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MINIREVIEWS

Percutaneous direct endoscopic pancreatic necrosectomy

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Abstract

Approximately 10%-20% of the cases of acute pancreatitis have acute necrotizing pancreatitis. The infection of pancreatic necrosis is typically associated with a prolonged course and poor prognosis. The multidisciplinary, minimally invasive "step-up" approach is the cornerstone of the management of infected pancreatic necrosis (IPN). Endosonography-guided transmural drainage and debridement is the preferred and minimally invasive technique for those with IPN. However, it is technically not feasible in patients with early pancreatic/peripancreatic fluid collections (PFC) (< 2-4 wk) where the wall has not formed; in PFC in paracolic gutters/pelvis; or in walled off pancreatic necrosis (WOPN) distant from the stomach/duodenum. Percutaneous drainage of these infected PFC or WOPN provides rapid infection control and patient stabilization. In a subset of patients where sepsis persists and necrosectomy is needed, the sinus drain tract between WOPN and skin-established after percutaneous drainage or surgical necrosectomy drain, can be used for percutaneous direct endoscopic necrosectomy (PDEN). There have been technical advances in PDEN over the last two decades. An esophageal fully covered self-expandable metal stent, like the lumen-apposing metal stent used in transmural direct endoscopic necrosectomy, keeps the drainage tract patent and allows easy and multiple passes of the flexible endoscope while performing PDEN. There are several advantages to the PDEN

procedure. In expert hands, PDEN appears to be an effective, safe, and minimally invasive adjunct to the management of IPN and may particularly be considered when a conventional drain is *in situ* by virtue of previous percutaneous or surgical intervention. In this current review, we summarize the indications, techniques, advantages, and disadvantages of PDEN. In addition, we describe two cases of PDEN in distinct clinical situations, followed by a review of the most recent literature.

Key Words: Infected pancreatic necrosis; Direct endoscopic necrosectomy; Percutaneous endoscopic necrosectomy; Sinus tract endoscopy; Stent-assisted percutaneous direct endoscopic necrosectomy

Core Tip: In expert hands, percutaneous direct endoscopic necrosectomy through the sinus drainage tract, established after percutaneous drainage or surgical necrosectomy drain, plays a vital role as a minimally invasive, safe, and effective adjunct in the management of infected pancreatic necrosis.

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INTRODUCTION

Acute necrotizing pancreatitis may be seen in about 10%-20% of the cases of acute pancreatitis and is frequently associated with a protracted course. The infection of pancreatic necrosis is a serious complication and carries a grave prognosis[1]. The multidisciplinary, minimally invasive "step-up" approach is favoured for the management of infected pancreatic necrosis (IPN)[2]. However, the clinical condition of the patient, local experience and expertise, anatomical position, and content of the collection, as well as the time from presentation and maturation of the wall of the collection, usually determine the treatment approach. A single treatment protocol cannot be used to manage IPN[3,4].

The minimally invasive and preferred endosonography-guided transmural drainage and debridement approach may be technically impossible in early pancreatic/peripancreatic fluid collections (PFC) (< 2-4 wk) where the wall has not formed; in PFC in paracolic gutters/pelvis; or in walled off pancreatic necrosis (WOPN) distant from the stomach/duodenum. In this group of patients, percutaneous drainage of the infected PFC helps to control the infection source rapidly and allows time to wall off pancreatic necrosis and stabilize an ill patient. A subset of patients with IPN will not recover with percutaneous drainage alone[2,5], and they will need necrosectomy. Percutaneous direct endoscopic necrosectomy (PDEN) is the minimally invasive technique used for the debridement of infected necrotic material with a flexible endoscope through the matured sinus tract connecting the WOPN and skin (the drainage tract formed after surgical necrosectomy or percutaneous drainage). Here, we review the indications, techniques, advantages, and disadvantages of PDEN with a description of two cases of PDEN with different clinical scenarios, followed by a review of the latest literature on PDEN.

INFECTED PANCREATIC NECROSIS

Acute necrotizing pancreatitis may be seen in about 10%-20% of the cases of acute pancreatitis and is frequently associated with a complex and prolonged course. Infection is a serious complication of pancreatic necrotic collection, with a mortality rate of 20%-30%[1]. The drainage and/or debridement of necrotic material are indicated for symptomatic necrotic collections, either for infection (the commonest indication) or if sterile, then for persistent pain, gastrointestinal luminal obstruction, biliary obstruction, fistulas, or persistent systemic inflammatory response syndrome[1].

PERCUTANEOUS DRAINAGE OF INFECTED PANCREATIC NECROSIS

The preferred modality for the drainage of infected WOPN is endoscopic ultrasonography-guided transmural drainage (transgastric/transduodenal) with a lumen-apposing metal stent or plastic stents

along with direct endoscopic necrosectomy, depending upon the symptoms and quantity of the solid component in the WOPN cavity[6,7]. Endoscopic transmural drainage is not technically feasible if: (1) Infection occurs during the early stage (< 2-4 wk) of acute necrotizing pancreatitis where pancreatic necrosis is not walled off; (2) WOPN is far away (> 10 mm) from the stomach/duodenum; (3) necrosis extends into paracolic gutters or pelvis; (4) the patient is very sick and unfit for the procedure; and (5) local expertise is not available. Image-guided percutaneous drainage of a symptomatic pancreatic necrotic collection is crucial in the treatment of these individuals. Percutaneous drainage of an infected PFC typically allows pancreatic necrosis to wall off and stabilize a sick patient while also controlling the infection source. Percutaneous drainage catheters are available in sizes ranging from 8 F to 32 F. It can be placed under imaging guidance by an interventional radiologist (Figure 1A). The drain size is usually gradually increased to around 28 F-32 F at regular intervals before PDEN. Percutaneous drainage with an esophageal fully covered self-expandable metal stent (SEMS) insertion may obviate the need for these multiple procedures[8]. Exclusive percutaneous drainage is effective in 35%-51% of symptomatic WOPN patients[2,9,10]. As a result, in the remaining subset of patients, debridement of infected necrotic debris is necessary. A matured sinus tract after percutaneous drainage or a surgically-placed drain after necrosectomy can be utilized for PDEN if there is an incomplete clinical improvement following percutaneous drainage.

PERCUTANEOUS DIRECT ENDOSCOPIC NECROSECTOMY

Indications

PDEN, also known as sinus tract endoscopy, is a minimally invasive technique that involves passing a flexible endoscope through the matured tract connecting WOPN and skin, the drainage tract established following surgical necrosectomy drain or percutaneous drainage-to debride infected necrotic material. If percutaneous or surgically-placed drain alone does not result in a complete clinical response, PDEN can be used to debride the infected necrotic material. In the literature, PDEN has been the subject of various case series and case reports[3,5,8,11-27] (Table 1). Although the retroperitoneal route is the preferred safe route for PDEN because there is no risk of peritoneal contamination, a transperitoneal route has been reported. A fully covered SEMS, when used for drainage tract dilatation, may help to prevent infectious material from escaping into the peritoneal cavity, thereby preventing peritonitis. The main indications of PDEN are summarized in Table 2.

Anaesthesia

Although PDEN has been performed under general anaesthesia in a few case series[11,19], it has mostly been done under conscious sedation or total intravenous anaesthesia without endotracheal intubation (TIVA)[14,18,21,27]. A deep plane of anaesthesia can be achieved with TIVA. Propofol is used for induction and maintenance, while ketamine is used to provide analgesia during spontaneous ventilation with an oxygen mask[28]. When compared to general, regional, and combined anaesthesia, TIVA is significantly associated with a reduction in inflammatory markers, particularly C-reactive protein, potentially reducing the post-procedure systemic inflammatory response and complications[29]. However, elderly patients or those with the American Society of Anaesthesiologists' poor physical status should be treated with extreme caution.

PROCEDURE/TECHNIQUE

Drainage tract dilation

After the sinus tract between the skin and WOPN has matured (usually 7-10 d after percutaneous drainage) (Figure 1B), it can be dilated with a wire-guided controlled radial expansion balloon or Amplatz dilators, depending on the length of the sinus tract, to facilitate an easy passage of the flexible endoscope into WOPN (Figure 1C). As Amplatz dilators have a smaller nose compared to Savary Gillard dilators, they can be used to dilate longer sinus tract more easily and safely. As the diameter of the upper gastrointestinal endoscope ranges from 9 to 10 mm, the sinus tract dilation is typically planned up to 10 to 12 mm. Another method for sinus tract dilatation is to gradually increase the drain size to around 28-32 F at regular intervals. If the drainage tract is longer and a patent tract is required for a longer period of time, an esophageal fully covered SEMS placement across the tract should be preferred to minimize repeated dilatation of the sinus tract (Figure 1D). Because of its wide diameter, the fully covered SEMS keeps the sinus tract patent and enables easy and several passes of the flexible endoscope during PDEN. Percutaneous drainage and tract dilatation with a fully covered SEMS placement followed by necrosectomy may be done in a single step, eliminating the multiple steps involved in PDEN[8].

Table 1 Case series of percutaneous direct endoscopic necrosectomy for infected pancreatic necrosis

Ref.	Number of patients	Initial intervention	PDEN/stent assisted PDEN	Anaesthesia	Median PDEN sessions	Additional intervention-number of patients	Clinical success rate (%)	Procedure related complications-number of patients	Mortality (%)
Carter *et al*[11], 2000	14	ON-4, PD-10	PDEN	GA	2	Surgery-1	85.7	Bleeding-1	14.3
Mui *et al*[12], 2005	13	ON-4, PD-10	PDEN	TIVA	3	ERCP-9, Surgery-1	76.9	Colonic perforation-1; catheter dislodgement-1	7.7
Dhingra *et al*[14], 2015	15	PD-15	PDEN	TIVA	4	Surgery-1	93.3	Bleeding-1; pancreatico-cutaneous Fistula-1	6.7
Mathers *et al*[15], 2016	10	PD-10	PDEN	TIVA; GA if clinically warranted	1.5	None	100	Pancreatico-cutaneous Fistula-1	0
Goenka *et al*[18], 2018	10	PD-10	PDEN	TIVA	2.3	Transmural, DEN-2, Surgery-1	90	Pneumo-peritoneum-2	0
Saumoy *et al*[19], 2018	9	PD-9	Stent-assisted PDEN	GA	3	None	88.9	None	11.1
Thorsen *et al*[20], 2018	5	PD-3; transmural; DEN-2	Stent-assisted PDEN	TIVA or GA	6	Transmural DEN-1	80	Abdominal Pain-5; pancreatico-cutaneous fistula-2	20
Tringali *et al*[21], 2018	3	PD-3	Stent-assisted PDEN	TIVA	3	0	100	None	0
Jain *et al*[5], 2020	53	PD-53	PDEN	TIVA	4	Surgery-8	79.2	Pancreatico-cutaneous fistula-4; bleeding-1; aspiration pneumonia-2; peritonitis-2; paralytic ileus-1; subcutaneous emphysema-1	20.8
Ke *et al*[25], 2021	37	PD-37	Stent-assisted PDEN	NA	4	Surgery-8	86.5	Bleeding-6; pancreatico-cutanoeus fistula-7; colonic fistula-4; gastro-duodenal fistula-4	13.5

ON: Open necrosectomy; PD: Percutaneous drainage; DEN: Direct endoscopic necrosectomy; PDEN: Percutaneous direct endoscopic necrosectomy; GA: General anaesthesia; TIVA: Total intravenous anaesthesia without endotracheal intubation; PFC: Pancreatic/peripancreatic collection; NA: Not available.

Table 2 Indications of percutaneous direct endoscopic necrosectomy

Indications
< 2-4 wk-Infected acute pancreatic/peripancreatic collection in which percutaneous drainage is required early and infection persists even after percutaneous drainage alone
> 2-4 wk-Infected walled off pancreatic necrosis unsuitable for transmural drainage: (1) Location (Paracolic/pelvic extension); (2) Distance > 1 cm; (3) Coagulopathy; (4) Multiple collaterals-Endosonography guided can be done

Percutaneous direct endoscopic necrosectomy

PDEN is carried out using carbon dioxide insufflation. The most crucial step for PDEN is to irrigate the cavity with sterile normal saline for the early evacuation of pus and liquefied necrotic debris. A rat-tooth forceps, a polyp retrieval basket, a snare, a dormia basket, or an automated rotor resection device can be used to remove necrotic debris (Figure 1E and F). The most important precaution to take during PDEN is to only remove loose debris with a gentle traction. Forceful traction will lead to intracavitary bleeding or perforation of the WOPN wall. After the necrosectomy session, it is preferable to keep a 30-32 F drain and a 7-8 F irrigation catheter in place to keep the tract dilated for easy passage of the scope during the subsequent necrosectomy and irrigation of the cavity with normal saline, respectively (Figure 1G). The necrosectomy sessions may vary depending on the infected solid component of WOPN. The key end

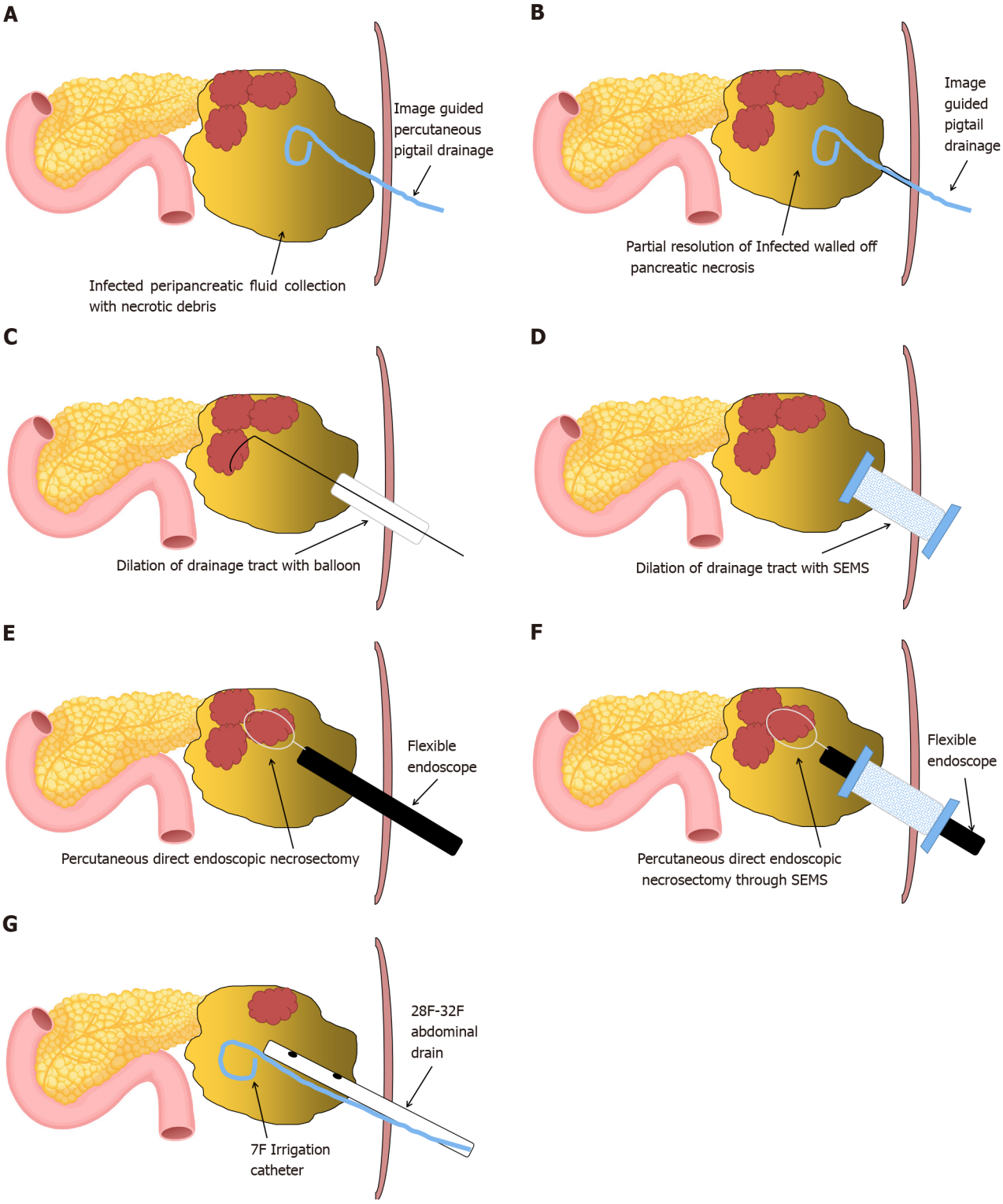

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Figure 1 Schematic representation of steps involved in percutaneous direct endoscopic necrosectomy. A: Image-guided pigtail drainage of infected pancreatic/peripancreatic collection; B: Partial resolution of infected walled off pancreatic necrosis (WOPN) with maturation of drainage tract between the skin and WOPN (usually 7-10 d approximately); C and D: Drainage tract dilation with (C) wire-guided controlled radial expansion balloon or (D) an esophageal fully covered self-expandable metal stent (SEMS); E and F: Percutaneous direct endoscopic necrosectomy with flexible endoscope through (E) the dilated tract or (F) a fully covered SEMS; G: Placement of large bore abdominal drain and irrigation catheter for drainage and irrigation of WOPN cavity, respectively.

objectives of PDEN are: (1) Symptom control with near-complete removal of the infected necrotic debris; and (2) visualization of healthy granulation tissue along the cavity wall[18]. The drainage catheter can be gradually changed with smaller diameter catheters every week after the PDEN sessions are completed and the patient's symptoms have improved, for an early sinus tract closure.

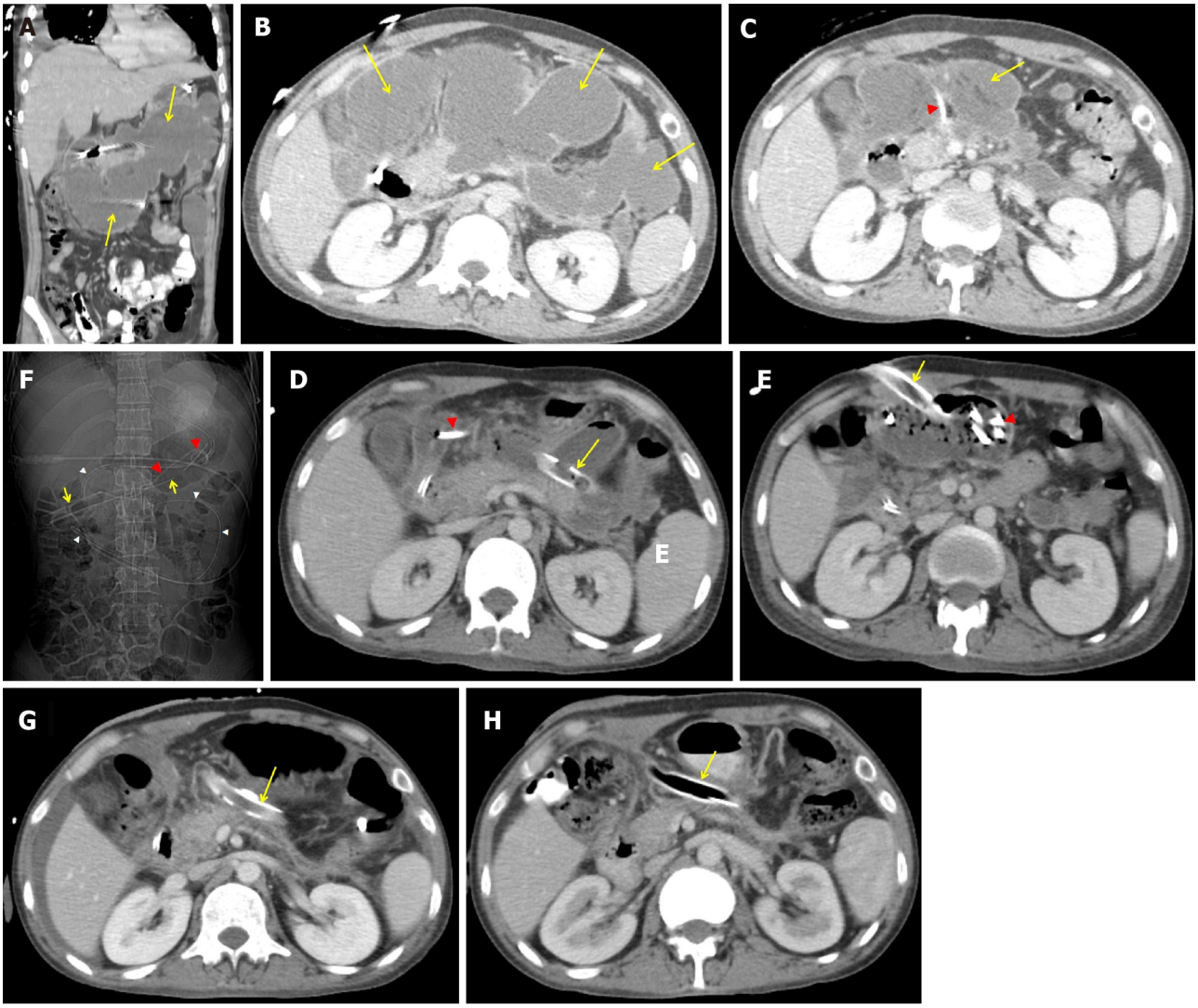

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Figure 2 Abdominal contrast enhanced computerized tomography. A and B: Large, irregular infected pancreatic/peripancreatic collection (PFC) (arrows) in upper abdomen in coronal and transverse sections; C: Partial resolution of PFC (arrow) with a 14 F pigtail (arrow head) *in situ*; D-F: A 26 F drain (arrows) and a 7 F pigtail irrigation catheter (red arrow head) in walled off pancreatic necrosis (WOPN), and nasojejunal tube (white arrow heads); G and H: A 32 F drain (arrow) *in situ* with complete resolution of WOPN after (G) 2 wk and (H) 4 wk of percutaneous direct endoscopic necrosectomy.

Advantages and disadvantages

PDEN can be carried out in a critically ill patient at bedside as it can be done under deep sedation. The main advantage of PDEN is an easier access to various extensions deep within the abdomen with a flexible endoscope as compared to a rigid laparoscope or nephroscope. Like a lumen-apposing metal stent, a fully covered SEMS used in PDEN reduces the need for frequent dilations while also eliminating peritoneal contamination in a transperitoneal approach. The significant adverse event of PDEN is pancreatico-cutaneous fistula, which can occur in up to 7% of the patients[5]. However, dual-percutaneous and transluminal drainage can help to minimize this complication[30]. Table 3 summarizes the advantages and disadvantages of PDEN.

APPLICATION OF PDEN IN IPN-CLINICAL CASE SCENARIO

To better perceive the PDEN case situation, a study of two IPN cases with contrasting clinical settings is provided. The PDEN was carried out using distinct procedures and approaches in both the situations. One case had image-guided percutaneous drainage done in the early phase of acute pancreatitis due to a poor general condition, while the other case had a surgically-placed drain after open-necrosectomy. PDEN was carried out under TIVA.

Table 3 Advantages and disadvantages of percutaneous direct endoscopic necrosectomy

No.	Advantages	Disadvantages
1	It can be done in critically ill patients where laparoscopy access is not possible- bed side	More invasive (compared to transmural necrosectomy) (Multiple interventions-percutaneous drainage followed by multiple tract dilation/drainage catheter exchanges, if not stent-assisted percutaneous direct endoscopic necrosectomy)
2	Subsequent liquefied necrosis drained by gravity	Small endoscopic accessories for necrosectomy-hence, time-consuming and labour-intensive procedure (compared to VARD/surgical necrosectomy)
3	No intraperitoneal transmission (retroperitoneal approach); a fully covered self-expandable metal stent may help to prevent intraperitoneal transmission in transperitoneal approach	The need for repeated procedures for effective drainage (compared to VARD/surgical necrosectomy)
4	Access various extensions deep within the abdomen using the flexible endoscope's angulation and versatility (Figures 3C and 6C)	Pancreatico-cutaneous fistula (compared to transmural necrosectomy)
5	Usually carried out under deep sedation; general anaesthesia avoided	-

VARD: Video-assisted retroperitoneal drainage.

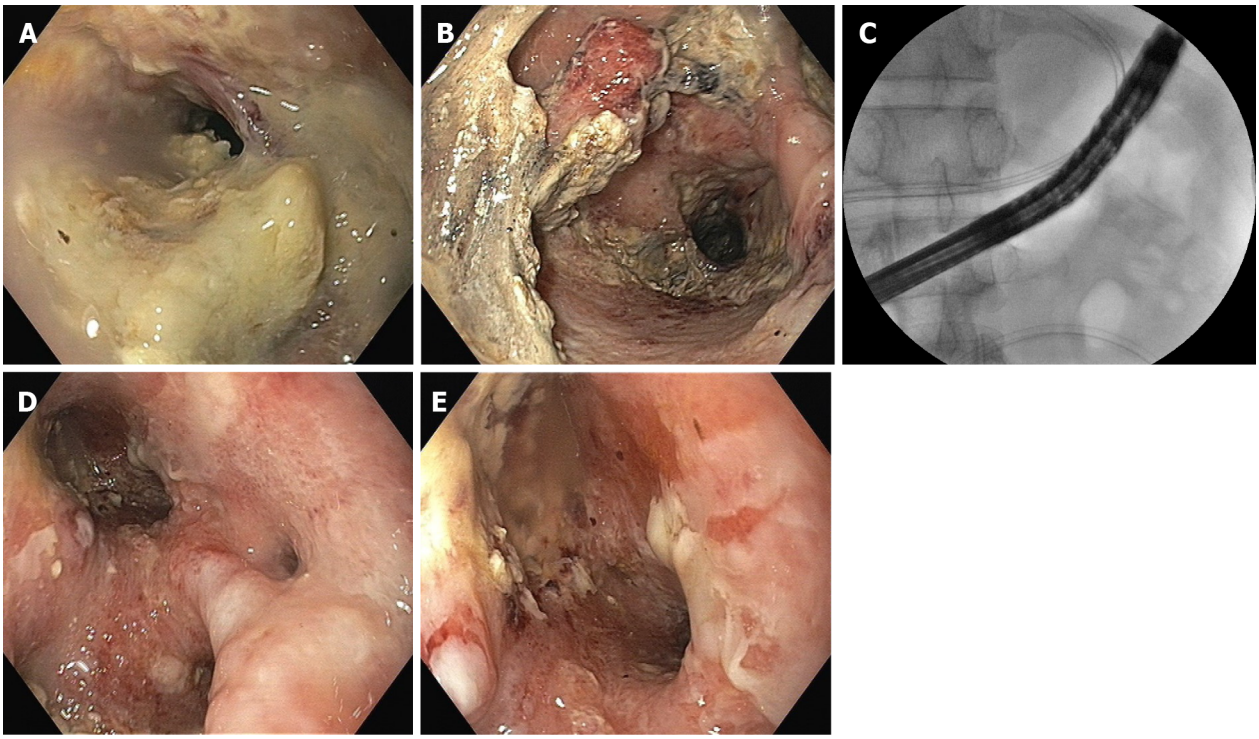

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Figure 3 Percutaneous direct endoscopic necrosectomy. A and B: Infected necrotic debris in walled off pancreatic necrosis (WOPN); C: A flexible upper gastrointestinal scope deep within the WOPN cavity for percutaneous direct endoscopic necrosectomy (PDEN); D and E: Clean WOPN cavity after PDEN.

Case 1

A 35-year-old male was treated for 2 wk for ethanol-induced moderately severe acute pancreatitis. On the 17th day of his illness, he was sent to our center with a persistent fever and loss of appetite. An abdominal contrast enhanced computed tomography (CECT) scan revealed a large irregular PFC in the upper abdomen (Figure 2A and B). Due to his poor health status and early PFC, an image-guided 14 F pigtail was inserted to drain the infected necrotic collection. *Klebsiella pneumoniae* was found in his pus culture, and it was sensitive to Carbepenams and Quinolones. The fever and leucocytosis continued even after the PFC was significantly reduced in size (Figure 2C). In order to irrigate the cavity, a 26 F drain and a 7 F irrigation catheter were inserted into the PFC following dilatation of the tract with a controlled radial expansion balloon over the guide-wire under fluoroscopy guidance (week 4) (Figure 2D). His health steadily improved, with fewer fever spikes and a lower leucocyte count. He did, however, continue to suffer from low-grade fever and systemic inflammatory response syndrome. As a result, following the dilatation of the tract with a controlled radial expansion balloon up to 12 mm, he

underwent PDEN with a flexible upper gastrointestinal endoscope at week 5. A snare and rat-tooth forceps were used to remove the infected necrotic debris (Figure 3). A 7 F irrigation catheter and a 32 F drain were inserted for irrigation and for the subsequent necrosectomy sessions, respectively (Figure 2E and F). He had a second session of PDEN after 2 d. His general condition began to improve subsequently with the resolution of WOPN (Figure 2G and H). The drain was gradually reduced in size over a period of 4 wk, and it was eventually removed after 5 wk of PDEN treatment. At the 12-mo follow-up, he remained asymptomatic.

Case 2

A 47-year-old male was managed for 4 wk for ethanol-induced moderately severe acute pancreatitis. At week 5, he had an exploratory laparotomy with WOPN drainage and necrosectomy for large symptomatic WOPN (not suited for transluminal drainage) with a 24 F drain *in situ*. He was admitted to our centre a week later with a fever, chills, and leucocytosis. The abdominal drain output was minimal with a residual WOPN on the CECT scan (Figure 4A and B). The sinus tract measured 9 to 10 cm in length. Hence, he was scheduled for stent-assisted PDEN. The drain was exchanged over the guide-wire with the catheter. The contrast was injected into the WOPN to delineate the cavity (Figure 5A). A 12-cm long esophageal fully covered SEMS with a 16 mm diameter was inserted across the tract after dilatation to 24 F using Amplatz dilators (Figure 4C; Figure 5B and C). The stent was secured to the skin with sutures (Figure 5C). The WOPN cavity was irrigated with a 7 F irrigation catheter, and a stoma bag was put over the SEMS to collect normal saline after the cavity was irrigated (Figure 4C; Figure 5D and E). He had PDEN through the fully covered SEMS 2 d later. He underwent three sessions of PDEN at 2-d intervals to remove the infected debris using a snare and rat tooth forceps (Figure 6). The fully covered SEMS was removed and replaced with a 32 F drain and a 7 F irrigation catheter after the clinical and haematological improvements. The irrigated normal saline was collected using the stoma bag. An abdominal CECT scan revealed complete resolution of WOPN (Figure 4D) after 1 wk. The drain size gradually decreased and the catheter was removed after 2 mo following stent removal, when the drain output was nil for a week. One month later, he again presented with abdominal pain with WOPN at the previous site on the CECT scan. The previously closed sinus tract spontaneously reopened with a discharge of clear liquid, indicating a pancreatico-cutaneous fistula. At the 10-mo follow-up, he remained asymptomatic with a pancreatico-cutaneous fistula.

Percutaneous direct endoscopic necrosectomy-literature review

To date, several case series and case reports on PDEN have been published[3,5,8,11-27] (Table 1). The largest observational study series of PDEN was reported by Garg *et al*[5], in which 53 patients with IPN underwent PDEN. 42 (79.2%) patients were successfully treated, with 34 patients recovering after PDEN alone and 8 patients recovering after the additional surgery. Eleven patients (7 after PDEN and 4 after surgery) died due to organ failure. The adverse events seen during PDEN included aspiration pneumonia, peritonitis, paralytic ileus, subcutaneous emphysema, and self-limiting haemorrhage. Four (7%) patients had pancreatico-cutaneous fistulas following the PDEN. Early organ failure and necrosis of more than 50% were found to be independent predictors of mortality. PDEN proved to be an effective therapy for IPN in the study[5].

Another observational study from the same group found that 14 of the 15 patients with IPN who received PDEN showed improvement. The adverse events were a pancreatico-cutaneous fistula and self-limiting haemorrhage. One patient required surgery but died as a result of organ failure. According to the authors, PDEN is a safe and effective minimally invasive technique for necrosectomy in IPN[14].

Carter *et al*[11] used PDEN in 4 and 10 patients with IPN along the drainage tract following previous open necrosectomy and percutaneous drainage, respectively. The procedure success rate was 78.6%, with a 14.3% mortality rate. The authors demonstrated a significant reduction in the postoperative organ dysfunction after PDEN[11]. A similar study was conducted by Mui *et al*[12] where PDEN was carried out in 4 and 9 patients with IPN *via* the drain tract following open necrosectomy and percutaneous drainage, respectively. Nine of the thirteen patients needed endoscopic retrograde cholangio-pancreaticography. The overall success rate and mortality rate of PDEN in the study were 76.9% and 7.7%, respectively. The authors concluded that PDEN and endoscopic retrograde cholangio-pancreaticography are useful adjuncts in the management of IPN[12].

A series by Goenka *et al*[18] of 10 patients with symptomatic, laterally-placed WOPN who underwent PDEN showed clinical success in 9 patients. Two patients developed pneumoperitoneum, which was managed conservatively. There was no mortality, cutaneous fistula, or recurrence during the follow-up. The authors concluded that PDEN can successfully manage laterally-placed WOPN[18].

In a recently published retrospective, historically-controlled cohort study by Ke *et al*[25], 37 patients with IPN who received stent-assisted PDEN were compared to 73 historically-control patients. While stent-assisted PDEN reduced hospital stay (38 d *vs* 48 d, $P = 0.035$) and new-onset sepsis (35% *vs* 56%, $P = 0.037$), and allowed for faster necrosectomy, it did not reduce the incidence of major complications and/or mortality (35% *vs* 52%, $P = 0.095$)[25].

All the studies in this regard have shown a comprehensive success rate with a minimal complication rate. Due to its minimally invasive nature, PDEN has been proven to significantly minimize the post-procedure organ dysfunction and new-onset sepsis, therefore improving outcomes in IPN patients.

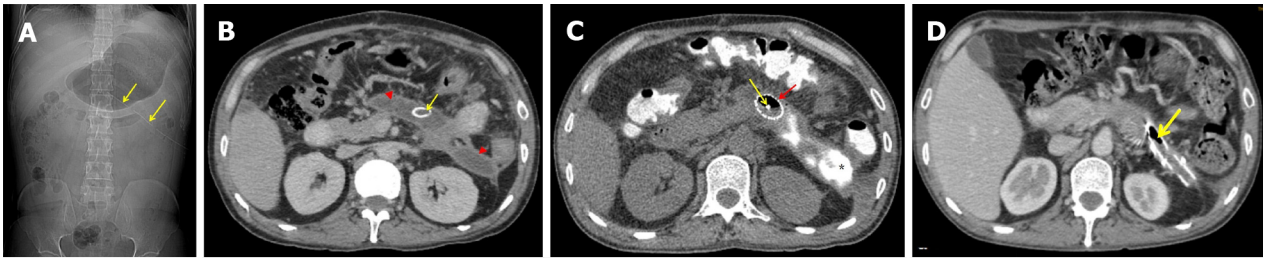

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Figure 4 Abdominal contrast enhanced computerized tomography. A and B: Residual walled off pancreatic necrosis (WOPN) (arrow heads) with post open necrosectomy drain (arrows) *in situ*; C: An esophageal fully covered self-expandable stent (red arrow) in WOPN with a 7 F irrigation catheter (yellow arrow). The asterisk (*) indicates injected contrast within WOPN cavity; D: Complete resolution of WOPN with the drain *in situ* (arrow).

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Figure 5 Drainage tract dilation and placement of a self-expandable metal stent. A: Coiling of the guide-wire along with contrast in walled off pancreatic necrosis (WOPN); B: Dilation of the drainage tract with Amplatz dilators over the guide-wire; C: An esophageal fully covered self- expandable metal stent (SEMS) secured to the skin with sutures; D: A 7 F irrigation catheter in WOPN through a fully covered SEMS; E: A stoma bag secured in place over fully covered SEMS with a 7 F irrigation catheter in place.

PDEN has been shown to treat laterally positioned WOPN that cannot be treated with transmural drainage. The stent-assisted PDEN has been shown to allow easy and multiple passes of the flexible endoscope, resulting in faster necrosectomy. Additionally, a fully covered SEMS prevents peritoneal contamination. The only unfavourable outcome of PDEN is pancreatico-cutaneous fistula. The major limitations of most of the above case series are: (1) The observational nature of the studies; (2) small sample size; (3) lack of uniformity in the procedural steps; and (4) biased case selection. However, large-scale studies may be challenging to conduct because IPN is a heterogeneous disease with substantial diversity in disease course and extent[4].

CONCLUSION

IPN is typically associated with a prolonged course and carries a poor prognosis with high mortality. The multidisciplinary, minimally invasive "step-up" approach is more favoured for the management of infected pancreatic necrotic collections. In a subset of patients in whom necrosectomy is essential, PDEN has emerged as a safe, effective, and minimally invasive adjunct in the armamentarium of IPN management. It may particularly be considered when a conventional drain is *in situ* by virtue of the previous percutaneous or surgical intervention.

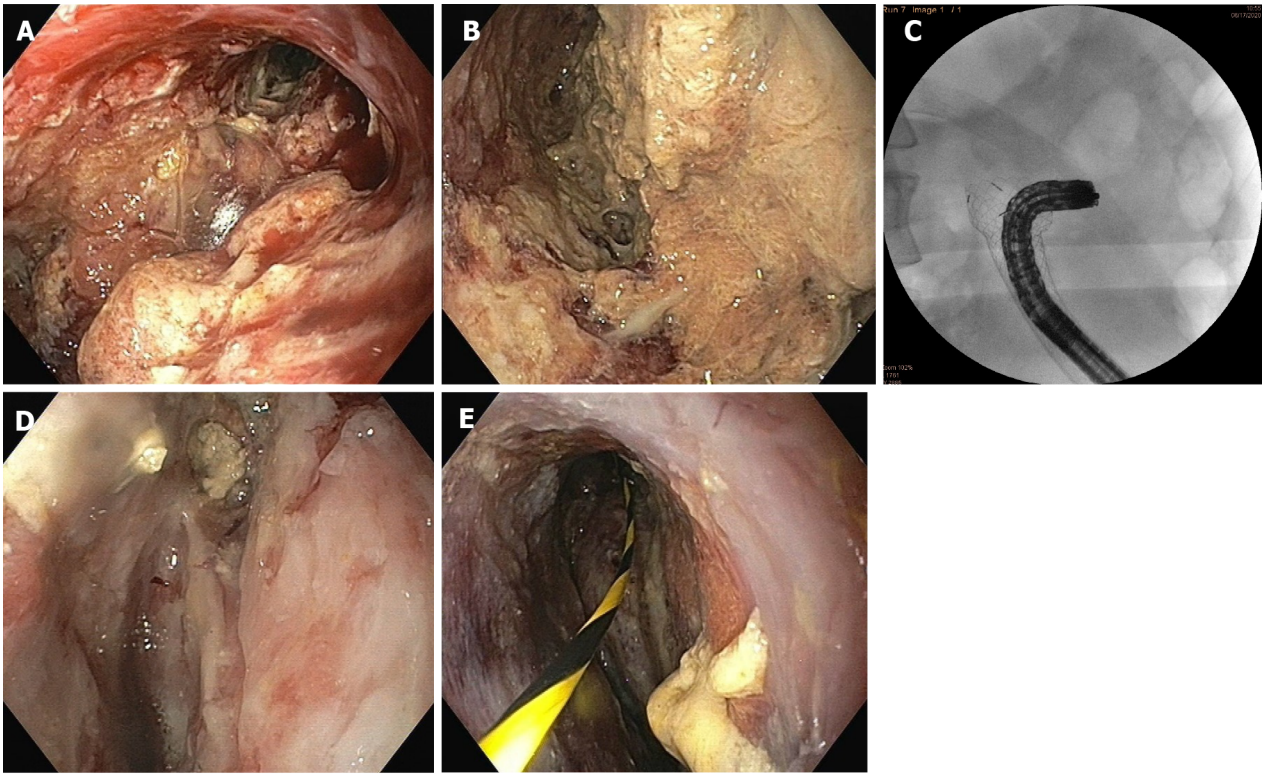

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Figure 6 Percutaneous direct endoscopic necrosectomy. A and B: Infected necrotic debris in walled off pancreatic necrosis (WOPN); C: A flexible endoscope through a fully covered self-expandable metal stent with ability to angulate to reach deep within the cavity; D and E: Clean WOPN cavity after percutaneous direct endoscopic necrosectomy.

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FOOTNOTES

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ORIGINAL ARTICLE

Case Control Study

Factors associated with hypertension remission after gastrectomy for gastric cancer patients

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Abstract

BACKGROUND

Previous studies reported hypertension remission after gastrectomy for gastric cancer patients, and the remission rate was 11.1%-93.8%. We have reported the factors of hypertension remission previously, however, the follow-up time was six months. It is necessary to identify risk factors for hypertension for a relatively longer follow-up time.

AIM

To analyze the predictive factors for hypertension remission one year after gastrectomy of gastric cancer patients and to construct a risk model for hypertension remission.

METHODS

We retrospectively collected the medical information of patients with concurrent gastric cancer and hypertension in a single clinical center from January 2013 to December 2020. Univariate and multivariate logistic regression of hypertension remission were conducted, and a nomogram model was established.

RESULTS

A total of 209 patients with concurrent gastric cancer and hypertension were included in the current study. There were 108 patients in the remission group and 101 patients in the non-remission group. The hypertension remission rate was 51.7% one year after gastrectomy. The remission group had younger aged patients (P = 0.001), larger weight loss (P = 0.001), lower portion of coronary heart disease (P = 0.017), higher portion of II-degree hypertension (P = 0.033) and higher portion of total gastrectomy (P = 0.008) than the non-remission group. Younger age (P =

0.011, odds ratio = 0.955, 95%CI: 0.922-0.990), higher weight loss (P = 0.019, odds ratio = 0.937, 95%CI: 0.887-0.989) and total gastrectomy (P = 0.039, odds ratio = 2.091, 95%CI: 1.037-4.216) were independent predictors for hypertension remission. The concordance index of the model was 0.769 and the calibration curve suggested great agreement. Furthermore, decision curve analysis showed that the model was clinically useful.

CONCLUSION

Younger age, higher weight loss and total gastrectomy were independent predictors for hypertension remission after gastrectomy for gastric cancer patients. The nomogram could visually display these results.

Key Words: Gastric cancer; Hypertension; Gastrectomy; Remission; Nomogram

Core Tip: The purpose of the current study is to analyze the predictive factors for hypertension remission one year after gastrectomy of gastric cancer patients and to construct a risk model for hypertension remission. We found that younger age, higher weight loss and total gastrectomy were independent predictors for hypertension remission after gastrectomy for gastric cancer patients. The nomogram could visually display these results.

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INTRODUCTION

Gastric cancer is the fifth most common cancer and the third most common cause of cancer-related death[1,2]. In China, gastric cancer patients account for about approximately 50% of the world's population[3]. Despite improvements in treatment strategies, radical gastrectomy remains the cornerstone of gastric cancer treatment[4-6].

Hypertension is a major risk factor for cardiovascular disease and an important cause of morbidity and mortality[7,8]. It is estimated that, in 2025, hypertensive patients will account for nearly one-third of adults worldwide[9,10]. In China, the prevalence of hypertension has increased significantly because of urbanization, economic growth, and the aging population[11]. A total of 26.6%-33.6% of the general population is diagnosed with hypertension, resulting in an estimated 23 million deaths per year[12].

Obese patients could experience hypertension remission after bariatric surgery[13,14]. Previous studies reported hypertension remission after gastrectomy for gastric cancer patients, and the remission rate was 11.1%-93.8%[15-20]. We have reported the factors of hypertension remission previously, however, the follow-up time was six months[15].

It is necessary to identify risk factors for hypertension for a relatively longer follow-up time. Therefore, the purpose of the current study was to analyze the predictive factors for hypertension remission one year after gastrectomy in gastric cancer patients; moreover, we constructed a nomogram to visually display these associated factors.

MATERIALS AND METHODS

Patients

We retrospectively collected the medical information of patients with concurrent gastric cancer and hypertension in a single clinical center from January 2013 to December 2020. This study was carried out in accordance with the World Medical Association Declaration of Helsinki. Ethical approval was obtained from the Institutional Ethics Committee of the local hospital (2022-133-2), and informed consent was obtained from all patients.

Inclusion and exclusion criteria

The analysis of this study was restricted to patients who: (1) Had concurrent gastric cancer and hypertension who underwent radical gastrectomy; and (2) had a pathology confirming R0 resection. On

the other hand, those excluded had: (1) Incomplete medical records (n = 32); (2) Irregular follow-up or death within the first year after gastrectomy (n = 37); (3) Irregular hypertension monitoring (n = 77); (4) Irregular antihypertensive medications use (n = 21); (5) Secondary hypertension (n = 4); and (6) had no cardiologist when changing antihypertensive medications (n = 44). Finally, a total of 209 patients with concurrent gastric cancer and hypertension were included in this study, and the flow chart of patient selection is shown in Figure 1.

Definition

Hypertension (HTN) was defined as follows: the average systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg at least three times on different days. Hypertension was classified into I, II and III degrees. Degree I HTN was an average SBP was between 140 and159 mmHg or an average DBP between 90 and 99 mmHg; the degree II-HTN was as follows: the average SBP was between 160 and 179 mmHg or the average DBP was between 100 and 109 mmHg; and the degree III was as follows: the average SBP ≥ 180 mmHg or the average DBP ≥ 110 mmHg.

Hypertension remission was divided into two groups: the remission group and the non-remission group. The remission group was defined as follows: (1) SBP and/or DBP decreased with the same antihypertensive medications; (2) The antihypertensive medications were reduced or ceased. The non-remission group was defined as the antihypertensive medications that remained the same or increased. Weight loss was defined as: weight (one year after gastrectomy) minus preoperative weight.

Surgery management and follow-up

Subtotal gastrectomy or total gastrectomy plus D2 Lymph node dissection was conducted according to the guidelines of the 2010 Japanese gastric cancer treatment guidelines (ver. 3)[21]. The gastrectomy type was based on the location and size of the tumor and the reconstruction methods included the Billroth I, Billroth II or Roux-en-Y methods. Patients were regularly followed up every three months for the first three years and every six months for the following two years.

Data collection

Patients' information was collected through the inpatient system, outpatient system and telephone interview. The collected information was as follows: age, sex, preoperative body mass index, preoperative weight, preoperative albumin, pre-operative hemoglobin, one-year postoperative weight, weight loss, smoking, drinking, type 2 diabetes mellitus (T2DM), coronary heart disease (CHD), hypertension classification, neoadjuvant chemotherapy, surgical techniques (subtotal gastrectomy or total gastrectomy), reconstruction methods, tumor stage, tumor size, hypertension duration and hypertension remission.

Statistical analysis

The continuous data are shown as the mean ± SD and the categorical data are shown as n (%). Chi-square tests, Fisher's exact test or independent samples t tests were used to compare the difference between the remission group and the non-remission group.

Parameters were analyzed by univariate regression analysis for potential predictors of hypertension remission. Multivariate regression analysis was used to identify independent risk factors for hypertension remission. Then, a nomogram was generated. Bootstraps with 300 resamples were performed for internal validation. The predictive performance was assessed by Harrell's concordance index (C-index). A calibration curve was plotted to evaluate the calibration of the nomogram. Decision curve analysis (DCA) was performed to evaluate the clinical usefulness of the nomogram.

Data were analyzed using SPSS (version 22.0) statistical software and R software (version 3.6.1). A bilateral P value of < 0.05 was considered statistically significant.

RESULTS

Patients

A total of 209 patients with concurrent gastric cancer and hypertension were included in the current study according to the inclusion and exclusion criteria (Figure 1). There were 108 patients in the remission group and 101 patients in the non-remission group. The hypertension remission rate was 51.7%.

Characteristics of the remission group and the non-remission group

We compared the baseline information and surgical information of the two groups. The remission group had younger patients (63.6 ± 8.7 years *vs* 67.4 ± 8.0 years, P = 0.001), larger weight loss (-8.2 ± 6.7 kg *vs* -5.6 ± 4.6 kg, P = 0.001), lower portion of CHD (8.3% *vs* 19.8%, P = 0.017), higher portion of II-degree hypertension (47.2% *vs* 31.7%, P = 0.033) and higher portion of total gastrectomy (31.5% *vs* 15.8%, P = 0.008) than the non-remission group. There was no significant difference in terms of other

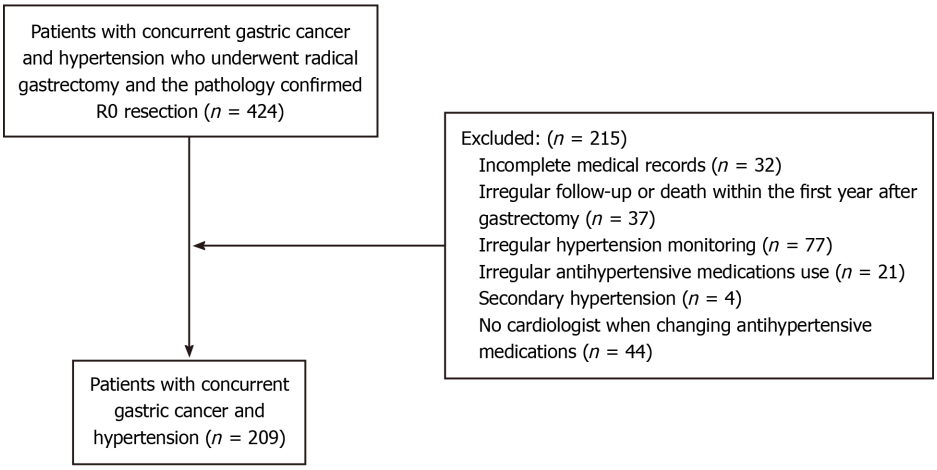

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Figure 1 Inclusion criteria and exclusion criteria of patients with concurrent gastric cancer and hypertension.

information ($P > 0.05$) (Table 1).

Univariate and multivariate logistic regression of hypertension remission

Univariate analyses were conducted to identify potential risk factors for hypertension remission. In univariate logistic regression, younger age ($P = 0.002$, odds ratio = 0.947, 95%CI: 0.916-0.980) and higher weight loss ($P = 0.002$, odds ratio = 0.922, 95%CI: 0.875-0.971), CHD ($P = 0.020$, odds ratio = 0.368, 95%CI: 0.159-0.853) and total gastrectomy ($P = 0.009$, odds ratio = 2.441, 95%CI: 1.248-4.775) were statistically significant (Table 2).

Multivariate logistic regression was conducted to identify independent risk factors. In multivariate logistic regression, younger age ($P = 0.011$, odds ratio = 0.955, 95%CI: 0.922-0.990) and higher weight loss ($P = 0.019$, odds ratio = 0.937, 95%CI: 0.887-0.989) and total gastrectomy ($P = 0.039$, odds ratio = 2.091, 95%CI: 1.037-4.216) were independent predictors (Table 2).

Nomogram, validation and clinical usefulness

The nomogram was built as shown in Figure 2A. The score of each variable could be calculated by drawing vertical line upward to the point scale. The risk factors for hypertension remission could be calculated by summing the total points.

