this patient with PPS as follows. The patient had multiple broad-based polyps, with the largest diameter of 2 cm. Multiple polyps were removed during each polypectomy, resulting in large intestinal mucosal wounds and severe electrocoagulation injuries. Multiple ulcers after polypectomy may facilitate bacterial entry to the circulation and sepsis. Blood culture results released on November 29 (samples sent on November 23) indicated *M. osloensis*. At the time of submitting the blood culture sample, the patient was suffering from a second bout of sepsis and developed septic shock. The Gram-negative aerobic bacterium *M. osloensis* is an opportunistic pathogen, and may cause infection in immunosuppressed adults and non-immunodeficient children[15]. It has previously been reported to cause brain tissue infection in patients with glioma[16]. *M. osloensis* can cause bacteremia in immunodeficient patients[17]. There was also a young patient on long-term peritoneal dialysis who developed diffuse peritonitis. *M. osloensis* was isolated from the peritoneal fluid, and eventually recovered after anti-infective treatment with cefazolin[18]. The patient had a history of oral cancer and was likely to have sepsis due to an opportunistic infection caused by *M. osloensis*. In summary, the patient's symptoms and laboratory results were in line with the diagnosis of local injury and infection of the intestinal wall after colonoscopic polypectomy, leading to bacterial entry into the blood and sepsis, followed by inflammatory storm, coagulation damage and shock. This was a particularly serious and life-threatening case of PPS.

Physicians should be aware of the risk of severe PPS with sepsis and gastrointestinal bleeding after polypectomy. The absence of abdominal pain does not rule out a diagnosis of PPS. At the same time, removing too many polyps at one time should be avoided, and caution should be exercised, given the risk of PPS, when removing polyps at dangerous sites, such as the ascending colon and cecum.

CONCLUSION

Abdominal pain is not a necessary symptom of PPS. PPS without abdominal pain may also lead to life-threatening sepsis and bleeding. When there is severe coagulopathy, it is necessary to stay alert for gastrointestinal bleeding. Physicians should take precautions against sepsis and septic shock caused by PPS. We recommend that patients with severe PPS should be transferred to the ICU for prompt treatment.

FOOTNOTES

Author contributions: Chen FZ and Zhou YY prepared the manuscript; Zhou YY, Ouyang L, and Zhong XL contributed to the clinical observations, material preparation, and image collection; Ouyang L and Zhong XL interpreted the laboratory results and computed tomography images; Chen FZ, Li JX and Zhou YY reviewed the manuscript; all authors contributed to the study conception and design and read and approved the final manuscript.

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CASE REPORT

Three-dimensional computed tomography reconstruction diagnosed digestive tract perforation and acute peritonitis caused by *Monopterus albus*: A case report

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Abstract

BACKGROUND

Few reports have described living foreign bodies in the human body. The current manuscript demonstrates that computed tomography (CT) is an effective tool for accurate preoperative evaluation of living foreign bodies in clinic. The three-dimensional (3D) reconstruction technology could clearly display anatomical structures, lesions and adjacent organs, improving diagnostic accuracy and guiding the surgical decision-making process.

CASE SUMMARY

Herein we describe a 68-year-old man diagnosed with digestive tract perforation and acute peritonitis caused by a foreign body of *Monopterus albus*. The patient pre-sented to the emergency department with complaints of dull abdominal pain, profuse sweating and a pale complexion during work. A *Monopterus albus* had entered the patient's body through the anus two hours ago. During hospitalization, the 3D reconstruction technology revealed a perforation of the middle rectum complicated with acute peritonitis and showed a clear and complete *Monopterus albus* bone morphology in the abdominal and pelvic cavities, with the *Monopterus albus* biting the mesentery. Laparoscopic examination detected a large (diameter of about 1.5 cm) perforation in the mid-rectum. It could be seen that a *Monopterus albus* had completely entered the abdominal cavity and had tightly bitten the mesentery of the small intestine. During the operation, the dead *Monopterus albus* was taken out.

CONCLUSION

The current manuscript demonstrates that CT is an effective tool for accurate preoperative evaluation of living foreign bodies in clinic.

Key Words: Digestive tract perforation; Acute peritonitis; *Monopterus albus*; Three-dimensional computed tomography reconstruction; Case report

Core Tip: Computed tomography (CT) is an effective tool for accurate preoperative evaluation of living foreign bodies in the human body. Three-dimensional (3D) CT reconstruction could clearly display anatomical structures, lesions and adjacent organs, improving diagnostic accuracy. In the present case, preoperative 3D CT reconstruction accurately showed a foreign body located outside the intestinal cavity with a perforation site, and revealed that the foreign body had damaged the mesentery in the small intestine, causing fluid and gas accumulation, as well as peritoneal thickening. These findings indicate preoperative 3D CT reconstruction may accurately locate perforation sites and foreign bodies, help diagnose peritonitis and guide surgical treatment.

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INTRODUCTION

Digestive tract perforation is a common acute abdominal pathology[1,2], often secondary to ulcers, trauma, inflammation, tumors, *etc*. Computed tomography (CT) constitutes an effective tool for accurate preoperative evaluation of foreign bodies in clinic[3]. Preoperative three-dimensional (3D) CT reconstruction accurately locates perforation sites and foreign bodies, helps diagnose peritonitis and guides surgical treatment[4]. In the present case, according to clinical symptoms and signs, combined with plain 3D CT reconstruction, it was determined that the patient had digestive tract perforation, and a *Monopterus albus* had died after entering the abdominal cavity[5]. As a result, the patient's abdominal cavity was seriously polluted, with a large amount of turbid yellow fluid and a small amount of feces attached to several intestinal areas, so it could be determined that the patient had "intestinal perforation" caused by a *Monopterus albus*[6]. The intestinal wall is relatively weak, and may burst out after *Monopterus albus* bites, which easily causes acute diffuse peritonitis [7]. If not timely treated, patients may develop septic shock, which is a serious and life-threatening condition. Surgical removal of foreign bodies, *e.g.*, *Monopterus albus*, is the best treatment method, and preoperative imaging evaluation is particularly important[8]. Living foreign bodies are rarely reported in the literature.

CASE PRESENTATION

Chief complaints

One patient, a 68-year-old man from China, presented to the hospital's emergency department after suffering from dull abdominal pain, profuse sweating and a pale complexion during the two-hour workday.

History of present illness

Symptoms started 2 h before presentation with complaints of dull abdominal pain, profuse sweating and a pale complexion during work.

History of past illness

The patient didn't have any remarkable history.

Personal and family history

The patient denied having a family history of any malignant tumors.

Physical examination

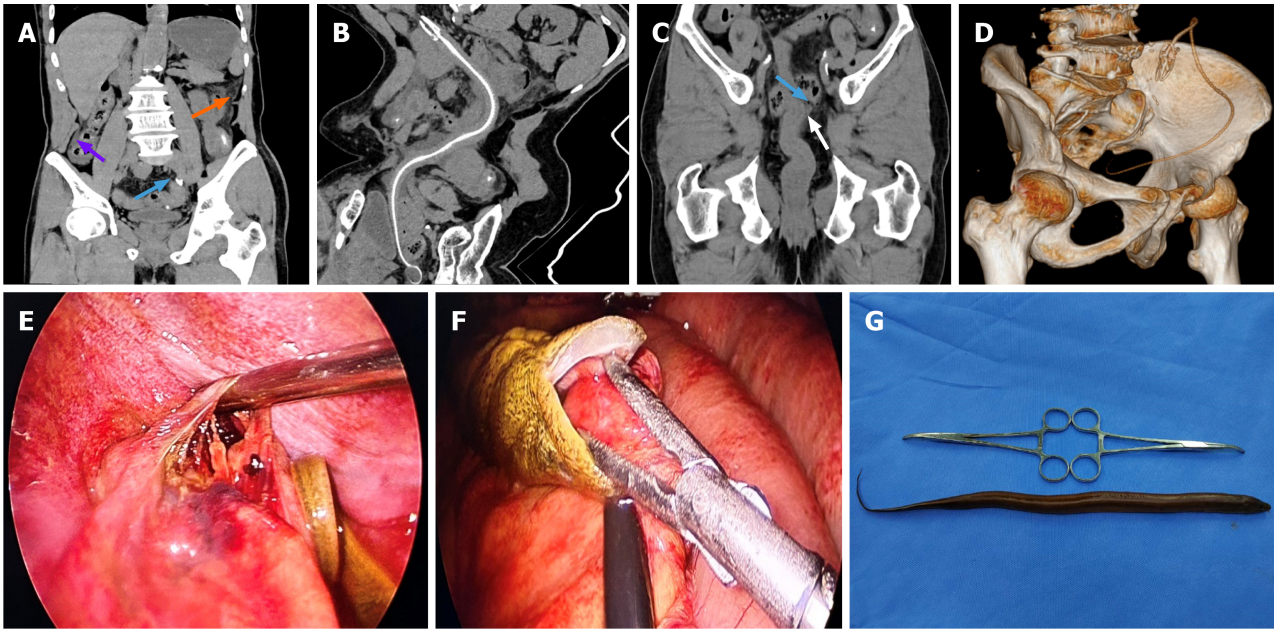
Using a physical examination, the results showed the following vital signs: Blood pressure, 118/69 mmHg; body temperature, 36.4 °C; heart rate, 81 beats/min; respiratory frequency, 18 breaths/min. Furthermore, total abdominal tenderness, plate-like abdomen, and liver dullness disappeared, with weak abdominal breathing and bowel sounds.

Table 1 Laboratory data at admission

Parameter	Value (admission)	Reference value	Unit
N-terminal-pro B-type natriuretic peptide	80	0-125	pg/mL
Urea	3.7	2.5-6.1	mmol/L
Creatinine	58	46-92	μmol/L
Troponin	< 0.01	0-0.04	ng/mL
Myoglobin	111.1	0-120	ng/mL
Carcinoembryonic antigen	4.5	0-5.0	ng/mL
Carbohydrate antigen 19-9	< 3	0-27	U/mL
Alpha-fetoprotein	3.2	0-7.000	ng/mL
Creatine kinase	102.2	30-135	U/L
Creatine kinase MB isoenzyme	11.3	0-16	U/L
Lactic dehydrogenase	145.88	120-246	U/L
D-dimer	0.28	0-0.5	μg/mL
White blood cell	9.10	4-10	10^9/L
Platelet	140	125-350	10^9/L
Hemoglobin	119	110-150	g/L
Alanine aminotransferase	18.28	5-40	IU/L
Aspartate aminotransferase	15.44	8-40	IU/L
Total bilirubin	16.48	5-21	μmol/L
Direct bilirubin	3.26	0-3.4	μmol/L
Indirect bilirubin	13.12	1.6-21	μmol/L
Albumin	42.73	35-52	g/L
Total cholesterol	3.67	3.0-5.7	mmol/L
Low density lipoprotein cholesterol	3.65	< 4.13	mmol/L
High density lipoprotein cholesterol	1.86	1.29-1.55	mmol/L
Fasting blood glucose	4.44	3.9-6.1	Mmol/L
Urinary protein	negative	negative	-
Hepatitis B surface antigen	0	< 0.05	IU/mL
Antibody to hepatitis C	6.04	< 1	S/CO
Immunodeficiency virus antigen and antibody	0.09	< 1	S/CO
Antibody to treponema pallidum	0.07	< 1	S/CO
Hepatitis C virus RNA	0	0	IU/mL
Anti-nuclear antibodies	negative	negative	-
Anti-cyclic citrullinated peptide antibody	13.89	< 25	RU/mL
Anti-cardiolipin antibody	2.23	0-12	RU/mL
Blood ammonia	22	9-30	μmol/L
Erythrocyte sedimentation rate	15	0-20	mm/h

Laboratory examinations

Laboratory tests showed normal liver function, alpha-fetoprotein, carbohydrate antigen 19-9, and carcinoembryonic antigen. No abnormality was found in routine blood and urine analyses. Primary laboratory data upon admission are summarized in Table 1.



