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

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REVIEW

From advanced diagnosis to advanced resection in early neoplastic colorectal lesions: Never-ending and trending topics in the 2020s

Francesco Auriemma, Sandro Sferrazza, Mario Bianchetti, Maria Flavia Savarese, Laura Lamonaca, Danilo Paduano, Nicole Piazza, Enrica Giuffrida, Lupe Sanchez Mete, Alessandra Tucci, Sebastian Manuel Milluzzo, Chiara Iannelli, Alessandro Repici, Benedetto Mangiavillano

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Abstract

Colonoscopy represents the most widespread and effective tool for the prevention and treatment of early stage preneoplastic and neoplastic lesions in the panorama of cancer screening. In the world there are different approaches to the topic of colorectal cancer prevention and screening: different starting ages (45-50 years); different initial screening tools such as fecal occult blood with immunohistochemical or immune-enzymatic tests; recto-sigmoidoscopy; and colonoscopy. The key aspects of this scenario are composed of a proper bowel preparation that ensures a valid diagnostic examination, experienced endoscopist in detection of preneoplastic and early neoplastic lesions and open-minded to upcoming artificial intelligence-aided examination, knowledge in the field of resection of these lesions (from cold-snaring, through endoscopic mucosal resection and endoscopic submucosal dissection, up to advanced tools), and management of complications.

Key Words: Colorectal lesions; Colorectal tumor; Endoscopic submucosal dissection; Endoscopic mucosal resection; Cold-endoscopic mucosal resection; FTRD®; Complications; Adverse events; Polypectomy

Core Tip: Appropriate bowel preparation is related with valuable outcomes in colorectal cancer screening. Artificial intelligence may represent an adjunctive methodology for standardizing endoscopy practice. Cold snare polypectomy emerged as a new approach for resection of superficial benign lesions. Endoscopic submucosal dissection has been widely recognized as an indispensable procedure for early superficial neoplastic lesions able to avoid unnecessary major surgery. Advanced techniques such as full-thickness resection and non-thermal avulsion represent valid tools for recurrent/non-lifting lesions.

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INTRODUCTION

Colonoscopy represents the most widespread and effective tool for the prevention and treatment of early stage preneoplastic and neoplastic lesions in the panorama of cancer screening. In the world there are different approaches to the topic of colorectal cancer (CRC) prevention and screening: different starting ages (45-50 years); different initial screening tools such as fecal occult blood with immunohistochemical or immune-enzymatic tests; recto-sigmoidoscopy; and colonoscopy.

The key aspects of this scenario are composed of a proper bowel preparation that ensures a valid diagnostic examination, an experienced endoscopist in the detection of preneoplastic and early neoplastic lesions and open-minded to upcoming artificial intelligence aided examination, know-how in the field of resection of these lesions [from cold-snaring, through endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), up to advanced tools], and management of complications.

BOWEL PREPARATION: WHICH BOWEL PREPARATION IS INDICATED FOR A QUALITY COLONOSCOPY?

Appropriate bowel preparation is crucial for a high-quality colonoscopy that is associated with favorable patient outcomes in CRC screening[1]; conversely inadequate preparation makes necessary to repeat the procedure with significant costs[2]. The updated 2019 European Society of Gastrointestinal Endoscopy (ESGE) guidelines provide practical advice on different aspects of bowel preparation as additional evidence on efficacy and safety of laxative and with a focus on diet, timing, type of laxative,

as well as patient information and specific scenarios[3].

Laxatives can be classified into high-volume solution (≥ 3 L) with polyethylene glycol (PEG) and low-volume solution (< 3 L) that includes PEG solution plus adjuvants such as ascorbate, citrate or bisacodyl, magnesium citrate with sodium pico-sulphate solution, and oral sulfate solution. The use of oral sodium phosphate is not recommended for the risk of acute kidney injury and alteration of electrolyte balance[4].

The optimal timing for administration of laxatives is a split-dose regimen because it improves bowel cleanliness[5,6], regardless of the type and dose of the cleansing agent. A "same day" regimen is provided only for an endoscopic procedure in the afternoon[7,8]. Furthermore, the last dose has to be started within 5 h of the colonoscopy[9,10] and to be completed 2 h before the procedure because an inverse correlation has been observed between the degree of mucosal cleanliness, the time of the last dose of bowel preparation, and the start of the colonoscopy[11].

Several metanalysis and randomized head-to-head trial compared bowel preparations to determine efficacy of laxatives. Low volume solutions have shown a noninferior efficacy for bowel cleansing compared with PEG high volume solutions[12-14] and have improved tolerability[15,16] and compliance[17,18]. The use of PEG agents or non-PEG agents have been validated for routine bowel preparation, but the choice of laxative should be individualized.

PEG high volume solution is contraindicated in patients with congestive heart failure (New York Heart Association III-IV). Maintaining iso-osmolar bowel lumen content is considered safe in renal failure and pre-existing electrolyte imbalance[19,20]; instead, low volume solutions are osmotically active, so they are not recommended in patients with congestive heart failure, severe renal insufficiency, ascites, and altered electrolyte homeostasis[21]. Furthermore, low volume solutions plus ascorbate or aspartame are contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency and phenylketonuria[22].

Other highlights of the clinical practice guidelines concern low fiber diet, associated with a higher willingness to repeat bowel preparation and better tolerability compared with a clear liquid diet[23-25] and use of bowel solution plus oral simethicone, associated with better bowel cleanliness and adenoma detection rate[26,27]. Prokinetic agents and enemas do not improve mucosal cleanliness[28-30].

The updated 2019 ESGE guidelines provide a focus on specific categories of patients. PEG high volume solutions with split-dose regime are preferred in elderly patients. However, the evidence does not allow a recommended specific solution[31]. There is insufficient evidence to suggest a special regimen or supplemental treatment for patients with chronic constipation[32,33]. In pregnant and lactating patients, if colonoscopy is strongly indicated[34], the use of PEG solutions or tap water enemas for sigmoidoscopy may be considered.

A special setting concerns patients with inflammatory bowel disease that could have a clinical exacerbation after colonoscopy with particular bowel preparations[35] and patients without colitis that could have a mucosal inflammation with sodium phosphate or sodium pico-sulphate solutions compared to PEG[36] solutions with a misdiagnosis of inflammatory bowel disease. Therefore, high or low volume PEG agents are recommended in this category of patients. In patients with lower gastrointestinal bleeding PEG high volume solutions are indicated for bowel preparation[37,38]. There is insufficient evidence about the use of low volume solutions, but preliminary results are encouraging[39].

Finally, which bowel preparation is indicated for a quality colonoscopy? ESGE defines evidence about efficacy and safety of different bowel preparation for screening colonoscopy and in particular categories of patients. Therefore, the clinician has to indicate the better solution following the guidelines and their clinical judgement.

EMR: THE STATE OF ART

EMR is a minimally invasive, organ-sparing endoscopic technique developed for removal of sessile or flat neoplasm confined to the superficial layers (mucosa and submucosa) of the gastrointestinal (GI) tract. Originally described by Deyle *et al*[40] as early as 1973, it has become sophisticated and widely used by many others since then. EMR is typically used for the en bloc and piecemeal removal of lesions smaller and larger than 2 cm, respectively[41]. Piecemeal EMR for large polyps is associated with moderate rates of recurrent adenoma (16% in a large prospective study), but these recurrent lesions can be removed at surveillance colonoscopy with a high success rate of 93%[42,43]. Flat lesions are difficult to capture and to resect with the snare. EMR addresses these issues as the injection of saline with or without adrenaline in close proximity to the lesion. The failure of the lesion to elevate after injection ("non-lifting sign") indicates that the tumor has invaded the muscle wall. Depressed lesions tend to have increased likelihood of submucosal invasion. This results in earlier microscopic dissemination and lymph node metastasis[44,45].

Indications

EMR has become a standard treatment for early GI cancers without regional lymph node metastasis because of its minimal invasiveness and excellent long-term survival comparable to surgical resection

[46-48]. The appropriate indications of EMR include: lesions that are type 0-IIa, less than the 2 cm; type 0IIb, less than 1 cm; type 0-IIc, less than 1 cm; or well-differentiated or moderately differentiated tumors confined to the mucosa. If cases of suspected superficial invasive carcinoma is indicated, then en bloc EMR can be performed if the lesion is ≤ 20 mm[49].

Technique

EMR can be subdivided into injection-assisted EMR, cap-assisted EMR (EMR-C), ligation-assisted EMR, EMR after circumferential precutting, and underwater endoscopic mucosal resection (UEMR).

Injection-assisted EMR

EMR can be performed with a polypectomy snare after the lesion has been lifted with a submucosal fluid injection (Figure 1). Conventionally normal saline + epinephrine (1:10000 dilution) + diluted indigo carmine is used as the submucosal injection fluid[50]. In this technique the polyp is raised off the muscularis propria, strangulated, and resected with an electrosurgical snare. Injection-assisted EMR can be further subdivided into "inject-and-cut" technique (using an electrocautery snare through a single-channel endoscope) and the "inject, lift and cut" technique (using grasping forceps to lift the lesion and an electrocautery snare through two separate channels of a double channel endoscope)[51,52].

EMR-C

A transparent plastic cap is preloaded on the endoscope tip. Caps are composed of clear plastic that may be soft or hard. The caps are cylindrical and available with flat circular (straight) or oblique-shaped tips both with outer diameters ranging from 12.9 to 18.0 mm. Oblique cap are used for resection of esophageal lesions, whereas straight caps are most commonly used in the stomach and colon[53]. Inside the cap is a gutter that positions the opened polypectomy snare. After submucosal injection, the cap is pressed against the mucosa, the lesion is aspirated into the cap, and resected (Figure 2). Caution is required in the gastric fundus, duodenum, and ascending colon, where limited thickness of the muscularis propria could result in its entrapment. Use of EMR-C in the colon has been limited for fear of entrapping the muscularis propria into the snare. The advantages of EMR-C are better visualization of the operative field and the possibility of resecting lesions in difficult locations.

Ligation-assisted EMR

EMR can be performed using a standard variceal ligation device (Figure 3) with or without prior submucosal injection. Suction is applied to retract the lesion into the banding device, and a band is deployed to capture the lesion. An artificial polyp is created, and resection is performed with a polypectomy snare. It has been used for minute gastric cancers (5 mm), the diameter of the resected mucosa being 10-15 mm[54,55].

EMR after circumferential precutting

After identifying the target lesion, marking dots are made circumferentially at 5 mm lateral to the margin of the lesion. After marking, a submucosal injection is performed around the lesion to lift it off the muscle layer. A circumferential mucosal incision is performed outside the marking dots to separate the lesion from the surrounding nonneoplastic mucosa. The lesion is removed by a polypectomy snare.

UEMR

UEMR is an alternative method to conventional EMR proposed by Binmoeller *et al*[56] in 2012. Water is injected into the colon instead of gas, thereby avoiding submucosal injection. It is based on the concept that after water immersion, the muscularis propria of the colon remains circular and does not go along with involutions of the folds.

Complications

Bleeding is the most common complication of EMR (4%-38%). Most bleeding is observed during the procedure or within the first 24 h thereafter. It can be controlled by endoscopic treatment, but in cases of delayed bleeding, transfusion, emergency endoscopic evaluation and even surgical procedures may be required. A delayed bleeding rate of 6.7% was reported in a recent multicenter study including > 2000 EMRs[18]. Risk factors for bleeding included the size of the lesion, polyp location in the right colon, and patient comorbidity[57].

Reported perforation rates in EMR are 0.3%-0.5%. In most cases conservative medical treatment is safe after endoscopic treatment. The frequency of perforation after EMR is between 0.4% and 1.3% and depends on the size and location of the resected lesion[58,59].

Outcomes

Many studies have shown that EMR is suitable for removing the majority of nonmalignant colonic polyps[60,61]. EMR is safe and effective compared to surgery. In one meta-analysis from 50 studies included 6442 patients and 6779 polyps, technical success rate of EMR was 90.3% [95% confidence

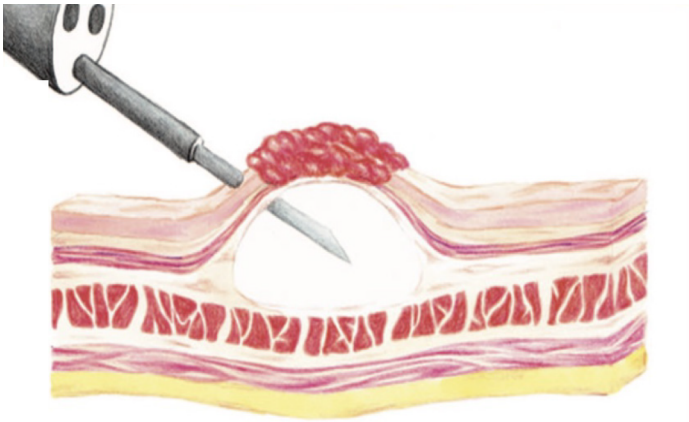

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Figure 1 The submucosal injection.

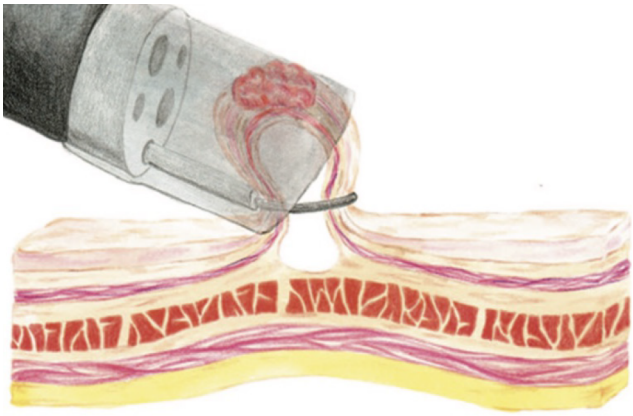

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Figure 2 The cap-assisted endoscopic mucosal resection technique.

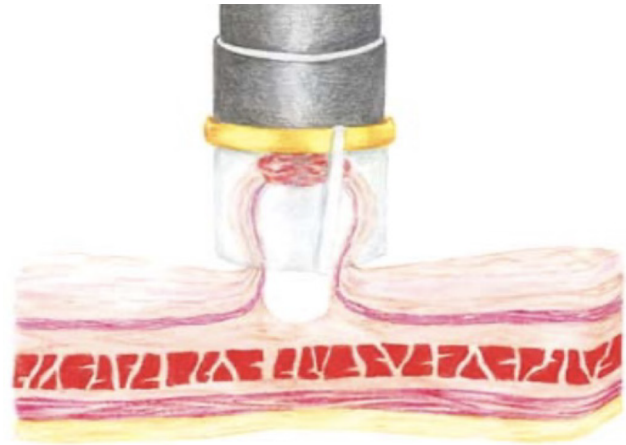

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Figure 3 "Suck-and-ligate" technique. The lesion has been aspirated into the variceal ligating device.

interval (CI): 88.2% to 92.5%]; mortality was 0.08% (95%CI: 0.01% to 0.15%)[62].

There are no randomized trials comparing the inject-and-cut technique with EMR-C. Given the complications profile and the high eradication rate reported by Kashani *et al*[63], EMR-C can be considered in high experienced centers for flat lesions when standard EMR cannot be attempted. Curcio *et al*

[64] demonstrated that UEMR could be safely performed by endoscopists skilled in EMR with no prior training in UEMR. A recent meta-analysis compared the effectiveness and safety of underwater *vs* conventional EMR for colorectal polyps[65]. There were a total of 1382 patients with 1511 polyps, including 722 patients who received UEMR and 789 who received EMR. In the UEMR and EMR groups, the en bloc resection rate was 85.87% and 73.89%, respectively, with a relative risk (RR) value of 1.14 (95%CI: 1.01-1.30; $P < 0.05$). A statistically significant difference was found between the EMR and UEMR groups for polyps equal to or greater than 20 mm in diameter. The post-endoscopic resection recurrence rates at 3-6 mo of the UEMR and EMR groups were 3.26% and 15.17%, respectively, with an RR value of 0.27 (95%CI: 0.09-0.83; $P < 0.05$). The post-endoscopic resection recurrence rates of UEMR and EMR at 12 mo were 6.25% and 14.40%, respectively, with an RR value of 0.43 (95%CI: 0.20-0.92; $P < 0.05$). Additionally, the incidence of adverse events was 8.17% and 6.21%, respectively, with an RR value of 1.07 (95%CI: 0.50-2.30; $P > 0.05$).

SMALL POLYPS AND COLD SNARING

The latest ESGE guidelines recommend cold snare polypectomy (CSP) as the preferred technique for removing diminutive polyps (size ≤ 5 mm), given the high percentages of complete resection, adequate tissue sampling for histology, and low complication rates. CSP for small sessile polyps (6-9 mm) is only suggested because evidence comparing efficacy with hot snare polypectomy (HSP) is lacking[41]. However, emerging data from recent literature are increasingly supporting the use of CSP for small polyps not only for the better safety profile compared to HSP but also for its comparable effectiveness in terms of complete resection.

The goal of the polypectomy is the removal of the entire polyp, ideally with a rim of normal tissue and in a single piece, with a low adverse event rate[66]. The optimal approach to CSP requires the polyp placement at the 5 to 7 o'clock position in order to match the location of the accessory channel of the scope and to maintain a short distance from the polyp[66]. There are at least two techniques that can be used for CSP: the snare tip can be anchored to the normal mucosa at the proximal edge of the polyp, the snare is then slowly opened so that the remainder of the polyp is surrounded by the snare; or the snare can be fully opened above the polyp and then laid down flat against the mucosa. At this point the snare is slowly closed to grasp and resect the lesion[66]. Before closing the snare, it is essential to ensure a margin of normal tissue of at least 2 mm to increase the R0 resection rate, defined as en bloc resection with pathologically negative resection margins.

Abe *et al*[67] compared extended CSP (with more than 1 mm resection margin) to conventional CSP, showing that the R0 resection rate was significantly higher in the extended CSP group [439/449 (98%)] than in the conventional one [222/263 (84%), $P < 0.001$]. The main challenge associated with the use of CSP is when the snare fails to cut through the polyp. This can be rescued by gently pulling the snare into the accessory channel of the colonoscope, to maximize force transmission down the snare wire. As an alternative, the snare can be slightly opened and closed again to release entrapped submucosa[66, 68]. Pale protrusions within the cold snare defect are episodically observed after CSP. The only variable that has been found to be associated with cold snare defect is a polyp size ≥ 6 mm. These protrusions often contain muscularis mucosae and submucosa but not residual neoplastic tissue. Therefore, no further treatment is required[69]. The mainstay of cold snaring is the mini snare, measuring 9 to 15 mm in opening diameter[70]. Horiuchi *et al*[71] compared cold snaring of small colorectal polyps by using a snare specifically designed for cold snaring and a traditional polypectomy snare designed for use with electrocautery. The resection was considered histologically complete if vertical and lateral margins were free of neoplastic tissue. The complete resection rate in the dedicated cold snare group was significantly higher than that in the traditional one (91% *vs* 79%; $P = 0.015$). The difference was most prominent for polyps 8 to 10 mm in size (83% *vs* 45%). Moreover, Makino *et al*[72] demonstrated that the use of dedicated cold snares resulted in a significantly lower rate of injuries to the arteries located in the submucosal layer when compared to the use of traditional snares [4.1% (4/98) *vs* 16% (17/105); $P = 0.009$].

The CRESCENT study compared the rate of complete resection of small sessile polyps between CSP and HSP in a multicenter randomized controlled trial (RCT) using the same traditional snare in both groups. Complete resection was defined by negative biopsy results from specimens obtained from the resection margin after polypectomy. The authors showed a comparable rate of complete resection for CSP and HSP (98.2% *vs* 97.4%, respectively)[73]. A meta-analysis of RCTs compared the incomplete resection rate between CSP and HSP when removing polyps between 4 and 10 mm in size. Incomplete resection rate was defined as the presence of any residual polypoid tissue in post-polypectomy biopsied specimens. Three RCTs and 1266 polyps were included in the final analysis with 630 polyps in the HSP group and 636 polyps in the CSP group. The difference in incomplete resection rate between HSP and CSP was not statistically significant [2.4% (15/630) and 4.7% (30/636), respectively][74]. The use of narrow-band imaging with magnification for the precise evaluation of a lateral neoplastic extent was found to be an independent predictor for R0 resection[75]. On the other hand, performance of the CSP by trainees was found to be an independent risk factor for incomplete polyp resection[76]. Moreover,

histopathological positive margin was found to be the only risk factor for recurrence[77].

By omitting electrocautery, cold resection avoids the risk of thermal injury to the colon wall, which can lead to post-polypectomy syndrome, perforation, or delayed bleeding. A better safety profile for CSP has been reported in several studies in terms of procedure time and post-polypectomy abdominal symptoms[78-80]. Delayed post-polypectomy bleeding is defined as bleeding occurring between 24 h and 30 d after polypectomy. The incidence of delayed post-polypectomy bleeding for CSP ranges from 0% to 1.8% in prospective studies[81]. Most of the RCTs comparing CSP and HSP have failed to demonstrate the superiority of CSP to reduce the risk of post-colonoscopy bleeding[82], probably due to small sample size.

Chang *et al*[83] compared the risk of delayed bleeding in a high-volume screening colonoscopy setting before and after universal implementation of CSP for resecting polyps < 10 mm. A total of 1822 and 1850 colorectal polyps were removed in CSP and HSP, respectively. The CSP cohort had significantly lower rates of bleeding, need for second-look colonoscopy, severe bleeding and Emergency Services visits compared with the HSP group[83]. In support of CSP safety, studies conducted on patients taking antithrombotic therapy showed that the use of single or even multiple antithrombotic agents did not increase the risk of delayed bleeding after CSP[84,85].

A prospective randomized comparison of CSP and HSP in anticoagulated patients showed a significant increase in delayed bleeding after HSP compared with CSP [14% (5/35) *vs* 0% (0/35); P = 0.027]. Moreover, injured submucosal arteries were seen significantly less frequently after CSP than after HSP (22% *vs* 39%; P = 0.023)[20]. While the RCTs failed to demonstrate the lower incidence of delayed bleeding after CSP compared to HSP, they showed higher rates of immediate bleeding after CSP than HSP[75,86]. Immediate bleeding is defined as spurting or oozing that lasts more than 30 s. The risk factors that were identified as being significantly and independently associated with the risk of immediate bleeding after CSP were polyp location in the rectum, polyp size ≥ 6 mm, polypoid growth pattern. and antithrombotic agent use[78,79]. However, the risk of immediate bleeding requiring treatment was not increased by CSP as compared with HSP[86].

In conclusion, CSP is a time-saving technique for the removal of small polyps (6-9 mm) with comparable effectiveness and safety to HSP. However, some issues need to be further addressed. Large-scale RCTs are needed to assess the superiority of dedicated cold snare to the traditional one. Large-scale RCTs with adequate sample size enrolling a general screening population are still warranted to confirm the lower rate of delayed bleeding after CSP compared with HSP. Large, multicenter long-term studies are needed to assess the recurrence rate when comparing the two techniques for the removal of small colorectal polyps.

ESD: THE STATE OF ART

ESD is a minimally invasive technique developed in Japan (its first appearance dates to 1988)[87] to overcome limitations of standard endoscopic resection techniques and to achieve higher en bloc and R0 resection rates in removing superficial GI tumors, regardless of their size and location[88].

ESD was initially introduced as a therapeutic option for early gastric cancer[89], but later its indications were broadened to include esophageal and colorectal lesions[90,91]. The colon-rectum ESD was shown to be an effective choice for managing difficult-to-resect lesions when en bloc resection is essential for an accurate pathologic assessment and for residual or recurrent colorectal adenomas[92].

While in Japan and Asian countries ESD has progressively become the standard method for endoscopic resection of large superficial lesions in any GI segment, its spread in Western countries has been slower[93]. Some of the reasons of this discrepancy include the underestimation of the need and benefit for ESD (*e.g.*, no need of short follow-up endoscopy like EMR), the bias of medical and surgical oncologists toward surgical resection, the propensity of endoscopists toward EMR, a slow learning curve, the need of high-level expertise to select appropriate lesions, the longer procedural time, the higher rate of adverse events compared to EMR, and finally the lack of proper training programs compared to Eastern countries[94]. Despite these limitations, the experience with ESD in Western countries has recently grown, mainly at tertiary referral centers.

Indications

The feasibility and the effectiveness of ESD is strictly linked to the proper selection of suitable lesions and the prediction of invasiveness. Specific factors able to predict the risk of nodal dissemination and need for surgery have been highlighted. Some of these factors are endoscopy-based and have to be evaluated at index examination: lesion diameter; lesion shape defined by Paris classification[95]; and mucosal pattern defined by several classifications (Kudo, narrow-band imaging international colorectal endoscopic, Japan narrow-band imaging expert team)[96-98].

In addition to the morphology and pattern of the lesions, in CRC we must always take into consideration the site of the lesion. In fact, lesions with the same morphology may have a higher risk of harboring early cancer if located in the left colon or rectum compared to other parts of the colon[99]. Furthermore, regarding the rectum and in particular the lower/middle rectum, we must consider the

greater complexity of the standard surgical alternative if endoscopic resection results are non-curative. Therefore, the en bloc resection for the lesion suspected of submucosal invasion should be mandatory, especially in the rectum (Figure 4). Therefore, the choice of ESD is tightly linked to the identification of lesions that actually require an en bloc resection. When the likelihood of submucosal invasion is high, especially for lesions larger than 20 mm, en bloc resection using ESD allows the most accurate pathology staging with a high chance of curative resection[100] (Table 1). ESD is also indicated to remove lesions that are technically difficult to treat with the conventional technique, which includes those that are non-lifting after submucosal injection and local recurrence after previous treatments (Figure 5).

Technique

To date ESD is a well-established technique. Unlike a few years ago, various types of ESD devices are currently available. In principle, familiarizing yourself with one of these is sufficient to complete most of the procedures. Occasionally, the combined use of different devices can improve dissection efficiency. It therefore remains essential to know the different types of knives and how they work as well as the advantages and disadvantages of each.

There are three popular groups of devices, namely the needle type, the insulated tip type, and the clamp type[101] including in the first group the Hybrid-Knife by ERBE. Using a needle knife with a water-jet function, such as the Dual-Knife J, Flush Knife or similar, or Hybrid Knife with water-jet-surgery system is very useful because it enables repeated submucosal injection without changing the injection needle[102]. Other knives such as the Hook-Knife or insulated tip knife-nano can be very useful to make colonic ESDs safer and increase dissection speeds. Hook-shape knives in general enable resection of the submucosal tissue, while pulling up on it is useful. For instance, in situations of severe fibrosis or perpendicular access to the cutting line the hook-shape knife allows tissue grasping and safe cutting far from muscular layer[103]. Insulated tip knives have an insulated ceramic tip at the end of the blade, which theoretically can prevent perforation[104]. Furthermore forceps-type knives are forceps-like devices that allow grasping before cutting so that the quality of the tissue bite can be assessed before cutting, and usually no coagulation forceps are needed during the procedure[105].

Several strategies are known to perform en bloc resection of a lesion with this technique. Basically, the direction of dissection should be parallel and horizontal rather than tangential[106]. Tangential or perpendicular approaches to the colonic wall raise the risk of perforation. Hence, we have to reach and keep an orientation whereby the endoscope is in line with the bowel wall rather than facing it end-on. Moreover, the line of dissection is important because though the risk of perforation is higher if the dissection is too close to the muscle layer, dissecting too superficially may damage the specimen, compromising the histopathological assessment[107].

ESD widely differs from the more common EMR, but it involves the injection of a substance under the targeted lesion to create a safety cushion before starting the mucosal incision with a dedicated knife [108]. Then, various approaches have been described. In the so called "standard ESD or conventional methods" an initial mucosal incision is made approximately 5-10 mm from the distal side of the lesion to expose the submucosal layer. As another option, initial mucosal incision can be started from the proximal side, and the procedure can be done in retroflexion if a good plane and a stable position can be maintained. A further possibility is to complete the mucosal incision circumferentially around the lesion and then begin the submucosal dissection.

A crucial step is represented by the insertion of the distal attachment under the exfoliated mucosa of the lesion side for safely and effectively dissecting the submucosal layer[109]. Submucosal dissection is started by the knife from the center toward the side of the submucosal space following a catting line between the mucosal and muscular layers. The dissection of the incised area is completed until en bloc resection is achieved[110].

New strategies such as pocket creation method and tunneling ESD were recently introduced to overcome some procedure issues like scope instability and quick dispersion of the injected fluid[111, 112]. In the pocket creation method-ESD, a 20 mm mucosal incision is made around 10 mm from the anal margin of the lesion. Subsequently, the endoscope is inserted into the incision, and submucosal dissection is started. A large submucosal pocket is then progressively created. After that submucosal dissection under the lesion is judged completed by the endoscopist, the remaining mucosa is incised, and the pocket completely open. Several studies have shown that the pocket creation method is associated with higher en bloc resection rate, R0 resection rate, and dissection speed[113].

The tunneling technique is conceptually similar. After an initial small mucosal incision, a submucosal tunnel is created all the way from the anal to oral side[114]. If the lesion is large, multiple small mucosal incisions with more than one tunnel can be made with the aim to connect them, subsequently obtaining a unique pocket under the lesion[115].

Outcomes

According to a recent systematic review and meta-analysis by Zhang *et al*[116], including 12 studies conducted in Asian countries, ESD was compared to EMR in terms of efficacy and safety, showing better results with higher en bloc resection [odds ratio (OR) = 7.06, 95%CI: 3.69-13.50, $P < 0.00001$] and lower recurrence rate (OR = 0.10, 95%CI: 0.05-0.18, $P < 0.00001$). In detail, ESD showed a significantly higher en bloc resection rate for lesions > 2 cm (OR = 9.62, 95%CI: 4.42-20.95, $P < 0.00001$), while no

Table 1 Indications for colon and rectum endoscopic submucosal dissection[95-100]

	Europe	United States	Japan
Colon and rectum	Lesions > 20 mm with high suspicion of limited submucosal invasion:	Submucosally invasive cancer	LST-NG, pseudo-depressed[1]
			Vi-type pit pattern lesions[1]
		Type V Kudo pit pattern	Carcinoma with shallow T1 (SM) invasion[1]
			Large depressed-type tumors[1]
		Paris 0-IIc	Large protruded-type lesions suspected to be carcinoma[1]
	Paris 0–IIa+c or 0–III	Paris (0-Is or 0-IIa+Is)	
	Nongranular surface	Rectosigmoid location	Mucosal tumors with submucosal fibrosis
	Advanced surface pattern	Nongranular LST ≥ 20 mm	Sporadic tumors in IBD
		Granular LST ≥ 30 mm	Local residual/recurrent early carcinomas
	Residual/recurrent lesions	Residual/recurrent adenomas	

[1]Not amenable to *en bloc* resection by endoscopic mucosal resection. IBD: Inflammatory bowel disease; LST: Laterally spreading tumor; NG: Nongranular; SM: Submucosal.

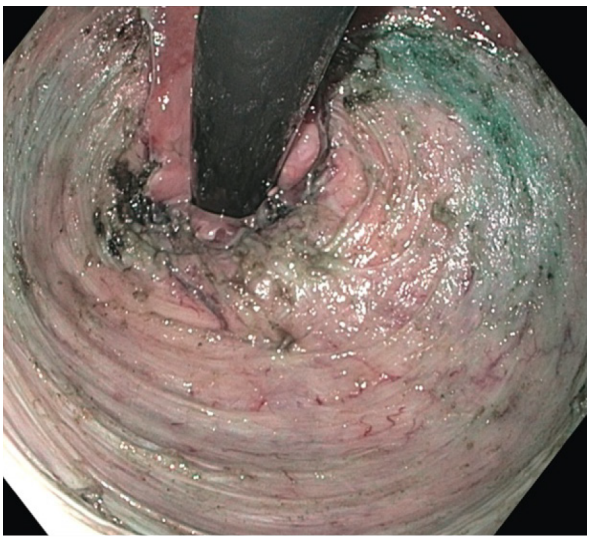

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Figure 4 Rectal endoscopic submucosal dissection.

statistically significance was reached for lesion ≤ 2 cm (OR = 2.16, 95%CI: 0.61-7.58, P = 0.23). Analyzing the safety, ESD showed a higher perforation rate (OR = 4.77, 95%CI: 2.87-7.93, P < 0.00001), while no statistically significance was observed for bleeding between the groups (OR = 1.15, 95%CI: 0.70-1.90, P = 0.59). The procedure time remained longer in the ESD group (standardized mean difference = 1.88, 95%CI: 0.42-3.34, P = 0.01). Similar results were shown in another systematic review and meta-analysis by Chao *et al*[117].