The C-index value of the nomogram was 0.769. The calibration curve of the nomogram suggested great agreement (Figure 2B).

The DCA for the nomogram is shown in Figure 2C, which indicated that when the threshold probability was larger than 0.33, the nomogram might add more benefit than the treat-all or treat-none strategies.

DISCUSSION

A total of 209 patients with concurrent gastric cancer and hypertension were included in the current study and the hypertension remission rate was 51.7% one year after gastrectomy. Younger age, higher weight loss and total gastrectomy were independent predictors for hypertension remission. The C-index of the model was 0.769 and the calibration curve suggested great agreement. Furthermore, decision curve analysis showed that the model was clinically useful.

Previous studies reported that patients with concurrent colorectal cancer and hypertension and/or T2DM could experience hypertension or T2DM remission[22,23]. In gastric cancer patients, remission of T2DM and hypertension was also observed after gastrectomy[20,24-28]. Onco-metabolic surgery was proposed because of the observation of hypertension and/or T2DM remission after gastrectomy for gastric cancer patients. Based on the current findings of hypertension and/or T2DM remission after gastric cancer and colorectal cancer surgery, we thought the onco-metabolic surgery might expand to gastrointestinal cancer surgery.

In terms of patients with concurrent gastric cancer and hypertension, the remission rate was 11.1%-93.8%[15-20]. We summarized these findings in Table 3. We previously reported that age and the surgical techniques used can predict the remission of hypertension six months after gastrectomy[15], however, the follow-up time was only 6 mo. Kim *et al*[16] reported that in early gastric cancer survivors with hypertension, gastrectomy resulted in better blood pressure control, which might be due to the gastrectomy itself, beyond weight loss. Therefore, it was necessary to identify exact risk factors for

Table 1 Baseline characteristics of the remission group and the non-remission group

Characteristics	Remission (*n* = 108)	Non-remission (*n* = 101)	*P* value
Age (yr)	63.6 ± 8.7	67.4 ± 8.0	0.001[b]
Sex			0.420
Male	70 (64.8)	60 (59.4)	
Female	38 (35.2)	41 (40.6)	
Pre-operative BMI (kg/m^2)	23.4 ± 3.0	23.3 ± 32.9	0.770
Pre-operative weight (kg)	63.1 ± 10.0	61.9 ± 10.1	0.366
Pre-operative albumin (g/L)	39.5 ± 5.9	39.4 ± 5.3	0.902
Pre-operative hemoglobin (g/L)	117.9 ± 28.5	118.3 ± 24.4	0.922
Weight loss (kg)	-8.2 ± 6.7	-5.6 ± 4.6	0.001[b]
Smoking	39 (36.1)	41 (40.6)	0.923
Drinking	44 (40.7)	31 (30.7)	0.130
T2DM	21 (19.4)	19 (18.8)	0.908
CHD	9 (8.3)	20 (19.8)	0.017[a]
Hypertension classification			0.033[a]
I	27 (25.0)	25 (24.8)	
II	51 (47.2)	32 (31.7)	
III	30 (27.8)	44 (43.6)	
Neoadjuvant chemotherapy	7 (6.5)	7 (6.9)	0.897
Surgical techniques			0.008[b]
Subtotal gastrectomy	74 (68.5)	85 (84.2)	
Total gastrectomy	34 (31.5)	16 (15.8)	
Reconstruction methods			0.771
B-I	37 (34.3)	36 (35.6)	
B-II	15 (13.9)	17 (16.8)	
R-Y	56 (51.8)	48 (47.6)	
Tumor stage			0.174
I	37 (34.3)	36 (35.6)	
II	15 (13.9)	17 (16.8)	
III	56 (51.8)	48 (47.6)	
Tumor size			0.556
< 5 cm	92 (85.2)	83 (82.2)	
≥ 5 cm	16 (14.8)	18 (17.8)	
Hypertension duration			0.346
≤ 5 yr	53 (49.1)	43 (42.6)	
> 5 yr	55 (50.9)	58 (57.4)	

[a]$P < 0.05$.
[b]$P < 0.01$.
Variables are expressed as the mean ± SD, *n* (%). T2DM: Type 2 diabetes mellitus; BMI: Body mass index; CHD: Coronary heart disease; B-I: Billroth I reconstruction; B-II: Billroth II reconstruction; R-Y: Roux-en-Y reconstruction.

hypertension remission.

Table 2 Univariate and multivariate logistic regression of hypertension remission

Risk factors	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Age (yr)	0.947 (0.916-0.980)	0.002[b]	0.955 (0.922-0.990)	0.011[a]
Sex (male/female)	0.794 (0.454-1.391)	0.421		
Pre-operative BMI (kg/m^2)	1.014 (0.925-1.112)	0.769		
Pre-operative weight (kg)	1.013 (0.986-1.040)	0.365		
Pre-operative albumin (g/L)	1.003 (0.956-1.053)	0.902		
Pre-operative hemoglobin (g/L)	0.999 (0.989-1.010)	0.922		
Weight loss (kg)	0.922 (0.875-0.971)	0.002[b]	0.937 (0.887-0.989)	0.019[a]
Smoking (yes/no)	0.973 (0.557-1.700)	0.923		
Drinking (yes/no)	1.552 (0.877-2.748)	0.131		
T2DM (yes/no)	1.042 (0.523-2.077)	0.908		
CHD (yes/no)	0.368 (0.159-0.853)	0.020[a]	0.517 (0.212-1.265)	0.148
Hypertension classification (III/II/I)	0.761 (0.533-1.087)	0.133		
Neoadjuvant chemotherapy (yes/no)	0.931 (0.315-2.753)	0.897		
Surgical techniques (Total gastrectomy/subtotal gastrectomy)	2.441 (1.248-4.775)	0.009[b]	2.091 (1.037-4.216)	0.039[a]
Reconstruction methods (R-Y/B-II/B-I)	1.318 (0.968-1.794)	0.080		
Tumor stage (III/II/I)	1.072 (0.795-1.445)	0.650		
Tumor size (≥ 5 cm/< 5 cm)	0.802 (0.384-1.674)	0.557		
Hypertension duration (> 5 yr/≤ 5 yr)	0.769 (0.446-1.328)	0.346		

[a]$P < 0.05$.
[b]$P < 0.01$.
OR: Odds ratio; CI: Confidence interval; T2DM: Type 2 diabetes mellitus; BMI: Body mass index; CHD: Coronary heart disease; B-I: Billroth I reconstruction; B-II: Billroth II reconstruction; R-Y: Roux-en-Y reconstruction.

Table 3 Previous studies reporting the remission of hypertension after gastrectomy for gastric cancer patients

Ref.	Year	Country	Sample size	Remission rate	Summary
Peng *et al* [15]	2020	China	143	55.3%	Age and the surgical techniques used can predict the remission of hypertension 6 mo after gastrectomy. However, the follow-up time was only 6 mo
Kim *et al* [16]	2019	South Korea	66	57.6%	In early gastric cancer survivors with hypertension, gastrectomy resulted in better blood pressure control, which may be due to the gastrectomy itself, beyond weight loss
Lee *et al* [17]	2015	South Korea	351	11.1%	The results came from a nationwide cohort study with limited baseline information, no further information could be found in terms of risk factors for hypertension remission
Park *et al* [18]	2020	South Korea	33	42.4%	The study focused on the comparison between the long-limb R-Y reconstruction between conventional R-Y reconstruction, the information for hypertension remission was limited
Wang *et al*[19]	2020	China	16	93.8%	Elaborate parameters of endocrine hormone change, however, the sample size was too small

The molecular mechanism of hypertension remission after gastrectomy for gastric cancer patients is unclear, but it might be related to bariatric surgery for obese patients[29,30]. There were many possible molecular mechanisms of hypertension remission for obese patients after bariatric surgery: elevated activation of the renin–angiotensin–aldosterone system in obese patients might normalize after surgery [31] and the improvement of gastrointestinal gut hormone levels and insulin resistance after surgery [32], a possible effect of these gut hormones on the sympathetic nervous system[33], adipokines and other inflammatory cytokines would lead to hypertension recovery[34]. Thus, similar to bariatric surgery, multiple factors might work together for hypertension remission after gastric cancer surgery

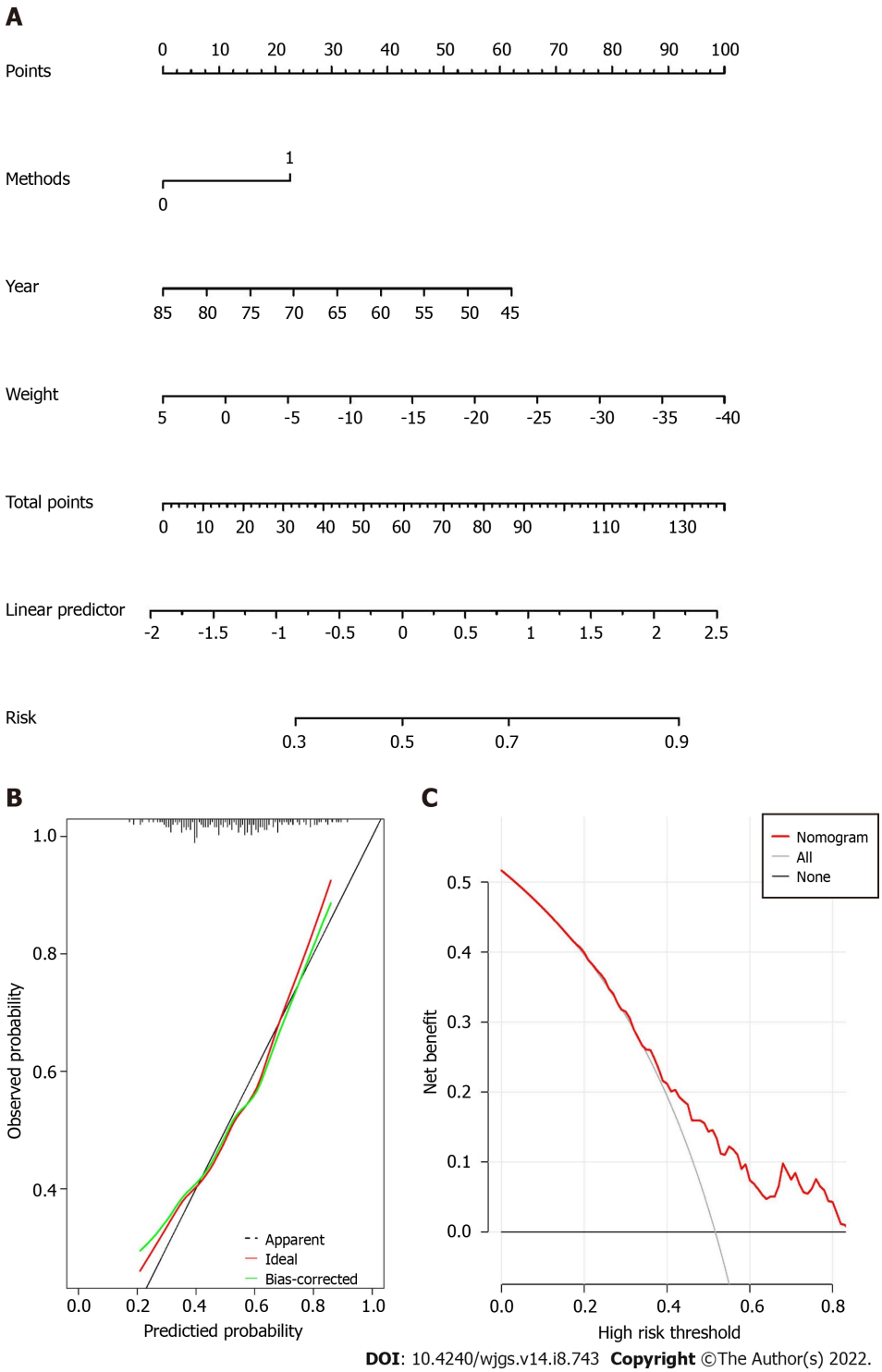

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Figure 2 Predictive model for hypertension remission. A: Nomogram for hypertension remission; B: Calibration curve of the nomogram; C: Decision curve analysis for predicting hypertension remission. TG: Total gastrectomy; SG: Subtotal gastrectomy.

[35-37]. Furthermore, it was reported that early hypertension remission might be related to endocrine hormones and late hypertension remission might be related to neurohumoral regulation[36,37].

For younger patients, vascular elasticity might contribute to the higher rate of hypertension remission [15]. Total gastrectomy had a wider extent than subtotal gastrectomy, and a larger volume of residual stomach in subtotal gastrectomy allowed more food than total gastrectomy, thus total gastrectomy might be associated with higher remission of hypertension[16]. The purpose of this study was different from previous studies reporting the remission of hypertension after gastrectomy for gastric cancer patients. Lee *et al*[17] found no risk factors for hypertension remission. Park *et al*[18] focused on the comparison between long-limb R-Y reconstruction and conventional R-Y reconstruction. The information for hypertension remission was limited. Another study from China focused on the elaborate parameters of endocrine hormone change, however, the sample size was too small[19]. In this study, we

identified three independent predictive factors including younger age, total gastrectomy and higher weight loss, which led to hypertension remission after gastrectomy. Weight loss was an important factor for hypertension control, which was related to lifestyle changes that promoted hypertension remission [38-40].

Some limitations existed in this study. First, this was a retrospective single center study, which might cause selection bias and some detailed data were lost; Second, the follow-up time was relatively short; Third, we only established internal validation, and external validation is needed in the future; Fourth, some blood parameters including leptin, adiponectin, renin, angiotensin II and aldosterone are needed in the following experiments. Therefore, multi-center, large-sample studies with more parameters are needed in future studies to elaborately analyze the factors of hypertension remission.

CONCLUSION

In conclusion, younger age, higher weight loss and total gastrectomy were independent predictors for hypertension remission after gastrectomy for gastric cancer patients one year after surgery. The nomogram could visually display these results. Our study predicted that younger hypertension patients who underwent gastrectomy for gastric cancer might decrease anti-hypertensive medication and relieve hypertension-related comorbidities.

ARTICLE HIGHLIGHTS

Research background

Previous studies reported hypertension remission after gastrectomy for gastric cancer patients, and the remission rate was 11.1%-93.8%. We have reported the factors of hypertension remission previously, however, the follow-up time was six months. It is necessary to identify risk factors for hypertension for a relatively longer follow-up time.

Research motivation

The purpose of the current study was to analyze the predictive factors for hypertension remission one year after gastrectomy in gastric cancer patients.

Research objectives

The purpose of the current study is to analyze the predictive factors for hypertension remission one year after gastrectomy of gastric cancer patients and to construct a risk model for hypertension remission.

Research methods

Univariate and multivariate logistic regression of hypertension remission were conducted, and a nomogram model was established.

Research results

A total of 209 patients with concurrent gastric cancer and hypertension were included in the current study and the hypertension remission rate was 51.7% one year after gastrectomy. Younger age, higher weight loss and total gastrectomy were independent predictors for hypertension remission. The C-index of the model was 0.769 and the calibration curve suggested great agreement. Furthermore, decision curve analysis showed that the model was clinically useful.

Research conclusions

Younger age, higher weight loss and total gastrectomy were independent predictors for hypertension remission after gastrectomy for gastric cancer patients. The nomogram could visually display these results.

Research perspectives

Our study predicted that younger hypertension patients who underwent gastrectomy for gastric cancer might decrease anti-hypertensive medication and relieve hypertension-related comorbidities.

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FOOTNOTES

Author contributions: Kang B and Liu XY contributed equally to this work; Tao W and Peng D contributed to conception and design of the study; all authors contributed to data collection; Cheng YX and Peng D contributed to the data analysis; Peng D led the quality assessments; Kang B and Liu XY write the origin draft; all the authors have agreed on the manuscript which will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Institutional review board statement: This study was conducted in accordance with the World Medical Association Declaration of Helsinki and was approved by the Medical Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (2022-133-2).

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

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ORIGINAL ARTICLE

Retrospective Cohort Study

3D laparoscopic-assisted *vs* open gastrectomy for carcinoma in the remnant stomach: A retrospective cohort study

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Abstract

BACKGROUND

Three-dimensional (3D) laparoscopic technique has gradually been applied to the treatment of carcinoma in the remnant stomach (CRS), but its clinical efficacy remains controversial.

AIM

To compare the short-term and long-term results of 3D laparoscopic-assisted gastrectomy (3DLAG) with open gastrectomy (OG) for CRS.

METHODS

The clinical data of patients diagnosed with CRS and admitted to the First Medical Center of Chinese PLA General Hospital from January 2016 to January 2021 were retrospectively collected. A total of 84 patients who met the inclusion and exclusion criteria were enrolled. All their clinical data were collected and a database was established. All patients were treated with 3DLAG or OG by experienced surgeons and were divided into two groups based on the different surgical methods mentioned above. By using outpatient and telephone follow-up, we were able to determine postoperative survival and tumor status. The postoperative short-term efficacy and 1-year and 3-year overall survival (OS) rates were compared between the two groups.

RESULTS

Among 84 patients with CRS, 48 were treated with OG and 36 with 3DLAG. All patients successfully completed surgery. There was no significant difference between the two groups in terms of age, gender, body mass index, ASA score, initial disease state (benign or malignant), primary surgical anastomosis method, interval time of carcinogenesis, and tumorigenesis site. Patients in the 3DLAG

group experienced less intraoperative blood loss (188.33 ± 191.35 mL *vs* 305.83 ± 303.66 mL; P = 0.045) and smaller incision (10.86 ± 3.18 cm *vs* 20.06 ± 5.17 cm; P < 0.001) than those in the OG group. 3DLAGC was a more minimally invasive method. 3DLAGC retrieved significantly more lymph nodes than OG (14.0 ± 7.17 *vs* 10.73 ± 6.82; P = 0.036), whereas the number of positive lymph nodes did not differ between the two groups (1.56 ± 2.84 *vs* 2.35 ± 5.28; P = 0.413). The complication rate (8.3% *vs* 20.8%; P = 0.207) and intensive care unit admission rate (5.6% *vs* 14.5%; P = 0.372) were equivalent between the two groups. In terms of postoperative recovery, the 3DLAGC group had a lower visual analog score, shorter indwelling time of gastric and drainage tubes, shorter time of early off-bed motivation, shorter time of postoperative initial flatus and initial soft diet intake, shorter postoperative hospital stay and total hospital stay, and there were significant differences, showing better short-term efficacy. The 1-year and 3-year OS rates of OG group were 83.2% [95% confidence interval (CI): 72.4%-95.6%] and 73.3% (95%CI: 60.0%-89.5%) respectively. The 1-year and 3-year OS rates of the 3DLAG group were 87.3% (95%CI: 76.4%-99.8%) and 75.6% (95%CI: 59.0%-97.0%), respectively. However, the 1-year and 3-year OS rates were similar between the two groups, which suggested that long-term survival results were comparable between the two groups (P = 0.68).

CONCLUSION

Compared with OG, 3DLAG for CRS achieved better short-term efficacy and equivalent oncological results without increasing clinical complications. 3DLAG for CRS can be promoted safely and effectively in selected patients.

Key Words: Carcinoma in the remnant stomach; Remnant gastric cancer; 3D laparoscopic-assisted gastrectomy; Open gastrectomy; Safe; Effective

Core Tip: The application of minimally invasive surgery in carcinoma in the remnant stomach (CRS) is affected by factors such as abdominal adhesion, anatomical displacement and unclear markers caused by previous partial gastrectomy. Most previous studies were case series or small-sample studies. This study explored the therapeutic efficacy of three-dimensional (3D) laparoscopic-assisted gastrectomy (3DLAG) *vs* open gastrectomy for CRS. 3DLAG has shown obvious short-term advantages and equivalent long-term oncological efficacy in the treatment of CRS without increasing the incidence of complications. This study provides evidence-based medical support for the treatment of CRS by 3DLAG.

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INTRODUCTION

Remnant gastric cancer (RGC) was initially defined as carcinoma arising in the residual stomach after gastrectomy for benign or malignant disease. The incidence of RGC is about 2%-3%, which is a relatively rare disease in the clinic[1-3]. However, as the long-term survival rate of patients with GC improves due to early detection and individual comprehensive therapy, the incidence of RGC is gradually increasing. As a unique type of GC, RGC had gained increasing attentions in recent years. The Japanese Gastric Cancer Association (JGCA) proposed the broad nomenclature of carcinoma in the remnant stomach (CRS), which contains new cancer, recurrent cancer, residual cancer, to replace the narrow definition of RGC[4].

At present, there is no consensus on the surgical and postoperative management of CRS. Completion gastrectomy of the RS combined with adequate lymph nodes dissection remains the mainstay treatment for resectable CRS[4-6]. In traditional opinion, most scholars believed that the history of upper abdominal surgery was contraindicated for laparoscopic surgery, and patients with RGC were treated with open surgery. With the development of minimally invasive techniques and equipment, three-dimensional (3D) laparoscopy is widely used in the treatment of GC, and displays advantages over two-dimensional (2D) laparoscopy and open surgery[7,8]. The emergence of 3D laparoscopy has pushed minimally invasive surgery into the stereoscopic era. 3D laparoscopy provides a sense of depth and

layering that allows surgeons to obtain a field of vision similar to open surgery. At the same time, compared with open surgery, 3D laparoscopic surgery has a magnified view of the local surgical field and a better and clearer view of the anatomical structure, thus making it easier and more precise to perform the delicate procedures such as dissection, separation of tissues, stopping bleeding and ligating vessels, especially in complicated surgery. However, there are limited reports and studies about the application of 3D laparoscopic-assisted techniques in the treatment of CRS. Our study retrospectively collected the clinical data of 3D laparoscopic-assisted and open surgery in the treatment of CRS, analyzed the short-term and long-term efficacy of the two groups, and provided a reference for the minimally invasive treatment of CRS.

MATERIALS AND METHODS

Inclusion and exclusion criteria

This retrospective cohort study was conducted in the First Medical Center of Chinese PLA General Hospital in China, and it was approved by the ethics committee of the hospital. This study set the inclusion and exclusion criteria of patients as follows.

Inclusion criteria: (1) Patients underwent function-preserving gastrectomy such as proximal or distal gastrectomy due to benign or malignant gastric lesions were diagnosed as CRS including new cancer, recurrent cancer, residual cancer, multifocal cancer by preoperative gastroscopy and biopsy pathology; (2) The surgical method was open or 3D laparoscopic-assisted total residual gastrectomy for RGC; (3) The clinical and pathological data were complete; (4) The operation was performed by experienced doctors, at least associate professor level; and (5) Patients and their relatives were fully aware of the surgical risks and signed the surgical informed consent.

Exclusion criteria: (1) Preoperative examination showed that CRS with distant metastasis such as liver, peritoneum and ovary, and other metastases could not be radically resected; (2) Patients confirmed other malignant tumors simultaneously; (3) Patients underwent palliative gastrectomy or RS-jejunal anastomosis due to acute tumor complications such as hemorrhage, obstruction and perforation; (4) Partial resection or palliative resection of the RS was performed during surgery; (5) Clinical and pathological data were missing or deficient; (6) Postoperative pathology confirmed high-grade epithelial neoplasia and other precancerous lesions; and (7) Patients received systemic chemotherapy or local radiotherapy within 1 mo before surgery.

Patients

A total of 102 patients with CRS who underwent gastrectomy in the First Medical Center of Chinese PLA General Hospital from January 2016 to January 2021 were retrospectively collected. Eight patients underwent subtotal resection of the RS, seven patients were pathologically confirmed to have precancerous lesions after surgery, and three patients underwent palliative surgery due to acute complications. Thus, a total of 18 patients were excluded. Finally, a total of 84 patients with CRS were enrolled in this study and divided into two groups according to different surgical methods. Of them, 48 patients underwent open gastrectomy (OG) for CRS and 36 patients underwent 3D laparoscopic-assisted gastrectomy (3DLAG) (Figure 1).

Observation indicators

The basic information of all patients who met the inclusion and exclusion criteria were collected based on the hospital records, including gender, age, body mass index (BMI), ASA score, initial gastric disease status (benign or malignant), operation type of initial gastrectomy, interval time from surgery to occurrence of CRS, tumor site (anastomotic or nonanastomotic), *etc.* The surgical information included surgical methods (3D laparoscopic-assisted or open surgery), grade of abdominal adhesions, operation time, intraoperative blood loss *etc.* The postoperative information included gastric tube removal time, time to first soft diet intake, time to first off-bed ambulation, time to first flatus and defecation, time to remove the drainage tube, visual analog score (VAS) of postoperative days 1, 3 and 5, intensive care unit (ICU) stay, postoperative hospital stay, and total hospital stay. Postoperative pathological information included pathological type, total number of harvested lymph nodes, number of positive lymph nodes, and TNM stage. Perioperative complications were registered and collected according to the Clavien-Dindo classification system.

Surgical procedures

Regardless of 3DLAG or OG for CRS, the common procedures of radical gastrectomy for RGC are adhesiolysis, lymph node dissection, total resection of the RS and digestive tract reconstruction. It is a major challenge for surgeons to perform adhesiolysis for CRS surgery. Severe adhesion always is a major cause of unplanned organ injury or combined resection. Laparotomy for RGC usually requires the middle incision of the upper abdomen, but it is necessary to pay attention to adhesion of the small intestine under the abdominal wall to avoid unnecessary injury. For regular LAG for GC, 1 cm below

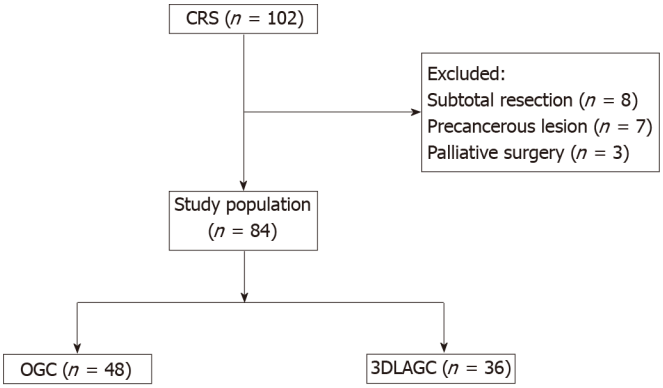

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Figure 1 Flow chart of this study. CRS: Carcinoma in the remnant stomach; OGC: Open gastrectomy for CRS; 3DLAGC: 3D laparoscopic assisted gastrectomy for CRS.

the navel is always selected for the location of the observation port. However, the location of the observation port needs to be changed according to abdominal adhesions caused by a history of upper-abdominal surgery in order to avoid unplanned intra-abdominal organ injury. The right lower-abdominal area is recommended as the optimum site for the observation port during surgery for RGC. The other trocars could be subsequently inserted carefully under visualization. Sometimes, one can also choose the left upper abdomen as the site of the observation port and then as the main operating port. When the initial operation is distal gastrectomy, lymph node dissection around the celiac axis, proximal splenic artery and paracardial nodes were routinely performed, and the left gastric artery is ligated at its base if it has been preserved. When proximal gastrectomy has been performed before, it is necessary to open the esophageal hiatus of the diaphragm and fully dissect the lower segment of the esophagus in order to obtain sufficient cutting edge and facilitate follow-up anastomosis. Meanwhile, the lymph node dissection around the celiac axis and infrapyloric and suprapyloric areas is routinely performed. Roux-en-Y anastomosis is the regular method of digestive tract reconstruction using circular stapler.

Follow-up

Postoperative follow-up was performed by outpatient and telephone to investigate the postoperative survival data and tumor conditions of the patients. Overall survival (OS) was defined as the time from radical operation for RGC to death due to any cause or last time of follow-up. The follow-up time was up to December 2021.

Statistical analysis

All observation indicators were included and a database of patients with CRS was established. All data were processed and analyzed using IBM SPSS Statistics 25 and R version.4.2.2. Continuous variables were analyzed using the *t*-test or Mann-Whitney *U* test; the latter was used for variables that did not meet the criteria for positivity and homogeneity. Categorical variables were compared using the ^{2} test or Fisher's exact probability test. OS was estimated using the Kaplan-Meier method, and curves were compared using the log-rank test. $P < 0.05$ was considered statistically significant.

RESULTS

Patients' characteristics

The demographic and clinicopathological characteristics and initial gastrectomy information of the 3DLAGC group compared with those of the OG group are summarized in Table 1. In this study, there were more men than women with RGC with a male-to-female ratio of 7.4:1. Among the reasons for initial gastrectomy, patients with benign diseases accounted for 39.3%, mainly due to gastrointestinal ulcerative diseases, while patients who performed gastrectomy due to malignant tumors accounted for 60.7% in the initial surgery. Main digestive tract reconstruction methods for distal gastrectomy included Billroth-I anastomosis, Billroth-II anastomosis, and Roux-en-Y anastomosis, accounting for 33.3%, 50.0%, and 6.0%, respectively. The main anastomosis method of proximal gastrectomy was esophageal residual gastric tube-like anastomosis, accounting for 10.7%. No patient underwent proximal gastrectomy with double tract anastomosis. The interval time is generally considered to be the time from primary gastrectomy to the occurrence of adenocarcinoma in the RS. Patients with benign gastric ulcer who underwent partial gastrectomy, the interval time of CRS took longer than those with malignant gastric disease (415.64 mo *vs* 98.16 mo). However, there was no significant difference in the interval time

Table 1 Demographic and clinicopathological characteristics for patients in two cohorts

	OG (*n* = 48)	3DLAG (*n* = 36)	*P* value
Age (yr)	60.62 (10.11)	61.19 (9.90)	0.797
Gender (%)			1.000
Male	42 (87.5)	32 (88.9)	
Female	6 (12.5)	4 (11.1)	
BMI (kg/m^2)	21.65 (3.22)	22.26 (2.59)	0.355
ASA (%)			0.384
1	1 (2.1)	0 (0.0)	
2	33 (68.8)	29 (80.6)	
3	14 (29.2)	7 (19.4)	
Previous disease (%)			0.54
Benign	17 (35.4)	16 (44.4)	
Malignant	31 (64.6)	20 (55.6)	
Primary reconstruction (%)			0.617
Billroth I	16 (33.3)	12 (33.3)	
Billroth II	22 (45.8)	20 (55.6)	
Roux-en-Y	4 (8.3)	1 (2.8)	
Tube-like Stomach esophagogastrostomy	6 (12.5)	3 (8.3)	
Interval time (d)	211.56 (197.35)	237.97 (209.01)	0.556
Site of CRS (%)			0.352
Non-anastomosis	22 (45.8)	12 (33.3)	
Anastomosis	26 (54.2)	66.7)	

All continuous variables were described by mean ± SD; enumeration data were presented by percentage (%). OGC: Open gastrectomy for carcinoma in the remnant stomach; 3DLAGC: 3D laparoscopic assisted gastrectomy for carcinoma in the remnant stomach; BMI: Body mass index; CRS: Carcinoma in the remnant stomach.

between the OG and 3DLAG groups (211.56 ± 197.35 mo *vs* 237.97 ± 209.01 mo; P = 0.556). The incidence of CRS occurring at anastomotic stoma was higher than that at nonanastomotic stoma, and the ratio was 1.47:1. However, there were no significant differences in age, gender, BMI, disease status of the initial surgery, reconstruction method of the initial surgery, interval time from the initial surgery to the occurrence of RGC, and location of RGC between the two groups.

Surgical outcomes and postoperative recovery

Clinical data of intraoperative and postoperative recovery in patients with CRS in the 3DLAG group compared with the OG group are shown in Table 2. The initial surgical operation often causes adhesion of the RS, anastomotic stoma and surrounding tissues, thus affecting exposure of the anatomical level. One of the difficulties in the surgical resection of RGC is intra-abdominal adhesion. Abdominal adhesions grades 2 and 3 were found in most patients in both groups, with no significant difference between the groups (P = 0.098). The mean operating time was shorter in the OG group than in the 3DLAG group (215.67 min *vs* 243.11 min), but the difference between the wo groups was not significant (P = 0.075). The 3DLAG group had less intraoperative blood loss (188.33 ± 191.35 mL *vs* 305.83 ± 303.66 mL; P = 0.045), and significantly shorter surgical incision (10.86 ± 3.18 *vs* 20.06 ± 5.17 cm; P < 0.001), which was minimally invasive. In terms of postoperative recovery, the 3DLAG group had a lower pain score according to VAS on d 1, 3 and 5 after surgery (P < 0.001). The indwelling time of the gastric and drainage tubes, time to early off-bed motivation, time to first flatus, time to first soft diet intake, postoperative hospital stay and total hospital stay in the 3DLAG group were significantly shorter than in the OG group (P < 0.001). There was no significant difference in the incidence of complications (P = 0.372) and ICU admission rate (P = 0.207) between the two groups.

Table 2 Intraoperative and postoperative results for patients in two cohorts

	OGC (*n* = 48)	3DLAGC (*n* = 36)	*P* value
Abdominal adhesion, *n* (%)			0.098
0	7 (14.6)	1 (2.8)	
I	10 (20.8)	3 (8.3)	
II	12 (25.0)	14 (38.9)	
III	12 (25.0)	14 (38.9)	
IV	7 (14.6)	4 (11.1)	
Operation time (min)	215.67 (73.80)	243.11 (61.97)	0.075
Blood Loss (mL)	305.83 (303.66)	188.33 (191.35)	0.045
Incision size (cm)	20.06 (5.17)	10.86 (3.18)	< 0.001
Postoperative VAS			
Day 1	7.17 (0.88)	6.03 (0.70)	< 0.001
Day 3	5.52 (0.80)	3.86 (0.68)	< 0.001
Day 5	3.73 (1.16)	2.06 (0.92)	< 0.001
Nasogastric tube removal time (d)	3.58 (1.93)	1.86 (1.46)	< 0.001
Abdominal drainage tube removal time (d)	8.21 (3.14)	5.83 (2.26)	< 0.001
Time to first ambulation (d)	2.58 (0.71)	1.81 (0.71)	< 0.001
Time to first flatus (d)	4.00 (1.03)	3.08 (0.55)	< 0.001
Time to first soft diet (d)	5.50 (3.58)	3.14 (1.73)	< 0.001
ICU, *n* (%)	10 (20.8)	3 (8.3)	0.207
Postoperative hospital stay (d)	11.19 (6.34)	7.56 (2.25)	0.002
Total hospital stay (d)	15.75 (7.37)	12.19 (4.02)	0.011
Complications (Grade ≥ III), *n* (%)	7 (14.5)	2 (5.6)	0.372
Anastomosis leakage	2 (4.2)	1 (2.8)	
Cardiac failure	1 (2.1)	0 (0.0)	
Anastomosis obstruction	2 (4.2)	0 (0.0)	
Abdominal bleeding	2 (4.2)	1 (2.8)	

All continuous variables were described by mean ± SD; enumeration data were presented by percentage (%). Incision size: primary incision excluding the wounds for drainage and trocar; Complications (Grade ≥ 3): According to classification of Clavien-Dindo; OGC: Open gastrectomy for carcinoma in the remnant stomach; 3DLAGC: 3D laparoscopic assisted gastrectomy for carcinoma in the remnant stomach; VAS: Visual analog score; ICU: Intensive care unit.

Pathology results

Table 3 depicts the pathological results for the 3DLAG and OGC groups. There were no significant differences between the two groups in postoperative pathological type, tumor size, tumor invasion depth or lymph node metastasis. However, the 3DLAG group exhibited a certain advantage in perigastric lymph node dissection. Total number of lymph nodes retrieved by 3DLAG was significantly higher than by OG (14.0 ± 7.17 *vs* 10.73 ± 6.82; $P = 0.036$).

Survival results

Figure 2 depicts the survival of the two groups. The median follow-up duration of the OG group was 34 mo, compared with 27 mo for 3DLAG. The 1-year and 3-year OS rates of the OG group were 83.2% (95%CI: 72.4%-95.6%) and 73.3% (95%CI: 60.0%-89.5%), respectively. The 1-year and 3-year OS rates of the 3DLAG group were 87.3% (95%CI: 76.4%-99.8%) and 75.6% (95%CI: 59.0%-97.0%), respectively. However, these OS rates did not differ significantly between the two groups ($P = 0.68$).

Table 3 Postoperative pathological results for patients in two cohorts

	OGC (*n* = 48)	3DLAGC (*n* = 36)	*P* value
Pathological type, *n* (%)			0.521
Well differentiated	24 (50.0)	21 (58.3)	
Moderately differentiated	19 (39.6)	10 (27.8)	
Poorly differentiated (including signet-ring cell carcinoma)	5 (10.4)	5 (13.9)	
Tumor size (mm)	38.67 (30.51)	35.22 (30.93)	0.612
TNM, *n* (%)			0.084
I	18 (37.5)	15 (41.7)	
IIa	11 (22.9)	8 (22.2)	
IIb	9 (18.8)	1 (2.8)	
IIIa	4 (8.3)	9 (25.0)	
IIIb	4 (8.3)	3 (8.3)	
IIIc	2 (4.2)	0 (0.0)	
Depth of tumor invasion, *n* (%)			0.826
T1	10 (20.8)	9 (25.0)	
T2	9 (18.8)	7 (19.4)	
T3	17 (35.4)	13 (36.1)	
T4	10 (25.0)	5 (19.5)	
Lymph nodes metastases, *n* (%)			0.205
N0	34 (70.8)	20 (55.6)	
N1	6 (12.5)	8 (22.2)	
N2	2 (4.2)	5 (13.9)	
N3	6 (12.5)	3 (8.3)	
Number of positive lymph nodes (*n*)	2.35 (5.28)	1.56 (2.84)	0.413
Total number of lymph nodes retrieved (*n*)	10.73 (6.82)	14.00 (7.17)	0.036

All continuous variables were described by mean ± SD; Enumeration data were presented by percentage (%). OGC: Open gastrectomy for carcinoma in the remnant stomach; 3DLAGC: 3D laparoscopic assisted gastrectomy for carcinoma in the remnant stomach; TNM: Pathological staging (pTNM) according to American Joint Committee on Cancer (AJCC) TNM Staging Classification for Carcinoma of the Stomach (8th ed).

DISCUSSION

RGC, first described by Balfour[9] in 1922, is defined as a carcinoma occurring in the RS after partial gastrectomy for peptic ulcer disease. Since then, RGC had been gradually known as a unique disease. In 1998, the concept of CRS was initially proposed and continuously used by the JGCA[10]. It was widely accepted that the adenocarcinoma occurring in the RS after gastrectomy was called CRS, regardless of whether the initial disease was benign or malignant, or the interval time.

As a subtype of GC with unique characteristics, the incidence of CRS showed a male preponderance, with a male-to-female incidence ratio of 3.1:1[11]. In our study, CRS was also more common in men, but the incidence ratio of male-to-female was 7.4:1, which was higher than the ratio reported in previous studies. Several studies clearly indicated that the RS after gastrectomy had a high risk of developing CRS, and the anastomosis had a higher prevalence to develop stump carcinomas in a shorter time interval than other site of the RS[12-14]. It has also been shown that CRS tends to arise from the sites of anastomosis in patients treated with Billroth II reconstruction, in contrast to nonanastomotic sites in patients treated with Billroth I reconstruction[5,15,16]. In our study, carcinoma in the RS at the anastomotic site accounted for about 59.5% of cases; of which, Billroth I reconstruction accounted for 32% and Billroth II for 52%, which was consistent with the epidemiological characteristics of previous studies.

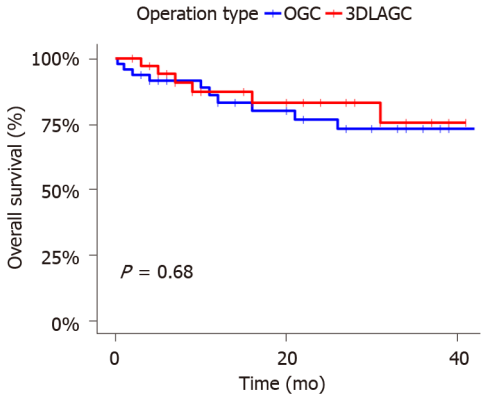

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Figure 2 Kaplan-Meier estimates of overall survival for open gastrectomy for carcinoma in the remnant stomach group and 3D laparoscopic assisted gastrectomy for carcinoma in the remnant stomach group. The 1-yr and 3-yr overall survival (OS) rates for the open gastrectomy group were 83.2% [95% confidence interval (CI): 72.4%-95.6%] and 73.3% (95%CI: 60.0%-89.5%) respectively. The 1-yr and 3-yr OS rates for the 3D laparoscopic assisted gastrectomy for carcinoma in the remnant stomach group were 87.3% (95%CI: 76.4%-99.8%) and 75.6% (95%CI: 59.0%-97.0%) respectively. However, there was no significant difference in 1-yr and 3-yr OS rates between the two groups, and the long-term survival results were comparable (P = 0.68). CRS: Carcinoma in the remnant stomach; OGC: Open gastrectomy for CRS; 3DLAGC: 3D laparoscopic assisted gastrectomy for CRS.

Intra-abdominal adhesions and anatomical displacement presented significant challenges for surgeons in both OG and 3DLAG for RGC[17-19]. Extensive and intensive intra-abdominal adhesions due to previous surgery may significantly prolong the operation time, increase intraoperative blood loss, and lead to unplanned collateral damage to the surrounding tissues and organs. In our study, the degree of abdominal adhesions was macroscopically inspected and scored using Knightly's grading system for assessment of the intensity and Linsky's grading system for assessment of the extent of adhesions[20]. Almost 13.1% of patients had grade 4 abdominal adhesions, which may lead to unplanned damage to peripheral organs. While most patients with CRS, approximately 56%, had abdominal adhesion below grade 3, the abdominal adhesion mainly existed in the previous operation area. However, there was no significant difference in abdominal adhesions between the 3DLAG and OG groups (P = 0.098). The first successful application of laparoscopic surgery in the treatment of RGC was reported by Yamada *et al*[17] in 2005. Other reports have shown the ever-increasing feasibility and safety of LAG for RGC; in some cases, even proving superior to traditional open surgery[18,19]. However, Son *et al*[21] suggested that although laparoscopic total gastrectomy was technically feasible, it did not show a definite clinical advantage over laparotomy in the treatment of RGC. 3D laparoscopy in the treatment of CRS has shown many advantages in the separation of abdominal adhesions. An outstanding advantage of laparoscopic surgery is that the establishment of carbon dioxide pneumoperitoneum can make the connective tissue space appear clearly and make it possible to identify the correct dissection layer[22]. In addition, 3D laparoscopy can overcome the disadvantages of traditional laparoscopy, such as lack of sense of space and distance, presenting a stereoscopic vision closer to open surgery[23]. However, compared with open surgery, the enlarged surgical field of 3D laparoscopy shows the anatomical structure more clearly, which is more conducive to delicate operations, making it easier to find the correct anatomical level, resulting in less surgical bleeding and adverse consequences. It also avoids unnecessary damage to surrounding tissues or organs due to adhesiolysis and decreases the probability of unplanned combined devisceration.

Our study found that the 3DLAG group showed obvious advantages in short-term postoperative outcomes. We attributed those advantages to the magnification effect, 3D sense, and spatial depth of the surgical field. Because 3D laparoscopic surgery made it easier to obtain the correct anatomical landmark and dissect important tissues accurately such as blood vessels, nerves and perigastric lymph nodes[24,25]. 3DLAGC group had less intestinal traction and flipping, damage to surrounding tissues during adhesiolysis, trauma and inflammatory response. Enhanced recovery after surgery (ERAS) protocols have been effective in improving postoperative recovery after major abdominal surgeries[26,27]. All patients with CRS enrolled in this study underwent preoperative education and evaluation, intraoperative stretch socks for thrombosis prevention, intraoperative warmth, postoperative multimode analgesia, encouragement of early ambulation, and postoperative enteral and parenteral nutrition support, which were in line with ERAS protocols. Take considerations that not every patient is eligible for all items of ERAS, we hold the opinion that patients who meet a few of the items should accept the management of ERAS. However, minimally invasive surgery is the cornerstone of ERAS. Through minimally invasive surgical methods, patients can remove the gastric tube and drainage tube early after surgery, thus reducing nausea, vomiting and other gastrointestinal reactions caused by gastric tube stimulation and reduce pain and discomfort caused by the abdominal drainage tube. Early removal of the gastric tube and drainage tube is beneficial to the early off-bed activity of patients, promoting

recovery of gastrointestinal function, facilitating early eating of patients and accelerating the rehabilitation process. The total number of dissected lymph nodes was significantly more in the 3DLAG than OG group, which may be related to the visual magnification and flexibility in tight spaces. While the staging system of CRS is not yet established, it generally follows the TNM staging of primary GC. The number of positive lymph nodes (pN) is key to determination of the N stage, but inadequate lymph nodes harvested in patients with CRS might influence the predictive value of pN. Some research has demonstrated that the lymph node ratio (LNR) has significant prognostic value for patients with CRS [28]. When the retrieved lymph node count is < 15, the LNR is superior to pN as an important and independent prognostic index of CRS[29]. In spite of the obvious postoperative short-term advantages shown by 3DLAG, the long-term survival results were similar between the 3DLAG and OG groups with the 1-year and 3-year OS rates comparable between the two groups.

Several limitations to our study warrant mention. Our study was a retrospective study, which had a potential for selection bias. The number of patients enrolled was small. Prospective randomized controlled trials with large samples and multiple centers are needed in the future. Despite these limitations, our study demonstrated the feasibility and efficacy of 3DLAG for CRS and showed some advantages over OG in short-term postoperative outcomes.

CONCLUSION

Nowadays, patients with GC can obtain long-term survival due to the application of comprehensive treatments, thus causing an increase in incidence of CRS. Compared with OG, 3DLAG for CRS can achieve better short-term efficacy and equivalent oncological results without increasing clinical complications. In some medical centers, 3DLAG for CRS can be applied and promoted in selected patients.

ARTICLE HIGHLIGHTS

Research background

Three-dimensional (3D) laparoscopy provides a 3D sense of depth and layering that allows surgeons to obtain a field of vision similar to open surgery. 3D laparoscopic techniques are gradually being applied in the treatment of carcinoma in the remnant stomach (CRS), but their clinical efficacy remains controversial.

Research motivation

There are limited reports and studies about the application of 3D laparoscopic-assisted techniques in the treatment of CRS. No study has shown whether 3D laparoscopic-assisted gastrectomy (3DLAG) is superior or non-inferior to open gastrectomy (OG) for CRS.

Research objectives

This study retrospectively collected the clinical data of 3DLAG and OG in the treatment of CRS, analyzed the short-term and long-term efficacy of the two methods, and provided a reference for the minimally invasive treatment of CRS.

Research methods

The authors retrospectively evaluated 84 patients with CRS who had undergone OG for carcinoma or 3DLAGC at the First Medical Center of Chinese PLA General Hospital from January 2016 to January 2021. The short-term and long-term outcomes were compared between the OG (n = 48) and 3DLAG (n = 36) groups.

Research results

Compared with the OG group, the 3DLAG group had less surgical trauma and faster recovery after surgery. However, the complication rate and intensive care unit admission rate were equivalent between the two groups. The 1-year overall survival (OS) and 3-year OS rates were similar between the two groups, which suggested comparable long-term survival results between the groups. Our research showed that 3DLAG for CRS can be promoted safely and effectively in selected patients.

Research conclusions

Compared with OG, 3DLAG for CRS can achieve better short-term efficacy and equivalent oncological results without increasing clinical complications.

Research perspectives

Prospective randomized controlled trials with large samples and multiple centers are needed in the

future.

FOOTNOTES

Author contributions: Wu D and Wang XX designed the experiment; Wu D and Song QY performed the experiment; Li XG and Xie TY collected data; Wu D, Lu YX and Zhang BL analyzed the data; Wu D and Li S created the tables and figures based on the data; Wu D wrote the initial draft; and Wang XX modified the draft.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Nomogram to predict permanent stoma in rectal cancer patients after sphincter-saving surgery

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Abstract

BACKGROUND

Approximately 20 percent of patients with a tumour localized in the low rectum still encounter the possibility of requiring permanent stoma (PS), which can cause drastic changes in lifestyle and physical perceptions.

AIM

To determine the risk factors for PS and to develop a prediction model to predict the probability of PS in rectal cancer patients after sphincter-saving surgery.

METHODS

A retrospective cohort of 421 rectal cancer patients who underwent radical surgery at Taipei Medical University Hospital between January 2012 and December 2020 was included in this study. Univariate and multivariate analyses were performed to identify the independent risk factors for PS. A nomogram was developed according to the independent risk factors obtained in the multivariate analysis. The performance of the nomogram was assessed using a receiver operating characteristic curve and a calibration curve.

RESULTS

The PS rate after sphincter-saving surgery was 15.1% (59/391) in our study after a

median follow-up of 47.3 mo (range 7–114 mo). Multivariate logistic regression analysis demonstrated that local recurrence, perirectal abscess, anastomosis site stenosis, perineural invasion, tumor size and operative time were independent risk factors for PS. These identified risk factors were incorporated into the nomogram, and the concordance index of this model was 0.903 (95%CI: 0.851-0.955). According to the calibration curves, the nomogram represents a perfect prediction model.

CONCLUSION

Several risk factors for PS after sphincter-saving surgery were identified. Our nomogram exhibited perfect predictive ability and will improve a physician's ability to communicate the benefits and risks of various treatment options in shared decision making.

Key Words: Nomogram; Permanent stoma; Risk factor; Shared decision making; Sphincter-saving operation; Rectal cancer

Core Tip: Approximately 20 percent of patients with a tumour localized in the low rectum still encounter the possibility of requiring permanent stoma (PS), which can cause drastic changes in lifestyle and physical perceptions. The study aimed to identify the risk factors for PS in rectal cancer patients after sphincter-saving surgery. Our results showed that the predictive models constructed by clinicopathological features exhibited perfect predictive ability and will allow physicians to inform patients about the possibility of PS prior to surgery.

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INTRODUCTION

Shared decision making (SDM) is a structured process that incorporates available scientific evidence, patient values, preferences, and life situation into screening decisions[1]. The benefits of SDM include improved medical quality, improved patient satisfaction, increased patient compliance to medical treatment, and reduced patient anxiety during treatment; SDM also helps patients understand the issues with which they should be familiar before they undergo treatment[2,3]. This discussion is particularly important in cancer treatment since patients are often provided with more than one available treatment strategy[4].

Despite innovative advancements, the management of rectal cancer remains a formidable endeavor, especially distally located rectal cancer[5]. It is extremely challenging to work in the low and narrow pelvis with laparoscopic straight instruments. Male sex, high body mass index (BMI), low rectal cancer, bulky tumor, and advanced stage are well known to increase the technical difficulty[6]. Moreover, a certain percentage of anastomosis-related complications will occur after colorectal surgery. Anastomosis complications, such as anastomotic leakage, perirectal abscess, and anastomotic stenosis, often lead to permanent stoma (PS). According to previous studies, 3%-24% of rectal cancer patients experience anastomosis complications after sphincter-saving surgery[7-9].

A nomogram is a statistical tool that can transform a complex regression equation result into a simple and visual graph[10]. Thus, the results of prediction models become more readable and valuable. The aim of this study was to develop and validate a nomogram that incorporated both the clinical and pathologic risk factors for individual preoperative prediction of PS in patients with rectal cancer who underwent sphincter-saving surgery.