DOI: 10.4240/wjgs.v15.i10.2351 **Copyright** ©The Author(s) 2023.

Figure 1 Imaging and laparoscopic exploration. A: Computed tomography (CT) with multi-plane reconstruction revealed scattered exudation, peritoneal thickening (orange arrow), peritoneal effusion (purple arrow), and free gas (blue arrow) in the abdominal cavity, suggesting gastrointestinal perforation complicated with acute peritonitis; B: Curved planar reconstruction (CPR) of CT images showed an abdominal *Monopterus albus* that has bitten the mesentery, indicating a foreign body outside the intestinal cavity; C: CPR of CT images revealed rough and raised outer margin of the wall of the mid-rectum (white arrow), as well as exudation and free gas in the surrounding mesentery (blue arrow), indicating a perforation in the mid-rectum; D: Volume reconstruction revealed clear and complete *Monopterus albus* bone morphology in the abdominal and pelvic cavities; E: Laparoscopic exploration revealed a large perforation in the mid-rectum, with a diameter approximating 1.5 cm; F: Laparoscopic exploration showed the *Monopterus albus* has perforated the mesentery of the small intestine; G: During the operation, the dead *Monopterus albus* was taken out, with a length of about 40 cm.

Imaging examinations

CT with multi-plane reconstruction revealed scattered exudation, effusion and free gas in the abdominal cavity, indicating gastrointestinal perforation complicated with acute peritonitis (Figure 1A). Curved planar reconstruction of CT images revealed an abdominal *Monopterus albus* biting the mesentery, suggesting a *Monopterus albus* outside the intestinal cavity (Figure 1B). The outer margin of wall of the mid-rectum was rough and raised, and exudation and free gas were detected in the surrounding mesentery, suggesting a perforation of the mid-rectum (Figure 1C). Volume reconstruction of CT images showed clear and complete eel bone morphology in the abdominal and pelvic cavities (Figure 1D).

Further diagnostic work-up

The patient consented to laparoscopic surgery. Laparoscopic exploration revealed abundant cloudy yellow fluid and small amounts of feces-like fluid in the abdominal and pelvic cavities, and a large perforation was detected in the mid-rectum, with a diameter approximating 1.5 cm (Figure 1E), alongside a small amount of stool. It could be observed that the *Monopterus albus* has completely entered the abdominal cavity and has tightly bitten the mesentery of the small intestine (Figure 1F). During the operation, the dead *Monopterus albus* was extracted, and was about 40 cm long (Figure 1G).

FINAL DIAGNOSIS

Based on the patient's previous medical history, the patient was eventually diagnosed with digestive tract perforation and acute peritonitis.

TREATMENT

Postoperatively, the patient recovered well and was discharged on postoperative 5 d.

OUTCOME AND FOLLOW-UP

The patient recovered without complications.

DISCUSSION

Few reports have described living foreign bodies in the human body[9]. CT constitutes an effective tool for accurate preoperative evaluation of living foreign bodies in clinic[3]. 3D CT reconstruction clearly displays anatomical structures, lesions and adjacent organs, improving diagnostic accuracy[6]. In the present case, preoperative 3D CT reconstruction accurately located a *Monopterus albus* outside the intestinal cavity with a perforation site, and the foreign body had damaged the mesentery in the small intestine, causing fluid and gas accumulation, as well as peritoneal thickening[5]. These findings suggest preoperative 3D CT reconstruction may accurately locate perforation sites and foreign bodies, help diagnose peritonitis and guide surgical treatment[4].

CONCLUSION

Preoperative 3D CT reconstruction can accurately locate perforation sites and living foreign bodies, help diagnose peritonitis and guide surgical treatment.

FOOTNOTES

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CASE REPORT

Gastric adenosquamous carcinoma with an elevated serum level of alpha-fetoprotein: A case report

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Abstract

BACKGROUND

Gastric adenosquamous carcinoma (ASC) is rare and characterized by coexisting of adenocarcinoma andsquamous carcinoma within the same tumor. We present a female patient with gastric ASC who had an elevated serum level of alpha-fetopro -tein (AFP), which decreased to normal levels after a laparoscopic distant radical gastrectomy in a short period. The clinicopathological features in AFP-producing gastric cancer (GC) are discussed, as well as potentially available prognostic predi -ctors.

CASE SUMMARY

A 50-year-old woman presented to our department with a chief complain of a 6-mo history of bloating. She had no basic diseases including heart diseases and respiratory diseases, and she also denied any prior history of dysphagia, hematemesis, melena, rectal bleeding, hematochezia, or unintentional weight loss. Based on her symptoms, an esophagogastroduodenoscopy was performed, showing an annular cavity lesion 3 cm from the pylorus with a diameter of 6 cm. A biopsy of the lesion showed gastric ASC, whereas the pylorus biopsy showed normal mucosa. The patient further received an enhanced computed tomography scan which demonstrated an invasive lesion close to the pylorus with a still clear margin of the tumor to peripheral organs such as the pancreas and liver. Scattered lymph nodes were visible around, whereas no sign of liver metastasis was discovered. Serum tumor markers including carcinoembryonic antigen (CEA), cancer antigen 199 (CA199), CA724, CA125, and CA242 were all normal, while the level of serum AFP increased to 172 ng/mL. A laparoscopic distant radical gastrectomy was performed after exclusion of surgical contraindications. Postoperative pathology

results showed that the tumor displayed an ulcerated ASC phenotype (90% of medium to highly-differentiated squamous cell carcinoma, 10% of poorly differentiated adenocarcinoma. Surprisingly, the serum level of AFP decreased to normal level on post operation day 5. The tumor cells were positive for CK5/6, p63, and CEA, and negative for AFP and Epstein-Barr encoding region.

CONCLUSION
We presented a rare case of gastric ASC with elevated serum AFP level, which may be new subtype of AFP-producing GC. Follow-up detection of serum AFP might be a useful tool to predict patient prognosis.

Key Words: Gastric cancer; Gastric adenosquamous carcinoma; Alpha-fetoprotein; Case report

Core Tip: Most patients diagnosed with gastric cancer (GC) have a pathological phenotype of adenocarcinoma, and gastric adenosquamous carcinoma (ASC) is rare. We presented a rare case of gastric ASC with elevated serum alpha-fetoprotein (AFP) level, which may be new subtype of AFP-producing GC. AFP-GC is an aggressive cancer with high incidence of liver or lymph node metastasis. Follow-up detection of serum AFP might be a useful tool to predict prognosis.

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INTRODUCTION

It is well known that gastric cancer (GC) is the fourth most common cancer worldwide with a third highest incidence and mortality in China[1]. With a change in population structure and population growth, it is also suggested that the incidence of GC has increased by 25% between 2007 and 2017[2]. 1 in 78 women and 1 in 33 men developed GC over a lifetime[2]. Most patients diagnosed with gastric carcinoma had a pathological phenotype of adenocarcinoma which has been studied well over the last decades, and National Comprehensive Cancer Network guidelines also present a detailed management strategy for GC with a adenocarcinoma phenotype. However, there also exist other histological types of gastric carcinoma including primary gastric squamous cell carcinoma, carcinoid, and primary adenosquamous carcinoma (ASC) which is characterized by coexisting of adenocarcinoma and squamous carcinoma within the same tumor. Gastric ASC is rare and clinical features of ASC were described largely in case reports or case series.

CASE PRESENTATION

Chief complaints

A 50-year-old woman presented to our department with a chief complain of a 6-mo history of bloating.

History of present illness

Symptoms started 6-mo before presentation.

History of past illness

She had no basic diseases including heart diseases, respiratory diseases, active or chronic hepatits, liver cirrhosis, and she also denied any prior history of dysphagia, hematemesis, melena, rectal bleeding, hematochezia, or unintentional weight loss.

Personal and family history

The patient denied any family history of malignant tumors.

Physical examination

On physical examination, the vital signs were as follows: Body temperature, 36.7 °C; blood pressure, 125/76 mmHg; heart rate, 78 beats per min; respiratory rate, 18 breaths per min. Furthermore, the abdomen is flat without touching any lumps, without tenderness, rebound pain, or muscle tension. Digital anal examination was not performed.

Laboratory examinations

Serum tumor markers including carcinoembryonic antigen (CEA), cancer antigen 199 (CA199), CA724, CA125, and CA242 were all normal, while the level of serum alpha-fetoprotein (AFP) increased to 172 ng/mL. Liver function indicators and pathogenic tests were all normal.

Imaging examinations

The patient further received an enhanced computed tomography scan which demonstrated an invasive lesion close to the pylorus with a still clear margin of the tumor to peripheral organs such as the pancreas and liver (Figure 1). Scattered lymph nodes were visible around, whereas no sign of liver metastasis was discovered.

FINAL DIAGNOSIS

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

TREATMENT

A laparoscopic distant radical gastrectomy was performed after exclusion of surgical contraindications.

OUTCOME AND FOLLOW-UP

Postoperative pathology results showed that the tumor displayed an ulcerated ASC phenotype, 90% of medium to highly-differentiated squamous cell carcinoma, 10% of poorly differentiated adenocarcinoma (Figure 2A) and metastatic lymph nodes (Figure 2B). Surprisingly, the serum level of AFP decreased to normal level on post operation day 5. The tumor cells were positive for CK5/6, p63, and CEA, and negative for AFP (Figure 2C) and Epstein-Barr encoding region.

DISCUSSION

In this case report, we presented a female patient with gastric ASC who had an elevated serum level of AFP. Although immunohistochemistry staining results for AFP protein in tumor tissues were negative, serum AFP level decreased to normal level after a laparoscopic distant radical gastrectomy in a short period. Therefore, it is possible that gastric ASC in our patient may be accompanied with or even produces soluble AFP. As far as we know, this is the first case of gastric ASC with elevated AFP level partly due to a very low incidence of gastric ASC, which was suggested to account for less than 1% of all gastric malignancies[3]. The whole story of gastric ASC has not been fully elucidated and only two case series with a total of 287 cases summarized clinicopathological features of gastric ASC[4]. The diagnosis of gastric ASC is supported by the presence of both actinic cheilitis (AC) and ASC components with squamous cell carcinoma (SCC) accounting for at least 25% of tumors. In our case, SCC component accounted for approximately 90% of tumor. In addition, the location of tumor in our case was close to pylorus instead of cardia or esophagus, which was in consistent with previous studies showing the most common location of lower third for gastric ASC[4]. No evidence of other AC or SCC was found elsewhere in the body which further confirmed the diagnosis of gastric ASC for our case.

It was suggested that gastric ASC was an extremely aggressive cancer and distant metastasis was usually found, with liver being the most common location for distant metastasis[3,4]. Detailed analysis showed that both AC and SCC components were capable for distant metastasis. The T stage in our case was T4 which was inconsistent with previous study showing that 52.7% cases were stage T4. Lymph node metastasis also occurred in our case with AC component but not SCC component found in metastatic lymph nodes. It is interesting that AC component in our case only accounted for 10% of the tumor but played a predominant role in lymph node metastasis.

Radical resection of tumor remains the optimal treatment for patients without distant metastasis, and the following adjuvant therapy has not been established. Whether to choose chemotherapy or radiotherapy or a combination largely depends on the predominant component presented in gastric ASC. Due to personal reason, this patient refused to receive to any further chemotherapy or radiotherapy. The prognosis of gastric ASC was worse than typical gastric AC with a low 3-year overall survival ranging from 15.4%-32.4%[3-5]. The patient in this report died one year after operation.