An interesting systematic review and meta-analysis by Fuccio *et al*[118] compared performances of ESD performed in Asian and non-Asian countries, showing that ESD is still failing to achieve acceptable levels of performance in the latter. R0 and en bloc resection rates were significantly lower in non-Asian countries, being 71.3% (95%CI, 66.2%-75.9%) and 81.2% (95%CI: 77.1%-84.7%) *vs* 85.6% (95%CI: 83.3%-87.7%) and 93% (95%CI: 91.4%-94.3%) of Asian countries, respectively. Comparing complications, the need for surgery, delayed bleeding, and perforations were also lower in non-Asian countries, being 3.1% (95%CI: 2.1%-4.7%), 4.2% (95%CI: 1.9%-5.9%), and 8.6% (95%CI: 5.9%-12.2%) *vs* 0.8% (95%CI: 0.6%-1.0%) 2.4% (95%CI: 1.9%-3.0%), and 4.5% (95%CI: 3.9%-5.3%) of Asian countries, respectively.

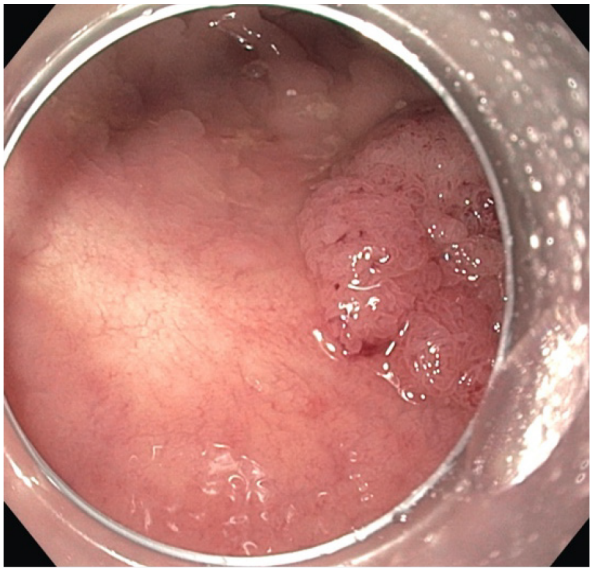

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Figure 5 Endoscopic submucosal dissection as treatment of post-endoscopic mucosal resection recurrence.

RECURRENT, NON-LIFTING, FIBROTIC RESIDUAL COLORECTAL LESIONS: ENDOSCOPIC FULL THICKNESS RESECTION WITH FULL THICKNESS RESECTION DEVICE AND ENDOROTOR

EMR and ESD are two endoscopic minimally invasive techniques usually applied for resection of large polyps of the colon. In cases of difficult location or non-lifting adenomas these approaches become challenging to the endoscopist given the risk of incomplete resection or adverse effects such as bleeding and perforation.

Full thickness resection

As early as 1980 the concept of endoscopic full thickness resection (EFTR) on a rigid system slowly took place from the trans-anal microsurgery for resection of lesions located in the rectum and sigmoid colon. Subsequently, EFTR was adapted to flexible instruments, and in September 2014 the Full Thickness Resection Device (FTRD®; Ovesco Endoscopy AG) was approved for use in Europe. The current major indications for EFTR are recurrent, non-lifting lesions, usually located in difficult sites such as the cecum, appendix, and peri-intra diverticula[119] (Figure 6).

Device description and endoscopic technique

The FTRD is an over-the-scope device used for flexible EFTR. The technique combines a full thickness resection together with closure and cutting of the colonic tissue by the deployment of a modified Ovesco clip. As results the procedure provides an en bloc resection with a full thickness specimen for histopathological assessment. The device is made of a 23-mm cap carrying a modified 14-mm over-the-scope clip with additional lateral teeth for improved tissue hold. A monofilament snare is preloaded in the tip of the cap with its handle running on the outer surface of the scope underneath a plastic sheath.

The procedure consists of a preliminary colonoscopy performed to reach the target lesion. Subsequently, the lesion is marked on the edges with a FTRD marking probe (Ovesco Endoscopy) or Argon Plasma Coagulation (ERBE APC 300, 25 W). For colonic lesions, prOVE CAP (Ovesco Endoscopy), a cap similar in size to the FTRD cap, is anchored on the instrument tip to assess accessibility and feasibility in terms of fitting the entire lesion inside the cap. Then a second colonoscopy is performed using another endoscope with the device mounted, and the lesion is pulled into the cap using the FTRD grasper (Ovesco Endoscopy) until all of the lateral markers are visible inside. The Over-The-Scope-Clip (OTSC) is deployed, and the lesion is resected by means of the preloaded snare.

Indications and size of lesions

FTRD is an endoscopic technique that arises between EMR, ESD, and surgery when these are difficult to apply or in specific settings, especially for patients unfit for surgery. The main indications for EFTR are non-lifting adenomas (primary or recurrence) of a previous polypectomy, small submucosal tumors such as GI stromal tumors or neuroendocrine tumors, adenomas at difficult anatomic sites (appendicular of inside diverticula), and early T1 carcinomas. It is also used for diagnostic workup of neuromotor bowel disorders[120-124].

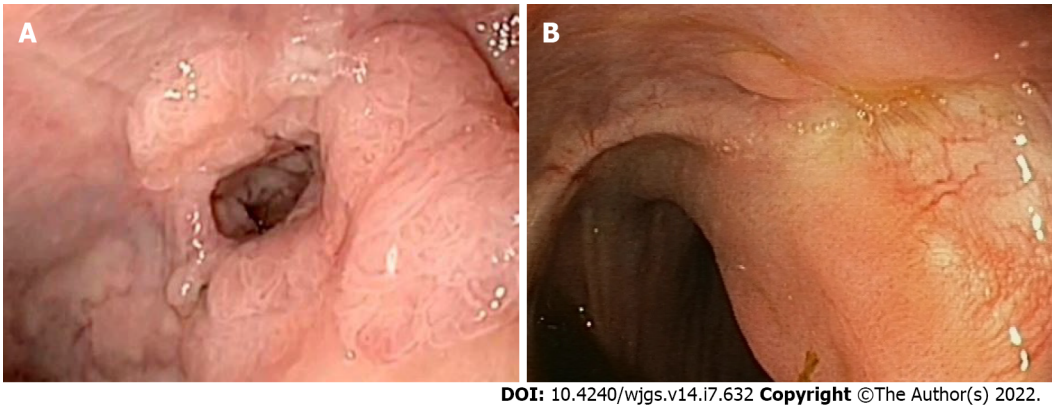

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Figure 6 Laterally spreading tumor granular in perianastomotic diverticula (A) and scar after full thickness resection (B).

Regarding its application in resection of colonic polyps and submucosal lesions, according to the literature, EFTR is usually suitable and indicated for non-lifting lesions ranging from 5 to 25 mm, with an indication of a maximum 20-25 mm in severe scarring, even if polyps up to 40 mm diameter and even larger have been successfully removed[121,125,126].

Efficacy and safety of procedure

The efficacy of the procedure takes into account several parameters: technical success (en bloc resection and macroscopically complete) and R0 resection in terms of histologically complete resection, defined as tumor-free lateral and deep resection margins. Another important parameter is histologically confirmed full-thickness resection (visibility of all layers of the colonic wall including serosa within the resection specimen). The technical resection rate of FTRD ranges from 75% to 100%[127-129].

In a retrospective study, resection was technically successful in 97%[128]. In the WALL RESECT study, the major prospective trial of EFTR, the rate was 89.5%[99]. This probably reflects the heterogeneity and the rate of technically difficult lesions treated in this trial that would have rather been treated surgically. In a recent multicenter Italian experience involving 110 patients the rate of technical success was 94.3%[130]. In a recent meta-analysis, the pooled outcome of technical success was 94% [131].

According to the literature, the R0 resection rate was lower for lesions > 20 mm (86.5%) than for lesions ≤ 20 mm (92.9%)[128]. In the WALL RESECT study, the resection rate was 81.6% for lesions between 10-20 mm and 58.1% for those above 20 mm[124]; the pooled outcome of R0 was 84.9% with significant heterogeneity perhaps attributable to different study design among the studies considered [131].

Complications and limitations of procedure

The reported complications of FTRD are bleeding, perforation, post-polypectomy syndrome indicated as occurrence of fever, abdominal pain, and an increase of white blood count after the procedure, and acute appendicitis. The risk of perforation is very low in expert hands, as reported in a retrospective study (1.4%)[128]. The pooled rates for bleeding and perforation were 2.2% and 0.19%, respectively, with no significant heterogeneity (I^2 = 53%, P = 0.04) in a recent meta-analysis[131]. In the study of Schmidt *et al*[124], 1 case of entero-colonic fistula due to the possible entrapment of small bowel into the clip during the resection procedure was reported.

FTRD appears to be a safe and effective procedure; as with other procedures it shows some limitations. R0 resection rates depend on the center experience, the dimension, site, and visibility of the lesion[120,121,124].

EndoRotor

A new minimally invasive technique is slowly taking place for treatment of recurrent scarred polyps. The EndoRotor device (Interscope medical, Inc. Worcester, MA, United States) is a non-thermal resection technique for benign scarred polyps (Figure 7). It consists of a single use disposable catheter passing though the channel of an endoscope. The catheter has a fixed outer cannula and an inner cannula capable of rotating at 1000 or 17000 rpm. Both cannulas have an orifice that allows suction together with an irrigation system that allows recovery of resected tissue. The fragments are then transported to a tissue trap located on the resection system. Rotation and suction are controlled by two foot pedals, and as a safety measure the cutting stops automatically after 8 s. As with EMR, the injection of the target lesion makes it easier to remove. Sizes of resected specimens vary from 2 to 5 mm, comparable to a sample from biopsy forceps. An improvement in histopathological assessment is due to the absence of thermal artefacts. The first study on animals demonstrated feasibility and safety of this

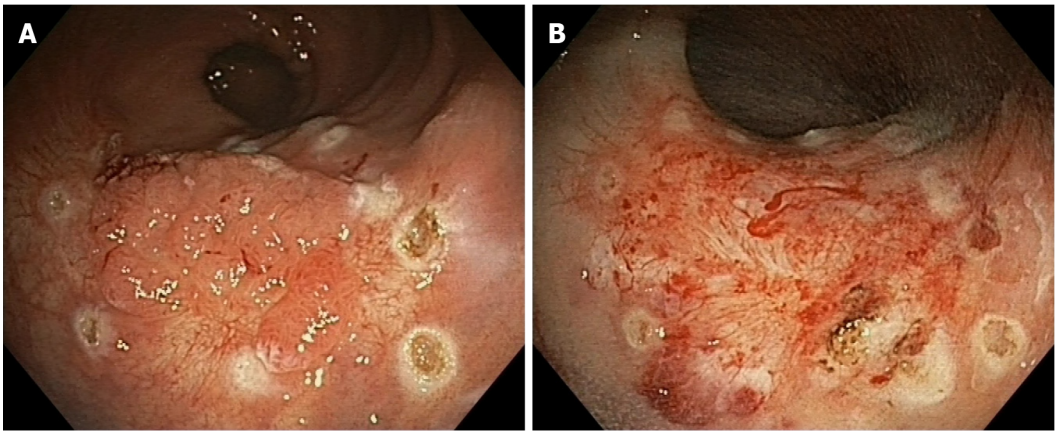

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Figure 7 Scar polyp residue of a large endoscopic mucosal resection (A) and result of EndoRotor treatment (B).

device[132]. EndoRotor has been used in different settings such as the resection of pancreatic walled-off necrosis and treatment of Barrett's esophagus[133,134].

The first pilot study was published in 2019 aiming to evaluate feasibility and safety of EndoRotor in scarred polyps[135]. Complete resection of the polyp was achieved in 84% of 19 patients in one or two sessions. Polyps were located in the rectum or sigma. The procedure was determined to be safe in this study since the only adverse events reported were intraprocedural bleeding in 2 patients that was successfully controlled with coagulation and endoscopic clips. No delayed bleeding or other adverse events have been described despite the small population. A large study[136], with up to 98% technical success and acceptable clinical success (79.2%) has been reported. To date no RCTs exist to compare EndoRotor with other standardized techniques.

In another case report by Tillinger *et al*[137], EndoRotor was used in a 90-year-old man with severe comorbidities, making him unfit for surgery, for the removal of a recurrent scarred big lesion located in the rectum. The only adverse effect was intraprocedural bleeding, successfully treated with adrenaline. In another case report[138], a large lesion with a deep scar was removed combining the ESD and EndoRotor techniques in two sessions. The only adverse event was intraprocedural bleeding controlled successfully with hot biopsy. The control after 3 mo showed no recurrence of the adenoma.

In conclusion, EndoRotor is a new technique with different applications in the GI tract. Its application in a definite setting, such as scarred, recurrent polyps with prior histology and in patients unfit for surgery with no other therapeutic chances, make this technique promising. The use of this nonthermal resection technique has been shown to be safe and feasible with low adverse events despite the lack of literature at the present time. Histopathological assessment can be done without thermal artefacts even though it is impossible to assess complete resection. Limitations of this technique are the difficulty of retroflexion and the required channel of 3.2 mm or more of the endoscope. Another concern regards the length of procedure that can be considerable and the handling of the device when the lesion is tangent to the catheter.

MANAGEMENT OF ADVERSE EVENTS IN COLONOSCOPY

Colonoscopy is usually a safe examination. Adverse events are not frequently reported and include mainly perforation and bleeding. Large studies reported a post-colonoscopy perforation rate of 0.005%-0.008%, rising to 0.6%-5.5% in therapeutic examinations, whereas bleeding rate is described in 0.001%-0.687% of the cases[139]. Risk of adverse events increases with age, comorbidity, and type of procedure and appears to be operator-dependent, decreasing in endoscopy centers with a volume of > 300 colonoscopies per year[140-142].

Perforation is the most feared adverse event because of its high morbidity and considerable mortality [143]. It is a full thickness tissue defect involving all four layers and can be classified on the basis of the cause of injury: thermal; post-polypectomy (more frequent in the right colon); and blunt (more frequent in the left colon)[144,145]. The main reported risks factors for perforation are therapeutic colonoscopy (polypectomy, stricture dilation ,and argon plasma coagulation use), age > 75 years, diverticular disease, previous intra-abdominal surgery, colonic obstruction, and female gender[146]. On the other hand, the use of CO_2 appears to be associated with a 62% decrease in the post-polypectomy admission rate[147]. In about one-third (30%) of the cases, the perforation is recognized during the endoscopic examination and when feasible a proper and timely endoscopic closure allows conservative management and can prevent unnecessary surgery[148].

The ESGE position statement and its recent update (2020) recommends considering endoscopic closure using through-the-scope endoclips for small holes and OTSC for larger ones[149]. Through-the-scope clips are an effective method for closing small post-polypectomy defects and suturing after endoscopic surgery. Their use for closing endoscopic perforations is limited by a small span and a low closure force, confined to the mucosal and submucosal layers. Therefore, they could be inadequate for a full thickness defect[150]. Nevertheless, immediate endoscopic closure of the defect and superficial apposition of the mucosa and submucosal layers seems sufficient to obtain adequate wound healing at the perforation site and to achieve a good nonsurgical outcome.

In the largest retrospective observational case series in Europe describing post-perforation outcomes, endoclips were successfully used to close perforations in 83.3% of cases where the perforation was visualized by the endoscopist[151]. OTSC (Ovesco Endoscopy AG, Tubingen, Germany) was introduced in 2007 and plays an important role for rescue therapy for GI perforation, refractory bleeding, and fistula. It is a nitinol-based clip that is placed over the scope (onto the tip) with a cap. In post-colonoscopy perforation the jaws used are usually blunt, and a successful closure is reported in 84.6%-89.0% of the cases[152].

Voermans *et al*[150] in a prospective multicenter study on 36 acute iatrogenic perforations treated 13 colonic perforations sized up to 3 cm, 8 of which were diagnostic examinations and 5 were therapeutic. They reported a successful closure in 12 out of 13 cases (92%) and 1 case of surgery performed after OTSC unsuccessful placement. Unfortunately, the patient died due to complications[150]. Jayaraman *et al*[153] observed that an effective closure of the perforation could be influenced by its size. They reported a higher successful rate in defects < 10 mm compared to defects > 10 mm (90% *vs* 60%; P = 0.36)[153]. Furthermore, shape of perforation and technique adopted appears to be important to obtain a stable closure. Mangiavillano *et al*[154] in a multicenter retrospective study, used different techniques of OTSC placement according to classification of shape perforation. An oval shape (type 2) was closed with OTSC only by suction and a round shape (type 1) by the twin grasper plus suction. They treated 10 colonic perforations with a technical success rate of 100% and a clinical success rate of 90%.

In addition to technical features and endoscopic solution, the ESGE position statement and its recent update stress another aspect. Adequate colon cleansing is an important factor when considering endoscopic treatment of iatrogenic perforation. If perforation is not promptly recognized, an interval less than 4 h has to be considered still safe and adequate for an endoscopic attempt. Administration of intravenous fluids, broad spectrum antibiotics, and close monitoring of vital signs are strongly recommended in each suspected or diagnosed colorectal perforation. All patients treated conservatively should be observed closely by a multidisciplinary team in the post-procedure period. Larger iatrogenic perforations or patients with failed closure or worsening clinical condition may require immediate surgical repair, preferring mini-invasive laparoscopic approaches[149].

Hemorrhage post-resection of colonic lesions (EMR and polypectomy) is another over-addressed topic in lower GI endoscopy. It may occur immediately or can be delayed for up to 4 wk after the procedure. The rate of bleeding is actually reported as 0.24%. In a recent meta-regression analysis, the percentage of colonoscopies involving a polypectomy strongly predicted rates of bleeding, with a 2.7% increase in risk of bleeding for every 1% increase in rate of polypectomy (P < 0.001). This association remained significant after adjustment for age and gender (P = 0.016)[155]. One of the most relevant risk factors for post-polypectomy bleeding is the size of the polyp[156,157], and other risk factors are the number of polyps removed[158,159], anticoagulant therapy[160,161], polyp location in the right colon, and the histology[162,163]. Patient comorbidities increase the risk for bleeding[164].

The prophylactic use of mechanical methods, such as clips, is commonly performed in practice; however, their efficacy in preventing delayed bleeding has not been totally established. Prospective, randomized studies and a meta-analysis have shown prophylactic clipping for polyps < 2 cm does not prevent delayed bleeding[165-167], but in cases of non-pedunculated polyps > 2 cm, endoscopic clip closure of the mucosal defect has been demonstrated to reduce the incidence of delayed bleeding events in the proximal colon after resection (see and ref to Serious adverse events related to advanced resection techniques, postprocedural bleeding). Injection of epinephrine during submucosal cushion before the resection was reported to reduce the incidence of intraprocedural bleeding, although there was no demonstrated effect on delayed bleeding[168,169]. Finally, a large series of 286 patients, with either upper GI bleeding (n = 214) or lower GI bleeding (n = 72), showed that the over-the-scope clip was used as first-line therapy was a technical success, and primary hemostasis rates were gained in 97.9% and 96.4% of the cases, respectively[170].

ARTIFICIAL INTELLIGENCE: WILL THE TECHNOLOGY BE TO SUPPORT OR TO REVOLUTIONIZE OUR PRACTICE?

CRC is the second and third-leading causes of cancer-related deaths in men and women, respectively [171]. Colonoscopy with complete resection of neoplastic lesions is considered a reliable measure to reduce both the incidence and mortality of CRC[172]. Adenoma detection rate (ADR) is an independent predictor for the risk of interval CRC[173]. Polyps can be missed, with reported miss rates of up to 27%

due to both polyp and operator characteristics[174]. In this field, artificial intelligence (AI) can solve human errors reducing inter-observer variability[175].

Recent trials have evaluated the efficacy of deep convoluted neural network-based AI system in colonoscopy for improving ADR and polyp detection rate[176]. The major roles of computer-aided diagnosis (CAD) for colonoscopy include automated polyp detection and characterization by indicating the presence and location of polyps in real time during colonoscopy by digital video marker or sound [177].

In a recent validation study of AI *vs* experienced endoscopists, the AI system (GI-Genius; Medtronic, Dublin, Ireland) was trained using a series of videos of 2684 polyps from 840 patients who underwent colonoscopy using high-definition white light endoscopy. The study showed that AI anticipated the detection of polyps against the average of the 5 endoscopists in 277/337 cases (82%). Moreover, the study showed a low rate of false-positives, demonstrating the high precision of the AI algorithm with sensitivity and specificity up to 99%[178].

In the first prospective RCT, Wang *et al*[179] investigated the effect of an automatic polyp detection system based on deep learning on polyp detection rate with or without assistance of a real-time automatic polyp detection system. A total of 1058 patients were included, 536 randomized to standard colonoscopy and 522 to CAD colonoscopy. The primary outcome was ADR. This study showed that the AI system significantly increased ADR (29.1% *vs* 20.3%; $P < 0.001$) and the mean number of adenomas per patient (0.53 *vs* 0.31; $P < 0.001$). This effect was mainly due to a higher rate of diminutive adenomas found. There was a total of 39 false positive (false alarm), which may be due to bubbles, stool, undigested debris, or local inflammation[179].

In another study, Mori *et al*[180] evaluated whether CAD may help endoscopists to characterize polyps in neoplastic adenomas, which require resection, from non-neoplastic polyps, which do not require resection, potentially reducing costs. The authors enrolled 791 consecutive patients undergoing colonoscopy with an endo-cytoscope after application of the narrow-band imaging and methylene blue staining modes. A CAD system was connected to the endoscope and provided a prediction of the pathologic status in real time. CAD predictions were compared with pathologic assessment of the excised polyps. Results were calculated based both on worst-case scenario, where polyps lacking either CAD or pathology were treated as false-positive or negative and best-case scenario, where they were treated as true-positive or negative. The primary endpoint was to evaluate if the CAD with the stained modality produced a negative predictive value of 90% in order to identify the minor rectosigmoid adenomas, to apply the concept of "diagnosing-and-leaving" non-neoplastic polyps. In total, 466 diminutive (including 250 rectosigmoid) polyps from 325 patients were assessed by CAD, with a pathologic prediction rate of 98.1% (457 of 466). The negative predictive value of CAD for diminutive rectosigmoid adenomas was > 93 with stained mode and > 95% with narrow-band imaging. Real-time CAD designed for endo-cytoscope can achieve the clinical level required for a "diagnose-and-leave" strategy for diminutive, non-neoplastic rectosigmoid polyps, which may help improve the cost-effectiveness of colonoscopy[180]. A recent add-on of this study by Mori *et al*[181] confirmed that use of AI to enable the diagnose-and-leave strategy resulted in substantial cost reductions for colonoscopy.

Another recent study by Liu *et al*[182] demonstrated the feasibility of a CAD system for increasing ADR and polyp detection rate (PDR). A total of 1026 patients were prospectively randomized to the CAD group and the control group. The detection rate of adenomas increased in the CAD group, the average number of adenomas increased, the number of small adenomas increased, the number of proliferative polyps increased, and the differences were statistically significant ($P < 0.001$). However, the comparison for the number of larger adenomas showed no significant difference between the groups ($P > 0.05$). Worse results were found in the cecum and ascending colon in detecting adenomas, probably for the high instability of colonoscopy in these areas with consequent reduced vision. In addition, there was no significant difference in the rectum, which may be due to the good visibility and stability of colonoscopy in this segment[182]. These aspects were also discussed and confirmed by the study of Wang *et al*[179].

In an old study in 2015, Kominami *et al*[183] compared the results of a CAD system with that of narrow-band imaging diagnosis and evaluated the correlation between the CAD system and the pathological results. The concordance between endoscopists and CAD system was 97.5%. Accuracy between histology and diagnosis by the CAD system was 93.2% with a negative predictive value of 93.3%, with sensitivity and specificity of 93.0% and 93.3%, respectively[183].

A new scenario is using AI for the assessment of disease activity in inflammatory bowel disease patients, especially ulcerative colitis (UC), in order to reduce interobserver variability. In a recent complex study, Bossuyt *et al*[184] used data from 29 consecutive patients with UC and 6 healthy controls in order to build a computer algorithm, named red density (RD). RD is an operator-independent computer-based tool to determine disease activity in patients with UC, based on evaluation of the redness map and vascular pattern. RD scores successively correlated with endoscopic (MAYO endoscopic sub-score, Ulcerative Colitis Endoscopic Index of Severity) and histological index (Robarts histological index) of UC activity in a multiple regression analysis. RD correlated with Robarts histological index ($r = 0.74$, $P < 0.0001$), Mayo endoscopic sub-scores ($r = 0.76$, $P < 0.0001$) and Ulcerative Colitis Endoscopic Index of Severity ($r = 0.74$, $P < 0.0001$). Therefore, RD may be an objective computer-based score that accurately assesses disease activity in UC[184].

Ozawa *et al*[185] built a CAD system using a deep convoluted neural network trained using 26304 colonoscopy images from 841 patients with UC. This data was linked with anatomic locations and Mayo endoscopic sub-score. The CAD system showed a good level of performance with area under the receiver operating characteristic of 0.86 and 0.98 to identify Mayo 0 and 0–1, respectively. CAD had better results for the rectum than for the right side and left side of the colon when identifying Mayo 0 [185].

Another recent field of application of AI is evaluation of bowel preparation. Several tools, such as the Boston Bowel Preparation Scale, are used to assess the quality of bowel preparation, which is an important factor that can affect the effectiveness of a colonoscopy. However, there are subjective biases and differences among endoscopists to evaluate this important aspect. Zhou *et al*[186] tried to develop an objective and stable method for the assessment of bowel preparation through AI by a deep convolutional neural network and machine-learning. They retrospectively collected colonoscopy images to train the system and then compared its performance with endoscopists. This model was applied to colonoscopy videos and developed a system named ENDOANGEL to provide bowel preparation scores every 30 s and to show the cumulative ratio of frames for each score during the withdrawal phase of the colonoscopy. This novel system achieved 93.33% accuracy, which was better than that of all endoscopists and 80.00% accuracy among 100 images with bubbles[186].

AI is a strategy for standardizing endoscopy practice, in order to mitigate human error, to support lesion detection and characterization, and improve ADR. This aspect was confirmed in a recent meta-analysis by Aziz *et al*[176] that demonstrated statistically significant results for ADR and polyp detection rate using AI colonoscopy. Moreover, this study showed a significant improvement in both flat adenoma per subject and adenomas < 10 mm using AI colonoscopy, which may have resulted in overall improved ADR and polyp detection rate. This evidence could prove to be a useful guide in therapeutic decision making in the future. Therefore, further high-quality clinical trials need to be conducted to accumulate evidence and understand how to obtain regulatory approval for clinical use.

CONCLUSION

Appropriate bowel preparation plays a pivotal role in high-quality colonoscopy, which is related to valuable outcomes in CRC screening. Even in the presence of largely comprehensive guidelines, clinicians have to tailor the efficacy and safety of different bowel preparations for screening colonoscopy in particular categories of patients. AI may represent an adjunctive methodology for standardizing endoscopy practice in order to minimize human inaccuracy and to support lesions detection and characterization. CSP emerged as a relatively new approach for resection of superficial benign lesions. The literature increasingly supports CSP not only for the better safety profile compared to HSP but also for its analogous effectiveness in terms of complete resection. While ESD has been widely recognized as an indispensable procedure for early superficial neoplastic lesions to be able to avoid unnecessary major surgery, advanced techniques such as full-thickness resection and non-thermal avulsion represent valid tools for recurrent/non-lifting lesions suitable for an endoscopic approach.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Adult patients with allied disorders of Hirschsprung's disease in emergency department: An 11-year retrospective study

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Abstract

BACKGROUND

In the past years, only a few studies with a limited number of adult patients analyzed clinical features of allied disorders of Hirschsprung's disease (ADHD), most of which were individual case reports or lacked detailed clinical information. Although many studies have reported patients presenting to the emergency department (ED) with recurrent abdominal symptoms for a number of disorders, there are few data involving ADHD. However, owing to a lack of awareness of the disease, misdiagnoses and mistreatments are common. Severe complications such as perforation, bleeding, malabsorption, and even death in ADHD had been reported by many studies.

AIM

To assist ED clinicians in having a more comprehensive understanding of this disease and making an early suspected diagnosis of ADHD more effectively.

METHODS

We enrolled 53 patients who visited the ED and were eventually diagnosed with ADHD over the past 11 years in our hospital. Their basic information, clinical manifestations, and imaging findings were analyzed. Blood indices were compared between the ADHD and irritable bowel syndrome (IBS) groups.

RESULTS

Adult patients with ADHD had a mean age of 48.8 ± 14.3 years, and 77.4% had been treated before admission. The transverse colon was the most common dilated part (73.6%), and constipation (67.9%) was the most common symptom.

ADHD patients can present with uncommon symptoms and false-negative imaging findings. Logistic regression analysis indicated that body mass index (BMI) [odds ratio (OR) = 0.786, P = 0.013], cholinesterase (per 1000 units; OR = 0.693, P = 0.008), and blood chlorine (OR = 0.816, P = 0.022) were determined to be independent related factors between the ADHD and IBS groups. The area under the receiver operating characteristics curve of these three indices combined was 0.812 (P < 0.001).

CONCLUSION

Emergency physicians should be vigilant regarding patients with chronic constipation, abdominal pain, or abdominal distension, and consider the possibility of ADHD despite its rarity. Abdominal computed tomography examination is recommended as a useful tool in the suspected diagnosis of ADHD. BMI, cholinesterase, and blood chlorine have good discriminative abilities between ADHD and IBS. The nutritional status of adult patients with ADHD is worthy of further attention. Surgical treatment for adult patients with ADHD is important and inevitable.

Key Words: Allied disorders of Hirschsprung's disease; Emergency department; Clinical characteristics; Misdiagnosis and mistreatment; Timely diagnosis

Core Tip: Emergency physicians should be vigilant regarding patients with chronic constipation, abdominal pain, or abdominal distension, especially those with recurrent and intolerable symptoms. Allied disorders of Hirschsprung's disease (ADHD) should be considered in such cases despite its rarity. Abdominal computed tomography examination is recommended as a useful tool to make a suspected diagnosis of ADHD. Clinicians should also be wary of uncommon symptoms and false-negative imaging findings. Body mass index, cholinesterase, and blood chlorine have good discriminative abilities between ADHD and irritable bowel syndrome. The nutritional status of adult patients with ADHD is worthy of further attention.