MATERIALS AND METHODS

Patient selection

We retrospectively reviewed records of patients with rectal cancer who underwent surgery at Taipei Medical University Hospital from January 2012 to December 2020. The inclusion criteria were as follows: (1) Patients older than 18 years; (2) Underwent radical surgery [low anterior resection,

intersphincteric resection, or abdominoperineal resection (APR)]; (3) Pathological diagnosis of malignancy; and (4) lesion located within 12 cm from the anal verge. The exclusion criteria were as follows: (1) Patients with stage IV disease; (2) Those who underwent emergency surgery; and (3) Those who underwent other organ resection during primary surgery. Defunctioning stoma was performed if any of the following conditions applied: (1) Positive air leak test; (2) Patient received preoperative chemoradiotherapy (CRT); (3) Anastomosis had tension or poor blood supply; (4) Presence of incomplete anastomotic ring; (5) Very low anastomosis; (6) Patients' clinical condition indicated defunctioning stoma; and (7) The surgeon elected to perform this procedure based on his/her experience. The condition of PS included non-reversal temporary stoma and stoma re-creation after reversal surgery (Figure 1). This study was approved by the Joint Institutional Review Board of Taipei Medical University (TMU-JIRB No: N202103023).

Data collection and definition of postoperative complications

Patient demographics and potential risk factors for PS were retrospectively collected and included sex, age, BMI, comorbidities (diabetes mellitus, hypertension, heart disease, chronic obstructive pulmonary disease, chronic kidney disease, liver disease), smoking status, clinical tumor-node-metastasis stage, whether the patient received neoadjuvant CRT, American Society of Anesthesiologists (ASA) score, tumor location (distance from the anal verge), tumor markers, such as carcinoembryonic antigen (CEA), preoperative lab data (hemoglobin and albumin), surgical approach, blood loss, operative time, stoma status, postoperative hospital stay, histologic grade, lymph vascular invasion, perineural invasion, circumferential resection margin (CRM) status, whether the patient received adjuvant chemotherapy, local recurrence, postoperative leakage, anastomosis site stenosis, perirectal abscess, and recto-visceral fistula.

Anastomotic leakage was defined as peritonitis that was clinically apparent (discharge containing pus or fecal material) or radiologically evident (contrast leakage or abscess around the anastomosis). Perirectal abscess (late anastomotic leak) was defined as a leak that was diagnosed more than 30 d after surgery. Anastomotic stricture was defined as the inability of a 12-mm proctoscope to pass through the anastomosis. A PS was defined when a closure procedure had not been performed or scheduled within the follow-up period (median, 47 mo; range, 7–114 mo).

Postoperative follow-up

Patients were followed-up every 3 mo during the first 2 years and then every 6 mo until the fifth year. Clinical examination and serum CEA testing were performed during each follow-up visit. Surveillance colonoscopy was performed within 12 mo after the initial surgery and every other year thereafter. Contrast-enhanced computed tomography scan of the thorax, abdomen, and pelvis was performed annually for 3 years and subsequently only when clinically indicated.

Data and risk factor analysis

Categorical variables are presented as counts and percentages, while continuous variables are depicted as the mean ± SD. Differences between both groups were assessed with the chi-square test or Fisher exact test depending on the sample size. Univariate analyses for risk factors related to a PS were performed. Multivariate logistic regression was conducted to identify the independent risk factors. A two-tailed P value < 0.05 was considered statistically significant. Statistical analyses were performed using SAS v9.4 (Cary, NY)

Nomogram development

Statistical analyses of the nomogram were conducted using SAS v 9.4 and R (ver. 3.0.1, Vienna, Austria). The rms package in R was used to plot the nomogram as a graphical calculating device that visualizes an approximation of mathematical function. Features of the nomogram are based on logistic regression models. The nomogram function in the rms package was adopted to generate nomograms from the fitted logistic statistical model. As a result, the performance of the nomogram is dependent on the regression models. We assessed the predictive power of the nomogram using receiver operating characteristic curve analysis. Calibration curves were used to explore the performance of the nomogram.

RESULTS

Patient characteristics

In all, 421 patients who underwent radical surgery are included in our study, including 391 (92.9%) who underwent sphincter-saving surgery and 30 (7.1%) who underwent APR. Moreover, 136/391 (34.8%) patients who underwent a sphincter-saving procedure had a temporary stoma after primary surgery. After a median follow-up of 47.3 mo (range 7–114 mo), 59/391 (15.1%) patients were confirmed to have PS, and the details of the stoma condition are shown in Figure 1. According to our data, 332 patients are in the stoma free group, while 89 patients are in the PS group. In summary, the PS rate after sphincter-

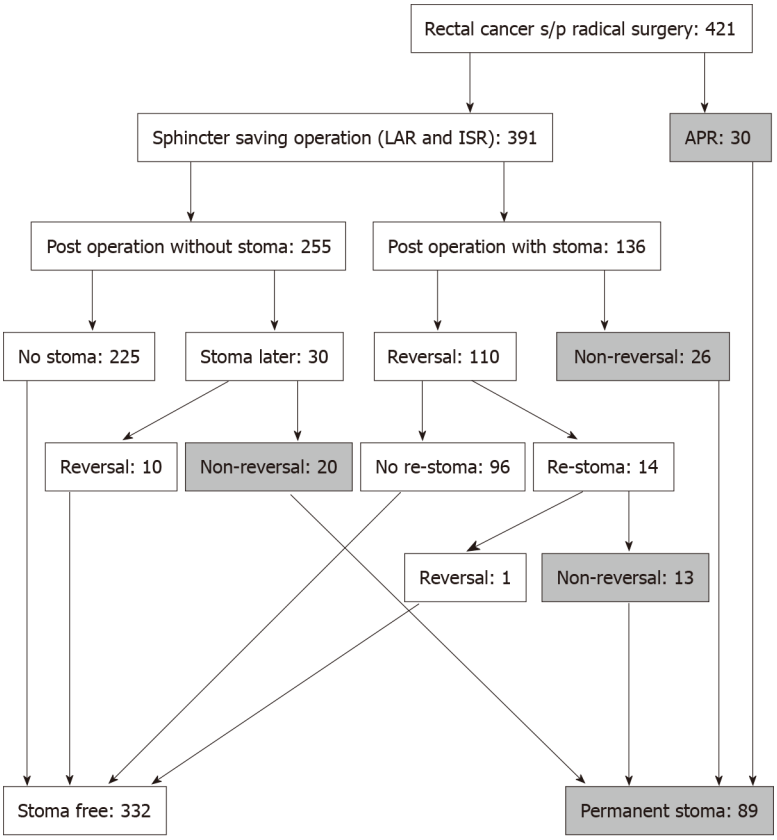

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Figure 1 Study flow chart.

saving surgery at our hospital from January 2012 to December 2020 is 15.1% (59/391), and the total sphincter-saving rate is 78.9% (89/421). All data compared between the stoma free and PS groups are presented in Table 1.

Feature selection

Data from the univariate and multivariate analyses for PS are provided in Table 2. According to the multivariate logistic regression analysis, seven features were significantly related to PS. The independent risk factors for PS by multivariate logistic regression were local recurrence [odd ratio (OR), 111.578; 95%CI: 7.964-> 999; $P < 0.001$], perirectal abscess (OR, 369.397; 95%CI: 17.137-> 999; $P < 0.001$), anastomosis site stenosis (OR, 211.256; 95%CI: 13.705-> 999; $P < 0.001$), perineural invasion (OR, 7.674; 95%CI: 1.138-51.745; $P = 0.036$), tumor size (OR, 1.076; 95%CI: 1.015-1.14; $P = 0.014$), liver disease (OR, 0.054; 95%CI: 0.004-0.698; $P = 0.025$), and operative time (min) (OR, 1.008; 95%CI: 1.002-1.014; $P = 0.01$). We excluded liver disease because of OR < 1. Thus, these six variables were selected to construct the nomogram.

Construction of the nomogram

The prognostic nomogram that integrated all potential risk factors for PS in the cohort is shown in Figure 2. The nomogram model was validated by computing the concordance index (C-index) of the nomogram sample. The nomogram provides a visualization of accumulated risk by mapping the predicted probabilities into points on a scale from 0 to 1 in a graphical interface. The total points accumulated by each covariate correspond to the predicted probability in a given patient. To further illustrate this, the point system functions by ranking the effect estimates, regardless of statistical significance, and this ranking is influenced by the presence of other covariates. Despite statistical significance, the risk factor whose absolute value has the largest regression coefficient will be assigned 100 points on the scale, while the remaining variables are assigned a smaller number of points proportional to their effect size. As shown in Figure 2, perirectal abscess has the highest effect, and thus, this variable is assigned 100 points. Whereas a patient with perirectal abscess would be assigned 100 points, a patient without perirectal abscess would be assigned 0 points. Similarly, a patient with perineural invasion would be assigned 40 points, while a patient with a tumor size of 20 mm would be assigned 10 points. For example, a patient with perirectal abscess, perineural invasion, and a tumor size of 20 mm would be assigned 150 points overall, which is mapped to an approximate predicted probability of 70%.

Table 1 Comparison of patient-related characteristics between the stoma free and permanent stoma groups

Characteristic	Stoma free (*n* = 332)	Permanent stoma (*n* = 89)	*P* value
Age, yr	60.78 ± 12.80	60.56 ± 12.60	0.888
Sex (*n*)			0.716
Male	196 (59.04%)	50 (56.18%)	
Female	136 (40.96%)	39 (43.82%)	
Body mass index, kg/m^2	24.00 ± 3.97	24.47 ± 4.32	0.331
Comorbidity (*n*)			
DM	68 (20.48%)	14 (15.73%)	0.393
Hypertension	103 (31.02%)	33 (7.08%)	0.339
Heart disease	25 (7.53%)	8 (8.99%)	0.816
COPD	2 (0.60%)	2 (2.25%)	0.421
Chronic kidney disease	36 (10.84%)	9 (10.11%)	0.996
Liver disease	39 (11.75%)	10 (11.24%)	1
Smoker (*n*)	49 (14.76%)	9 (10.11%)	0.339
Distance to anus verge, cm	7.06 ± 3.52	4.68 ± 3.96	< 0.001
Clinical T stage (*n*)			0.002
T0	8 (2.41%)	1 (1.13%)	
T1	12 (3.61%)	1 (1.13%)	
T2	50 (15.06%)	8 (8.98%)	
T3	218 (65.66%)	56 (62.92%)	
T4	20 (6.03%)	17 (19.10%)	
Data loss	24 (7.23%)	6 (6.74%)	
Clinical N stage (*n*)			0.44
N0	108 (32.53%)	23 (25.84%)	
N1	100 (30.12%)	31 (34.83%)	
N2	100 (30.12%)	29 (32.59%)	
Data loss	24 (7.23%)	6 (6.74%)	
AJCC c TNM stage (*n*)			0.002
Stage 0	8 (2.41%)	1 (1.13%)	
Stage I	49 (14.76%)	7 (7.86%)	
Stage II	52 (15.66%)	15 (16.85%)	
Stage III	199 (59.94%)	60 (67.42%)	
Data loss	24 (7.23%)	6 (6.74%)	
NACR (*n*)	222 (66.87%)	69 (77.53%)	0.026
Hb, g/dL	12.78 ± 1.57	12.52 ± 1.72	0.169
Albumin, g/dL	4.14 ± 0.36	4.08 ± 0.37	0.19
CEA, ng/mL	4.81 ± 8.58	6.15 ± 8.69	0.198
ASA score (*n*)			0.182
I	26 (7.83%)	3 (3.37%)	
II	271 (81.63%)	73 (82.02%)	
III	30 (9.03%)	12 (13.48%)	
Data loss	5 (1.51%)	1 (1.13%)	

ASA: American Society of Anesthesiologists; COPD: Chronic obstructive pulmonary disease; CEA: Carcinoembryonic antigen; DM: Diabetes mellitus; AJCC: American Joint Committee on Cancer; Hb: Hemoglobin; NCRT: Neoadjuvant chemoradiotherapy; TNM: Tumor-node-metastasis; NACR: Neoadjuvant chemoradiation.

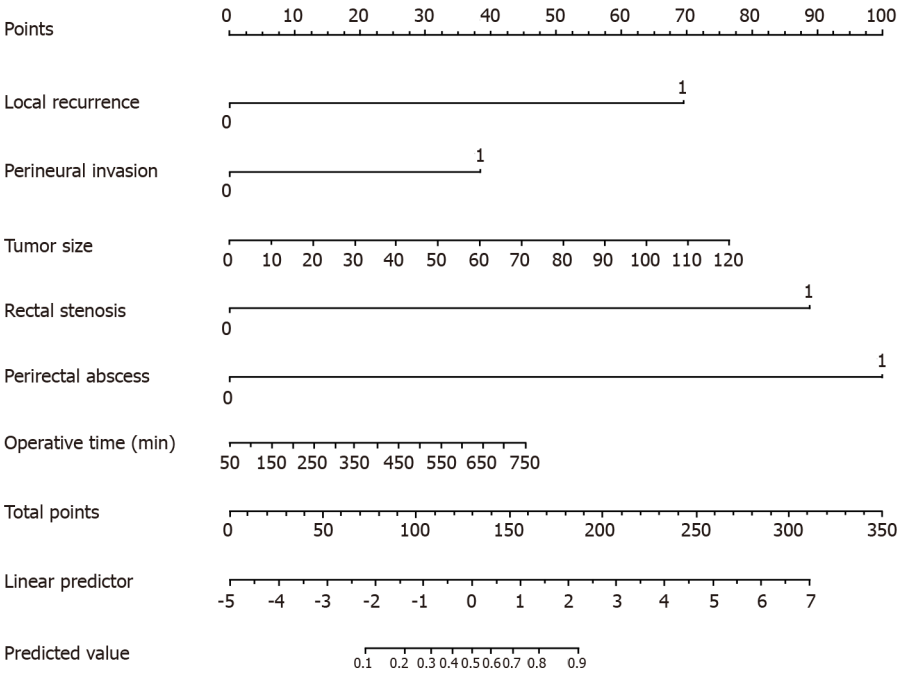

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Figure 2 The established nomogram for predicting permanent stoma was developed by incorporating the following six parameters: Local recurrence, perineural invasion, tumor size (mm), rectal stenosis, perirectal abscess and operative time. First, the nomogram is used by giving each variable a score on the "Points" scale. The scores for all variables are then added to obtain the total score after which a vertical line is drawn from the "Total points" row to estimate the predicted probability of permanent stoma.

Validation and performance of the nomogram

After these six factors were incorporated, the nomogram achieved an outstanding C-index of 0.903 (95%CI: 0.851–0.955). The area under the receiver operating characteristic curve of our model (0.903) was higher than that of any single factor (local recurrence: 0.641; perineural invasion: 0.636; tumor size: 0.638; rectal stenosis: 0.645; perirectal abscess: 0.565**;** operative time: 0.669), which indicates that this model was more accurate than other models (Figure 3A). According to the calibration curve, the nomogram calibration plot demonstrated high reliability (Figure 3B). Predicted PS rates based on the model and the observed outcomes on calibration fit best at PS probability rates above 40%. However, the nomogram showed less consistent but high performance in the lower PS rate ranges, as the calibration curve fluctuates below 40% probability.

DISCUSSION

For the past three decades, dramatic improvements have been made in rectal cancer treatment, including advances in surgical pathology, refinements in surgical techniques and instrumentation, new imaging modalities, and the widespread use of neoadjuvant therapy[11]. No matter how advanced the surgical technique, restoration of bowel continuity in patients with rectal cancer is still currently a challenge. Whenever possible, sphincter preservation should be sought. The sphincter can generally be preserved if the tumor can be resected with a 1-cm distal margin[12]. However, not all patients meet the surgical indications for sphincter-saving surgery. Even if patients undergo resection for rectal cancer, a common dilemma faced by surgeons is whether or not to create a defunctioning stoma. According to a recent meta-analysis published in 2017, which included ten studies consisting of 8568 patients, the rate of non-reversal of temporary stoma was 19%[13]. Patients still encounter multiple possible complications and the risk of perioperative mortality after surgery. Anastomotic complications are the primary reason for the necessity of a PS, and thus, these complications are more frequent than local recurrence [14-16]. Therefore, surgical decision making in the setting of rectal cancer is often complex, and detailed meetings for SDM are necessary. Patients and physicians arrive at treatment decisions together based on

Table 2 Risk factors for permanent stoma after sphincter-preserving surgery according to univariate and multivariable analyses

Variable	Univariable analysis OR (95%CI)	*P* value	Multivariable analysis OR (95%CI)	*P* value
Age, yr	0.99 (0.969-1.012)	0.369	0.959 (0.895-1.027)	0.232
Sex (Ref. = female)				
Male	0.822 (0.472-1.443)	0.491	0.273 (1.044-1.7)	0.164
Body mass index, kg/m^2	1.022 (0.953-1.092)	0.532	0.949 (0.807-1.116)	0.525
DM (Ref. = No)				
Yes	0.792 (0.363-1.586)	0.532	0.307 (0.032-2.9)	0.303
Hypertension (Ref. = No)				
Yes	1.229 (0.678-2.179)	0.488	0.819 (0.121-5.542)	0.838
Heart disease (Ref. = No)				
Yes	0.893 (0.256-2.413)	0.84	0.229 (0.008-6.382)	0.385
COPD (Ref. = No)				
Yes	5.795 (0.684-49.02)	0.082	451.125 (0.376->999)	0.091
CKD (Ref. = No)				
Yes	0.931 (0.34-2.172)	0.878	0.421 (0.019-9.234)	0.583
Liver disease (Ref. = No)				
Yes	1.179 (0.488-2.55)	0.694	0.054 (0.004-0.698)	0.025
Smoker (Ref. = No)				
Yes	0.906 (0.379-1.932)	0.81	0.125 (0.007-2.148)	0.152
Distance to anus verge, cm	0.838 (0.758-0.921)	< 0.001	0.834 (0.618-1.127)	0.238
Clinical T stage (Ref. = T0)				
T1	< 0.001 (NA-4.239)	0.98	1.081 (< 0.001-> 999)	0.999
T2	1.28 (0.193-25.357)	0.827	> 999 (< 0.001-> 999)	0.968
T3	1.394 (0.246-26.24)	0.757	> 999 (< 0.001-> 999)	0.976
T4	3.2 (0.468-64.31)	0.308	> 999 (< 0.001-> 999)	0.971
Clinical N stage (Ref. = N0)				
N1	1.697 (0.831-3.568)	0.152	0.017 (< 0.001-> 999)	0.986
N2	1.466 (0.701-3.129)	0.313	0.003 (< 0.001-> 999)	0.981
AJCC c TNM stage (Ref. = Stage 0)				
Stage I	0.98 (0.139-19.76)	0.986	0.015 (< 0.001-> 999)	0.986
Stage II	1.077 (0.159-21.492)	0.948	0.007 (< 0.001-> 999)	0.983
Stage III	1.648 (0.291-30.993)	0.642	NA	NA
Pre-operative CCRT (Ref. = No)				
Yes	1.332 (0.731-2.533)	0.364	1.873 (0.137-25.575)	0.638
Hb, g/dL	0.987 (0.832-1.18)	0.887	1.404 (0.768-2.568)	0.27
Albumin, g/dL	0.821 (0.361-1.928)	0.643	0.66 (0.041-10.497)	0.769
CEA, ng/mL	1.011 (0.978-1.038)	0.443	0.936 (0.804-1.09)	0.396
ASA score (Ref. = I)				
II	2.02 (1.046-3.891)	0.036	7.967 (0.64-99.127)	0.107
III	NA	NA	NA	NA
Surgical Approach way (Ref. = 0)				

LPS (1)	NA	NA	> 999 (< 0.001-> 999)	0.859
Robotic (2)	NA	NA	> 999 (< 0.001-> 999)	0.872
Type of operation (Ref. = LAR)				
CAA	3.46 (1.958-6.266)	< 0.001	0.221 (0.027-1.796)	0.158
Estimated blood loss	1.002 (1-1.005)	0.072	1.001 (0.987-1.016)	0.889
Operative time	1.004 (1.002-1.007)	< 0.001	1.011 (1.001-1.02)	0.026
Histologic tumor grade (Ref. = Grade I)				
Grade II	1.622 (0.883-3.05)	0.124	1.203 (0.22-6.586)	0.831
Grade III	2.507 (0.645-8.203)	0.147	1.53 (0.038-61.785)	0.822
Tumor size, mm	1.026 (1.011-1.041)	< 0.001	1.076 (1.015-1.14)	0.014
Circumferential resection margin (Ref. = No)				
Yes	6.575 (2.955-14.604)	< 0.001	0.936 (0.064-13.699)	0.961
Lymph vascular invasion (Ref. = No)				
Yes	1.99 (1.071-3.617)	0.026	0.94 (0.132-6.715)	0.951
Perineural invasion (Ref. = No)				
Yes	3.085 (1.726-5.518)	< 0.001	7.674 (1.138-51.745)	0.036
Postoperative hospital stays	1.05 (1.02-1.083)	0.001	1.003 (0.911-1.104)	0.953
Postoperative chemotherapy (Ref. = No)				
Yes	1.907 (0.963-4.134)	0.079	4.281 (0.247-74.107)	0.318
Anastomosis site stenosis (Ref. = No)				
Yes	11.648 (5.499-25.374)	< 0.001	211.256 (13.705-> 999)	< 0.001
Local recurrence (Ref. = No)				
Yes	12.584 (5.874-27.885)	< 0.001	111.578 (7.964-> 999)	< 0.001
Postoperative leakage (Ref. = No)				
Yes	2.659 (0.982-6.557)	0.041	0.743 (0.047-11.833)	0.833
Perirectal abscess (Ref. = No)				
Yes	11.037 (3.22-43.367)	< 0.001	369.397 (17.137-> 999)	< 0.001
Recto visceral fistula (Ref. = No)				
Yes	44.557 (7.71-841.643)	< 0.001	> 999 (< 0.001-> 999)	0.963

ASA: American Society of Anesthesiologists; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; AJCC: American Joint Committee on Cancer; CCRT: Concurrent chemoradiotherapy; CEA: Carcinoembryonic antigen; CAA: Coloanal anastomosis; DM: Ciabetes mellitus; Hb: Hemoglobin; LPS: Laparoscopic surgery; LAR: Low anterior resection; OR: Odd ratio; TNM: Tumor-node-metastasis.

clinical evidence within the context of a patient's personal preferences[4]. Prior to surgery, patients should be informed that a certain percentage of postoperative anastomosis complications may occur, which in turn may lead to PS. In addition, the physician should carefully judge whether sphincter-saving surgery or APR should be performed. Many factors should be carefully considered, including the effects of neoadjuvant CRT, sufficient tumor resection margins, the patient's functional status/comorbid disease, and his or her personal wishes[17]. If patients who are at a higher risk of a PS after surgery can be identified, a physician's ability to communicate the benefits and risks of various treatment options in an SDM setting will be improved.

Postoperative leakage and stricture are the most well-known anastomotic healing complications that have continued to plague surgeons. Both are primary reasons for PS. Although numerous studies have attempted to determine the healing process of colorectal anastomoses, the pathophysiologic mechanisms that govern the process of anastomotic regeneration remain poorly understood[18]. One major obstacle has been the lack of access to observe, sample, and analyze an anastomosis as it heals. Traditional dogma suggests that the most common factors implicated in anastomotic healing include

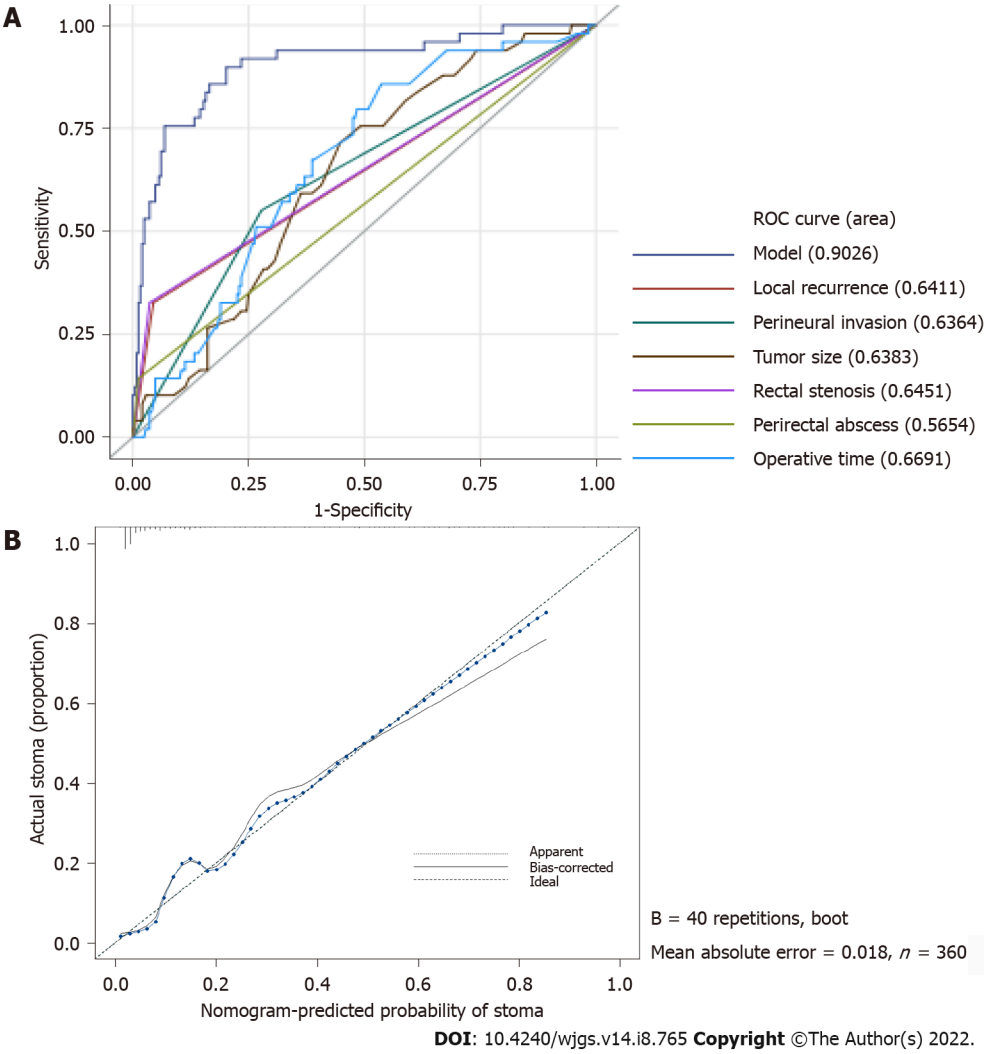

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Figure 3 The nomogram calibration plot demonstrated high reliability. A: The area under the receiver operating characteristic curve for the nomogram was 0.903 (95%CI: 0.851–0.955); B: In the calibration curve, the predicted probability of stoma is plotted on the x-axis, while the actual probability of stoma is plotted on the y-axis. The dotted line represents an ideal nomogram, and the solid blue line represents the current nomogram.

tissue perfusion/ischemia, tissue tension, and patient nutritional status[19]. However, surgeons still cannot predict which anastomoses will leak or undergo stenosis. Even a well-constructed anastomosis by the most skilled surgeon with good perfusion and no tension can still develop leakage or stricture. Therefore, many retrospective studies attempt to determine the incidence and potential risk factors of anastomotic complications, which can help us predict the probability of PS. According to recent studies, the incidence of anastomotic leakage in the literature varies from 1% to 29%[20], and over half of patients with symptomatic anastomotic leakage will have PS[21,22]. A systematic search by Qu *et al*[23] indicated that common risk factors for anastomotic leakage include male gender, high BMI, high ASA score, large tumor size, preoperative chemotherapy, intraoperative adverse events, and low rectal anastomosis. While many studies have thoroughly analyzed the risk factors of anastomotic leakage, relatively few studies have focused on risk factors of anastomotic stricture. Rates have been shown to vary from 2%–30% in the literature, but these rates are usually under-reported due to the requirement for long-term follow-up[24]. In addition, while high-grade strictures are immediately recognized due to patient symptoms, low-grade strictures are not always identified[18]. According to recent studies, neoadjuvant CRT, clinical anastomotic leakage, and hand-sewn coloanal anastomosis have all been shown to be associated with independent risk factors of anastomotic stricture[25,26]. Endoscopic balloon dilation is the most common and effective way to treat symptomatic anastomotic stricture, but the recurrence rates after this procedure range from 6%–25%[27]. Some patients with recurrent anastomotic stricture have to accept PS to avoid the symptoms of anastomotic stricture and maintain a good quality of life.

Histology and pathology have played an important role in cancer diagnosis and prognostic prediction for decades. Some markers may potentially reflect the biological aggressiveness of the tumor, such as tumor type, tumor differentiation, growth pattern, tumor budding, and involvement of the serosa, nerves, lymphatic vessels, intramural, and extramural veins[28]. Patients with these high-risk

tumor patterns may easily develop local recurrence (LR), which can lead to PS. Perineural invasion and lymphovascular invasion have been demonstrated to be independent prognostic factors of recurrence in many cancers. Perineural invasion is characterized by tumor invasion of nervous structures and spread along nerve sheaths, while lymphovascular invasion is characterized by tumor invasion of small lymphatic or blood vessels[29]. According to a study in rectal cancer by Peng *et al*[30], the 5-year LR rate of the perineural invasion-positive group was more than 2.5-fold higher than that of the perineural invasion-negative group (22.7% *vs* 7.9%; $P = 0.017$). In addition, in terms of lymphovascular invasion, Dresen *et al*[28] indicated that the presence of lymphovascular invasion (OR 4.66, $P < 0.001$) was associated with an increased risk for the development of local recurrence in patients with rectal cancer. Another key factor for the development of local recurrence is positive CRM. Agger *et al*[31] reported that the local recurrence rate was 17.0% in patients without any microscopic margin (CRM 0 mm) and 6.7% in patients with a CRM of 0–1 mm. With advancements in surgical techniques, the ratio of CRM has continued to decrease. In the study by Quentin *et al*[32], the rate of positive CRM decreased significantly after perineal dissection compared with after abdominal rectal dissection (4% *vs* 18%; $P = 0.025$). Moreover, it was beyond our expectations that tumor size was an independent risk factor for PS according to the results of the multivariate analysis. In previous studies, the results of the correlation between tumor size and the prognosis of rectal cancer are often contradictory, and multivariate analyses are seldom performed. However, in more recent studies, Kornprat *et al*[33] indicated that tumors larger than 4.5 cm are associated with high T and N classification, UICC stage, and tumor grade. Moreover, Chen *et al*[34] reported that pathological tumor size ≥ 5 cm is an independent prognostic factor for local recurrence in rectal adenocarcinoma. In our current study, the univariate analysis revealed that the independent risk factors for PS were lymphovascular invasion (OR, 1.99; 95%CI: 1.071–3.617; $P = 0.026$) and positive CRM (OR, 6.575; 95%CI: 2.955–14.604; $P < 0.001$), while the multivariate analysis revealed that the independent risk factors for PS were perineural invasion (OR, 3.085; 95%CI: 1.726–5.518; $P < 0.001$) and tumor size (OR, 1.076; 95%CI: 1.015-1.14; $P = 0.014$). The above four factors have been confirmed to be related to tumor recurrence, which can cause intestinal obstruction and affect intestinal continuity. The patient has no choice but to accept PS when the disease recurs because it is impossible for the physician to close the stoma in these patients.

Here, we developed a nomogram to predict the incidence of PS in patients with rectal cancer who undergo sphincter-saving surgery. To our knowledge, nomograms are widely used in many cancers to predict patient prognosis and cancer behavior (*e.g.*, lymph node metastasis, recurrence, and distant metastasis)[35-37]. In addition, some studies have used nomograms to predict the rate of postoperative complications, such as infection, anastomotic leakage, and stenosis[38,39]. Currently, only a few predictive models of PS for patients with rectal cancer have been published[40-42]. We collected 391 cases for analysis, which is the largest case number to date among all relevant studies. The C-index for the nomogram is 0.903 (95%CI: 0.851–0.955), which indicates a perfect prediction model. According to the calibration curve, the nomogram calibration plot demonstrated high reliability. Patients with these risk factors would be classified as high-risk patients with PS, and they should be informed of their status prior to surgery. We propose that this nomogram provides more individualized outcome predictions and could aid clinicians and patients in the treatment decision making process.

The present study has some limitations. First, this was a retrospective study and was not randomized in nature. In some incomplete patient records, the details of stoma complications after hospital discharge may be difficult to evaluate. Second, the study period was relatively long, and differences may exist in surgeon discretion and surgical techniques. Finally, this analysis was based on data from a single center. External validation using data from other centers is needed to certify the discriminatory ability of this model. More representative prediction models can be developed using data from multiple centers.

CONCLUSION

This study reports that risk factors leading to PS were highly correlated with local recurrence, perirectal abscess, anastomosis site stenosis, perineural invasion, tumor size and operative time (min). Our established nomogram enables a relatively accurate assessment of the risk of PS after sphincter-saving surgery. The ease of use of this nomogram can improve a physician's ability to communicate the benefits and risks of various treatment options in SDM.

ARTICLE HIGHLIGHTS

Research background

Despite innovative advancements, the management of rectal cancer remains a formidable endeavor, especially distally located rectal cancer. According to previous studies, 3%-24% of rectal cancer patients experience anastomosis complications after sphincter-saving surgery, which may lead to permanent

stoma (PS).

Research motivation

Patients fail to achieve stoma closure can cause drastic changes in lifestyle and physical perceptions.

Research objectives

The purpose of this study was to determine the risk factors for PS and to develop a prediction model to predict the probability of PS in rectal cancer patients after sphincter-saving surgery.

Research methods

A retrospective cohort of 421 rectal cancer patients who underwent radical surgery at Taipei Medical University Hospital between January 2012 and December 2020 was included in this study. Univariate and multivariate analyses were performed to identify the independent risk factors for PS. A nomogram was developed according to the independent risk factors obtained in the multivariate analysis. The performance of the nomogram was assessed using a receiver operating characteristic curve and a calibration curve.

Research results

The PS stoma rate after sphincter-saving surgery was 15.1% (59/391) in our study after a median follow-up of 47.3 mo (range 7-114 mo). Multivariate logistic regression analysis demonstrated that local recurrence, perirectal abscess, anastomosis site stenosis, perineural invasion, tumor size, liver disease, and operative time were independent risk factors for PS. After exclude liver disease, these identified risk factors were incorporated into the nomogram, and the concordance index of this model was 0.903 (95%CI: 0.851-0.955). According to the calibration curves, the nomogram represents a perfect prediction model.

Research conclusions

This study reports that risk factors leading to PS were highly correlated with local recurrence, perirectal abscess, anastomosis site stenosis, perineural invasion, tumor size and operative time (min). Our established nomogram enables a relatively accurate assessment of the risk of PS after sphincter-saving surgery. The ease of use of this nomogram can improve a physician's ability to communicate the benefits and risks of various treatment options in shared decision making.

Research perspectives

The present study has some limitations. First, this was a retrospective study and was not randomized in nature. In some incomplete patient records, the details of stoma complications after hospital discharge may be difficult to evaluate. Second, the study period was relatively long, and differences may exist in surgeon discretion and surgical techniques. Finally, this analysis was based on data from a single center. External validation using data from other centers is needed to certify the discriminatory ability of this model. More representative prediction models can be developed using data from multiple centers.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Pre-colonoscopy special guidance and education on intestinal cleaning and examination in older adult patients with constipation

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Abstract

BACKGROUND

The prevalence of constipation in the Chinese population over 60 years of age is 11.5%, and this prevalence increases with age, which seriously affects the quality of life in older adults. Therefore, reducing the incidence of constipation in older adults is necessary to promote a healthy lifestyle as well as biochemical health.

AIM

To explore the value of preoperative guidance and education to improve the effects of bowel cleaning in older adult patients undergoing colonoscopy.

METHODS

In this study, 160 older adult patients with constipation requiring colonoscopy at Shandong Provincial Hospital between January 2019 and March 2021 were selected and randomly divided into a study group and a control group, with 80 patients in each group. The study group received medication guidance and targeted educational guidance before the operation, while the control group received only medication and dietary guidance. The baseline data, colonoscopy duration, bowel preparation compliance, Boston bowel preparation (BBPS) assessment score, intestinal bubble score, the incidence of adverse reactions during bowel preparation, and nursing appointment satisfaction were compared between the two groups.

RESULTS

The colonoscopy duration times and intestinal bubble scores of the study group were shorter than those of the control group, with statistically significant differences. The BBPS scores for the right, left, and interrupted colon in the study

group were also higher than those in the control group, and the difference was statistically significant. Additionally, the study group had a higher rate of liquid diet one day before the examination, higher rate of correct bowel-clearing agent dilution method, higher rate of accurate time of ingesting the bowel-clearing agent, and a higher proportion of patients ingesting bowel-clearing agent at the specified time than the control group, with statistically significant differences. The incidence of nausea and vomiting during bowel clearance in the study group was significantly lower than that in the control group. The incidence of abdominal pain, abdominal distension, dizziness, and fatigue was compared between the two groups, but the difference was not statistically significant. The scores of service attitude, detailed notification of dietary precautions, clear and easy-to-understand health educational content, and receiving care and comfort in the study group were significantly higher than those in the control group.

CONCLUSION

Preoperative special guidance and education were shown to significantly improve bowel clearance and compliance and reduce the incidence of adverse reactions in older adult patients with constipation undergoing colonoscopy. These factors are beneficial for improving patient satisfaction with nursing services.

Key Words: Special guidance education; Older adults; Constipation; Colonoscopy; Intestinal cleansing effect

Core Tip: Oral education on bowel preparation before colonoscopy in digestive endoscopy room, so some patients cannot understand the requirements of bowel preparation, especially in elderly patients with hearing impairment and lower education level patients, cannot be very good bowel preparation.

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INTRODUCTION

Colonoscopy is the most important screening test for colon and anal diseases because it provides a realistic picture of diseased sections, which allows early diagnosis of diseases[1]. Intestinal preparation before a colonoscopy examination is usually performed using an enema or an oral intestinal cleaning agent, which is crucial in ensuring that the desired examination effects are achieved for older adult patients with constipation[2]. The ideal method of intestinal preparation allows the patient to empty the intestine in a short time, and the colonic mucosa does not change. The patient feels comfortable, water and electrolytes levels are stable, and the procedure has few or no complications[3,4]. At present, most of the informational literature and educational methods for intestinal preparation before colonoscopy are delivered orally, and nurses must provide education on medication and other topics within a limited time[5]. Some patients are unable to understand the instructions of intestinal preparation, especially older adult patients with hearing impairment and patients with low education levels. Hence, these patients cannot adequately perform intestinal preparation. Therefore, to improve the quality of bowel preparation in older adult patients, we must explore personalized and targeted methods for delivering guidance to these patients. This study discusses the value of special preoperative guidance and educational methods for older adult patients with constipation undergoing colonoscopy.

MATERIALS AND METHODS

Information

This study was conducted on 160 older adult patients with constipation, who were scheduled for colonoscopy at Shandong Provincial Hospital between January 2019 and March 2021. Patients were selected and randomly divided into a study group and a control group, with 80 patients in each group. The age range of the subjects was 60–85 years, and all had the typical manifestations of chronic

constipation and met the diagnostic criteria for constipation (Rome III). Patients had healthy understanding and communication skills. Those suspected of having intestinal organic lesions or polyps were required to undergo intestinal endoscopy. There was detailed communication with the patients and their families before the implementation of this study, and patients did not use laxatives for one week prior to the study. Exclusion criteria were: (1) any examination contraindications; (2) gastrointestinal perforation; (3) electrolyte disorders, dehydration, severe infection, or galactose intolerance; and (4) lactation, pregnancy, or occurrence of a menstrual period.

Procedure

The control group received oral health education in which patients were asked to refrain from high-fiber food intake 2 d before the examination and were advised to consume semi-liquid or liquid foods with less residual fiber. Liquid diet was prescribed 1 d before the examination, and the use of compound polyethanol electrolyte powder (Heshuang, Shenzhen Wanhe Pharmaceutical Co., Ltd.) and medication administration were both explained to the patients. The following were confirmed the day before examination: dinner had been consumed (with water allowed) and medication was administered 1 h after dinner (oral dosage, with 2 L administered at a rate of approximately 1 L per hour). On the day of the examination, medication was checked, breakfast was not allowed (with water allowed), and medication was administered about 6 h before the scheduled examination. Medication was terminated once the discharge liquid became transparent; however, if the defecation form was not up to the standard, the doctor advised to continue administration, with the total dose not exceeding 4 L.

The study group received special guidance and education beyond what was given to the control group. To fully understand the patient's situation, nursing staff conducted a multi-dimensional assessment of the patient's condition, including age, personality, living habits, rest, bowel routine, and other basic conditions. Information tables were prepared, including detailed records of the patients' basic conditions, colonoscopy duration times, main condition, convenient time for telephone follow-up, and other contact details required for nurses to individualize education and care. If the patients had any doubts, they can consult by telephone. The language and behavior of the patients was observed, and their psychological status was evaluated to fully understand their condition. During the special guidance sessions, patients were informed about the basic principles and importance of bowel preparation and the role of prescriptions to encourage compliance. This was done to increase patients' cooperation and establish good nurse–patient relationships. Nursing staff printed out the basic points for bowel preparation, used a written form, and guided patients to watch a video regarding bowel preparation medication and precautions to increase the impact of the information. Defecation standards were also placed in the toilet to facilitate comparisons for patients. Medication was kept consistent within the control group, and patients and their families were guided to massage the abdomen, engage in moderate exercise to increase gastrointestinal peristalsis, and check for intestinal cleanliness. Patients were also able to communicate with doctors through the WeChat platform, and telephone, so that doctors could respond to any sudden issues quickly, and nurses were able to strengthen ward inspection work.

Colonoscopy

All patients underwent electronic colonoscopy. Patients were placed on the left lateral position and instructed to bend their knees. The colonoscope was then slowly inserted into the patients' anus to explore the rectum, sigmoid colon, transverse colon, ascending colon, and terminal ileum. Pathological manifestations in the intestinal mucosa and intestine were recorded.

Evaluation method

The colonoscopy duration time, bowel preparation compliance, Boston bowel preparation assessment scale (BBPS) score, intestinal bubble score, the incidence of adverse reactions during bowel preparation, and nursing appointment satisfaction were compared between the two groups.

The BBPS score[7] divided the patient's colon into the right, left, and middle colon. The score of each colon ranged from 0 to 3 points, where 3 points indicated that the bowel was prepared very well, the vision was clear, and the internal intestinal structure was observed; 2 points: the bowel was ready, the vision was clear, and did not affect the observation of the internal structure of the bowel; 1 point: the intestinal tract was well prepared; however, the visual field clarity was poor, which affected the observation of internal intestinal wall under endoscopy; and 0 point: poor bowel preparation, fecal water, and feces in the intestinal wall, which seriously affected visualization.

The total score of bubbles in intestinal endoscopy was also 0–3 points, with 3 points indicating: bubbles in the intestinal cavity and a large number of bubbles in the intestinal tract; 2 points: a moderate number of bubbles in the intestinal tract; 1 point: a small number of bubbles were detected; and 0 points: no bubbles were detected.

The factor of nursing appointment satisfaction took into account the treatment environment, service attitude, medication guidance, detailed information on bowel preparation and dietary precautions, health education content being clear and easy to understand, care and comfort provided, and attention to privacy protection. Each aspect was divided into very satisfied (3 points), satisfied (2 points), general

(1 point), or dissatisfied (0 points).

The evaluation of intestinal preparation compliance mainly included the type of diet (solid, liquid, or semi-liquid diet) consumed on the day before the colonoscopy, whether fasting was observed on the day of the examination (yes/no), whether the correct dilution method of the intestinal cleaning agent was followed (yes/no), whether the time taken for the intestinal cleaning agent was accurate (yes/no), and whether the intestinal cleaning agent was consumed within the specified time (yes/no).

Statistical analysis

In this study, colonoscopy time, intestinal bubble score, and other measurement indexes of the patients were tested by normal distribution, which was in line with either the approximate normal distribution or normal distribution and expressed as mean ± SD. A *t*-test was used for comparisons between the two groups. The non-counting data were represented as percentages, and the comparison was performed using the χ^2 test; SPSS 21.0, software was used for data processing with a test level $\alpha = 0.05$.

RESULTS

Comparison of general information between the study group and the control group

Statistical analysis comparison was conducted between the study group and the control group using the factors of age, BMI, duration of constipation, sex, and comorbidities ($P > 0.05$, Table 1).

Comparison of colonoscopy time and intra-intestinal bubble score between the study group and the control group

The colonoscopy time of the study group was shorter than that of the control group, and the intestinal bubble score of the study group was lower than that of the control group; these differences were statistically significant ($P < 0.05$, Table 2).

Comparison of BBPS scores between the study group and the control group

The BBPS scores of the right colon, left colon, and transverse colon in the study group were higher than those in the control group, and the difference was statistically significant ($P < 0.05$, Table 3, Figure 1).

Comparison of bowel cleansing compliance between the study group and the control group

The study group had a higher fluid diet rate 1 d before examination, the correct bowel-clearing agent dilution method, an accurate time of ingesting the bowel-clearing agent, and a higher proportion of patients ingesting the bowel-clearing agent within the specified time compared to the control group, and the difference was statistically significant ($P < 0.05$, Table 4).

Comparison of the incidence of adverse bowel cleansing reactions between the study group and the control group

The incidence of nausea and vomiting in the study group was lower than that in the control group, and the difference was statistically significant ($P < 0.05$). The incidence of abdominal pain, bloating, dizziness, and fatigue was compared between the two groups, and the difference was not statistically significant ($P > 0.05$, Table 5).

Evaluation of nursing satisfaction in the study group and the control group

The scores measuring service attitude, detailed diet instructions, clear and understandable health education content, and care and comfort in the study group were higher than those in the control group, and the difference was statistically significant ($P < 0.05$, Table 6).

DISCUSSION

Before a colonoscopy, a patient's diet and drug intake can influence the effectiveness of intestinal preparation, thereby affecting the effectiveness of the examination and increasing the possibility of complications such as intestinal perforation and intestinal bleeding[8]. Early studies have shown[9,10] that the provision of health education before a colonoscopy is closely related to the degree of intestinal cleanliness, which can indirectly affect the diagnosis and treatment of the procedure. Thus, helping patients master the pertinent health knowledge prior to the procedure improves the effectiveness of colonoscopy[11]. In the past, patient preparation by the nurses before colonoscopy was often too procedural and not targeted, frequently ignoring the occurrence of complications, resulting in insufficient bowel preparation and incomplete bowel clearance that directly decreased the effectiveness of colonoscopy. When nursing staff guide patients to prepare their intestinal tracts, special instruction methods must be adopted and individualized. Standardized and targeted guidance should be provided

Table 1 Comparison of general information between the study group and the control group, *n* (%)

Normal information	Research group (*n* = 80)	Control group (*n* = 80)	t/χ^2	*P* value
Age (yr)	68.2 ± 5.4	68.4 ± 5.4	-0.218	0.827
BMI (kg/m^2)	24.5 ± 2.7	24.1 ± 2.7	1.009	0.158
Duration of constipation (yr)	6.3 ± 1.6	6.4 ± 2.3	040	0.158
Sex			0.905	0.341
Male	46 (57.50)	40 (50.00)		
Female	34 (42.50)	40 (50.00)		
Hypertension			0.227	0.634
Yes	38 (47.5)	35 (43.75)		
No	42 (52.5)	45 (56.25)		
Diabetes			0.038	0.845
Yes	17 (21.25)	16 (20.00)		
No	63 (78.75)	64 (80.00)		
Smoking			0.000	1.000
Yes	14 (17.50)	14 (17.50)		
No	66 (82.50)	66 (82.50)		
Drinking			0.316	0.574
Yes	20 (25.00)	17 (21.25)		
No	60 (75.00)	63 (78.75)		

BMI: Body mass index.

Table 2 Comparison of colonoscopy time and intestinal bubble score (mean ± SD)

Groups	Colonoscopy time (min)	Intestinal bubble score (points)
Research group (*n* = 80)	15.21 ± 1.81	0.59 ± 0.22
Control group (*n* = 80)	16.28 ± 2.04	1.00 ± 0.26
t value	-3.509	-10.767
P value	0.001	0.000

Table 3 Comparison of Boston bowel preparation scores between the study group and the control group (mean ± SD, scores)

Groups	Right colon	Left colon	Mid colon
Research group (*n* = 80)	2.25 ± 0.52	2.34 ± 0.50	2.31 ± 0.47
Control group (*n* = 80)	2.04 ± 0.37	2.13 ± 0.46	2.13 ± 0.49
t value	2.943	2.765	2.371
P value	0.004	0.006	0.019

regarding medication, diet, and prevention of complications, with suggestions that patients take medicine as directed on time.

The results of this study showed that the colonoscopy duration time in the study group was shorter, and the intestinal bubble scores were lower compared to those in the control group. The BBPS scores of the right, left, and transverse colon of patients in the study group were higher than those in the control group ($P < 0.05$). This shows that the intestinal preparation of the study group is better, which is consistent with previous research results[12,13]. Special guidance can enhance adherence to correct behavior in older adult patients, deepen patients' memory of bowel preparation, improve compliance

Table 4 Comparison of bowel cleansing compliance between the study group and the control group, *n* (%)

Compliance index	Research group (*n* = 80)	Control group (*n* = 80)	χ^2	*P* value
Check the diet of the day before			5.010	0.025
Liquid or semi-liquid	77 (96.25)	69 (86.25)		
Solid	3 (3.75)	11 (13.75)		
Check if fasting on the day			1.858	0.173
Yes	79 (98.75)	76 (95.00)		
No	1 (1.25)	4 (5.00)		
The correct method of diluting bowel cleansers			4.113	0.043
Yes	73 (91.25)	64 (80.00)		
No	7 (8.75)	16 (20.00)		
Is the time of taking the bowel cleansing correct			4.440	0.035
Yes	74 (92.50)	65 (81.25)		
No	6 (7.50)	15 (18.75)		
Drink the bowel cleanser within the specified time			4.113	0.043
Yes	73 (91.25)	64 (80.00)		
No	7 (8.75)	16 (20.00)		

Table 5 Comparison of the incidence of adverse bowel cleansing reactions between the study group and the control group, *n* (%)

Adverse reactions	Research group (*n* = 80)	Control group (*n* = 80)	χ^2	*P* value
Nausea			5.301	0.022
Yes	22 (27.50)	36 (45.00)		
No	58 (72.50)	44 (55.00)		
Vomiting			6.144	0.013
Yes	6 (7.50)	17 (21.25)		
No	74 (92.50)	63 (78.75)		
Stomach ache			1.002	0.317
Yes	7 (8.75)	11 (13.75)		
No	73 (91.25)	69 (86.25)		
Bloating			1.406	0.236
Yes	13 (16.25)	19 (23.75)		
No	67 (83.75)	61 (76.25)		
Dizziness			1.441	0.230
Yes	4 (5.00)	8 (10.00)		
No	76 (95.00)	72 (90.00)		
Fatigue			1.707	0.191
Yes	7 (8.75)	3 (3.75)		
No	73 (91.25)	77 (96.25)		

with bowel preparation guidance content, and improve the quality of bowel preparation. This indicated that the special guidance education method was effective, patients more easily accepted the information, health knowledge was mastered faster and better, and the nurse–patient relationship was greatly improved. Nurses could increase patients' trust at a professional level to encourage patients to listen to their medical advice.