Based on the change of serum AFP in this patient before and after operation, we speculated that gastric ASC in this patient may be a new subtype of AFP-producing GC (AFPGC). Commonly, increased serum level of AFP could be seen in AFPGC or in hepatoid adenocarcinoma of the stomach (HAS). AFPGC is defined as primary GC with serum AFP level more than 20 ng/mL or positive immunohistochemistry staining of AFP in the tumor. The diagnosis of HAS is mainly dependent on the pathological character of hepatocellular carcinoma-like differentiation of GC. We didn't find any proof of HAS in our case and the biological behavior in our case also partly matched those found in AFPGC. The most common location of AFPGC was gastric antrumand corpus[6], and the serum level of AFP predicted the 5-year overall survival[7]. AFPGC is also an aggressive cancer with high incidence of liver or lymph node metastasis[7]. We identified an elevation of serum AFP 6 mo after surgery in this patient, and the level of AFP remained high 3 mo before his death. No evidence

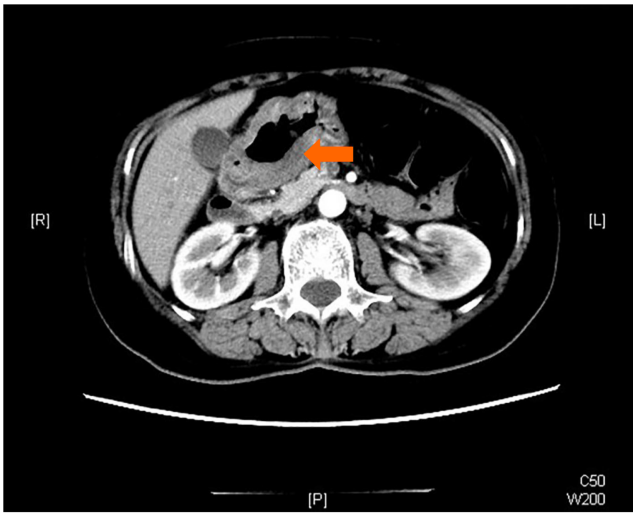

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Figure 1 Enhanced computed tomography examination of the abdomen. Invasive lesion close to the pylorus can be seen, and the edges between the tumor and peripheral organs such as the pancreas and liver are still clear (arrow).

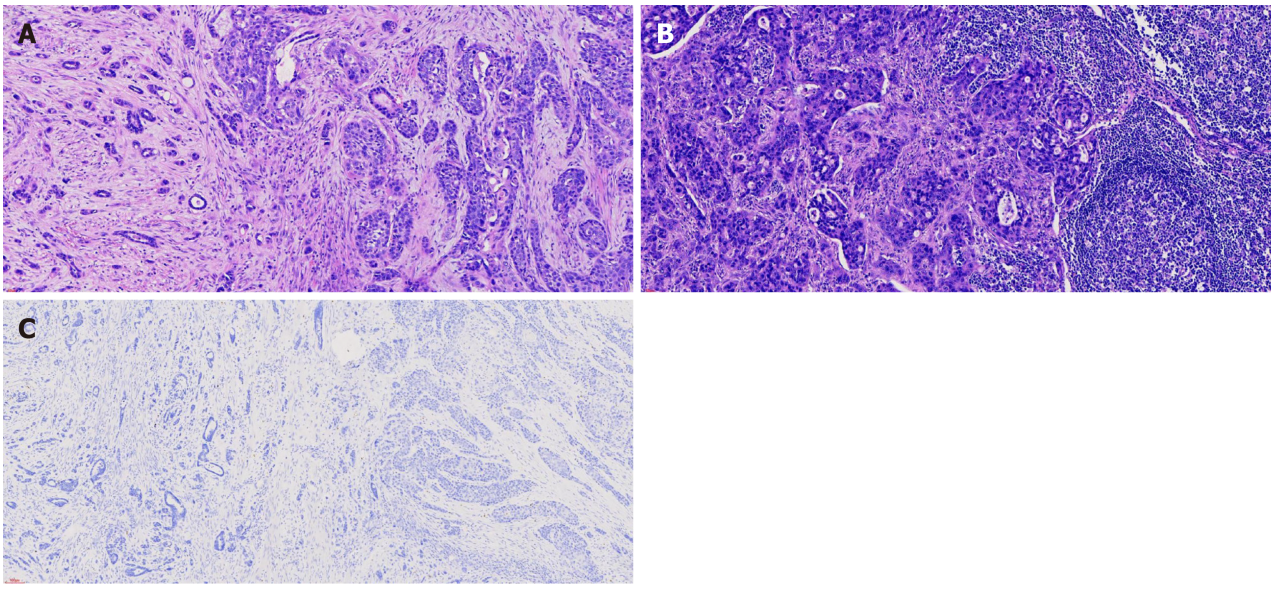

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Figure 2 Histopathological analysis and immunohistochemical examination. A and B: Histopathological analysis and immunohistochemical examination of the resected specimen. Gastric adenosquamous carcinoma (20 ×), lymph node metastasis (20 ×); C: Immunohistochemistry staining for alpha-fetoprotein (AFP) of the resected specimen. Immunohistochemistry staining for AFP (10 ×).

of liver metastasis was identified during the follow-up period.

CONCLUSION

In conclusion, we presented a rare case of gastric ASC with elevated serum AFP level, which may be new subtype of AFP-producing GC. Follow-up detection of serum AFP might be a useful tool to predict patient prognosis.

FOOTNOTES

Author contributions: Sun L and Wei JJ contributed equally to this work, contributed to the conceptualization and writing-original draft; An R, Cai HY, Li T, Lv Y and Shen XF provided technical support for the staining of the sections and performed standard pathologic analysis; Du JF and Chen G involved in the writing-review and editing; the work reported in the article has been performed by the

authors, unless clearly specified in the text; and all authors read and approved the final manuscript.

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CASE REPORT

Mucocutaneous ulcer positive for Epstein–Barr virus, misdiagnosed as a small bowel adenocarcinoma: A case report

Ji Hyeong Song, Ji Eun Choi, Jin Soo Kim

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Abstract

BACKGROUND

Epstein–Barr virus (EBV)-positive mucocutaneous ulcers (MCUs) are an uncommon disorder characterized by ulcerative lesions in the skin, oral cavity or gastrointestinal tract in patients with iatrogenic or aging-induced immunosuppression. The nonspecific lesions are difficult to differentiate from small bowel adenocarcinomas. We present the case of a 69-year-old woman who was initially misdiagnosed with a small bowel adenocarcinoma but was later surgically diagnosed with and treated for EBV-MCU. Through this case, we aim to emphasize the importance of accurately distinguishing between the two conditions.

CASE SUMMARY

The patient presented with an incidental finding of a small bowel tumor during computed tomography (CT) examination performed for hematuria. The CT scan showed irregular thickening of the distal ileum, which was suggestive of a malignant small bowel tumor. An exploratory laparotomy revealed an 8-cm mass in the distal ileum; thus, a segment of the small intestine, including the mass, was resected. Histopathological analysis revealed an ulceroinfiltrative mass-like lesion with luminal narrowing, marked inflammatory cell infiltration, and large atypical lymphoid cells (positive for EBV-encoded small RNA). A final diagnosis of an EBV-MCU was established. The postoperative course was uneventful, and the patient was discharged on postoperative day 7. The patient remained recurrence-free until 12 mo after surgery.

CONCLUSION

This case highlights the diagnostic challenges for EBV-MCUs and emphasizes the importance of comprehensive evaluation and accurate histopathological analysis.

Key Words: Epstein–Barr virus; mucocutaneous ulcer; Misdiagnosis; Small bowel adenocarcinoma; Surgery; Case report

Core Tip: We report a case that highlights the diagnostic challenges of distinguishing an Epstein–Barr virus-mucocutaneous ulcer from a small bowel adenocarcinoma in a 69-year-old woman. It emphasizes the importance of performing comprehensive evaluation and accurate histopathological analysis to guide appropriate management. Awareness of this rare entity is crucial for its timely diagnosis and prevention of unnecessary invasive procedures.

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INTRODUCTION

Epstein–Barr virus (EBV)-positive mucocutaneous ulcer (MCU) is an uncommon disorder characterized by ulcerative lesions in the skin, oral cavity, or gastrointestinal (GI) tract. Previous reports have revealed that EBV-MCU is primarily associated with drug-induced immunosuppression or age-related immunosenescence[1]. Most cases of EBV-MCU respond well to conservative treatment, such as reduction of immunosuppressive drugs; surgical resection is required in only a minority of cases[2].

However, EBV-MCU diagnosis is challenging due to the nonspecific nature of the ulcerative lesions, which makes it difficult to distinguish from other tumorous conditions (such as small bowel adenocarcinoma). Small bowel adenocarcinoma is rare, accounting for ~3% of all GI cancers[3]. The rarity of cases and the presence of nonspecific symptoms often pose a challenge to achieving early and accurate diagnosis[4]. The complex etiology and histopathological heterogeneity of small bowel adenocarcinoma further contribute to the difficulty in establishing a definitive diagnosis[5].

A diagnostic challenge arises when EBV-MCU occurs in the GI tract, thereby mimicking small bowel adenocarcinoma. Potential misdiagnosis may subject patients to unnecessary invasive procedures or inappropriate treatment. Thus, both conditions must be differentiated to ensure appropriate management. In this case report, we present a rare case of surgically diagnosed and treated EBV-MCU that was initially misdiagnosed as small bowel adenocarcinoma. By highlighting this case, we aim to raise awareness of the importance of accurately distinguishing between these two conditions to ensure effective management and prevent potential harm to the patients.

CASE PRESENTATION

Chief complaints

A 69-year-old woman presented with hematuria during routine screening.

History of present illness

Computed tomography (CT) urography was performed at the Department of Nephrology. Incidentally, a small bowel tumor was detected on the CT scan, prompting a referral to our department.

History of past illness

The patient had no other underlying diseases, except for hypertension, and did not complain of GI symptoms (such as nausea, vomiting, or abdominal pain). There was no history of previous pulmonary tuberculosis.

Personal and family history

The patient had no relevant family history.

Physical examination

A physical examination revealed normoactive bowel sounds, no abdominal distention, and no prominent tenderness. The vital signs were as follows: blood pressure, 141/86 mmHg; pulse rate, 70 beats/min; respiratory rate, 18 breaths/min; and body temperature, 36.2°C.

Laboratory examinations

Laboratory tests indicated anemia, with the following findings: hemoglobin, 9.2 g/dL (reference: 12–16 g/dL); mean corpuscular volume, 87.8 fL (reference: 80–100 fL); mean corpuscular hemoglobin, 29.8 pg (reference: 26–38 pg); serum

iron, 82 μg/dL (reference: 29–164 μg/dL); ferritin, 116 ng/mL (reference: 13–150 ng/mL); and unsaturated iron binding capacity, 135 μg/dL (reference: 191–269 μg/dL). Tumor markers, namely carcinoembryonic antigen and carbohydrate antigen 19-9, were within their normal limits (0.697 ng/mL and 3.8 U/mL, respectively). No other abnormalities were noted.

Imaging examinations

A CT scan revealed irregular thickening of the distal ileum, which caused proximal small bowel dilatation, and several enlarged lymph nodes in the mesentery and preaortic area (Figure 1). These findings suggested the presence of a malignant small bowel tumor with lymph node metastasis. No findings indicative of GI bleeding were observed during an endoscopic evaluation.