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INTRODUCTION

Patients with abdominal pain, abdominal distension, constipation, and intestinal obstruction in the emergency department (ED) are very common. However, during the follow-up of these patients over the years, we found that a small percentage were diagnosed with allied disorders of Hirschsprung's disease (ADHD). We also noticed that they often visited the ED because of recurrent symptoms. It was reported that ADHD clinically resembled HD, despite the presence of ganglion cells in the rectum[1]. The first reported case was termed "pseudo Hirschsprung's disease" by Ravitch[2] in 1958. In recent years, there have been many studies on the molecular mechanism, signaling pathway, and biomarkers associated with HD[3-5]. Researchers from Ireland reported that the diagnosis of ADHD is made after consideration of the presenting symptoms, radiographic findings, and histopathological examination [6]. Researchers from Japan have expounded on the specifics regarding the clinical symptoms, disease classification, and diagnostic criteria of ADHD[1,7,8]. According to their studies, ADHD can be classified into two categories: Diseases with intestinal ganglion cell abnormality (immature ganglia, isolated hypoganglionosis, and intestinal neuronal dysplasia) and diseases without intestinal ganglion cell abnormality (megacystis microcolon intestinal hypoperistalsis syndrome, segmental intestinal dilatation, internal anal sphincter achalasia, and chronic idiopathic intestinal pseudo-obstruction). All these studies have greatly increased our knowledge of ADHD. However, before a definite pathological diagnosis is made, making a suspected diagnosis of ADHD based on clinical manifestations alone is challenging because common intestinal disorders can present with these similarly[9]. Although many studies have reported patients presenting to the ED with recurrent abdominal symptoms for a number of disorders[10-13], there are few data involving ADHD. It is hard for most ED doctors to associate common abdominal symptoms with ADHD specifically. Consequently, potential diagnoses of ADHD are often missed or ignored in patients presenting with abdominal symptoms in the ED. Unfortunately, if the disease is not suspected, the subsequent treatment may be incorrect, and thus, further examination

or targeted follow-up might not be implemented in such patients.

Owing to a lack of awareness of the disease, misdiagnoses and mistreatments are common. Severe complications such as perforation, bleeding, malabsorption, and even death in ADHD had been reported by many studies[14-18]. Moreover, we found that some patients repeatedly visited our ED or underwent one or more surgeries but still had recurrent symptoms. This prompted us to consider two important questions: What are the clinical characteristics of these patients? How can we make an early suspected diagnosis of ADHD more effectively?

However, the low prevalence of ADHD makes this difficult. A 10-years nationwide survey in Japan that included almost all ADHD cases from 2001 to 2010 showed that only 355 cases had a definite or suspicious diagnosis of ADHD[1]. Special attention should be given to addressing the difficulty of emergency clinicians in making a suspected diagnosis of ADHD. In past years, only a few studies with a limited number of adult patients analyzed its clinical features, most of which were individual case reports or lacked detailed clinical information. Herein, we performed a retrospective study to analyze the clinical manifestations, imaging findings, blood test indexes, treatment, and prognosis of adult ADHD patients. We hope to assist ED clinicians in having a more comprehensive understanding of this disease and making an early suspected diagnosis of ADHD more effectively.

MATERIALS AND METHODS

Patients and study design

This single-center, retrospective observational study was carried out at the ED of the First Affiliated Hospital, School of Medicine, Zhejiang University. We enrolled patients from May 2009 to October 2020 who once visited the ED because of disease worsening and then, after receiving specialized treatment in our hospital, were finally diagnosed with ADHD. The diagnosis was consistent with existing guidelines and diagnostic criteria[1,7]. Figure 1 illustrates the specific screening procedure for ADHD patients. The patients were enrolled if they: (1) Were over 18 years old; and (2) Conformed to the diagnostic criteria for ADHD. The exclusion criteria included the following: (1) Patients who had missed important information; and (2) Patients who were suffering from heart, liver, brain, lung, kidney, or other vital organ failure. Finally, 53 patients with ADHD were included in this study, and among them, 39 had isolated hypoganglionosis and 14 had intestinal neuronal dysplasia on pathological analysis. Irritable bowel syndrome (IBS) is recognized as one of the most common functional gastrointestinal disorders presenting with abdominal pain and changes in bowel habits[19,20]. The diagnosis of IBS was in line with the Rome IV criteria[21]. To analyze blood indices in the adult ADHD patients, 58 patients diagnosed with IBS during the same period were included as a control group, who were all over 18 years and free of heart, liver, brain, lung, kidney, other vital organ failure and cachexia. This study was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (No. 2021271).

Data collection

Data was collected from the electronic medical record system of the First Affiliated Hospital, School of Medicine, Zhejiang University. All 53 patients had confirmed pathology reports, and when they were finally diagnosed with ADHD at the specialty ward, the following data was recorded: Age, sex, hospital days, chief complaints, onset time, duration time, pre-hospitalization treatment, imaging findings, routine blood examination, biochemical test indexes, surgical procedures, and postoperative complications. The blood indices of both the ADHD and IBS groups were the first results on admission. The symptom duration was classified into the following: < 1 year, 1-5 years, 5-10 years, and > 10 years. We also identified the dilated sites of the bowel, if any (small intestine, transverse colon, ascending colon, descending colon, sigmoid colon, rectum, and no dilation) through radiological findings.

Statistical analysis

The data was analyzed using the SPSS statistical software package (version 23.0, SPSS Inc., IBM, Chicago, IL, United States). Continuous variables are described as the mean with standard deviation if they followed a normal distribution and median with interquartile range if they did not follow a normal distribution. Categorical variables are described as numbers (*n*) with percentage (%) in the group. The Kolmogorov-Smirnov normality test was used to determine if the quantitative variables had a normal distribution. The independent sample *t*-test or Mann-Whitney *U* test was used to evaluate continuous data, whereas the Chi-square test was used to analyze categorical variables. Variables with $P < 0.05$ in the univariate analysis were selected for the multivariate logistic regression to examine the independent related factors between ADHD and IBS. The stepwise procedure (forward: LR) was used to isolate the factors. Odds ratios (OR) and 95% confidence intervals (CI) were calculated, and a two-tailed *P* value < 0.05 was considered statistically significant. The area under the receiver operating characteristics curve (AUROC) was measured to evaluate the discriminative power of these blood test indices.

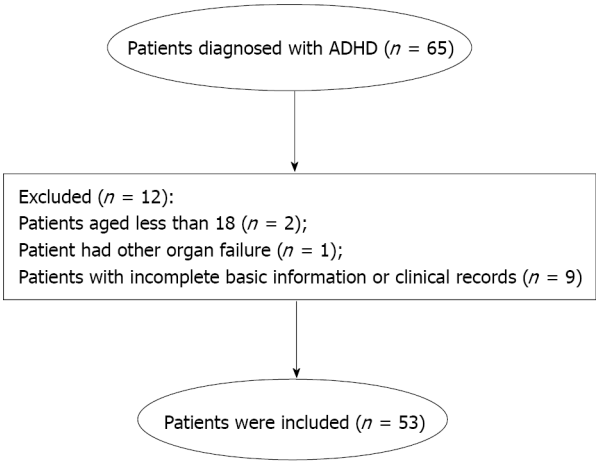

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Figure 1 Flowchart of selection of allied disorders of Hirschsprung's disease patients. ADHD: Allied disorders of Hirschsprung's disease.

RESULTS

Patient characteristics

Among all 53 ADHD patients, the female-to-male ratio was 35:18 (35 females and 18 males) (Table 1). The mean age was 48.8 ± 14.3 years (range: 18-72 years), while the median length of hospital stay on first admission at our hospital was 14 d. Surgical history was classified into two categories: Abdominal (*e.g.*, cesarean section, cholecystectomy, laparoscopic exploratory surgery, enterostomy, enterectomy, and inguinal hernia repair) and non-abdominal. Moreover, false negatives were found in 11 and 5 cases examined *via* enteroscopy and barium enema (BE), respectively. Lastly, all cases underwent either plain or contrast-enhanced abdominal computed tomography (CT) scans, and only one patient had a false-negative diagnosis.

Clinical information

Among the 53 patients enrolled, 43 (81.1%) were either wrongly diagnosed or treated upon the first ED admission. On average, 17 mo passed from the first ED visit before arriving at the final diagnosis. The clinical information is presented in Figure 2. Notably, patients with < 1-year symptom duration were the most common. Furthermore, before a correct diagnosis was formulated, most patients were treated conservatively (*i.e.*, medication, fasting, gastrointestinal decompression, or enema therapy). A total of 30 patients (56.6%) had a history of admission for abdominal symptoms; 22 cases were treated conservatively and 8 underwent enterectomy, including 3 cases who underwent bowel resection surgery twice in other hospitals. The transverse colon (73.6%) was the most involved dilated intestinal segment, while one case had no dilatations in the bowel. Abdominal pain, abdominal distension, constipation, and bowel obstruction were relatively common. Surprisingly, vomiting, weight loss, diarrhea, and abdominal mass were also found. Subtotal colectomy and total colectomy were the most common procedures, done in 42 cases (79.2%). Concomitant treatments mainly involved maintaining electrolyte balance, regulating intestinal flora, and symptomatic treatment. Postoperative complications were mainly bowel obstruction and infection.

Radiographic images and pathological sections

Typical radiographic images obtained from three cases are shown in Figure 3. Patient A was a 70-year-old man with chief complaints of intractable constipation, abdominal distension, and abdominal pain for 1 mo. Abdominal CT showed significant dilatation of gas in the colon (Figure 3A), whereas BE showed a dilated sigmoid colon and barium retention in the sigmoid colon and rectum (Figure 3D). Patient B was a 51-year-old man with intermittent lower abdominal pain and no defecation for 1 mo. Abdominal CT showed a dilated colon with a large amount of fecal content (Figure 3B), while BE showed a dilated middle and upper rectum and a narrow lower rectum (Figure 3E). Patient C was a 22-year-old girl with paroxysmal abdominal pain around the umbilicus and severe constipation for 2 mo. She was the only case that had marked narrowing of the intestinal lumen on enteroscopy. Abdominal CT showed that the whole colon was obviously distensible with gas accumulation and fecal retention (Figure 3C), while enteroscopy revealed significant narrowing of the intestine 40 cm from the anus, which could not be further examined (Figure 3F). The pathological sections of the normal intestinal ganglion and of the resected bowel of ADHD patients (hematoxylin-eosin staining) are shown in Figure 4, respectively. In Figure 4A, the black arrows indicate normal ganglion cells. In Figure 4B, the black arrow indicates the degenerated ganglion cell. The proliferation of nerve fibers and reduction of

Table 1 Basic characteristics of adult patients with allied disorders of Hirschsprung's disease

Basic characteristic	Data (*n* = 53)
Age (yr)	48.8 ± 14.3
Onset age (yr)	42.8 ± 17.9
Hospitalization days	14.0 (10.0, 21.0)
Sex (*n*, %)	
Male	18 (34.0)
Female	35 (66.0)
Blood type (*n*, %)	
A	10 (18.9)
B	17 (32.1)
AB	6 (11.3)
O	19 (35.8)
Unknown	1 (1.9)
All surgical history (*n*, %)	25 (47.2)
Abdominal	18 (34.2)
Non-abdominal	7 (13.2)
Smoking (*n*, %)	
Yes	5 (9.4)
No	48 (90.6)
Drinking (*n*, %)	
Yes	2 (3.8)
No	51 (96.2)
Enteroscopy (*n*, %)	
Abnormality	5 (9.4)
Non-abnormality	11 (20.8)
Unexamined	37 (69.8)
Barium enema (*n*, %)	
Intestinal dilation	17 (32.1)
No abnormality	5 (9.4)
Unexamined	31 (58.5)

ganglion cells were also observed.

Laboratory data

As shown in Table 2, there were no statistically significant differences in age or sex between the case and control groups ($P > 0.05$). ADHD patients had a significantly lower body mass index (BMI) than IBS patients (20.2 *vs* 22.6 kg/m^2, $P < 0.001$). Similarly, cholinesterase and blood chlorine in ADHD patients were remarkably lower than those in IBS patients ($P < 0.001$). In addition, when compared with the control group, the case group had lower total protein and albumin levels (64.2 *vs* 69.3 g/L; and 41.2 *vs* 44.1 g/L, respectively, $P < 0.05$). Likewise, creatinine, triglyceride, total cholesterol, serum sodium, and blood calcium levels in the case group were distinctly lower than those in the control group ($P < 0.05$). No significant differences in other indices were found between the two groups ($P > 0.05$). After initial analysis, variables with a P value < 0.05 were selected and multivariate logistic regression analysis was performed. Since the values of cholinesterase varied widely (from 2020 U/L to 13252 U/L), we included it in the regression by dividing by 1000 according to the method of a previous study[22]. Logistic regression suggested that BMI (OR = 0.786, $P = 0.013$), cholinesterase (per 1000 units; OR = 0.693, $P = 0.008$), and blood chlorine (OR = 0.816, $P = 0.022$) were determined to be independent related factors between ADHD and IBS (Table 3). The AUROC of these three indices combined was 0.812 (95%CI:

Table 2 Blood test indices between allied disorders of Hirschsprung's disease (case group) *versus* irritable bowel syndrome (control group) patients

Parameter	Case group (*n* = 53)	Control group (*n* = 58)	*P* value
Age (yr)	48.8 ± 14.3	49.8 ± 14.5	0.715
Male (*n*, %)	18 (34.0%)	24 (41.4%)	0.421
Body mass index (kg/m^2)	20.2 (18.8, 21.6)	22.6 (20.3, 25.0)	< 0.001[c]
White blood cells (× 10^9/L)	5.4 (3.9, 6.8)	5.4 (4.7, 6.4)	0.512
Neutrocyte proportion (%)	61.0 ± 14.5	57.9 ± 10.0	0.190
Lymphocyte proportion (%)	30.0 ± 14.2	32.1 ± 9.5	0.371
Red blood cells (× 10^{12}/L)	4.3 (4.0, 4.6)	4.4 (4.0, 4.8)	0.064
Hemoglobin (g/L)	128.5 ± 16.2	133.9 ± 21.9	0.141
Platelet count (× 10^9/L)	214.0 (171.0, 260.5)	213.0 (161.8, 245.0)	0.445
Total protein (g/L)	64.2 ± 9.6	69.3 ± 5.7	0.001[b]
Albumin (g/L)	41.2 ± 7.1	44.1 ± 4.3	0.014[a]
Alanine aminotransferase (U/L)	13.0 (9.5, 19.0)	17.0 (10.8, 27.3)	0.061
Aspartate aminotransferase (U/L)	14.0 (17.0, 21.5)	19.0 (15.0, 26.0)	0.090
Cholinesterase (U/L)	6331.0 (4900.5, 7575.0)	7534.0 (6877.8, 9216.8)	< 0.001[c]
Creatinine (μmol/L)	61.0 ± 14.2	67.2 ± 13.3	0.018[a]
Triglyceride (mmol/L)	1.0 (0.7, 1.3)	1.2 (0.9, 1.7)	0.013[a]
Total cholesterol (mmol/L)	3.9 ± 1.0	4.3 ± 0.9	0.013[a]
Fasting blood glucose (mmol/L)	4.8 (4.3, 5.8)	4.8 (4.0, 5.2)	0.225
Serum potassium (mmol/L)	4.0 ± 0.5	4.1 ± 0.4	0.139
Serum sodium (mmol/L)	141.0 (139.0, 142.0)	142.0 (140.0, 143.0)	0.011[a]
Blood chlorine (mmol/L)	103.0 (101.0, 105.0)	104.0 (103.0, 106.0)	0.009[b]
Blood calcium (mmol/L)	2.2 (2.1, 2.3)	2.2 (2.1, 2.3)	0.254
Serum phosphorus (mmol/L)	1.1 ± 0.3	1.2 ± 0.2	0.327

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.

0.734-0.890, $P < 0.001$) (Figure 5). The optimal cutoff value was 0.488 (sensitivity 71.7%, specificity 74.1%, and Euclidean index 0.491). These findings imply that BMI, cholinesterase, and blood chlorine have good discriminative abilities between ADHD and IBS.

DISCUSSION

The rarity of ADHD makes it difficult to respond to its clinical features and suspect its diagnosis. To our best of knowledge, our study on the clinical characteristics of adults with ADHD has the largest sample in China, as well as more detailed clinical information about the subjects than previous studies. Our analysis was also from an ED perspective, thus enabling other ED physicians to have a more systematic and comprehensive understanding of the characteristics of ADHD patients. Moreover, we found that the atypical symptoms and negative radiological outcomes of ADHD could also make it more difficult to suspect its diagnosis. Another novel finding was that BMI, cholinesterase, and blood chlorine have good discriminative abilities between ADHD and IBS. We believe that our findings could be helpful for emergency clinicians to lessen the chance of misdiagnosis and mistreatment of adult patients with ADHD.

It is known that 80%-90% of HD patients with delayed passage of meconium and abdominal distension or serious chronic constipation are diagnosed in the neonatal period[23]. Conversely, adult ADHD patients usually have mild symptoms with later onset that are hard to associate with ADHD,

Table 3 Prediction of the allied disorders of Hirschsprung's disease *vs* irritable bowel syndrome based on multivariate logistic regression model

Value	*P* value	OR	95%CI
Body mass index	0.013	0.786	0.649-0.951
Cholinesterase, per 1000 units	0.008	0.693	0.527-0.910
Blood chlorine	0.022	0.816	0.686-0.971

OR: Odds ratio; CI: Confidence interval.

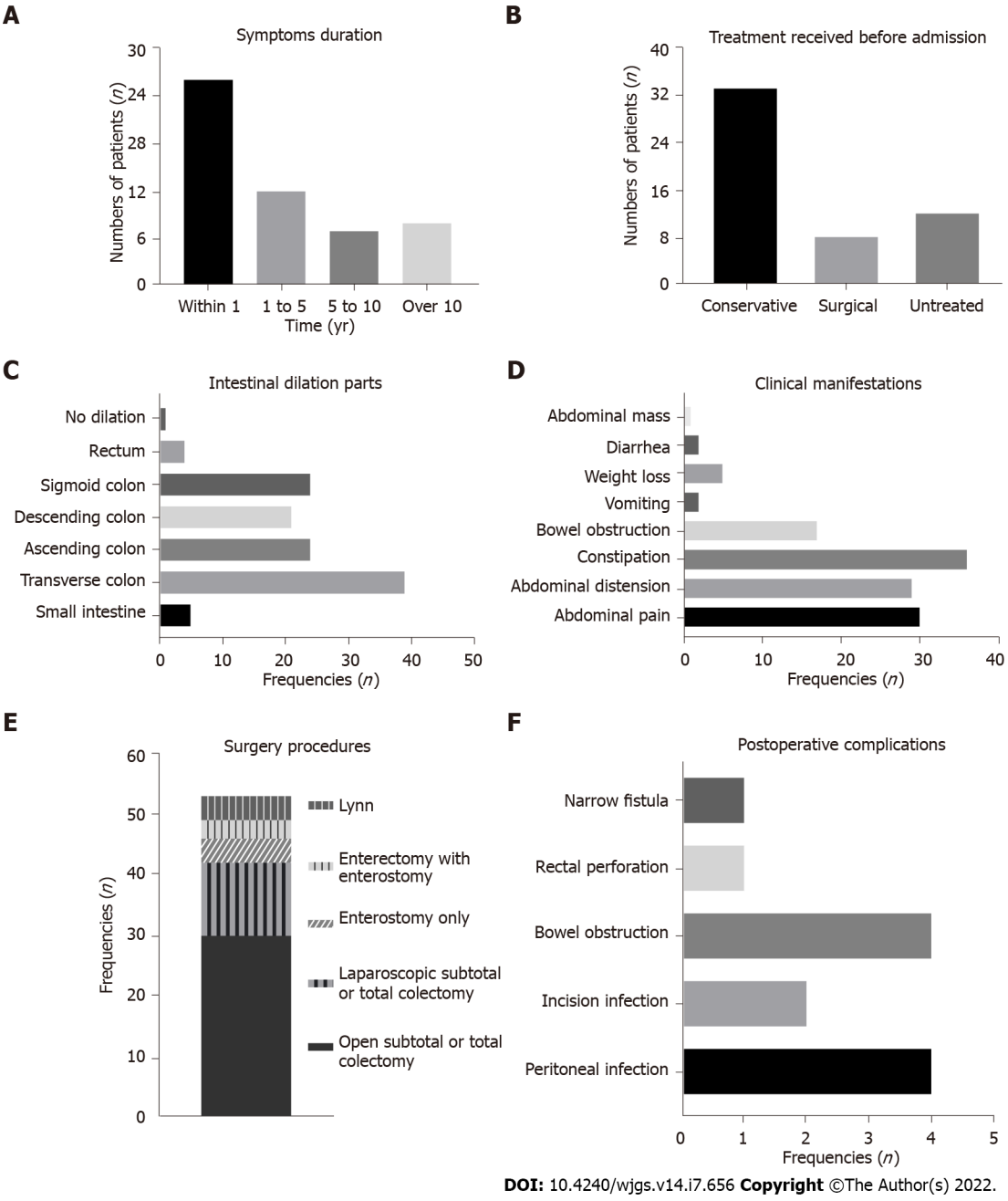

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Figure 2 Clinical information of adult patients with allied disorders of Hirschsprung's disease. A: Symptoms duration; B: Treatment received before admission; C: Intestinal dilation parts; D: Clinical manifestations; E: Surgery procedures; F: Postoperative complications.

thus causing delayed treatment. Many previous studies have described the clinical manifestations of patients with ADHD[24,25], which are in line with the most common symptoms that we found in our study (*i.e.*, abdominal pain, abdominal distension, and constipation). However, we also found

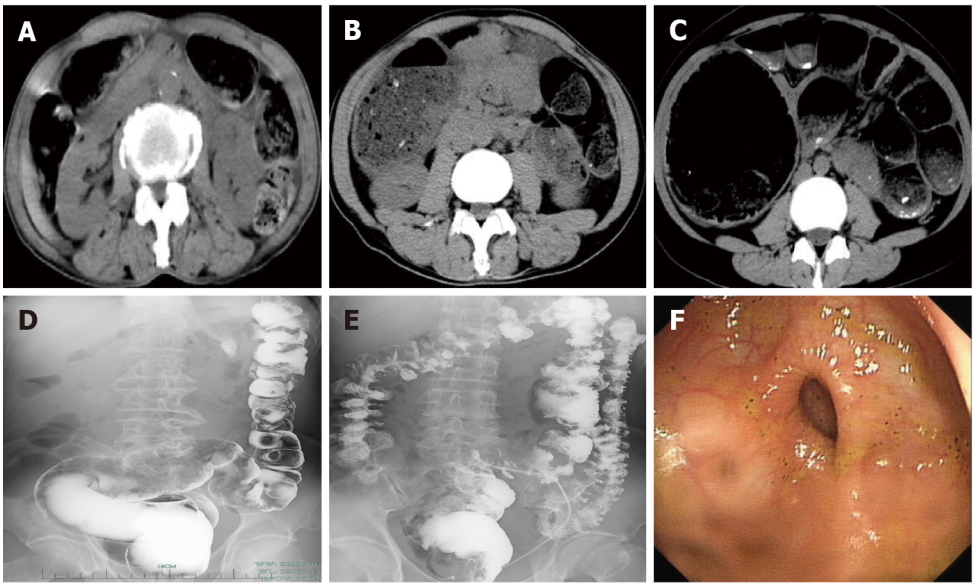

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Figure 3 Classic imaging findings of three patients with allied disorders of Hirschsprung's disease. A: Computed tomography (CT) revealed significant dilatation of gas in the colon in a 70-year-old man; B: CT dilated colon with a large amount of fecal content in a 51-year-old man; C: CT obvious dilation in the total colon in a 22-year-old girl; D: Enteroscopy revealed dilated sigmoid colon and barium retention in the sigmoid colon and rectum in the 70-year-old man; E: Enteroscopy dilated middle and upper rectum and narrow lower rectum in the 51-year-old man; F: Enteroscopy significant narrowing of the intestine 40 cm from the anus in the 22-year-old girl.

uncommon symptoms. We found a right abdominal mass that was caused by dilation of the intestinal cavity in one patient who had difficulty in defecation for a long time. Two cases also presented with severe diarrhea, but their onset symptoms were abdominal distension. This might be related to the progression of the disease; however, these atypical symptoms could also be accidental and concomitant. Nevertheless, this means that the emergency doctor should not only focus on the common symptoms but also be aware of the uncommon ones that may mislead the diagnosis. Notably, 43.4% of the patients had a symptom duration of over 5 years. However, chronic constipation or abdominal distension due to ADHD can be life-threatening. In Japan, an adult female with ADHD died of circulatory failure due to the megacolon compressing the heart, lungs, and inferior vena cava[15]. Another study reported an adult male with ADHD who died of shock caused by intestinal necrosis due to extremely high intra-intestinal pressure[16]. Similarly, both cases had chronic onset at the beginning and also had a long history of intractable constipation, showing no improvements or recurrent attacks after conservative treatment, without further clinical visits or examination. We speculated that these mortalities were due to the late diagnosis and incorrect treatment. Thus, emergency physicians should consider the medical history of ADHD patients, especially those with chronic symptoms who showed no improvement or relapsed despite medication. Further examinations or targeted follow-ups are recommended for patients suspected of having ADHD.

Previous studies have also recommended imaging examinations to make a diagnosis. BE has been effectively used for preoperative evaluation to identify the extent of bowel disease in ADHD[26]. In our study, 17 out of 22 cases examined *via* BE presented with intestinal dilation and barium retention, while the rest had normal findings. Similar false-negative results were also reported by others in an approximate proportion compared to our study[27,28]. We believe that this could be another reason related to the progression of disease. Although BE has its limitations as a diagnostic tool, it should not be ignored because it can assess both dilated bowels and intestinal motility. Nowadays, enteroscopy has been widely used as the standard procedure for the diagnosis, screening, treatment, and follow-up of many colorectal diseases[29]. This was used in 16 cases in our study, but a large proportion presented with normal results. Only one case had a notably narrow lumen, while a small number of cases had intestinal mucosal abnormalities. Thus, we suggest that the role of colonoscopy in ADHD still needs to be verified in larger samples. In addition, researchers from New York University reported that CT could be used to identify bowel obstruction, with a sensitivity of 94% and specificity of 96%, revealing the correct cause of obstruction in 73% of cases[30]. Rubin[31] also pointed out that, as a key means of examination, CT provides great support for the diagnosis of abdominal diseases. Likewise, Wang *et al*[32] reported that coronal images on CT scans of the abdomen and pelvis may provide a complete assessment of the overall diameter of the colon. In our study, almost all patients had severe multistage intestinal dilatation, but surprisingly, there was one patient without intestinal dilatation. Thus, emergency clinicians need to be aware that not all adult ADHD patients present with intestinal dilation. Nevertheless, CT can detect sites of intestinal dilatation or stenosis with higher sensitivity and

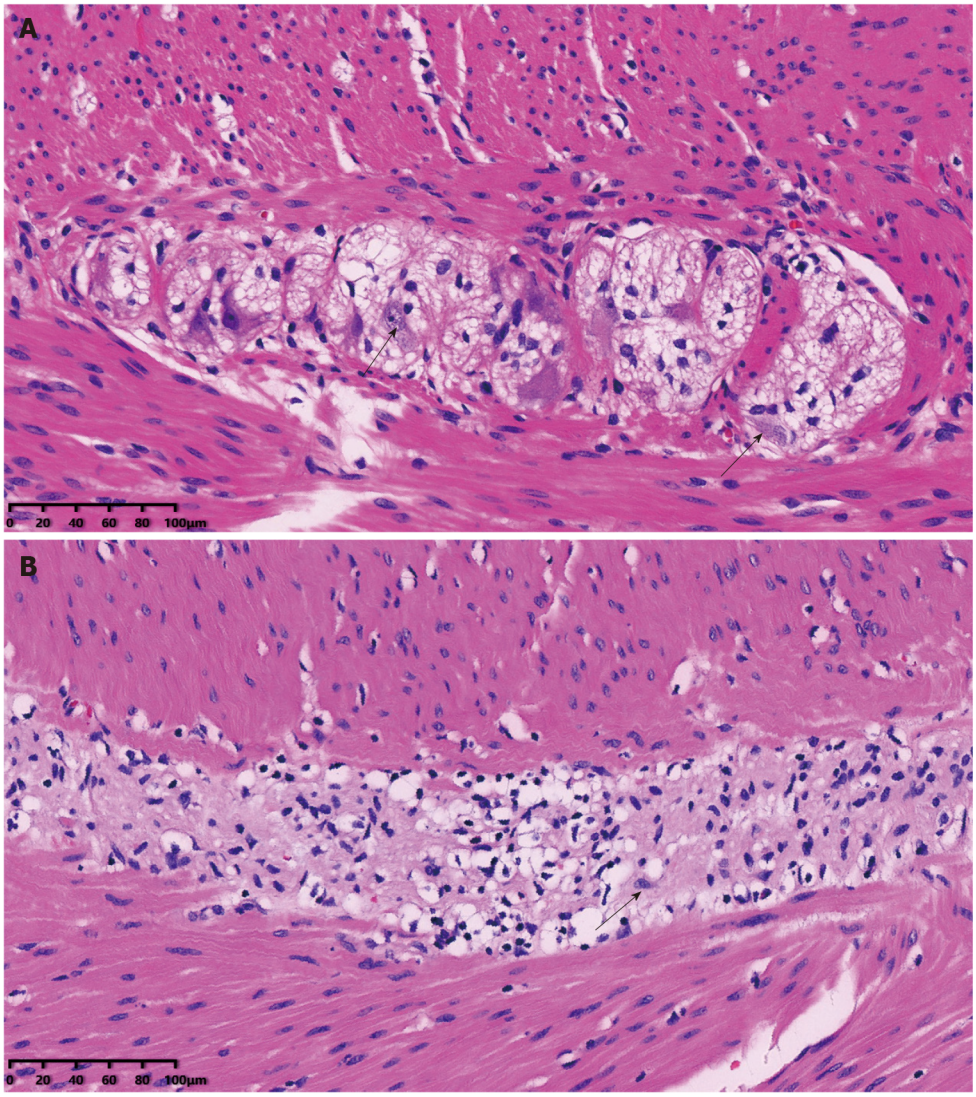

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Figure 4 Typical pathological sections of normal intestinal ganglion and resection bowel of allied disorders of patients with Hirschsprung's disease (hematoxylin-eosin staining). A: Black arrows indicate normal ganglion cells; B: The black arrow indicates the degenerated ganglion cell. The proliferation of nerve fibers and reduction of ganglion cells were also observed. Magnification, × 200.

specificity than abdominal radiography[33]. Therefore, we strongly recommend that CT be used to identify ADHD, but if a patient suspected of ADHD has negative results on plain or enhanced CT, the suspicion cannot be ruled out. According to the patient's medical history and features of symptoms, seeking specialty consultation was conducive, and further examinations were needed in our cases. However, it is also very possible that IBS might be considered by doctors, because IBS would be suspected in a patient with negative imaging examinations combined with obvious abdominal symptoms. Intestinal disorders similar to IBS have also been reported in patients who had previously undergone bowel resection[34]. All patients in our study had undergone enterectomy, implying that some patients may return to the hospital because of such symptoms even after being discharged.