Table 6 Evaluation of nursing satisfaction of study group and control group (mean ± SD, scores)

Nursing satisfaction	Research group (*n* = 80)	Control group (*n* = 80)	*t* value	*P* value
Appointment and consultation environment	2.09 ± 0.46	1.98 ± 0.42	1.580	0.116
Service attitude	2.20 ± 0.40	2.08 ± 0.35	2.019	0.045
Medication guidance	2.15 ± 0.39	2.09 ± 0.43	0.924	0.357
Inform in detail about dietary precautions	2.14 ± 0.33	1.91 ± 0.41	3.909	0.000
Health education content is clear and easy to understand	2.04 ± 0.37	1.84 ± 0.48	2.952	0.004
Give care and comfort	2.14 ± 0.47	1.91 ± 0.36	3.475	0.001
Pay attention to privacy protection	1.98 ± 0.55	1.95 ± 0.35	0.412	0.681

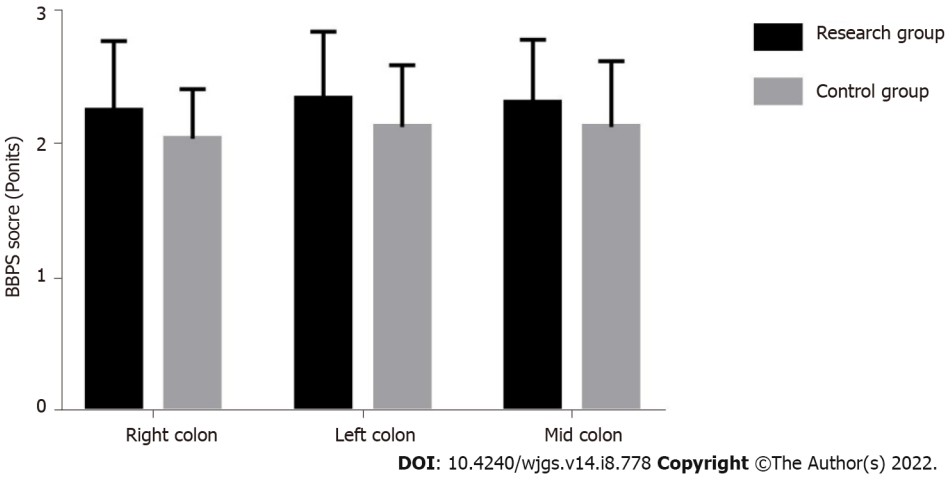

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Figure 1 Histogram of Boston bowel preparation scores of the study group and the control group. BBPS: Boston bowel preparation scores.

Fear of autonomic nervous system disturbances induced by colonoscopy in elderly patients can also lead to symptoms such as nausea and vomiting[14,15]. The incidence of nausea and vomiting during bowel clearance in the study group was significantly lower than that in the control group. Our results show that special guidance prior to ingesting intestinal cleaning agents can increase the incidence of correct intestinal preparation in older adult patients and reduce adverse reactions caused by emotional and timing factors. The results of this study are consistent with those of existing studies[16,17]. Analysis of the reasons mainly before the inspection and effective methods are necessary to alleviate the stressful emotions of patients so that they realize these emotions could trigger physical problems, listen to the guidance of medical staff, and improve the quality of their bowel preparation. The nurses in this study took care in explaining matters needing special attention during intestinal preparation, such as the pace of ingestion of intestinal cleaning agents (not too fast or too slow), and ingesting them within 2 h, thereby relieving tension and helping to reduce the incidence of adverse reactions in older adult patients.

The scores of service attitude, detailed notification of dietary precautions, clear and easy-to-understand health education content, and providing care and comfort in the study group were significantly higher than those in the control group. The method used to educate the control group was cursory and cannot take into account the individual differences of elderly patients, while the method used in the research group overcomes these drawbacks and meets the requirements of nursing, with high rationality and accurate targeting of patients. Knowledge gaps and biases may compromise the quality of bowel preparation. The special guidance adopted by the research group can provide a one-to-one personalized education reminder service. Patients should feel that they have received attention and that nursing staff would answer their questions patiently. It is easier to accept health education plans that are individualized to the patient, which significantly improves patient's understanding of their condition or disease and helps to improve the relationship between nurses and patients. Special guidance health education is based on the basic concept of modern high-quality nursing and patient-centeredness. In the implementation process, nursing staff must master the knowledge of colonoscopy, bowel preparation methods, influencing factors, related drug contraindications, adaptive population, usage and dosage of medication, and be able to adjust the bowel preparation plan flexibly according to each situation. When this is done, compliance and satisfaction of patients are significantly improved,

reflecting the strong effectiveness of health education.

In this study, we used existing nursing studies[18-20] to guide our investigation of whether personalized preoperative special guidance for colonoscopy has a better effect on bowel preparation, patient acceptance, and safety in older adult patients with constipation, and whether the practice is worthy of clinical application. However, the sample size of this study was small, and the inclusion criteria were not representative. In future follow-up studies, it will be necessary to further expand the sample range to make the research results more representative and further explore the education methods used to improve the quality of bowel preparation for colonoscopy subjects.

CONCLUSION

In summary, preoperative special guidance and education significantly improve bowel clearance compliance and bowel clearance effect and reduce the incidence of adverse reactions in older adult patients with constipation undergoing colonoscopy. This is also conducive to improving the satisfaction of patients interacting with nursing staff.

ARTICLE HIGHLIGHTS

Research background

The prevalence of constipation in the Chinese population over 60 years of age is 11.5%. Intestinal preparation before a colonoscopy examination is usually performed using an enema or an oral intestinal cleaning agent, which is crucial in ensuring that the desired examination effects are achieved for older adult patients with constipation.

Research motivation

Oral education was provided on bowel preparation before colonoscopy in the digestive endoscopy room.

Research objectives

This study aimed to improve the quality of bowel preparation in older adult patients, we must explore personalized and targeted methods for delivering guidance to these patients.

Research methods

Nurses could increase patients' trust at a professional level to encourage patients to listen to their medical advice.

Research results

Preoperative special guidance and education significantly improve bowel clearance compliance and bowel clearance effect and reduce the incidence of adverse reactions in older adult patients with constipation undergoing colonoscopy.

Research conclusions

This study discusses the value of special preoperative guidance and educational methods for older adult patients with constipation undergoing colonoscopy.

Research perspectives

This is conducive to improving the satisfaction of patients interacting with nursing staff.

FOOTNOTES

Author contributions: Wang H, Wang Y and Ren WX design the experiment; Wang H and Wang Y drafted the work; Wang H and Wang Y contributed equally to this study, and are considered as co-first authors; Wang H, Wang Y, Yuan JH collected the data; Wang XY and Ren WX analyzed and interpreted data; Wang H and Wang Y wrote and revised the manuscript.

Institutional review board statement: This study was reviewed and approved by the Provincial Hospital Affiliated to Shandong First Medical University Institutional Review Board.

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ORIGINAL ARTICLE

Retrospective Study

Model established based on blood markers predicts overall survival in patients after radical resection of types II and III adenocarcinoma of the esophagogastric junction

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Abstract

BACKGROUND

In recent years, the incidence of types II and III adenocarcinoma of the esophagogastric junction (AEG) has shown an obvious upward trend worldwide. The prognostic prediction after radical resection of AEG has not been well established.

AIM

To establish a prognostic model for AEG (types II and III) based on routine markers.

METHODS

A total of 355 patients who underwent curative AEG at The First Affiliated Hospital of Anhui Medical University from January 2014 to June 2015 were retrospectively included in this study. Univariate and multivariate analyses were

performed to identify the independent risk factors. A nomogram was constructed based on Cox proportional hazards models. The new score models was analyzed by C index and calibration curves. The receiver operating characteristic (ROC) curve was used to compare the predictive accuracy of the scoring system and tumor-node-metastasis (TNM) stage. Overall survival was calculated using the Kaplan-Meier curve amongst different risk AEG patients.

RESULTS

Multivariate analysis showed that TNM stage (hazard ratio [HR] = 2.286, P = 0.008), neutrophil-to-lymphocyte ratio (HR = 2.979, P = 0.001), and body mass index (HR = 0.626, P = 0.026) were independent prognostic factors. The new scoring system had a higher concordance index (0.697), and the calibration curves of the nomogram were reliable. The area under the ROC curve of the new score model (3-year: 0.725, 95% confidence interval [CI]: 0.676-0.777; 5-year: 0.758, 95%CI: 0.708-0.807) was larger than that of TNM staging (3-year: 0.630, 95%CI: 0.585-0.684; 5-year: 0.665, 95%CI: 0.616-0.715).

CONCLUSION

Based on the serum markers and other clinical indicators, we have developed a precise model to predict the prognosis of patients with AEG (types II and III). The new prognostic nomogram could effectively enhance the predictive value of the TNM staging system. This scoring system can be advantageous and helpful for surgeons and patients.

Key Words: Adenocarcinomas of the esophagogastric junction; Neutrophil-to-lymphocyte ratio; Platelet-to-lymphocyte ratio; Prognosis; Tumor-node-metastasis

Core Tip: Based on the serum markers and other clinical indicators, we developed a precise model to predict the prognosis of patients with adenocarcinomas of the esophagogastric junction (types II and III). This scoring system can be advantageous for surgeons and patients.

Citation: Wei ZJ, Qiao YT, Zhou BC, Rankine AN, Zhang LX, Su YZ, Xu AM, Han WX, Luo PQ. Model established based on blood markers predicts overall survival in patients after radical resection of types II and III adenocarcinoma of the esophagogastric junction. *World J Gastrointest Surg* 2022; 14(8): 788-798
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INTRODUCTION

Adenocarcinomas of the esophagogastric junction (AEG), which are located within 5 cm of the esophagogastric junction, are classified into three subgroups: Types I, II, and III. Type I AEG (adenocarcinoma of the distal esophagus) is most prevalent in Western countries; types II and III AEG are more prevalent than type I in Asia and are mostly treated as gastric cancer[1,2]. The incidence rate of AEG has significantly increased over the past two decades and is increasing more rapidly than any other type of neoplasm[3,4].

Surgery is considered the only curative treatment for patients with AEG; however, the survival rate is not good even with surgery[5].

At present, many studies are exploring non-invasive and sensitive biomarkers that can accurately predict the prognosis of patients with AEG. Among these, carcinoembryonic antigen (CEA) has been used for the early diagnosis of cancer[6]. Cancer-related systemic inflammatory responses, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), play an important role in the progression and outcome of tumors[7,8]. Patients with a high NLR have a poor prognosis[9]. Malnutrition is also related with the prognosis of patients; however, few studies have assessed the predictive value of inflammatory, nutritional, and blood tumor markers for overall survival (OS) in patients with AEG (types II and III)[10]. This research established a nomogram to explore the value of blood markers.

MATERIALS AND METHODS

We collected blood and clinical data of patients with AEG (types II and III) who were hospitalized at the First Affiliated Hospital of Anhui Medical University between January 2014 and June 2015. Patients were analyzed retrospectively according to the inclusion and exclusion criteria. The inclusion criteria were as follows: (1) Patients confirmed with AEG (types II and III) by pathological diagnosis; (2) Radical resection of the tumor; (3) Absence of heart diseases or organ failure; and (4) Peripheral blood test results obtained within 1 wk before surgery. The exclusion criteria were as follows: (1) Previously untreated malignancy; (2) Previously accepted radiation treatment or chemotherapy before the treatment; (3) Presence of certain diseases, such as infection, which could influence the peripheral blood cell counts; (4) Patients who died within 30 d after surgery because of sudden accidents, such as pulmonary embolism; and (5) Patients with incomplete data. In accordance with the inclusion criteria, 440 patients with AEG were included in the study. Finally, a cohort of 355 patients was analyzed based on the exclusion criteria. The patient admission process is shown in Supplementary Figure 1. This study was conducted conforming to the TRIPOD guidelines. This study included 355 patients and the testing group, including 120 patients, who were hospitalized at the First Affiliated Hospital of Anhui Medical University between January 2018 and June 2018.

Data on patients' demographic and clinicopathological features were gathered from the medical records of our hospital, including age, gender, body mass index (BMI), tumor size, differentiation grade, tumor-node-metastasis (TNM) stage, tumor location, surgery time, cancerous node, smoking, and comorbidities. The pathological tumor stage was categorized according to the 7th edition of the American Joint Committee on Cancer TNM staging system. The routine laboratory data evaluated were as follows: Neutrophil, lymphocyte, and platelet counts; prealbumin, albumin, hemoglobin, CEA, CA199, and fibrinogen levels.

Peripheral blood tests were performed within 1 wk before surgery, and the following indices were determined: NLR, PLR, and prognostic nutritional index (PNI). The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, and the PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count. The PNI was calculated as serum albumin (g/L) + 5 × total lymphocyte count (10^9/L)[11]. The NLR, PLR, and PNI were grouped into low and high groups according to the Youden index (maximum [sensitivity + specificity-1])[12]. The BMI (kg/m^2) was divided into the following three groups: < 18.5 (low group), 18.5-24.9 (normal group), and ≥ 25 (high group). The CEA, CA199, albumin and prealbumin levels were grouped based on their normal values.

All patients with Siewert type II/III AEG underwent radical surgery with celiac and mediastinal lymphadenectomy. All the patients underwent radical D2 lymphadenectomy. They received four to six cycles of first-line adjuvant combination chemotherapy after surgery with oxaliplatin plus 5-fluorouracil/leucovorin or a prodrug of 5-fluorouracil (capecitabine; CapeOX).

Statistical analysis

Multivariate and univariate survival analyses were performed using the Cox proportional hazard pattern. Harrell's concordance index (C-index) was used in the nomogram to evaluate the model performance for the prognosis of patients with AEG. Calibration and receiver operating characteristic (ROC) curves were used to verify the accuracy of the new scoring system. Survival analysis was compared using Kaplan-Meier method, and the nomogram was constructed using the R package "rms," "Hmisc," "lattice," "Formula," and "foreign." The data are presented using the Statistical Package for the Social Sciences software (16.0 version) and RStudio software (version 1.1.447- 2009-2018; RStudio, Inc.). A P value < 0.05 was considered statistically significant.

RESULTS

The baseline characteristics of 355 patients are presented in Table 1. Overall, 281 (79.1%) male and 74 (20.9%) female patients were included. The median age of the patients was 65 years (range, 29-85 years). The median follow-up period was 52 mo (range, 1.5-72 mo).

Table 2 shows the results of univariate risk factors. Age, prealbumin, TNM stage, tumor size, histological type, CEA, PNI, PLR, NLR, BMI, hemoglobin, and cancerous nodes were significant indicators. The variables with a P value < 0.05, as determined by the univariate analysis, were included in the multivariate analysis. Among them, TNM stage (hazard ratio [HR] = 2.286, P = 0.008), NLR (HR = 2.979, P = 0.001), and BMI (HR = 0.626, P = 0.026) were independent prognostic factors (Table 3).

A model was constructed to predict OS of AEG patients based on the Cox analysis (Figure 1). Each subgroup variable was assigned a score. A scoring system was used to assign a score to each variable (Table 4). To apply the nomogram, a vertical line was delineated to indicate the row to assign point values for each variable. Subsequently, the corresponding scores were summed to obtain the total score. Finally, a vertical line from the total point was drawn to obtain the 3-year and 5-year survival probability.

Table 1 Characteristics of the recruited patients

Characteristic	Surviving	Dead
Gender		
Male	148 (78.3)	134 (80.7)
Female	41 (21.7)	32 (19.3)
Age (yr)	65.00 (60.00-71.00)	63.00 (59.00-69.25)
Tumor size	5.00 (4.00-7.00)	4.00 (2.50-5.50)
TNM stage		
I-II	49 (25.9)	105 (63.3)
III	140 (74.1)	61 (36.7)
Differentiation grade		
Low	59 (31.2)	70 (42.2)
High	130 (68.8)	96 (57.8)
BMI (kg/m^2)	21.23 (19.88-23.85)	22.96 (20.96-25.00)
Tumor location		
Siewert II	104 (55.0)	98 (59.0)
Siewert III	85 (45.0)	68 (41.0)
NLR	2.37 (1.61-3.62)	2.20 (1.55-2.86)
PLR	122.75 (87.98-182.94)	108.03 (81.43-152.54)
CEA	3.60 (1.95-9.30)	2.20 (1.44-6.85)
CA199	10.34 (5.64-20.26)	9.88 (5.75-16.88)
PNI	48.80 (45.30-53.15)	50.35 (47.20-53.45)
Albumin	41.60 (38.40-44.80)	42.40 (39.48-44.30)
Prealbumin	187.00 (153.50-234.00)	239.50 (201.75-264.25)
Neutrophil count	3.41 (2.72-4.53)	3.26 (2.38-4.48)
Platelet count	188.00 (143.00-235.50)	176.00 (145.00-219.50)
Lymphocyte count	1.43 (1.10-1.82)	1.63 (1.26-1.97)

Categorical values are expressed as number (percentage), and continuous variable are expressed as median (25th percentile and 75th percentile). NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; BMI: Body mass index; PNI: Prognostic nutritional index; CEA: Carcinoembryonic antigen.

Calibration curves were used to verify the performance of the model in predicting OS of patients with AEG (Figures 2 and 3), and the results showed that the actual OS curve of the nomogram fits the predicted OS curve. Besides, the calibration curve in the testing group for 3-year OS was also good (Figure 4), and the C-index of the model was 0.697 (95% confidence interval [CI]: 0.660-0.734), indicating that this model was reliable. Besides, the area under the ROC curve (AUC) of the new score model (3-year: 0.725, 95%CI: 0.676-0.777; 5-year: 0.758, 95%CI: 0.708-0.807) was larger than that of the TNM stage (3-year: 0.630, 95%CI: 0.585-0.684; 5-year: 0.665, 95%CI: 0.616-0.715) (Figures 5 and 6), which indicated that the constructed nomogram was a reliable scoring system.

In addition, we divided the patients into two groups according to the total nomogram score (low-risk: < 58 and high-risk: ≥ 58) (Figure 7). The results showed that high-risk patients with AEG had a poor prognosis. The Kaplan-Meier curves indicated that the nomogram had excellent results in predicting survival.

DISCUSSION

Early detection of AEG is often difficult, owning to the limitations of diagnostic techniques, resulting in a poor prognosis. At present, the 5-year survival rate of patients with AEG is less than 30%[13]. The

Table 2 Univariate analysis of adenocarcinoma of the esophagogastric junction (types II and III) patients

Characteristic	Coefficient	HR (95%CI)	*P* value
Gender (men/women as reference)	0.078	1.081 (0.765, 1.528)	0.660
Age	0.019	1.019 (1.002, 1.037)	0.031
NLR	0.176	1.193 (1.112, 1.280)	< 0.001
Tumor size	0.178	1.195 (1.134, 1.260)	< 0.001
TNM stage	1.042	2.836 (2.046, 3.930)	< 0.001
Histologic type	0.390	1.477 (1.086, 2.009)	0.013
CA199	0.000	1.000 (0.998, 1.002)	0.948
PNI	-0.034	0.966 (0.940, 0.993)	0.013
PLR	0.003	1.003 (1.001, 1.005)	0.009
Fibrinogen	0.010	1.030 (0.970, 1.095)	0.332
Albumin	-0.289	0.557 (0.479, 1.008)	0.056
Prealbumin	-0.102	0.362 (0.271, 0.484)	< 0.001
Surgery time	0.017	1.017 (0.755, 1.369)	0.912
BMI	-0.580	0.560 (0.431, 0.727)	< 0.001
Cancerous node	0.219	1.245 (1.150, 1.347)	< 0.001
Hemoglobin	-0.006	0.994 (0.988, 1.000)	0.033
Tumor location	0.719	1.127 (0.855, 1.487)	0.397
Smoking	0.006	0.994 (0.970, 1.019)	0.624
Comorbidities	0.017	0.983 (0.953, 1.013)	0.264

NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; BMI: Body mass index; PNI: Prognostic nutritional index; CEA: Carcinoembryonic antigen.

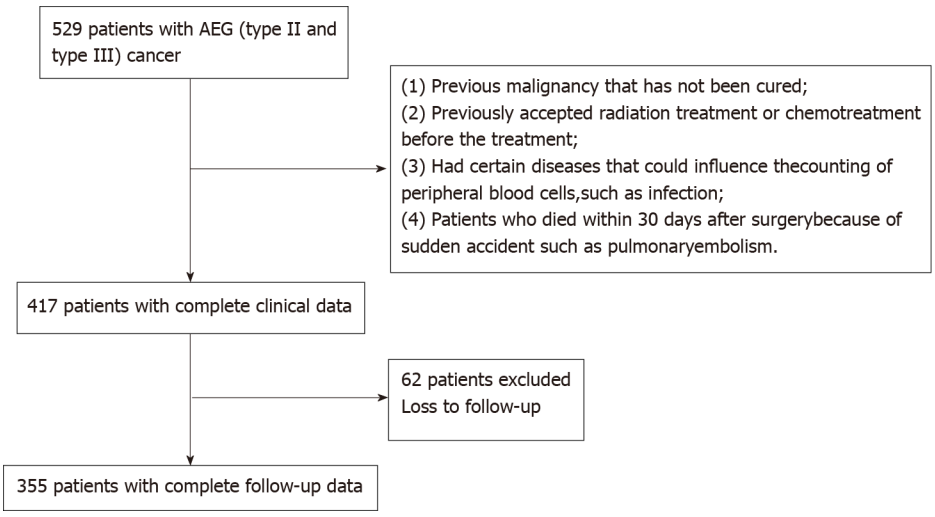

Figure 1 Nomogram for predicting overall survival after curative resection of gastric cancer.

epidemiology, genetics, spread pattern, and prognosis of neoplasms in the esophagus, esophagogastric junction, and stomach remain unclear. The process of tumor development is complex. Gastroesophageal reflux disease and *Helicobacter pylori* have been reported as risk factors for AEG[14,15]. Therefore, many researchers have made significant contributions to improve the prognosis of AEG. Lymph node metastasis, tumor size, differentiation grade, and TNM stage have been defined as prognostic factors[16, 17]. However, these prognostic factors are difficult to judge before surgery; therefore, research on prognostic serum markers has been widely conducted in recent years. To the best of our knowledge, this

Table 3 Multivariate analysis of adenocarcinoma of the esophagogastric junction (types II and III) patients

Characteristic	Coefficient	HR (95%CI)	*P* value
TNM stage	0.827	2.286 (1.236, 4.227)	0.008
BMI	-0.470	0.625 (0.413, 0.946)	0.026
NLR	1.092	2.979 (1.565, 5.674)	0.001
CEA	0.008	1.008 (0.997, 1.019)	0.143
Age	0.031	0.970 (0.556, 1.691)	0.914
Tumor size	0.143	1.154 (0.651, 2.045)	0.624
PNI	0.347	1.415 (0.783, 2.557)	0.250
PLR	0.040	1.041 (0.567, 1.912)	0.897
Hemoglobin	0.197	0.821 (0.479, 1.408)	0.474
Prealbumin	0.122	0.885 (0.496, 1.578)	0.678
Differentiation grade	0.073	1.075 (0.630, 1.836)	0.791
Cancerous node	0.084	1.088 (0.587, 2.016)	0.789

NLR: neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; BMI: Body mass index; PNI: Prognostic nutritional index; CEA: Carcinoembryonic antigen.

Table 4 Nomogram scoring system

NLR	Points	TNM stage	Points	BMI	Points
Low (1)	0	I and II (1)	0	Low (1)	0
High (2)	26	III and IV (2)	20	Normal (2)	58
				High (3)	100

NLR: Neutrophil-to-lymphocyte ratio; BMI: Body mass index.

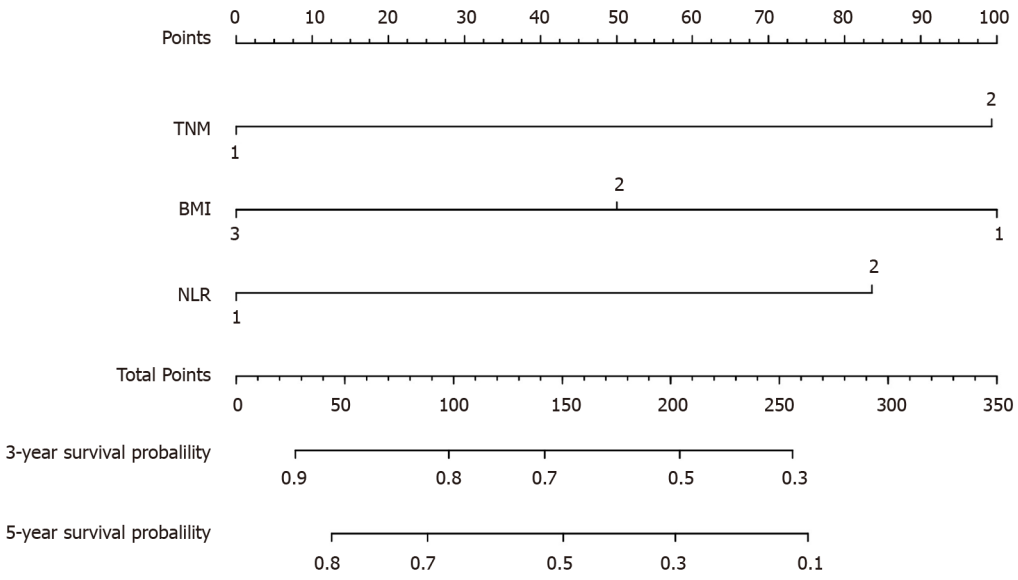

Figure 2 Calibration curves of the prognostic nomogram for 3-year overall survival. TNM: Tumor-node-metastasis; BMI: Body mass index; NLR: Neutrophil-to-lymphocyte ratio.

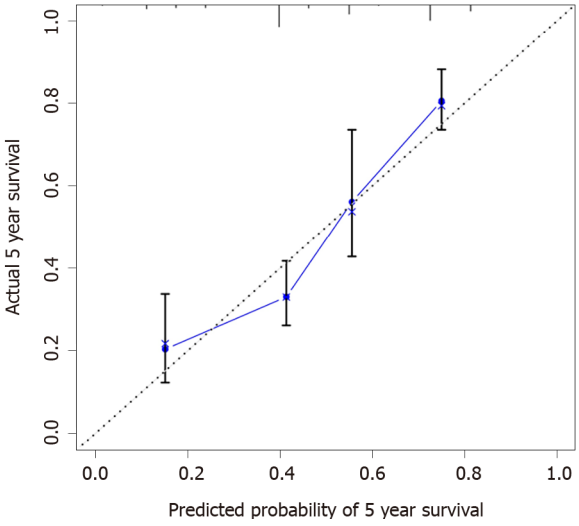

Figure 3 Calibration curves of the prognostic nomogram for 5-year overall survival.

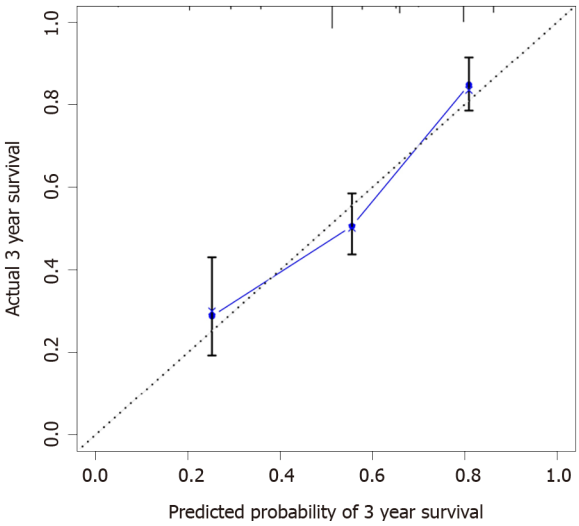

Figure 4 Calibration curves in the testing group for 3-year overall survival.

study is the first attempt to develop a prognostic nomogram that combines serum markers (including inflammatory markers, nutritional indices, and tumor markers) and clinicopathological characteristics to estimate the 3-year and 5-year survival probability, which was highly accurate in predicting the prognosis of patients with AEG (types II and III).

The multivariate analysis revealed that TNM stage, NLR, and BMI were important factors. Therefore, a model was built by these markers. Moreover, the calibration and ROC curves showed that the nomogram was reliable and precise.

In recent years, nomogram has been used to predict the prognosis of many cancers[18,19]. This model has been identified as a new standard that can integrate multiple predictive variables in a weighted manner and intuitively show the influence of variables on individual predictive values. Similar conclusions were obtained in the present study. The AUC of the nomogram was larger than that of TNM stage; therefore, the nomogram and TNM staging system can help in predicting the survival of patients with AEG. Furthermore, this nomogram can be applied in clinical practice to help surgeons evaluate the prognosis of patients and choose appropriate treatment.

Our nomogram contained three variables, and previous studies also got to the same conclusion[9,20]. Inflammatory indexes were related with the prognosis of gastrointestinal cancer patients[21]. This research found that NLR was an independent risk factor, and the possible mechanism is that systemic inflammation caused by tumors can release a large number of pro-inflammatory mediators, such as C-reactive protein, fibrinogen, vascular endothelial growth factor, and transforming growth factor-α. These factors stimulate the process of tumors[22]. Meanwhile, neutrophils could prevent natural killer cells and T cells in the system contacting and killing the tumor cells[23,24]. Therefore, the NLR should be included in the regular assessment index for patients with AEG.

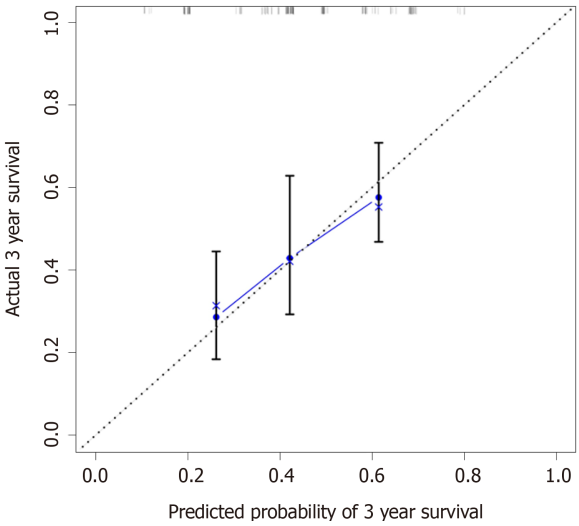

Figure 5 The receiver operating characteristic curves of the prognostic nomogram and tumor-node-metastasis staging for 3-year overall survival.

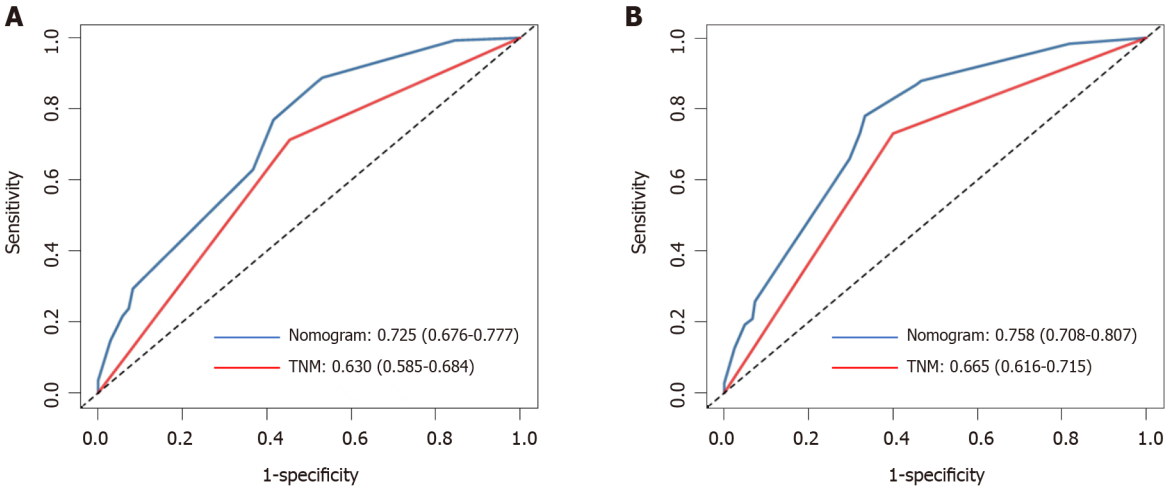

Figure 6 The receiver operating characteristic curves of the prognostic nomogram and tumor-node-metastasis staging for 5-year overall survival.

As an independent prognostic indicator of tumor-related diseases, BMI has raised increasing concerns for researchers in recent years. BMI is related to the prognosis of breast carcinoma, non-small-cell lung cancer, and colorectal cancer, among others[25-27]. In this study, we found that BMI was significantly correlated with the prognosis of patients with AEG. However, the underlying mechanism remains unclear. Patients with AEG with a low BMI may have poor nutritional status and immune function[28]. This may have an adverse effect on disease progression; therefore, these patients may have a shorter OS.

Our research has two potential limitations. First, this study was a single-center study that did not include a sufficient number of cases to verify the results. Second, the included patients who underwent surgical resection for AEG cannot account for all patients with AEG.

CONCLUSION

TNM stage, NLR, and BMI are risk factors for the prognosis of patients with AEG. The novel nomogram accurately and reliably predicts the OS after radical resection of patients with AEG (types II and III). This may help clinicians formulate personalized treatment plans.

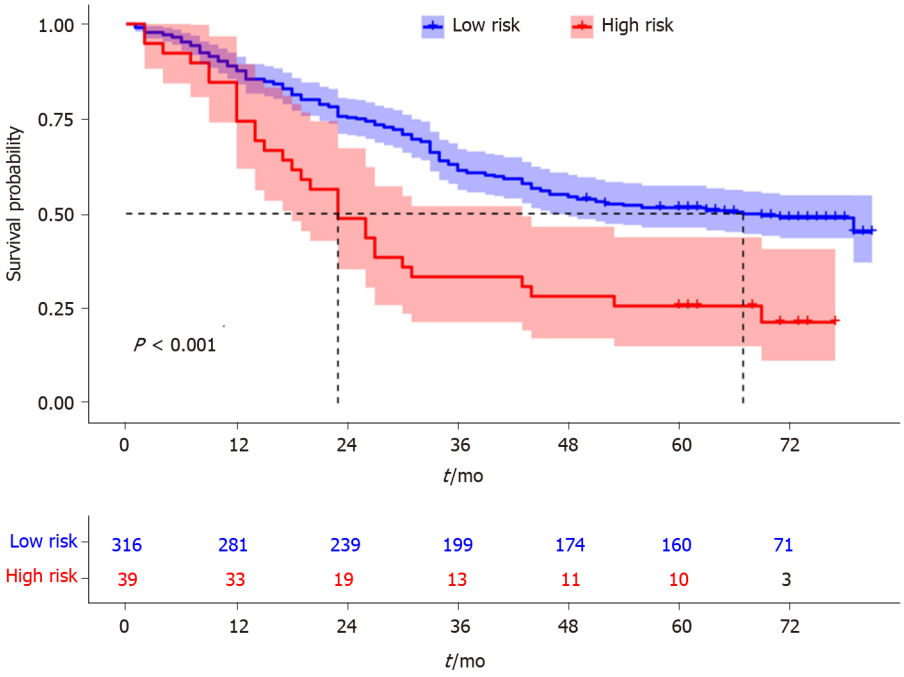

Figure 7 Survival curves stratified by the score calculated by the nomogram (low risk: < 58 and high risk: ≥ 58).

ARTICLE HIGHLIGHTS

Research background

In recent years, the incidence of types II and III adenocarcinoma of the esophagogastric junction (AEG) has shown an obvious upward trend worldwide.

Research motivation

The prognostic prediction after radical resection of AEG has not been well established.

Research objectives

To establish a prognostic model for AEG (types II and III) based on routine markers.

Research methods

The construction of the nomogram was based on Cox proportional-hazards models. The new score model was analyzed by C index and calibration curves. The receiver operating characteristic (ROC) curve was used to compare the predictive accuracy of the scoring system and tumor-node-metastasis (TNM) staging. Overall survival (OS) was calculated using the Kaplan-Meier curve amongst different risk AEG patients.

Research results

Multivariate analysis showed that TNM stage (hazard ratio [HR] = 2.286, P = 0.008), neutrophil-to-lymphocyte ratio (NLR) (HR = 2.979, P = 0.001), and body mass index (BMI) (HR = 0.626, P = 0.026) were independent prognostic factors. The new scoring system had a higher concordance index (0.697), and the calibration curves of the nomogram were reliable. The area under the ROC curve of the new score model (3-year: 0.725, 95% confidence interval [CI]: 0.676-0.777; 5-year: 0.758, 95%CI: 0.708-0.807) was larger than that of TNM staging (3-year: 0.630, 95%CI: 0.585-0.684; 5-year: 0.665, 95%CI: 0.616-0.715).

Research conclusions

This model has been identified as a new standard that can integrate multiple predictive variables in a weighted manner and intuitively show the influence of variables on individual predictive values. To the best of our knowledge, this study is the first attempt to develop a prognostic nomogram that combines serum markers (including inflammatory markers, nutritional indices, and tumor markers) and clinicopathological characteristics to estimate the 3-year and 5-year survival probability, which is highly accurate in predicting the prognosis of patients with AEG (types II and III). TNM stage, NLR, and BMI were risk factors for the prognosis of patients with AEG and then a model was built which can predict the prognosis of patients.

Research perspectives

The novel nomogram accurately and reliably predicts the OS after radical resection of patients with AEG (types II and III). This may help clinicians formulate personalized treatment plans.

FOOTNOTES

Author contributions: Wei ZJ and Qiao YT designed this study and drafted the manuscript, and they contributed to this work equally; Zhou BC collected and organized the data; Abigail NR polished the article; Zhang LX, Su YZ, Xu AM, Han WX, and Luo PQ performed the study and participated in the work; Zhang LX, Su YZ, Xu AM, Han WX, and Luo PQ contributed this work equally, and they are all the corresponding author. All authors read and approved the final manuscript.

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

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Retrospective Study

Over-the-scope-grasper: A new tool for pancreatic necrosectomy and beyond - first multicenter experience

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Abstract

BACKGROUND

Endoscopic treatment of pancreatic necrosis can be challenging and time-consuming because sticky necrotic debris is sometimes difficult to remove. The over-the-scope-grasper, a new tool that has recently become available for this purpose, might also be useful for other indications. However, clinical data on the efficacy and safety of this new device are lacking.

AIM
To evaluate the technical success and safety of the device in a multicenter setting.

METHODS
The over-the-scope-grasper was used in nine selected endoscopic centers between November 2020 and October 2021 for appropriate indications. Overall, 56 procedures were included in the study. We retrospectively evaluated procedural parameters of all endoscopic interventions using a predefined questionnaire, with special respect to technical success, indications, duration of intervention, type of sedation, and complications. In the case of pancreatic necrosectomy, the access route, stent type, number of necrosis pieces removed, and clinical handling were also recorded.

RESULTS
A total of 56 procedures were performed, with an overall technical success rate of 98%. Most of the procedures were endoscopic pancreatic necrosectomies (33 transgastric, 4 transduodenal). In 70% of the procedures, access to the necrotic cavity was established with a lumen apposing metal stent. The technical success of pancreatic necrosectomy was 97%, with a mean of 8 pieces (range, 2-25 pieces) of necrosis removed in a mean procedure time of 59 min (range, 15-120 min). In addition, the device has been used to remove blood clots (n = 6), to clear insufficiency cavities before endoluminal vacuum therapy (n = 5), and to remove foreign bodies from the upper gastrointestinal tract (n = 8). In these cases, the technical success rate was 100%. No moderate or severe/fatal complications were reported in any of the 56 procedures.

CONCLUSION
These first multicenter data demonstrate that the over-the-scope-grasper is a promising device for endoscopic pancreatic necrosectomy, which is also appropriate for removing foreign bodies and blood clots, or cleaning insufficiency cavities prior to endoluminal vacuum therapy.

Key Words: Over-the-scope-grasper; Endoscopic pancreatic necrosectomy; Grasper; Direct endoscopic necrosectomy; Pancreatic necrosis; Endoscopic tool

Core Tip: The objective of our retrospective multicenter study was to evaluate the efficacy and safety of the over-the-scope-grasper, a new endoscopic grasping tool, originally designed for endoscopic pancreatic necrosectomy. A total of 56 procedures were evaluated, including 37 pancreatic necrosectomies with a technical success of 97%. In the other indications - removal of foreign bodies and blood clots or cleaning of insufficiency cavities before endoluminal vacuum therapy - the technical success rate was 100%. These first multicenter data show the over-the-scope-grasper as a promising tool for endoscopic pancreatic necrosectomy and beyond.

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INTRODUCTION

Interventional endoscopy continues to evolve with new techniques, which allows minimally invasive treatment of gastroenterological diseases. The development and improvement of these methods have always been accompanied by the development of new, optimized equipment and tools[1-4].

In the case of endoscopic pancreatic necrosectomy, some new tools for endoscopic ultrasound (EUS) guided access to the necrotic cavity have been developed, such as lumen apposing metal stents (LAMS) [5]. Dedicated instruments for necrosectomy are scarce, although a new motorized device (EndoRotor™) has been tested for this indication, providing encouraging data[6]. Therefore, in addition to suction and irrigation, various snares, baskets, or forceps are usually used to remove the tough and sticky necrotic tissue from the retroperitoneal cavity. Since these instruments are less suitable for this purpose, they often slip off from the necrotic tissue and necrosectomy is cumbersome and time consuming. Inci-

dentally, the same problems occur during removal of larger foreign bodies or blood clots from the gastrointestinal tract.

The over-the-scope-grasper, an extra-large grasper attached to the tip of the endoscope, is a new tool developed to overcome the mentioned limitations, especially to facilitate pancreatic necrosectomy[7]. The aim of this retrospective study was to evaluate the efficacy and safety of the new device in a multicenter setting.

MATERIALS AND METHODS

Description of the device

The over-the-scope-grasper (OTSG Xcavator™ - Ovesco Endoscopy AG, Tübingen, Germany) is an approved single use extra-large grasper attached to the tip of the endoscope. The device is made of transparent plastic to restrict the endoscopic view as little as possible. With a diameter of 14.7 mm (forceps closed), the grasping tool can be well inserted through large caliber LAMS. The diameter of open forceps (28.4 mm) allows grasping larger pieces of tissue or necrotic debris. The volume inside the closed grasper is just over 1 cm^3. A central 1.1 mm opening at the tip of the device allows additional guidance and stiffening of the endoscope by a guidewire, if necessary. The instrument is connected to a semi-rigid spout that is fixed onto the endoscope's tip (Figure 1). The 1650 mm flexible shaft of the instrument is fixed to the ring and connected proximally to a standard handgrip for opening and closing the grasping tool. To prevent the mucosa from becoming trapped between the endoscope and the cable, both (system and endoscope) are covered with a transparent plastic sheath.

Application of the device in pancreatic necrosectomy

The device was applied as follows: The endoscope with the attached grasping tool was inserted into the necrosis cavity. Inside the cavity, the necrotic tissue was grasped by opening the tool and advancing the endoscope while the tissue was sucked into the grasper. After closing the device, the endoscope was withdrawn into the stomach, the grasper was opened, and the tissue was pushed out of the grasper by irrigation through the working channel (Figures 2 and 3, Video).

Study design

In this multicentric retrospective study, the over-the-scope-grasper was used in selected centers in the early phase of its market launch and 5 mo beyond (from November 2020 to October 2021). After a dedicated introduction into the system, the device was applied by experienced endoscopists for appropriate indications. Preparation and application of the system took place as previously described [7].

The main study objective was to evaluate the technical success of the device application, defined as the smooth advancement of the grasper into the target region, capturing and removing the foreign body/necrotic tissue.

Other outcome parameters were indications, duration of intervention, type of sedation, and complications. In the case of necrosectomy, the access route, stent type, number of necrosis pieces removed, and clinical handling (cleaning, additional instruments, *etc*.) were also considered. Complications were classified according to the American Society for Gastrointestinal Endoscopy Lexicon[8]. The overall procedure time was calculated from the first insertion to the last removal of the endoscope, while the "grasper on time" corresponds to the time period during which the grasper was attached to the endoscope.

Data acquisition and statistics

To evaluate procedural parameters in a standardized manner, for each procedure a predefined questionnaire was retrospectively completed by the endoscopist. Data were extracted from the clinical database at each center and submitted in an anonymous form to the coordinating center, where all data were collected centrally and in an anonymized form. A complete case analysis was performed for all 56 procedures. Experience of at least four procedures was mandatory to have patients included in our prospective registry.

Data analyses were performed using Microsoft Excel (version 16.54). Due to the non-interventional study design, no between-group significance tests were performed, and only descriptive statistics were used (mean and range). Before each endoscopic procedure, the patients gave their written consent to the procedure. Retrospective analysis of clinical data was approved by the local ethics committee without requiring separate written informed consent from each patient for data analysis (Ethics Committee of the University of Würzburg).

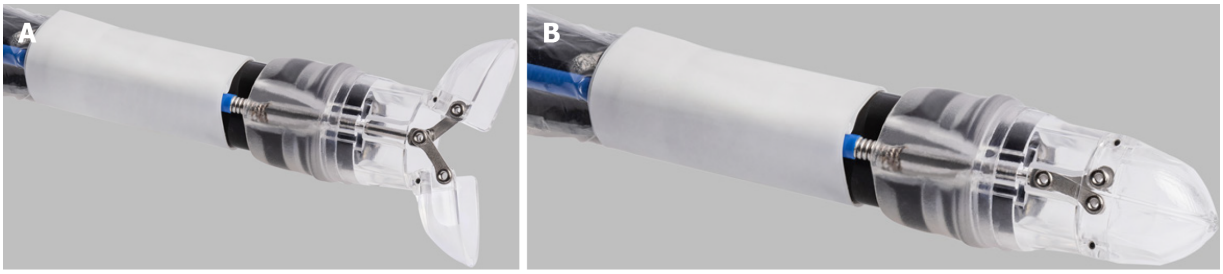

Figure 1 Over-the-scope-grasper attached to an endoscope. A: Open position; B: Closed position. With permission from Ovesco Endoscopy AG, Tübingen, Germany. Available from: http://www.ovesco.com/de.

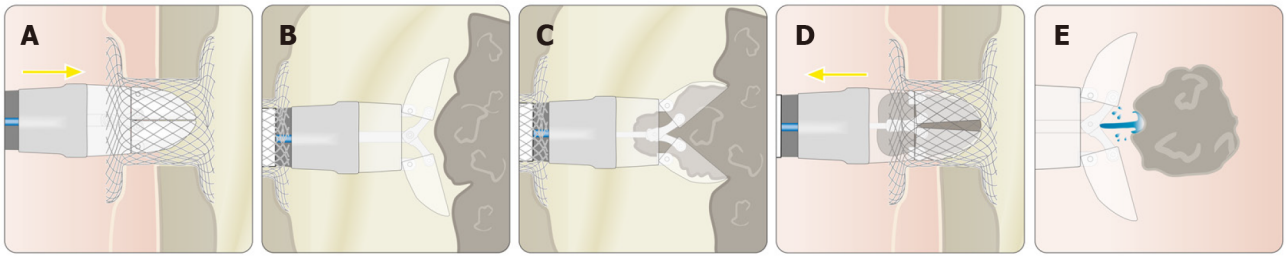

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Figure 2 Application of the over-the-scope-grasper in pancreatic necrosectomy through a lumen apposing metal stent. A: Insertion into the necrotic cavity; B: Opening the device; C: Grasping necrotic tissue; D: Withdrawal from the necrotic cavity; E: Flushing out the tissue by irrigation. LAMS: Lumen apposing metal stent. With permission from Ovesco Endoscopy AG, Tübingen, Germany. Available from: http://www.ovesco.com/de.

RESULTS

In nine centers, the over-the-scope-grasper was used in 56 procedures (in 50 patients) performed between November 2020 and October 2021. All procedures were on-label uses. Details about the number of patients from each center are shown in the supplementary data (Supplementary Table 1).

Primary outcome

The overall technical success of the device application was 98% (55 of 56 procedures). In one case (pancreatic necrosectomy with transduodenal access), the device could not be inserted into the necrosis cavity due to an unfavorable angle of entry.

Pancreatic necrosectomies

Most of the procedures (66%, *n* = 37) were pancreatic necrosectomies, with preferred transgastric approach (33 transgastric *vs* 4 transduodenal). EUS-guided access to the necrosis cavity was achieved *via* LAMS (70%, *n* = 26) or *via* double pigtail stents (30%, *n* = 11). Three different types of SEMS were used. Almost all LAMS (25/26) had a small diameter (15 or 16 mm). The first necrosectomy session was performed in a mean of 35.7 (14 – 90) d after the beginning of the pancreatitis (Table 1).

The technical success of necrosectomy was 97%, with a mean of 8 pieces (2-25 pieces) of necrosis removed. The mean overall procedure time was 59 min (range, 15-120 min), of which the grasper was used for a mean of 32 min (range, 10-70 min). In eight cases, an additional snare was used to pull the tissue into the grasping tool. In all cases, an irrigation pump was used to push the necrotic tissue out of the grasper. However, in 51%, removal of the endoscope was necessary to clean the device outside the patient. Almost all necrosectomies were performed under sedation. In three patients, the procedure was performed under general anesthesia because prolonged ventilation was required due to the severity of the pancreatitis.

Other indications

In addition to endoscopic necrosectomy, the device has been used for other appropriate indications (19 cases, Table 2). In eight patients, the tool was used to remove foreign bodies from the upper gastrointestinal tract (Figure 4). In each case, complete removal of the foreign body was achieved. In six cases, the device was used to remove large blood clots in case of upper gastrointestinal bleeding. In addition to pancreatic necrosectomy, the device was also used to clear insufficiency cavities prior to endoluminal vacuum therapy (*n* = 5). In all these cases, the technical success rate was 100%.

Table 1 Over-the-scope-grasper in endoscopic pancreatic necrosectomy - procedural parameters

Number of cases	37
Number of patients	31
Sedation	34× NAPS
	3× anesthesia
Mean time to first necrosectomy	35.7 d (14-90 d)
Mean dimension of won	10.1 cm × 6.5 cm × 4.8 cm
Estimated percentage of necrosis within each collection	57% (20%-90%)
Mean number of DEN session for WON resolution	4.5 (1-13)
Access route/mean duration	Total (*n* = 37/59 min)
	33× transgastric (58 min)
	4× transduodenal (65 min)
LAMS (type, diameter)	26× LAMS
	15× Plumber™ (16 mm)
	8× hot Axios™ (15 mm)
	1× hot Axios™ (20 mm)
	2× Spaxus™ (16 mm)
	11× double pigtail stents
Additional tool	37× irrigation pump
	8× snare
Handling	19× endoscope removed for cleaning
	18× removal of endoscope not necessary

NAPS: Nurse administrated propofol sedation; LAMS: Lumen apposing metal stent; WON: Walled-off necrosis; DEN: Direct endoscopic necrosectomy; Plumber™: M.I.Tech, Pyeongtaek, South Korea; Hot Axios™: Boston Scientific, Marlborough, United States; Spaxus™: Taewoong Medical, Gimpo, South Korea.