FINAL DIAGNOSIS

The resected specimen was analyzed histopathologically. Grossly, the specimen showed a single ulcerative lesion with luminal obstruction, and the adjacent mucosa was edematous (Figure 2A). Microscopically, the mucosal surface showed ulceration with the formation of granulation tissue formation and marked inflammatory cell infiltration in all the layers of the colon wall; the inflammatory cells comprised a variable number of lymphocytes, plasma cells, eosinophils, and neutrophils, as well as a small number of large atypical lymphoid cells (Figure 2B and 2C). Immunohistochemical analyses revealed that these lymphoid cells were B cells with CD20 and CD30 positivity (Figure 2D and 2E). *In situ* hybridization further revealed that these cells were also positive for EBV-encoded small RNA (Figure 2F). No evidence of definite malignancy or tuberculosis was noted. Thus, a final diagnosis of EBV-MCU was established.

TREATMENT

An exploratory laparotomy was performed for definitive diagnosis and treatment. During surgery, a mass of ~8 cm was identified at the distal ileum, 30 cm from the ileocecal valve. A 50-cm segment of the small intestine (including the mass) was resected, and D2 lymphadenectomy was performed. Anastomosis was performed using the hand-sewn method. The resected specimen showed a 7 cm × 4.5 cm ulceroinfiltrative mass-like lesion with luminal narrowing.

OUTCOME AND FOLLOW-UP

The patient had an uneventful postoperative course, and was discharged on postoperative day 7. The patient remained recurrence-free until 12 mo after surgery.

DISCUSSION

EBV-MCU was first identified as a B-cell lymphoproliferative disorder in 2010 by Dojcinov *et al*[1]. They reported a series of 26 EBV-MCU cases involving the oropharyngeal mucosa, skin, and GI tract; these were associated with drug-induced immunosuppression or age-related immunosenescence. Since then, several cases have been reported, and the 2016 World Health Organization classification recognized the condition as a newly identified entity[6]. Based on the absence of immunosuppression in the present case, the patient was considered to have developed EBV-MCU due to age-related immunosenescence.

A review by Sinit *et al*[2] discussed the first 100 reported cases of EBV-MCU, which revealed that the most commonly affected site was the oropharyngeal mucosa, followed by the GI tract and skin. The treatments administered included reduction of immunosuppressive drugs, systemic therapy, radiotherapy, and surgical resection in 50, 22, 10, and six cases, respectively. Only one of the six surgically treated cases involved the GI tract[7]. Only two out of the 100 small intestinal cases did not require surgical treatment. Conversely, the present case involved surgical resection of a tumorous lesion in the small intestine, which was initially misdiagnosed as small bowel adenocarcinoma but subsequently confirmed to be EBV-MCU through histopathological analysis.

Ishikawa *et al*[8] summarized 30 reported cases of EBV-MCUs involving the GI tract. The large intestine was the most commonly affected site, while the small intestine was only involved in three cases. Surgical treatment was undertaken in 10 of the 30 cases. Our case, however, presented with EBV-MCU-induced intestinal obstruction that required surgery; this is consistent with the findings reported by Morita *et al*[7]. Nonetheless, preoperative endoscopic access was challenging due to the location of the lesion in the small intestine. To the best of our knowledge, the present case is the first reported instance of an EBV-MCU causing small intestinal obstruction and necessitating surgical treatment.

For EBV-MCU, the pivotal aspect in clinical practice is its accurate differentiation from other related conditions, such as small bowel adenocarcinoma or intestinal tuberculosis. This differentiation hinges upon comprehensive assessment of the clinical manifestations and imaging features, which enables precise diagnosis and development of tailored treatment strategies. EBV-MCUs frequently emerge in immunocompromised patients, especially those receiving immunosup-

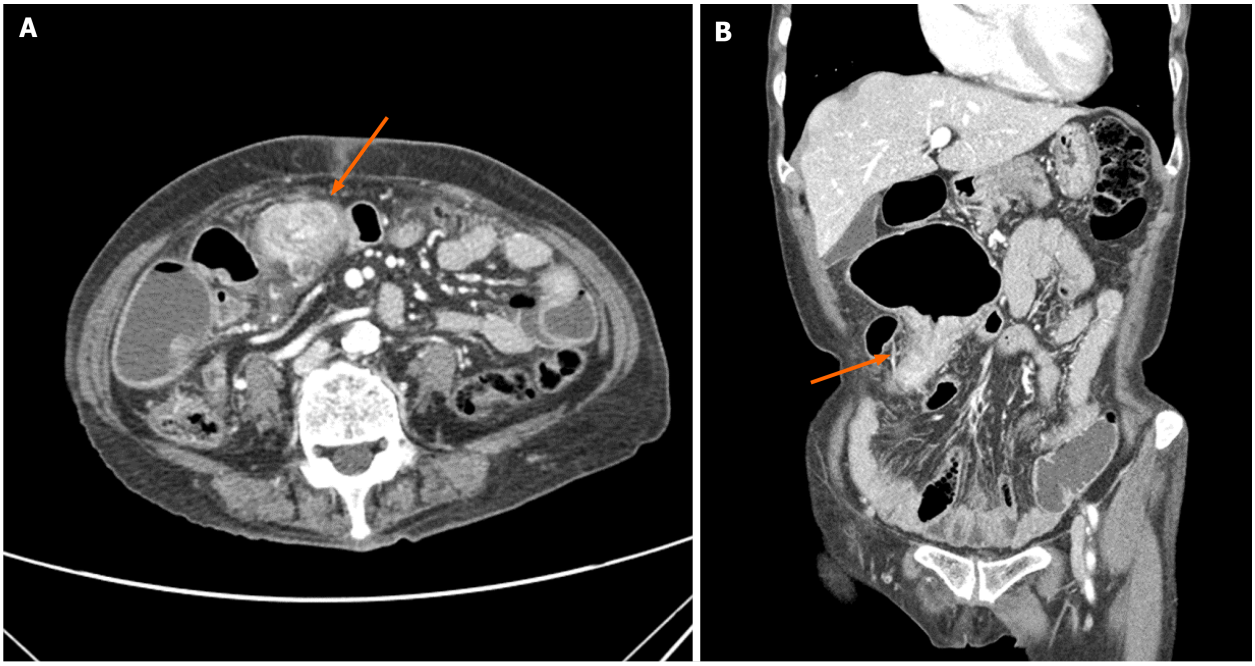

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Figure 1 Computed tomography scan demonstrating irregular thickening of the distal ileum, resulting in proximal small bowel dilatation (arrow). A: Axial view; B: Coronal view.

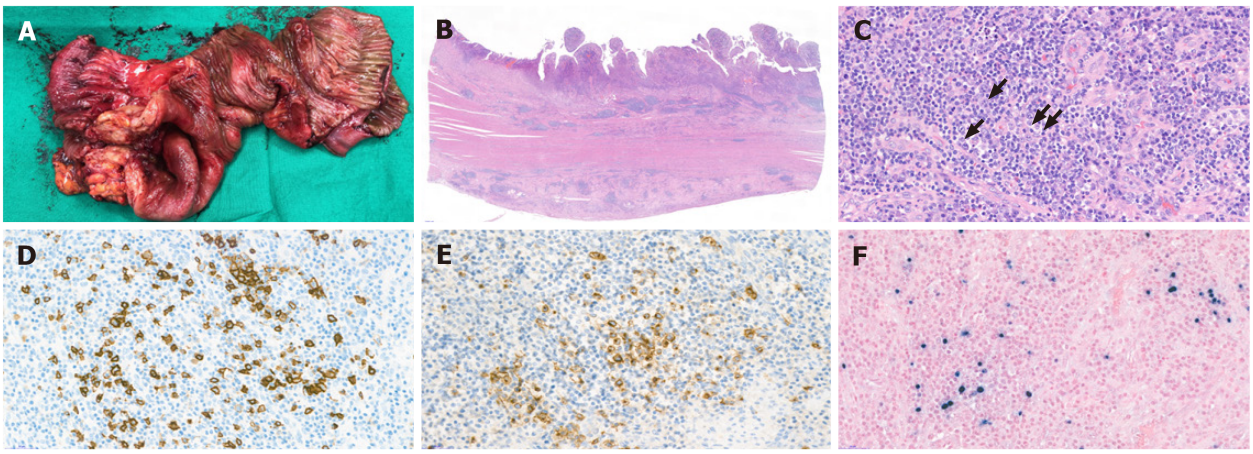

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Figure 2 Histopathological analysis of the resected specimen. A: The resected specimen showed a single ulcerative lesion with luminal obstruction; B: Histopathologically, the mucosal surface was ulcerated with granulation tissue formation. Beneath the ulcer, the specimen revealed marked infiltration of various inflammatory cells as well as dense fibrosis in all layers of the colon wall (hematoxylin–eosin stain, scan view); C: The infiltrated inflammatory cells consisted of lymphocytes, plasma cells, eosinophils and neutrophils, as well as a few scattered large atypical lymphoid cells (arrow) (hematoxylin–eosin stain, original magnification, 400×); D–F: The large atypical lymphoid cells were CD20-positive, CD30-positive, and Epstein–Barr virus (EBV)-positive. CD20 (D), CD30 (E), and *in situ* hybridization for EBV-encoded RNA (F) (original magnification, 400×).

pressive therapy or undergoing age-related immunosenescence[8]. A reduction in immunosuppressant dose often leads to an improvement in the lesions, which offers a diagnostic clue for EBV-MCU. EBV-MCUs often present as ulcerative lesions with infiltrative margins in mucosal areas on imaging studies.

For small bowel adenocarcinoma, clinical manifestations may include nonspecific signs, such as weight loss, anemia, and abdominal discomfort[9]; conversely, common imaging findings include nodular or irregular thickening of the small bowel wall, which is often accompanied by luminal narrowing. In case of intestinal tuberculosis, patients may present with constitutional symptoms, such as fever, night sweats, and weight loss; imaging findings may include thickened intestinal walls or nodules, mostly in the ileocecal area[10].

While these clinical manifestations and imaging features could help differentiate EBV-MCU from small bowel adenocarcinoma or intestinal tuberculosis, there may be cases with overlapping characteristics. Thus, diagnosis of GI-tract-associated EBV-MCU remains challenging without surgery, and accurate diagnosis requires a combination of

clinical assessment, imaging studies, and histopathological analysis[7,8,11].

CONCLUSION

Although EBV-MCUs rarely affect the GI tract, particularly the small intestine, they should be considered when chronic inflammation with ulceration is observed. The overlapping clinical features between EBV-MCUs and small bowel adenocarcinoma may lead to misdiagnosis, which emphasizes the need for comprehensive evaluation and accurate histopathological analysis. Increased awareness of this rare entity is crucial for timely diagnosis, optimal patient care, and prevention of unnecessary invasive procedures.

FOOTNOTES

Author contributions: Song JH contributed to formal analysis, investigation, and writing the original draft; Choi JE contributed to writing review, editing, and data curation; Kim JS contributed to conceptualization, methodology, project administration, supervision, validation, and visualization; and all authors have read and approved the final manuscript.

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CASE REPORT

Hereditary hemorrhagic telangiectasia involving portal venous system: A case report and review of the literature

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Abstract

BACKGROUND

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant genetic disorder with an incidence of approximately 1 in 5000 in the general population. It is characterized by vasodilation, which affects specific organs, such as the skin, mucous membranes, brain, lungs, gastrointestinal tract, liver, and others. However, HHT rarely involves the portal venous system to cause serious clinical compli-cations.