To date, no specific blood index has been reported to identify ADHD. Our regression model showed that BMI, cholinesterase, and blood chlorine have good discrimination between ADHD and IBS (AUROC = 0.812). BMI was recognized as the most popular and common method for nutritional status assessment[35]. It was worth noting that BMI in the case group was significantly influenced by ADHD. There are a few possible reasons for this. First, ADHD patients are more likely to reduce food intake owing to difficulties in smooth defecation, which would result in a lower BMI. Second, ADHD patients usually take laxatives. Regular use of laxatives can give rise to electrolyte loss, steatorrhea, and kidney disturbances including hypokalemia and volume depletion[36]. IBS may also have those problems, but we considered that these behaviors may vary in degree. Meanwhile, ADHD patients had significantly lower levels of cholinesterase. It was reported that cholinesterase could be used as a biomarker of malnutrition[37]. In addition, acetylcholinesterase controls cholinergic nerve and chemical transmission by hydrolyzing the neurotransmitter acetylcholine[38], a major excitatory neuromodulator in the intestinal nervous system[39]. It was also reported that malnourishment caused by chronic obstruction

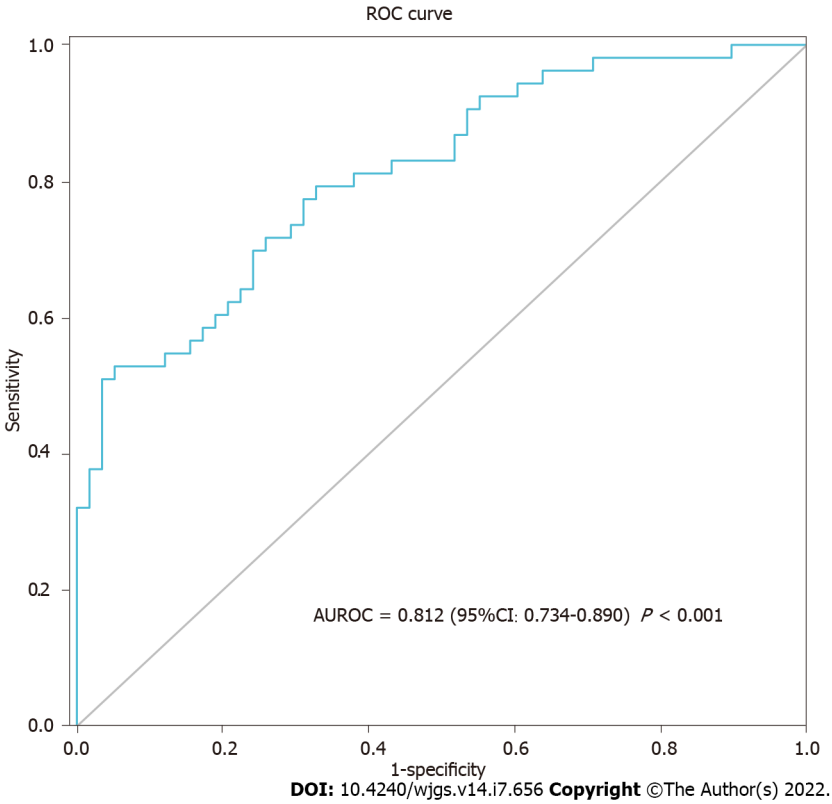

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Figure 5 Receiver operating characteristic curve. Receiver operating characteristic curve analysis showed that body mass index, cholinesterase, and blood chlorine had good discriminative abilities between allied disorders of Hirschsprung's disease and irritable bowel syndrome. ROC: Receiver operating characteristics; AUROC: Area under the receiver operating characteristics curve; CI: Confidence interval.

associated with HD can affect the digestion and absorption of nutrients including iron and other blood-forming materials, leading to intractable anemia[40]. Considering all of the above, we concluded that patients with ADHD had worse nutritional status than patients with IBS. The nutritional status of adult patients with ADHD is worthy of further attention. On the other hand, our regression model has good power of discrimination between ADHD and IBS. Further studies are required to evaluate the impact of ADHD on malnourishment.

It was reported that suction rectal biopsy could be used to identify ADHD[41]. However, the procedure is controversial because it collects less amount of mucosa and submucosa, which carries a risk of producing false negatives[42]. Wedel *et al*[43] also reported that superficial submucous biopsies were not suitable for the diagnosis of hypoganglionosis and its severity. Since it is conducted 2 and 5 cm above the dentate line, this method is effective only if the distance from the lesion is within reach. Meanwhile, biopsy-related complications including perforation, bleeding, and infection were also reported[44]. Full-thickness pathological examination is the gold standard for the diagnosis of ADHD [45]. Immunohistochemistry was widely used in the histopathological diagnosis of ADHD[46]. Currently, hematoxylin and eosin staining, acetylcholinesterase staining, Hu C/D, CD56, S-100 protein, and SOX10 are all used by investigators for diagnosing ADHD[47]. However, full-thickness histopathological examination undoubtedly means that the definitive diagnosis depends on surgical resection of the intestine, which creates a confusing paradox between diagnosis and surgery.

No global consensus has been reached on whether an adult ADHD patient should undergo surgical therapy. For emergency clinicians, understanding the ultimate treatment of this disease can help patients get timely specialist treatment. It was reported that surgical treatment is only appropriate for patients whose symptoms have not improved after at least 6 mo of conservative treatment[8]. In contrast, many studies indicated that pharmaceutic therapy could not fundamentally relieve constipation and abdominal distension in ADHD and that surgical treatment is unavoidable[7,26,48]. In our study, we confirmed that surgical intervention is indeed necessary. All 53 of our patients underwent surgical treatment, and most of them who underwent radical surgery obtained a good prognosis. However, the surgical preference of an ADHD patient is also a factor that should be not ignored. It was reported that a 24-year-old woman underwent subtotal colectomy with a postoperative pathological diagnosis of ADHD, owing to her third recurrence of abdominal pain and no bowel movements for 4 d. The patient had a history of two episodes of bowel obstruction and was planning a second pregnancy; she was worried that such obstruction would probably occur again[49]. Postoperatively, it is important for emergency clinicians to know the possibilities and reasons for recurrence. In our study, three

patients had recurrent episodes of constipation and had previously undergone intestinal resection surgery twice before admission. Consequently, two of them developed a peritoneal infection after the third operation. The occurrence of infection might be related to the multiple operations. However, based on the pathological reports of the third operation, they were diagnosed with ADHD, and thus, the infections may have been due to the progression of the disease. However, the possibility of insufficient resection of diseased intestinal segments in previous surgeries also exists. In HD surgery, Kapur *et al*[50] strongly recommended using intraoperative multipoint frozen rapid examination to ensure that the preserved intestine had a reasonable number of normal ganglion cells. The ganglia-to-nerve fiber ratio could be used in the decision of ADHD surgery[48]. Zhang *et al*[26] pointed out that the resection range of the bowel could be estimated using BE and 24-h delayed X-ray findings, though unavoidable false negatives may mislead the outcomes. Thus, a surgeon needs to ensure a complete resection of the diseased bowel in ADHD patients.

There were some limitations in our study. First, we enrolled patients who met our inclusion criteria as much as possible, but the sample size was still not large enough, which may result in sampling bias. An additional limitation was that our cases were limited to those diagnosed with ADHD pathologically. Second, as this is a retrospective study, we were limited in our ability to gather detailed outcome data after hospital discharge. Finally, this was a single-center study in a single institution. We intend to conduct a multicenter prospective study to validate our results.

CONCLUSION

In conclusion, emergency physicians should be vigilant regarding patients with chronic constipation, abdominal pain, or abdominal distension, especially those with recurrent and intolerable symptoms. ADHD should be considered in such cases despite its rarity. Abdominal CT examination is recommended as a useful tool to make a suspected diagnosis of ADHD. Clinicians should also be wary of uncommon symptoms and false-negative imaging findings. BMI, cholinesterase, and blood chlorine have good discriminative abilities between ADHD and IBS. The nutritional status of adult patients with ADHD is worthy of further attention. Surgical treatment for adult patients with ADHD is important and inevitable.

We believe that these findings are beneficial for emergency clinicians to make appropriate suspected diagnoses earlier and reduce misdiagnosis and mistreatment of adult patients with ADHD. In the future, a large-scale study will be used to verify our results and discover more powerful models for ADHD. In addition, we will follow up with the patients for a longer period, including postoperative quality of life, and comparison of nutritional status before and after surgery. Future work requires more in-depth research on the molecular mechanisms, signal pathways, and biomarkers of ADHD.

ARTICLE HIGHLIGHTS

Research background

In the past years, only a few studies with a limited number of adult patients analyzed the clinical features of allied disorders of Hirschsprung's disease (ADHD).

Research motivation

Although many studies have reported patients presenting to the emergency department (ED) with recurrent abdominal symptoms for a number of disorders, there are few data involving ADHD. It is hard for most ED doctors to associate common abdominal symptoms with ADHD specifically.

Research objectives

To assist ED clinicians in having a more comprehensive understanding of this disease and making an early suspected diagnosis of ADHD more effectively.

Research methods

We enrolled 53 patients who visited the ED and were eventually diagnosed with ADHD over the past 11 years in our hospital. Their basic information, clinical manifestations, and imaging findings were analyzed. Blood indices were compared between the ADHD and irritable bowel syndrome (IBS) groups.

Research results

About 77.4% of adult patients with ADHD had been treated before admission. The transverse colon was the most common dilated part (73.6%), and constipation (67.9%) was the most common symptom. ADHD patients can present with uncommon symptoms and false-negative imaging findings. Logistic regression analysis indicated that body mass index (BMI), cholinesterase, and blood chlorine were

determined to be independent related factors between ADHD and IBS.

Research conclusions

Emergency physicians should be vigilant regarding patients with chronic constipation, abdominal pain, or abdominal distension, and consider the possibility of ADHD despite its rarity. Abdominal computed tomography examination is recommended as a useful tool in the suspected diagnosis of ADHD. BMI, cholinesterase, and blood chlorine have good discriminative abilities between ADHD and IBS. The nutritional status of adult patients with ADHD is worthy of further attention. Surgical treatment for adult patients with ADHD is important and inevitable.

Research perspectives

Large samples will be used to verify our results and discover more powerful models for ADHD. In addition, we will follow up with the patients for a longer period, including postoperative quality of life, and comparison of nutritional status before and after surgery. Future work requires more in-depth research on the molecular mechanisms, signal pathways, and biomarkers of ADHD.

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FOOTNOTES

Author contributions: Jiang S and Lu YQ conceived and designed the study; Jiang S and Feng MX collected the clinical data; Jiang S and Song CY provided statistical advice on study design and analyzed the data; Jiang S drafted the manuscript; and all authors contributed substantially to manuscript revision; Lu YQ takes responsibility for the paper as a whole.

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

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ORIGINAL ARTICLE

Retrospective Study

Impact of comorbid renal dysfunction in patients with hepatocellular carcinoma on long-term outcomes after curative resection

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. However, the number of patients with chronic kidney disease (CKD) is on the rise because of the increase in lifestyle-related diseases.

AIM

To establish a tailored management strategy for HCC patients, we evaluated the impact of comorbid renal dysfunction (RD), as stratified by using the estimated glomerular filtration rate (EGFR), and assessed the oncologic validity of hepatectomy for HCC patients with RD.

METHODS

We enrolled 800 HCC patients who underwent hepatectomy between 1997 and 2015 at our university hospital. We categorized patients into two (RD, EGFR < 60 mL/min/1.73 m^2; non-RD, EGFR ≥ 60 mL/min/1.73 m^2) and three groups (severe CKD, EGFR < 30 mL/min/1.73 m^2; mild CKD, 30 ≤ EGFR < 60 mL/min/1.73 m^2; control, EGFR ≥ 60 mL/min/1.73 m^2) according to renal function as defined by the EGFR. Overall survival (OS) and recurrence-free survival (RFS) were compared among these groups with the log-rank test, and we also analyzed survival by using a propensity score matching (PSM) model to exclude the influence of patient characteristics. The mean postoperative observation period was 64.7 ± 53.0 mo.

RESULTS

The RD patients were significantly older and had lower serum total bilirubin, aspartate aminotransferase, and aspartate aminotransferase levels than the non-RD patients ($P < 0.0001$, $P < 0.001$, $P < 0.05$, and $P < 0.01$, respectively). No patient received maintenance hemodialysis after surgery. Although the overall postoperative complication rates were similar between the RD and non-RD patients, the proportions of postoperative bleeding and surgical site infection were significantly higher in the RD patients (5.5% *vs* 1.8%; $P < 0.05$, 3.9% *vs* 1.8%; $P < 0.05$, respectively), and postoperative bleeding was the highest in the severe CKD group ($P < 0.05$). Regardless of the degree of comorbid RD, OS and RFS were comparable, even after PSM between the RD and non-RD groups to exclude the influence of patient characteristics, liver function, and other causes of death.

CONCLUSION

Comorbid mild RD had a negligible impact on the prognosis of HCC patients who underwent curative hepatectomy with appropriate perioperative management, and close attention to severe CKD is necessary to prevent postoperative bleeding and surgical site infection.

Key Words: Hepatocellular carcinoma; Hepatectomy; Renal dysfunction; Estimated glomerular filtration rate

Core Tip: This retrospective study revealed that comorbid renal dysfunction (RD) had a negligible impact on the prognosis of hepatocellular carcinoma patients who underwent curative hepatectomy with appropriate perioperative management, and close attention to severe chronic kidney disease is necessary to prevent postoperative bleeding and surgical site infection. Of particular interest is the finding that regardless of the degree of comorbid RD, the overall survival rate and recurrence-free survival rate were comparable, even when using a propensity model to exclude the influence of patient characteristics, liver function, and other causes of death. Moreover, no RD patient, even severe RD patients, received maintenance hemodialysis after hepatectomy.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death in many parts of the world and is estimated to be the fourth most common cause of cancer-related death worldwide[1-3]. Hepatectomy for the treatment of HCC has the highest controllability among local treatments and results in a good survival rate[4,5]. However, chronic kidney disease (CKD) affects 8% to 16% of the population worldwide, especially in developed countries, and the number of patients with CKD is on the rise; additionally, CKD is most commonly attributed to diabetes and/or hypertension[6]. Several studies have shown that patients with CKD who undergo any major surgery are at risk because they have more comorbidities, including coagulopathy and systemic atherosclerosis[7-9]. Previous reports have shown a relationship between preoperative renal dysfunction (RD) and prognosis and postoperative complications in patients with HCC who underwent hepatectomy; however, these relationships remain controversial[10-12]. Moreover, previously, the serum creatine (Cr) value was used as an indicator of renal function, but recently, it has been common to use the estimated glomerular filtration rate (EGFR) to determine the stage of RD because the level of serum Cr is influenced by age, sex, muscle quantity, and lifestyle[6,13]. To date, only one study has reported the effects of preoperative RD defined by using the EGFR in patients with HCC[14], but little is known about the impact of preoperative RD on the long-term prognosis of or postoperative complications, including acute kidney disease and the initiation of hemodialysis, in HCC patients who underwent hepatectomy. In this study, we evaluated the impact of comorbid RD as stratified by the EGFR and assessed the oncologic validity of hepatectomy for HCC patients with RD, such as end-stage renal disease (ESRD), on short- and long-term outcomes after curative resection.

MATERIALS AND METHODS

Patients

We enrolled 800 HCC patients who underwent hepatectomy between January 1997 and December 2015 at the Gastroenterological Surgery Unit of Hokkaido University Hospital in Sapporo, Japan. Baseline information, including the etiology of chronic liver disease, serum biochemistry, severity of cirrhosis, performance status, and cancer stage, was recorded when the diagnosis was established. This study was conducted with the approval of the Institutional Review Board of Hokkaido University Hospital (No. 016-0354) and was performed in accordance with the Helsinki Declaration guidelines. Informed consent was obtained in the opt-out form on the website of Hokkaido University Hospital.

Diagnosis and definitions

The diagnosis of HCC, disease progression and resectability status were assessed *via* general status, physical findings, serological tests, and imaging studies, including contrast-enhanced computed tomography, magnetic resonance imaging, and ultrasonography. Liver function was assessed with a blood liver function test, the Child-Pugh grade, the estimated indocyanine green retention rate at 15 min [15,16], and the technetium-99 m-galactosyl human serum albumin scintigraphy index[17]. To evaluate the feasibility of hepatectomy in HCC patients with RD, the primary endpoint of the present study was long-term outcomes [median survival time (MST)] after hepatectomy. The secondary endpoint was postoperative complications.

Diagnostic criteria for RD

Preoperative RD was defined by the preoperative EGFR. CKD stage 3a (45 ≤ EGFR < 60 mL/min/1.73 m^2) or higher according to KDIGO CKD guideline is reportedly associated with an increase in the risk of various diseases and mortality[18-20], so the RD group comprised patients with an EGFR < 60 mL/min/1.73 m^2, and the non-RD group comprised patients with an EGFR ≥ 60 mL/min/1.73 m^2. Moreover, we also categorized patients into three groups according to the RD as defined by the EGFR (severe CKD, EGFR < 30 mL/min/1.73 m^2; mild CKD, 30 ≤ EGFR < 60 mL/min/1.73 m^2; control, EGFR ≥ 60 mL/min/1.73 m^2) because patients with ESRD who were undergoing dialysis were likely to be at high risk of developing HCC[21].

Treatment and perioperative management of patients with severe CKD

The criteria for hepatectomy were decided regardless of renal function. Surgical procedures were determined according to the patient's liver function and general status, including the extent of disease [22], and were classified as anatomical resection (subsegmentectomy, segmentectomy, bisegmentectomy, and trisegmentectomy) or nonanatomical resection (partial resection). Postoperative complications of class II or higher according to the Clavien-Dindo classification system were recorded[23]. Postoperative mortality was defined as death within 90 d after surgery.

All the patients were managed pre- and postoperatively according to previous reports[22]. In particular, the nephrology team was consulted on cases of severe CKD, and preparations for emergency hemodialysis were made prior to surgery. For six patients in the RD group on maintenance hemodialysis, hemodialysis was scheduled to be performed the day before surgery, one day postoperatively, and then three times per week thereafter.

Statistical analysis

Categorical data were compared with the χ^2 test. Continuous data were compared between the RD and non-RD groups by the Mann-Whitney *U* test and among the three groups (severe CKD, mild CKD, and non-RD) by the Kruskal-Wallis *U* test. The EGFR values before and one month after hepatectomy in patients with severe CKD were compared by a paired *t* test. Overall survival (OS) and recurrence-free survival (RFS) curves were drawn using the Kaplan-Meier method with the generalized log-rank test for in all 800 patients, and 110 pairs of matched HCC patients were selected by using a propensity score matching (PSM) model. This PSM model was constructed with patients' age, etiology, and laboratory data such as the levels of serum total bilirubin (T-bil), aspartate aminotransferase (AST), aspartate aminotransferase (ALT), and hemoglobin A1c (HbA1c). Univariate and multivariate analyses were performed using Cox proportional hazards regression models. A *P* value less than 0.05 was considered statistically significant. All statistical analyses were conducted with JMP 16 software (SAS Institute Inc., Cary, NC, United States) or GraphPad Prism 7 (GraphPad Software, Inc., La Jolla CA, United States).

RESULTS

Patient characteristics

The patients in the RD group (128 patients, 16.0%) were significantly older ($P < 0.0001$), had a lower prevalence of hepatitis B ($P < 0.001$), had lower serum T-bil, AST, ALT, alpha-fetoprotein (AFP), and

Table 1 Characteristics of the patients with and without renal dysfunction

	RD (EGFR < 60), *n* = 128	Non-RD (EGFR ≥ 60), *n* = 672	*P* value
Age (yr)	69.5 ± 8.6	63.0 ± 10.4	< 0.0001
Sex			
Male	111 (86.7)	549 (81.7)	0.17
Female	17 (13.3)	123 (18.3)	-
Etiology			
HBV	29 (22.7)	263 (39.1)	< 0.001
HCV	41 (32.0)	218 (32.4)	0.93
NBNC	58 (45.3)	191 (28.5)	< 0.001
Child-Pugh grade			
A	124 (96.9)	649 (96.6)	0.86
B	4 (3.1)	23 (3.4)	-
Laboratory data			
Plt (×10^4/μL)	16.2 ± 6.2	15.5 ± 7.3	0.26
PT (%)	94.9 ± 13.7		0.08
Alb (g/dL)	4.0 ± 0.4	4.1 ± 0.4	0.32
T-bil (mg/dL)	0.7 ± 0.3	0.8 ± 0.4	< 0.001
AST (IU/L)	35.5 ± 31.2	43.0 ± 43.4	< 0.05
ALT (IU/L)	31.5 ± 30.0	40.0 ± 36.1	< 0.01
ChE (IU/L)	238.0 ± 89.8	245.0 ± 81.3	0.92
ICG15R (%)	14.4 ± 7.3	13.6 ± 10.6	0.61
HbA1c (%)	5.7 ± 1.1	5.3 ± 1.1	< 0.05
BUN (mg/dL)	20.0 ± 10.8	14.0 ± 4.0	< 0.0001
Cr (mg/dL)	1.1 ± 1.6	0.7 ± 0.1	< 0.0001
AFP (ng/mL)	10.3 (1.4-164321.4)	19.9 (0-5986980)	< 0.01
AFP-L3 (%)	0.0 ± 23.8	3.1 ± 24.4	< 0.05
PIVKA-II (mAU/mL)	11385.0 (0-436410)	136.0 (0-664680)	0.68

P values were determined by the χ^2 test or the Mann-Whitney *U* test. RD: Renal dysfunction; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NBNC: Non-hepatitis B virus or hepatitis C virus; Plt: Platelet count; PT: Prothrombin time; Alb: Serum albumin; T-bil: Total bilirubin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ChE: Choline esterase; ICGR15: Indocyanine green rate at 15 min; HbA1c: Hemoglobin A1c; BUN: Blood urea nitrogen; Cr: Creatinine; AFP: Alpha-fetoprotein; AFP-L3: Alpha-fetoprotein isoform, lectin affinity; PIVKA-II: Protein-induced vitamin K absence-II; EGFR: Estimated glomerular filtration rate.

AFP isoform, lectin affinity (AFP-L3) levels ($P < 0.001$, $P < 0.05$, $P < 0.01$, $P < 0.01$, and $P < 0.05$, respectively), had a higher prevalence of non-hepatitis B virus (HBV) and non-hepatitis C virus (HCV) (NBNC) ($P < 0.001$), and had higher serum HbA1c, blood urea nitrogen (BUN), and Cr levels ($P < 0.05$, respectively) than the patients in the non-RD group (Table 1). The preoperative characteristics of the severe CKD, mild CKD and non-RD patient groups are summarized in Table 2. Nineteen patients had severe CKD, including six patients who received routine preoperative hemodialysis, and 109 patients had mild CKD. Age (73.0, 69.0, and 63.0 years; $P < 0.0001$), female ratio (31.6%, 10.1%, and 18.3%; $P < 0.05$), BUN (38.0 mg/dL, 19.0 mg/dL, and 14.0 mg/dL; $P < 0.0001$), and Cr (2.4 mg/dL, 1.0 mg/dL, and 0.7 mg/dL; $P < 0.0001$) and AFP-L3 levels (21.7%, 0%, and 3.1%; $P < 0.05$) in the severe CKD patient group were significantly higher than those in the other patient groups. On the other hand, the serum albumin (3.8 g/dL, 4.1 g/dL, and 4.1 g/dL; $P < 0.01$), T-bil (0.4 mg/dL, 0.7 mg/dL, and 0.8 mg/dL; $P < 0.001$), ALT (21.0 IU/L, 34.0 IU/L, and 40.0 IU/L; $P < 0.05$), and cholinesterase levels (181.0 IU/L, 249.0 IU/L, and 245.0 IU/L; $P < 0.01$) in the severe CKD group were significantly lower than those in the other patient groups. The NBNC ratio (31.6%, 47.7%, and 28.5%; $P < 0.001$) and HbA1c level (5.5%, 5.9%, and 5.3%; $P < 0.05$) in the mild CKD patient group were higher and the HBV ratio (26.3%, 22.0%, and

Table 2 Characteristics of the patients with severe and mild chronic kidney disease and without renal dysfunction

	CKD stage			*P* value
	Severe (EGFR < 30), *n* = 19	Mild (30 ≤ EGFR < 60), *n* = 109	Non-RD (EGFR ≥ 60), *n* = 672	
Age (yr)	73.0 ± 8.9	69.0 ± 8.6	63.0 ± 10.4	< 0.0001
Sex				
Male	13 (68.4)	98 (89.9)	549 (81.7)	< 0.05
Female	6 (31.6)	11 (10.1)	123 (18.3)	-
Etiology				
HBV	5 (26.3)	24 (22.0)	263 (39.1)	< 0.01
HCV	8 (42.1)	33 (30.3)	218 (32.4)	0.59
NBNC	6 (31.6)	52 (47.7)	191 (28.5)	< 0.001
Child-Pugh grade				
A	19 (100.0)	105 (96.3)	649 (96.6)	0.71
B	0 (0.0)	4 (3.7)	23 (3.4)	-
Laboratory data				
Plt ($\times 10^4/\mu L$)	14.5 ± 5.2	16.3 ± 6.4	15.5 ± 7.3	0.76
PT (%)	94.9 ± 10.1	95.2 ± 14.3	91.7 ± 14.7	0.35
Alb (g/dL)	3.8 ± 0.3	4.1 ± 0.4	4.1 ± 0.4	< 0.01
T-bil (mg/dL)	0.4 ± 0.2	0.7 ± 0.3	0.8 ± 0.4	< 0.001
AST (IU/L)	27.0 ± 17.4	38.0 ± 32.5	43.0 ± 43.4	0.07
ALT (IU/L)	21.0 ± 19.0	34.0 ± 30.9	40.0 ± 36.1	< 0.05
ChE (IU/L)	181.0 ± 68.1	249.0 ± 90.0	245.0 ± 81.3	< 0.01
ICG15R (%)	10.5 ± 6.2	15.3 ± 7.3	13.6 ± 10.6	0.18
HbA1c (%)	5.5 ± 1.0	5.9 ± 1.1	5.3 ± 1.1	< 0.05
BUN (mg/dL)	38.0 ± 15.8	19.0 ± 5.2	14.0 ± 4.0	< 0.0001
Cr (mg/dL)	2.4 ± 3.2	1.0 ± 0.2	0.7 ± 0.1	< 0.0001
AFP (ng/mL)	51.5 (2.1-164321.4)	6.5 (1.4-37525.5)	19.9 (0-5986980)	0.61
AFP-L3 (%)	21.7 ± 30.6	0.0 ± 21.6	3.1 ± 24.4	< 0.05
PIVKA-II (mAU/mL)	1309.0 (10-167600)	105.0 (0-436410)	136.0 (0-664680)	0.93

P values were determined by the $\chi 2$ test or by the Kruskal-Wallis *U* test. RD: Renal dysfunction; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NBNC: Non-hepatitis B virus or hepatitis C virus; Plt: Platelet count; PT: Prothrombin time; Alb: Serum albumin; T-bil: Total bilirubin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ChE: Choline esterase; ICGR15: Indocyanine green rate at 15 min; HbA1c: Hemoglobin A1c; BUN: Blood urea nitrogen; Cr: Creatinine; AFP: Alpha-fetoprotein; AFP-L3: Alpha-fetoprotein isoform, lectin affinity; PIVKA-II: Protein-induced vitamin K absence-II; CKD: Chronic kidney disease; EGFR: Estimated glomerular filtration rate.

39.1%; $P < 0.01$) in the severe and mild CKD groups was lower than those in the non-RD group. The mean follow-up time was 64.7 ± 53.0 mo after hepatectomy.

Intraoperative variables and tumor characteristics

As listed in Table 3, the proportion of curability A or B was significantly higher in the RD patients than in the non-RD patients (91.4% *vs* 83.8%; $P < 0.05$). Vascular invasion and advanced fibrosis (F stage 3 and 4) were significantly lower in the RD patients than in the non-RD patients (8.6% *vs* 21.6%; $P < 0.001$, 32.0% *vs* 53.2%; $P < 0.0001$, respectively). The intraoperative variables and other tumor characteristics of the severe, mild CKD and non-RD groups were almost comparable for all groups. In this analysis, the curability of the severe and mild CKD group patients was higher than that of the non-RD group patients ($P < 0.05$); on the other hand, the proportion of vascular invasion and advanced fibrosis in the patients with severe and mild CKD was significantly lower than that of the non-RD group patients ($P < 0.01$ and $P < 0.001$, respectively). The resected liver weight (365 g, 222 g, and 252 g, $P = 0.24$) in the severe CKD

Table 3 Intraoperative parameters in the patients with and without renal dysfunction

	CKD stage		*P* value
	RD (EGFR < 60), *n* = 128	Non-RD (EGFR ≥ 60), *n* = 672	
Intraoperative variables			
Operative time (min)	323.0 ± 125.0	329.0 ± 108.0	0.70
Blood loss (mL)	380.0 ± 3230.1	425.0 ± 1577.3	0.42
Procedure of resection			
Anatomical resection	99 (77.3)	498 (74.1)	0.44
Nonanatomical resection	29 (22.7)	174 (25.9)	-
Resected liver weight (g)	239.0 ± 459.3	252.0 ± 630.0	0.57
Curability			
A + B	117 (91.4)	563 (83.8)	< 0.05
C	11 (8.6)	109 (16.2)	-
Tumor characteristics			
Tumor size (cm)	4.5 ± 3.9	4.4 ± 4.6	0.85
Tumor number	1.0 ± 1.7	1.0 ± 2.8	0.55
PStage[1]			
I	8 (6.3)	53 (7.9)	0.11
II	62 (48.4)	272 (40.5)	-
III	40 (31.3)	207 (30.8)	-
IV	18 (14.1)	140 (20.8)	-
Pathological grade			
Well	24 (18.7)	95 (14.1)	0.29
Mod-por	104 (81.3)	577 (85.9)	-
Vascular invasion[1]			
Yes	11 (8.6)	145 (21.6)	< 0.001
No	117 (91.4)	527 (78.4)	-
Liver fibrosis score[2]			
0-1	44 (34.4)	143 (21.2)	< 0.0001
2	43 (33.6)	172 (25.6)	-
3	22 (17.2)	149 (22.2)	-
4	19 (14.8)	208 (31.0)	-

[1]Liver Cancer Study Group of Japan, 6th edition.
[2]Liver fibrosis was graded and staged according to the New Inuyama classification system as follows: F1 (periportal expansion), F2 (porto-portal septa), F3 (porto-central linkage or bridging fibrosis), and F4 (cirrhosis).
P values were determined by the χ^2 test or the Mann-Whitney *U* test. The liver fibrosis score was assessed by expert pathologists using a noncancerous lesion from the resected specimen. RD: Renal dysfunction; CKD: Chronic kidney disease; EGFR: Estimated glomerular filtration rate.

patient group tended to be higher than that in the other patient groups, although the difference was not statistically significant (Table 4).