Safety and complications

Overall, five mild complications occurred. In three cases, dislocation of the LAMS occurred during endoscopic necrosectomy. None of these cases resulted in further problems (bleeding, *etc*.). In all three cases, pigtail stents were inserted instead to keep access to the necrosis open.

In one case, superficial laceration of the upper esophageal sphincter occurred during insertion of the device. In another case, minor bleeding occurred during necrosectomy, which could be treated endoscopically (no transfusion required). No moderate or severe/fatal complications were reported in any of the 56 procedures.

DISCUSSION

Direct endoscopic necrosectomy (DEN) of pancreatic necrosis is an important development in interventional endoscopy and has significantly improved the prognosis of these patients[9]. The method is well established and has been further developed in recent years, especially with new, specially shaped LAMS that facilitate EUS-guided access to the necrosis cavity[5]. To our knowledge, new devices designed for necrosectomy have not yet been developed[10-12]. Therefore, DEN is often performed by a combination of sucking debris through the working channel, removing necrotic material with a removal device, and applying irrigation. This method is often time consuming, as effective suction needs a free working channel, therefore used devices (snares, *etc*.) have to be introduced and removed frequently. The devices used so far also have disadvantages in necrosectomy. Frequently, snares or baskets cannot be fully opened in the narrow retroperitoneal necrosis cavity, thus grabbing of tissue can be difficult. In addition, snares often cut through the soft necrotic tissue rather than capturing it. Therefore, other systems for necrosectomy have been tested recently, such as the EndoRotor™ (Interscope Inc., Northbridge, Massachusetts, United States), a technically complex device originally developed for

Table 2 Over-the-scope-grasper in other indications - procedural parameters

Foreign bodies	
Number of cases	8
Number of patients	8
Sedation	7× NAPS
	1× anesthesia
Mean duration	31.5 min (15-60 min)
Location	5× esophagus
	3× stomach
Type of foreign body	5× meat bolus
	2× tablets (intoxication)
	1× button cell batteries
Additional tool	1× forceps
	1× net
Blood clots/bleeding:	
Number of cases	6
Number of patients	6
Sedation	5× NAPS
	1× anesthesia
Mean duration	52.2 min (20-100 min)
Location	4× stomach
	2× duodenum
Additional treatment	3× OTSC
	1× TTS clip
	2× no treatment required
Prior to endoluminal vacuum therapy:	
Number of cases	5
Number of patients	5
Sedation	5× NAPS
Mean duration	22 min (20-30 min)
Location	5× rectum
Additional tool	4× irrigation pump
	1× snare

NAPS: Nurse administrated propofol sedation; OTSC: Over-the-scope-clip; TTS: Through-the-scope.

polypectomy and available only in a few centers[6,13,14].

The over-the-scope-grasper is a simple tool developed that can overcome several of the problems mentioned above. Since the grasper is mounted on the tip of the endoscope, the working channel remains free, allowing the necrotic tissue to be captured and aspirated simultaneously. The new device also cuts through the soft tissue, but the captured material remains in the grasper and can be removed. Furthermore, the grasping tool is easy to open even in tight space and can be even used in half-opened position. However, in foxhole-like branched necrotic cavities, the device is less applicable due to its size. Since the system can be attached to a standard gastroscope, it is quickly and easily ready for use and does not require any special additional equipment.

In our study, the new device was used in nine centers after a dedicated introduction into the system. No moderate or severe/fatal complications were reported in a total of 56 cases, underlining the ease of use and safety of the system.

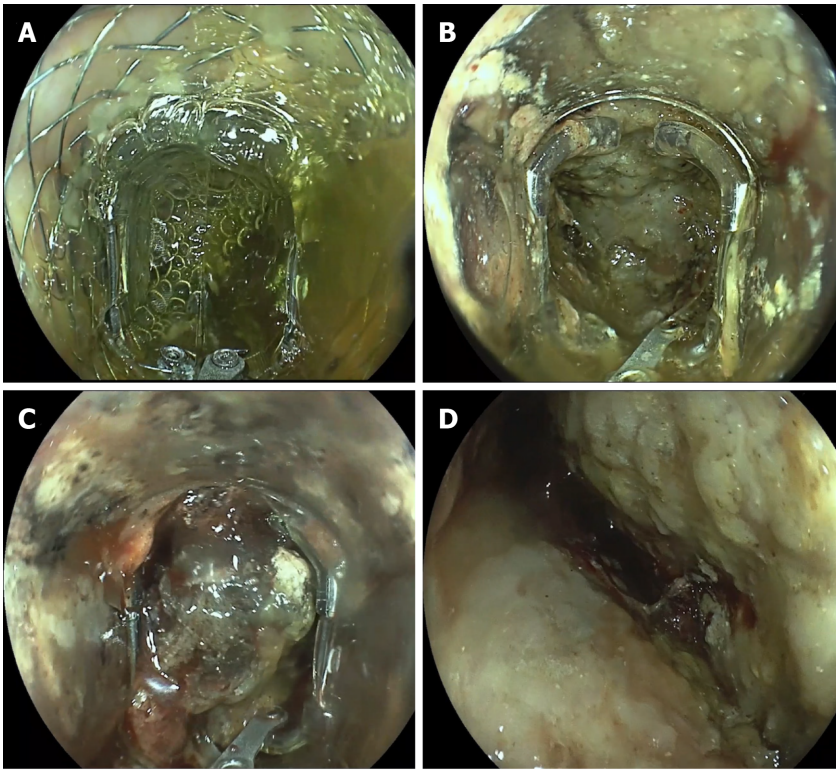

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Figure 3 Pancreatic necrosectomy through a lumen apposing metal stent with the over-the-scope-grasper. A: Insertion through the lumen apposing metal stent; B: Opening the device inside the necrosis; C: Grasping necrotic tissue; D: Cleaned necrotic cavity.

Insertion of the device through the pharynx and esophagus but also entry into the necrosis cavity was usually straightforward. However, the transgastric approach to necrosis appears to be more favorable because the device significantly extends the tip of the endoscope, which may hinder manipulation within the duodenum. This should already be considered when creating the EUS access, as an unfavorable access angle (*e.g.*, in the duodenum) can make insertion of the grasping tool impossible.

Removal of necrotic material with new device works well, even in small LAMS diameters (15 to 16 mm). However, there is little a risk of stent dislocation, especially if the grasper has captured much tissue. LAMS with a larger diameter (20 mm) may be advantageous in this situation. For effective use, a therapeutic gastroscope with a large working channel is recommended. To improve the suction performance, we recommend using a combined suction-irrigation attachment directly at the upper end of the working channel. Irrigation with a pump is also helpful to flush the necrotic pieces out of the grasper. Cleaning the grasper outside the patient is time consuming and frequent passage through the upper esophageal sphincter is an additional burden to the patient. Therefore, we recommend wetting the surface of the device with an Anti-Fog solution, to reduce the necrotic material sticking at the grasper and to improve the visibility through the transparent plastic cover.

Insufficiency cavities after gastrointestinal surgery are often treated by endoluminal vacuum therapy [15]. To achieve rapid healing of the insufficiency, the cavity is previously cleansed of pus and necrotic tissue. For this purpose, the new grasping tool can be used in the same way as for pancreatic necrosectomy if the access to the insufficiency cavity is large enough.

With respect to endoscopic removal of foreign bodies from the gastrointestinal tract, examiners experience that in case of extra-large or hard foreign bodies, the grasper may slip off the foreign body. Here, additional use of a snare might be helpful to pull the foreign body firmly into the grasper[7]. In case of small foreign bodies, the grasping tool completely encloses the foreign body, preventing it from being lost in the pharynx and eliminating the risk of aspiration. Therefore, the system is particularly suitable for removing button cell batteries and small magnets.

Last but not least, the new device appeared to be a helpful tool in the management of upper gastrointestinal bleeding. In addition to quick removal of large blood clots, the transparent plastic scoops of the grasper can be used to compress the bleeding vessel. Thus, after removal of the blood clot, the bleeding source can be compressed while an instrument (clip, injection needle, *etc.*) is inserted through the free working channel. After opening the device, the source of bleeding can then be treated directly, making hemostasis potentially easier and faster.

In summary, our data highlight the usefulness of this new device in several indications, but the study has several limitations. Due to the retrospective design, the study may be affected by selection bias in favor of the device. The multicenter study design with heterogeneous patient populations and operator

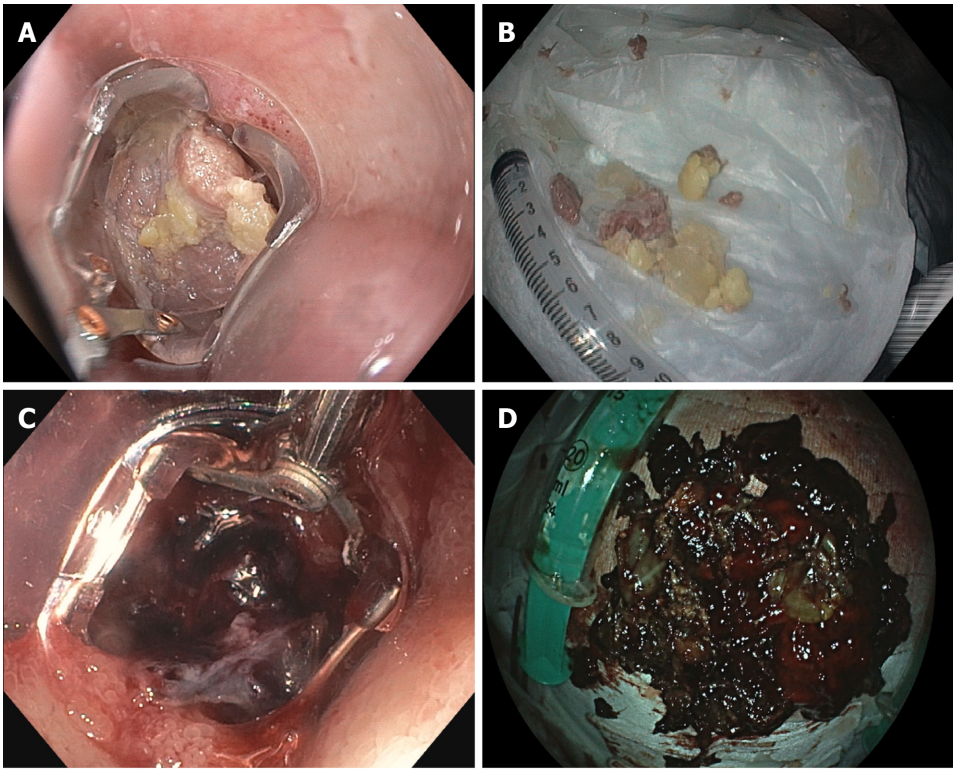

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Figure 4 Removing food bolus and blood clots with the over-the-scope-grasper. A: Grasping a meat chunk in the esophagus; B: Food pieces removed with the new device; C: Grasping a duodenal blood clot; D: Blood clots removed from the stomach with the new device.

experience may also lead to bias (*e.g.*, referral bias). Since this is a retrospective study, a standardized approach to the necrosectomy was not possible. Therefore, only descriptive statistical methods are used and any benefit from the device cannot be quantified or statistically proven.

CONCLUSION

These first multicenter data demonstrate that the over-the-scope-grasper is a promising device for endoscopic pancreatic necrosectomy. Other appropriate indications seem to be cleaning insufficiency cavities prior to endoluminal vacuum therapy and removal of foreign bodies. In the management of upper gastrointestinal bleeding, the grasping tool has been reported to be a useful device beyond the removal of blood clots. However, prospective studies including more patients should be conducted to demonstrate the efficacy and clinical utility of the device and to gather even more information on the safety of the device.

ARTICLE HIGHLIGHTS

Research background

Endoscopic treatment of pancreatic necrosis can be challenging and time consuming because sticky necrotic debris is sometimes difficult to remove. The over-the-scope-grasper, a new tool that has recently become available for this purpose, might also be useful for other indications.

Research motivation

To evaluate the technical success and safety of the new over-the-scope-grasper in a multicenter setting.

Research objectives

We retrospectively evaluated the use of the over-the-scope-grasper in nine selected endoscopic centers and aimed to investigate the technical success and safety of device use.

Research methods

We retrospectively evaluated 56 procedures performed between November 2020 and October 2021. In addition to technical success and complications, we evaluated procedural parameters such as the indications, duration of the procedure, type of sedation, and, in the case of pancreatic necrosectomy, the access route, stent type, and number of pieces of necrosis removed.

Research results

The overall technical success rate was 98%. The technical success of pancreatic necrosectomy (37 cases) was 97%, with a mean of eight pieces of necrosis removed in a mean of 59 min. In addition, the device has been used to remove blood clots (n = 6) to clear insufficiency cavities before endoluminal vacuum therapy (n = 5), and to remove foreign bodies from the upper gastrointestinal tract (n = 8). In these cases, the technical success rate was 100%. No moderate or severe/fatal complications were reported.

Research conclusions

The over-the-scope-grasper is a promising device for endoscopic pancreatic necrosectomy, which is also appropriate for removing foreign bodies and blood clots, or cleaning insufficiency cavities prior to endoluminal vacuum therapy.

Research perspectives

Prospective studies including more patients should be conducted to demonstrate the efficacy and clinical utility of the device.

FOOTNOTES

Author contributions: Brand M and Meining A designed the study concept and drafted the manuscript; Brand M, Bachmann J, Schlag C, Huegle U, Rahman I, Wedi E, Walter B, Möschler O, Sturm L, and Meining A performed endoscopic interventions and undertook critical revision of the article.

Institutional review board statement: This retrospective analysis of clinical data was approved by the local ethics committee (Ethik-Kommission of university Würzburg).

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

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

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Country/Territory of origin: Germany

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ORIGINAL ARTICLE

Retrospective Study

Identifying survival protective factors for chronic dialysis patients with surgically confirmed acute mesenteric ischemia

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Abstract

BACKGROUND

Mesenteric ischemia is significantly more common in end-stage kidney disease patients undergoing chronic dialysis than in the general population and is associated with high morbidity and mortality. However, reports on prognostic factors in this population are limited.

AIM

To elucidate the in-hospital outcomes of acute mesenteric ischemia in chronic dialysis patients and to analyze protective factors for survival.

METHODS

The case data of 426 chronic dialysis patients who were hospitalized in a tertiary medical center for acute mesenteric ischemia over a 14-year period were retrospectively reviewed. Of these cases, 103 were surgically confirmed, and the patients were enrolled in this study. A Cox regression analysis was used to evaluate the protective factors for survival.

RESULTS

The in-hospital mortality rate among the 103 enrolled patients was 46.6%. Univariate analysis was performed to compare factors in survivors and nonsurvivors, with better in-hospital outcomes associated with a surgery delay (defined as the time from onset of signs and symptoms to operation) < 4.5 d, no shock, a higher potassium level on day 1 of hospitalization, no resection of the colon, and a

total bowel resection length < 110 cm. After 1 wk of hospitalization, patients with lower white blood cell count and neutrophil counts, higher lymphocyte counts, and lower C-reactive protein levels had better in-hospital outcomes. Following multivariate adjustment, a higher potassium level on day 1 of hospitalization (HR 1.71, 95%CI 1.19 to 2.46; P = 0.004), a lower neutrophil count (HR 0.91, 95%CI 0.84 to 0.99; P = 0.037) at 1 wk after admission, resection not involving the colon (HR 2.70, 95%CI 1.05 to 7.14; P = 0.039), and a total bowel resection length < 110 cm (HR 4.55, 95%CI 1.43 to 14.29; P = 0.010) were significantly associated with survival.

CONCLUSION

A surgery delay < 4.5 d, no shock, no resection of the colon, and a total bowel resection length < 110 cm predicted better outcomes in chronic dialysis patients with acute mesenteric ischemia.

Key Words: Mesenteric ischemia; Chronic dialysis; End-stage kidney disease; Surgery; Protective factors; Survival

Core Tip: One hundred and three chronic dialysis patients with surgically confirmed acute mesenteric ischemia in a tertiary medical center over 14 years were retrospectively analyzed. Demographic data and clinical characteristics were compared between in-hospital survivors and nonsurvivors. Cox regression analysis was used to evaluate the protective factors for survival. Only 53.4% of the patients survived the index admission, and a surgery delay < 4.5 d, no shock, no resection of the colon, and a total bowel resection length < 110 cm predicted better outcomes in chronic dialysis patients with mesenteric ischemia.

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INTRODUCTION

Mesenteric ischemia is significantly more common in end-stage kidney disease (ESKD) patients undergoing chronic dialysis than in the general population and is associated with high morbidity and mortality. In chronic dialysis patients, mesenteric ischemia occurs in approximately 0.3%-1.9% of patients annually[1,2], whereas mesenteric ischemia is rare in the general population, with a frequency of 0.09%-2.0% per patient annually[3,4]. The nonocclusive type of mesenteric ischemia (NOMI) is a predominant feature in dialysis patients[5-8] and results from splanchnic hypoperfusion, vasoconstriction, and ischemia–reperfusion injury[9]. Previous investigations have reported mortality rates reaching 45% to 73%[2,5,6,10] in hemodialysis patients. However, reports on prognostic factors in this population are limited.

Acute mesenteric ischemia is usually surgically managed, and early surgical intervention is thought to favor NOMI survival in nondialysis patients. In an analysis of 54 nondialysis patients with mesenteric ischemia who underwent surgery, Duran *et al*[11] demonstrated a significantly worse prognosis in patients over 70 years of age and a higher mortality rate among those with delayed surgery, defined as the time from admission to surgery being > 24 h compared with ≤ 24 h. Aliosmanoglu *et al*[12] retrospectively analyzed 95 nondialysis patients who underwent emergent surgery for mesenteric ischemia and reported that advanced age, high leukocyte levels, a duration from the onset of symptoms to the operation of more than 24 h, and colon involvement had negative effects on the mortality rate. Similarly, among nondialysis patients, Acosta-Merida *et al*[13] found that age, time to surgery, shock, and acidosis significantly increased the risk of mortality due to acute mesenteric ischemia, whereas intestinal resection had a protective effect. A recent systematic review and meta-analysis analyzed 10425 patients with acute mesenteric ischemia and concluded that age, chronic renal disease, diabetes, patient dependency, arrhythmias, cardiac failure, hypotension, large bowel involvement, small and large bowel involvement, creatinine, lactate, delay to surgery, and inotropes were significantly associated with mortality, while anticoagulants, revascularization and bowel thickening on computerized tomography were associated with decreased mortality[14]. However, the in-hospital prognostic factors for survival among chronic dialysis patients with acute mesenteric ischemia are not well established. Moreover, the effect of bowel resection length, as the most important precipitating factor of short bowel syndrome, on

the in-hospital survival of chronic dialysis patients with mesenteric ischemia has not been elucidated.

This retrospective study sought to identify the protective factors for mesenteric ischemia in chronic dialysis patients to promote earlier initiation of aggressive therapy in this targeted population and improve their poor prognosis.

MATERIALS AND METHODS

Patient selection

The medical records of chronic dialysis patients who had been admitted to a tertiary medical center for mesenteric ischemia between January 2002 and December 2015 were retrospectively reviewed. The diagnosis of mesenteric ischemia was defined using the International Classification of Diseases, Ninth Revision, Clinical Modification codes 5570, 5571 and 5579 during the index admission. In total, 426 chronic dialysis patients with acute mesenteric ischemia were identified over a 14-year period. Of these patients, 103 received a surgically confirmed diagnosis and were therefore enrolled in this study. The study was approved by the Institutional Review Board of Chang Gung Medical Foundation (approval number: 202001647B0), which waived the requirement for written informed consent from each participant because personal information was anonymized for this study.

Patient characteristics and outcomes

Baseline characteristics, including sex, age, body weight/height, ESKD-associated comorbidities (diabetes mellitus, hypertension, coronary artery disease, heart failure, atrial fibrillation, history of prior stroke, peripheral artery disease, cirrhosis, peptic ulcer disease, chronic obstructive pulmonary disease, malignancy, and immunosuppressive status), left ventricular ejection fraction (EF), and modality of renal replacement therapy were retrieved. For each patient, surgery delay, defined as the time from the onset of signs and symptoms to surgery, and complications during admission (shock, respiratory failure) were documented. The results of blood examinations upon admission and on day 7 of hospitalization were recorded. The etiology of mesenteric ischemia and the bowel resection sites and length were also documented. Each patient was followed for 3 years from the time of admission or until death.

Statistical analysis

This investigation was a retrospective cohort study. Demographic data and clinical information are presented as means ± SD and counts (%) for categorical data. The *t* test or chi-square test was used to compare continuous or categorical variables between survivors and nonsurvivors.

In the univariate and multivariate analyses, Cox regression analysis was used to identify the protective factors for in-hospital survival. Variables that were determined to be significant in the univariate analysis were calculated. Kaplan–Meier survival curves were plotted for groups with a surgery delay < 4.5 d or more, resection involving the colon or not, and total bowel resection length < 110 cm or more. We used the predictive model of classification and regression tree to define a cutoff value of 4.5 days for surgery delay and 110 cm for total bowel resection length.

R 3.0.2 statistical analysis software (Copyright the R Foundation for Statistical Computing, Vienna, Austria) was used. All reported P values were two-sided, and $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Demographic data and outcomes of chronic dialysis patients with acute mesenteric ischemia

Of the 426 chronic dialysis patients who were hospitalized with mesenteric ischemia, 103 patients whose diagnosis was surgically confirmed were enrolled in this study. The mean age was 68.3 ± 11.3 years, and the male-to-female ratio was 1:1.64 (Table 1). The distributions of age and sex did not differ between survivors and nonsurvivors. The number of patients who survived hospitalization was 55 (53.4%), and the number who did not survive hospitalization was 48 (46.6%). The average age of those who survived hospitalization was 68.5 ± 10.6 years, and that of those who did not survive hospitalization was 68.0 ± 12.3 years ($P = 0.811$). Among the chronic dialysis patients with acute mesenteric ischemia, 63.1% had hypertension, 54.4% had diabetes, 23.3% had peptic ulcer disease, 17.5% had coronary artery disease, 14.6% suffered a prior stroke, 12.6% had malignancy, 10.7% had heart failure, 9.7% had peripheral artery occlusive disease, 4.9% had atrial fibrillation, 2.9% had cirrhosis, 2.9% had chronic obstructive airway disease, and 1.9% had an immunosuppressed status. Hypertension and diabetes mellitus were the two most common comorbidities. No significant differences in baseline comorbidities existed between in-hospital survivors and nonsurvivors. Overall, 100 (97.1%) patients underwent hemodialysis, 8 (7.8%) underwent peritoneal dialysis, and 5 (4.9%) of 103 chronic dialysis patients underwent both hemodialysis and peritoneal dialysis. The frequencies of peritoneal dialysis as a renal replacement therapy modality differed significantly between in-hospital survivors (12.5%, $n = 1$) and nonsurvivors

Table 1 Demographic data of chronic dialysis patients with acute mesenteric ischemia

Variable	Total (*n* = 103)	Survival (*n* = 55)	Death (*n* = 48)	*P* value
Age (yr) (mean ± SD)	68.3 ± 11.3	68.5 ± 10.6	68.0 ± 12.3	0.811
BMI	23.8 ± 3.7	23.5 ± 2.9	24.3 ± 4.6	0.323
Sex, *n* (%)				0.495
Male	39 (37.9)	23 (59.0)	16 (41.0)	
Female	64 (62.1)	32 (50.0)	32 (50.0)	
Comorbidities, *n* (%)				
Diabetes mellitus	56 (54.4)	32 (57.1)	24 (42.9)	0.527
Hypertension	65 (63.1)	35 (53.8)	30 (46.2)	1.000
Coronary artery disease	18 (17.5)	10 (55.6)	8 (44.4)	1.000
Heart failure	11 (10.7)	6 (54.5)	5 (45.5)	1.000
Atrial fibrillation	5 (4.9)	2 (40.0)	3 (60.0)	0.662
Prior stroke	15 (14.6)	10 (66.7)	5 (33.3)	0.404
Peripheral arterial occlusive disease	10 (9.7)	4 (40.0)	6 (60.0)	0.508
Cirrhosis	3 (2.9)	1 (33.3)	2 (66.7)	0.597
Peptic ulcer disease	24 (23.3)	11 (45.8)	13 (54.2)	0.539
Chronic obstructive pulmonary disease	3 (2.9)	1 (33.3)	2 (66.7)	0.597
Malignancy	13 (12.6)	8 (61.5)	5 (38.5)	0.740
Immunosuppressive status	2 (1.9)	1 (50.0)	1 (50.0)	1.000
RRT modality				
Hemodialysis	100 (97.1)	55 (55.0)	45 (45.0)	0.098
Peritoneal dialysis	8 (7.8)	1 (12.5)	7 (87.5)	0.024[a]

[a]$P < 0.05$.

BMI: Body mass index; RRT: Renal replacement therapy.

(87.5%, $n = 7$; $P = 0.024$), but the frequencies of hemodialysis did not.

Analysis of clinical characteristics of chronic dialysis patients with acute mesenteric ischemia

The average surgery delay, defined as the time from the onset of signs and symptoms to surgery, was 2.6 ± 3.1 d, without a significant difference between in-hospital survivors (2.3 ± 2.8 d) and nonsurvivors (2.9 ± 3.5 d; $P = 0.296$) (Table 2). The frequencies of shock defined as vasopressor or inotrope use during hospitalization, including norepinephrine, dopamine, and vasopressin (47.1% survivors *vs* 52.9% nonsurvivors; $P < 0.007$), significantly differed between the two groups. Patient hemogram and biochemical data on days 1 and 7 of hospitalization were recorded. On the first day of admission, the white blood cell (WBC) count was significantly lower (11.69 ± 5.49 k/μL *vs* 14.21 ± 6.74 k/μL, $P = 0.041$), and the serum potassium level was significantly higher (4.71 ± 1.08 g/dL *vs* 4.19 ± 0.89 g/dL; $P < 0.008$) in survivors than in nonsurvivors. On day 7 of hospitalization, a lower WBC count (10.05 ± 5.04 k/μL *vs* 13.96 ± 8.19 k/μL; $P = 0.004$) and a lower C-reactive protein (CRP) level (119.34 ± 81.27 mg/L *vs* 191.94 ± 82.54 mg/L; $P = 0.000$) were associated with higher in-hospital survival.

Reduced EF, defined as an EF determined by echocardiography of less than 50% at the time of initial hospitalization, was not common in either group, and the EF did not differ significantly between survivors and nonsurvivors. NOMI (95.1%) was the most frequent etiology of acute mesenteric ischemia, followed by arterial thrombosis (4.9%). The etiology of acute mesenteric ischemia did not differ significantly between survivors and nonsurvivors. The ileum (80.4%) was the most common resection site, followed by the colon (41.2%), jejunum (27.5%), and rectum (2.0%). The frequency of resection in the ileum were significantly higher in survivors than in nonsurvivors (58.5% *vs* 41.5%, respectively; $P = 0.041$); however, the Cox regression analysis revealed that bowel resection not involving the colon was more powerful in predicting survival (see later text). The average total bowel resection lengths were 78.8 ± 58.36 cm and 65.39 ± 58.86 and 14.23 ± 23.93 cm in the small intestine and colon, respectively. The length of bowel resection did not differ significantly between the groups.

Table 2 Clinical characteristics of chronic dialysis patients with acute mesenteric ischemia

Characteristics	Total (*n* = 103)	Survival (*n* = 55)	Death (*n* = 48)	*P* value
Surgery delay (d) (mean ± SD)	2.6 ± 3.1	2.3 ± 2.8	2.9 ± 3.5	0.296
Complications, *n* (%)				
Shock	87 (84.5)	41 (47.1)	46 (52.9)	0.007[a]
Laboratory data				
Hospital day 1				
WBC (k/μL)	12.86 ± 6.21	11.69 ± 5.49	14.21 ± 6.74	0.041[a]
Hemoglobin (g/dL)	11.06 ± 2.40	11.22 ± 2.30	10.88 ± 2.53	0.476
Platelet (k/μL)	195.47 ± 76.10	189.76 ± 65.39	202.00 ± 87.03	0.418
PMN (%)	82.36 ± 10.74	80.87 ± 11.59	84.08 ± 9.50	0.126
Lymphocytes (%)	9.28 ± 6.10	10.12 ± 6.34	8.32 ± 5.72	0.132
CRP (mg/L)	180.12 ± 138.86	167.23 ± 136.09	193.60 ± 142.03	0.377
Potassium (mEq/L)	4.47 ± 1.02	4.71 ± 1.08	4.19 ± 0.89	0.008[a]
Albumin (g/dL)	2.82 ± 0.59	2.91 ± 0.41	2.70 ± 0.74	0.080
Total bilirubin (mg/dL)	0.86 ± 0.61	0.78 ± 0.34	0.94 ± 0.79	0.230
Hospital day 7				
WBC count (k/μL)	11.87 ± 6.94	10.05 ± 5.04	13.96 ± 8.19	0.004[a]
Hemoglobin (g/dL)	9.56 ± 1.74	9.39 ± 1.76	9.75 ± 1.72	0.297
Platelets (k/μL)	159.35 ± 94.81	173.94 ± 72.26	142.94 ± 113.62	0.099
PMN (%)	79.71 ± 11.77	78.69 ± 8.83	80.90 ± 14.49	0.347
Lymphocytes (%)	10.16 ± 8.08	10.19 ± 5.60	10.13 ± 10.33	0.975
CRP (mg/L)	157.71 ± 89.16	119.34 ± 81.27	191.94 ± 82.54	0.000[a]
Potassium (mEq/L)	4.08 ± 0.85	3.94 ± 0.68	4.24 ± 1.00	0.075
Albumin (g/dL)	2.50 ± 0.43	2.50 ± 0.47	2.50 ± 0.41	0.977
Total bilirubin (mg/dL)	1.62 ± 1.93	1.11 ± 1.75	2.05 ± 2.00	0.053
Echocardiographyin hospital				
LVEF	0.65 ± 0.13	0.66 ± 0.11	0.62 ± 0.16	0.199
Etiology of mesenteric ischemia, *n* (%)				
Arterial embolism	0 (0)	0 (0.0)	0 (0.0)	NA
Arterial thrombosis	5 (4.9)	2 (40.0)	3 (60.0)	0.664
Venous thrombosis	0 (0)	0 (0.0)	0 (0.0)	NA
Nonocclusive	97 (95.1)	52 (53.6)	45 (46.4)	0.664
Bowel resection site, *n* (%)				
Jejunum	28 (27.5)	12 (42.9)	16 (57.1)	0.302
Ileum	82 (80.4)	48 (58.5)	34 (41.5)	0.041[a]
Colon	42 (41.2)	18 (42.9)	24 (57.1)	0.132
Rectum	2 (2.0)	0 (0.0)	2 (100.0)	0.219
Bowel resection length (cm) (mean ± SD)				
Small intestine	65.39 ± 58.86	59.84 ± 48.80	71.64 ± 68.43	0.314
Colon	14.23 ± 23.93	11.88 ± 24.30	16.88 ± 23.47	0.294
Total	78.85 ± 58.36	70.41 ± 48.18	88.52 ± 67.43	0.117

[a]*P* < 0.05.

WBC: White blood cell; PMN: Polymorphonuclear leukocytes; CRP: C-reactive protein; LVEF: Left ventricular ejection fraction.

Univariate and multivariate protective factor analyses of in-hospital survival of chronic dialysis patients with acute mesenteric ischemia

A Cox regression analysis was used to identify important in-hospital protective factors (Table 3). In the univariate analysis, our results demonstrated that a surgery delay < 4.5 d (HR 2.63, 95%CI 1.11 to 6.25; *P* = 0.028) (Figure 1), no shock (HR 2.86, 95%CI 1.49 to 5.26; *P* = 0.001), a higher potassium level on day 1 of hospitalization (HR 1.44, with a 95%CI 1.13 to 1.83; *P* = 0.003), no resection of the colon (HR 2.08, 95%CI 1.15 to 3.85; *P* = 0.015) (Figure 2), and a total bowel resection length < 110 cm (HR 2.33, 95%CI 1.18 to 4.76; *P* = 0.015) (Figure 3) were correlated with survival. After 1 wk of hospitalization, patients with a lower WBC count (HR 0.93, 95%CI 0.88 to 0.98; *P* = 0.006), lower neutrophil count (HR 0.96, 95%CI 0.93 to 0.99; *P* = 0.005), higher lymphocyte count (HR 1.06, 95%CI 1.01 to 1.11; *P* = 0.030), and lower CRP level (HR 0.99, 95%CI 0.99 to 1.00; *P* = 0.009) also had better in-hospital outcomes. After multivariate adjustment, only higher potassium levels on day 1 of hospitalization (HR 1.78, 95%CI 1.25 to 2.54; *P* = 0.001), a lower neutrophil count (HR 0.92, 95%CI 0.84 to 1.00; *P* = 0.038) 1 wk after admission, no resection of the colon (HR 2.70, 95%CI 1.05 to 7.14; *P* = 0.039), and a total bowel resection length < 110 cm (HR 3.85, 95%CI 1.41 to 11.11; *P* = 0.009) were independently associated with survival.

DISCUSSION

This retrospective study assessed differences between survivors and nonsurvivors among patients with acute mesenteric ischemia who underwent chronic dialysis in terms of in-hospital survival, as previous reports are limited. The univariate analysis revealed that a surgery delay < 4.5 d, no shock, no resection of the colon, a total bowel resection length < 110 cm, and improved hemogram and biochemistry data 1 wk after admission were significantly associated with a better in-hospital prognosis. There were no differences in age, sex or baseline comorbidities between the survivors and nonsurvivors. According to the multivariate analysis, with respect to in-hospital survival, a higher potassium level on day 1 of hospitalization, a lower neutrophil level after 1 wk of admission, no resection of the colon, and a total bowel resection length < 110 cm were associated with higher in-hospital survival. Our results emphasize the importance of early diagnosis and early surgical intervention in chronic dialysis patients with mesenteric ischemia.

The relevant literature reports in-hospital mortality rates of 45% to 73%[2,5,6,10], and a similarly high in-hospital mortality rate (46.6%) was observed in this study. Previous investigations reported that early surgical intervention was associated with better survival. Duran *et al*[11] reviewed 54 nondialysis patients with acute mesenteric ischemia who underwent open surgery and found that the mortality rate was related to surgery time (from admission to surgery), with 27% mortality in the < 12-h group, 20% mortality in the 12-24-h group, and 50% mortality in the > 24-h group. In chronic dialysis patients, Charra *et al*[15] found that the 1-mo mortality rate was limited to 15% when 75% of patients were surgically treated in the first 24 h. Similarly, Bender *et al*[2] observed an increased mortality rate (85.7%, 6 of 7) when surgery was delayed for more than 24 h after the onset of abdominal pain compared with no mortality (100%, 4 of 4) when the interval was within this critical period. Among 11 chronic dialysis patients with mesenteric ischemia, Picazo *et al*[10] demonstrated that only 3 (27%) who underwent surgery less than 8 h from the time of their arrival at the emergency room survived. In our work, higher mortality was associated with a longer surgery delay, defined as the time from the onset of signs and symptoms to operation (57%, 8 of 14 in the ≥ 4.5-d group *vs* 47.1%, 42 of 89 in the < 4.5-d group). There are three possible explanations for the slightly longer surgery delay in our work compared with those in other studies. First, the definitions of surgery delay differ among studies. Second, since surgical risk is higher in chronic dialysis patients than in nondialysis patients, most physicians prefer to administer supportive treatment first, including gastrointestinal decompression, aggressive intravascular volume resuscitation, hemodynamic monitoring and support, correction of electrolyte abnormalities, pain control, and initiation of broad-spectrum antibiotics, which may prolong the time of surgery delay. Third, chronic bowel ischemia due to atherosclerosis is prominent in chronic dialysis patients; thus, mesenteric ischemia may be more tolerable in this population than in nondialysis patients, which may explain the longer surgery delay among chronic dialysis patients. Although a short surgery delay was not significantly associated with survival after multivariate adjustment, the protection afforded by a short surgery delay may have been masked or confounded by other factors, such as total bowel resection length, potassium level, or site of operation. The present work reported an important finding: a shorter surgery delay is associated with better survival and the acceptable surgery delay may be longer among chronic dialysis patients than among nondialysis patients.

Table 3 Univariate and multivariate Cox regression analysis of protective factors for in-hospital survival

Variable	Protective measurement univariate	Protective measurement multivariate
	Hazard ratio (95%CI)	Hazard ratio (95%CI)
Surgery delay < 4.5 d	2.63 (1.11-6.25)[a]	2.70 (0.69-10.0)
No shock	2.86 (1.49-5.26)[a]	1.67 (0.33-8.33)
Potassium level in hospital on day 1	1.44 (1.13-1.83)[a]	1.78(1.25-2.54)[a]
WBC count in hospital on day 7	0.93 (0.88-0.98)[a]	0.94 (0.85-1.03)
Neutrophil count in hospital on day 7	0.96 (0.93-0.99)[a]	0.92 (0.84-1.00)[a]
Lymphocyte count in hospital on day 7	1.06 (1.01-1.11)[a]	0.89 (0.76-1.04)
CRP level in hospital on day 7	0.99 (0.99-1.00)[a]	0.99 (0.99-1.00)
No resection of colon	2.08 (1.15-3.85)[a]	2.70 (1.05-7.14)[a]
Total resection length < 110 cm	2.33 (1.18-4.76)[a]	3.85 (1.41-11.11)[a]

[a]$P < 0.05$

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

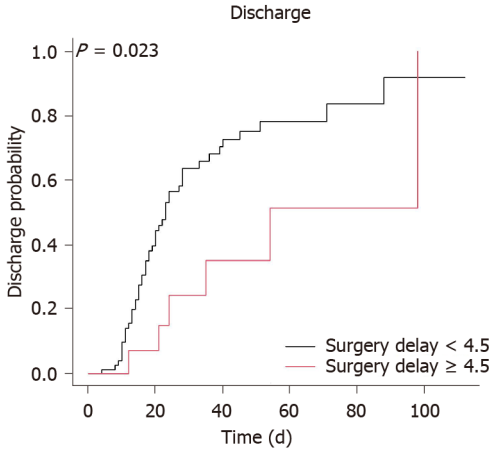

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Figure 1 Kaplan–Meier plot for in-hospital survival with a surgery delay less than or not less than 4.5 d. In patients with a surgery delay < 4.5 d, the 20-d discharge probability was 44.4%, whereas the discharge probability was 50% on day 22. For surgery delays ≥ 4.5 d, the 20-d discharge probability was 14.9%, whereas the discharge probability was 50% on day 54. Surgery delay was defined as the time from the onset of signs and symptoms of acute mesenteric ischemia to surgery.

Tran *et al*[16] analyzed 212 patients undergoing surgery for acute mesenteric ischemia with a predominant etiology of embolism or in situ thrombosis and found that the time to revascularization was associated with predicted 30-d and all-cause 2-year mortality, total bowel resection length and postoperative short-bowel syndrome. They emphasized that early and routine vascular surgery consultation and definitive revascularization may mitigate outcomes of patients suspected to have acute mesenteric ischemia. However, in the present study, all of our study population received bowel resection without documented revascularization procedures before or after intestinal resection. The reason for the lack of revascularization procedures may be that NOMI, rather than vascular occlusion, was the leading cause of acute mesenteric ischemia among the chronic dialysis patients.

Correlations with the bowel involvement site, bowel resection length, and survival have not been well described in chronic dialysis patients with acute mesenteric ischemia. A previous investigation showed a worse mesenteric ischemia prognosis when the colon was involved. Acosta-Merida *et al*[13] demonstrated a significantly higher mortality rate of mesenteric ischemia when the large bowel was involved (78% *vs* 22%), and Aliosmanoglu *et al*[12] also concluded that colon involvement had a negative effect on the mortality rate. Similarly, in the present study, we found that bowel resection not involving the colon independently predicted survival. One of the reasons for the higher mortality rate in these patients may be that more extensive resection is necessary, including colon resection. Second, colon continuity may be important. According to previous reports, short-bowel syndrome is unavoidable after resection if more than 70% of the small intestine or less than 100 cm of small bowel is

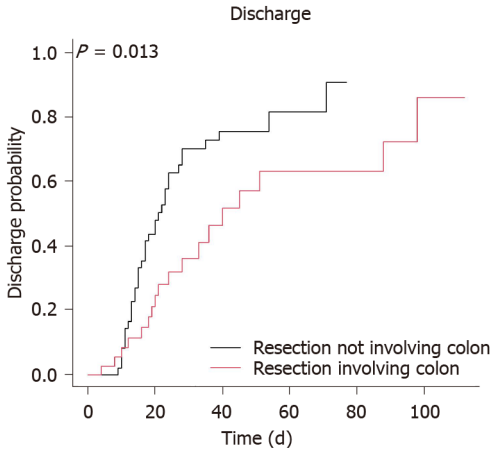

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Figure 2 Kaplan–Meier plot for in-hospital survival with bowel resection involving or not involving the colon. For resection not involving the colon, the 20-d discharge probability was 48.0%, whereas the discharge probability was 50% on day 21. For resection involving the colon, the 20-d discharge probability was 24.7%, whereas the discharge probability was 50% on day 36.

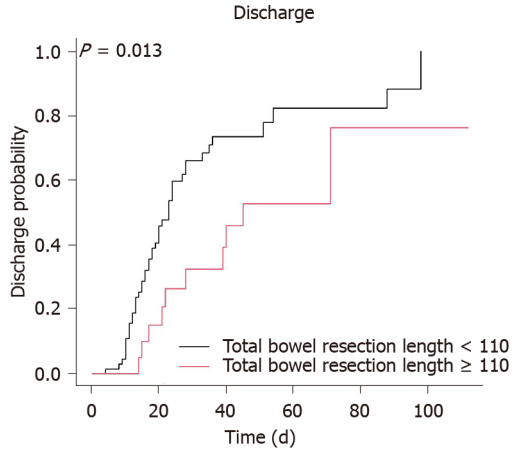

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Figure 3 Kaplan–Meier plot for in-hospital survival with a total bowel resection length less than or not less than 110 cm. In patients with a total bowel resection length < 110 cm, the 20-d discharge probability was 45.8%, whereas the discharge probability was 50% on day 21. In patients with a total bowel resection length ≥ 110 cm, the 20-d discharge probability was 20.1%, whereas the discharge probability was 50% on day 40.

left[17]. Since the colon has important digestive and absorption functions, additional resection of the ileocecal region or the colon increases the severity of short-bowel syndrome. Patients with a short small bowel and no colon are likely to require long-term parental nutrition and fluids; however, if more than half of the colon is brought into continuity, parental nutrition is less likely to be needed unless shorter than 50-cm jejunum remains[18]. A third explanation may involve the intense microbiologic flora in the colon, bacterial translocation, and systemic effects[12]. Our study found an independent protective effect of a total bowel resection length < 110 cm in this population, which has not been described previously. Based on the above findings, we emphasize the importance of bowel continuity and colon preservation in chronic dialysis patients with acute mesenteric ischemia; to maximally reduce the extent of bowel resection, early diagnosis and aggressive surgical intervention are important.

Watershed areas of circulation are more vulnerable to NOMI[19]. A higher frequency of involvement of the right colon and the cecum has been reported in dialysis patients[1,10,15,20]. This intestinal segment seems to be particularly susceptible to nonocclusive ischemia since natural collateral circulation struggles to keep up with tissue demands if the main arterial source is lost[21]. In addition, the right colonic vasa recta are longer and originate from a more distant site than those in the left colon, which may increase resistance to reperfusion after an ischemic insult from arterial hypotension[22]. However, in our study, the ileum (80.4%) was the intestinal segment most involved, followed by the colon (41.2%), likely due to hypoperfusion at the superior mesenteric artery level and often to severe episodes of arterial hypotension. NOMI has only rarely been reported to be associated with peritoneal dialysis, possibly due to the lower occurrence of abruptly hypotensive episodes[23]. Despite having a more stable blood pressure than patients on hemodialysis, peritoneal dialysis patients may experience severe

hypotensive conditions with less symptoms. Contributing factors are inappropriate use of dialysate, resulting in excessive fluid removal; diuretics, and a very low-salt diet coupled with the tendency of dialysate to remove endogenous aldosterone, which is needed for adequate sodium absorption by the gastrointestinal tract[7]. An extremely high mortality rate among peritoneal dialysis patients with mesenteric ischemia has been reported (8 of 10 cases, 80%)[7]. In our study, consistent with a previous investigation, the mortality rate among peritoneal dialysis patients with acute mesenteric ischemia was even higher (7 of 8 cases, 87.5%). Since the presentation of NOMI is similar to that of peritonitis, the presence of peritonitis may mask the condition, and the key to a correct diagnosis is a high index of suspicion in predisposed patients. The high mortality rate is a reflection of the failure to recognize the syndrome at an early, treatable stage[24].

Whether the CRP level predicts in-hospital mortality in acute mesenteric ischemia patients is controversial. Yu *et al*[25] analyzed 12 dialysis patients with mesenteric ischemia and found comparable CRP levels among survivors and nonsurvivors. In contrast, Destek *et al*[26] demonstrated that the CRP level was significantly correlated with the total lengths of stay in the hospital and intensive care unit (ICU). Kaçer *et al*[27] found that the CRP/albumin ratio was a powerful predictor of in-hospital mortality in patients with acute mesenteric ischemia, and it was superior to the WBC count, neutrophil to lymphocyte ratio, and lactate level. In the present study, we found that a lower CRP level after 7 d of admission predicted better survival in these patients, but the protective effect was masked after multivariate adjustment, probably because of confounding by total bowel resection length. We suggest the close monitoring of CRP levels during hospitalization in treatment response monitoring.

Leukocytosis is a common finding among patients with mesenteric ischemia[2,5,6,28]. Yu *et al*[25] disclosed that not all dialysis patients with mesenteric ischemia had leukocytosis initially, but all deceased patients had leukocytosis; however, the difference was not statistically significant. In our work, we observed lower leukocyte counts at baseline (11.69 ± 5.49 k/μL *vs* 14.21 ± 6.74 k/μL; $P = 0.041$) and 1 wk after treatment (10.05 ± 5.04 k/μL *vs* 13.96 ± 8.19 k/μL; $P = 0.004$) in survivors. Improvement in leukocytosis after 1 wk of treatment significantly predicted better survival, but the protective effect was masked after multivariate adjustment, possibly due to confounding by other factors, such as total bowel resection length. We suggest monitoring leukocyte levels during hospitalization and treatment response monitoring.

Shock is also a common clinical feature in dialysis patients with mesenteric ischemia. In a literature review, shock developed in 27%-60%[1,10] of dialysis patients with mesenteric ischemia at the time of diagnosis, and septic shock was the main cause of early death[1]. Schoenberg *et al*[29] found that the mortality rate of systemic inflammatory response syndrome ranged from 6% to 7% and that of septic shock exceeded 50% in an ICU population. Unsurprisingly, the frequency of shock was higher among nonsurvivors in this study. Univariate analysis revealed that no shock during hospitalization, which was associated with milder disease activity, was associated with higher in-hospital survival, but the protective effect disappeared after multivariate adjustment.

Diamond *et al*[28] demonstrated that hyperkalemia (6 of 12), metabolic acidosis (10 of 12), and leukocytosis (8 of 12) were the most consistently noted laboratory findings in dialysis patients with mesenteric ischemia; however, these data are difficult to interpret in dialysis patients since some of them are already increased due to uremia itself and/or due to the time elapsed from the last dialysis session [30]. In chronic dialysis patients, hyperkalemia beginning at a serum potassium level ≥ 5.7 mEq/L was associated with all-cause mortality, and mortality risk estimates increased ordinally through ≥ 6.0 mEq/L[31]. Paradoxically, in our work, both the univariate and multivariate analyses demonstrated a protective value of a higher potassium level on the first day of hospitalization. However, the mean potassium level was still within the normal range among survivors and nonsurvivors in our study, which may explain the paradox, and we suggest keeping the potassium level within the normal range in this population.

Cardiac diseases, such as congestive heart failure, cardiac arrhythmia, low cardiac output states, recent myocardial infarction, and severe valvular cardiac disease, are acknowledged risk factors for acute mesenteric ischemia[32], but the prognostic value of heart failure has not been elucidated in chronic dialysis patients. In our work, there were no significant differences in left ventricular EF among survivors and nonsurvivors.

This study has several limitations. First, this was a retrospective study at a single medical center that enrolled predominantly Asian patients; thus, its findings may not apply to the general population. Second, since this study involved a single center, the number of considered cases was limited, reducing the capacity to detect significance with respect to some variables. Third, only chronic dialysis patients were enrolled, and the in-hospital outcomes of mesenteric ischemia in chronic dialysis patients and nondialysis patients were not compared. Therefore, further study is needed. Fourth, the quick Sepsis-related Organ Failure Assessment (qSOFA) score, with a cutoff value ≤ 3, was found to be a reliable predictor of survival in NOMI patients treated with conservative management[33]. We did not analyze the qSOFA score in the present work, and further study of the prognostic value of the qSOFA score in NOMI patients treated with surgery is needed. Fifth, frequent and severe hypotension when receiving dialysis occurred more commonly in patients who developed bowel ischemia[34], but in this work, we did not analyze the impact of blood pressure on in-hospital mortality. Further investigation is warranted. Nevertheless, this work provides important information about protective factors for survival

in patients with mesenteric receiving chronic dialysis.

CONCLUSION

Outcomes of acute mesenteric ischemia in chronic dialysis patients were poor, and only 53.3% of these patients survived the index hospitalization. A surgery delay less than 4.5 d, no shock during admission, bowel resection not involving the colon, and a total bowel resection length < 110 cm were associated with better in-hospital survival. This study emphasizes that early diagnosis and prompt surgical intervention in chronic dialysis patients with acute mesenteric ischemia are beneficial.

ARTICLE HIGHLIGHTS

Research background

Mesenteric ischemia is significantly more common in end-stage kidney disease patients undergoing chronic dialysis than in the general population and is associated with high morbidity and mortality. However, reports on prognostic factors in this population are limited.

Research motivation

Reports on prognostic factors in chronic dialysis patients with acute mesenteric ischemia are lacking.

Research objectives

The aim of this retrospective study was to identify the protective factors for mesenteric ischemia in chronic dialysis patients to promote earlier initiation of aggressive therapy in this targeted population and improve their poor prognosis.

Research methods

One hundred and three chronic dialysis patients with surgically confirmed acute mesenteric ischemia in a tertiary medical center over 14 years were retrospectively analyzed. Cox regression and Kaplan-Meier analysis were used for prognostic analysis by R statistical analysis software.