CASE SUMMARY

A 68-year-old woman was admitted to the emergency department due to four consecutive days of abdominal pain and bloody stool and was subsequently diagnosed with HHT. Computed tomography angiography confirmed the presence of an arteriovenous fistula (AVFs). Considering this specific manifestation, whole exome sequencing was performed. After a comprehensive evaluation, a selective superior mesenteric artery embolization was prioritized to avoid intestinal ischemia. The postoperative symptoms of the patient were quickly relieved. Unfortunately, two months post-procedure the patient died from intestinal necrosis and

abdominal infection related to remaining AVFs.

CONCLUSION
For patients with diffuse superior mesenteric AVFs, selective mesenteric arterial embolization may lead to positive short-term outcomes.

Key Words: Hereditary hemorrhagic telangiectasia; Portal system; Arteriovenous fistula; Arteriovenous malformation; Selective artery embolization; Case report

Core Tip: This case report describes a rare case of hereditary hemorrhagic telangiectasia (HHT) involving the portal system and identified a possible gene mutation site. For patients with diffuse superior mesenteric arteriovenous fistulas (AVFs), a selective mesenteric arterial embolization may lead to positive short-term outcomes. In the future, more studies are needed to determine the suitability of this treatment for patients with diffuse superior mesenteric AVFs (SMAVFs) associated with HHT. Additionally, more studies are required to investigate whether new sites of gene mutations can cause or contribute to the development of diffuse SMAVFs in patients with HHT.

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INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is a common autosomal dominant genetic disease, with an estimated incidence of 1 in 5000[1]. HHT is characterized by vascular malformations that affect specific organs such as the skin, mucosa, brain, lungs, gastrointestinal tract, liver, and others. The most common clinical symptoms of HHT are epistaxis, gastrointestinal bleeding, iron deficiency anemia, and characteristic cutaneous-mucosal telangiectasia[2]. However, HHT rarely affects the portal venous system to cause severe clinical complications. HHT involving the portal venous system is an extremely rare clinical manifestation, with only six similar cases reported in the literature. Patients exhibiting this clinical presentation often experience severe symptoms and have a poor prognosis. Here, we report a case of HHT with mesenteric arteriovenous fistulas (AVFs). We performed whole-exome sequencing and selective embolization of the mesenteric arteries in the patient, which achieved some positive outcomes. This study aims to analyze the diagnosis and treatment of HHT involving the portal venous system and provide a reference for the effective clinical treatment of these patients.

CASE PRESENTATION

Chief complaints

A 68-year-old female patient presented to the Emergency Department of our hospital with the chief complaint of abdominal pain and bloody stool for four days, worsening for two days.

History of present illness

Prior to admission, there was no obvious cause for abdominal stabbing pain, which continued to worsen and changed to dull pain in the left lower abdomen. She had experienced two episodes of dark red bloody stools (approximately 200 mL each time). After defecation, there was no improvement in abdominal pain, and these symptoms were accompanied by abdominal distension, nausea, and low back pain. The patient had no fever, vomiting, or other symptoms over the course of the disease.

History of past illness

The patient had a history of spontaneous epistaxis for 20 years and intermittent rectal bleeding for 10 years, which had been previously neglected in terms of sufficient attention and medical intervention.

Personal and family history

Some of her family members also had a long-term history of spontaneous epistaxis (Figure 1).

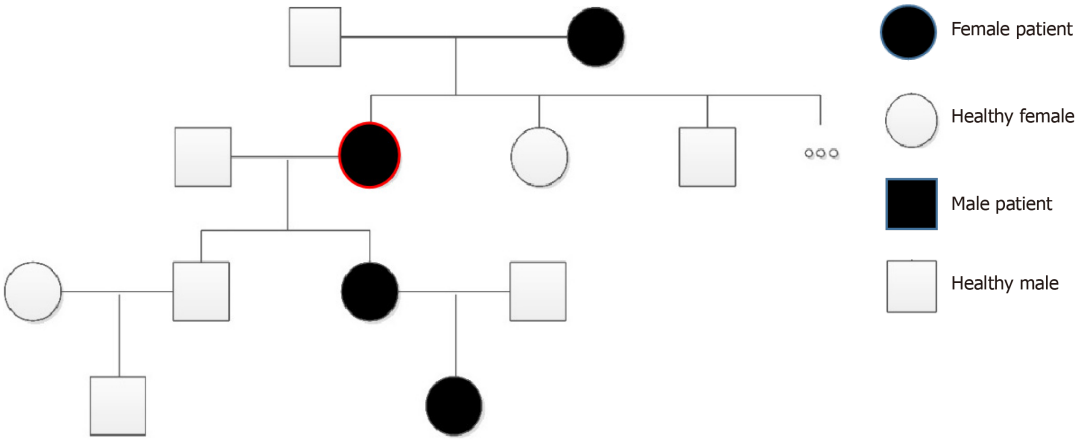

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Figure 1 Pedigree chart. Black circles refer to female patients with a history of epistaxis, open circles refer to healthy women; black squares refer to male patients with a history of epistaxis, open squares refer to healthy men. Red circle highlights the patient in this case study.

Physical examination

During the physical examination, capillary dilatation was identified in the patient's lips. The patient's abdomen was distended with tenderness in the lower left quadrant with no signs of rebound tenderness. Bowel sounds were 10 times per minute. No other identifiable abnormalities were found.

Laboratory examinations

The routine blood examination revealed hemoglobin of 115 g/L (normal range: 110-150 g/L), white blood cell count of 8.7 × 10^9 [normal range: (4-10) × 10^9], and 81.6% neutrophils (normal range: 50%-70%). A fecal occult blood test was positive. Coagulation function indexes showed varying degrees of decline.

Imaging examinations

A gastroscopy revealed scattered congestion and edema of the duodenal descending and transverse mucosa, while a colonoscopy showed a blue venous aneurysm or varicose in the ileum at 10 cm from the ileocecal valve. The cecum and ascending colon showed migrated veins and varicose veins (Figures 2A and B). The mucosa was cracked and scale-like (Figures 2C and D). Computed tomography angiography (CTA) of abdominal vessels revealed early mesenteric venous perfusion in the arterial phase that involved the right lower abdomen and left middle abdominal superior mesenteric veins. In the venous phase, there were tortuous vessels around the right upper abdominal intestine, which were connected to the superior mesenteric vein. Tortuous vessels were also visible in the posterior central abdomen (Figures 3A and B). CT showed patchy contrast enhancement in multiple parts of the drainage/supply area of the superior mesenteric artery, mainly involving the jejunal and ileal branches (Figures 3C and D). Whole-exome sequencing was conducted and a comprehensive analysis of the data was performed (Supplementary material).

FINAL DIAGNOSIS

Based on the above information, the patient was ultimately diagnosed with HHT.

TREATMENT

Due to the diffuse congestion and ischemia of the small intestine secondary to the superior mesenteric AVFs (SMAVFs), surgical intervention would involve resection of extensive intestinal segments, leading to adverse effects such as short bowel syndrome, anastomotic stenosis, and others. After being informed of these risks, the patient opted for interventional treatment. Therefore, selective embolization of the SMAVFs was performed. After careful evaluation, it was found that not all sites of the AVFs could be embolized during the selective procedure. If all fistula tracts had been occluded, the patient would have likely developed intestinal ischemic necrosis. Hence, the proportion of embolism had to be appropriate. As no similar cases existed, we selected the most severe shunt site for embolization (Figures 3E and F).

OUTCOME AND FOLLOW-UP

After the procedure, the patient experienced an improvement in abdominal pain, bloating, and diarrhea. An abdominal

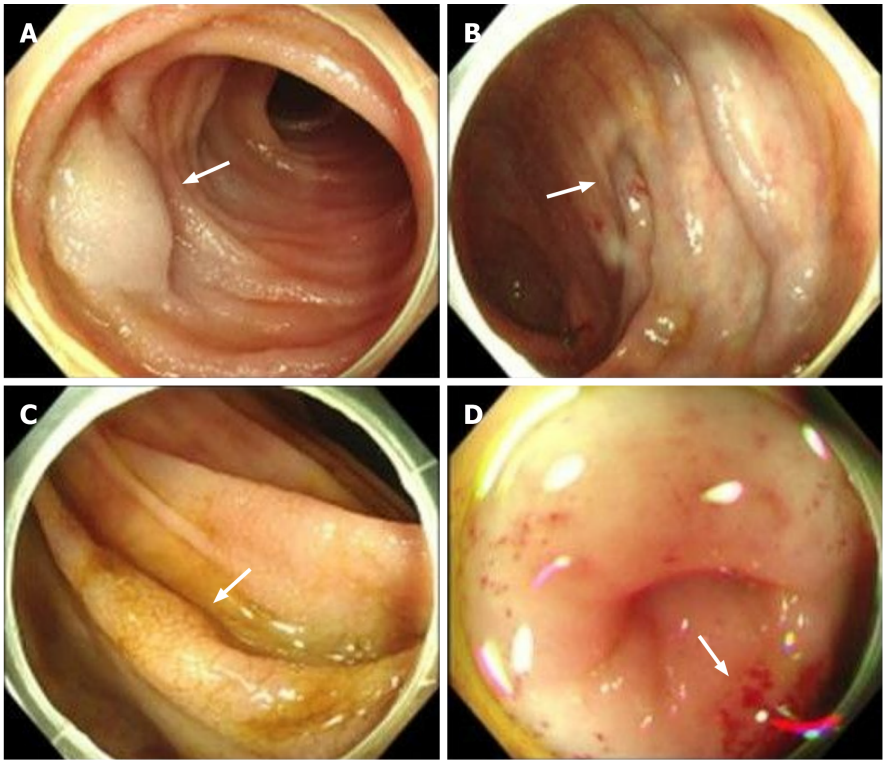

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Figure 2 Endoscopy images. A: Aneurysm (arrows) on intestinal mucosa; B: Varicose vein (arrows) on intestinal mucosa; C: Cracked and scale-like mucosa (arrows) on intestinal mucosa; D: Scattered sites of bleeding sites (arrows) on intestinal mucosa.

CT showed reduced intestinal wall edema with no abnormal perfusion at the embolization site (Figures 3G and H). One week later, the patient had recovered well and was discharged. One month after discharge, the patient was readmitted with abdominal pain and bloody stools. Remaining AVFs were identified and evaluated, and were believed to have caused secondary bowel necrosis. However, due to financial difficulties, the patient declined surgery and conservative treatment had to be adopted. One month later, the patient died from bowel necrosis and abdominal infection.

DISCUSSION

After searching various databases, we ultimately identified six cases similar to the one reported herein (Table 1). According to the Curaçao criteria, all six cases can be diagnosed as HHT[3]. However, since these reports were from an earlier time period, considerable patient information was missing and no sequencing was performed, which is undoubtedly a significant loss. In this report, we performed whole exome sequencing on the patient and conducted a comprehensive analysis of the data (Supplementary material). Common gene mutations associated with HHT, including endoglin (ENG), activin receptor-like kinase 1 (ACVRL1), and soluble (cytosolic) malate dehydrogenase (SMDH), were not found in this case. This indicates that the patient had a unique gene mutation that had not been detected previously.