Postoperative complications

Although the overall postoperative complication rates were similar between the RD and non-RD patients, the proportions of postoperative bleeding and surgical site infection were significantly higher in the RD patients (5.5% *vs* 1.8%; $P < 0.05$, 3.9% *vs* 1.8%; $P < 0.05$, respectively) (Table 5). In the comparison between the patients with severe CKD and those with mild CKD, there was no difference in postoperative complications. Postoperative complications were also not significantly different among

Table 4 Intraoperative parameters in the patients with severe and mild chronic kidney disease and without renal dysfunction

	CKD stage			*P* value
	Severe (EGFR < 30), *n* = 19	Mild (30 ≤ EGFR < 60), *n* = 109	Non-RD (EGFR ≥ 60), *n* = 672	
Intraoperative variables				
Operative time (min)	311.0 ± 112.0	331.0 ± 127.0	329.0 ± 108.0	0.52
Blood loss (mL)	389.0 ± 1254.1	380.0 ± 3464.9	425.0 ± 1577.3	0.64
Procedure of resection				
Anatomical resection	13 (68.4)	86 (78.9)	498 (74.1)	0.46
Nonanatomical resection	6 (31.6)	23 (21.1)	174 (25.9)	-
Resected liver weight (g)	365.0 ± 388.5	222.0 ± 471.3	252.0 ± 630.0	0.24
Curability				
A + B	19 (100.0)	98 (89.9)	563 (83.8)	< 0.05
C	0 (0.0)	11 (10.1)	109 (16.2)	-
Tumor characteristics				
Tumor size (cm)	5.8 ± 4.0	4.5 ± 3.8	4.4 ± 4.6	0.41
Tumor number	1.0 ± 2.1	1.0 ± 1.6	1.0 ± 2.8	0.44
pStage[1]				
I	1 (5.3)	7 (6.4)	53 (7.9)	0.45
II	8 (42.1)	54 (49.5)	272 (40.5)	-
III	7 (36.8)	33 (30.3)	207 (30.8)	-
IV	3 (15.8)	15 (13.8)	140 (20.8)	-
Pathological grade				
Well	2 (10.5)	22 (20.2)	95 (14.1)	0.84
Mod-por	17 (89.5)	87 (79.8)	577 (85.9)	-
Vascular invasion[1]				
Yes	2 (10.5)	9 (8.3)	145 (21.6)	< 0.01
No	17 (89.5)	100 (91.7)	527 (78.4)	-
Liver fibrosis score[2]				
0-1	7 (36.8)	37 (34.0)	143 (21.2)	< 0.001
2	8 (42.1)	35 (32.1)	172 (25.6)	-
3	3 (15.8)	19 (17.4)	149 (22.2)	-
4	1 (5.3)	18 (16.5)	208 (31.0)	-

[1]Liver Cancer Study Group of Japan, 6th edition.
[2]Liver fibrosis was graded and staged according to the New Inuyama classification system as follows: F1 (periportal expansion), F2 (porto-portal septa), F3 (porto-central linkage or bridging fibrosis), and F4 (cirrhosis).
P values were determined by the χ^2 test or by the Kruskal-Wallis *U* test. The liver fibrosis score was assessed by expert pathologists using a noncancerous lesion from the resected specimen. RD: Renal dysfunction; CKD: Chronic kidney disease; EGFR: Estimated glomerular filtration rate.

the three groups, except for bleeding, which was higher than that in the severe CKD group ($P < 0.05$) (Table 6). Regarding these bleeding complications, three RD patients (2.3%) and eight non-RD patients (1.2%) required reoperation to control postoperative bleeding. There were no complications of ascites, pleural effusion, liver failure, or surgical site infection in six patients who required maintenance hemodialysis before surgery. The duration of postoperative hospital stay was not significantly different among the three groups (16.0, 16.0, and 16.0 d; $P = 0.92$). There was no mortality during hospitalization in the severe CKD group, but one patient each in the mild CKD and non-RD groups died during hospitalization. In the mild CKD group, one patient died due to postoperative gastrointestinal perforation and

Table 5 Postoperative complications in the patients with and without renal dysfunction

	CKD stage		*P* value
	RD (EGFR < 60), *n* = 128	Non-RD (EGFR ≥ 60), *n* = 672	
All complications	33 (25.8)	169 (25.1)	0.96
Major complication (Grade ≥ 2)	20 (15.6)	112 (16.7)	0.91
Bile leakage	12 (9.8)	44 (6.5)	0.33
Ascites	6 (4.7)	27 (4.0)	0.90
Pleural effusion	4 (3.1)	37 (5.5)	0.41
Pneumonia	6 (5.3)	12 (1.8)	0.70
Bleeding	7 (5.5)	12 (1.8)	< 0.05
Liver failure	1 (0.8)	9 (1.3)	0.55
Surgical site infection	5 (3.9)	12 (1.8)	< 0.05
Duration of postoperative hospital stay (d)	16.0 ± 14.5	16.0 ± 19.3	0.17
Died during hospitalization	1[1] (0.8)	1[2] (0.1)	0.96

[1]One patient in the renal dysfunction group died due to postoperative gastrointestinal perforation and an intraabdominal abscess.
[2]One patient in the non-renal dysfunction group died due to postoperative liver failure.
P values were determined by the χ^2 test or the Mann-Whitney *U* test. RD: Renal dysfunction; CKD: Chronic kidney disease; EGFR: Estimated glomerular filtration rate.

Table 6 Postoperative complications in the patients with severe and mild chronic kidney disease and without renal dysfunction

	CKD stage			*P* value
	Severe (EGFR < 30), *n* = 19	Mild (30 ≤ EGFR < 60), *n* = 109	Non-RD (EGFR ≥ 60), *n* = 672	
All complications	5 (26.3)	28 (25.7)	169 (25.1)	0.99
Major complication (Grade ≥ 2)	3 (15.8)	17 (15.6)	112 (16.7)	0.98
Bile leakage	2 (10.5)	10 (9.2)	44 (6.5)	0.40
Ascites	2 (10.5)	4 (3.7)	27 (4.0)	0.45
Pleural effusion	0 (0.0)	4 (3.7)	37 (5.5)	0.68
Pneumonia	1 (5.3)	5 (4.6)	12 (1.8)	0.84
Bleeding	2 (10.5)	5 (4.6)	12 (1.8)	< 0.05
Liver failure	0 (0.0)	1 (0.9)	9 (1.3)	0.55
Surgical site infection	0 (0.0)	5 (4.6)	12 (1.8)	0.07
Duration of postoperative hospital stay (d)	16.0 ± 15.3	16.0 ± 14.4	16.0 ± 9.3	0.92
Died during hospitalization	0 (0.0)	1[1] (0.9)	1[2] (0.1)	0.96

[1]One patient in the renal dysfunction group died due to postoperative gastrointestinal perforation and an intraabdominal abscess.
[2]One patient in the non-renal dysfunction group died due to postoperative liver failure.
P values were determined by the χ^2 test or the Mann-Whitney *U* test. RD: Renal dysfunction; CKD: Chronic kidney disease; EGFR: Estimated glomerular filtration rate.

an intraabdominal abscess. In the non-RD group, one patient died due to postoperative liver failure.

Impact of hepatectomy on postoperative RD

We compared the EGFR values before and one month after hepatectomy in the patients with CKD stage 4 or 5 according to the KDIGO CKD guidelines who did not receive maintenance hemodialysis (n = 13) [18] (Figure 1). The EGFR values did not decrease after the operation; furthermore, no patient received maintenance hemodialysis after hepatectomy.

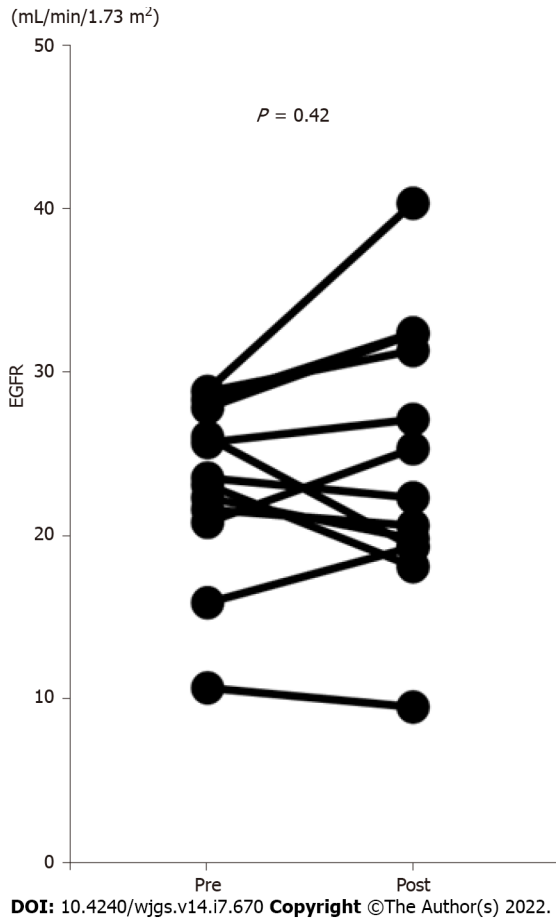

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Figure 1 Comparison of the estimated glomerular filtration rate before and after hepatocellular carcinoma resection in patients with stage 4 or 5 chronic kidney disease. In patients with stage 4 or 5 chronic kidney disease who did not require maintenance hemodialysis, the estimated glomerular filtration rate (EGFR) values did not decrease after the operation (n = 13). Furthermore, no patient received maintenance hemodialysis after the operation. The EGFR values were measured before and one month after hepatectomy. CKD: Chronic kidney disease; EGFR: Estimated glomerular filtration rate.

Survival and recurrence after hepatectomy for HCC

The MST was 70.6 mo in the RD patients and 72.4 mo in the non-RD patients (P = 0.524). The 1-, 3-, 5-, and 10-year OS rates were 87.3%, 74.0%, 60.2%, and 20.6% in the RD patients and 89.9%, 74.1%, 64.6%, and 23.1% in the non-RD patients, respectively (Figure 2A). Moreover, the MST was 40.8 mo in the severe CKD group, 70.9 mo in the mild CKD group and 72.4 mo in the non-RD group (P = 0.605). The 1-, 3-, 5-, and 10-year OS rates were 78.2%, 64.5%, 48.4%, and 9.7% in the severe CKD group, 89.0%, 75.5%, 62.2%, and 22.5% in the mild CKD group and 89.9%, 74.1%, 64.6%, and 23.1% in the non-RD group, respectively (Figure 2B). The median RFS time was 46.2 mo in the RD patients and 27.4 mo in the non-RD patients (P = 0.464) (Figure 2C). The median RFS time was 17.0 mo in the severe CKD group, 47.5 mo in the mild CKD group and 27.4 mo in the non-RD group (P = 0.762) (Figure 2D).

OS and RFS between the RD and non-RD groups after PSM

Regarding patient characteristics, the RD patients were significantly older, had a lower proportion of HBV and a higher proportion of NBNC, and had lower serum T-bil, AST, and ALT levels and higher serum HbA1c levels than the non-RD patients. Therefore, we examined the impact of preoperative RD on the OS and RFS rates, excluding the influence of these factors, by using a propensity model. This PSM model was constructed with patients' age, etiology, and laboratory data, such as the levels of serum T-bil, AST, ALT, and HbA1c, so a total of 110 pairs of matched HCC patients undergoing hepatectomy were selected in this model (Supplementary Table 1). The comparison of the OS and RFS rates between the matched patients with and without RD showed no significant difference (P = 0.343, P = 0.314, respectively) (Figure 3). In addition, considering the influence of liver function or other causes of death, we also analyzed survival in patients with Child-Pugh grade A disease and in those who died from cancer-related causes. The OS rate was similar between the RD and non-RD patients with Child-Pugh grade A disease (P = 0.489, Figure 4A) and in those who died from cancer-related causes (P = 0.993, Figure 4B).

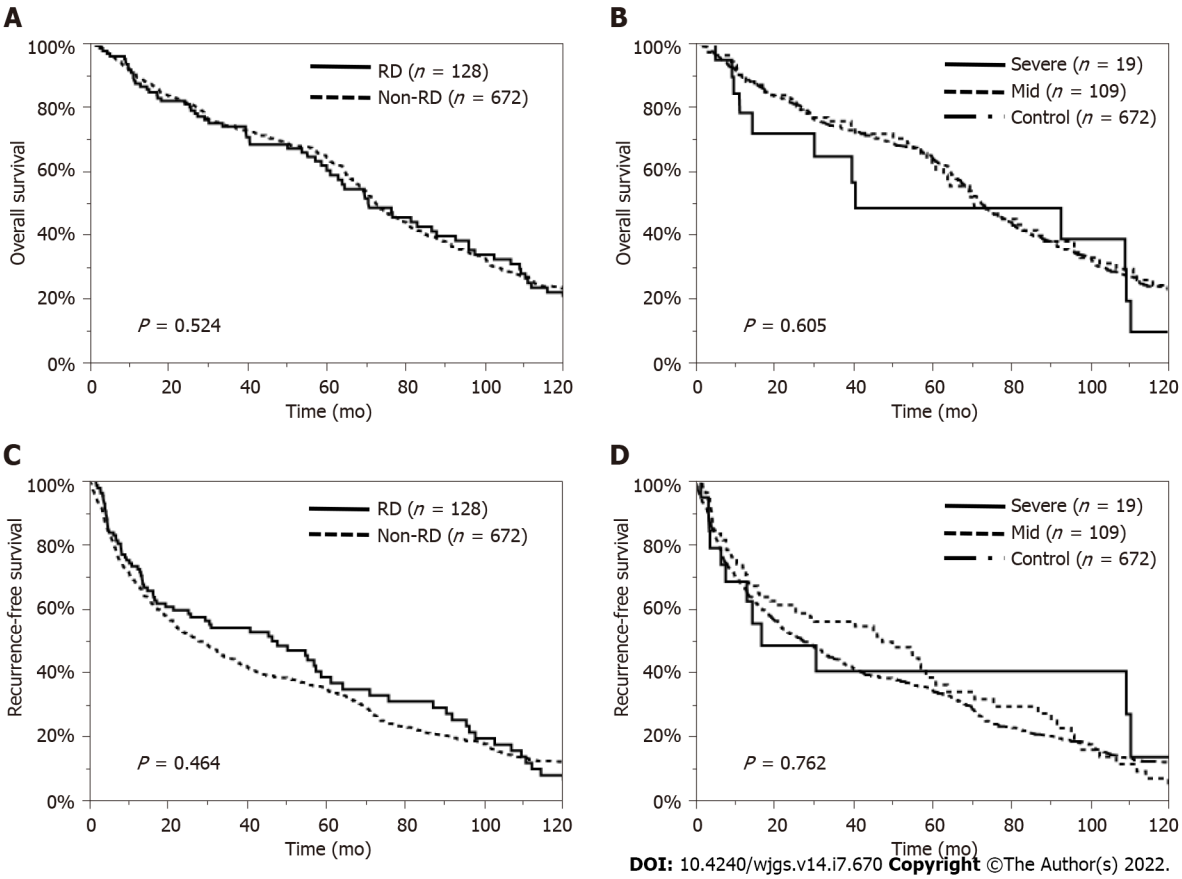

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Figure 2 Overall survival and recurrence-free survival rates of patients with or without renal dysfunction. A: Overall survival (OS) was similar between the renal dysfunction (RD) and non-RD groups (P = 0.524); B: OS was also similar among the severe, mild, and control groups (P = 0.605); C: Recurrence-free survival (RFS) was similar between the RD and non-RD groups (P = 0.464); D: RFS was also similar among the severe, mild, and control groups (P = 0.762). RD: Renal dysfunction.

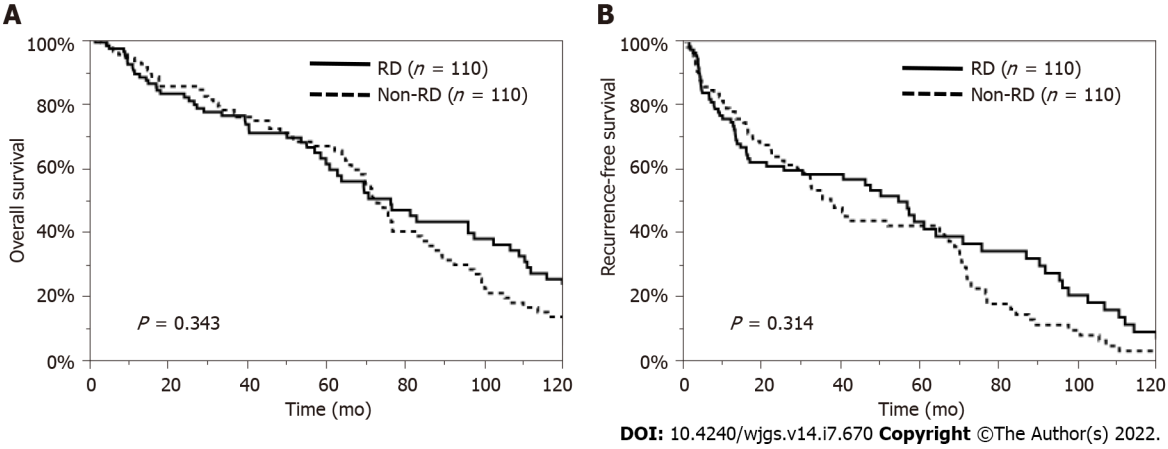

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Figure 3 Overall survival and recurrence-free survival rates of patients with renal dysfunction after propensity score matching. A: The median survival time was 76.5 mo in patients with renal dysfunction (RD) and 73.0 mo in patients without RD, so overall survival was similar between the RD and non-RD groups (P = 0.343) after propensity score matching (PSM); B: Recurrence-free survival also did not differ significantly between the RD and non-RD groups after PSM (P = 0.314) after PSM. RD: Renal dysfunction.

Prognostic factor analysis in HCC patients with RD

Table 7 shows the prognostic factors for OS and RFS in the HCC patients with RD in this cohort. In the RD patients, the multivariate analysis showed that the presence of multiple tumors was an independent factor for both OS and RFS [OS: hazard ratio (HR) = 2.44, 95% confidence interval (CI): 1.04-5.75, P = 0.040, RFS: HR = 3.77, 95%CI: 1.61-8.97, P = 0.002].

Table 7 Prognostic factors for overall survival and relapse-free survival in the hepatocellular carcinoma patients with renal dysfunction

Variable (RD patients)	Univariate analysis (OS)		Multivariate analysis (OS)		Univariate analysis (RFS)		Multivariate analysis (RFS)	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age > 60 yr	2.33 (1.14-5.63)	< 0.05	3.85 (0.81-22.53)	0.092	2.08 (1.01-5.01)	< 0.05	0.98 (0.26-4.76)	0.978
Male	1.37 (0.73-2.82)	0.371			1.66 (0.88-3.48)	0.122		
HBV+	1.00 (0.56-1.67)	0.995			1.02 (0.57-1.73)	0.947		
HCV+	0.97 (0.60-1.52)	0.899			1.03 (0.64-1.63)	0.889		
NBNC	1.03 (0.66-1.60)	0.898			0.96 (0.61-1.50)	0.849		
Child-Pugh grade B	2.16 (0.12-10.17)	0.44			0.90 (0.05-4.13)	0.919		
Plt < 13.8	0.88 (0.54-1.40)	0.598			0.76 (0.46-1.22)	0.257		
PT < 80	0.89 (0.47-1.57)	0.706			1.05 (0.57-1.81)	0.858		
Alb < 4.0	1.25 (0.80-1.95)	0.321			1.23 (0.78-1.92)	0.376		
T-bil > 1.2	0.87 (0.30-2.01)	0.772			1.03 (0.40-2.18)	0.95		
AST > 38	1.15 (0.74-1.79)	0.534			1.31 (0.85-2.05)	0.223		
ALT > 44	0.71 (0.43-1.14)	0.162			1.21 (0.76-1.90)	0.421		
ChE < 168	2.40 (1.22-4.32)	< 0.01	1.06 (0.31-3.15)	0.921	3.15 (1.59-5.79)	< 0.01	2.21 (0.17-1.35)	0.147
ICGR15 > 15	0.94 (0.60-1.48)	0.800			1.36 (0.87-2.14)	0.176		
HbA1c > 5.6	1.49 (0.87-2.55)	0.145			0.94 (0.57-1.56)	0.823		
AFP > 10	1.51 (0.97-2.39)	0.068			2.07 (1.32-3.28)	< 0.01	0.79 (0.29-2.03)	0.634
AFP-L3 > 10	2.97 (1.74-5.01)	< 0.0001	2.57 (0.99-6.70)	0.051	2.21 (1.33-3.59)	< 0.01	2.22 (0.87-5.98)	0.095
PIVKA-II > 40	1.85 (1.17-3.00)	< 0.01	2.57 (0.64-11.50)	0.186	1.53 (0.97-2.46)	0.067		
Operative time > Ave	0.96 (0.62-1.50)	0.868			0.98 (0.62-1.53)	0.916		
Blood loss > Ave	1.31 (0.78-2.13)	0.282			1.17 (0.70-1.89)	0.533		
Anatomical resection	1.06 (0.64-1.85)	0.833			0.79 (0.48-1.37)	0.391		
Resected liver weight > Ave	2.05 (1.18-3.44)	< 0.01	0.99 (0.37-2.66)	0.978	1.53 (0.87-2.59)	0.137		
Tumor size > Ave	1.94 (1.18-3.10)	< 0.01	1.06 (0.33-3.30)	0.918	1.88 (1.14-3.04)	< 0.05	1.86 (0.63-5.40)	0.258
Tumor number > 1	2.13 (1.30-3.45)	< 0.01	2.44 (1.04-5.75)	< 0.05	3.46 (2.04-5.85)	< 0.0001	3.77 (1.61-8.97)	< 0.01
Pathological grade (mod-por)	1.23 (0.70-2.34)	0.505			1.32 (0.76-2.47)	0.337		
Vascular invasion (Vp+, Vv+)	4.92 (2.21-9.84)	< 0.0001	1.88 (0.61-5.14)	0.26	4.08 (1.86-8.00)	< 0.01	1.89 (0.70-4.60)	0.198
Liver fibrosis score 3, 4	1.29 (0.80-2.03)	0.278			1.37 (0.86-2.16)	0.186		

OS: Overall survival; RFS: Recurrence-free survival; HR: Hazard ratio; CI: Confidence interval; RD: Renal dysfunction; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NBNC: Non-hepatitis B virus or hepatitis C virus; Plt: Platelet counts; PT: Prothrombin time; Alb: Serum albumin; T-bil: Total bilirubin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ChE: Choline esterase; ICGR15: Indocyanine green rate at 15 min; HbA1c: Hemoglobin A1c; BUN: Blood urea nitrogen; Cr: Creatinine; AFP: Alpha-fetoprotein; AFP-L3: Alpha-fetoprotein isoform, lectin affinity; PIVKA-II: Protein-induced vitamin K absence-II; Ave: Average; Mod: Moderately differentiated; por: Poorly differentiated; Vp: Portal vein invasion; Vv: Hepatic vein invasion.

DISCUSSION

We revealed here that the prognoses for survival and recurrence in HCC patients with and without RD who underwent curative hepatectomy were similar, even if patients had severe CKD. This finding indicated that comorbid RD had a negligible impact on the prognosis of HCC patients who underwent curative hepatectomy. However, preoperative RD affected some kinds of postoperative complications, such as postoperative bleeding and surgical site infection. It has been reported that progressive CKD is associated with adverse clinical outcomes, including ESRD, cardiovascular disease, and increased

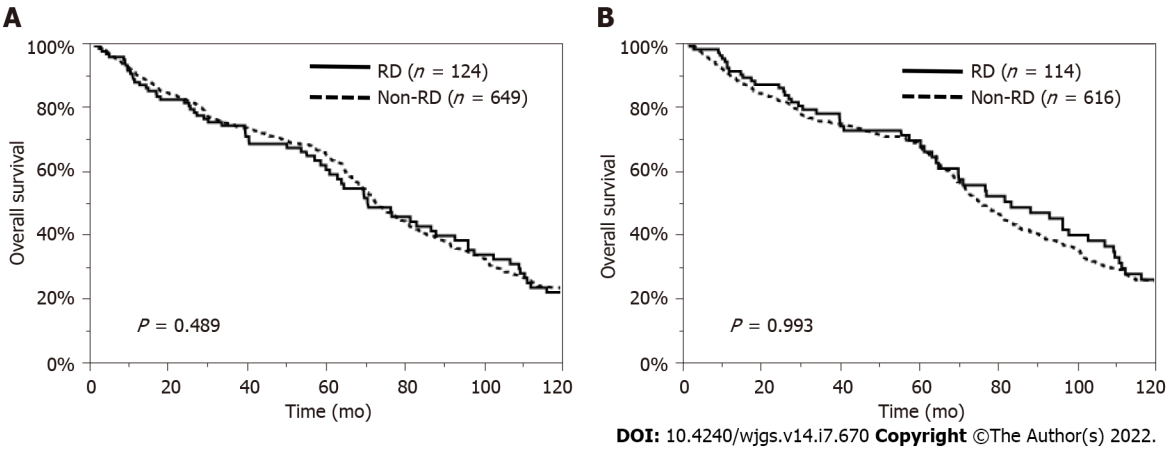

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Figure 4 Overall survival rates of patients with renal dysfunction. A: Overall survival (OS) rates of patients with renal dysfunction (RD) Child-Pugh grade A disease. The OS rate was similar between the RD (*n* = 124) and non-RD (*n* = 649) hepatocellular carcinoma (HCC) patients with Child-Pugh grade A disease (*P* = 0.489); B: OS rates of patients with RD who died from only HCC. The OS rate was similar between the RD (*n* = 114) and non-RD (*n* = 616) HCC patients who died from only HCC (*P* = 0.993).

mortality[24,25]. The prognosis of HCC patients with RD might be affected by these comorbidities. In addition, Toyoda *et al*[21] reported that the survival rate of patients who required dialysis was significantly lower than that of nondialysis controls. On the other hand, Shirata *et al*[14] mentioned that liver resection for Child-Pugh A patients with RD is safe and has comparable oncological outcomes compared to those for non-RD patients, but the selection of liver resection candidates among Child-Pugh B patients with RD should be stricter. In our study, there was no significant difference in either OS or RFS between the patients with and without RD, even if the patients had severe CKD. Moreover, because there were some differences in patient characteristics, such as age, etiology, liver function, and HbA1c levels, between patients with and without RD, we also performed PSM. The OS and RFS rates were comparable between the patients with and without RD after PSM. These results indicated that curative hepatectomy might be effective for the long-term prognosis of HCC patients, regardless of the presence of concomitant RD.

RD has been reported to be a risk factor for the development of massive ascites, pleural effusion, respiratory failure, and acute renal failure in patients after hepatectomy[11,12]. Our study showed that the proportion of patients who experienced these complications was similar between those with and without RD. The following reasons might explain these results. First, there were low frequencies of ascites and pleural effusion. Second, we might perform hepatectomy in RD patients whose liver function was better because serum T-bil, AST, and ALT levels were lower in the RD patients than in the non-RD patients. Regarding acute renal failure, the EGFR values did not decrease after liver resection; furthermore, no patient with stage 4 or 5 disease who was not on hemodialysis was treated after hepatectomy; instead, they were given appropriate perioperative care. Some reports have also shown that blood loss is higher in RD patients than in non-RD patients[11], but the amounts of blood loss were similar between the RD and non-RD patients in our study. On the other hand, the rate of postoperative bleeding was significantly higher in the RD patients. Regarding the higher proportion of postoperative bleeding in the RD patients, especially in those with severe CKD, some degree of coagulopathy and tissue weakness in patients with CKD might influence this complication[26]. Surgical site infection might also be related to the immune dysfunction of CKD patients[27]. Therefore, we should ensure blood stanching before closing the abdomen.

In the present study, the proportion of postoperative surgical site infections was also higher in the RD patients than in the non-RD patients, so more careful postoperative management is needed for RD patients. In addition to curative liver resection, hepatectomy requires careful follow-up of patients. As demonstrated in the univariate and multivariate analyses, the RD patients with multiple tumors tended to have a poor prognosis. We might have to carefully monitor and perform additional treatments for patients with multiple tumors. Moreover, from an oncological point of view, some reports have shown an increased risk of various cancers in patients with severe CKD, especially those on dialysis[28-30]. The incidences of various cancers, including kidney, bladder, and thyroid cancers, other endocrine tumors, and multiple myeloma, are higher in ESRD patients than in non-ESRD patients[31,32]. Patients who require dialysis are likely to be at risk of developing HCC, and patients with ESRD may be at high risk of developing HCC[21].

There are some limitations to this study. First, the liver function of the RD patients was better than that of the non-RD patients because physicians might exclude RD patients with severe liver function. Second, the number of HCC patients with RD, especially those with severe CKD who underwent hepatectomy, was rather small; therefore, we could not investigate rehepatectomy for patients with RD

who experienced HCC recurrence, and we could not entirely conclude that severe RD has a negligible impact on the prognosis of HCC patients. Third, this study was a retrospective study. Additional studies on larger cohorts of HCC patients with RD are required to reveal the pathogenesis of HCC and RD.

CONCLUSION

We revealed that comorbid mild RD has a negligible impact on the prognosis of HCC patients who undergo curative hepatectomy with appropriate perioperative management, and close attention to severe CKD is necessary to prevent postoperative bleeding and surgical site infection.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, on the other hand, the number of patients with chronic kidney disease (CKD) is on the rise because of the increase in lifestyle-related diseases.

Research motivation

To establish a tailored management strategy for HCC patients with CKD.

Research objectives

To evaluate the impact of comorbid renal dysfunction (RD), as stratified by using the estimated glomerular filtration rate (EGFR), and assessed the oncologic validity of hepatectomy for HCC patients with RD.

Research methods

We enrolled 800 HCC patients who underwent hepatectomy between 1997 and 2015 at our university hospital. We categorized patients into two and three groups according to renal function as defined by the EGFR. Overall survival (OS) and recurrence-free survival (RFS) were compared among these groups and we also analyzed survival by using a propensity score matching (PSM) model to exclude the influence of patient characteristics.

Research results

The RD patients were significantly older and had lower serum total bilirubin, aspartate aminotransferase, and aspartate aminotransferase levels than the non-RD patients, and no patient received maintenance hemodialysis after surgery. Although the overall postoperative complication rates were similar between the RD and non-RD patients, the proportions of postoperative bleeding and surgical site infection were significantly higher in the RD patients, and postoperative bleeding was the highest in the severe CKD group. Regardless of the degree of comorbid RD, OS and RFS were comparable, even after PSM between the RD and non-RD groups to exclude the influence of patient characteristics, liver function, and other causes of death.

Research conclusions

Comorbid mild RD had a negligible impact on the prognosis of HCC patients who underwent curative hepatectomy with appropriate perioperative management, and close attention to severe CKD is necessary to prevent postoperative bleeding and surgical site infection.

Research perspectives

The present study will be useful for management of HCC patients with CKD in future.

FOOTNOTES

Author contributions: Sakamoto Y, Shimada S, Kamiyama T contributed to the conception and design; Kamiyama T, Kamachi H, Taketomi A involved in the provision of study materials or patients; Sakamoto Y, Shimada S, Sugiyama K, Asahi Y, Nagatsu A, Orimo T, Kakisaka T contributed to the collection and assembly of data; Sakamoto Y, Shimada S, Kamiyama T, Ito YM involved in the data analysis and interpretation; all authors contributed to the manuscript writing; and all authors approved final manuscript.

Institutional review board statement: This study was conducted in accordance with the Declaration of Helsinki (as

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ORIGINAL ARTICLE

Retrospective Study

Individualized risk estimation for postoperative pulmonary complications after hepatectomy based on perioperative variables

Li-Ning Xu, Ying-Ying Xu, Gui-Ping Li, Bo Yang

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Abstract

BACKGROUND

At present, there is no perfect system to evaluate pulmonary complications of liver surgery using perioperative variables.

AIM

To design and verify a risk assessment system for predicting postoperative pulmonary complications (PPCs) after hepatectomy based on perioperative variables.

METHODS

A retrospective analysis was performed on 1633 patients who underwent liver surgery. The variables were screened using univariate and multivariate analyses, and graded scores were assigned to the selected variables. Logistic regression was used to develop the liver operation pulmonary complication scoring system (LOPCSS) for the prediction of PPCs. The LOPCSS was verified using the receiver operating characteristic curve.

RESULTS

According to the multivariate correlation analysis, the independent factors which influenced PPCs of liver surgery were age [≥ 65 years old/< 65 years old, odds ratio (OR) = 1.926, P = 0.011], medical diseases requiring drug treatment (yes/no,

OR = 3.523, $P < 0.001$), number of liver segments to be removed (≥ 3/≤ 2, OR = 1.683, $P = 0.002$), operation duration (≥ 180 min/< 180 min, OR = 1.896, $P = 0.004$), and blood transfusion (yes/no, OR = 1.836, $P = 0.003$). The area under the curve (AUC) of the LOPCSS was 0.742. The cut-off value of the expected score for complications was 5. The incidence of complications in the group with ≤ 4 points was significantly lower than that in the group with ≥ 6 points (2.95% *vs* 33.40%, $P < 0.001$). Furthermore, in the validation dataset, the corresponding AUC of LOPCSS was 0.767.

CONCLUSION

As a novel and simplified assessment system, the LOPCSS can effectively predict PPCs of liver surgery through perioperative variables.

Key Words: Liver surgery; Complication; Pulmonary; Prediction

Core Tip: In this study, a binomial logistic regression model was established to obtain the liver operation pulmonary complication scoring system (LOPCSS). The area under the curve of the LOPCSS was 0.742. As a novel and simplified assessment system, the LOPCSS can effectively predict postoperative pulmonary complications of liver surgery through perioperative factors; therefore, it can be used to evaluate the risk of liver surgical pulmonary complications.