Research results

The in-hospital mortality rate among the 103 enrolled patients was 46.6%. Univariate analysis was performed to compare factors in survivors and nonsurvivors, with better in-hospital outcomes associated with a surgery delay (defined as the time from onset of signs and symptoms to operation) < 4.5 d, no shock, no resection of the colon, and a total bowel resection length < 110 cm. Following multivariate adjustment, resection not involving the colon (HR 2.70, 95%CI 1.05 to 7.14; P = 0.039), and a total bowel resection length < 110 cm (HR 4.55, 95%CI 1.43 to 14.29; P = 0.010) were significantly associated with survival.

Research conclusions

A surgery delay < 4.5 d, no shock, no resection of the colon, and a total bowel resection length < 110 cm predicted better outcomes in chronic dialysis patients with acute mesenteric ischemia.

Research perspectives

This study emphasizes that early diagnosis and prompt surgical intervention in chronic dialysis patients with acute mesenteric ischemia are beneficial.

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FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Efficacy of staple line reinforcement by barbed suture for preventing anastomotic leakage in laparoscopic rectal cancer surgery

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Abstract

BACKGROUND

Anastomotic leakage (AL) is a severe complication in rectal cancer surgery. Various methods, including intracorporeal reinforcing suturing, have been used to reduce the incidence of AL. However, little is known about the efficacy of staple-line reinforcement by barbed suture for preventing AL.

AIM

To evaluate the efficacy of staple-line reinforcement using barbed suture for preventing AL in laparoscopic surgery for rectal cancer.

METHODS

We retrospectively reviewed the clinical datum of 319 patients undergoing laparoscopic low anterior resection combined with double stapling technique between May 1, 2017 and January 31, 2021. All surgeries were performed by the same surgical team specializing in colorectal surgery. Patients were divided into two groups depending on whether they received reinforcing sutures. Patients' baseline characteristics did not show any significant difference between the two groups. We analyzed patient-, tumor-, as well as surgery-related variables using univariate and multivariate logistic analyses.

RESULTS

There were 168 patients in the reinforcing suture group and 151 patients in the non-reinforcing suture group. AL occurred in 25 cases (7.8%). Its incidence was significantly higher in the non-reinforcing suture group than in the reinforcing suture group (4.8% *vs* 11.3%, $P = 0.031$). The multivariate analyses demonstrated that the tumor site, tumor size and presence of staple-line reinforcement were independent risk factors for AL. We divided these patients into two risk groups based on the combination of tumor site and tumor size. Patients without any risk factor were assigned to the low-risk group ($n = 177$), whereas those having one or two risk factors were assigned to the high-risk group ($n = 142$). In the high-risk

group, the AL incidence considerably decreased in the reinforcing suture group compared with that in the non-reinforcing suture group (P = 0.038). Nonetheless, no significant difference was found in the low-risk group between the two groups.

CONCLUSION
Staple-line reinforcement by barbed suture may decrease the incidence of AL. A large-scale prospective randomized controlled trial is needed for evaluating the efficacy of staple-line reinforcement for preventing AL.

Key Words: Reinforcing suture; Anastomotic leakage; Laparoscope; Rectal cancer; Double-stapling technique; Barbed suture

Core Tip: Double stapling technique (DST) has been extensively applied in rectal surgery. However, the drawbacks of DST cannot be ignored, particularly because the linear cutter application as the distal rectum incision is not completely matched with a circular incision in the proximal intestinal tract. This leads to crossing at least two staple lines, which is referred as the "dog ear" structure. Some studies have reported that such intersection induced the vulnerable area causing anastomotic leakage (AL). This study was aimed to investigate the efficacy of reinforcing anastomosis with barbed suture in preventing AL after laparoscopic DST, and evaluate its feasibility and safety.

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INTRODUCTION

Colorectal cancer ranks 4th among global cancers in terms of mortality, it causes nearly 900000 deaths every year, and surgery is still the cornerstone of curative intent treatment[1]. Laparoscopic surgery exhibited better clinical and oncologic outcomes and demonstrated its noninferiority in comparison with open surgery in numerous trials, including Colorectal Cancer Laparoscopic or Open Resection II and Comparison of Open Versus Laparoscopic Surgery for Mid or Low Rectal Cancer After Neo-adjuvant Chemoradiotherapy (COREA), and has been extensively applied in rectal cancer surgery[2,3]. Recently, with the constant and intensive investigation of the anatomy, pathology, biological characteristics, and lymph node metastasis mechanisms of rectal cancer, as well as the introduction and popularization of the total mesorectal excision (TME) concept, specification of surgical procedures and innovation of surgical instruments, the sphincter preservation rate in the middle and low rectal cancer surgery has been increased[4,5]. With an increase in sphincter-preserving operations, anastomotic leakage (AL) has become an unavoidable problem. AL is related to a high short-/long-term morbidity, increased local recurrence and impaired quality of life[5-7], with rates varying between 1% and 30%[8-10]. AL is possibly induced by the combination of local, systemic, and technical factors, as well as certain risk factors. It is associated with a male sex, obesity, old age, diabetes, intraoperative blood loss, longer operation duration, lower tumor location and larger tumor size[11,12]. The double stapling technique (DST), originally proposed by Griffen and Knight[13], has been extensively used in colorectal surgery because anastomosis can be made at a low pelvic location during this procedure while preserving the anal sphincter. Nonetheless, the safety of DST has attracted wide concern, particularly because the linear cutter application as the distal rectum incision is not completely matched with a circular incision in the proximal digestive tract. This leads to crossing at least two staple lines, which is referred as the "dog ear" structure (Figure 1)[14,15]. Some studies have reported that such intersection induces the vulnerable area causing AL[16,17]. Therefore, we conducted a retrospective evaluation to determine whether reinforced circular-stapled anastomosis using barbed suture can reduce the incidence of AL after laparoscopic DST, and investigate whether this surgical approach is feasible and safe.

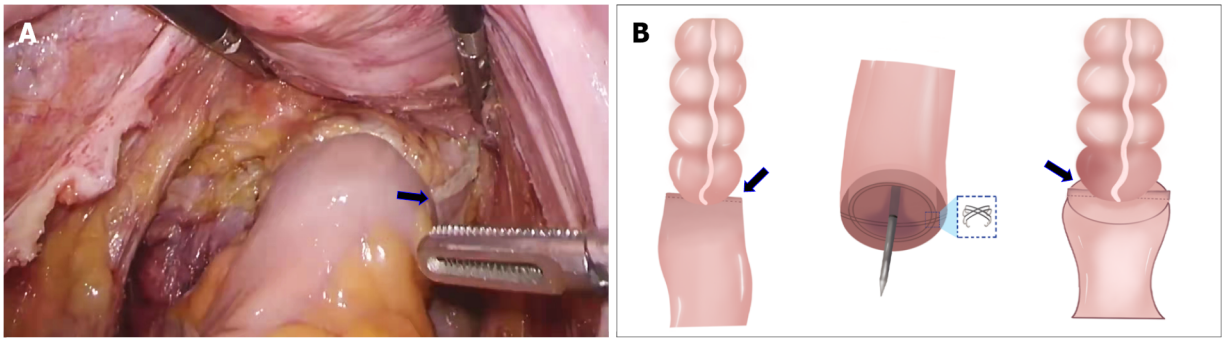

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Figure 1 "Dog ear" structure. A: The intersection of the staple lines (arrow); B: schematic diagram of the intersection of the staple lines (arrow).

MATERIALS AND METHODS

Patients

The study protocol was approved by the Ethics Committee of the Second Hospital of Jilin University. This work was carried out in line with the Helsinki Declaration of the World Medical Association. Patients were carefully selected, and finally, 319 patients undergoing laparoscopic low anterior resection (LAR) with DST between May 1, 2017 and January 31, 2021, at colorectal center of Jilin University were included in the study. All patients were divided into two groups: Those who received reinforcing sutures (n = 168) as experimental group and those who did not receive reinforcing sutures (n = 151) as control group. The tumor was located within 10 cm from the anal verge. The inclusion criteria were: Primary rectal cancer confirmed by colonoscopy and biopsy, American Society of Anesthesiologists (ASA) Grades I-III, and clinical TNM stage of cT1-4aN0-2M0 based on imaging examinations. The exclusion criteria were: Patients with terminal ileal protective stoma or patients receiving colostomy, emergency surgery, intersphincteric resection, preoperative chemotherapy or radiotherapy, and patients with incomplete follow-up data. All surgeries were performed by the same surgical team specializing in colorectal surgery. We have routinely reinforced anastomotic structure using barbed sutures since January 2019; therefore, most of the patients with reinforcing sutures received surgical treatment between 2019 and 2021.

Surgical procedures

Each patient lay in the modified lithotomy position following general anesthesia. In the laparoscopic surgery, a 5-port technique was used. Surgeons evaluated whether the left colonic artery should be preserved on the basis of the condition of the patient and their experiences. The standard surgical technique was used according to the principle of TME, which was sharp mesorectal dissection with nerve preservation. If necessary, splenic flexure was mobilized. After the rectal division using a linear cutter stapler, the circular stapler was used for end-to-end anastomosis. Routine evaluation of the blood supply of the anastomotic stoma was completed by intraoperative indocyanine green (ICG) fluorescence angiography. After anastomosis, each patient underwent an air leakage test. Patients showing risk factors, such as uncertain blood perfusion, insufficient circular stapling donut, and positive results in the air leakage test, underwent temporary diverting stoma. In the reinforcing group, running full-layer stitches were adopted using the unidirectional absorbable 3–0 V-Loc 180 sutures (Covidien, Mansfield, MA, United States) to reinforce the intersection of the cutting lines and anterior anastomosis wall (Figure 2). Pelvic drainage was used in all cases in this study.

Definition of AL

AL is defined as the defect of the intestinal wall at the anastomotic site causing the communication between the intra-and extraluminal compartments[18]. In our colorectal surgery center, all patients routinely received contrast enema radiography 5–7 d after surgery to evaluate asymptomatic AL. Symptomatic AL was confirmed based on the following symptoms: Discharge of feces, pus, or gas from the pelvic drainage, peritonitis, fever, sepsis with pelvic abscess and abdominal pain. We performed computed tomography, digital rectal examination, and surgical to confirm the suspicious cases. AL severity was graded according to the guidelines given by the international study group on rectal cancer [18].

Variables related to AL

The following 24 factors were identified as potential risk factors for AL: Gender, age at the time of operation, body mass index (BMI ≥ 25 or < 25 kg/m^2), diabetes mellitus, hypertension, heart disease, chronic obstructive pulmonary disease, tumor site (≥ 5 or < 5 cm from anal verge), tumor size (≥ 4 or < 4

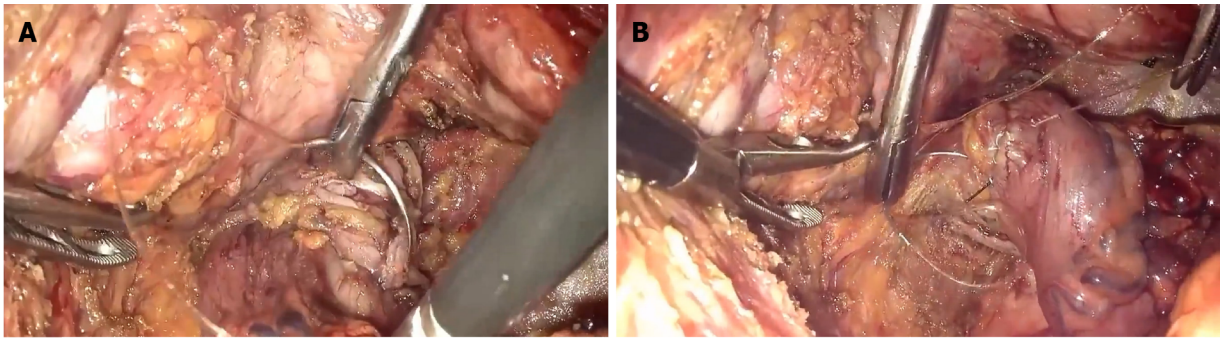

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Figure 2 Continuous suture reinforcement. A: Use of a 3-0 barbed suture at the intersection of the staple lines; B: Completion of the suture on the other side of staple line intersection.

cm), tumor infiltration depth, lymph node metastasis, previous abdominal surgery, preoperative carcinoma embryonic antigen (≥ 5 or < 5 ng/mL), preoperative albumin level (≥ 35 or < 35 g/L), preoperative hemoglobin levels (≥ 90 or < 90 g/L), preoperative serum C-reactive protein level (≥ 10 or < 10 mg/L), ASA scores, ligation of left colic artery (LCA), operation time (≥ 150 or < 150 min), number of staple firings (≥ 3 or < 3), intraoperative blood transfusion, intraoperative blood loss (≥ 60 or < 60 mL), the placement of reinforcing sutures and postoperative intestinal obstruction. All blood samples were collected 3-5 d preoperatively. Thresholds of tumor size, operation time, intraoperative blood loss, and anal exhaust time were determined by average value. The cutoff level for BMI was 25 kg/m^2 as a BMI of ≥ 25 is considered obesity in Chinese people.

Definition of postoperative defecation dysfunction and anastomotic stricture

Patients with a LAR syndrome score ≥ 21 were considered to have postoperative defecation dysfunction [19]. Follow-up was performed at 3, 6, and 12 mo postoperatively by specialized follow-up personnel *via* a telephonic interview. The anastomotic stricture was defined as tight stenosis of anastomosis associated with the inability to traverse a flexible endoscope[20-22]. In the present study, the anastomotic stricture was referred to as the tight stenosis of anastomosis narrower than the 12-mm diameter colonoscope. Colonoscopy was routinely performed for 6-9 mo postoperatively in our hospital.

Statistical analysis

IBM SPSS26.0 was used for data analysis. Continuous variables were represented as mean ± SD (range). Student's *t*-test was used for comparison. Ranked data were analyzed using Mann-Whitney U-test. Moreover, the categorical variables were shown by numbers (percentage). Fisher's exact test and $\chi 2$ test were used for comparison. Multivariate logistic regression was performed for identifying distinct factors that independently predicted the risk of AL. After univariate regression, variables satisfying $P < 0.05$ were enrolled in the multivariate regression. $P < 0.05$ was considered statistically significant.

RESULTS

Between May 2017 and January 2021, we recruited a total of 636 patients who underwent laparoscopic surgery for rectal cancer at the Second Affiliated Hospital of Jilin University. Among them, 498 meeting our pre-determined inclusion criteria were selected for further analysis, whereas 179 were excluded based on the exclusion criteria (34 undergoing colostomy, 43 with a terminal ileal protective stoma, 40 undergoing intersphincteric resection, 6 undergoing emergency surgery, 26 receiving preoperative chemotherapy or radiotherapy, and 30 patients with incomplete clinical data) (Figure 3). Finally, we enrolled 319 patients (153 male and166 female cases). Correlations between various clinicopathological factors in the two groups are presented in Table 1. There were 168 patients in the reinforcing suture group and 151 patients in the non-reinforcing suture group. Among them, 237 patients (74.3%) had middle rectal cancer, and the remaining 82 patients (25.7%) had low rectal cancer. Patients' features did not show any significant difference between the two groups. Surgery-related information is presented in Table 2. LCA preservation rate, number of staple firings, intraoperative transfusion, or intraoperative blood loss did not show any significant difference between the two groups. The experimental group had a longer operation time than the control group, with no significant difference. In terms of complications, the incidence of AL was 7.8% (25/319), with 8 patients from the reinforcing suture group and 17 patients from the control group. There was no significant difference in anastomotic stricture and postoperative defecation dysfunction. The incidence of postoperative defecation dysfunction decreased gradually with the increase in recovery time. Table 3 shows the AL-related information. The experi-

Table 1 Baseline characteristics of patients (*n* = 319)

Variables	Reinforcing sutures		*P* value
	Yes, *n* = 168	No, *n* = 151	
Age (yr)	61.8 ± 8.7	63.0 ± 9.7	0.229
Men/Women	80/88	73/78	0.897
BMI (kg/m^2)	23.2 ± 3.6	22.8 ± 3.8	0.378
ASA score, *n* (%)			0.948
1	60 (35.7)	54 (35.8)	
2	67 (39.9)	61 (40.4)	
3	41 (24.4)	36 (23.8)	
Tumor diameter (cm)	4.4 ± 1.7	4.1 ± 1.8	0.178
Tumor site (from anal verge, cm), *n* (%)			0.641
≥ 5	123 (73.2)	114(75.5)	
< 5	45 (26.8)	37(24.5)	
Depth of tumor invasion, *n* (%)			0.295
T1-T2	33 (19.6)	37 (24.5)	
T3-T4	135 (80.4)	114 (75.5)	
Lymph node metastases, *n* (%)			0.493
Yes	77 (45.8)	75 (49.7)	
No	91 (54.2)	76 (50.3)	
Diabetes mellitus, *n* (%)	31 (18.5)	22 (14.6)	0.352
Hypertension, *n* (%)	37 (22.0)	25 (16.6)	0.218
Heart disease, *n* (%)	18 (10.7)	11 (7.3)	0.287
COPD, *n* (%)	9 (5.4)	7 (4.6)	0.768
Previous abdominal surgery, *n* (%)	17 (10.1)	14 (9.3)	0.799
Preoperative CEA (ng/mL), *n* (%)			0.430
≥ 5	57 (33.9)	45 (29.8)	
< 5	111 (66.1)	106 (70.2)	
Preoperative hemoglobin levels (g/L), *n* (%)			0.239
≥ 90	138 (82.1)	116 (76.8)	
< 90	30 (17.9)	35 (23.2)	
Preoperative serum albumin level (g/L), *n* (%)			0.301
≥ 35	139 (82.7)	118 (78.1)	
< 35	29 (17.3)	33 (21.9)	
Preoperative serum CRP level (mg/L), *n* (%)			0.375
≥ 10	28 (16.7)	28 (20.5)	
< 10	140 (83.3)	123 (79.5)	

BMI: Body mass index; ASA: American society of anesthesiologists; COPD: Chronic obstructive pulmonary disease; CEA: Carcinoma embryonic antigen; CPR: C-reactive protein.

mental group had considerably decreased severity of AL compared with that of the control group (P = 0.020). A total of 15 patients (60.0%) underwent reoperations (laparoscopy and terminal ileostomy) because of failure in conservative management. Meanwhile, the control group had evidently increased reoperation rate compared with that of the experimental group (P = 0.028). With regard to nonoperative treatment, no statistical difference was found between the two groups. Table 4 shows the univariate and

Table 2 Surgical outcomes and postoperative complications

Variables	Reinforcing sutures		*P* value
	Yes, *n* = 168	No, *n* = 151	
Left colic artery ligation, *n* (%)			0.637
Yes	79 (47.0)	75 (49.7)	
No	89 (53.0)	76 (50.3)	
Number of staple firings, *n* (%)			0.902
≥ 3	16 (9.5)	15 (9.9)	
< 3	152 (90.5)	136 (90.1)	
Operation time (min)	150.4 ± 25.1	146.6 ± 20.2	0.135
Intraoperative transfusion, *n* (%)	20 (11.9)	15 (9.9)	0.574
Intraoperative blood loss (mL)	60.5 ± 43.9	58.2 ± 46.3	0.652
Complications, *n* (%)			
Anastomotic leakage	8 (4.8)	17 (11.3)	0.031
Postoperative intestinal obstruction	25 (14.9)	17 (11.3)	0.339
Anastomosis stricture	12 (7.1)	17 (13.1)	0.202
Postoperative defecation dysfunction, 3 mo	31 (18.5)	25 (16.6)	0.657
Postoperative defecation dysfunction, 6 mo	23 (13.7)	21 (13.9)	0.955
Postoperative defecation dysfunction, 12 mo	12 (7.1)	9 (6.0)	0.671

Table 3 Anastomotic leakage related indices (*n* = 25)

	Reinforcing sutures		*P* value
	Yes, *n* = 8	No, *n* = 17	
AL classification			0.020
Grade A	3	2	
Grade B	3	2	
Grade C	2	13	
AL time (d)	5 (2–7)	4 (1–7)	0.715
Treatment			
Trans-anal lavage and drainage	2	1	0.231
Peritoneal lavage and drainage	1	1	1.000
Reoperation	2	13	0.028

AL: Anastomotic leakage.

multivariate analysis results in AL-related risk factors. The tumor site, tumor size, and reinforcing sutures were associated with AL upon univariate and multivariate regression. AL-related risk factors were stratified, then subgroup analyses on reinforcing sutures' efficacy were performed (Table 5). All patients were divided into two risk groups by combining AL-associated risk factors (low rectal cancer and tumor diameter of ≥ 4 cm). Patients without any risk factor were assigned to the low-risk group (n = 177), whereas those having one or two risk factors were assigned to the high-risk group (n = 142). In the high-risk group, the AL incidence considerably decreased in the experimental group compared with that in the control group (P = 0.038). Nonetheless, no statistically significant difference was found in the low-risk group between experimental group and control group.

Table 4 Univariate and multivariate regression on anastomotic leakage-related factors (*n* = 319)

Variables	Univariate regression			Multivariate regression		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Male gender	1.189	0.523–2.705	0.680			
Age ≥ 60 (yr)	2.123	0.824–5.473	0.119			
BMI ≥ 25 (kg/m^2)	1.115	0.448–2.775	0.814			
Diabetic mellitus	2.604	1.060–6.394	0.037	1.662	0.588–4.669	0.338
Hypertension	1.039	0.374–2.888	0.941			
Heart disease	2.050	0.652–6.441	0.219			
COPD	1.739	0.372–8.124	0.482			
Low tumor location < 5 (cm)	2.954	1.289–6.769	0.010	2.856	1.133–7.198	0.026
Tumor diameter ≥ 4 (cm)	3.010	1.313–6.901	0.009	2.994	1.185–7.563	0.020
T3-T4	1.135	0.410–3.142	0.807			
Lymph node metastases	1.719	0.748–3.951	0.202			
Previous laparotomy	1.884	0.602–5.890	0.276			
Preoperative CEA ≥ 5 (ng/mL)	1.216	0.518-2.852	0.653			
Preoperative serum albumin level < 35 (g/L)	1.690	0.673–4.244	0.264			
Preoperative hemoglobin levels < 90 (g/L)	1.582	0.631–3.967	0.328			
Preoperative serum CRP level, ≥ 10 (mg/L)	2.242	0.918–5.476	0.076			
ASA score ≥ 3	1.244	0.499–3.102	0.639			
Ligation of left colic artery	2.435	1.019–5.819	0.045	2.195	0.869–5.546	0.096
Operation time ≥ 150 (min)	2.437	1.059–5.613	0.036	1.837	0.750–4.495	0.183
Number of staple firings ≥ 3	2.577	0.893–7.434	0.080			
Intraoperative transfusion	1.116	0.316–3.939	0.864			
Intraoperative blood loss ≥ 60 (mL)	1.223	0.537–2.787	0.632			
Reinforcing sutures	0.394	0.165–0.942	0.036	0.293	0.114–0.750	0.010
Postoperative intestinal obstruction	2.263	0.848–6.041	0.103			

OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CEA: Carcinoma embryonic antigen; CPR: C-reactive protein; ASA: American society of anesthesiologists.

DISCUSSION

AL is a main concern in a surgical procedure for rectal cancer. Among AL risk factors, the surgical procedure is most important, because it is the only controllable factor. The use of DST leads to the formation of at least two intersections of staple lines, creating ischemic corners that result in AL[23,24]. In the present study, after performing the DST procedure, we used a barbed suture to reinforce the intersection of the cutting lines and anterior anastomosis wall to eliminate vulnerable corners and prevent AL. The three main findings of our study are as follows. First, tumor diameter ≥ 4 cm, low rectal cancer, and reinforcing sutures are independent risk factors for AL. Second, reinforcing sutures reduce AL severity and decrease the reoperation rate. Finally, for patients with risk factors, reinforcing sutures can significantly lower AL incidence.

There are different approaches adopted for reducing the AL rate caused by the DST procedure or other risk factors. Asao *et al*[25] used a mattress suture to let the linear stapler line clump around the dummy shaft to eliminate dog ears and improve DST. However, the approach was technically restricted, which also required relatively upper anastomotic positions, making it difficult to popularize. Marecik *et al*[26] adopted a single-stapled, double-pursestring approach for colorectal anastomosis in 160 cases receiving LAR, resulting in a low AL rate. However, technical difficulties limited its

Table 5 Subgroup analysis of the effectiveness of reinforcing sutures

Reinforcing sutures	Anastomotic leakage		*P* value
	Yes	No	
Low-risk group			0.368
Yes	1	87	
No	4	85	
High-risk group			0.038
Yes	7	73	
No	13	49	

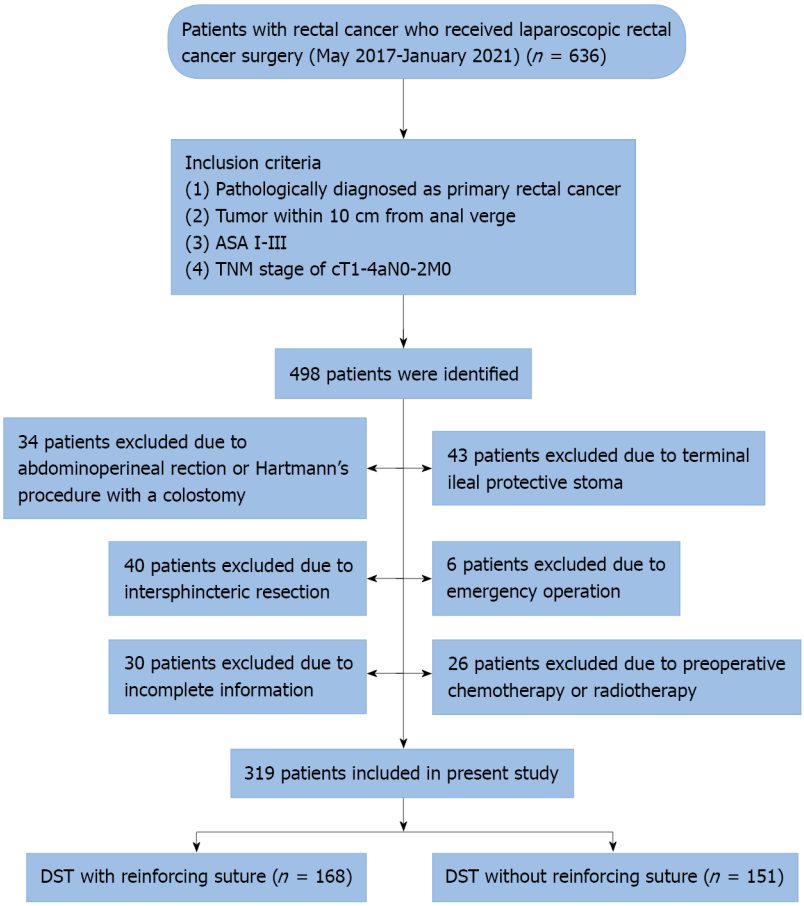

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Figure 3 Consort diagram of patient flow. DST: Double stapling technique; ASA: American Society of Anesthesiologists.

application in laparoscopic surgery. Baek *et al*[27] used transanal reinforcing sutures to improve DST and found that the procedure decreased the demand for diverting ileostomy. However, their sample size was relatively small, and no decrease was observed in the AL rate. Gadiot *et al*[28] compared 76 cases receiving anti-traction sutures with 77 non-suture cases, and found that AL occurrence remarkably decreased in the sutured group. In addition, several studies reported that trans-anal drainage tube could effectively decrease the incidence of AL after rectal surgery[29-32]. Among them, Xiao *et al*[29] retrospectively analyzed the clinical data of 398 patients undergoing LAR for rectal cancer and found that patients in transanal tube group were associated with lower AL and reoperation rates. According to their research, the potential benefits of transanal tube may be multifactorial, including promotion of gastrointestinal peristalsis, drainage, and reducing endoluminal pressure.

In this study, we evaluated whether a continuous suture using a barbed suture at the intersection of staple lines and anterior anastomosis wall was efficient in reducing the AL rate. We showed that AL incidence remarkably decreased in the reinforcing suture group than in the non-reinforcing suture group. In stratified risk factor analysis, though the low-risk group did not exhibit any distinct difference,

high-risk group showed significantly lower AL incidence in the reinforcing suture group than in the non-reinforcing suture group. Consequently, a reinforcing suture is considered an efficient approach to reduce AL for high-risk cases, and it is possibly not necessary for low-risk cases. Additionally, AL severity markedly decreased in the suture group compared with that in the non-suture group; the former had markedly decreased the demand for temporary diverting ileostomy. The possible reason for this is that anastomotic sutures may reinforce the anastomotic structure strength, while adding thickness to the staple line, distributing the tension of any individual staple across the length of the reinforcement strip and removing the risk of "dog ear" structures[33,34]. Moreover, a knotless barbed suture used in the present study makes it easier for a laparoscopic suture, as it requires no knot with the self-maintenance of tension in sutures running and does not require repetitive re-tightening of the sutures during stitching. This technique showed increased security and bursting pressure compared with those of the non-barbed monofilaments[35]. Several retrospective studies have verified its short- and long-term safety and efficacy in laparoscopic gastrointestinal operation[36-38]. As shown in the present study, reinforcing suture using barbed suture exhibited feasibility and safety as it does not prolong operation time, add to laparoscopic operation difficulty, or increase the complication rate, including defecation dysfunction and anastomosis stricture.

Based on our multivariate regression, tumor diameter ≥ 4 cm, and low rectal cancer are the other two factors that independently predict the risk of AL. Tumor size is related to AL, which is consistent with the results of previous studies[17,39]. The large tumor can make pelvic anastomosis and rectal transection difficult[40]. Furthermore, patients with a larger tumor or more advanced TNM stage always suffer from poorer systemic physical conditions, in some cases, the intestines can be oedematous, and pelvic adhesion may occur[39]. We also found that low tumor position influences the occurrence of AL. The lower tumor position is associated with an increased AL rate. Notably, the low tumor position can add technical difficulty in laparoscopic LAR, which can reduce the blood supply, and increase tension and local tissue trauma. Many studies have confirmed low tumor location as the AL-related independent risk factor[11,41].

In recent years, intraoperative ICG fluorescence angiography has been gaining recognition as an important intraoperative approach that provides real-time perfusion evaluation in anastomosis. Notably, ICG-based fluorescence angiography can decrease AL incidence by changing the surgical strategy[42,43]. In our study, patients with doubtful anastomotic blood perfusion, as well as other risk factors including insufficient circular stapling donut and positive results in air leakage tests, underwent a temporary diverting stoma. Therefore, these patients were excluded from this study. Moreover, the LCA was preserved in 52.2% of patients (165/319) in the present study, which was a relatively high rate of LCA preservation. It is controversial whether to conduct a high or low tie of the inferior mesenteric artery during laparoscopic rectal resections. Several studies[44,45] have reported that LCA preservation is associated with lower AL. This can be seen in the results of the univariate analysis in the present study, with *P* value of 0.045. Based on the above reasons, the incidence of AL was lower compared with that of other studies, with the overall and symptomatic AL rates of 7.5% (25/319) and 6.3% (20/319), respectively.

The present study had certain limitations. Firstly, the present study was a single-centered, retrospective, and non-randomized study. It is not possible to control all biases with this study design. Although the differences in the preoperative general clinical data of the patients were not significant between the two groups, there might still be residual or confounding variables. Second, there were chronological differences in operation between the two groups. Most patients in the suture group received treatment during the late period, when laparoscopic skills may have been better compared with the early period, and these may have influenced the incidence of complications. Hence, we should consider the impact of the learning curve. However, we believe that this limitation is slight because all procedures were performed by experienced surgeons and the incidence of AL in both groups did not differ from year to year. Third, patients in present study did not receive trans-anal drainage tube, which was also an effective method for preventing AL, as mentioned before. The combination of reinforcing sutures and trans-anal drainage tube may be more effective than the technique alone. However, we emphasize the efficacy and safety of reinforcing sutures for preventing AL in laparoscopic surgery for rectal cancer. Therefore, the combined effect of reinforcing sutures and trans-anal drainage tube remains unclear and deserves further investigation.

CONCLUSION

We demonstrated the safety and efficacy of barbed suture-based reinforcing sutures for patients with primary rectal cancer receiving laparoscopic LAR with a double-stapled anastomotic approach. This procedure can decrease AL incidence. However, large-scale prospective randomized controlled trials are required for evaluating the efficacy of reinforcing sutures for the prevention of AL.

ARTICLE HIGHLIGHTS

Research background

Anastomotic leakage (AL) is a severe complication in rectal cancer surgery. Various methods have been used to reduce the incidence of AL.

Research motivation

We hypothesized that staple-line reinforcement using barbed suture could reduce the incidence of AL in laparoscopic surgery for rectal cancer.

Research objectives

To evaluate the efficacy of staple-line reinforcement using barbed suture for preventing AL in laparoscopic surgery for rectal cancer.

Research methods

We compared the incidence of AL and other operative complications between two groups and analyzed patient-, tumor-, as well as surgery-related variables using univariate and multivariate logistic analyses.

Research results

AL incidence was significantly lower in the reinforcing suture group than in the control group (4.8% *vs* 11.3%, $P = 0.031$). The multivariate analyses demonstrated that the tumor site, tumor size and presence of staple-line reinforcement were independent risk factors for AL. In patients with risk factors, the AL incidence considerably decreased in the experimental group compared with that in the control group ($P = 0.038$). However, for patients without risk factor, no significant difference was found between experimental group and control group.

Research conclusions

Staple-line reinforcement can significantly lower AL incidence for patients with risk factors, while reducing AL severity and decreasing the reoperation rate. Besides, this technique does not increase the occurrence of postoperative complications.

Research perspectives

A large-scale prospective randomized controlled trial is needed for evaluating the efficacy of staple-line reinforcement for preventing AL.

FOOTNOTES

Author contributions: Ban B designed the research and wrote the manuscript; Shi J designed the research and supervised the manuscript; Shang A performed the research and contributed to the statistical analysis.

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Early detection of colorectal cancer based on circular DNA and common clinical detection indicators

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Abstract

BACKGROUND

Colorectal cancer (CRC) is the third most common cancer worldwide, and it is the second leading cause of death from cancer in the world, accounting for approximately 9% of all cancer deaths. Early detection of CRC is urgently needed in clinical practice.

AIM

To build a multi-parameter diagnostic model for early detection of CRC.

METHODS

Total 59 colorectal polyps (CRP) groups, and 101 CRC patients (38 early-stage CRC and 63 advanced CRC) for model establishment. In addition, 30 CRP groups, and 62 CRC patients (30 early-stage CRC and 32 advanced CRC) were separately included to validate the model. 51 commonly used clinical detection indicators and the 4 extrachromosomal circular DNA markers *NDUFB7*, *CAMK1D*, *PIK3CD* and *PSEN2* that we screened earlier. Four multi-parameter joint analysis methods:

binary logistic regression analysis, discriminant analysis, classification tree and neural network to establish a multi-parameter joint diagnosis model.

RESULTS

Neural network included carcinoembryonic antigen (CEA), ischemia-modified albumin (IMA), sialic acid (SA), *PIK3CD* and lipoprotein a (LPa) was chosen as the optimal multi-parameter combined auxiliary diagnosis model to distinguish CRP and CRC group, when it differentiated 59 CRP and 101 CRC, its overall accuracy was 90.8%, its area under the curve (AUC) was 0.959 (0.934, 0.985), and the sensitivity and specificity were 91.5% and 82.2%, respectively. After validation, when distinguishing based on 30 CRP and 62 CRC patients, the AUC was 0.965 (0.930-1.000), and its sensitivity and specificity were 66.1% and 70.0%. When distinguishing based on 30 CRP and 32 early-stage CRC patients, the AUC was 0.960 (0.916-1.000), with a sensitivity and specificity of 87.5% and 90.0%, distinguishing based on 30 CRP and 30 advanced CRC patients, the AUC was 0.970 (0.936-1.000), with a sensitivity and specificity of 96.7% and 86.7%.

CONCLUSION

We built a multi-parameter neural network diagnostic model included CEA, IMA, SA, *PIK3CD* and LPa for early detection of CRC, compared to the conventional CEA, it showed significant improvement.

Key Words: Colorectal cancer; Colorectal polyps; Multi-parameter; Circular DNA; Neural network

Core Tip: Most patients with colorectal cancer (CRC) are diagnosed at an advanced stage. The high morbidity and mortality of advanced CRC indicates an urgent need for clinical improvements in early CRC detection and individualized management. Compared with free linear DNA, extrachromosomal circular DNA is not easily degraded by nucleases, and its structure is more stable. In this study, we aimed to build a multi-parameter diagnostic model for early detection of CRC.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide, and it is the second leading cause of death from cancer in the world, accounting for approximately 9% of all cancer deaths. Currently, surgery is the most common treatment for nonmetastatic CRC[1]. Most patients with CRC are diagnosed at an advanced stage. The high morbidity and mortality of advanced CRC indicates an urgent need for clinical improvements in early CRC detection and individualized management[2].

In the era of precision oncology, liquid biopsy has become the primary method for characterizing circulating tumor components present in body fluids[3]. This noninvasive tool can identify relevant molecular alterations in CRC patients, including some that indicate disruption of epigenetic mechanisms. Epigenetic alterations found in solid and liquid biopsies have shown great utility as biomarkers for the early detection, prognosis, monitoring, and assessment of the treatment response in CRC patients[4]. Therefore, the term "liquid biopsy" includes blood, the most commonly used human fluid sample, as well as other fluids, such as urine, ascites, pleural effusion, cerebrospinal fluid, and saliva[5,6]. Both primary tumors and metastases can release tumor material into these body fluids, mainly comprised of circulating tumor cells (CTCs), nucleic acids (cNA), and extracellular vesicles (cEVs)[7]. These circulating elements constitute a valuable source of noninvasive biomarkers[8-11].

At present, single-stranded or double-stranded DNA is detected based on ctDNA. With the development of high-throughput sequencing technology and single-cell gene amplification technology, new types of circular cell-free DNA have been discovered such as extrachromosomal circular DNA (eccDNA)[12,13]. eccDNA refers to a closed circular DNA located outside the chromosome in the form of single-stranded or double-stranded DNA, which is widely found in eukaryotes, including humans [14,15]. Compared with free linear DNA, eccDNA is not easily degraded by nucleases, and its structure is more stable.

In our study, we aimed to build a multi-parameter diagnostic model based on the commonly used clinical detection indicators and the 4 eccDNA markers for early detection of CRC which is urgently needed in clinical practice.

MATERIALS AND METHODS

Study samples

After approval by the ethics committee, the research subjects signed informed consent forms. This project included 59 patients with colorectal polyps (CRP) and 101 CRC patients (38 early-stage CRC and 63 advanced CRC) for building the model. An additional 30 CRP and 62 CRC patients (30 early-stage CRC and 32 advanced CRC) were used to validate the model (Table 1).

The inclusion criteria for the CRP group were those with villous/tubular adenoma, with or without mild-to-moderate hyperplasia, confirmed by colonoscopy and pathologically confirmed after adenoma removal, or confirmed by pathology and immunohistochemistry as focal high-grade neoplasia of villous tubular adenoma. All biochemical examinations and auxiliary examinations showed no abnormality, no complaints of gastrointestinal discomfort, no signs of a tumor, adenoma with a diameter less than 1 cm, no villous adenoma or mixed adenoma, and no adenoma with moderate to severe dysplasia.

In the early CRC group, it was confirmed by tumor surgery that the adenocarcinoma of the intestinal wall was confined to the mucosa or submucosa without lymphatic metastasis, that is, stage 1 or 2, and it was pathologically confirmed villous tubular adenoma with focal high-grade neoplasia or intestinal wall glands.

For the advanced CRC group based on tumor staging according to the American Joint Committee on Cancer tumor node metastasis staging, we defined colorectal cancer stages 3 and 4 as advanced stage with pathologically confirmed colorectal cancer; no treatment was performed before sample collection, including surgery, chemotherapy, radiotherapy, or other treatments; and no blood transfusion had occurred within the past 3 mo.

All enrolled patients provided colorectal cancer or polyp specimens and the corresponding clinical examination data. None of the patients received chemotherapy, radiotherapy or immunotherapy before surgery, and other tumors and gastrointestinal diseases were excluded by examination at the time of admission.

Peripheral blood was collected from all subjects included in this study on an empty stomach in the morning. The anticoagulant in the plasma collection tube was EDTA and after collection, the blood was centrifuged at 3000 rpm for 10 min, and the plasma was placed into a new sterile Eppendorf tube. Serum samples were early morning fasting peripheral blood samples collected in tubes containing separation gel and a clot activator. The samples were centrifuged at 3000 rpm for 10 min, and the serum was transferred to new sterile Eppendorf tubes and stored at -80 °C until assayed. The plasma was also stored at -80 °C. During the sample collection process, hemolyzed and chyle blood samples were removed to avoid repeated freezing and thawing. When testing was conducted, normal temperature recovery was performed.

Detection of commonly used clinical indicators

There were 51 commonly used clinical detection indicators, including 13 common tumor-related markers and 38 clinical biochemical indicators. Among them, 13 tumor-related indicators included carcinoembryonic antigen (CEA), alpha fetoprotein (AFP), carbohydrate antigen 125 (CA125), CA199, CA153, CA724, cytokeratin fragment 211 (Cyfra211), ferritin (Ferr), neuron-specific enolase (NSE), squamous cell carcinoma (SCC), pepsinogen (PG) I, PG II and PGI/II. The 38 clinical biochemical indicators included alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP), albumin (ALB), total bilirubin (TB), direct bilirubin (DB), total bile acid (TBA), alkaline phosphatase (ALP), γ-glutamyl transfer enzyme (GGT), glucose (GLu), urea nitrogen (UN), creatinine (Cr), uric acid (UA), cholesterol (CHO), triglyceride esters (TG), creatine kinase (CK), lactate dehydrogenase (LDH), creatine kinase isoenzyme (CKMB), calcium (Ca), phosphorus (P), magnesium (Mg), potassium (K), sodium (Na), chlorine (Cl), carbon dioxide (CO_2), lipoprotein a (LPa), high-density lipoprotein (HDL), low-density lipoprotein (LDL), apolipoprotein A1 (ApoA1), apoB, cysteine (CYS), sialic acid (SA), homocysteine (HCY), C-reactive protein (CRP), amylase (AMY), lipase (LPS), superoxide dismutase (SOD) and ischemia-modified albumin (IMA).

Among the 51 detection indicators, CEA, AFP, CA199, CA724, CA125, CA153, Cyfra211, Ferr, NSE, ALT, AST, TP, ALB, ALP, GGT, Glu, UN, CR, UA, CHO, TG, CK, Ca, P, Mg, K, Na, CL, CO2, HDL, LDL, CRP, AMY, and LPS standards and controls and detection kits were purchased from Roche Diagnostics Ltd. ApoA1, ApoB, CYS, LPa, and CKMB standards and controls and detection kits were purchased from Beijing Leadman Biochemical Co., Ltd. SCC, PG I and PG II standards and controls and test kits were purchased from Abbott Diagnostics. TBA and HCY standards and quality controls and detection kits were purchased from Beijing Jiuqiang Biotechnology Co., Ltd. TB and DB standards and controls and assay kits were purchased from Hitachi Diagnostics Co., Ltd. IMA standards, quality control products, and detection kits were purchased from Changsha Yikang Technology Development

Table 1 General clinical characteristics of study subjects

Clinical features	Model building		Model validation	
	CRC (*n* = 101)	CRP (*n* = 59)	CRC (*n* = 62)	CRP (*n* = 30)
Age				
Average	58	56	57	57
Range	29-81	31-76	33-74	35-69
Sex				
Male	60	34	37	19
Female	41	25	25	11
Location				
Ascending colon	21		17	
Descending colon	15		12	
Transverse colon	3		4	
Sigmoid colon	59		28	
Rectal	3		1	
Differentiation				
Well	21		15	
Moderate	57		33	
Poorly	23		14	
TNM stage				
T1	11		11	
T2	27		21	
T3	44		7	
T4	19		23	

CRP: Colorectal polyps; CRC: Colorectal cancer; TNM: Tumor node metastasis.

Co., Ltd. SA standards, quality control products, and detection kits were purchased from Zhejiang Dongou Diagnostic Products Co., Ltd. SOD standards, quality control products and detection kits were purchased from Fujian Fuyuan Biotechnology Co., Ltd. A modular 7600 automatic biochemical analyzer, Roche E170 immunoassay analyzer and Architect i2000 immunoassay system were used to complete the pre-assay quality control and calibration. After the analysis, the experimental data of each instrument were exported for statistical analysis.

Detection of differential eccDNA based on ddPCR

Cell-free DNA was extracted from plasma samples using the QIAamp DNA Blood Kit (Qiagen, 51192) according to the ddPCR detection method established in the second part of this study. ATP-dependent DNase (Epicenter, E310K) was added to the free DNA and digested at 37 °C for 1.5 h to a final concentration of 0.4 U/μL to remove linear double-stranded DNA. The reaction was continued at 70 °C for 30 min to inactivate ATP-dependent DNase activity, and the product was then stored until analysis.

Based on the eccDNA sequence incorporated into the model, primers were designed using Primer3 software. After a homology search was performed with BLAST, the primers were synthesized by Invitrogen. The 5' ends of the primers were modified with a FAM fluorophore, and the 3' ends were modified with a BHQ1 quenching group. (1) *NDUFB7*. Forward sequence: TACCGTCAGCATCCACAGCCAT; reverse sequence: GCCTTCTCAGAAGGATGCCAGT; (2) *CAMK1D*. Forward sequence: TGAGCAGATCCTCAAGGCGGAA; reverse sequence: GTCCTTCTCCATCAGGTTCCGA; (3) *PIK3CD*. Forward sequence: TGCCAAACCACCTCCCATTCCT; reverse sequence: CATCTCGTTGCCGTGGAAAAGC; and (4) *PSEN2*. Forward sequence: GCTGTTTGTGCCTGTCACTCTG; reverse sequence: TGTGTCCTCAGTGAATGGCGTG.

Primers and probes were diluted with deionized water to the storage concentration of 200 μmol/L, and the working concentration was 10 μmol/L. The total PCR volume was 20 μL, including 2-fold ddPCRTTM Super mix 10 μL, forward and reverse primers 1.8 μL each (final concentration 900

nmol/L), probe 0.5 μL (final concentration 250 nmol/L), template DNA 4 μg, and ddH_2O to make it up to 20 μL. Then, 20 μL of the reaction system mixture was added to the droplet generation card for droplet generation. All of the resulting droplets were transferred to a 96-well plate for PCR amplification. The PCR conditions were: 95 °C/10 min; 94 °C/30 s, 60 °C/1 min, 40 cycles; 98 °C/10 min. Finally, Quanta Soft 1.6 software (Bio-Rad, USA) was used to analyze the results and the Flush System was used before each experiment. After the setup is complete, the sample droplets are analyzed. We analyzed the results of the run and view channels, scatterplots, concentration data, ratio data, and the number of events.

Evaluation of the diagnostic value of a single indicator

Second, we compared the 51 common clinical indicators and 4 kinds of eccDNA between the CRP group and CRC group based on the difference indicator, tested by the area under the curve (AUC) and the *P* value, for potential markers to evaluate their diagnostic value for distinguishing the CRP and CRC groups, CRP and early CRC groups, colon polyps and advanced CRC groups.

Establishment and evaluation of the multiparameter diagnosis model

Based on the differential diagnostic value (CRP group *vs* CRC group), we established a multiparameter combined auxiliary diagnostic model. The models are binary logistic regression analysis, discriminant analysis, classification tree and neural network. Binary logistic regression analysis was used for the Forward: Conditional method. Discriminant analysis applied the Bayes discriminant method, and stepwise discriminant analysis was used in the fitting function process. A classification tree was the CHAID classification tree method, and a cross-validation evaluation was conducted to establish the classification tree model. An artificial neural network was the neural network's multilayer perceptron used to build the model.

Validation of the multiparameter diagnosis model

After comparing the diagnostic value of the binary logistic regression analysis, the discriminant analysis, classification tree and neural network with the diagnostic value of a single index were conducted. The optimal multiparameter auxiliary diagnosis model was selected, and 30 CRP groups and 62 CRC patients (30 early-stage CRC patients and 32 advanced CRC patients) were enrolled to validate the multiparameter model. Then, the stability of the model was evaluated. Finally, the validated model was compared with the commonly used clinical detection index CEA, and its clinical application value was evaluated by comparing the sensitivity, specificity, and AUC.

Statistical analysis

SPSS 22.0 was used for statistical analysis. Measurement data were expressed as medians (25%, 75%). If the data were normally distributed, they were compared by two independent samples *t*-tests. If nonnormally distributed, comparisons were made by the rank-sum test. The AUC was used to assess the diagnostic value of the index. Four multiparameter analysis methods (binary logistic regression analysis, discriminant analysis, classification tree and neural network) were used to establish a multiparameter joint diagnosis model. The binary logistic regression model used the forward conditional method. The discriminant analysis used the Bayes discriminant method. The classification tree used the CHAID classification tree method, and the established classification tree model was evaluated by cross-validation. Artificial neural networks used multilayer perceptrons of neural networks to build the models. Univariate and multivariate logistic regression were used to analyze Exp (B) of the index. The *Z* score test was used to compare the AUC of the different groups. $P < 0.05$ indicates that the difference is statistically significant.

RESULTS

Comparison of 51 common clinical indicators and 4 kinds of eccDNA between the colon polyp group and the colorectal cancer group

Thirteen tumor markers (CEA, AFP, CA125, CA199, CA153, CA724, CY211, Ferr, NSE, SCC, PG I/II, PG II, and PG I) and 38 blood biochemical indices (ALT, AST, TP, ALB, TB, DB, TBA, ALP, GGT, GLu, UN, Cr, UA, CHO, TG, CK, LDH, CKMB, Ca, P, Mg, K, Na, Cl, CO_2, LPa, HDL, LDL, ApoA1, ApoB, CYS, SA, HCY, CRP, AMY, LPS, SOD, and IMA) were compared between the 59 CRP patients and the 101 CRC patients. Among the 51 commonly used clinical indicators, 22 indicators, including IMA, CEA, SA, LPa, CK, TB, HDL, NSE, ALT, Ferr, DB, CA125, LDH, AMY, CY211, CA724, HCY, CHO, P, LDL, Cl and CKMB, were significantly different between the CRP and CRC groups ($P < 0.05$). The remaining 29 indicators were not significantly different. By comparison, among the four eccDNA indices, two indices, *CAMK1D* and *PIK3CD*, showed significant differences between the CRP and CRC groups ($P < 0.05$). The other two indicators were not significantly different, as shown in Table 2.