Internationally, the clinical diagnosis of HHT is mainly based on the Curacao criteria[3]. These criteria have a broad application, especially for the identification of patients and non-patients[1]. The development of genetic technology enables us to diagnose HHT more accurately, particularly for adolescents and children who have no clinical manifestations of epistaxis or visible telangiectasia but do have unknown vascular malformations[4]. HHT can be divided into six common types based on different genotypes (Table 2). Primarily, sequencing methods of the *ENG* and *ACVRL1* genes are currently used[5-8]. Although, a negative result in genetic testing cannot rule out the diagnosis of HHT, since many sporadic cases have unique gene mutations that are not one of the common variations. Many studies have found new variations in the above two gene loci. For example, in a study of a Canadian family, nine new mutation loci were found in the *ENG* and *ACVRL1* genes[5]. In another investigation of a Chinese family, no significant mutation was found in the *ENG*, *ACVRL1*, or *SMDH* genes. After whole exome sequencing, new and unreported variations were found in the N-ethylmaleimide-sensitive factor attachment protein gamma gene[9]. In a genomic investigation conducted in the United Kingdom, comprehensive whole-genome sequencing uncovered a previously unknown heterozygous GDF2 sequence variation in all three affected individuals within an HHT family. Notably, gene screening results for ACVRL1, ENG, and mothers against decapentaplegic homolog 4 (SMAD4) yielded negative findings. *In vitro* experiments provided compelling evidence that the identified mutation interfered with the normal protein cleavage process, subsequently contributing to the pathogenesis of HHT[10]. Consequently, the pathogenic genes associated with HHT may extend beyond our current scope of comprehension. Further analysis is required to discover novel mutations after performing whole exome

Table 1 Publications that describe similar cases

Serial number	Publication date	Gender	Age	Clinical manifestation	Treatment	Prognosis	Ref.
1	1978	Male	63	Severe epistaxis; gastrointestinal bleeding; ileocolic AVM	NA	NA	[29]
2	2003	Male	68	Gastrointestinal bleeding; epistaxis; telangiectasia of skin; pulmonary AVM	Embolization for AVM	No recurrence after 6 mo of follow-up	[30]
3	2006	Female	73	Epistaxis; hemolytic anemia; mesenteric AVM	NA	NA	[31]
4	2007	Male	72	Epistaxis; gastric telangiectasia; superior mesenteric AVM	Treatment for ascites and varicose veins	NA	[32]
5	2016	Female	46	Epistaxis; telangiectasia of skin; AVM of splenic flexure of colon	NA	NA	[33]
6	2014	Female	68	Duodenal AVM	NA	NA	[34]

AVM: Arteriovenous malformations; NA: Not available.

Table 2 Common genetic variants in hereditary hemorrhagic telangiectasia patients

Type	HHT1	HHT2	HHT3	HHT4	HHT5	HHT + JPS
Mutated gene locus	ENG	ACVRL1	No specific gene	No specific gene	BMPq/GDF2	MADH4
Location	9q34	12q3	5q31	7q14	NA	NA
Affected protein	Endoglin protein	AKL1 protein	NA	NA	NA	SMAD4 protein
Proportion	61%	37%	NA	NA	NA	2%

JPS: Juvenile polyposis syndrome; NA: Not available; ENG: Endoglin; HHT: Hereditary hemorrhagic telangiectasia; SMAD4: Mothers against decapentaplegic homolog 4; ACVRL1: Activin receptor-like kinase 1.

sequencing. In this case, the existing database only contains commonly reported gene mutations, making it easy to exclude new gene mutations through comparative analysis and ultimately leading to false negative results. To solve this problem, it is necessary to compare the gene sequencing data of multiple similar patients to better screen for meaningful variations.

The different genotypes of HHT can also lead to different clinical manifestations in patients. Studies have found that HHT1 is more prone to cerebral arteriovenous malformations, while HHT2 is more prone to hepatic arteriovenous malformations[11], and the age at diagnosis of HHT1 patients is generally young[12]. A specific type of HHT caused by MADH4 mutations is usually accompanied by juvenile polyposis syndrome[13]. Prior studies have suggested that the *ENG*, *ACVRL1*, and *MADH4* genes all play a role in regulating cell signaling through the transforming growth factor beta (TGF-β) signaling pathway. The TGF-β family activates the ENG glycoprotein and ALK1 on the cell membrane, leading to changes in gene transcription levels within the cell nucleus that regulate cell proliferation, differentiation, migration, apoptosis, and secretion, ultimately affecting vascular structure and function[14]. Furthermore, studies have found that clinical manifestations differ amongst patients within families, with vascular malformations only appearing in specific organs, suggesting that interpretation solely from a genetic variation perspective cannot fully explain the occurrence of HHT. Therefore, another hypothesis known as the "second strike" theory has been suggested[15]. Firstly, heterozygous variations in the HHT gene lead to the loss of a single allele that encodes for endothelium, which is the first strike. Secondly, environmental or genetic factors provide the second strike. These two factors can also have a synergistic effect. The appearance of HHT clinical symptoms may be the result of multiple factors working together, controlled by complex molecular mechanisms. The cause of the mesenteric AVFs in this patient is currently unknown and requires further study. The "second-strike" hypothesis has been proposed for many years but previously lacked convincing evidence. However, with the advancement of sequencing technologies, Snellings *et al*[16] have successfully validated three hypotheses pertaining to the second-strike theory. These hypotheses involve the presence of telangiectasia containing a somatic mutation in the same gene as a germline mutation responsible for HHT, bi-allelic somatic and germline mutations, with both mutations leading to loss of function. This strong evidence has substantiated the plausibility of the two-hit hypothesis and provided a new direction for the development of HHT therapies.

Common clinical manifestations of HHT include epistaxis, cerebral vascular malformations, pulmonary arteriovenous malformations (PAVM), gastrointestinal bleeding, and hepatic arteriovenous malformations (Figure 4). HHT patients typically exhibit lower social index values for EuroQol-visual analogue scale scores, indicating a reduced quality of life compared to the general population. Notably, they attribute a substantial impact on their quality of life to epistaxis (nose-

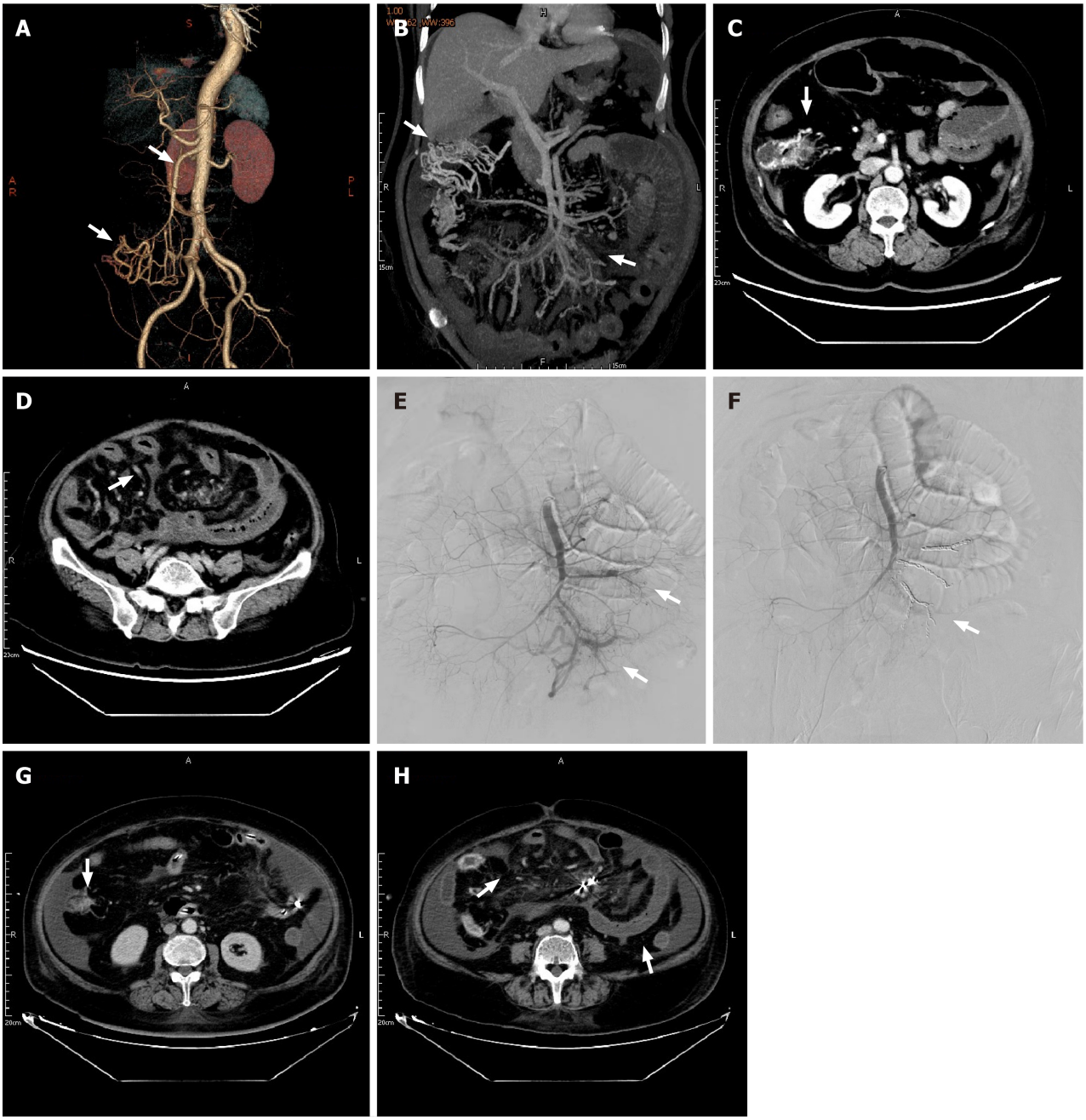

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Figure 3 Pre- and post-procedure computed tomography images. A: Computed tomography (CT) angiography examination of abdominal blood vessels. The superior mesenteric vein (upper arrow), and tortuous blood vessels connecting with the superior mesenteric vein (lower arrow); B: Tortuous vessels (left arrow), and the superior mesenteric arteriovenous fistula (right arrow); C: CT examination. Tortuous vessels (arrow); D: Considerable edema of the intestinal segment receiving blood supply from the jejunal and ileal branches of the superior mesenteric artery (arrow); E: Two arteriovenous fistulas (arrows); F-H: After embolization, arteriovenous fistulas were not present (F), the range of tortuous vessels was decreased (G), and edema of the intestinal segment receiving blood supply from the jejunal and ileal branches of the superior mesenteric artery was relieved (H).

bleeds), particularly among older patients[17]. AVMs are present in 42.2% of patients, most of which are small. However, one-fifth of these AVMs rupture, and nearly half of these patients have related symptoms including headache, epileptic seizures, and focal neurological deficits[18]. PAVM is present in as many as 49% of HHT patients. PAVM can cause life-threatening events including massive bleeding from a ruptured PAVM, pulmonary hypertension, paradoxical embolism with stroke, and brain abscess[19]. Approximately 30% of HHT patients experience gastrointestinal bleeding due to mucosal telangiectasias in the stomach, small intestine, or colon, with the main consequence being anemia, and the incidence increases with age[20]. The probability of hepatic vascular malformations in HHT patients is 41%-78%[21]. Among these patients, only 8% had clinical symptoms such as high-output heart failure, portal hypertension, or bile duct necrosis, which are all known clinical manifestations of HHT. Currently, the proportion of patients with mesenteric AVFs is unknown, which is a clinical manifestation that doctors may easily overlook. It is concerning that patients with this manifestation have poor gastrointestinal function and may suffer from serious gastrointestinal ischemia and hypoxia. If