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INTRODUCTION

Compared to other surgical areas, liver surgery is still a relatively complex discipline that requires continuous theoretical exploration and accumulated experience[1,2]. However, liver surgery technology has developed rapidly as a result of the development of information science and encouragement of liver allograft transplantation[3]. The key reason hepatectomy is not applied globally is the high incidence of postoperative complications and high operative mortality[4]. Appropriate preoperative prevention strategies should, therefore, be considered to reduce the risk of postoperative complications. Predicting, evaluating, and intervening in surgical risk and preventing complications of liver surgery have become major clinical problems[5-7]. Postoperative pulmonary complications (PPCs) are important adverse events associated with surgery and anesthesia. The main PPCs include pulmonary insufflation, pneumonia, respiratory failure, and deterioration of potential pulmonary diseases. The treatment cost related to pulmonary complications is high and the average hospital stay is long. PPCs are a major cause of delayed recovery and worse outcomes after hepatectomy[8], their incidence is much higher than that of other important organ complications, and the associated complications can be life-threatening. Current clinical guidelines strongly recommend evaluation of the risk of PPCs. The prediction of PPCs enables individual application of preventive measures and perhaps even early treatment if a PPC eventually starts to develop[9]. Appropriate perioperative prevention strategies should be considered to reduce the risk of PPCs where possible. Since the 1970s, many risk assessment systems have been established and applied; however, these risk assessment systems still have many problems in guiding clinical practice. Currently, there is no perfect prediction and evaluation system for pulmonary complications in liver surgery. Although many factors have been implicated as predictors, few models have been developed using the rigorous methodology required for clinically useful tools[10]. Therefore, establishing a set of risk prediction and evaluation systems for perioperative pulmonary complications with strong clinical operability and improving the safety of liver surgery has become an urgent problem in the clinic.

In this study, perioperative risk factors for PPCs of liver surgery were screened and assessed according to the odds ratio (OR), and the total value of the perioperative risk factors for each patient was calculated. The results of the regression analysis will be used to create a scoring system for PPCs incidence and an associated cut-off value to make perioperative evaluation more intuitive.

MATERIALS AND METHODS

Case selection

Personal medical information files were established for patients undergoing perioperative liver surgery. The inclusion criteria were as follows: (1) Perioperative patients; (2) Complete medical records; and (3) Nonrecent secondary surgery. A total of 1633 cases were collected between January 1990 and December 2020 at the PLA General Hospital. Data were obtained from the medical records department of PLA General Hospital. Among these patients, 682 (41.76%) were diagnosed with benign hepatobiliary disease, including hepatolithiasis, and 951 (58.24%) were diagnosed with malignant hepatobiliary disease, mainly primary hepatocellular carcinoma and intrahepatic cholangiocarcinoma. The mean patient age was 47.80 ± 12.09 years old (range 2–83), with 1017 (62.28%) men and 616 (37.72%) women. After the evaluation formula was obtained, 100 consecutive patients were enrolled in the validation for verification.

Selection of indicators to be screened

Based on other commonly used surgical risk scoring systems and the project team's previous clinical research experience, the perioperative factors analyzed included the patient's basic information, diagnosis, laboratory examination, type of surgery, associated medical diseases, medication history, tumor position, and intraoperative variables (such as operative time, blood loss, blood transfusion). Postoperative conditions included complications and death.

The clinical risk factors were screened according to the occurrence of PPCs in liver surgery

The grouping variables were PPCs and the test variables were perioperative variables. The variables were set according to the grade for ordered classification variables, such as age and bilirubin level. The main risk factors and their relative risk values were determined using Pearson's correlation analysis. All factors that were significantly correlated with postoperative adverse outcomes were included in the multivariate logistic regression analysis. A scoring system was introduced based on the OR values for these factors, which were rounded off to be clinically usable (the risk index was assigned according to the nearest integer for clinical application). The sum of the risk scores of all risk factors for a single patient was considered to be the patient's total risk score for complications. The risk index for all patients with complications was calculated to establish the evaluation system for the risk of pulmonary complications: The liver operation pulmonary complication scoring system (LOPCSS). The cut-off value was used to determine the critical point of complications.

Method for verifying LOPCSS

Receiver operating characteristic (ROC) curves were used to evaluate the resolution of the LOPCSS. The area under the curve (AUC) and cut-off values were calculated.

Statistical analysis

Statistical software (SPSS 25.0) was used for the data analysis. The measurement data are expressed as mean ± SD. Pearson's correlation analysis was used to analyze the relationship between the complications and preoperative factors. Regression analysis was used to conduct a multivariate analysis of the factors affecting surgical complications, and $P < 0.05$ was considered statistically significant.

RESULTS

Incidence of pulmonary complications after liver surgery

A total of 250 pulmonary complications were observed in 205 patients, of whom 26 patients had multiple complications, with an incidence of 12.55% (Table 1).

Screening the perioperative clinical risk factors for postoperative complications

According to the univariate correlation analysis, the preoperative clinical risk factors for different levels of postoperative liver complications were age ($P < 0.001$), medical diseases requiring drug treatment ($P < 0.001$), Child-Pugh grade ($P < 0.001$), number of total liver segments to be removed ($P < 0.001$), blood transfusion ($P < 0.001$), blood loss ($P < 0.001$), operation duration ($P < 0.001$), adjacent organ invasion ($P = 0.007$), and preoperative hospital stay ($P < 0.001$) (Table 2).

According to multivariate correlation analysis, the independent factors influencing postoperative complications of liver surgery were age, medical diseases requiring drug treatment, number of liver segments to be removed, operation duration, and blood transfusion, as shown in Table 3. A scoring system was introduced based on the OR values for these factors, which were rounded to improve the ease of applying the scale clinically, as shown in Table 4.

Table 1 Post-surgical pulmonary complications

Complication-pulmonary	*n*	Ratio (*n*/total number of patients), %
Pleural cavity infection	1	0.06
Respiratory tract infection	3	0.18
Pneumothorax	3	0.18
Respiratory insufficiency	7	0.43
Atelectasis	22	1.35
Pneumonia	30	1.84
Pleural effussion	184	11.27

Predictive efficacy of the simplified scoring system

The ROC curves for each identified independent risk factors are plotted in Figure 1.

The ROC curves of the five combined variables are shown in Figure 2A. The AUC of the five combined variables was 0.742, and the corresponding standard error was 0.019. The cut-off value of the total score, calculated by adding the values of all risk factors, was 5. With this threshold, the incidence of pulmonary complications was 2.95% (33/1118) for patients with a score ≤ 4 and 33.40% (172/515) for patients with a score ≥ 6. The incidence of PPCs between patients with ≤ 4 points and ≥ 6 points was significantly different ($\chi^2 = 297.731$, $P < 0.001$), as shown in Figure 2B.

Validation of the LOPCSS

One hundred consecutive patients were enrolled in the validation group to verify LOPCSS. We analyzed the discrimination ability using ROC curves. The AUC of LOPCSS is 0.767, as shown in Figure 3.

DISCUSSION

Hepatectomy has always been characterized by complexity and a high incidence of complications and mortality. However, in recent years, the safety of hepatectomy has been significantly improved by optimizing the selection of surgical patients, anesthesia, and perioperative management, and especially with the establishment of hepatobiliary surgery as a specialty. For the past fifty years, the safety of hepatectomy has always been at the forefront of liver surgery[11]. With the rapid development of liver surgery, hepatectomy has changed from a risky procedure to a relatively safe one[12]. However, there is still a high incidence of complications and mortality with liver surgery, and appropriate preoperative prevention strategies must be considered to reduce the risk of postoperative complications[13]. However, a complete system for predicting complications of liver surgery based on perioperative factors remains unavailable[14]. Therefore, establishing a set of clinically applicable preoperative risk prediction and evaluation systems for surgical liver complications has become an urgent clinical problem[15,16].

Among the complications of liver surgery, the incidence of pulmonary complications is high[17]. This has a great impact on postoperative rehabilitation, so avoiding pulmonary complications should be considered as a priority by doctors. PPCs not only affect the recovery course and quality of life of patients, but also significantly increase the overall perioperative complication rate and mortality. Previous studies have reported that the incidence of PPCs was 2%–70%[18,19]. PPCs mainly include atelectasis, bronchitis, pneumonia, respiratory failure (postoperative mechanical ventilation time exceeding 48 h or unplanned reintubation), hypoxemia, COPD, or asthma attack. Various risk factors can increase the incidence of PPCs[20]. At present, the clear risk factors mainly include the operation site (such as the upper abdomen), emergency surgery, age > 65 years, duration of operation > 3 h, and poor overall health. Strengthening perioperative airway management, protecting pulmonary function, and reducing pulmonary complications are important to ensure the success of the operation and improve prognosis. In this study, a simplified prediction and evaluation system for PPCs of liver surgery which integrated multiple risk factors was established and verified, and is expected to provide new means for early intervention and treatment.

There are three major difficulties in performing surgery for elderly patients: (1) The decline in organ function and poor tolerance to the operation; (2) Elderly patients often have a variety of accompanying diseases; and (3) Elderly patients recover slowly after surgery. In this study, age was an independent risk factor for PPCs after liver surgery (≥ 65 years/< 65 years, OR = 1.926, $P = 0.011$). Elderly individuals are prone to pulmonary complications, such as pleural effusion and infection after surgery, and some elderly individuals also experience problems such as respiratory failure. This leads to high requirements

Table 2 Univariate analysis of preoperative clinical risk factors related to pulmonary complications of hepatectomy

Variable	*n*	Pearson coefficient	*P* value[1]
Age (years old)		0.087	0.000
≥ 65	147		
< 65	1486		
Medical diseases requiring drug treatment		0.200	< 0.001
Yes	248		
No	1385		
Child-pugh grade		0.093	< 0.001
A	1463		
B, C	170		
Number of segments resected		0.124	< 0.001
≤ 2 segments resected	1046		
≥ 3 segments resected	587		
Blood transfusion		0.182	0.000
Yes	689		
No	944		
Blood loss (mL)		0.103	< 0.001
≥ 800	204		
< 800	1429		
Operation duration (min)		0.169	0.000
≥ 180	922		
< 180	711		
Adjacent organ invasion		0.066	0.007
Yes	18		
No	1615		
Preoperative hospital stay (days)		0.098	0.000
≤ 7	1142		
> 7	491		

[1]Pearson's correlation analysis.

for intraoperative and perioperative management. Therefore, perioperative management strategies should be improved.

Many patients who require surgery often have one or more other medical conditions or comorbidities [21], and this is more common in elderly patients[22]. The physiological function of elderly people decreases with age, and is evidenced by: Decreases in height and body surface area; muscle atrophy; decreases in the total number of metabolically active cells; and decreased function of the heart, blood vessels, respiration, kidney, and other organs. These changes in physiological function lowers the reserve ability to maintain the stability of the internal environment under stress. The stress of surgery increases the burden on the organ systems and oxygen consumption of the body, and myocardial oxygen consumption[23]. With the continuous breakthrough of the traditional surgical exclusion zone, a large number of high-risk surgery patients with liver, kidney, and lung insufficiency have been operated upon, and the number of surgical patients with diabetes, hypertension, heart disease, and other diseases has also increased rapidly. In these high-risk patients, perioperative comorbidities exist alone or in combination with several diseases, and are closely associated with postoperative complications and mortality. In this study, concomitant medical conditions requiring medication were independent risk factors for postoperative complications after liver surgery (yes/no, OR = 3.523, P < 0.001).

Table 3 Multivariate analysis to screen and assign independent influencing factors of post-hepatectomy pulmonary complications

Variable	Odds ratio	*P* value[1]
χ_1: Age (≥ 65 years old/< 65 years old)	1.926	0.011
χ_2: Medical diseases requiring drug treatment (Yes/No)	3.523	< 0.001
χ_3: Number of segments resected (≥ 3/≤ 2)	1.683	0.002
χ_4: Operation duration (≥ 180 min/< 180 min)	1.896	0.004
χ_5: Blood transfusion (Yes/No)	1.836	0.003

[1]Logistic regression.

Table 4 New scoring system

Variable	Conditions	Scores
χ_1: Age	< 65 years old	0
	≥ 65 years old	2
χ_2: Medical diseases requiring drug treatment	No	0
	Yes	4
χ_3: Number of segments resected	≤ 2	0
	≥ 3	2
χ_4: Operation duration	< 180 min	0
	≥ 180 min	2
χ_5: Blood transfusion	No	0
	Yes	2

Note: The total score was calculated as the sum of the five variables.

In recent years, due to the increasing maturity of liver surgery technology, the success rate of resection of giant liver tumors has increased[24], and postoperative complications and mortality have decreased greatly, such that large liver tumors that were considered inoperable in the past can now be safely resected. The main reasons for this are as follows: (1) The development of stereo positioning technology for liver tumors; (2) The development of liver bleeding, hemostasis, and blood transfusion technology; (3) More accurate liver and vascular surgery techniques; (4) Excellent anesthesia management; and (5) Advances in perioperative management. However, the amount of liver resected, and therefore the residual functional liver volume, remains the main factor affecting the curative effect of hepatectomy[25]. This study showed that the number of liver segments removed was an independent risk factor for complications after liver surgery (≥ 3/≤ 2, OR = 1.683, P = 0.002).

However, there are some limitations to measuring the scope of resection based on the number of liver segments. The volume of the left lobe of the liver is smaller than that of the right lobe. Consequently, resection of the two segments of the left lobe is not equivalent to resection of segments 6-7 or 7-8. There are also differences in the surgical difficulty and scope of resection. In this study, considering the complexity of liver anatomy and the possible infiltration of liver tumors into adjacent organs, three indicators (lesion size, number of liver segments removed, and presence of adjacent organ infiltration) were used to evaluate the scope of liver resection. Even with all of these considerations taken into account, the results of this study showed that the removal of > 2 liver segments was an independent risk factor for pulmonary complications.

The surgical duration has long attracted the attention of doctors as an important factor affecting rehabilitation after general anesthesia. The surgical duration mainly reflects the complexity of the operation. With the development of modern surgical medicine, operation durations are shorter than ever before; however, under existing conditions, the operation duration is still one of the main factors hindering rehabilitation after general anesthesia. The extension of the operation duration has a great impact on postoperative respiration, digestion, physiological response, and the recovery of autonomic function, and affects the quality of postoperative rehabilitation. Additionally, the operation duration can affect the occurrence of PPCs[26]. A longer duration of surgery has a significant impact on postoperative respiratory function. Owing to the residual effect of general anesthesia drugs, the respiratory center will

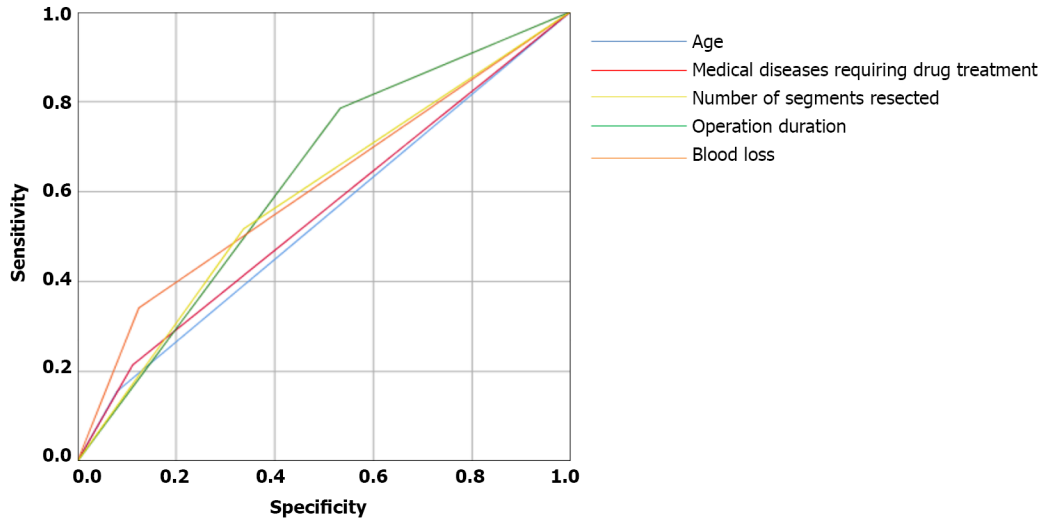

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Figure 1 Predictive efficacy of the five variables. Predictive efficacy of the five variables: The area under the curves for diagnoses of postoperative complication were 0.538, 0.551, 0.626, 0608, and 0.590 for age, blood loss, operation duration, medical diseases requiring drug treatment, and number of segments resected, respectively.

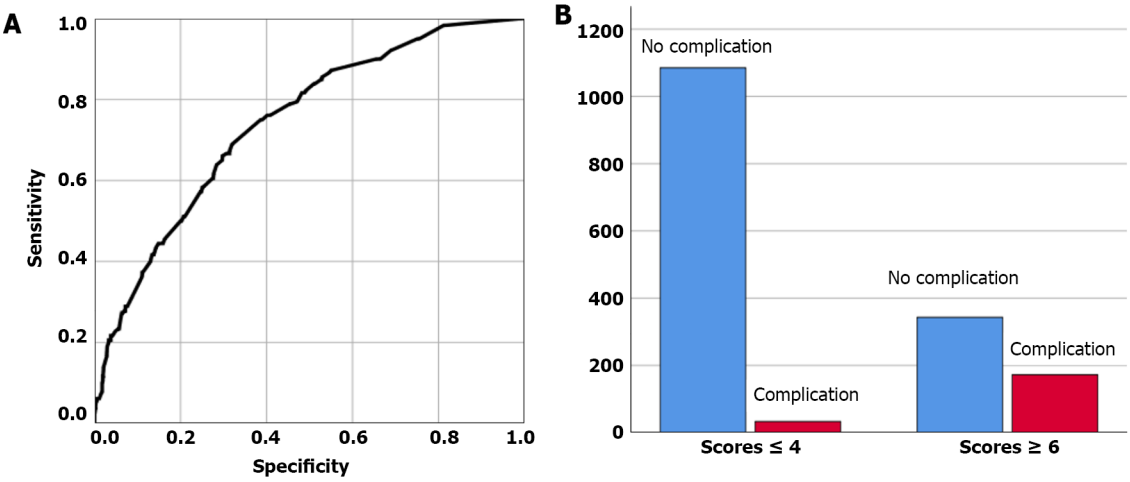

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Figure 2 The predictive efficacy of the combined variables in the liver operation pulmonary complication scoring system. A: The area under the curve of the combined variables was 0.742; B: The incidence of complications in two groups divided based on liver operation pulmonary complication scoring system.

be inhibited to varying degrees, resulting in a weakening of ventilation function, a reduction in tidal volume, and a change in respiratory rate. In addition, the residual effects of muscle relaxants can cause incomplete respiratory tract obstruction and insufficient ventilation. Simultaneously, long-term airway intubation can cause pulmonary infection, and the incidence of PPCs increases. Therefore, it is necessary to actively improve respiratory function. We should make preoperative and emergency plans, optimize the operation process, and shorten the operation time as much as possible. This study showed that the operation duration was an independent risk factor for complications after liver surgery (≥ 180 min/< 180 min, OR = 1.896, P = 0.004).

Blood transfusion is directly related to massive blood loss during surgery, which reflects a wider scope of resection. Because the estimation of intraoperative and postoperative acute bleeding is often inaccurate, the amount of blood transfused is often used as an alternative index of blood loss. As an effective treatment to correct intraoperative blood loss, blood transfusion is widely used in almost all hospitals; however, some negative effects can arise during its use, such as the spread of infectious diseases. In addition, blood transfusion also leads to some related complications[27], such as blood transfusion-related acute lung injury, blood transfusion-related graft-versus-host disease, blood transfusion-related circulatory overload, hemolytic reaction, and immunosuppression. Patients

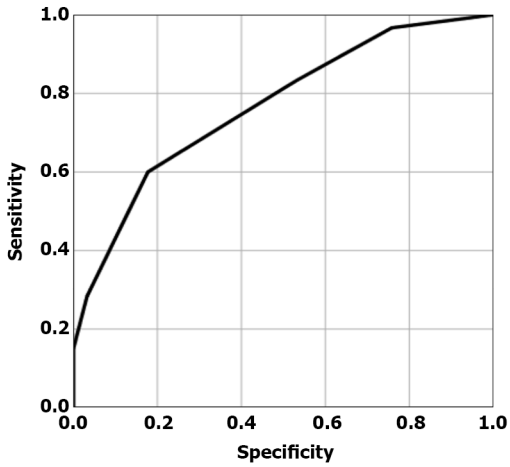

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Figure 3 Validation of the liver operation pulmonary complication scoring system. The area under the curve of the liver operation pulmonary complication scoring system was 0.767.

receiving blood transfusions tend to be older, have more complications, worse basic conditions, and more serious diseases. The adverse consequences of blood transfusion are related to factors such as blood transfusion-related immunosuppression, acute lung injury, changes in the coagulation cascade. Transfusion may cause infection and transfusion-related lung injury, which have an important impact on patient prognosis. Perioperative blood transfusions should be highly valued. Blood transfusions often lead to a significant increase in early mortality of the recipient and affects the prognosis. Attention should be paid to the risk factors for blood transfusions. For patients with risk factors, we should intervene as soon as possible, pay attention to the prevention and treatment of bleeding and blood transfusion-related complications, and prepare for blood transfusion when necessary. In this study, blood transfusion was an independent risk factor for PPCs after liver surgery (yes/no, OR = 1.836, P = 0.003).

Perioperative scoring systems have been developed to assess the risk of PPCs. An important example is the pulmonary complication risk score (PCRS) developed by the National Surgical Quality Improvement Program[28]. However, the PCRS also has limitations. The PCRS is a real-time network calculator based on big data that can only be used after registration with the model software on the internet. Although the prediction model comes from a large multicenter study, it has not been fully validated in countries outside the United States. Moreover, the surgical risk is different in China and the United States, and should be adjusted according to the actual situation in China.

In this study, a binomial logistic regression model was established to obtain the LOPCSS. The AUC of LOPCSS was 0.742 and the cut-off value of the expected score for complications was 5. Furthermore, in the validation dataset, the corresponding AUC of LOPCSS was 0.767. The scoring system has only five parameters, and the values are all integers (0-4); therefore, the calculation is simple to perform. If the patient's score is higher than the cut-off value, the lung function of the patient should be fully adjusted before surgery to achieve the optimum conditions; if the lung function is poor and surgery is necessary, the surgical method should be adjusted to shorten the operation time as much as possible and reduce trauma to the patient.

This study has some limitations. Due to the limited number of cases with pulmonary complications, only internal validation was used in this study. Before the beginning of this study, considering that open liver surgery had more pulmonary complications than laparoscopic liver surgery, it was of great practical significance to study open liver surgery. Therefore, only cases of open liver surgery were included in the present study. At present, with the rapid growth in the number of cases of laparoscopic liver surgeries performed, the significance of studying the risk factors for complications of laparoscopic liver surgery is more prominent, and we plan to study this in future.

CONCLUSION

As a novel and simplified assessment system, the LOPCSS can effectively predict the PPCs of liver surgery through perioperative factors and can be used to evaluate the risk of pulmonary complications associated with liver surgery.

ARTICLE HIGHLIGHTS

Research background

Predicting, evaluating, and intervening in surgical risk and preventing pulmonary complications of liver surgery have become major clinical problems.

Research motivation

Postoperative pulmonary complications (PPCs) are important adverse events associated with surgery and anesthesia. At present, there is no perfect system to evaluate the risk of pulmonary complications following liver surgery using perioperative variables.

Research objectives

This study aimed to design and verify a risk assessment system for predicting PPCs after hepatectomy based on perioperative variables.

Research methods

A retrospective analysis was performed on 1633 patients undergoing liver surgery. All factors that were significantly correlated with postoperative adverse outcomes were included in the multivariate logistic regression analysis. A scoring system [the liver operation pulmonary complication scoring system (LOPCSS)] was introduced based on the odds ratio (OR) values for these factors. The sum of the risk scores of all risk factors for a single patient was the total risk score of the patient's complications. The cut-off value was used to determine the critical point of complications.

Research results

The independent factors influencing PPCs of liver surgery were age (≥ 65 years old/< 65 years old, OR = 1.926, P = 0.011), medical diseases requiring drug treatment (yes/no, OR = 3.523, P < 0.001), number of liver segments to be removed (≥ 3/≤ 2, OR = 1.683, P = 0.002), operation duration (≥ 180 min/< 180 min, OR = 1.896, P = 0.004), and blood transfusion (yes/no, OR = 1.836, P = 0.003). The cut-off value of the expected score for complications was 5.

Research conclusions

As a novel and simplified assessment system, the LOPCSS can effectively predict PPCs of liver surgery using perioperative variables.

Research perspectives

We screened for perioperative risk factors associated with pulmonary complications in liver surgery and established a scoring system to predict the occurrence of complications.

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FOOTNOTES

Author contributions: Xu LN, Xu YY and Li GP contributed equally to this work; Xu LN and Xu YY were the gastroenterologists; Li GP and Yang B performed the radiological diagnosis; Xu LN and Yang B analyzed the data and wrote the manuscript; Xu LN, Xu YY, Li GP and Yang B designed the research, performed the primary literature and data extraction, they were responsible for revising the manuscript for important intellectual content; and all authors read and approved the final version.

Institutional review board statement: The study was approved by the Medical Ethics Committee of the Chinese PLA General Hospital.

Informed consent statement: This is a retrospective study, so informed consent is not involved.

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

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SYSTEMATIC REVIEWS

Skeletal muscle metastasis from colorectal adenocarcinoma: A literature review

Nikhil Kulkarni, Ahmed Khalil, Shruti Bodapati

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Abstract

BACKGROUND

Colorectal adenocarcinoma is the third most common cancer worldwide. It accounts for almost 10% of all cancer-related deaths. Skeletal muscle is a very unusual site for metastasis from colorectal cancers and is associated with a poor prognosis and high mortality.

AIM

To review the literature for cases of skeletal muscle metastasis (SMM) from colorectal adenocarcinoma.

METHODS

A systematic literature search using a validated search strategy was carried out to identify the incidence of SMM associated with colorectal adenocarcinoma. The studies identified were tabulated in a PRISMA, and data was extracted in a tabulated form.

RESULTS

Twenty-nine studies were included in this literature review. SMM was most commonly detected in the thigh muscles. Most of the tumours had originated from the rectum or the right colon. The histopathology of the primary tumour was generally advanced. The mean time interval between the primary tumour and onset of SMM was 22 mo. In 3 cases, asymptomatic SMM had been picked up by advanced imaging systems, like fluorodeoxyglucose-positron emission tomography scan.

CONCLUSION

SMM from colorectal adenocarcinomas is a rare complication. However, it is possible that the low incidence could be due to under-reporting. Early use of

advanced imaging techniques and a high index of clinical suspicion might increase the reporting of SMM from colorectal adenocarcinoma.

Key Words: Skeletal muscle; Metastasis; Colorectal cancer; Adenocarcinoma; Systematic review

Core Tip: Skeletal muscle metastasis (SMM) from a colorectal adenocarcinoma is a rare complication. Presentation usually occurs at a late stage, and prognosis remains poor. However, with a high index of suspicion and early use of advanced investigative modalities, like fluorodeoxyglucose-positron emission tomography scan, SMM can be detected and treated at an earlier stage. Further research is required to better understand the prognosis and pathophysiology of SMM.

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INTRODUCTION

Colorectal cancer is the third most common cancer worldwide, with at least 1.8 million new cases reported across the globe in 2018, and accounting for almost 10% of all cancer-related deaths worldwide [1,2]. Fortunately, there have been significant improvements in the life expectancy and survival rates after colorectal cancer. In particular, over the last 40 years, 5-year survival rates after a diagnosis of colorectal cancer have increased from 22% to 57%[2]. The improvement in survival has been attributed to a plethora of reasons, including screening and surveillance programmes, advanced endoscopic diagnostic and therapeutic techniques, use of minimally invasive surgical approaches (like laparoscopic and robotic techniques), and refined adjuvant and neoadjuvant chemotherapy and radiotherapy options.

Metastasis of colorectal cancer occurs *via* lymphatic, hematogenous and direct-spread routes, with the most common secondary sites being the liver, lungs, peritoneum, lymph nodes, and bones[3]. Intriguingly, although skeletal muscles constitute almost 50% of the total body mass, the incidence of metastasis to skeletal muscles from all forms of cancers is extremely low[4]. Many studies have commented on the possible reasons for the relatively low incidence of metastases to skeletal muscles. Hypotheses include variable blood flow to skeletal muscles, rare incidence of microvasculature damage due to cancer cells in skeletal muscles, and production of a low molecular weight non-protein factor that may inhibit tumour cell proliferation[5].

The aim of this study was to review the literature for cases of skeletal muscle metastasis (SMM) from colorectal adenocarcinoma.

MATERIALS AND METHODS

A systematic literature search was carried out in December 2021, using a validated search strategy as described below.

Search strategy

The search was performed using Reference Citation Analysis, PubMed, Medline, Embase, Cochrane Library and Google Scholar databases. Journals, as well as society websites, were also searched using the search terms "skeletal muscle metastasis", "colorectal cancer", "case reports", and "review." The search strategy was standardized using the PRISMA guidelines. Two researchers (Khalil A, Bodapati S) reviewed the summary and abstracts of the articles. A full-text review was then performed by all three authors.

Inclusion criteria

Articles that were not available in English language were excluded from the study. Only studies with full texts available that included data for pathological evidence of SMM from colorectal origin were considered. Studies with pathology data other than adenocarcinoma were excluded. No other exclusion criteria were used. The data were extracted by the three researchers and included patient characteristics,

year of publication, site of primary tumour, presenting symptom, type of surgery performed for the primary lesion, site of skeletal and non-skeletal metastasis, time interval for onset of skeletal metastasis, and final outcome.

Information about the number of relevant citations, number and reasons of studies excluded after full assessment, as well as number of studies included in the systematic review fit in a well-designed PRISMA diagram, as presented in Figure 1.

RESULTS

Characteristics of studies

The initial search yielded 138 eligible studies, of which 29 ultimately fit our inclusion criteria for the review (all case reports). These studies covered a total of 30 patients. Detailed characteristics of the studies are shown in Table 1.

Patient profiles

The median age of the patients was 67 years (range: 23-83 years), with 19 male patients and 11 female patients. The primary tumour was present in the right colon in 10 patients, transverse colon in 4, left colon in 5, and rectum in 11. The presenting symptoms were pain (6 patients), palpable lump (4 patients), painful lump (9 patients), and ocular symptoms (2 patients). Three of the patients had the SMM incidentally diagnosed by imaging. Only 3 of the reported cases mention an early primary lesion (tubulovillous adenoma with high-grade dysplasia or T2 stage tumours). Six cases reported indicated that the primary lesion was of an advanced nature (T3 or T4). The tumours were either moderately or poorly differentiated in 6 cases. Four of the reported cases indicated that the primary lesion was either a mucin-secreting tumour or signet ring cell tumour.

SMM distribution

The mean time interval between the diagnosis of the primary tumour and presentation of SMM was 22 mo. Six cases were diagnosed synchronously with the metastasis. There were a wide range of skeletal muscles that were involved in the metastasis, as follows: Upper limb (extensor carpi ulnaris, thenar, deltoid, biceps); lower limb (thigh, tibialis anterior, semimembranous, adductor, sartorius, vastus lateralis); trunk (teres major, glutei, external oblique, neck muscles, paraspinal, rectus abdominus, intercostal, psoas, piriformis); and, extraocular muscles (lateral rectus, superior rectus). However, the most common site of metastasis was the thigh muscle. In 8 cases, the skeletal muscles were the only site of metastasis.

There was no detailed information about the duration of follow-up and final outcome of the disease; however, 10 case reports mentioned that the patients did not survive the disease.

DISCUSSION

Colorectal cancers account for 10.7% of all new cancers reported worldwide[2]. Our literature review has shown that since 1970, only 30 cases of SMM due to colorectal adenocarcinomas have been reported. This highlights the extremely low incidence of skeletal muscle as a metastatic site due to colorectal adenocarcinoma.