Table 2 Comparison of 51 common clinical indicators between colon polyp group and colorectal cancer group

Index	CRP (*n* = 59)	CRC (*n* = 101)	*F* value	Sig	*P* value
CEA	1.86 (1.17, 2.43)	3.9 (1.67, 13.87)	11.39	< 0.01	< 0.01
AFP	2.58 (1.87, 3.59)	2.41 (1.75, 3.36)	0.02	0.90	0.41
CA125	9.78 (6.77, 13.55)	11.63 (7.98, 19.9)	4.80	0.03	0.04
CA199	8.57 (5.44, 14.38)	13.43 (7.22, 26.48)	3.62	0.06	0.22
CA153	9.5 (7.08, 13.09)	9.25 (6.6, 13)	1.53	0.22	0.49
CA724	1.63 (1.16, 4.39)	2.55 (1.36, 7.33)	5.54	0.02	0.07
CY211	1.82 (1.4, 2.89)	2.3 (1.63, 3.58)	9.29	< 0.01	< 0.01
Ferr	150.9 (85.62, 269.5)	72.12 (17.02, 161.5)	0.11	0.74	0.01
NSE	8.06 (6.52, 9.16)	10 (7.71, 12.63)	4.58	0.03	< 0.01
SCC	1.1 (0.7, 1.5)	0.8 (0.6, 1.2)	2.96	0.09	0.19
PG I/II	4.576 (2.835, 5.914)	5.12 (3.7, 6.53)	0.10	0.76	0.08
PG II	15.9 (9, 28.3)	14.6 (9.7, 24.2)	1.08	0.30	0.64
PG I	75.5 (38.5, 101.3)	71.7 (51.45, 96.3)	0.49	0.49	0.82
ALT	16.8 (12.1, 25)	12.7 (9.3, 17.75)	0.59	0.44	0.03
AST	17.1 (14.1, 20.6)	16.6 (12.25, 19.3)	0.87	0.35	0.43
TP	68.3 (64.1, 71.9)	67.3 (63.15, 70.65)	0.03	0.86	0.29
ALB	41.8 (39.6, 44.4)	39.5 (36.95, 41.45)	0.63	0.43	0.07
TB	12.5 (10, 16.4)	9.7 (7.4, 12.8)	0.75	0.39	< 0.01
DB	4.1 (3.2, 5.2)	3.6 (2.3, 4.2)	0.05	0.82	0.01
TBA	4.2 (2.5, 7.2)	3.5 (2.2, 5.7)	2.15	0.14	0.11
ALP	61.4 (54.8, 73.6)	67 (56.4, 80.05)	2.38	0.13	0.59
GGT	23.6 (13.5, 37.6)	22.3 (14.75, 33.95)	0.01	0.95	0.98
GLu	5.02 (4.79, 5.51)	5.12 (4.74, 5.81)	0.00	0.97	0.97
UN	5.49 (4.64, 6.08)	5.23 (4.08, 6.29)	5.94	0.02	0.43
Cr	70.2 (61.6, 78.6)	65.2 (56.35, 75.6)	0.22	0.64	0.06
UA	312.3 (257.9, 386.9)	292.8 (224, 339.4)	0.19	0.67	0.06
CHO	4.5 (4.04, 5.27)	4.36 (3.88, 5.09)	2.31	0.13	0.02
TG	1.43 (1.01, 2.01)	1.25 (0.93, 1.62)	7.94	0.01	0.45
CK	69.8 (55.5, 118.9)	54.4 (35.2, 71.05)	15.60	< 0.01	0.04
LDH	137 (122.2, 153.3)	148.4 (129.75, 177.75)	4.13	0.04	< 0.01
CKMB	6.6 (4, 9.8)	6.14 (4.05, 9.6)	1.81	0.18	0.02
Ca	2.26 (2.19, 2.31)	2.21 (2.14, 2.27)	0.10	0.75	0.47
P	1.27 (1.14, 1.39)	1.25 (1.07, 1.38)	0.01	0.93	0.01
Mg	0.93 (0.85, 1.01)	0.91 (0.84, 0.97)	0.01	0.94	0.29
K	4.03 (3.78, 4.18)	4.09 (3.87, 4.33)	4.98	0.03	0.53
Na	143.8 (141.6, 145.4)	143.1 (141.45, 144.7)	0.17	0.68	0.12
Cl	105.6 (103.4, 107.2)	105.3 (103.5, 107.4)	2.08	0.15	0.04
CO_2	22.6 (20.7, 26.1)	24.9 (22.9, 26.65)	2.31	0.13	0.40
LPa	7.83 (3.01, 12.74)	15.65 (7.82, 31.65)	13.29	< 0.01	0.01
HDL	1.27 (1.03, 1.41)	1.02 (0.89, 1.23)	0.10	0.76	< 0.01
LDL	2.63 (2.26, 3.28)	2.54 (2.07, 3.27)	1.33	0.25	< 0.01

ApoA1	1.39 (1.17, 1.54)	1.13 (1.01, 1.34)	0.66	0.42	0.55
ApoB	0.83 (0.72, 1.02)	0.83 (0.72, 1.01)	0.09	0.76	0.62
CYS	1.07 (0.95, 1.16)	0.97 (0.84, 1.08)	0.34	0.56	0.70
SA	59.3 (55, 66.5)	67.1 (60.8, 82.4)	13.50	< 0.01	0.04
HCY	15.19 (11.54, 19.68)	13.92 (11.18, 17.42)	4.71	0.03	< 0.01
CRP	0.7 (0.4, 1.5)	3.9 (1, 10.55)	30.41	< 0.01	0.11
AMY	59.5 (50, 73.7)	51.8 (38.95, 64.7)	1.18	0.28	< 0.01
LPS	33.1 (25.1, 42.7)	32.9 (22.25, 44.25)	2.87	0.09	0.06
SOD	136.1 (125, 147)	136.5 (115.8, 156.9)	4.82	0.03	0.35
IMA	63.8 (60.1, 66.3)	62.1 (59.45, 67.5)	0.11	0.74	< 0.01
NDUFB7	1.34 (0.94, 2.42)	2.10 (1.29, 3.08)	2.666	0.105	0.155
CAMK1D	34.21 (17.82, 103.44)	70.39 (35.26, 155.57)	3.045	0.083	0.030
PIK3CD	105.90 (36.69, 308.35)	333.22 (259.40, 417.90)	3.700	0.056	0.001
PSEN2	6.46 (4.44, 11.03)	8.69 (6.00, 11.67)	0.144	0.705	0.154

CRP: Colorectal polyps; CRC: Colorectal cancer; CEA: Carcinoembryonic antigen; AFP: Alpha fetoprotein; CA125: Carbohydrate antigen 125; NSE: Neuron-specific enolase; SCC: Squamous cell carcinoma; PG: Pepsinogen; ALT : Alanine aminotransferase; AST: Aspartate aminotransferase; TP: Total protein; ALB: Albumin; TB: Total bilirubin; DB: Direct bilirubin; TBA: Total bile acid; ALP: Alkaline phosphatase; GGT: γ-glutamyl transfer enzyme; Glu: Glucose; UN: Urea nitrogen; Cr: Creatinine; UA: Uric acid; CHO: Cholesterol; TG: Triglyceride esters; CK: Creatine kinase; LDH: Lactate dehydrogenase; CKMB: Creatine kinase isoenzyme; Ca: Calcium; P: Phosphorus; Mg: Magnesium; K: Potassium; Na: Sodium; Cl: Chlorine; CO_2: Carbon dioxide; LPa: Lipoprotein a; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; ApoA1: Apolipoprotein A1; CYS: Cysteine; SA: sialic acid; HCY: Homocysteine; CRP: C-reactive protein; AMY: Amylase; LPS: Lipase; SOD: Superoxide dismutase; IMA: Ischemia-modified albumin.

Diagnostic value of the differential indicators between the CRP and CRC groups

Based on the 22 commonly used clinical indicators and 2 kinds of eccDNA that showed significant differences between the CRP and CRC groups, receiver operating characteristic (ROC) curves were used to evaluate the diagnostic value, as shown in Table 3. Fifteen commonly used clinical indicators and 2 kinds of eccDNA (IMA, CEA, SA, LPa, CK, TB, HDL, NSE, ALT, Ferr, DB, CA125, LDH, AMY, CY211, *CAMK1D* and *PIK3CD*) showed statistically significant differences in the area under the curve ($P < 0.05$) while the other 7 commonly used clinical indicators (CA724, HCY, CHO, P, LDL, Cl and CKMB) showed no significant difference. Therefore, 15 commonly used clinical indicators and 2 kinds of eccDNA with significant differences between the groups and the areas under the ROC curve were selected for subsequent multiparameter combined auxiliary diagnosis model analysis.

Univariate logistic regression and multivariate logistic regression analysis

Indices with statistically significant differences between the CRP and CRC groups and the ROC included IMA, CEA, SA, LP (a), CK, TB, HDL, NSE, ALT, Ferr, DB, CA125, LDH, AMY, CY211, *CAMK1D* and *PIK3CD* ($P < 0.05$). First, univariate logistic regression analysis was performed, as shown in Table 4. The Exp (B)s of CEA, IMA, SA, E3 and LPa were significantly different ($P < 0.05$), while that of CK, TB, HDL, NSE, CHO, P, LDL, Cl, CKMB and *CAMK1D* were not significantly different. Second, multivariate logistic regression analysis was performed on the differences in CEA, IMA, SA, E3 and LPa. As shown in Table 5, the Exp (B)s were significantly different for all of them ($P < 0.05$). CEA, IMA, SA, *PIK3CD* and LPa were included in the subsequent multiparameter joint auxiliary diagnosis model.

Multiparameter combined auxiliary diagnosis model building

Based on CEA, IMA, SA, *PIK3CD* and LPa, a multiparameter combined auxiliary diagnosis model was built to distinguish the 59 CRP group and 101 CRC group (including 38 cases of early CRC and 63 cases of advanced CRC).

As shown in Table 6, binary logistic regression analysis based on CEA, IMA, SA, *PIK3CD* and LPa showed that the correct rate of CRP was 76.3%, the correct rate of CRC was 85.1%, and the overall accuracy was 81.9%. The predicted probability of each sample was used as an independent variable, as shown in Figure 1A, and the AUC was 0.900 (0.855-0.946).

The discriminant analysis based on CEA, IMA, SA, *PIK3CD* and LPa showed that the correct rate of CRP was 86.4%, the correct rate of CRC was 69.3%, and the overall accuracy was 75.6%. Taking the predicted probability of each sample as an independent variable, as shown in Figure 1B, the AUC was 0.855 (0.794-0.916).

Table 3 Evaluation of the diagnostic value of 26 commonly used clinical indicators with statistical differences (colon polyp group vs colorectal cancer group)

Indicator	AUC	SE	*P* value	95% CI	
				Lower	Upper
IMA	0.787	0.036	< 0.001	0.716	0.859
CEA	0.734	0.038	< 0.001	0.658	0.809
SA	0.728	0.039	< 0.001	0.651	0.804
LPa	0.715	0.042	< 0.001	0.633	0.797
CK	0.702	0.042	< 0.001	0.619	0.784
TB	0.672	0.044	< 0.001	0.585	0.758
HDL	0.670	0.044	< 0.001	0.583	0.758
NSE	0.668	0.044	< 0.001	0.580	0.755
ALT	0.667	0.044	< 0.001	0.580	0.754
Ferr	0.663	0.045	0.001	0.575	0.751
DB	0.646	0.044	0.002	0.559	0.733
CA125	0.642	0.044	0.003	0.557	0.728
LDH	0.621	0.045	0.011	0.534	0.709
AMY	0.611	0.045	0.019	0.522	0.700
CY211	0.602	0.046	0.032	0.513	0.691
CA724	0.583	0.046	0.081	0.492	0.673
HCY	0.570	0.048	0.138	0.476	0.664
CHO	0.556	0.046	0.240	0.465	0.646
P	0.543	0.047	0.361	0.451	0.636
LDL	0.536	0.046	0.453	0.445	0.626
Cl	0.525	0.047	0.603	0.432	0.618
CKMB	0.516	0.047	0.736	0.424	0.608
CAMK1D	0.652	0.046	0.001	0.561	0.742
PIK3CD	0.753	0.047	< 0.001	0.660	0.845

AUC: Area under the curve; CEA: Carcinoembryonic antigen; AFP: Alpha fetoprotein; CA125: Carbohydrate antigen 125; NSE: Neuron-specific enolase; PG: Pepsinogen; ALT : Alanine aminotransferase; AST: Aspartate aminotransferase; TP: Total protein; ALB: Albumin; TB: Total bilirubin; DB: Direct bilirubin; TBA: Total bile acid; ALP: Alkaline phosphatase; GGT: γ-glutamyl transfer enzyme; CK: Creatine kinase; LDH: Lactate dehydrogenase; CKMB: Creatine kinase isoenzyme; Ca: Calcium; P: Phosphorus; Cl: Chlorine; LPa: Lipoprotein a; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; ApoA1: Apolipoprotein A1; CYS: Cysteine; SA: sialic acid; HCY: Homocysteine; CRP: C-reactive protein; AMY: Amylase; IMA: Ischemia-modified albumin.

In the classification tree analysis based on CEA, IMA, SA, *PIK3CD* and LPa, the final independent variables included CEA, IMA, SA, *PIK3CD* and LPa, the number of nodes was 3, the number of terminal nodes was 2, and the depth was 1. Among them, the correct rate of CRP was 91.5%, the correct rate of CRC was 58.4%, and the overall accuracy rate was 70.6%. Taking the predicted probability of each sample as an independent variable, as shown in Figure 1C, the AUC was 0.750 (0.674-0.826).

The artificial neural network analysis based on CEA, IMA, SA, *PIK3CD* and LPa, CEA, IMA, SA, *PIK3CD* and LPa all entered the input layer. The number of hidden layers included 1 Layer, and the output layer included 2 Layers. The training set included 39 cases of CRP and 70 cases of CRC, among which the correct rate of identifying healthy controls was 79.5%, the correct rate of identifying colorectal cancer was 97.1%, and the overall accuracy rate was 90.8%. The test set included 20 cases of CRP and 31 cases of CRC, among which the correct rate of identifying CRP was 90.0%, the correct rate of identifying CRC was 87.1%, and the overall accuracy rate was 88.2%. Taking the predicted probability of each sample as an independent variable, as shown in Figure 1D, the AUC was 0.959 (0.934-0.985).

Table 4 Univariate Logistic Regression Analysis between the colon polyp group and the colorectal cancer group with statistically significant between-group and receiver operating characteristic indicators

Indicator	B	SE	Wals	*P* value	Exp (B)	95% CI	
						Lower	Upper
CEA	0.335	0.138	5.864	0.015	1.398	1.066	1.834
IMA	-0.138	0.048	8.352	0.004	0.871	0.793	0.956
SA	0.078	0.034	5.347	0.021	1.081	1.012	1.155
LPa	0.085	0.027	9.844	0.002	1.089	1.032	1.148
CK	-0.004	0.008	0.207	0.649	0.996	0.980	1.013
TB	-0.065	0.054	1.463	0.226	0.937	0.843	1.041
HDL	-0.949	0.822	1.331	0.249	0.387	0.077	1.941
NSE	0.160	0.084	3.656	0.056	1.174	0.996	1.383
CHO	-0.004	0.017	0.053	0.817	0.996	0.964	1.029
P	0.886	1.104	0.644	0.422	2.426	0.279	21.139
LDL	0-.585	0.368	2.534	0.111	0.557	0.271	1.145
Cl	0.112	0.086	1.682	0.195	1.119	0.944	1.325
CKMB	-0.025	0.057	0.202	0.653	0.975	0.872	1.089
CAMK1D	0.003	0.003	1.189	0.275	1.003	0.998	1.009
PIK3CD	0.003	0.001	4.429	0.035	1.003	1.000	1.005

CEA: Carcinoembryonic antigen; TB: Total bilirubin; CKMB: Creatine kinase isoenzyme; P: Phosphorus; Cl: Chlorine; LPa: Lipoprotein a; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SA: sialic acid; IMA: Ischemia-modified albumin.

Table 5 Multivariate Logistic Regreesion Analysis Exp (B) Indicators with Statistical Differences (Colon polyp group *vs* colorectal group)

Indicator	B	SE	Wals	*P* value	Exp (B)	95% CI	
						Lower	Upper
CEA	0.326	0.109	8.904	0.003	1.385	1.118	1.716
IMA	-0.136	0.035	14.765	< 0.001	0.873	0.815	0.936
SA	0.092	0.027	11.601	0.001	1.097	1.040	1.156
PIK3CD	0.002	0.001	5.852	0.016	1.002	1.000	1.004
LPa	0.064	0.022	8.888	0.003	1.066	1.022	1.112

CEA: Carcinoembryonic antigen; IMA: Ischemia-modified albumin; LPa: Lipoprotein a; SA: sialic acid.

Optimal multiparameter combined auxiliary diagnosis model selection and diagnostic evaluation

Based on CEA, IMA, SA, *PIK3CD* and LPa, binary logistic regression analysis, discriminant analysis, classification tree and neural network were used to predict the CRP and CRC groups, and the accuracy rates were 81.9%, 75.6%, 70.6%, and 90.8%, respectively. Therefore, we chose the neural network as the optimal multiparameter joint auxiliary diagnosis model. As shown above, the overall accuracy rate was 90.8%, as shown in Figure 2A. The area under the curve was 0.959 (0.934-0.985), and the sensitivity and specificity were 91.5% and 82.2%, respectively. As shown in Figure 2B, when the CRP and early CRC groups were differentiated, the area under the curve was 0.956 (0.921-0.992), and the sensitivity and specificity were 89.8% and 86.8%, respectively. As shown in Figure 2C, when the CRP and advanced CRC groups were differentiated, the area under the curve was 0.961 (0.932-0.990), and the sensitivity and specificity were 88.1% and 87.3%, respectively.

Table 6 Multi-parameter combined auxiliary diagnosis model building

Observed	Predicted		
	CRP	CRC	Correct percentage
Binary logistic regression analysis building			
CRP	45	14	76.30%
CRC	15	86	85.10%
Total percentage			81.90%
Discriminant analysis building			
CRP	51	8	86.40%
CRC	31	70	69.30%
Total percentage			75.60%
Classification tree building			
CRP	54	5	91.50%
CRC	42	59	58.40%
Total percentage			70.60%
Neural network building			
CRP	31	8	79.50%
CRC	2	68	97.10%
Total percentage			90.80%
Neural network validation			
CRP	18	2	90.00%
CRC	4	27	87.10%
Total percentage			88.20%

CRP: Colorectal polyps; CRC: Colorectal cancer.

Validation of the multi-index joint auxiliary diagnosis model

For distinguishing the CRP group from the CRC group, after comparing the multiple multiparameter joint analysis methods, the neural network based on CEA, IMA, SA, *PIK3CD* and LPa was the optimal multiparameter joint auxiliary diagnosis model. Thirty independent CRP patients and 62 CRC patients (32 in the early-stage CRC group and 30 in the advanced CRC group) were enrolled to validate the model. After validation, as shown in Figure 3A, for distinguishing CRP and CRC, the area under the curve of the neural network for CEA, IMA, SA, *PIK3CD* and LPa was 0.965 (0.930-1.000), its sensitivity and specificity were 66.1% and 70.0%, the area under the curve of the commonly used clinical indicator CEA was 0.723 (0.622-0.823), and its sensitivity and specificity were 96.8% and 86.7%, respectively. As shown in Figure 3B, for distinguishing CRP and 32 early-stage CRC, the area under the curve of the neural network model was 0.960 (0.916-1.000), with a sensitivity and specificity of 87.5% and 90.0%, the area under the curve of the commonly used clinical indicator CEA was 0.684 (0.548-0.821), and its sensitivity and specificity were 62.5% and 60.0%, respectively. As shown in Figure 3C, for distinguishing CRP and advanced CRC patients, the area under the curve of the neural network model was 0.970 (0.936, 1.000), with a sensitivity and specificity of 96.7% and 86.7%, the area under the curve of the commonly used clinical indicator CEA was 0.763 (0.632-0.895), and its sensitivity and specificity were 76.7% and 63.3%, respectively.

DISCUSSION

A biomarker is a biological molecule found in blood, other body fluids, or tissues that is a marker of a normal or abnormal process or disease. Biomarkers are primarily based on DNA, RNA, microRNA (miRNA), epigenetic changes, or antibodies. The term tumor marker, considered by some researchers to be synonymous with biomarkers, refers to substances that represent biological structures (most typically proteins, glycolipids) that can be attributed to normal cell development or to different stages of cell

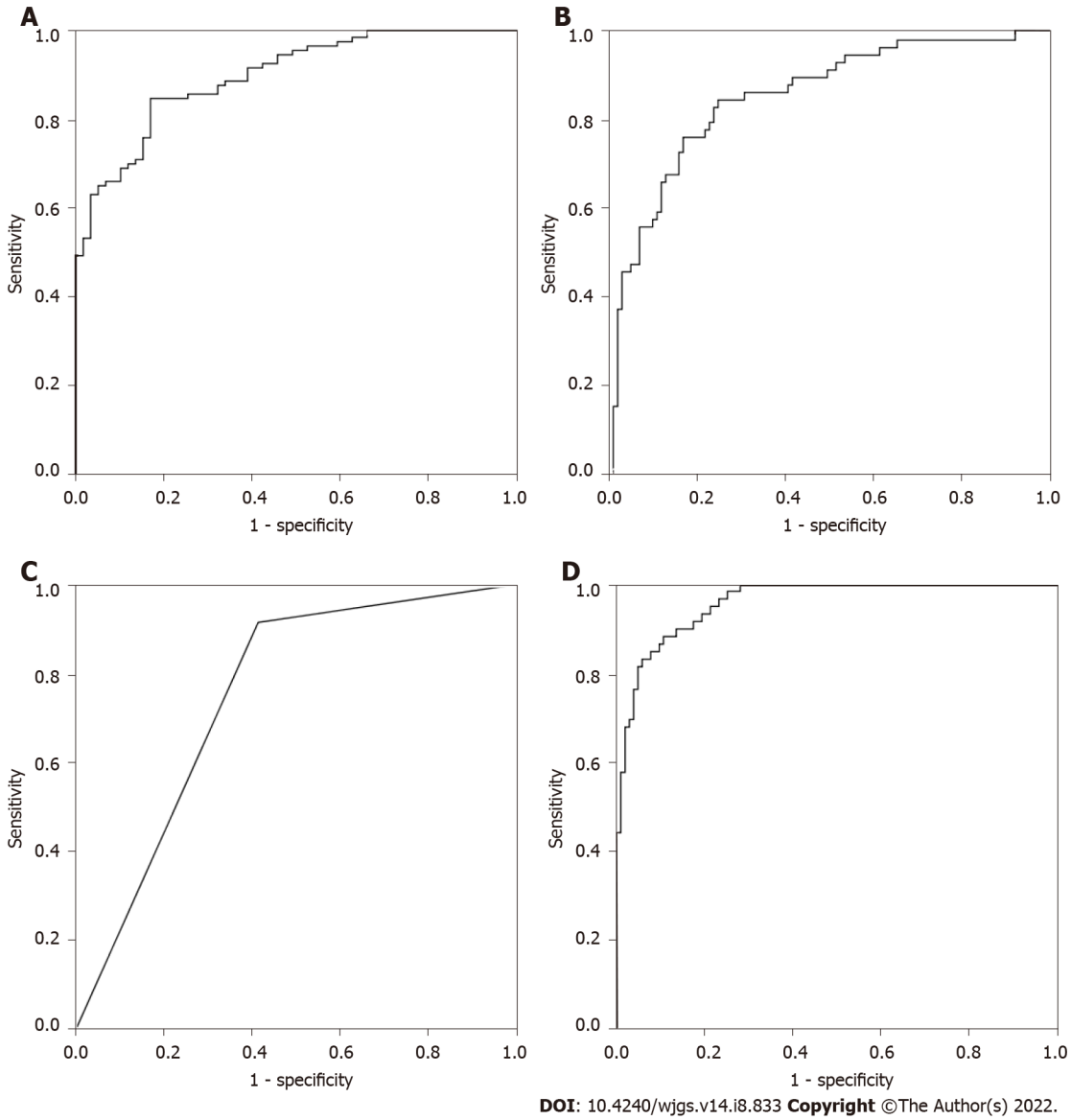

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Figure 1 Diagnostic evaluation of multi-parameter combined auxiliary diagnosis model building. A: Binary logistic regression analysis; B: Discriminant analysis; C: Classification tree analysis; D: Neural network.

development. For example, carcinogenesis-associated antigens (TAAs) are the largest group of clinically meaningful markers. Therefore, the concentration of TAA usually correlates with the quantity (or quality) of specific tumor cells.

Discovered 50 years ago in 1965, CEA is still the only tumor marker with proven efficacy in monitoring treatment in CRC patients. CEA was initially thought to be CRC specific, but elevated CEA levels have since been detected in other tumors, *e.g.*, gastric and pancreatic cancer, and inflammatory states. Rarely, elevated CEA concentrations are found in CRC stage I[16]. Furthermore, CEA cannot differentiate between benign and malignant polyps. Recently, several studies have explored the advantages of mRNA molecules encoding CEA for the detection of CRC, but the results were not superior to CEA[17]. In some studies, high CEA concentrations in patients with CRC stages II and III may be indicative of a more aggressive cancer type. CEA is the marker of choice for monitoring disseminated disease during systemic therapy. Sustained increases in CEA levels are often associated with disease progression, even though radiological examination may prove otherwise. However, chemotherapy may also cause a temporary increase in CEA concentrations, which must be taken into account. Therefore, it is not recommended to measure CEA levels within 2 wk after chemotherapy but only after 4 to 6 wk in oxaliplatin-treated patients. Cancer antigen 19-9 (CA 19-9) is a glycoprotein whose relevance in the diagnosis of CRC remains unclear. Most investigators concluded that the sensitivity of CA 19-9 was much lower than that of CEA and that elevated CA 19-9 Levels indicated a poor prognosis[18]. Other carbohydrate antigens, CA 19-5 and CA 50, have also been investigated with relatively disappointing results. CA 72-4 is a biomarker with poor sensitivity, ranging from 9% to 31%, and good specificity, ranging from 89% to 95%, for screening patients for CRC. The diagnostic

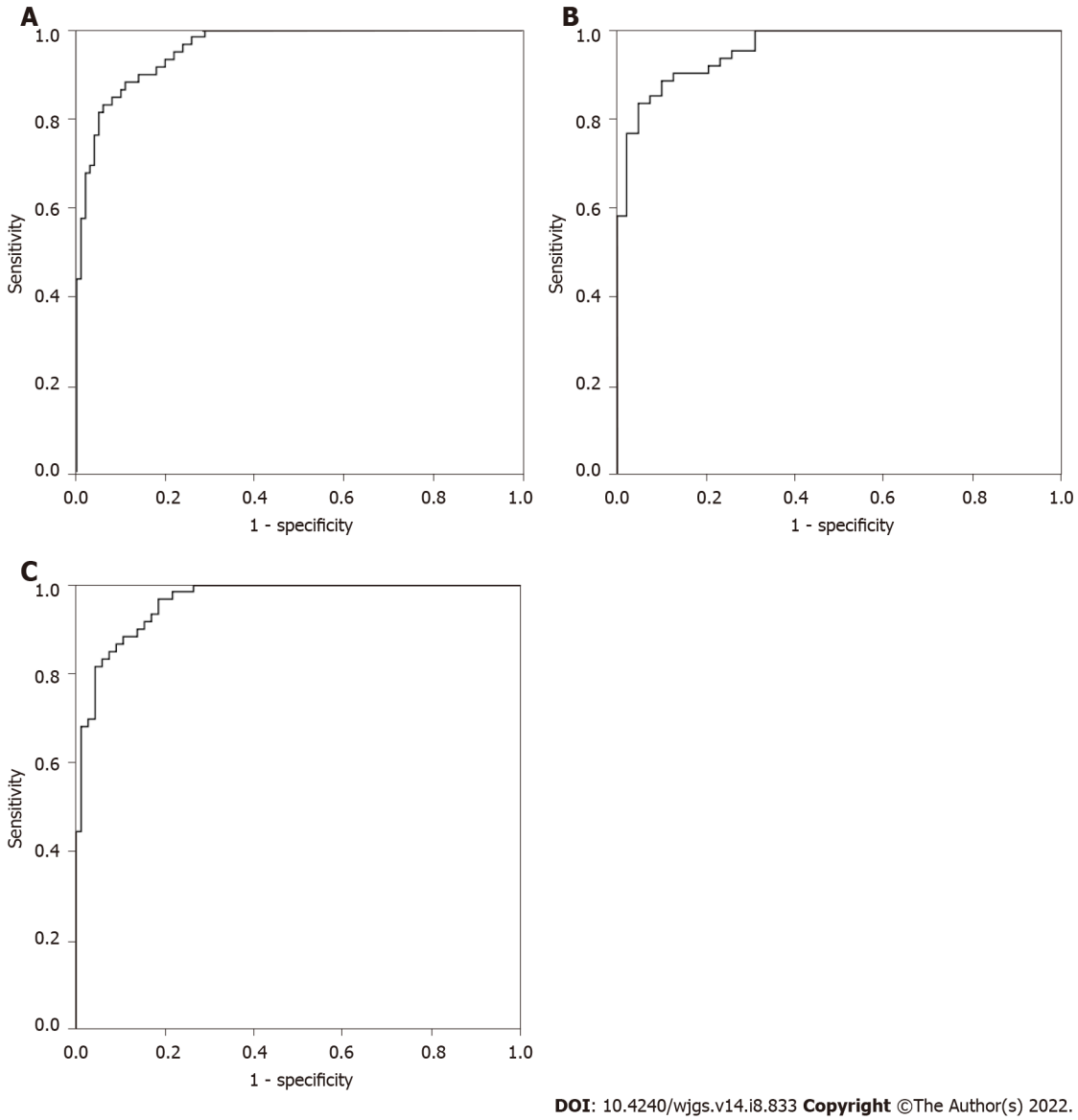

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Figure 2 Diagnostic evaluation of the neural network multi-parameter diagnostic model building. A: Colorectal polyps (CRP) *vs* colorectal cancer (CRC); B: CRP *vs* early stage of CRC; C: CRP *vs* advanced stage of CRC.

information provided by CA 72-4 in recurrent CRC is borderline and far inferior to that of CEA. There is a consensus that CA 72-4 has a rather low sensitivity and incomplete specificity in the screening and follow-up of CRC patients[19]. Tissue polypeptide-specific antigen (TPS) and tissue polypeptide antigen (TPA), which detect cytokeratin 8, 18, and 19 fragments, are not recommended for CRC screening due to their lack of sensitivity and specificity. Most investigators found that elevated levels of TPA and TPS were observed in the metastatic stage of CRC. Further studies showed that the combination of TPA and CEA improved the sensitivity of these biomarkers in identifying patients with CRC recurrence. Other biomarkers, such as thymidine phosphorylase and DNA ploidy, were found to have no utility in the detection, staging or follow-up of CRC patients.

NDUFB is an accessory subunit of *NADH* dehydrogenase (com-plex I) of the mitochondrial membrane respiratory chain, encoded by nuclear genes[20]. Mutations in *NDUFB* may promote tumor metastasis[21]. In addition, a SNP (rs7830235) associated with prostate cancer risk is located in the *NDUFB* gene[22]. In addition to this, most of the other subunits of *NADH* dehydrogenase (*NDUFB1-8/11*) family were found to have significant prognostic value (DMFS) in breast cancer patients, and it was the mainstay of MDA-MB-231 breast cancer cell proliferation, inhibition of migration and invasion [23]. Its high expression is positively correlated with the prognosis of gastric cancer, suggesting that these proteins may serve as new candidate diagnostic and prognostic biomarkers for gastric cancer[24]. *CAMK1D* is a member of the calcium/calmodulin-dependent protein kinase 1 family[25]. It involved in a variety of physiological processes, including activation of CREB-dependent gene transcription, differentiation and activation of neutrophils, and regulation of apoptosis in erythrocytic leukemia[26]. Recent studies have shown that overexpression of *CAMK1D* can promote the proliferation of breast cancer[27].

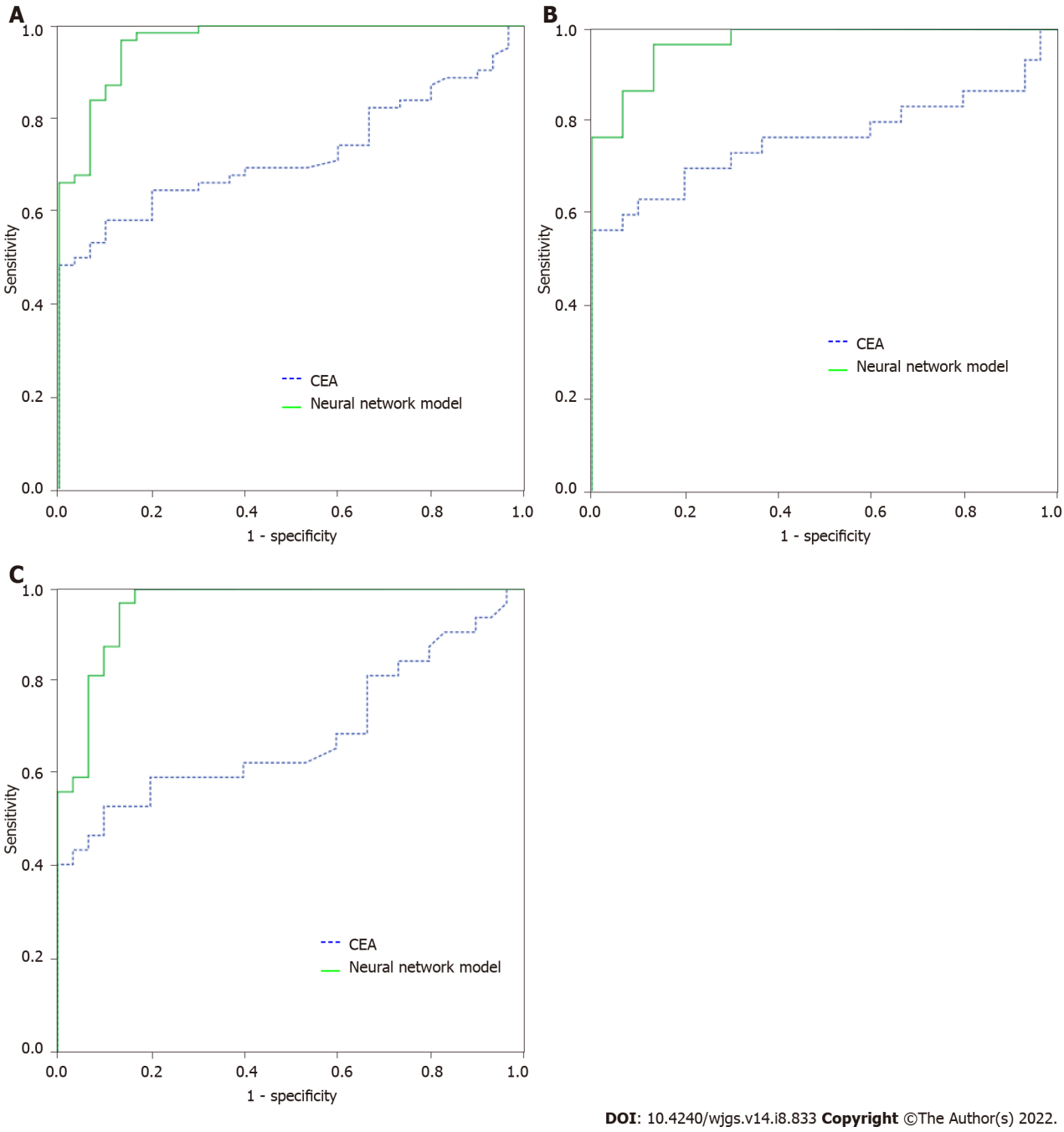

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Figure 3 Diagnostic evaluation of the neural network multi-parameter diagnostic model and carcinoembryonic antigen validation. A: Colorectal polyps (CRP) *vs* colorectal cancer (CRC); B: CRP *vs* early stage of CRC; C: CRP *vs* advanced stage of CRC. CEA: Carcinoembryonic antigen.

Knockdown of *CAMK1D* in HT-29 and SW480 cells significantly reduced cell proliferation, invasion/migration capacity, and significantly increased apoptosis[28]. Activation of phosphoinositide 3-kinase (PI3K) signaling is one of the most common events in several human cancers, including CRC. PI3K is a family of lipid kinases that phosphorylate phosphatidylinositol 4, 5-bisphosphate to generate phosphatidylinositol-3, 4, 5-triphosphate, which in turn activates serine-threonine[29-31]. PI3Ks are classified into 3 classes according to their substrate specificity and structure in mammals. Of these, class I PI3Ks appear to be most associated with human cancers. Class I PI3Ks are further divided into subclasses IA and IB based on their adapters. Class IA PI3Ks contain a p110 catalytic subunit and a p85 regulatory subunit. The class IA catalytic isoforms p110α, p110β and p110δ are encoded by the genes *PIK3CA*, *PIK3CB* and *PIK3CD*, respectively. *PIK3CB* and *PIK3CD* are often overexpressed or amplified in cancer[32,33]. *PIK3CD* is mainly expressed in leukocytes and plays a key role in some hematological malignancies. Furthermore, *PIK3CD* has recently been associated with several human solid tumors, including hepatocellular carcinoma, glioma, glioblastoma, neuroblastoma, and breast cancer[33,34]. *PIK3CD* induces cell growth and invasion in colorectal cancer by activating AKT/GSK-3β/β-catenin signaling[35]. Presenilin 2 (*PSEN2*) is a protein-coding gene. Diseases associated with *PSEN2* include

Alzheimer's disease[36]. Its related pathways include EPH-Ephrin signaling and p75 NTR receptor-mediated signaling. Presenilin (*PSEN1* or *PSEN2*) mutations are generally thought to be present in Alzheimer's disease patients with inherited disorders[37,38]. Although We have built a multi-parameter neural network diagnostic model for CRC, however, multi-centers and larger sample size still needed in the future study.

CONCLUSION

In conclusion, we built a multi-parameter neural network diagnostic model included CEA, IMA, SA, *PIK3CD* and LPa for early detection of CRC, compared to the conventional CEA, it showed significant improvement.

ARTICLE HIGHLIGHTS

Research background

Most patients with colorectal cancer (CRC) are diagnosed at an advanced stage. The high morbidity and mortality of advanced CRC indicates an urgent need for clinical improvements in early CRC detection and individualized management.

Research motivation

Early detection of CRC is urgently needed in clinical practice. Commonly biomarker and extra-chromosomal circular DNA (eccDNA) may have potential diagnostic value for CRC.

Research objectives

This study aimed to build a multi-parameter diagnostic model for early detection of CRC.

Research methods

Total 59 colorectal polyps (CRP) groups, and 101 CRC patients (38 early-stage CRC and 63 advanced CRC) for model establishment. In addition, 30 CRP groups, and 62 CRC patients (30 early-stage CRC and 32 advanced CRC) were separately included to validate the model. 51 commonly used clinical detection indicators and the 4 eccDNA markers *NDUFB7*, *CAMK1D*, *PIK3CD* and *PSEN2* that we screened earlier. Four multi-parameter joint analysis methods: binary logistic regression analysis, discriminant analysis, classification tree and neural network to establish a multi-parameter joint diagnosis model.

Research results

Neural network included carcinoembryonic antigen (CEA), ischemia-modified albumin (IMA), sialic acid (SA), *PIK3CD* and lipoprotein a (LPa) was chosen as the optimal multi-parameter combined auxiliary diagnosis model to distinguish CRP and CRC group, when it differentiated 59 CRP and 101 CRC, its overall accuracy was 90.8%, its area under the curve (AUC) was 0.959 (0.934, 0.985), and the sensitivity and specificity were 91.5% and 82.2%, respectively. After validation, when distinguishing based on 30 CRP and 62 CRC patients, the AUC was 0.965 (0.930, 1.000), and its sensitivity and specificity were 66.1% and 70.0%. When distinguishing based on 30 CRP and 32 early-stage CRC patients, the AUC was 0.960 (0.916, 1.000), with a sensitivity and specificity of 87.5% and 90.0%, distinguishing based on 30 CRP and 30 advanced CRC patients, the AUC was 0.970 (0.936, 1.000), with a sensitivity and specificity of 96.7% and 86.7%.

Research conclusions

We built a multi-parameter neural network diagnostic model included CEA, IMA, SA, *PIK3CD* and LPa for early detection of CRC, compared to the conventional CEA, it showed significant improvement.

Research perspectives

Larger sample size and multi-center study should be performed to validate the diagnostic model in future studies.

FOOTNOTES

Author contributions: Li J and Xian GA designed the study; Li J, Ren ZC and Jiang T performed the research; Li J, Wang ZL and Jiang T analyzed the date; Li J wrote the paper; Xiang GA and Zhang PJ revised the manuscript for final submission; Li J and Jiang T contributed equally to this study; Zhang PJ and Xiang GA the co-corresponding

author.

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

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Data sharing statement: No data was to share.

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CASE REPORT

Recurrent small bowel obstruction secondary to jejunal diverticular enterolith: A case report

Chanyang Lee, Geoffrey Menezes

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Abstract

BACKGROUND

Small bowel diverticulosis is an uncommon condition which is usually asymptomatic and is discovered incidentally. One rare complication is enteroliths forming in the diverticula causing bowel obstruction. Only a few cases of such have been described in literature, and recurrence from this aetiology has not been reported previously. This case report outlines the management of a 68-year-old male who presented with recurrent small bowel obstruction secondary to jejunal diverticular enterolith impaction, seven months following a previous episode.

CASE SUMMARY

A 68-year-old male presented with symptoms of small bowel obstruction. Computed tomography (CT) of the abdomen demonstrated small bowel obstruction from an enterolith formed in one of his extensive jejunal diverticula. He required a laparotomy, an enterotomy proximal to the enterolith, removal of the enterolith, closure of the enterotomy, and resection of a segment of perforated ileum with stapled side-to-side anastomosis. Seven months later, he represented to emergency department with similar symptoms. Another CT scan of his abdomen revealed a recurrent small bowel obstruction secondary to enterolith impaction. He underwent another laparotomy in which it was evident that a large enterolith was impacted at the afferent limb of the previous small bowel anastomosis. A part of the anastomosis was excised to allow removal of the enterolith and the defect was closed with cutting linear stapler. In the following two years, the patient did not have a recurrent episode of enterolith-related bowel obstruction.

CONCLUSION

The pathophysiology underlying enterolith formation is unclear, so it is difficult to predict if or when enteroliths may form and cause bowel obstruction. More research could provide advice to prevent recurrent enterolith formation and its sequelae.

Key Words: Small bowel diverticulosis; Jejunal diverticulosis; Bowel obstruction; Recurrent enterolith; Acute care surgery; Case report

Core Tip: Enterolith formation in small bowel diverticula followed by impaction is a rare cause of small bowel obstruction. Small bowel diverticulosis in itself is a rather rare entity. As such, the management of this acute surgical problem can vary widely depending on the situation. Only a few case reports of this pathology have been described, and the management of this condition was variable. Of note, the management of a recurrent episode in the same patient is not previously described. This case report adds to the current knowledge base of the management of this rare pathology.

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INTRODUCTION

Small bowel diverticulosis is an uncommon condition whose prevalence increases with age[1]. It is thought to arise due to high intraluminal pressure in the bowel that leads to sac-like protrusions of the mucosa and/or submucosa through mural weak points[2]. This condition is usually asymptomatic and is discovered incidentally. It can, however, be complicated by conditions such as diverticulitis, haemorrhage, and perforation[3,4]. One rare complication is bowel obstruction caused by formation of enteroliths in these diverticula[5].

Enteroliths are categorised as primary or secondary enteroliths. Primary enteroliths are those that form within the bowel, be it *via* precipitation of bowel content or clumping of ingested materials. Secondary enteroliths are stones that form in other viscera, such as gallstones. Primary enteroliths are thought to form due to stasis of intestinal content in the bowel. Such stasis can occur in diverticula, but can also be seen in other conditions such as intestinal strictures and anastomoses with blind pouches.

A few cases of small bowel obstruction from enterolith formation in jejunal diverticula have been described in literature[5-8], but recurrent small bowel obstruction from this aetiology has not been described previously. Here, we report a case of a 68-year-old male who presented with recurrent small bowel obstruction secondary to impaction of an enterolith formed in jejunal diverticula.

CASE PRESENTATION

Chief complaints

A 68-year-old Caucasian male was brought by ambulance to a regional emergency department with a three-day history of epigastric pain, vomiting, and reduced oral intake. He also reported a two-day history of obstipation.

History of present illness

This patient reported that his symptoms were strikingly similar to an episode seven months ago, when he underwent a laparotomy and small bowel resection for small bowel obstruction caused by an enterolith. At that time, enterolith impaction caused small bowel obstruction and ileal perforation, leading to purulent peritonitis. Extensive jejunal diverticulosis was also noted. A longitudinal enterotomy was made proximal to the impacted enterolith, the large enterolith was milked out, and the enterotomy was closed transversely (Figure 1A). The perforated ileal segment was resected separately and anastomosed side-to-side with a cutting linear stapler. The jejunal diverticula were not resectable, given the extensive jejunal involvement (Figure 1B). The final pathology of the enterolith revealed degenerate adipose and vegetable matter intermingled with bacteria, crystalline material, and red blood cells. This was suggestive of a primary enterolith with calcifications.

History of past illness

The patient's past history included open cholecystectomy, open appendicectomy, type 2 diabetes, hypertension, hypercholesterolaemia, and knee osteoarthritis. His medications were: Rosuvastatin 10

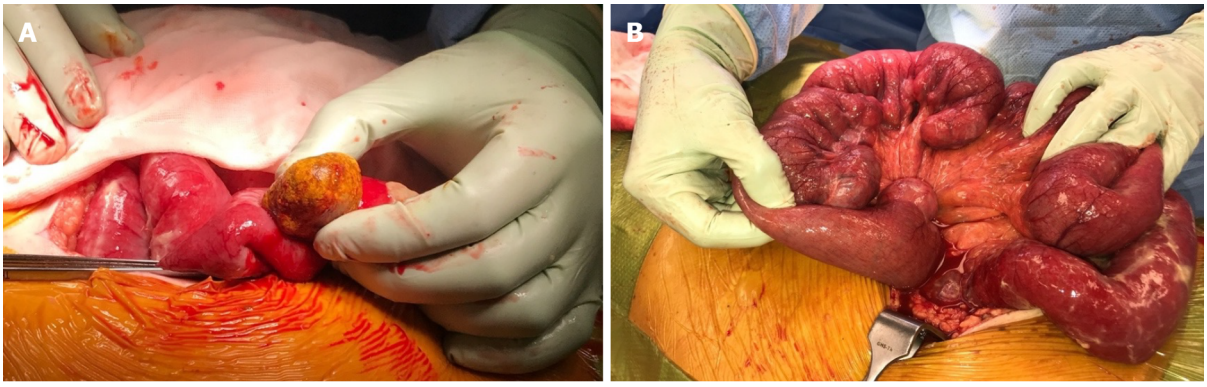

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Figure 1 Intraoperative photographs during the patient's initial laparotomy. A: Offending enterolith removed *via* longitudinal enterotomy; B: Extensive jejunal diverticulosis.

mg nocte, sitagliptin/metformin 50 mg/850 mg twice daily, telmisartan 80 mg mane, and meloxicam 15 mg nocte, with good adherence to his regimen. He did not have any known adverse drug reactions.

Personal and family history

The patient is a non-smoker and does not drink alcohol. He was not aware of any relevant family history.

Physical examination

On examination, the patient's temperature was 36 ˚C, heart rate was 88 bpm, blood pressure was 120/60 mmHg, respiratory rate was 20 breaths per minute, and oxygen saturation was 100% in room air. The abdomen was soft without peritonitis, but distended and moderately tender generally.

Laboratory examinations

Blood analysis showed a normal white cell count of 7.1 × 10^9/L, a mild rise in serum C-reactive protein level at 50 mg/L, a serum lactate level of 1.2 mmol/L, and pH of 7.39. He had an acute kidney injury with a serum creatinine level of 195 μmol/L.

Imaging examinations

A computed tomography (CT) scan of the abdomen and pelvis suggested small bowel obstruction with a transition point at the previous small bowel anastomosis site. The scan was reviewed again with the radiologist, who was provided with the pertinent recent surgical history from seven months ago. It was at this point that the offending enterolith was evident on the CT scan (Figure 2). The findings were explained to the patient, and he was booked and consented for an exploratory laparotomy.

FINAL DIAGNOSIS

The final diagnosis of this case is recurrent small bowel obstruction secondary to impacted enterolith related to extensive jejunal diverticulosis.

TREATMENT

Intraoperatively, extensive adhesions from the previous operation were divided. A bowel run revealed a large obstructive enterolith impacted at the afferent limb of the previous anastomosis (Figure 3A). All examined bowel was viable and extensive jejunal diverticulosis was once again noted. An enterotomy was made at the blind end of the afferent limb, and the enterolith was milked out (Figure 3B). The enterotomy was closed with a cutting linear stapler (Figure 3C). The patient recovered well and was discharged on postoperative day 5.

OUTCOME AND FOLLOW-UP

In the two years following his second laparotomy, there was no recurrence of enterolith-related bowel

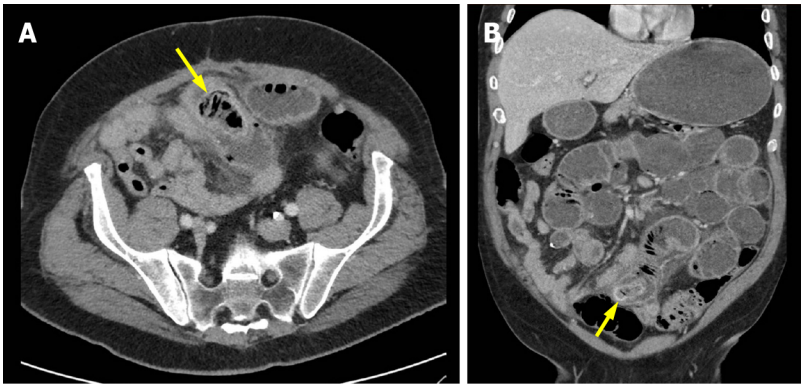

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Figure 2 Obstructing enterolith on computed tomography of abdomen and pelvis. A: Axial image of offending enterolith (yellow arrow); B: Coronal image of offending enterolith (yellow arrow).

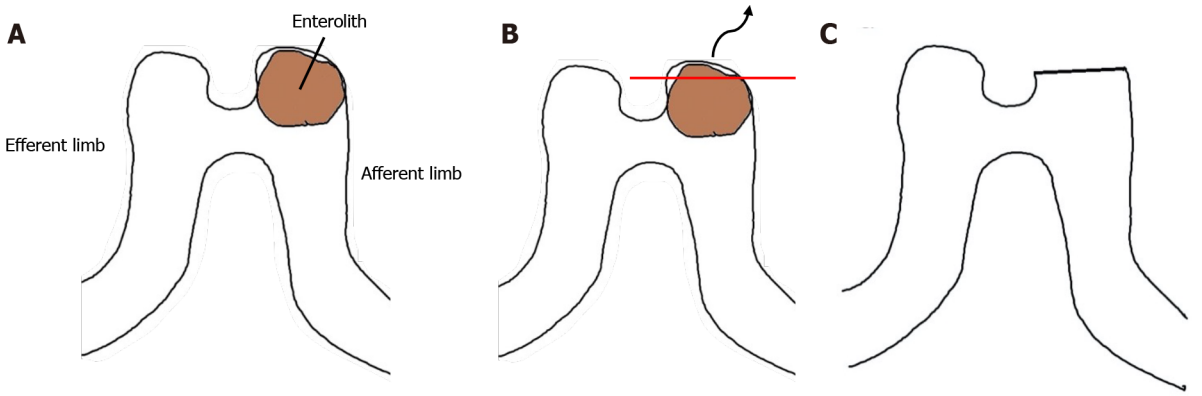

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Figure 3 Animated depiction of intraoperative management of recurrent enterolith impaction. A: Enterolith impaction in blind-ended pouch of previous side-to-side stapled anastomosis; B: Enterotomy at blind-ended pouch with enterolith extraction; C: Final configuration following closure of enterotomy with a linear stapler.

obstruction. Serum calcium and uric acid levels were measured and found to be within normal limits. The pathological analysis of the enterolith revealed degenerate food particles and vegetable matter, again indicative of a primary enterolith.