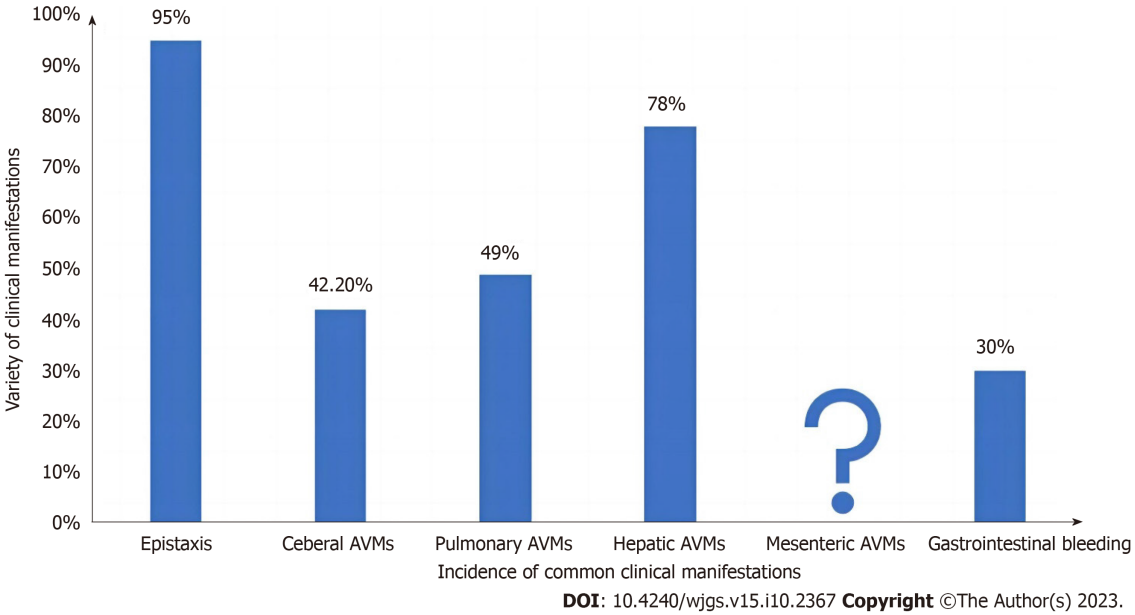

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Figure 4 Common clinical manifestations of hereditary hemorrhagic telangiectasia patients. AVM: Arteriovenous malformation; HHT: Hereditary hemorrhagic telangiectasia.

left untreated, mesenteric AVFs may seriously affect patient quality of life and even result in death.

The most common treatment for anemia caused by gastrointestinal bleeding in HHT patients is iron supplementation or blood transfusion, which is not sustainable for long-term treatment. Currently, the treatment options for chronic gastrointestinal bleeding in HHT patients include medication and endoscopic treatment, but they cannot cure AVFs. Al-Samkari and Eng[22] presented several cases of drug therapy for complex HHT-related vascular malformations, all of which achieved favorable treatment outcomes. However, these cases involved more severe manifestations of common symptoms rather than rare clinical presentations similar to the present case. Therefore, the treatment has limited relevance for this particularly rare clinical scenario. The main problem with the patient described in this study was the SMAVF, as conventional treatments were not an option. AVFs are abnormal direct connections between high-pressure arteries and low-pressure veins[23]. While AVFs are commonly found in the extremities, superior and inferior mesenteric AVFs are extremely rare[24,25]. The incidence of a SMAVF is 0.09%, and the mortality rate is 39%-77%[25]. Treatment methods for AVFs include interventional closure and surgery[26,27]. If vascular interventional treatment is ineffective, the second-line treatment generally involves surgical ligation of the AVF or the removal of the portion of the jejunum most affected by the fistula[28]. Although surgery was previously considered the most effective treatment method for SMAVF[27], with the development of interventional techniques and improvements in embolization materials, embolization has become the preferred treatment for SMAVF[28]. Due to the broad range of AVFs in this patient and the many adverse consequences, such as short bowel syndrome and anastomotic stenosis, superior mesenteric artery embolization was chosen as the treatment for the SMAVFs in this case. After the procedure, the patient's abdominal pain, bloating, and diarrhea improved. Unfortunately, the patient eventually died. Therefore, we believe that selective mesenteric artery embolization can lead to short-term benefits, but the long-term benefits require further. From this case, we found that clinical symptoms in HHT patients also include SMAVFs, which carries a high risk and should be treated appropriately. Furthermore, the gene mutations associated with this symptom do not appear to be the common mutations identified in previous studies.

CONCLUSION

The patient in this case did not exhibit a genetic mutation commonly associated with HHT. Furthermore, for patients with diffuse SMAVF, selective mesenteric arterial embolization may produce some positive outcomes. However, it is still unclear whether selective superior mesenteric arterial embolization is always advantageous in the long term or whether immediate surgery would be more beneficial in cases of intestinal necrosis. Researchers need to continue exploring new pathogenic mutations and the most appropriate treatment methods for rare HHT symptoms, to provide a basis for future prevention and diagnosis, and to deepen our understanding of HHT.

FOOTNOTES

Author contributions: Wu JL wrote the initial draft of the manuscript; Sun G and Wang SF provided critical analysis and review of the manuscript; Chen J, Zhang HW, Zhao ZZ, and Luan Z analyzed the patient's whole genome sequencing data; Zhao YM, Li CY, and Jing

YJ collected the clinical data; and all authors read and approved the manuscript.

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CASE REPORT

Giant dedifferentiated liposarcoma of the gastrocolic ligament: A case report

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Abstract

BACKGROUND

Dedifferentiated liposarcoma (DDLS) has a worse prognosis and occurs most commonly in the retroperitoneal region and rarely in the intraperitoneal region. Histological diagnosis was revolutionized by the combined contributions of histo-immuno-chemistry and molecular biology. Aside from surgery, there is no consensus on the optimal treatment for this chemoresistant cancer.

CASE SUMMARY

A thirty-year-old black female presented with a large painful abdominal mass occupying nearly the entire abdomen and progressive weight loss was admitted for surgery. Abdominal computed tomography showed a large heterogeneous mass of the mesentery that was sized 18 cm × 16 cm in size and had heterogeneous contrast enhancement. During laparotomy, en bloc excision of the large and multilobulated gastrocolic ligament mass was performed. The initial post-operative histopathological diagnosis was undifferentiated sarcoma. Finally, the results of immunohistochemistry and molecular biology allowed us to confirm the diagnosis of DDLS. The tumour followed an aggressive evolution with diffuse metastasis, causing the death of the patient less than 5 mo after the operation.

CONCLUSION

Dedifferentiated liposarcomas are rare tumours that typically originate in the retroperitoneum but may arise in unexpected locations.

Key Words: Dedifferentiated liposarcoma; Gastrocolic ligament mass; En bloc excision; Immunohistochemistry; Molecular biology; Worse prognosis; Case report

Core Tip: Dedifferentiated liposarcoma has a worse prognosis and occurs most commonly in a retroperitoneal location but rarely in an intraperitoneal location. Complete surgical excision with a negative microscopic margin (R0) remains the ideal treatment when the tumour is still localized. Here, we report the case of a young woman with disseminated giant dedifferentiated liposarcoma of the gastrocolic ligament. This case demonstrates the poor prognosis of dedifferentiated liposarcomas. To the best of our knowledge, a giant dedifferentiated liposarcoma of the gastrocolic ligament has not yet been reported.

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INTRODUCTION

Liposarcoma is a rare malignant tumour of mesodermic origin that derives from adipose tissue[1,2]. Well-differentiated and dedifferentiated liposarcomas (DDLSs) are the most common retroperitoneal types[3]. Liposarcoma is one of the most common soft-tissue sarcomas that mostly affects adults in their 50s or 60s[4,5].

DDLS, a variant of malignant adipocytic tumours, has a worse prognosis and occurs most commonly in a retroperitoneal location but rarely in an intraperitoneal location[6,7,8,9]. Typically in these locations, the tumour is paucisymptomatic or even asymptomatic until it becomes large enough to compress the surrounding organs[10]. The challenges of histological diagnosis and the lack of consensus on the optimal therapy complicate the management of this cancer[8,11]. Histological diagnosis was revolutionized by the combined contributions of histo-immuno-chemistry and molecular biology[12]. When the tumour is still localized, complete surgical excision with a negative microscopic margin (R0) remains the ideal treatment[10,13]. Additional surgery, chemotherapy, radiotherapy and targeted therapies are also useful in the treatment of advanced or metastatic forms[11,14,15].

Herein, we report the case of a thirty-year-old black female with a giant DDLS of the gastrocolic ligament. To the best of our knowledge, DDLS originating from this unusual location has not been reported.

CASE PRESENTATION

Chief complaints

A thirty-year-old black female was admitted to our surgical unit with a large painful abdominal mass occupying nearly the entire abdomen.

History of present illness

This abdominal mass appeared eight months earlier. A gradual increase in its volume had been associated with the onset of abdominal pain, constipation and progressive weight loss.

History of past illness

The patient had a good health history.

Personal and family history

No notable events were mentioned in her personal and family history.

Physical examination

The patient was visibly underweight. She presented with an irregular and painful hard abdominal mass with a diameter of approximately 28 cm.

Laboratory examinations

Blood analysis revealed severe nutritional impairment and anaemia. The total protein level was 4.2 g/dL (normal range: 5.8-6.5 g/dL), the albumin level was 2.8 mg/dL (normal range: 3.5-5.5 mg/dL) and the haemoglobin level was 10.5 g/dL (normal range: 12-16 mg/dL).

Imaging examinations

Abdominal computed tomography (CT) showed a large heterogeneous mesentery mass measuring 18 cm × 16 cm × 10.4 cm, and it was compressing the third part of the duodenum with heterogeneous contrast enhancement (Figure 1).

FINAL DIAGNOSIS

The final diagnosis of the presented case was DDLS of the gastrocolic ligament.

TREATMENT

At laparotomy, a large multilobulated mass that was sized 30 cm × 20 cm × 12 cm and arose from the gastrocolic ligament was found (Figure 2A). In addition, many other smaller synchronous lesions were discovered in the liver, small bowel mesentery and peritoneum. An en bloc excision of the giant mass of the gastrocolic ligament was carried out, and associated biopsies of the small lesions were taken. The other smaller lesions virtually ruled out any possibility of curative excision.

OUTCOME AND FOLLOW-UP

Symptomatic treatment, such as nutritional support, was given postoperatively. After two days, the patient was gradually redirected to a normal diet. The patient was discharged 8 d after surgery without any complications. The patient did not undergo any adjuvant treatment for economic reasons. Three months later, follow-up abdominal CT studies revealed multiple peritoneal and vascular implants. The tumour followed an aggressive evolution with diffuse metastasis, causing the death of the patient less than 5 mo after the operation.

Macroscopic examination showed a large yellowish, nodular and myxoid mass with focal areas of haemorrhage and necrosis (Figure 2B).

The histological examination revealed tumorous nodules that were poorly limited, often haemorrhagic, and located in fibrous or fibro-adipose tissue or in the peritoneum. The tumour proliferation was made up of masses with some fusiform cells (Figure 3A), which were sometimes more epithelioid (Figure 3B) and sometimes had pleomorphic nuclei. The mitotic rate was 10/10 per high power field. The tumour was not differentiated and was largely vascularized without necrosis. Immunohistochemical staining revealed that the tumour cells were negative for actin, desmin, calretinin, PS100, melana A, ERG, P63, AE1/AE3, EMA, chromogranin A and CDK4. BAP1 and P16 were partially positive in the neoplastic cells, while MDM2 was strongly expressed. The histo-pathological diagnosis was initially an undifferentiated sarcoma with fusiform and pleomorphic cells. The tumour was reclassified as DDLS according to the histopathological report and immu-nohistochemical test results.