The primary pathology in the majority of the patients was in the rectum (11 patients) and the right colon (10 patients). Left-sided colonic tumours accounted for 5 of the cases and transverse colon for 4. A large meta-analysis carried out by Prasanna *et al*[6] highlighted the different metastatic patterns of colorectal cancers, depending on the site of the primary tumour. This study showed that right colonic tumours were more frequently associated with peritoneal seeding, and rectal tumours were more frequently associated with lung, brain and bone metastases compared to left colonic tumours. Though SMMs were not mentioned in this meta-analysis, the general pattern of higher metastases in right colonic and rectal tumours was also seen in our review. Only 8 patients had no documented simultaneous metastasis in non-skeletal muscles. The other patients had metastases in non-skeletal muscle sites.

The most common presenting symptom of the SMM was a painful lump (9 patients). Six patients had a palpable lump with no description of pain, and 6 patients had pain as the presenting symptom. Three patients had the SMM diagnosed incidentally by imaging. The importance of advanced imaging techniques, especially fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning, for diagnosis of SMM has been highlighted by Emmering *et al*[7]. Lesions that cannot be detected by routine contrast computed tomography or magnetic resonance imaging can be observed by FDG-PET scans. FDG-PET had a significant impact on early diagnosis and patient management in 51% of cases with muscle metastasis. Hence, if there is a suspicion of SMM, the early use of FDG-PET should be encouraged for diagnosis.

Table 1 Characteristics of case reports of skeletal muscle metastasis in colorectal adenocarcinoma

Case	Ref.	Age/sex	Site of primary tumour	Presenting symptom	Surgery of primary tumour	Histology of primary	Site of skeletal metastasis and treatment	Non-skeletal metastases	Time interval in mo	Follow-up/outcome
1	Hasegawa *et al*[14], 2000	60/M	Transverse colon	Not described	Transverse colon resection and lymph node dissection + FOLFOX	Adenocarcinoma	Right extensor carpi ulnaris muscle; a major part of the right extensor carpi ulnaris and the extensor digiti minimi muscle were resected, warranting a sufficient margin of 5 cm of normal tissue from the tumour	Multiple hepatic metastases detected 14 mo after primary resection and was resected	24	Alive
2	Buemi *et al* [3], 2019	69/F	Right colon	Pain when mobilizing left leg + elevated CEA of 7.7 ng/mL	Right hemicolectomy	pT3N0M0 (0/44 lymph nodes)	Left gluteus muscle; lesion was resected en bloc		7	Alive; 6 yr after colectomy and 65 mo after resection of the muscular metastasis she was tumour free with normal CEA level
3	Yi *et al*[17], 2015	67/M	Caecum	Swelling and pain	Right hemicolectomy and subsequent chemotherapy with a regimen containing oxaliplatin	Poorly differentiated	Right thenar muscles	Liver, right kidney, right abdominal wall, left axillary and right subclavicular lymph nodes, skin of right thigh; treatment was given with palliative systemic chemotherapy (FOLFIRI)	Synchronous	Dead (9 mo after diagnosis)
4	Araki *et al* [18], 1994	66/M	Ascending colon	Painful lump	Right hemicolectomy		Right teres major; excision of the mass was performed		6	Dead (31 mo after surgery)
5	Manafi-Farid *et al*[19], 2019	23/M	Rectum	Incidentally detected in FDG-PET studies	Proctocolectomy preceded by neoadjuvant chemotherapy and followed by adjuvant chemotherapy, including the FOLFOX regimen	pT3N1	Multiple: Deltoid, external oblique, biceps, tongue; excisional biopsy of the deltoid muscle lesion proved to be metastatic adenocarcinoma; commenced chemotherapy (FOLFIRI)	Lung/adrenal gland/scalp	24	Alive
6	Torosian *et al* [20], 1987	69/M	Transverse colon		Extended right colectomy		Left thigh; en bloc resection was performed		60	Not specified
7	Okada *et al* [21], 2009	70/M	Rectum	Painful lump	Rectal resection		Right thigh; resection and chemotherapy were given	Lung	12	Alive; the resection of SMM made a positive contribution to his quality of life
8	Chang *et al* [22], 1994	62/M	Descending colon	Painful lump			Left tibialis anterior; excision of the mass was performed		Synchronous	Not specified
9	Yoshikawa *et al*[23], 1999	54/M	Sigmoid colon	Severe buttocks pain	Partial sigmoid colectomy		Right buttocks; en bloc resection performed	Multiple metastases	24	Died after 8 mo from multiple metastases

10	Guo *et al*[16], 2021	43/M	Ascending colon	Right thigh mass 4 cm × 4 cm with intolerable pain	Laparoscopic extended right hemicolectomy and four cycles of chemotherapy with CapeOX	PT4N2bM0; poorly differentiated adenocarcinoma	Right thigh; a complete resection was suggested but was refused by the patient; unresponsive to FOLFIRI; switched to bevacizumab, irinotecan, and capecitabine	Bony metastasis and multiple lymph node metastases around the abdominal aorta	5	Deteriorated and died 9 mo after primary resection
11	Tatsuta *et al* [24], 2022	83/M	Ascending colon	Pain in the back of his neck	Curative resection	Adenocarcinoma	Cervical (neck muscle); he was prescribed palliative radiation therapy because of his poor performance status	None	11	Died 2 mo after diagnosis of muscle metastasis
12	Iusco *et al* [25], 2005	73/F	Ascending colon	Painful lump	Right hemicolectomy	Dukes C	Left calf; the mass was excised and received adjuvant radiotherapy	None	24	Alive; no sign of recurrence at a 2-yr follow-up
13	Landriscina *et al*[9], 2013	71/F	Right colon	Detected on PET/CT scan	Right hemicolectomy with subsequent systemic neoadjuvant chemotherapy for liver metastasis followed by radical hepatectomy	Poorly differentiated adenocarcinoma	Deltoid, sternocleidomastoid and other multiple sites; chemotherapy with FOLFOX was administered for 3 cycles but discontinued due to traumatic femur fracture	Liver/lung	23	Disease progression and death
14	Hattori *et al* [26], 2008	64/F	Rectum	Asymptomatic; increased CEA; discovered by FDG-PET	Abdominoperineal rectal resection	Moderately differentiated adenocarcinoma	Right thoracic paraspinal muscles; *en bloc* excision was performed including the paraspinal muscles	Solitary lung metastasis, which was resected 3 yr previously by lobectomy with subsequent immunochemotherapy	96	Alive
15	Choi *et al* [27], 2008	83/F	Rectum	Painful lump	Low anterior resection and right liver lobectomy	T2N1M1	Semimembranous muscle of right thigh	Solitary pulmonary nodule in left lobe	48	Died of heart failure on second postoperative day
16	Doroudinia *et al*[28], 2019	48/M	Rectum	Subcutaneous lump	Abdominoperineal rectal resection followed by adjuvant radiotherapy and chemotherapy	High grade mucinous adenocarcinoma	Right proximal thigh; the patient became a candidate for tumour excision (metastasectomy) followed by additional course of chemotherapy.	None	38	Not specified
17	Tunio *et al* [29], 2013	28/M	Transverse colon	Abdominal pain and hard nodule at anterior abdominal wall	Extended right hemicolectomy; radiotherapy; FOLFOX4	Mucinous moderately differentiated adenocarcinoma T4N2bM0	Rectus abdominis muscle and right gluteus maximus; underwent palliative radiotherapy followed by systemic chemotherapy	None	11	Alive at time of publication with progressive disease
18	Simeunovic *et al*[30], 2014	55/F	Rectum	Lower back pain and left hip pain as first manifestation of the primary tumour	Radiotherapy; chemotherapy with FOLFOX	Poorly differentiated adenocarcinoma	Left adductor muscle	None	Synchronous	Not specified
19	Prabhu *et al* [31], 2017	69/M	Rectum	Severe low back ache	Neoadjuvant; abdominoperineal resection; capecitabine	Adenocarcinoma with signet ring cell features T3N2; Dukes C1	Multiple skeletal muscles: left sartorious, left vastus lateralis, left infraspinatus, left levator scapulae, left tenth	None	4	Not specified

							Intercostal muscle, right subscapularis muscle			
20	Tai *et al*[32], 2014	81/M	Caecum	Severe right shoulder pain	Palliative chemotherapy; palliative right hemicolectomy	Poorly differentiated adenocarcinoma	Right supraspinatus muscle	Right lobe of lung	Synchronous	Patient transitioned to hospice
21	Farraj *et al* [33], 2021	52/F	Rectum	Noted with preoperative staging	Low anterior resection; adjuvant combination of oxaliplatin, capecitabine, and pelvic external beam radiation therapy	Moderately differentiated adenocarcinoma T2N1a	Left psoas muscle	None	Synchronous	Patient is currently maintained on platinum doublet chemotherapy with control of metastatic disease
22	Salar *et al* [34], 2012	67/F	Rectum	Deep pelvic and left buttock pain	EUA; submucosal polypectomy	Tubullovillous adenomatous polyp with high grade dysplasia	Left piriformis muscle	None	18	Patient began cycles of chemoradiotherapy with plans for further surgical resection
23	Homan *et al* [35], 2000	72/F	Descending colon		Surgical resection; FOLFOX		Thigh			NA
24	Takada *et al* [36], 2011	71/M	Sigmoid colon		Radiotherapy; FOLFOX; resection "Hartmann"	Stage III adenocarcinoma	Left iliopsoas muscle; received radiotherapy and 15 courses of FOLFOX + bevacizumab for decreasing large and unresectable tumour; then resection was performed	GI metastasis	60	5 mo after resection of muscle metastasis, there was no recurrence
25	Naik *et al* [37], 2005	56/M	Ascending colon	A lump	Resection; chemotherapy FOLFOX; radiotherapy	Mucin secreting adenocarcinoma	Rectus abdominis muscle; resection was performed	NA	60	Not specified
26	Burgueño Montañés and López Roger[38], 2002	60/M	Rectosigmoid	Exophthalmos	Radiotherapy; FOLFOX		Lateral rectus muscle			Not specified
27	García-Fernández *et al* [39], 2012	32/M	Colon	Palpebral oedema, conjunctival chemosis, severe exophthalmos, complete ptosis in left eye and limitation in eye movement mainly in abduction and supraversion	Resistant to chemotherapy	Stage IV	Superior rectus elevator muscle of upper eyelid complex and external rectus muscle			Due to the patient generally feeling unwell, radiotherapy was not considered, and an intravenous bolus of corticoids was given, without response, resulting in the death of the patient
28	Lampenfeld *et al*[40], 1990	75/F	Rectum	Progressive growth of left buttock mass	Excision of mass	Adenocarcinoma	Left gluteus maximus and medius		24	
29	Laurence and Murray[41], 1970; Case 1	70/F	Caecum	Painful mass in posteroexternal aspect of right calf and leg	Right hemicolectomy	Ulcerated villous adenocarcinoma	Right calf; en bloc resection was performed	Generalized metastasis	24	Died due to generalized metastasis

				oedema				
30	Laurence and Murray[41], 1970; Case 2	51/M	Transverse colon	Right colectomy	Right forearm; en bloc resection was performed	Generalized metastasis	Synchronous	Died due to generalized metastasis

CapeOX: Combination of capecitabine and oxaliplatin; CEA: Carcinoembryonic antigen; EUA: Examination under anaesthesia; F: Female; FDG-PET: Fluorodeoxyglucose positron emission tomography; FOLFOX: Combination of folinic acid, 5-fluorouracil and oxaliplatin; FOLFOX4: Combination of 5-fluorouracil, leucovorin and oxaliplatin; FOLFIRI: Combination of leucovorin, 5-fluorouracil and irinotecan; GI: Gastrointestinal; M: Male; NA: Not available; PET/CT: Positron emission tomography computed tomography; SMM: Skeletal muscle metastasis.

Our review showed that most of the primary tumours were of an advanced nature (either T3 or T4 with positive lymph node status and poor differentiation). Three patients had mucinous features, and 1 patient had signet ring cell features. This raises the possibility that colorectal cancers with advanced aggressive features on the primary pathology have a higher incidence of SMM. Studies have shown that colorectal cancers with advanced pathological features have worse outcomes than early cancers[8]. It has been proposed that the presence of other coexisting pathologies could increase the chances of getting SMM due to colorectal adenocarcinomas. Landriscina *et al*[9] commented that dermatomyositis and other paraneoplastic syndromes could increase the chances of getting SMM. Kanani *et al*[10] also documented a case of multiple SMM associated with colorectal adenocarcinoma and non-Hodgkin's lymphoma with ulcerative colitis. However, no other studies in our literature review commented on any other coexisting pathologies.

The use of minimally invasive approaches has revolutionized the surgical treatment of colorectal cancers. Colorectal resections are now routinely undertaken with the laparoscopic and robotic approaches. Patients have smaller incisions, shorter hospital stays and equal oncological outcomes[11]. The use of laparoscopic surgery for colorectal procedures started in 1990 but became more widespread only in the 21st century. Our case reports were from a lengthy time period, beginning in 1970. Only two case reports specifically mention the use of a laparoscopic approach for the resection. Previous studies have shown that the incidence of distant metastasis and peritoneal seeding is not different between laparoscopic and open approaches[12]. In our search. we did not find any studies that observed that the laparoscopic approach led to fewer distant metastases. However, due to the advantage of decreased environmental exposure due to operating in closed cavities and smaller incisions, the possibility always remains that peritoneal seeding and subsequent metastasis incidence could be lower in minimally invasive approaches.

The incidence of SMM was detected in up to 5.6% of patients in a post-mortem series of cancer patients[13]. However, the incidence of SMM due to colorectal cancers is still extremely low and has been reported to be about 0.028%[14]. The outcome from SMM is generally poor. A large study investigating soft tissue metastases postulated that the survival time from diagnosis to death is 5.4 mo[15]. The studies included in our review were all case reports, and the duration of follow-up was not documented in most of these studies. Hence, it is not possible to comment on the exact mortality of SMM from our study. However, the presence of SMM generally indicates disseminated disease, which would indicate a very poor prognosis.

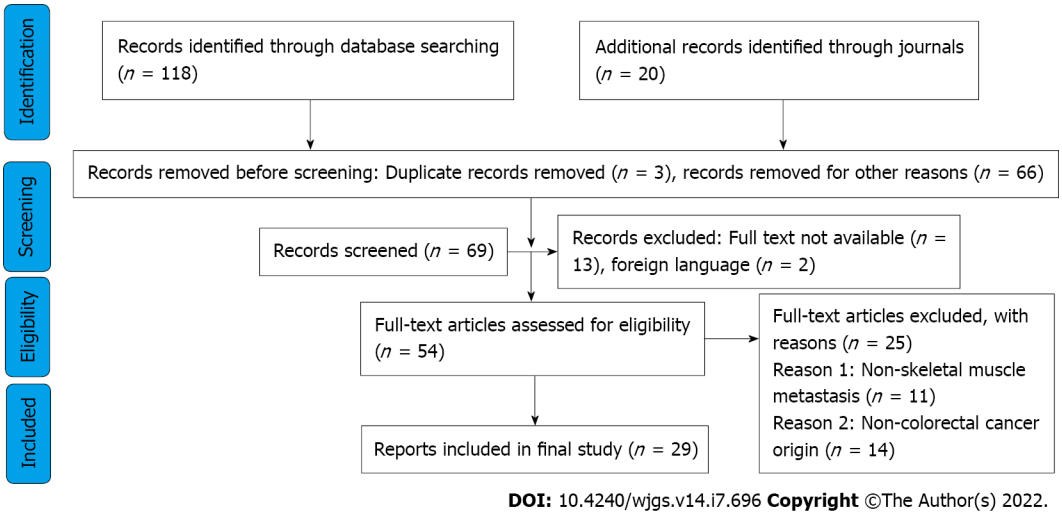

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Figure 1 Flow diagram of the study design according to PRISMA 2009.

There have been previous studies that have studied the incidence of SMM due to colorectal cancer [16]. However, we found SMM has been documented in 30 patients in the literature. We believe that this is the maximum number of cases of SMM due to colorectal cancers that have been reported in the literature. All the studies identified were case reports, and very few of these had long-term follow-up. Hence, it is not possible to definitely comment on the treatment strategies and long-term outcomes for these patients. This study again highlights that there is a paucity of literature on SMM due to colorectal adenocarcinoma. This is certainly a field that needs more research in the future.

CONCLUSION

Our review showed that SMM from colorectal adenocarcinomas is a rare complication. However, it is possible that the low incidence could be due to under-reporting. Early use of advanced imaging techniques like FDG-PET and a high index of clinical suspicion might increase the reporting of SMM from colorectal adenocarcinoma.

ARTICLE HIGHLIGHTS

Research background

Skeletal muscle metastasis (SMM) is a rare complication of colorectal adenocarcinomas. The study was conducted to explore, in more detail, the present literature of this unusual finding.

Research motivation

The study encompassed a thorough review of the present literature on SMM due to colorectal adenocarcinoma. Our goal was to highlight the significance of this type of metastasis and increase awareness for early diagnosis and detection.

Research objectives

The aim of this study was to review the literature for cases of SMM from colorectal adenocarcinoma.

Research methods

A systematic literature search was carried out in December 2021. The search strategy was standardized using the PRISMA guidelines.

Research results

SMM were most commonly detected in the thigh muscles. Most of the tumours originated from the rectum or the right colon. The mean time interval between the primary lesion and onset of SMM was 22 mo.

Research conclusions

Our review showed that SMM from colorectal adenocarcinomas is a rare complication. However, it is possible that the low incidence could be due to under-reporting. Early use of advanced imaging techniques, like fluorodeoxyglucose-positron emission tomography, and a high index of clinical suspicion might increase the reporting of SMM from colorectal adenocarcinoma.

Research perspectives

This study again highlights that there is a paucity of literature on SMM after colorectal adenocarcinoma. This is certainly a field that needs more research in the future.

FOOTNOTES

Author contributions: Kulkarni N conceptualized and designed the review; Khalil A and Bodapati S performed the initial literature review; all authors analysed the data; Kulkarni N and Khalil A wrote the final manuscript.

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CASE REPORT

Percutaneous aspiration and sclerotherapy of a giant simple hepatic cyst causing obstructive jaundice: A case report and review of literature

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Abstract

BACKGROUND

Giant simple hepatic cysts causing intrahepatic duct dilatation and obstructive jaundice are uncommon. A variety of measures with different clinical efficacies and invasiveness have been developed. Nonsurgical management, such as percutaneous aspiration and sclerotherapy, is often applied.

CASE SUMMARY

The case is a 39-year-old female with a 5-mo history of cutaneous and scleral icterus, loss of appetite, and dark urine. Lab tests showed jaundice and liver function abnormalities. Imaging revealed a giant simple hepatic cyst obstructing the intrahepatic bile ducts. A combination of percutaneous catheter aspiration and lauromacrogol sclerotherapy was successfully performed and the effects were satisfactory with the size of cyst decreasing from 13.7 cm × 13.1 cm to 3.0 cm × 3.0 cm. Further literature review presented the challenges of managing giant simple hepatic cysts that cause obstructive jaundice and compared the safety and efficacy of a combination of percutaneous aspiration and lauromacrogol sclerotherapy with other management strategies.

CONCLUSION

Giant simple hepatic cysts can cause obstructive jaundice, and a combination of percutaneous catheter aspiration and sclerotherapy with lauromacrogol are suggested to treat such cases.

Key Words: Simple hepatic cyst; Obstructive jaundice; Aspiration; Sclerotherapy; Lauromacrogol; Case report

Core Tip: Giant simple hepatic cysts causing obstructive jaundice are uncommon. Here we presented the challenges of managing giant simple hepatic cysts causing obstructive jaundice and compared the safety and efficacy of percutaneous aspiration and lauromacrogol sclerotherapy with other management strategies. The case is a 39-year-old female with jaundice and liver function abnormalities. Images revealed a giant simple hepatic cyst with obstruction of intrahepatic bile ducts. A combination of percutaneous catheter aspiration and lauromacrogol sclerotherapy was conducted successively, achieving satisfactory efficacy. Therefore, a combination of percutaneous aspiration and lauromacrogol sclerotherapy may be suggested to solve such cases.

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INTRODUCTION

Hepatic cysts occur in 2.5%-18% of the population[1-3]. They generally include a cluster of diseases with heterogeneous pathogenesis and etiology, including simple hepatic cysts, infectious cysts, cystic neoplasms, biliary duct-related cysts and some congenital polycystic liver diseases[4]. Most simple cysts are asymptomatic and are incidentally identified during imaging examinations, including ultrasonography (US), computed tomography (CT) or magnetic resonance imaging[5,6]. Only 5%-16% of simple hepatic cysts become symptomatic due to mass effects, rupture, hemorrhaging, or infection[5,7,8]. They mainly present as abdominal pain, nausea, vomiting and occasional jaundice[9,10].

The management of simple hepatic cysts widely differs according to clinical manifestations, imaging features, and, sometimes, patient preference. A watch-and-see strategy is acceptable for asymptomatic simple cysts, whereas interventions are required if cysts cause severe symptoms or complications. Various treatment methods with different clinical efficacies and levels of invasiveness have been developed. For nonsurgical management, percutaneous aspiration, sclerotherapy, and internal drainage are often used[8,9]. Surgical treatment mainly includes unroofing, cyst fenestration, hepatectomy, and open or laparoscopic liver transplantation[11]. Treatment selection depends on cyst location, size, surroundings and other factors[12,13].

Here, we report a case of a giant simple hepatic cyst in the hepatic hilum causing intrahepatic duct dilatation and obstructive jaundice. A combination of percutaneous aspiration and lauromacrogol sclerotherapy was performed and achieved satisfactory effects. The related literature was reviewed to better understand management in similar patients.

CASE PRESENTATION

Chief complaints

A 39-year-old female was admitted for cutaneous and scleral icterus, loss of appetite, and dark urine for 5 mo.

History of present illness

A 39-year-old female was admitted for cutaneous and scleral icterus, loss of appetite, and dark urine for 5 mo.

History of past illness

The patient used to be in good health and had no previous medical history.

Personal and family history

The patient's personal habits, customs, and family history were unremarkable.

Physical examination

Physical examination revealed moderate jaundice without abdominal tenderness, hepatomegaly, or Murphy's sign.

Laboratory examinations

Lab tests showed jaundice [total bilirubin (TBil) level was 149.8 μmol/L, and direct bilirubin (DBil) level was 118.7 μmol/L], liver function abnormalities (liver function test levels included the following: Alanine transaminase (ALT) was 175 U/L, aspartate aminotransferase (AST) was 130 U/L, gamma-glutamyl transpeptidase was 454 U/L, alkaline phosphatase was 314 U/L) and moderate anemia [the hemoglobin (HGB) level was 75 g/L]. Tumor markers were unremarkable except for a slightly elevated carcinoma embryonic antigen (CEA) level of 6.1 ng/mL (normal range: 0-5). Antibodies for hepatitis virus, primary biliary cholangitis and autoimmune hepatitis were all within the normal limits.

Imaging examinations

The abdominal US and the endoscopic US showed an enlarged liver (3.7 cm below the xiphoid process) and an anechoic area (increasing from 11.2 cm × 9.9 cm to 13.7 cm × 13.1 cm in three months) with a clear boundary and no peripheral blood flow, and the intrahepatic bile duct of the left lateral segment was approximately 0.6 cm wide. Magnetic resonance cholangiopancreatography showed several hepatic cysts. The largest cyst was approximately 9.5 cm × 11 cm in size, located in the hilum, and obstructed the intrahepatic bile ducts. Three-dimensional reconstruction of the biliary tract showed dilatated intrahepatic bile ducts and compressed hepatic vessels and branches of the portal vein (Figure 1).

Notably, esophagogastroduodenoscopy and colonoscopy were performed and excluded gastrointestinal neoplastic diseases.

FINAL DIAGNOSIS

A giant simple hepatic cyst complicated with obstructive jaundice was the diagnosis.

TREATMENT

We successfully performed a combination of percutaneous catheter aspiration and sclerotherapy with lauromacrogol. During percutaneous catheter aspiration under the guidance of US, the giant cyst was punctured with an 18-gauge pig-tail catheter. Postoperative drainage was favorable, and a total of 800 milliliters of clear yellow fluid was drained; bilirubin levels, tumor markers (such as CEA level) and cytology tests were unremarkable. Jaundice (TBil was 66.4 μmol/L, DBil was 51.2 μmol/L) and liver function anomalies (ALT was 90 U/L, AST was 59 U/L) were significantly relieved soon after drainage.

Then, two sessions of sclerotherapy (lauromacrogol) of the hepatic cyst were performed (30 mL and 20 mL lauromacrogol mixed with triple amounts of air) at one week. Of note, before sclerotherapy, the communications of the cyst with the surrounding bile ducts were ruled out by injecting a diluted contrast medium into the cyst cavity. After sclerotherapy, a small amount of cyst fluid was drained, and the tube was removed. The patient was generally in good condition. He was discharged and experienced further improvement in his liver function (ALT level was 38 U/L, TBil level was 34.9 μmol/L, and DBil level was 33.5 μmol/L; Figure 2).

OUTCOME AND FOLLOW-UP

During follow-up, the patient reported continued resolution of his symptoms. Three months after treatment, the size of the liver cyst decreased to 6.5 cm × 5.6 cm, and liver function returned to normal limits. Fourteen months after treatment, the size of the cyst had decreased to 3.0 cm × 3.0 cm on US.

DISCUSSION

Most simple liver cysts are asymptomatic and stable in size and structure, which allows for observation. However, some of these tumors gradually grow and eventually cause symptoms due to large size, rupture, hemorrhaging, infection, or neoplasm in rare cases[8,14]. Symptoms, including abdominal discomfort or pain, nausea, vomiting, jaundice, early satiety, and even dyspnea[9,10], are largely related to cyst size and location and are more often attributed to larger cysts and right-sided cysts[9,15]. In a recent review, abdominal pain was reported to be the most common symptom of simple hepatic cysts and was reported by 60% (456 of 764) of the patients[16].

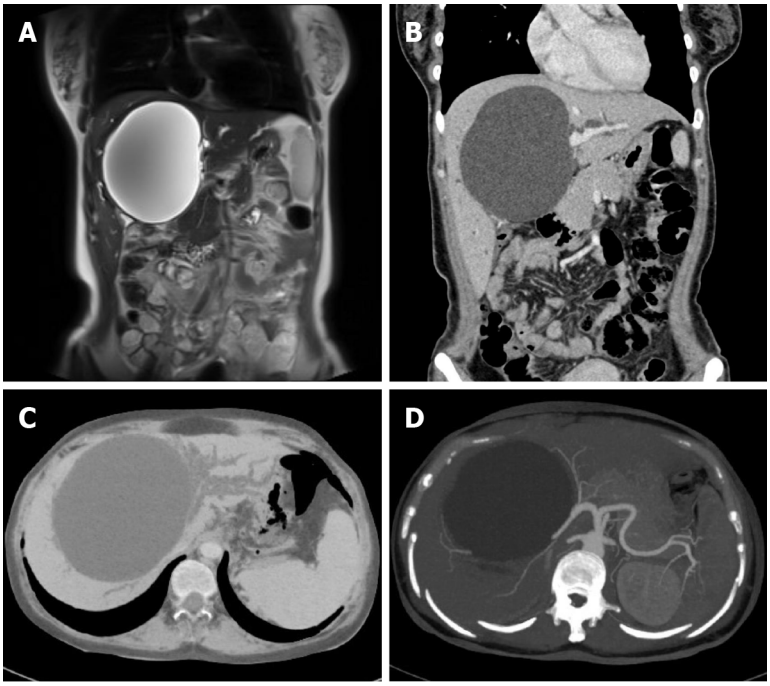

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Figure 1 Initial radiographic assessments of the cyst. A: Magnetic resonance cholangiopancreatography displayed a giant hepatic cyst approximately 9.5 cm × 11 cm in size located in the hilum and obstructed intrahepatic bile ducts; B-D: Abdominal contrast-enhanced computed tomography and three-dimensional reconstruction of the biliary tract displayed a hepatic cyst 11.0 cm × 10.6 cm × 12.7 cm in size with compressed hepatic arteries and veins and dilatated intrahepatic bile ducts. Multiple portal vein branches were also involved, and tortuous vessels were seen around the gastric fundus and the spleen.

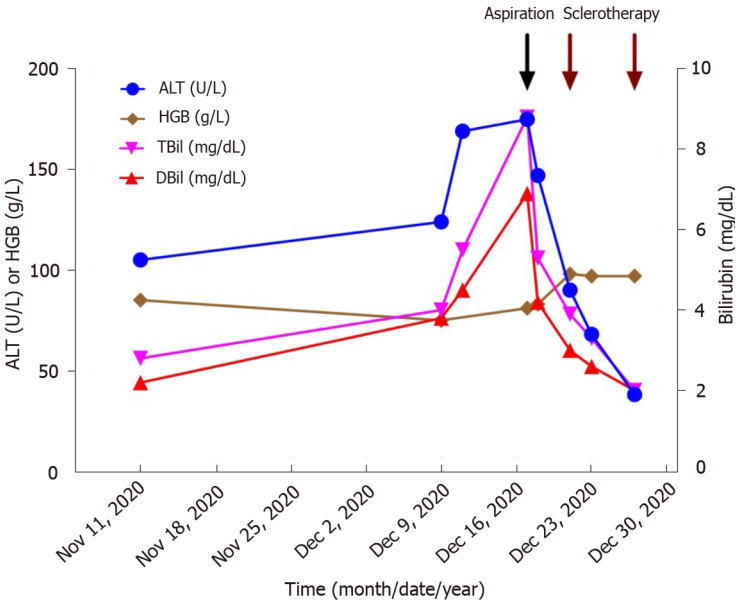

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Figure 2 Changes in hepatic indicators after treatment. The patient successfully underwent percutaneous catheter aspiration on December 17, 2020, and then two lauromacrogol sclerotherapies on December 21 and December 27. After treatment, liver function continuously dropped to normal limits. ALT: Alanine transaminase; HGB: Hemoglobin; TBil: Total bilirubin; DBil: Direct bilirubin.

Obstructive jaundice caused by solitary simple liver cysts is quite rare. A total of 17 cases of simple or benign liver cysts accompanied by obstructive jaundice were reviewed (Table 1)[17-33]. The average age of the patients was 65.2 years old, with a 7:10 female to male ratio. These cysts tended to be large (greater than 10 cm) and centrally located when compression of the main intrahepatic duct or even the hepatic hilum was present. Treatment for these patients varied from aspiration to resection. In recent years, a combination of drainage, sclerosing agent injection, and deroofing seem to be the most common treatment methods. Choledochoscopy was also proven to effectively treat these patients[33]. In our

Table 1 Published cases with simple or benign hepatic cysts causing obstructive jaundice

No.	Ref.	Age/sex	Cyst (cm)	Location (segments)	Total bilirubin (mg/dL)	Treatment	Prognosis	Follow-up period
1	Caravati *et al*[17], 1950	33/M	NA	IV, V	NA	Aspiration + marsupialization	Improved	7 mo
2	Hudson[18], 1963	55/F	25	III, IV, V	14	Cystenterostomy	Improved	1 mo
3	Dardik *et al*[19], 1964	69/F	15	V	9	Cystectomy	Improved	1 mo
4	Sacks *et al*[20], 1967	81/M	20	IV	19	Aspiration	Improved	2 mo
5	Santman *et al*[21], 1977	61/M	15	IV	29	Partial resection	Improved	NA
6	Machell *et al*[22], 1978	67/F	NA	III, IV, V	NA	Drainage + transhepatic T-tube	Improved	7 mo
7	Morin *et al*[23], 1980	80/M	17	IV, V	15	Aspiration only	Improved	10 mo
8	Fernandez *et al* [24], 1984	61/F	30	III, IV, V	22	Partial resection	Improved	24 mo
9	Clinkscales *et al* [25], 1985	80/M	8	IV	8	Aspiration only	Improved	1 mo
10	Cappel *et al*[26], 1988	44/F	12	IV, V	5	Aspiration	Improved	3 mo
11	Spivey *et al*[27], 1990	73/M	11	IV, V	10	Drainage + deroofing	Improved	NA
12	Terada *et al*[28], 1993	71/F	12	III, IV, V	9	Drainage + cystectomy	Improved	1 mo
13	Yoshihara *et al* [29], 1996	88/M	16	IV, V	8	Drainage + minocycline injection	Improved	9 mo
14	Kanai *et al*[30], 1999	71/M	15	IV, V, VIII	5	Drainage + deroofing	Improved	15 mo
15	Ishikawa *et al*[31], 2002	70/M	18	IV, V, VIII	9	Drainage + minocycline injection	Improved	20 mo
16	Ogawa *et al*[32], 2004	64/M	9	NA	NA	Drainage + minocycline injection	Improved	NA
17	Zhang *et al*[33], 2018	41/F	5	IV	24	Choledochoscopic high-frequency needle-knife electrotomy	Improved	36 mo

NA: Not available.

patients, the giant liver cyst caused obstructive jaundice and dilatation of the intrahepatic bile duct of the left lateral segment of the liver, which largely accounted for the patient's symptoms.