About one year following the second laparotomy, this patient was admitted for an episode of small bowel obstruction secondary to postoperative adhesions. This was non-operatively managed with success. Furthermore, he developed incisional hernias related to the laparotomy wound for which he has been wait-listed for elective repair. This patient had a follow up colonoscopy six months following his first laparotomy at which sigmoid diverticulosis was noted. Subjectively, the patient was satisfied with the treatment he received. There were no adverse or unanticipated events in the perioperative periods.

DISCUSSION

Bowel diverticula are abnormal sac-like mural outpouchings which can involve the small or large bowel. Small bowel diverticulosis is most common in the duodenum at 79% followed by the jejunum or ileum at 18%[9]. Overall, jejunoileal diverticulosis is quite rare, evident in 0.5% to 2.3% of individuals in radiographic studies. It is most commonly reported in 60 to 70-year-old males[7]. The exact pathophysiology is unclear, but intestinal dysmotility, high intraluminal pressures, and weak points in the alimentary tract are thought to be strong contributors to this condition. About 10% of individuals with jejunoileal diverticulosis may develop complications such as bowel obstruction, haemorrhage, and diverticulitis[9-11].

Enterolith impaction causing bowel obstruction should be on the list of differential diagnoses in individuals known to have small bowel diverticulosis. Such cases have been managed operatively with enterotomy and stone removal as in this case. Another method described was to crush the enterolith in

the small bowel and milking distally into the colon[12]. Quek and Tanase[13] also recently described a case which was managed non-operatively for the first time with success.

Recurrent enterolith formation is possible in individuals with small bowel diverticulosis. Three episodes of recurrent bowel obstruction from primary enterolith in a three-year time period was described only once previously by Shrestha and Shrestha[14], but there were no small bowel diverticula noted in that patient. It is not possible to resect all affected segments in individuals with extensive diverticular involvement due to the result of unacceptably short small bowel length. Current evidence to prevent recurrent formation of enteroliths in these patients is lacking. Surgically, anatomical alterations that avoid stasis of intestinal content probably should be implemented. More research is required to explore the mechanism by which enteroliths form. Evidence-based dietary advice for these patients with extensive small bowel diverticulosis could decrease the risk of recurrent enterolith formation and its sequelae.

CONCLUSION

This case report sheds new light on the pathophysiology of bowel obstruction caused by primary enterolith formation in small bowel diverticula. This is the first case in literature of a recurrent small bowel obstruction caused by a primary enterolith associated with jejunal diverticulosis. In particular, this case highlighted the time frame between episodes of enterolith related bowel obstruction: seven months. The current knowledge base of the pathophysiology of enterolith formation supports the practice of avoiding anatomical alterations that promote stasis of intestinal content. More research on dietary modifications may prove to be beneficial for individuals with unresectable extensive small bowel diverticulosis.

FOOTNOTES

Author contributions: Lee C designed and drafted the manuscript; Menezes G was the original surgeon and he reviewed and approved the manuscript for submission.

Informed consent statement: Written informed consent was obtained from the patient for the publication of this report with relevant radiographic and intraoperative images.

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CASE REPORT

Interventional radiology followed by endoscopic drainage for pancreatic fluid collections associated with high bleeding risk: Two case reports

Ning Xu, Long-Song Li, Wen-Yi Yue, Dan-Qi Zhao, Jing-Yuan Xiang, Bo Zhang, Peng-Ju Wang, Ya-Xuan Cheng, En-Qiang Linghu, Ning-Li Chai

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Abstract

BACKGROUND

Endoscopic ultrasound (EUS)-guided transluminal drainage is an advanced technique used to treat pancreatic fluid collections (PFCs). However, gastric varices and intervening vessels may be associated with a high risk of bleeding and are, therefore, listed as relative contraindications. Herein, we report two patients who underwent interventional embolization before EUS-guided drainage.

CASE SUMMARY

Two 32-year-old males developed symptomatic PFCs after acute pancreatitis and came to our hospital for further treatment. One patient suffered from intermittent abdominal pain and vomiting, and computed tomography (CT) imaging showed an encapsulated cyst 7.93 cm × 6.13 cm in size. The other patient complained of a mass inside the abdomen, which gradually became enlarged. Gastric varices around the ideal puncture site were detected by EUS when we evaluated the possibility of endoscopic drainage in both patients. Interventional embolization was recommended as the first procedure to decrease the risk of bleeding. After that, EUS-guided transluminal drainage was successfully conducted, without vascular rupture. No postoperative complications occurred during hospitalization, and no recurrence was detected at the last follow-up CT scan performed at 1 mo.

CONCLUSION

Interventional embolization is a safe, preoperative procedure that is performed

before EUS-guided drainage in PFC patients with gastric varices or at high risk of bleeding.

Key Words: Interventional embolization; Endoscopic drainage; Endoscopic ultrasound; Pancreatic fluid collections; Gastric varices; Case report

Core Tip: Endoscopic ultrasound-guided drainage has previously proved to be an excellent method to cure pancreatic fluid collections (PFCs). However, it is not recommended for PFCs with the gastric varices and the abundant surrounding vessels because of the high bleeding risk. Preoperative interventional embolization decreases the possibility of hemorrhage when a transluminal tunnel is established between the stomach and cyst. In our cases, the patients underwent this new preoperative arrangement and transgastric drainage was performed. No bleeding or other intraoperative complications occurred. We recommend this modality as a new strategy for PFCs drainage in patients with high bleeding risk.

Citation: Xu N, Li LS, Yue WY, Zhao DQ, Xiang JY, Zhang B, Wang PJ, Cheng YX, Linghu EQ, Chai NL. Interventional radiology followed by endoscopic drainage for pancreatic fluid collections associated with high bleeding risk: Two case reports. *World J Gastrointest Surg* 2022; 14(8): 855-861
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INTRODUCTION

Pancreatic fluid collections (PFCs), including walled-off necrosis (WON) and pancreatic pseudocysts (PPCs), are local complications of acute or chronic pancreatitis according to the updated Atlanta classification[1]. European Society of Gastrointestinal Endoscopy (ESEG) recommends endoscopic or percutaneous drainage as a first-line therapy for symptomatic PFCs[2]. A previous study found that endoscopic transmural drainage is more effective than surgery because of its minimal invasiveness[3]. However, the gastric varices and the abundant vessels surrounding PFCs might be ruptured while establishing the tunnel between the stomach and cyst, thus resulting in uncontrollable bleeding that is unresponsive to endoscopic clips or electrocoagulation[4]. In the two patients described here, lumen-metal apposing stents were successfully placed to drain PFCs under endoscopic ultrasound (EUS) guidance during preoperative embolization of potential bleeding vessels. Herein, we share our successful experience in the form of two case reports to help endoscopists prevent bleeding during the endoscopic drainage procedure.

CASE PRESENTATION

Chief complaints

Case 1: A 32-year-old male was admitted to our department with the symptoms of abdominal pain and vomiting.

Case 2: A 32-year-old male with abdominal distension was referred to our hospital for therapeutic management.

History of present illness

Case 1: The patient experienced continuous abdominal pain and vomiting and was sent to the emergency department of our hospital. The symptoms gradually disappeared after fasting and acid suppression. Abdominal ultrasound indicated the presence of cystic lesions in the body of the pancreas. Then, he was transferred to our inpatient area.

Case 2: In December 2020, the patient who was diagnosed with PPC from an outside hospital was admitted to the Department of Hepatobiliary Surgery to undergo open surgery. However, he was unsuitable for the surgical operation because of renal insufficiency. He came to our department for further treatment of PPC until renal function returned to normal in September 2021.

History of past illness

Case 1: Three years ago, he was admitted to a local hospital to receive treatment for severe acute pancre-

atitis.

Case 2: The patient suffered from acute pancreatitis for the first time five years prior to hospitalization, and recovered after symptomatic treatment. Intermittent pancreatitis occurred frequently between 2017 and 2020. The patient was hospitalized in the intensive care unit, at least once, for severe abdominal pain combined with continuous vomiting and fever.

Personal and family history

Cases 1 and 2: The personal and family histories were unremarkable.

Physical examination

Case 1: Abdominal distension was visible even when the patient lay flat.

Case 2: An obvious mass was palpable in the left upper abdomen, but the size of the mass might not have been evaluated accurately.

Laboratory examinations

Case 1: No pancreatitis-related abnormalities were found by blood biochemical examination.

Case 2: A slight increase in the carbohydrate antigen 125 level was detected by blood biochemical examination, as well as a sharp increase in the carbohydrate antigen 19-9 level. Amylase (501 U/L) and lipase levels (559 U/L) were much higher than normal (normal ranges: 0-150 U/L and 13-60 U/L).

Imaging examinations

Case 1: Contrast-enhanced abdominal computed tomography (CECT) showed a cystic lesion in the body of the pancreas, with a size of 7.93 cm × 6.13 cm (Figure 1A). A cystic lesion of the same size and the presence of blood vessels around the cyst were observed on linear EUS (Figure 2A).

Case 2: A cyst with a maximum diameter of 14 cm was detected by CECT (Figure 1B). Linear EUS showed signs of several vessels around the fundus of the stomach, which may have been a potential puncture site (Figure 2B).

FINAL DIAGNOSIS

Case 1

Based on the patient's history of illness and the direct endoscopic visualization of the cystic cavity contents, his diagnosis ultimately concluded as being WON.

Case 2

According to the characterization of the cystic cavity contents, he was diagnosed with PPC.

TREATMENT

Case 1

Coil embolization was performed before the endoscopic drainage (Figure 3A and B). Then the patient was prepared to undergo EUS-guided cystogastrostomy and a lumen-metal apposing stent (LAMS: 16 mm × 26 mm, Micro-Tech Co., Ltd., Nanjing, Jiangsu Province, China) placement.

Case 2

Under fluoroscopy guidance, endovascular embolization was conducted first (Figure 3C and D). Four days later, EUS-guided cystogastrostomy and placement of a LAMS were successively performed.

OUTCOME AND FOLLOW-UP

Case 1

Subsequent monitoring showed that the patient's temperature was maintained within the normal range. However, he experienced unexplained nausea and vomiting during hospitalization after the LAMS was placed. Four days after stent placement, postoperative endoscopic observation showed that the contents were almost fully discharged to the stomach cavity. Thus, after irrigation of the cystic cavity with sterile water only, the stent was retrieved, and thereby eliminated all discomforting symptoms. One month

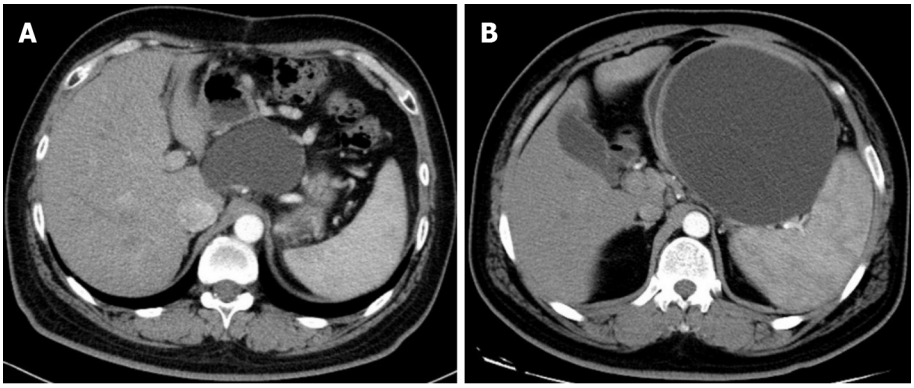

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Figure 1 Preoperative images of contrast-enhanced computed tomography. A: Preoperative contrast-enhanced computed tomography (CECT) image of the first patient showed a cystic lesion in the body of the pancreas, with a size of 7.93 cm × 6.13 cm; B: Preoperative CECT image of the second patient showed a cystic lesion with a maximum diameter of 14 cm.

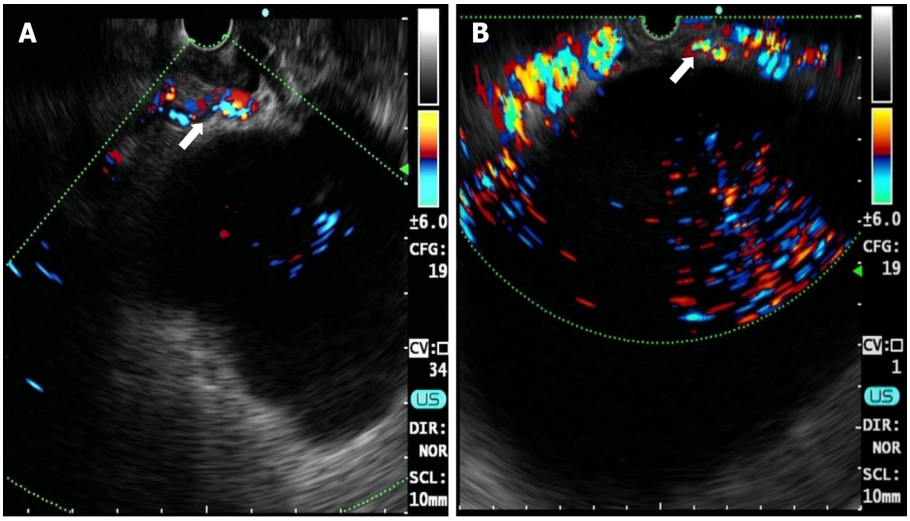

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Figure 2 Multiple vasculature (white arrow) detected by Doppler endoscopic ultrasound. A: Endoscopic ultrasound (EUS) imaging of the first patient; B: EUS imaging of the second patient.

after endoscopic drainage, CECT of the abdomen revealed that WON in the patient has resolved.

Case 2

The patient's vital signs were stable during hospitalization. Postoperative endoscopy was used to perform direct endoscopic necrosectomy. Sterile water was used to rinse the small amount of liquid content that remained in the cystic cavity followed by withdrawal of the stent. CECT obtained one month after the procedure showed shrinkage of the PPC**.** No abdominal symptoms or postoperative complications were observed.

DISCUSSION

PFCs are local complications of acute pancreatitis that frequently occur more than 4 wk after the onset of pancreatitis[5]. Some PFCs patients might suffer from symptoms of abdominal pain, vomiting, and other digestive-related discomfort, but the majority of patients are asymptomatic and their symptoms resolve spontaneously[6]. For symptomatic PFCs, especially those that seriously affect normal life, drainage of the collections is vital for effective treatment[7,8]. Although there are other drainage methods, endoscopic drainage is minimally invasive and has improved safety and efficacy when compared to open surgery or percutaneous drainage, so endoscopic drainage is recommended as the first-line treatment.

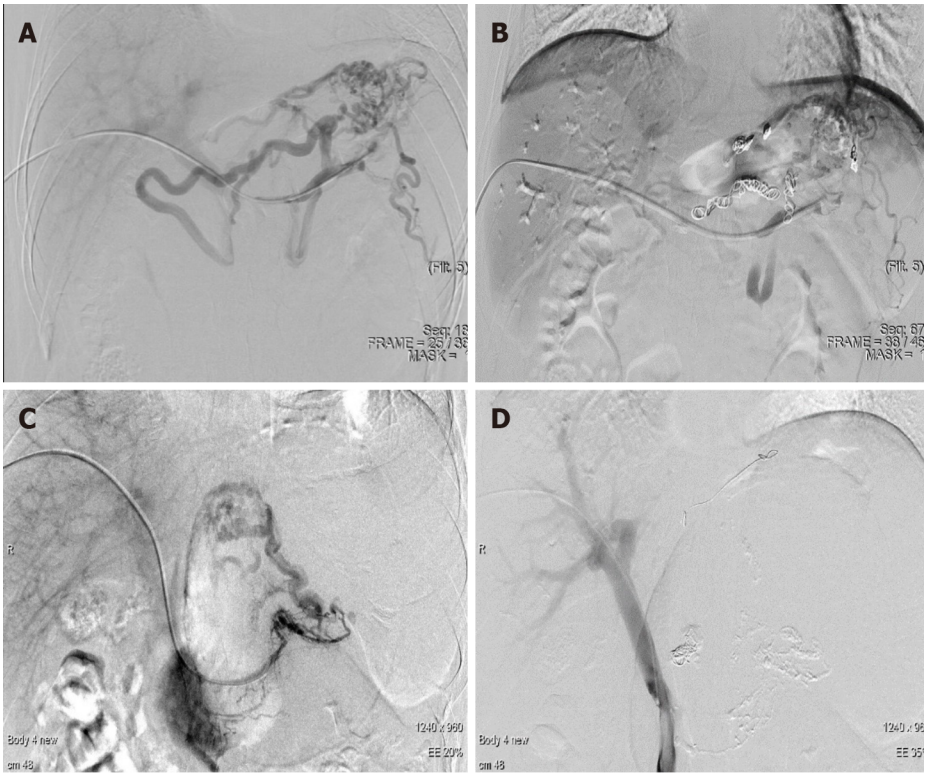

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Figure 3 Typical imaging of interventional radiology. A: Angiogram of the first patient prior to coil embolization; B: Angiogram of the first patient after coil embolization; C: Angiogram of the second patient prior to coil embolization; D: Angiogram of the second patient after coil embolization.

Endoscopic drainage is a well-established therapy for PFCs; however, bleeding complications still haunt endoscopists[9,10]. In the past, PFCs associated with gastric varices or abundant surrounding vessels were referred to the surgical department for further treatment[11]. Previous studies have reported attempts to treat PFC-associated diseases with high bleeding risks, such as arterial pseudoaneurysms, with a combination of minimally invasive endoscopic and radiological interventions[12,13]. However, this combined treatment is rare because of its association with the gastric varices or the surrounding vessels, thus limiting is applicability due to the demand for expertise in interventional radiology and therapeutic endoscopy.

Endovascular embolization, an advanced technique, is the preferred treatment of choice for esophageal or gastric varices and has been widely used to stop and prevent bleeding[14,15]. However, clinicians have limited experience in the clinical management of PFCs that present with gastric varices. Moreover, ideal management depends on the patient's hemodynamic stability[16]. The development of interventional radiological techniques has led to better outcomes of hemostasis with angioembolization. One report indicated that angioembolization alone is an effective treatment for a pseudocyst associated with pseudoaneurysms[17].

In the presence of gastric varices or pseudoaneurysms, EUS-guided endoscopic drainage is contraindicated because of the increased risk of vessel rupture[18]. In our study, we show that endoscopic drainage combined with coil embolization is an effective treatment for varices. These two patients underwent EUS-guided puncture and a small incision was made in the wall of the stomach and PFC cysts after interventional radiology. No intraoperative complications, such as bleeding or infection, occurred. We did not encounter any complications while removing the necrotic solid debris or the metal stent. However, we did not determine the cause of intermittent nausea and vomiting that occurred in one patient. All symptoms disappeared after the stent was removed.

One limitation is associated with this combined treatment method. For patients with PFCs less than 6 cm, a LAMS cannot be used to establish a tunnel between the two lumens[19]. Therefore, EUS-guided endoscopic drainage combined with interventional radiology would not be feasible.

CONCLUSION

The application of endovascular embolization before EUS-guided endoscopic drainage prevents vessel rupture. This combined treatment has the potential to be a solution for PFC patients with high bleeding risks and warrants further investigation to substantiate its use.

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FOOTNOTES

Author contributions: Xu N and Li LS contributed equally to this manuscript; Chai NL and Xu N contributed to manuscript drafting; Xu N and Yue WY wrote the manuscript; Li LS, Zhao DQ, Xiang JY, Zhang B, Wang PJ and Cheng YX were responsible for the revision of the manuscript for significant content; Chai NL and Linghu EQ were the patient's endoscopists and reviewed the literature; all authors issued final approval for the version to be submitted.

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LETTER TO THE EDITOR

Sirolimus *vs* tacrolimus: Which one is the best therapeutic option for patients undergoing liver transplantation for hepatocellular carcinoma?

Faiza Ahmed, Faiza Zakaria, Godsgift Enebong Nya, Mohamad Mouchli

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Abstract

Liver transplantation (LT) withstands as the most preferred therapeutic option for patients afflicted with hepatocellular carcinoma (HCC) and cirrhosis. To improve prognosis post-transplant, as well as to prevent the occurrence of rejection, a life-long immunosuppression strategy is implemented. The following letter to the editor highlights and provides novel evidence from recently published literature on topics discussed within the review article titled "Trends of rapamycin in survival benefits of liver transplantation for hepatocellular carcinoma" in *World J Gastrointest Surg* 2021; 13: 953-966. In the recent manuscript, the authors compared immunosuppressive drugs such as the newer option first-generation mammalian target of rapamycin inhibitor, also known as sirolimus, with the most widely used first-generation calcineurin inhibitors, such as tacrolimus (TAC). TAC is commonly known as the most effective immunosuppressive drug after LT, but it has been reported to cause intolerable side effects such as nephrotoxicity, neurotoxicity, diabetes, hypertension, gastrointestinal disturbances, increased risk of infections, and malignancies. It is necessary for physicians to be aware of recent advances in tacrolimus and sirolimus therapies to compare and understand distinctly the effectiveness and tolerability of these drugs. This will assist clinicians in making the best treatment decisions and improve the clinical prognosis of LT recipients with HCC.

Key Words: Rapamycin; Tacrolimus; Sirolimus; Immunosuppressants; Hepatocellular carcinoma; Liver transplantation

Core Tip: Post-transplant rejection holds significance in the long-term survival of patients with hepatocellular carcinoma (HCC) receiving a liver transplant (LT). The role of the mammalian target of rapamycin inhibitor (mTOR inhibitors) in preventing HCC recurrence after LT is still under debate. The major goal of this letter is to summarize the most relevant existing data on sirolimus, an mTOR inhibitor, and tacrolimus, a calcineurin inhibitor, therapy involvement in the progression of such patients.

Citation: Ahmed F, Zakaria F, Enebong Nya G, Mouchli M. Sirolimus *vs* tacrolimus: Which one is the best therapeutic option for patients undergoing liver transplantation for hepatocellular carcinoma? *World J Gastrointest Surg* 2022; 14(8): 862-866
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TO THE EDITOR

We read with profound interest the review by Zhao *et al*[1], "Trends of rapamycin in survival benefits of liver transplantation for hepatocellular carcinoma", published in the September 2021 issue of the *World Journal of Gastrointestinal Surgery*.

Hepatocellular carcinoma (HCC) is the second greatest cause of cancer fatalities worldwide and three times more frequent among males[2,3]. According to the World Health Organization, 905677 new cases were identified globally in 2020, with 830180 deaths[4]. By 2030, the worldwide burden of HCC mortality is anticipated to surpass one million[5]. Apart from poor prognosis, HCC has a five-year survival rate of less than 10%, and the outcome is worsened by the lack of therapy options. If detected early, HCC can be treated with surgery or liver transplantation (LT). However, more than 85% of cases are discovered at an advanced stage, when surgical treatment is not possible[6].

The most important indication for LT is concurrent HCC and cirrhosis. For end-stage liver diseases, LT is the most effective strategy[7]. However, tumor recurrence remains a significant challenge. The risk of HCC recurrence postoperatively within five years after LT is as high as 30% and remains the primary reason for mortality in such patients[8]. Life-long immunosuppression is required to prevent rejection. In recent years, post LT immunosuppression remains the subject of intense research.

In the article, Zhao *et al*[1] highlight investigations involving the use of different types of potential options to treat post-LT recurrence in HCC patients. The study also compares immunosuppressive drugs such as the newer option first-generation mammalian target of rapamycin (mTOR) inhibitor, also known as sirolimus (SRL), with the most widely used first-generation calcineurin inhibitors (CNIs), such as tacrolimus (TAC). However, CNIs have been proven to increase malignant development, with studies indicating a dose-dependent connection with tumor recurrence in HCC patients[9]. TAC is commonly known as the most effective immunosuppressive drug after LT, but it has been reported to cause side effects such as nephrotoxicity, neurotoxicity, diabetes, hypertension, gastrointestinal disturbances, increased risk of infections, and malignancies[10]. In contrast, mTOR inhibitors are considered to have anti-tumor properties *via* inhibiting angiogenesis, cellular proliferation, and have demonstrated tolerable safety with promising outcomes[11]. However, since there is inadequate data available to support the use of mTOR inhibitors in the treatment of HCC recurrence after transplantation, their role is yet to be determined. Nevertheless, we would like to draw the authors' attention to several recently published literature on this topic.

Five studies individually evaluated SRL therapy. A retrospective cohort study[12] compared the mTOR inhibitors group with a control group that did not receive any mTOR inhibitor therapy. The authors' demonstrated that the use of mTOR inhibitors, either SRL or everolimus (EVL), a rapamycin derivative, in the immunosuppressive regime of LT recipients increased survival after recurrence (median 21.0 ± 4.1 *vs* 11.2 ± 2.5 mo, $P = 0.04$). The mTOR inhibitors group had decreased recurrent tumors (2 *vs* 5, $P = 0.02$) compared to the control group. Supportive care was provided to a small number of patients (4% *vs* 36%, $P < 0.001$), and more aggressive therapies such as radiation (39% *vs* 22%, $P = 0.03$) and targeted therapy (59% *vs* 23%, $P < 0.001$) were actively utilized in mTOR inhibitors group. The results also confirmed that mTOR inhibitors enhanced survival, and subgroup analysis of patients who received SRL or EVL had no significant change in survival outcomes (19.1 ± 5.7 *vs* 21.0 ± 4.4 mo, $P = 0.88$). Furthermore, the study reported no changes in survival between patients who received mTOR inhibitors alone and those who received mTOR inhibitors in combination with TAC.

A systematic review and meta-analysis reported that SRL or EVL improved one, two, three and five-year overall survival (OS) [randomised controlled trials: 1-year, relative risk (RR) =1.04, 95%CI: 1.00-1.08; 2-year, RR = 1.09, 95%CI: 1.02-1.16; 3-year, RR = 1.13, 95%CI: 1.04-1.24; 5-year, RR = 1.13, 95%CI: 1.02-1.26) *vs* (cohort studies: 1-year, RR = 1.13, 95%CI: 1.06-1.20; 2-year, RR = 1.24, 95%CI: 1.16-1.32; 3-year, RR = 1.24, 95%CI: 1.15-1.34; 5-year, RR = 1.17, 95%CI: 1.10-1.24)), respectively[7]. A 13% improvement in OS was demonstrated over five years, with 14% survival benefit in three years, and minimal risk of nephrotoxicity was noticed (RR = 0.75, 95%CI: 0.60-0.93) in the mTOR inhibitors group.

Ye *et al*[13] was the first study that retrospectively integrated a molecular index, tuberous sclerosis 1-tuberous sclerosis 2 complex (TSC 1/2) expression levels, in predicting the SRL's impact on the prognosis of HCC-LT patients exceeding the Milan criteria. According to the researchers, SRL enhanced outcomes in HCC-LT patients with low TSC 1/2 expression [disease-free survival (DFS): P = 0.046, OS: P = 0.006 for TSC1; DFS: P = 0.05, OS: P = 0.003 for TSC2). However, the influence of lower dosages of CNIs, which have been reported to improve the anticancer activity of SRL, cannot be ruled out. Wei *et al*[14] also analyzed TSC mutations in LT for HCC and resulted in no notable disparity in survival rates among the SRL and non-SRL patients (P = 0.761). There was no distinction noted between the two treatment groups for the five-year disease-free survival rate. Overall, patients with TSC 1/2 mutations achieved a good prognosis from the use of SRL.

Zhao *et al*[1] also cited the SiLVER trial, which demonstrated in the first three to five years an improved recurrence-free survival (RFS) and OS, especially in low-risk patients with tumor characteristics within Milan criteria[15]. Research conducted by Ekpanyapong *et al*[16] also supports this benefit.

One recent article by Gastaca *et al*[17] retrospectively evaluated TAC therapy. The authors aimed to assess the impact of early post LT TAC trough levels on prognosis after LT. They concluded that no significant effect was appreciated on the function of the kidneys, immunosuppression-related morbidity, and five-year patient or graft survival. Therefore, small variations in mean TAC levels during the first month were reported to be insignificant predictors of long-term immunosuppression-related morbidity and patient survival; hence, long-term results appeared to be influenced by increased exposure.

Finally, we found three comparative research published on SRL and TAC regimens. A prospective, randomized, multicenter phase II trial compared both drugs' oncological outcomes in living donor LT patients exceeding the Milan criteria. The three-year RFS and OS rates were higher in the TAC group compared to the SRL group (77.3% *vs* 60%; and 81.8% *vs* 77%), respectively. On multivariate analysis, serum alpha-fetoprotein level > 150 ng/mL and positron emission tomography standardized uptake value ratio (tumor/background liver) > 1.15 were crucial risk factors for both RFS and OS. SRL therapy enhanced OS (TAC hazard ratio: 15.0, 95%CI: 1.302-172.8, P = 0.03) but had no impact on RFS. In regards to adverse events, the authors reported a higher incidence of wound complication and dyslipidemia in the SRL group; however, the variation was not statistically relevant. Overall, SRL did not reduce HCC recurrence, but it did extend the patients' OS time[18].

In a retrospective study, Sung *et al*[19] found that individuals with impaired renal function improved significantly after 12 mo of using mTOR inhibitors. The median eGFR values at 1, 3, 6, and 12 mo after switching to mTOR inhibitors were 90, 75.5, 74.5, and 76.8 mL/min. Moreover, the mean eGFR in TAC-withdrawn individuals after switching to mTOR inhibitors at 1, 3, 6, and 12 mo was 110, 98, 87.5, and 82 mL/min, respectively. In comparison, TAC-minimized patients at 1 and 6 mo after switching to mTOR inhibitors had significantly lower eGFR compared to the TAC withdrawn group. Hence, the TAC-withdrawn group demonstrated enhanced kidney function compared to the TAC-minimized group. Common adverse events such as thrombocytopenia (7.1%), proteinuria (11.9%), mouth ulceration (6%), and gastrointestinal adverse effects (9.5%) occurred within 2 mo after mTOR inhibitor use. Comprehensively, the authors confirmed that substituting with mTOR inhibitors is advantageous when renal function diminishes.

The authors, Zhao *et al*[1], also mentioned one of the side effects of SRL, which is delayed wound healing, as a generally moderate and easy to treat condition. They stated that adverse reactions were subsided by lowering the installation rate or stopping the medicine, whereas a case report by Lao *et al*[20] presents a different scenario. Initially, the 54-year-old woman patient with *CYP3A* mutation was provided TAC for treatment, but later on, was substituted with SRL at the first sign of acute renal injury. The transition was undertaken since SRL is not known to induce kidney and liver toxicity; however, the arterial anastomosis ruptured unexpectedly a few days after the medication was initiated. Before the arterial anastomosis ruptured, a postoperative Doppler ultrasonography was performed every 2-3 d and displayed no signs of either an abscess or a pseudoaneurysm. She received 6 mg of SRL as a loading dose for 2 d followed by a 2 mg maintenance dose. The loading dose and increased levels of SRL exposure damaged the durability of the arterial anastomosis, contributing to its rupture. Thus, the authors concluded that it is better to avoid using SRL at the early stage after LT considering its effect on wound healing.

In conclusion, Zhao *et al*[1] presented interesting points concerning LT for HCC patients by the usage of SRL and TAC therapy. We agree with the authors' insight that TAC significantly influences renal function, leading to acute and chronic kidney diseases after LT. However, further investigations are warranted regarding the safety profile of SRL to better understand its impact as a substitution for TAC. In addition, studies discussing cost-effectiveness analysis of these drugs are also necessary since they

will aid physicians in decision-making and individualizing treatment to improve OS and RFS with minimal adverse effects.

FOOTNOTES

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LETTER TO THE EDITOR

Statistical proof of *Helicobacter pylori* eradication in preventing metachronous gastric cancer after endoscopic resection in an East Asian population

Mohsen Karbalaei, Masoud Keikha

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Abstract

We conducted a comprehensive literature review and meta-analysis study on the efficacy of *Helicobacter pylori* (*H. pylori*) eradication in preventing metachronous gastric cancer after endoscopic resection among an East Asian population. Our results showed that the eradication of this pathogen significantly reduced the risk of susceptibility to metachronous gastric cancer in these patients. However, based on the available evidence, several factors such as increasing age, severe atrophy in the corpus and antrum, and intestinal metaplasia all may increase the risk of metachronous gastric cancer in *H. pylori* eradicated patients.

Key Words: *Helicobacter pylori*; Gastric cancer; Eradication rate; Metachronous gastric cancer

Core Tip: Gastrointestinal infections caused by *Helicobacter pylori* (*H. pylori*) is one of the most well-known infections in the human digestive tract. This bacterium successfully has been colonized in the stomach of more than 4 billion people worldwide. In many developing countries, these microorganisms are colonized in childhood, which in later years may develop to severe complications, particularly gastric adenocarcinoma. In the present study, we statistically evaluated the effectiveness of *H. pylori* eradication in reducing the risk of tend to metachronous gastric cancer (MGC) in Asian populations. Our results suggested that the eradication of this pathogen significantly reduced the risk of susceptibility to MGC in these patients. However, based on the available evidence, several factors such as increasing age, severe atrophy in the corpus and antrum, and intestinal metaplasia all may increase the risk of MGC in *H. pylori* extirpated patients. Unfortunately, there is no detailed information about the location of the stomach where the reduction of gastric cancer can be achieved after *H. pylori* eradication. Therefore, in future studies, more research should be done on the recent puzzle.

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TO THE EDITOR

Helicobacter pylori (*H. pylori*) is a Gram-negative, microaerophilic, and helical microorganism that colonizes the gastric mucosa in half of the world's population[1]. This bacterium is the main etiologic cause of gastritis, dyspepsia, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, gastric cancer, and peptic ulcer[1-3]. According to the literature, *H. pylori* also contributes in extragastrointestinal disorders such as insulin resistance, non-alcoholic liver disease, diabetes mellitus, coronary artery disease, and neurodegenerative disease[3,4]. In 1994, the International Agency for Research on Cancer (IARC) identified this bacterium as a group I gastric carcinogen[5]. There is ample evidence about the positive relationship between *H. pylori* infection and gastric cancer; primary infection with this bacterium has been proven to lead to cancer by inducing atrophic gastritis, intestinal metaplasia, and dysplasia[6]. According to previous randomized controlled trials (RCTs), it seems that the eradication of this pathogen is not effective in preventing the occurrence of primary gastric cancer[7-12]. Doorakkers *et al*[13] in a recent meta-analysis found that the eradication of this microorganism fundamentally reduced the incidence of primary gastric cancer.

Antrectomy (distal gastric resection) is a rare surgical procedure to treat early distal gastric cancer, in which the pyloric antrum is excised; although the presence of *H. pylori* may be decreased in the residual stomach, both untreated bacterial infection and biliopancreatic reflux damage the residual gastric mucosa, which can be considered as precursors for gastric stump cancer (GSC)[14]. Endoscopic resection (ER) procedures such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are known as accepted therapeutic strategies for treating early gastric cancer (EGC); although the effect of ER on EGC treatment is greater than that of gastrectomy, the risk of metachronous gastric lesions in the remnant stomach is higher after ER than gastrectomy[15].

Based on documents, the incidence of metachronous gastric cancer (MGC) has been estimated at 2.7%-15.6% in 3-5 years after EGC[16]. The efficacy of eradication of infection in the prevention of metachronous recurrence is controversial[15,17]. In the present study, we determined the beneficial effect of *H. pylori* eradication to prevent the recurrence of MGC after ER in an East Asian population.

We searched scientific databases such as Scopus, PubMed, Google Scholar, Cochrane Library, as well as Embase regardless of restriction in date and language by November 2020. The titles and abstracts of all papers were assessed to select the relevant articles. Then, eligible studies related to the effect of definitive treatment of infection on the recurrence of MGC after ER were collected. The inclusion criteria were: (1) RCTs or cohort studies on the effect of standard bacterial eradication on metachronous recurrence; (2) comparative studies of people with conventional *H. pylori* eradication and those who do not receive conventional eradication procedure; and (3) studies on the East Asian population. On the other hand, criteria such as (1) review articles, letters, or congress abstracts; (2) duplication studies; (3) non-clinical studies; and (4) studies with insufficient materials and findings were considered as the exclusion criteria. We collected the essential information using Comprehensive Meta-Analysis software, version 2.2. The incidence of metachronous recurrence was reported in each group as a percentage with 95% confidence interval (95%CI). Moreover, the clinical achievement of *H. pylori* eradication in reduction of metachronous recurrence was also measured using odds ratio (OR) with 95%CI. Heterogeneity was determined *via* I^2 value and Cochran's Q test; a random-effect model was applied in high heterogeneity cases ($I^2 > 25\%$ and Cochran's-Q $P > 0.05$) according to the Dersimonian and Laird

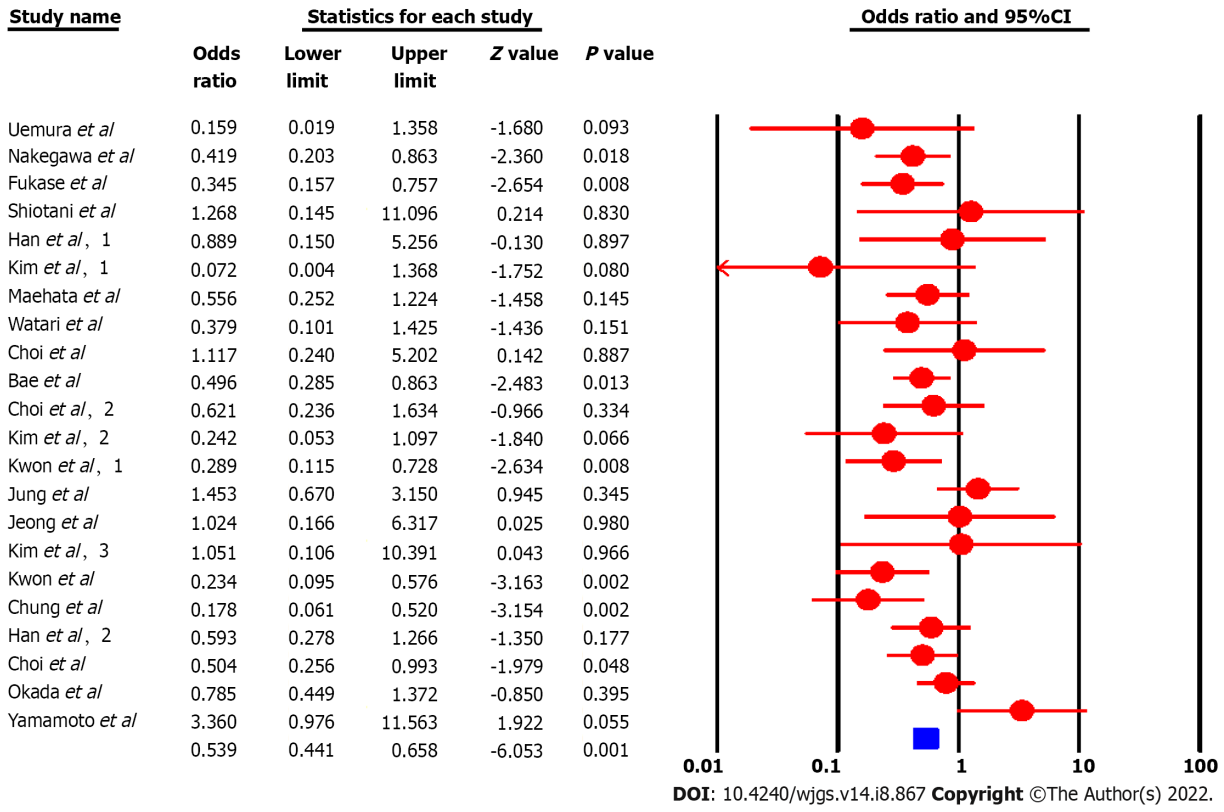

Figure 1 Forest plot for incidence of metachronous gastric cancer between *Helicobacter pylori*-eradicated group and non-eradicated group in 23 studies. 95%CI: 95% confidence interval.

method. The potential study bias was assessed by the Egger's test and Begg's test[18,19].

A total of 1753 documents were retrieved during the initial literature search. Finally, we selected 23 articles as eligible articles according to the inclusion criteria[20-42]. The demographic information such as first author, date of publication, country, follow-up years, metachronous lesions, frequency of metachronous recurrence in both eradicated and persistent cases, and references are summarized in Table 1. These studies were conducted during 1997-2019. Of all the studies, 10 were from Korea, and 10 from the Japan. In the current analysis, we evaluated the data of 9233 *H. pylori* positive cases to determine the efficacy of complete eradication in preventing metachronous events.

The frequency of metachronous recurrence in both *H. pylori* extirpated and persistently infected cases was 7.2% (95%CI: 6.4-8.1, $P = 0.01$; $I^2 = 81.68$, $Q = 125.56$, $P = 0.01$; Egger's $P = 0.08$, Begg's $P = 0.05$) and 17.7% (95%CI: 16.1-19.5, $P = 0.01$; $I^2 = 92.68$, $Q = 314.26$, $P = 0.01$; Egger's $P = 0.01$, Begg's $P = 0.54$), respectively.

According to the statistical analysis, there is an inverse relation between *H. pylori* elimination and metachronous recurrence (OR = 0.53, 95%CI: 0.44-0.65, $P = 0.01$; $I^2 = 39.22$, $Q = 34.55$, $P = 0.03$; Egger's $P = 0.08$, Begg's $P = 0.09$). We showed that the eradication of *H. pylori* can significantly reduce the risk of metachronous recurrence (Figure 1).

Although most of included studies had not investigated the positive effect of *H. pylori* eradication in reducing MGC in each location of the stomach, in patients with *H. pylori* eradication, the risk of MGC was significantly associated with other conditions such as severity of corpus atrophy and intestinal metaplasia[21-23,27,39,40]. However, Han *et al*[39] showed that antrum/body atrophy and old age can meaningfully increase the risk of metachronous cancer after *H. pylori* eradication[24]. In some studies, there was no significant relationship between this cancer and the eradication of *H. pylori*[26,31,36].

Gastric cancer is one of the most prevalent cancers worldwide, especially in East Asian countries; today, the incidence of secondary gastric cancer after ER has become a major public health concern[34]. Unfortunately, in some cases, the eradication of *H. pylori* has not been able to prevent MGC in patients with ER. In general, the clinical eradication of *H. pylori* seems to be effective in preventing secondary gastric cancer and improving quality of life and survival of patients with gastric cancer[43]. In the present study, using data from 9233 *H. pylori* positive cases, we showed an inverse association between the elimination of *H. pylori* and progression to MGC in patients with a record of ER. In previous studies, we have shown that eradicating *H. pylori* in patients with gastric ulcers can reduce the risk of gastric cancer[44]. In general, it is suggested that eradicating *H. pylori* after primary gastric cancer can reduce the risk of MGC and increase survival in gastric cancer population[15,34,45].

Table 1 Characteristics of included studies

First author	Country	Year	Follow-up years	Metachronous lesions	*H. Pylori* positive samples	Frequency		Mean age (yr)		Gender		Antrum/body/cardia		Ref.
						Eradicated	Persistent	Eradicated	Persistent	Eradicated (M/F)	Persistent (M/F)	Eradicated	Persistent	
Uemura	Japan	1997	3 years	EGC	132	1/65	6/67	69.4	68.7	47/18	49/18	48/24/3	42/31/2	[20]
Nakagawa	Japan	2006	2 years	EGC	2825	8/356	129/2469	NA	NA	NA	NA	NA	NA	[21]
Fukase	Japan	2008	3 years	EGC	505	9/255	24/250	68	69	195/60	191/59	130/96/29	114/103/33	[22]
Shiotani	Japan	2008	24-48 mo	EGC	91	9/80	1/11	66		82/18		NA	NA	[23]
Han	Korea	2011	18-57 mo	EGC	116	4/94	2/22	70		NA	NA	NA	NA	[24]
Kim	Korea	2011	60 mo	EGC	55	0/28	5/27	62	60	19/10	17/9	14/10/4	15/7/5	[25]
Maehata	Japan	2012	3 years	EGC	268	15/177	13/91	68	72	128/49	66/25	70/91/16	34/48/9	[26]
Watari	Japan	2012	1 year	ER	185	3/79	10/106	NA	NA	NA	NA	NA	NA	[27]
Seo	Japan	2012	27 mo	EGC	74	0/61	0/13	NA	NA	NA	NA	NA	NA	[28]
Kim	Korea	2014	12 mo	EGC	156	2/49	16/107	59	64	39/10	73/34	39/7/3	90/12/5	[29]
Bae	Korea	2014	60 mo	EGC/dysplasia	667	34/485	24/182	62	64	380/105	145/37	NA	NA	[30]
Choi	Korea	2014	36 mo	EGC	880	10/439	17/441	59	61	291/148	305/136	325/101/13	313/113/15	[31]
Kwon	Korea	2014	3 years	EGC	283	10/214	10/69	61	60	141/73	49/20	197/10/7	63/4/2	[32]
Jung	Korea	2015	42 mo	EGC/dysplasia	675	10/169	21/506	NA	NA	NA	NA	NA	NA	[33]
Jeong	Korea	2015	NA	EGC	148	3/88	2/60	NA	NA	NA	NA	NA	NA	[34]
Kim	Korea	2016	30 mo	EGC	162	3/120	1/42	64	67	86/34	29/13	75/35/10	23/14/5	[35]
Ami	Japan	2017	53 mo	EGC	226	0/212	0/14	69		NA	NA	NA	NA	[36]
Kwon	Korea	2017	47 mo	EGC/dysplasia	395	33/368	8/27	NA	NA	NA	NA	NA	NA	[37]
Chung	Korea	2017	61 mo	EGC/dysplasia	185	17/167	7/18	67		NA	NA	NS	NA	[38]
Han	Korea	2017	60 mo	EGC	408	12/212	18/196	61	61	165/47	144/52	133/70/9	136/50/10	[39]
Choi	Korea	2018	5.9 years	EGC	396	14/194	27/202	59	59	141/53	157/45	160/25/9	166/27/9	[40]
Okada	Japan	2019	2 years	ESD	348	27/174	33/174	65	65	129/45	133/41	45/66/68	49/66/64	[41]
Yamamoto	Japan	2019	31.7 mo	Dysplasia	53	12/17	15/36	67	67	14/3	28/8	6/11/1	15/18/3	[42]

ESD: Endoscopic submucosal dissection; EGC: Early gastric cancer; ER: Endoscopic resection; *H. pylori*: *Helicobacter pylori*; NA: Not available.

Unfortunately, there is no detailed information about the location of the stomach where the reduction of gastric cancer can be achieved after *H. pylori* eradication. Therefore, in future studies, more research should be done on the recent puzzle.

FOOTNOTES

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LETTER TO THE EDITOR

Risk prediction of common bile duct stone recurrence based on new common bile duct morphological subtypes

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Abstract

Stones in the common bile duct (CBD) are reported worldwide, and this condition is majorly managed through endoscopic retrograde cholangiopancreatography (ERCP). CBD stone recurrence is an important issue after endoscopic stone removal. Therefore, it is essential to identify its risk factors to determine the necessity of regular follow-up in patients who underwent endoscopic removal of CBD stones. The authors identified that the S and polyline morphological subtypes of CBD were associated with increased stone recurrence. New morphological subtypes of CBD presented by the authors can be important risk predictors of recurrence after endoscopic stone removal. Furthermore, the new morphological subtypes of CBD may predict the risk of residual CBD stones or technical difficulty in CBD stone removal. Further studies with a large sample size and longer follow-up durations are warranted to examine the usefulness of the newly identified morphological subtypes of CBD in predicting the outcomes of ERCP for CBD stone removal.

Key Words: Endoscopic retrograde cholangiopancreatography; Common bile duct stone; Stone removal; Recurrence; Common bile duct morphology; Risk prediction

Core Tip: It is important to identify the risk factors associated with the recurrence of common bile duct (CBD) stones after endoscopic treatment as it helps determine the necessity of regular follow-up in patients who underwent endoscopic CBD stone removal. CBD morphology can be an important predictor of stone recurrence after endoscopic stone removal. Further studies with a large sample size and a longer follow-up period are warranted to examine the efficacy of the new CBD morphological subtypes presented by the authors for predicting endoscopic retrograde cholangiopancreatography outcomes after CBD stone removal.

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TO THE EDITOR

We read with interest the retrospective cohort study by Ji *et al*[1]. In their study, the authors presented that the morphologies of the common bile duct (CBD), especially the S and polyline types, were associated with increased recurrence of CBD stones. Identifying the risk factors for recurrence after endoscopic stone removal is important to determine the necessity of regular follow-up examination for patients who underwent endoscopic removal of CBD stones.

Several studies have reported the risk factors of CBD stone recurrence after endoscopic treatment[2-6]. To the best of our knowledge, this is the first study to demonstrate that CBD morphology can be associated with CBD stone recurrence after endoscopic treatment. The new morphological subtypes of CBD presented in this study can be important predictors of the risk of CBD stone recurrence after endoscopic CBD stone removal.

Several aspects of this study need to be discussed. First, the recurrence of cholesterol CBD stones, which account for 10% of all CBD stones[7], was not evaluated in this study because CBD stones reported in this study were diagnosed using abdominal computed tomography. Furthermore, the follow-up protocol for evaluating stone recurrence was unclear. Second, CBD morphology was evaluated using a cholangiogram from an endoscopic nasobiliary drainage (ENBD) tube; however, evaluating CBD morphology using magnetic resonance cholangiopancreatography before endoscopic treatment may be a better option as the shape of the ENBD tube may affect the CBD morphology. Third, the new CBD morphological subtypes suggested by the authors may be useful for predicting residual stones after endoscopic removal as the CBD morphology may be responsible for the technical difficulties associated with endoscopic CBD stone removal. Finally, the authors' new CBD morphological subtypes were not risk predictors of multiple stone recurrence in this study, which included a small sample size and a short follow-up period of 19 mo; however, the author's new CBD morphological subtypes may have the potential to predict multiple stone recurrence. Therefore, further studies with a larger sample size and a longer follow-up period are warranted to investigate the usefulness of the new CBD morphological subtypes for predicting the outcomes of endoscopic retrograde cholangiopancreatography for endoscopic CBD stone removal.

FOOTNOTES

Author contributions: Saito H wrote the letter; Tada S revised the letter.

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