DISCUSSION

The patient's young age, unlike the cases usually reported and the rarity of its location at the gastrocolic ligament, makes our observation peculiar. Liposarcoma is the most common soft-tissue sarcoma in adults, with a peak incidence in the 5th-6th decade of life[4,5]. According to the World Health Organization, liposarcoma is classified into five main subtypes: Well-differentiated, dedifferentiated, myxoid, pleomorphic, and myxoid pleomorphic[6,14]. DDLS is a higher grade, often nonlipogenic, sarcoma with metastatic potential that is genetically similar to well-differentiated liposarcoma[16]. However, DDLS arises *de novo* in more than 90% of cases[17] and can exist without any well-differentiated cells[18]. Usually, DDLS are rare, located in the retroperitoneum and occasionally in the peritoneal cavity[6]. Localizations in the ascending colon, sigmoid colon, mesentery of the small bowel and oesophagus have been described, but no localization in the gastrocolic ligament has been reported to our knowledge[7,19,20,21]. Well-differentiated liposarcoma is typically associated with an adipose mass containing nonlipomatous components on abdominal CT and magnetic resonance imaging; the additional presence of a focal, nodular nonlipomatous region greater than 1 cm in size suggests DDLS[22]. Histo-pathological diagnosis is difficult; initially, this case was diagnosed as an undifferentiated sarcoma with fusiform and pleomorphic cells. In fact, tumours are generally diagnosed as an undifferentiated pleomorphous sarcoma on histology; the diagnosis is suspected in the presence of a well-differentiated liposarcoma[23]. It should be noted, however, that this well-differentiated component may be missing, as noted above. It has been reported that many cases of histological diagnosis of undifferentiated or poorly differentiated sarcoma located in the retroperitoneum were in fact DDLS[8]. The molecular features of DDLS overlap with well-differentiated liposarcoma[24,25]. In immunohistochemistry, both express MDM2 and CDK4 amplifications; MDM2 overexpression confirmed by fluorescence *in situ* hybridization helps distinguish it from pleomorphic liposarcoma and myxoid liposarcoma[16]. Radical surgery with R0 en bloc resection when possible, seems to offer longer survival and disease-free interval[14,18,26]. In all reported cases, radical surgery was performed as the first-line treatment. However, surgically, it is difficult to distinguish the well-differentiated components of healthy fat, which complicates complete excision surgery[16]. The most important prognostic factor for

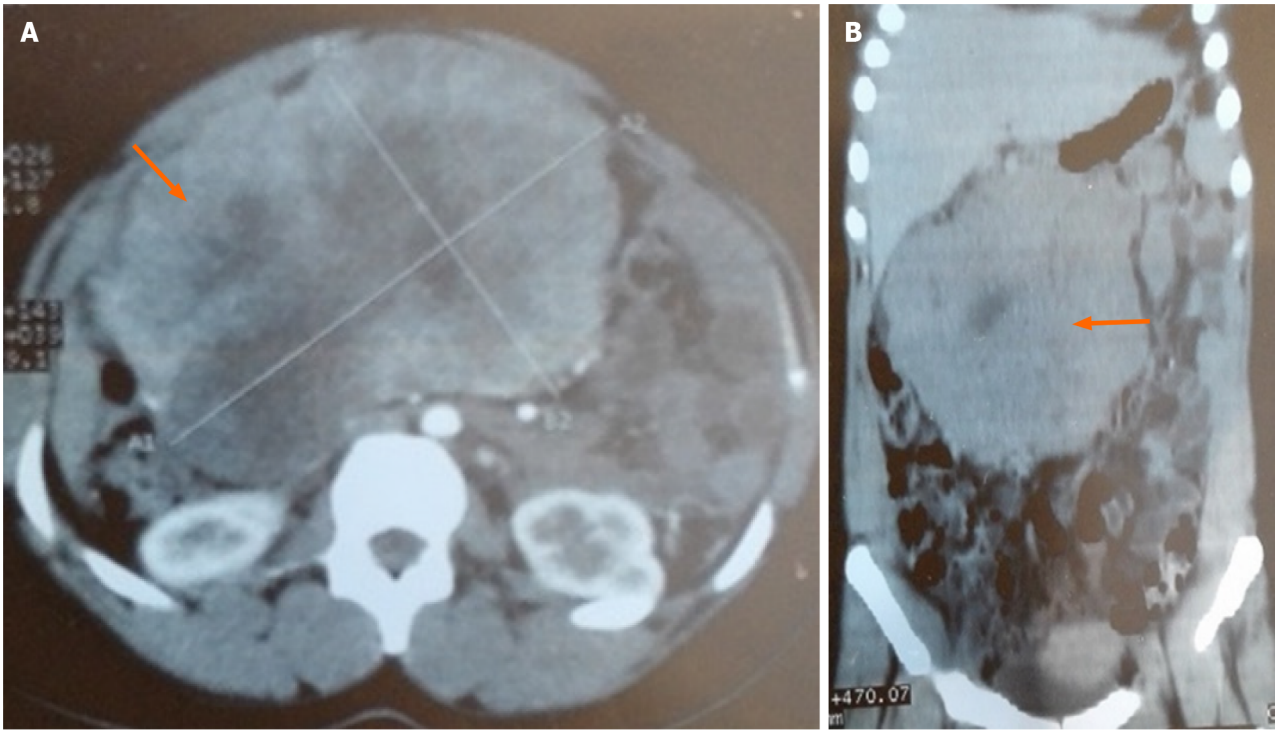

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Figure 1 Abdominal computed tomography showed a huge heterogeneous mesentery mass. A: Transverse view; B: Coronal view.

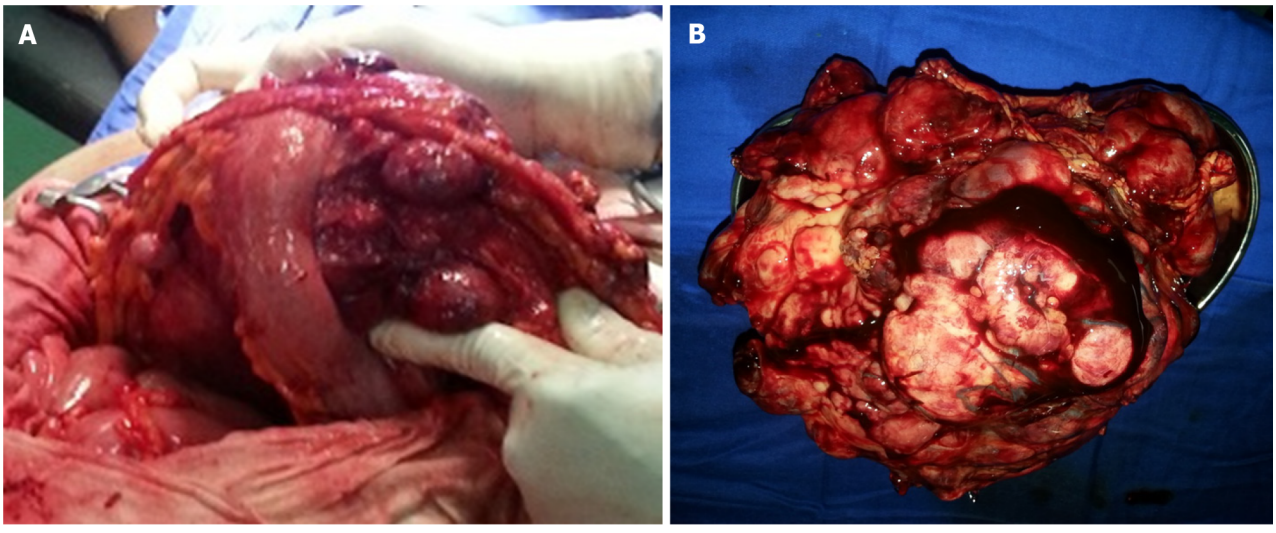

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Figure 2 Operatives images of this case report. A: Intraoperative procedure found multi-lobulated mass of gastrocolic ligament; B: Macroscopic aspect of removed giant mass of gastrocolic ligament.

DDLS is the anatomic site, with retroperitoneal sites having an overall worse prognosis. In our observation, the numerous small lesions did not allow for curative excision, suggesting relapse, as seen three months later. Chemotherapy and radiotherapy remain poorly codified, and their therapeutic benefit has not yet been demonstrated[18]. DDLS is not very sensitive to chemotherapy, so new molecular targets are based on an understanding of disease biology, usually targeting a specific, aberrant genetic or molecular pathway[27,28]. Pazopanib, a tyrosine kinase inhibitor, may provide clinical benefit for patients with DDLS according to recent data[29].

The patient did not undergo any adjuvant treatment for economic reasons. Approximately 40% of DDLS will have local recurrence, 17% will metastasize, and 28% will have tumour-related mortality[6]. Three months later, follow-up abdominal CT studies revealed multiple peritoneal and vascular implants with necrotic areas. The patient died less than five months after surgery.

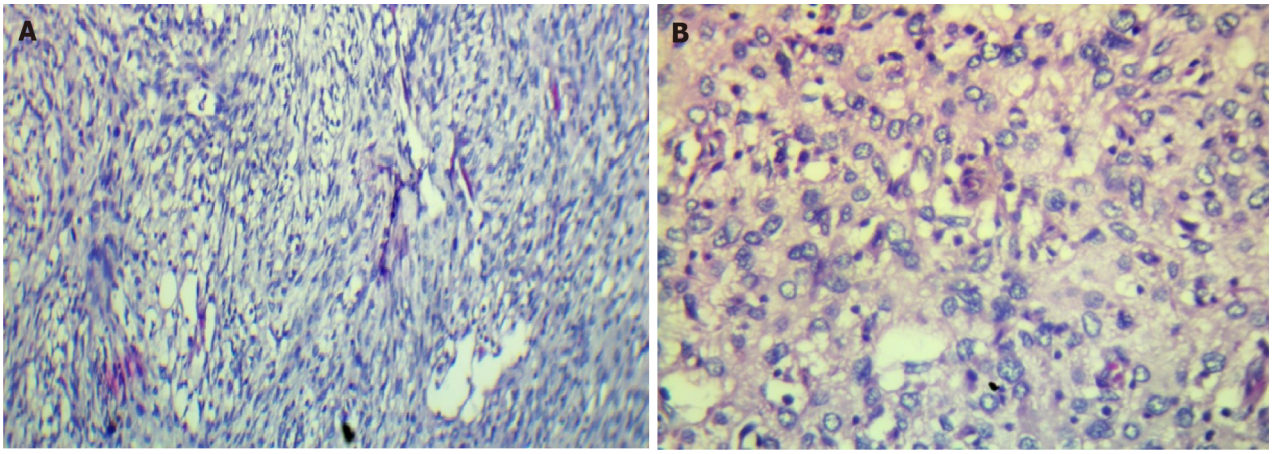

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Figure 3 Histopathological analysis. Immunohistochemical results show that the tumours cells are positive for Bap1 (A), p16 (A) and MDM2 (B) and negative for actin, desmin, calretinin, PS100, melana A, ERG, p63, cytokeratin AE1/AE3, EMA, chromogranin A and CDK4. A: A population of fusiform cells (× 200); B: A population of epithelioid cells and atypical adipose cells in a myxoid and vascularized matrix (× 200).

CONCLUSION

DDLSs are rare tumours that typically originate in the retroperitoneum but may arise in unexpected locations. The extremely rare primary gastrocolic liposarcoma presented here is an example. Immunohistochemistry and molecular biology are essential to confirm histological diagnosis. Surgical excision with oncologically appropriate margins is the gold standard of treatment.

FOOTNOTES

Author contributions: Kassi ABF proposed the idea, analyzed the literature, wrote and revised the manuscript according reviewers suggestions; Yenon KS supervised and revised the manuscript; Kassi FMH collected the data; Adjemé AJ and Diarra KM assisted with data collection; Kassi ABF, Yenon KS, Bombet-Kouamé C and Kouassi M were the patient's surgeons and participated in the entire operation; All the authors have read and approved the revised manuscript.

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