Aspiration is generally associated with high recurrence rates[34]. In recent years, percutaneous aspiration combined with sclerotherapy has been widely used as a minimally invasive procedure for simple hepatic cysts with satisfactory results[35-39]. During percutaneous aspiration and sclerotherapy, US- or CT-guided aspiration and drainage are combined with the injection of a sclerosing agent[7,40,41]. Sclerosing agents with good efficacy include ethanol, iophendylate, tetracycline chloride, doxycycline, minocycline chloride, and hypertonic saline solution[42].

While liquid sclerosing agents may mix with cyst contents and reduce sclerosing effects, foam sclerotherapy was initially used for vascular malformations and has evolved as an alternative for treating simple hepatic cysts[43]. The agents in a foam vehicle can completely destroy the intimal barrier after 2 min of exposure, causing endothelial edema, exfoliation from the tunica media, and thrombogenesis in the tunica media in 30 min[44]. Sclerotherapy using lauromacrogol foam is rarely reported for treating hepatic cysts. In one case report, laparoscopic lauromacrogol sclerotherapy surgery was reported to be safe and effective in patients with IVa, VII and VIII segment simple hepatic cysts, but more studies are needed to confirm their conclusion[45]. Our case report is the first to combine percutaneous aspiration with sclerotherapy using lauromacrogol in treating a giant simple hepatic cyst, thus proving the safety and efficacy of the therapy. Single or multiple sessions of percutaneous aspiration and sclerotherapy for persistent or recurrent symptoms are adaptable based on cyst features, efficacy and doctor or patient

preference[7]. In our patients, sclerotherapy with lauromacrogol was planned and administered twice to achieve a better sclerosing effect.

Surgical treatment of simple hepatic cysts, such as open or laparoscopic cyst deroofing or hepatectomy, can be effective but may contribute to recurrence and complications[46,47]. Generally, percutaneous aspiration combined with sclerotherapy and laparoscopic deroofing is reasonable for most symptomatic simple hepatic cysts. A systematic review showed that the outcome of percutaneous aspiration and sclerotherapy was excellent, with symptoms that persisted in less than 4% of patients, and both complication and recurrence rates were < 1%[16]. Major complications were reported in 2/265 (0.8%), 6/348 (1.7%) and 3/123 (2.4%), and cyst recurrence rates were 0.0%, 5.6% and 7.7% in patients treated with percutaneous aspiration and sclerotherapy and laparoscopic and open surgery, respectively[16]. Other studies on the advantage of percutaneous aspiration and sclerotherapy compared to surgical techniques reported similar results[13]. These results supported the safety and efficacy of percutaneous aspiration and sclerotherapy in treating symptomatic simple hepatic cysts prior to surgical procedures. Our patient's outcome suggested that percutaneous aspiration and sclerotherapy could effectively treat simple giant hepatic cysts. Studies concerning cost, hospitalization time, and quality of life are needed to further compare these measures.

CONCLUSION

Giant simple hepatic cysts can obstruct the intrahepatic bile ducts and cause obstructive jaundice. A combination of percutaneous catheter aspiration and sclerotherapy using lauromacrogol can achieve satisfactory results without evident complications compared to surgical interventions.

FOOTNOTES

Author contributions: He XX and Sun MX compiled all relevant information concerning that case and did the literature research; He XX did the drafting and review of the manuscript; Lv K and Cao J did the radiological analysis; Zhang SY did the study concept and design; Zhang SY and Li JN evaluated the whole treatment of the patient and supervised the study; all authors had reviewed and approved the final version of this manuscript.

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CASE REPORT

Indocyanine green fluorescence imaging for spleen preservation in laparoscopic splenic artery aneurysm resection: A case report

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Abstract

BACKGROUND

Splenic artery aneurysm (SAA) is a rare vascular lesion conventionally treated by resection or interventional therapy. The surgical procedure usually involves splenectomy, and interventional therapy may cause post-embolization syndromes. Preservation of the spleen and its function is rarely reported during the management of SAA.

CASE SUMMARY

We report a patient with an asymptomatic SAA (3.5 cm in diameter), which was en-bloc resected laparoscopically using indocyanine green (ICG) fluorescence imaging to preserve the spleen and its function.

CONCLUSION

ICG fluorescence imaging for spleen preservation in laparoscopic SAA resection is safe and may be beneficial in avoiding splenectomy and maintaining splenic function.

Key Words: Laparoscopic; Indocyanine green; Fluorescence imaging; Splenic artery; Aneurysm; Spleen-preserving; Case report

Core Tip: Currently, there are three main treatment methods for splenic artery aneurysm (SAA): Endovascular treatment, open surgery, and laparoscopic surgery. Laparoscopic SAA resection is inevitably concomitant with splenectomy due to end-organ ischemia at times. We here present a case of SAA treated by laparoscopic resection using indocyanine green fluorescence imaging for preserving spleen and its function. This is the first case successfully treated by this method reported in the literature.

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INTRODUCTION

With further understanding of spleen function, and occurrence of complications such as overwhelming post-splenectomy infection, thrombocytosis, and portal vein thrombosis after splenectomy, surgeons have realized the importance of splenic preservation[1]. Protecting normal splenic artery blood flow is the key to maintain spleen function[2]. Preserving the spleen and its function is an important issue in the management of splenic artery aneurysm (SAA). We here report the application of indocyanine green (ICG)-enhanced fluorescence for spleen preservation in a patient during laparoscopic SAA resection. We also review the relevant literature.

CASE PRESENTATION

Chief complaints

A 50-year-old man was admitted to hospital due to an asymptomatic SAA found on medical examination.

History of present illness

Abdominal ultrasound showed a posterior pancreatic mass, which was diagnosed as an SAA 3.5 cm in diameter three days ago without any symptoms.

History of past illness

The patient denied a history of surgery or abdominal trauma, and had a free previous medical history.

Personal and family history

His personal history and family history were unremarkable. He denied history of consuming alcohol, tobacco, and psychoactive drugs.

Physical examination

No positive signs were found on abdominal examination and other physical examinations.

Laboratory examinations

Blood tests, blood biochemistry, coagulation function, urine and routine stool tests were all normal.

Imaging examinations

Ultrasound showed a posterior pancreatic mass and an SAA was considered. A contrast-enhanced celiac trunk (CT) scan revealed an SAA 3.5 cm in diameter with thrombosis located in the posterior pancreas. 3D virtual imaging revealed a 3.5 cm SAA located at approximately 3 cm from the CT (Figure 1).

FINAL DIAGNOSIS

The final diagnosis of the presented case is an asymptomatic SAA (3.5 cm in diameter).

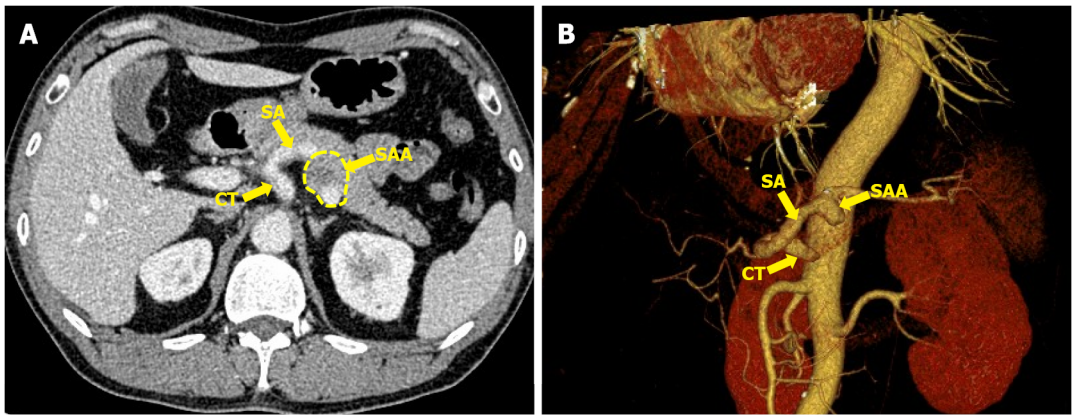

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Figure 1 Contrast-enhanced celiac trunk and 3D reconstruction imaging. A: A 3.5 cm splenic artery aneurysm (SAA) in the proximal splenic artery located in the posterior pancreas; B: 3D reconstruction imaging shows a 3.5 cm SAA at the same location. CT: Celiac trunk; SA: Splenic artery; SAA: Splenic artery aneurysm;

TREATMENT

Surgical treatment was selected based on the anatomic location of the aneurysm, possible rupture of the SAA and the patient's choice. Endovascular treatment was not proposed as endovascular repair may increase the risk of subsequent complications and re-interventions during long-term follow-up[3]. Thus, laparoscopic SAA resection with ICG fluorescence imaging was performed.

Five ports were inserted in the abdomen at a 15 mmHg pressure pneumoperitoneum. After that, the patient was placed in the reverse trendelenburg position. First, the gastrocolic ligament was divided to expose the pancreatic edge, identify splenic artery and aneurysm, then the proximal and distal parts were separated and ligated, respectively. An aneurysm, about 3.5 cm × 3.0 cm in size, was located approximately 3 cm from the CT, it had grown into the retroperitoneal pancreas parenchyma and was densely adhered to the splenic vein (Figure 2). It was partially ruptured with a 0.5 cm cleft, and protruded into the pancreatic parenchyma with thrombogenesis. The collateral vessels of the aneurysm were completely dissected, thus the aneurysm was en-bloc resected following separation of the surrounding tissues using an ultrasonic knife (Figure 2). At the end of the procedure, 2.5 mg ICG was injected into the peripheral vein, the whole spleen was stained green 6 min 50 s later, and the color faded completely 12 min 20 s after ICG injection, respectively (Figure 3). We irrigated the surgical field with normal saline and a tube was placed to drain the fluid. The operative time was approximately 140 min and blood loss was 50 mL.

OUTCOME AND FOLLOW-UP

Three days later, contrast-enhanced CT showed no splenic ischemia, localized fluid collections or splenic vein thrombosis, and the abdominal drainage tube was removed. The patient was discharged on postoperative day 8 after well recovery without any complications. Histopathology confirmed an aneurysm of the splenic artery. During the follow-up period, the blood platelet count was normal, and no abdominal pain, pancreatic insufficiency or recurrence of the aneurysm as well as no splenic infarction were observed.

DISCUSSION

SAAs are the most common visceral aneurysms accounting for 60%-70% of all cases, with an estimated prevalence of 1% in the population[4]. Early recognition and treatment of an SAA are essential, as 2%-10% present with rupture, resulting in a mortality rate of 25%-70% depending on the underlying pathology[5]. The management of an asymptomatic SAA is still controversial. SAAs with high-risk characteristics for rupture such as lesions > 2 cm in size, pregnancy and portal hypertension should be treated[6]. The mean diameter of non-ruptured SAAs was 2.2 cm, while that of ruptured SAAs was 3.1 cm according to one of the largest series published[7]. Investigators have been inclined to raise the standard to 2.5 cm due to the very low rupture risk in aneurysms below the standard, which is supported by retrospective studies[8].

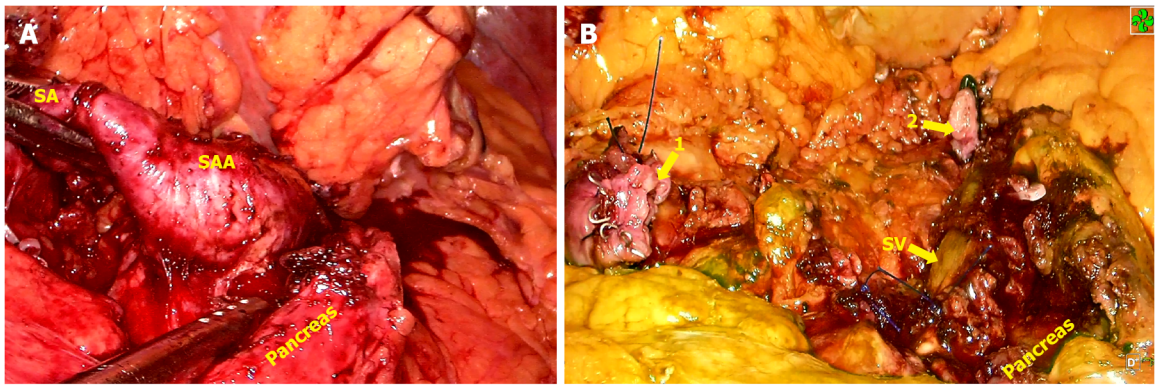

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Figure 2 Intraoperative imaging. A: The splenic artery aneurysm protruded into the pancreatic parenchyma adhered to the surrounding tissues; B: Both the proximal (1) and distal (2) aneurysms were occluded with aneurysmectomy. SA: Splenic artery; SAA: Splenic artery aneurysm; SV: Splenic vein.

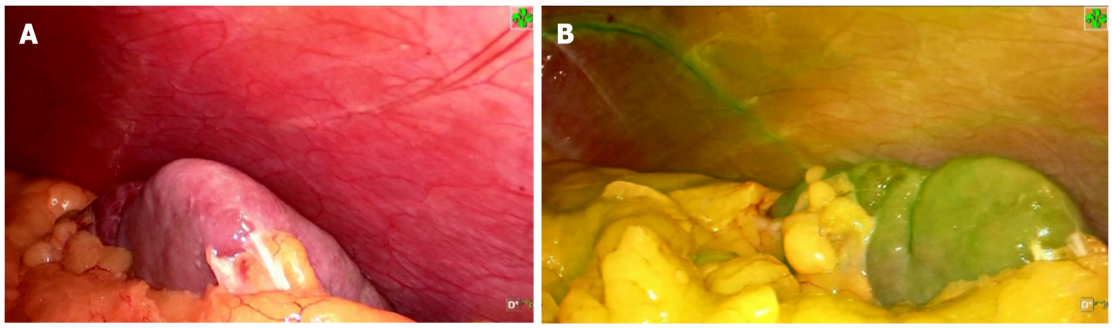

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Figure 3 Indocyanine green fluorescence imaging at the end of surgery. A: Spleen before indocyanine green (ICG) injection; B: The whole spleen was stained green 6 min 50 s after ICG injection.

Aneurysmectomy and endovascular repair are usually performed to treat SAAs. However, the splenectomy rate is approximately 76% during surgical treatment regardless of the size of the aneurysm [9]. Moreover, distal pancreatectomy or aneurysmectomy with vascular reconstruction have occasionally been performed concomitantly[10]. Even with spleen preservation, end-organ ischemia risk can occur after surgery and after interventional therapy. The most common ischemic incidents were post-embolization syndromes presenting as fever, abdominal pain, elevated leukocyte level and multiple splenic abscesses at the high rate of 31.8%[2]. Moreover, recanalization, coil migration and splenic infarction with abscess formation may occur. Laparoscopic ligation of a SAA in the proximal splenic artery is another method of preventing potential rupture of the SAA; however, there is still a risk of deficient residual blood flow to the spleen, thus leading to splenic infarction and possible evolution into a splenic abscess[11]. In the present case, the SAA was 3.5 cm in diameter, located approximately 3 cm from the CT, and it ruptured and eroded into the pancreatic parenchyma, indicating that it required immediate treatment. We chose SAA resection instead of ligation or other procedures for the following reasons: First, the SAA protruded into the pancreatic parenchyma with thrombogenesis and could potentially cause an abdominal infection; second, SAA may recur if the collateral circulation of the SAA was not blocked completely; third, the SAA' anatomical position nearby the CT, leading to a high risk of recanalization and coil migration with interventional therapy. It was crucial to find a way of assessing the blood supply to the spleen after surgery and to determine the optimal surgical strategy during preoperative evaluation. Preoperative 3D virtual reconstruction and intraoperative ultrasound are usually used to confirm the residual blood flow in the spleen[11]. However, collateral vessels of the splenic hilum are difficult to confirm due to abundant blood vessels in the posterior wall of the stomach and the pancreatic tail, surrounding the splenic hilum. In the present case, the collateral vessels of the spleen were too abundant and small to be seen clearly on the 3D images. ICG is widely used in general surgery for staining liver segments, locating hepatic carcinoma, visualizing bile ducts and evaluating anastomotic blood supply due to its special attribute of fluorescence imaging[12-14]. The price of ICG is affordable for most patients at $18.8 United States dollars. Based on the characteristics of ICG and experience of fluorescence imaging-guided laparoscopic hepatectomy, ICG fluorescence imaging can detect segmental blood supply to spleen theoretically. However, it is rarely reported in splenic surgery.

A recent study showed that ICG could visualize the spleen to assess the splenic blood supply, facilitating laparoscopic partial splenectomy[15]. Based on the characteristics of ICG visualization, we injected 2.5 mg ICG into a peripheral vein at the end of surgery, the whole spleen was stained green 6 min 50 s later, which indicated that fluorescence staining was complete and the splenic blood supply was satisfactory. The staining faded completely 12 min 20 s after ICG injection, which indicated that the splenic vein reflux was normal with a low risk of congestive splenomegaly. During the follow-up period, the blood platelet count was normal at all time points after surgery, and no abdominal pain, pancreatic insufficiency or recurrence of the aneurysm as well as no splenic infarction were observed. ICG fluorescence imaging is an effective and easy way to assess residual blood supply to the spleen and determine whether to preserve the spleen after surgical treatment of SAA.

CONCLUSION

ICG fluorescence imaging for spleen preservation in laparoscopic SAA resection is safe and may be beneficial in avoiding splenectomy and maintaining splenic function.

FOOTNOTES

Author contributions: Cheng J, Liu J and Zhang CW performed the operation; Cheng J and Sun LY collected case data and wrote the manuscript; Zhang CW proofread and revised the manuscript; all authors approved the version to be published; Sun LY and Cheng J contributed equally to this work.

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LETTER TO THE EDITOR

Total mesopancreas excision is the better staging tool of the mesopancreas in pancreatic head carcinoma

Nadia Peparini

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Abstract

Preoperative imaging staging based on tumor, node, metastasis classification cannot be effective to avoid R1 resection because only further improvements in imaging technologies will allow the precise assessment of perineural and lymphatic invasion and the occurrence of microscopic tumour deposits in the mesopancreas. However, waiting for further improvements in imaging technologies, total mesopancreas excision remains the only tool able to precisely assess mesopancreatic resection margin status, maximize the guarantee of radicality in cases of negative (R0) mesopancreatic resection margins, and stage the mesopancreas.

Key Words: Pancreatic head carcinoma; Mesopancreas; Total mesopancreas excision; Staging; Preoperative imaging; Surgery

Core Tip: To date, among all therapeutic tools, total mesopancreas excision remains the only tool able to precisely assess mesopancreatic resection margin status, maximize the guarantee of radicality in cases of negative (R0) mesopancreatic resection margins, and stage the mesopancreas.

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TO THE EDITOR

We read with great interest the article by Feng *et al*[1]. The authors note that most R1

resections are related to the insufficient removal of retroperitoneal tissue of the anatomical space recognized as the mesopancreas, and total mesopancreas excision (TMpE) has been proposed to increase the R0 rate of pancreaticoduodenectomies. Consequently, precise preoperative imaging evaluation of pancreatic head carcinoma should include all the nerves, lymphatic vessels, and fatty tissue in the mesopancreas (particularly the structures around the celiac artery and superior mesenteric artery) instead of only traditional masses, vascular invasion, lymph nodes and distant metastasis evaluation. The authors noted that unfortunately, further research is needed to identify the mesopancreas by imaging. To date, neither computed tomography nor magnetic resonance imaging has allowed preoperative evaluation of extrapancreatic perineural invasion, which is important for effective TMpE.

It has been reported that mesopancreatic fat stranding on preoperative multidetector CT scans predicts mesopancreatic cancerous infiltration, which is a significant indicator for incomplete surgical resection and worse overall survival[2].

We think that the following issues should be considered: Imaging evaluation of the mesopancreas facilitates the avoidance of R2 resection risk but not R1 resection risk; Tumour deposits (TDs), *i.e.*, macroscopic or microscopic nests or nodules found in the lymph drainage area of a primary carcinoma without evidence of residual lymph node in the nodule, may occur in pancreatic cancer as well as other digestive carcinomas; TMpE has been conceived to obviate the impossibility of preoperative detection of perineural and lymphatic invasion as well as microscopic TDs in the mesopancreas and to minimize the likelihood of R1 resection or else of "not radical" R0 resection (*i.e.*, unidentified residual TDs after resection with negative margins)[3].

Preoperative imaging staging based on tumor, node, metastasis (TNM) classification cannot be effective to avoid R1 resection because only further improvements in imaging technologies will allow the precise assessment of perineural and lymphatic invasion and the occurrence of microscopic TDs in the mesopancreas. To date, among all therapeutic tools, TMpE remains the only tool able to precisely assess mesopancreatic resection margin status, maximize the guarantee of radicality in cases of negative (R0) mesopancreatic resection margins, and stage the mesopancreas.

Moreover, the occurrence of TDs, the pathologic and prognostic significance of which remains to be determined (T, discontinuous primitive tumour; N, regional nodal metastasis; M, distant metastasis or something else?), underscores the need to overcome the preoperative staging and consequent treatment strategies based on pathological categorization of T, N, and M per the TNM classification system. In the staging and treatment of pancreatic head carcinoma, other pathological pathways and factors beyond T, N, and M that are involved in the modulation of tumour spread should be taken into account.

Precise preoperative imaging evaluation should include all the anatomical structures within the mesopancreas. However, waiting for further improvements in imaging technologies, TMpE remains the better staging tool of the mesopancreas.

FOOTNOTES

Author contributions: Peparini N conceived, drafted and critically revised the manuscript and gave the final approval.

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LETTER TO THE EDITOR

Three-dimensional visualization and virtual reality simulation role in hepatic surgery: Further research warranted

Faiza Ahmed, Vinay Jahagirdar, Sravya Gudapati, Mohamad Mouchli

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Abstract

Artificial intelligence (AI) is the study of algorithms that enable machines to analyze and execute cognitive activities including problem solving, object and word recognition, reduce the inevitable errors to improve the diagnostic accuracy, and decision-making. Hepatobiliary procedures are technically complex and the use of AI in perioperative management can improve patient outcomes as discussed below. Three-dimensional (3D) reconstruction of images obtained *via* ultrasound, computed tomography scan or magnetic resonance imaging, can help surgeons better visualize the surgical sites with added depth perception. Pre-operative 3D planning is associated with lesser operative time and intraoperative complications. Also, a more accurate assessment is noted, which leads to fewer operative complications. Images can be converted into physical models with 3D printing technology, which can be of educational value to students and trainees. 3D images can be combined to provide 3D visualization, which is used for pre-operative navigation, allowing for more precise localization of tumors and vessels. Nevertheless, AI enables surgeons to provide better, personalized care for each patient.

Key Words: Artificial intelligence; Three-dimensional printing; Liver surgery; Virtual reality; Preoperative planning; Simulation

Core Tip: One of the applications of artificial intelligence in hepato-biliary and pancreatic surgery is to generate three-dimensional (3D) imaging, models, and virtual reality for preoperative planning. 3D visualization and navigation can facilitate identification of the exact location of tumors and vessels, reducing vascular injury, operative time, and postoperative complications, thereby leading to better patient outcomes. Upcoming surgeons and students can utilize 3D models and virtual reality to gain expertise in the field of hepatobiliary and pancreatic surgery and share their experiences with their peers.

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TO THE EDITOR

We have read with great interest the paper "Role of Artificial Intelligence in Hepatobiliary and Pancreatic Surgery", published by Bari *et al*[1] in your well-regarded journal "*World Journal of Gastrointestinal Surgery*". Concerning the data reported on three-dimensional visualization (3DV) and virtual simulation on hepatic patients, we would like to make a contribution towards the discussion and draw your attention to several interesting aspects from recently published literature.

The role of artificial intelligence (AI) in healthcare delivery has become an increasingly important avenue of medical research and practice. AI is a vast field, which includes machine learning as a subfield, is steadily being integrated into healthcare settings to provide a more precise and individualized approach[2]. At present, before the surgery to determine treatments, hepatobiliary and pancreatic (HPB) surgeons utilize ultrasonography, computed tomography, and magnetic resonance imaging which provide two-dimensional (2D) views. Surgeons utilize the shadows, textures, and shades from the 2D displays to extrapolate three-dimensional (3D) information in their brains. This 2D image commonly causes loss of depth perception and exerts more workload on the operating physicians[3]. 3DV, a new type of computer-assisted imaging technology, exhibits clear and accurate images for post-processing to help surgeons stratify surgical risks and outline their surgical plan for intraoperative navigation[4].

We came across two recent studies that compared 3D and 2D visualization reconstruction techniques in liver diseases. Bari *et al*[1] referenced in their paper, the research conducted by Fang *et al*[5] which demonstrated significantly shorter operation time (P = 0.028), less hepatic inflow occlusion (P = 0.029), and decreased high grade (Clavien Grade III - V) postoperative complications in hepatocellular carcinoma patients using 3D models. Zhang *et al*[6] and Zhang *et al*[7] also reported similar benefits. Zhang *et al*[7] is the first to conduct research in the Tibet population for hepatic echinococcosis and his results revealed the 3DV technology contributing towards improved diagnosis and treatment of patients. Moreover, the 3DV technology accurately formulated a preoperative plan with a high compliance rate and reduced surgical time (210 *vs* 135; $P \leq 0.05$). Also, fewer cases were seen with blood flow blockage (83 *vs* 50), reduced blood flow blockage time (30.1 min *vs* 18.2 min), reduced volume of intraoperative blood transfusion and hemorrhage [(550 mL *vs* 310 mL) and (613 mL *vs* 312 mL); $P \leq 0.05$)], and a significantly lower incidence of postoperative biliary fistula was noted. A meta-analysis on video-assisted hepatectomy by Zhang *et al*[7] indicated significant shorter operating time [mean difference (MD = -34.39; 95%CI: -59.50, -9.28; P = 0.007), less blood loss (MD = -106.55; 95%CI: -183.76, -29.34; P = 0.007), small transfusion volume (MD = -88.25; 95%CI: -141.26, -35.24; P = 0.001)], and reduced postoperative complications [odds ratio (OR) = 0.57; 95%CI: 0.35, 0.91] with the utilization of 3D application. Furthermore, 3D video-assisted system is a better option than a 2D system since it provides a simple anatomical image combined with improved depth perception, allowing surgeons to operate precisely and in a shorter time.

Another new tool, the immersive 3D virtual reality (VR), allows for preoperative 3D liver models *via* an immersive VR application. It is not well investigated, so there is limited available literature on this modality. Most obtainable publications on hepatic models are described by means of 3D prints or 3D portable document formats (PDFs) for preoperative planning[8-10]. To date, we found three current studies comparing 3D PDFs, 3D printed models (PR), and 3DV models in liver surgery.

Boedecker *et al*[10] engineered a VR application that allows liver resection planning *via* a preoperative 3D liver. The study summarized that the drawbacks of visualization on a 2D screen and surface reflection, which arise from 3D print models, are avoided in the VR technique. VR not only includes almost all the benefits of 3D printing but also allows viewing of the various interactions of overlapping pathologies and hepatic vessels. This is not possible with a 3D print. Furthermore, when it comes to education, 3D models are widely used due to their availability and sustainability[11]. Nascent HPB trainees can utilize the benefits of immersive VR, including the ability to interact with other trainees and

mentors who are a long distance away, as supported by Kenngott *et al*[12] in their research, where they describe the benefits of VR application in medical education. However, the disadvantage of using VR is that it is unable to make volume calculations, which is only possible through a 3D PDF format. Also, the haptic interaction with the 3D model and surgeon's own hands is limited to the VR application[10]. This needs further investigations.

Out of all three modalities, the fastest and most cost-efficient tool is 3D PDF[10]. Often the 3D PR models are billed per case. Though the VR application equipment is more expensive than the PR model, VR technology is a better choice since they are only a one-time investment. Additionally, stereolithography files can be dragged and dropped to create the 3D VR model almost instantly without any delay. Prior to choosing a tool for preoperative surgical planning, the above factors must be reviewed.

Huettl *et al*[13] concluded that even though 3D PDF is more cost-effective, the 3D PDFs and 3D VR models have the advantage of providing more precise tumor localization. Comparatively, the majority of surgeons preferred VR application over the other modalities. The study also reported 3D PR as superior for faster tumor localization while 3D PDF and 3D PR showed no difference.

Overall, Bari *et al*[1] put in great efforts towards outlining the potential of applying currently available 3D presentation modalities in the perioperative evaluation of those who come in for HPB surgery. Further research is necessary to evaluate the reliability and validity of the results already existing on the 3DV and VR technology. This will help surgeons better understand these modalities, utilize, and design personalized surgical plans for each patient.

FOOTNOTES

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LETTER TO THE EDITOR

Signs and syndromes in acute appendicitis: A pathophysiologic approach

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Abstract

Physical examination signs have not been well studied, and their accuracy and reliability in diagnosis remain unknown. The few studies available are limited in that the method of performing the sign was not stated, the technique used was not standardized, and the position of the appendix was not correlated with imaging or surgical findings. Some appendiceal signs were written in a non-English language and may not have been appropriately translated (*e.g.*, Blumberg-Shchetkin and Rovsing). In other cases, the sign described differs from the original report (*e.g.*, Rovsing, Blumberg-Shchetkin, and Cope sign, Murphy syndrome). Because of these studies limitations, gaps remain regarding the signs' utility in the bedside diagnosis of acute appendicitis. Based on the few studies available with these limitations in mind, the results suggest that a positive test is more likely to be found in acute appendicitis. However, a negative test does not exclude the diagnosis. Hence, these tests increase the likelihood of ruling in acute appendicitis when positive but are less helpful in ruling out disease when negative. Knowledge about the correct method of performing the sign may be a valuable adjunct to the surgeon in further increasing their pretest probability of disease. Furthermore, it may allow surgeons to study these signs further to better understand their role in clinical practice. In the interim, these signs should continue to be used as a tool to supplement the clinical diagnosis.

Key Words: Appendicitis; Signs and symptoms; Psoas; Rovsing; Signs and symptoms; Syndrome

Core Tip: This paper describes the pathophysiologic mechanism of disease presentation and reports the signs of acute appendicitis as initially reported. Physical examination signs and syndromes have not been well studied in patients with acute appendicitis. Knowledge of how to appropriately perform these bedside maneuvers in diagnosing appendicitis may provide further knowledge about the likelihood of the disease. Understanding the mechanism of disease and these bedside maneuvers may further enhance the ability of surgeons to diagnose acute appendicitis.

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TO THE EDITOR

We read with interest the paper by Teng *et al*[1] titled "Acute appendicitis-advances and controversies." Several points regarding the physical examination require further clarification as they pertain to patient management and pathophysiologic mechanism of disease, which are critical in assessment. Additionally, we report information about the signs and syndromes as originally described, emphasizing how they are frequently incorrectly used, accounting for their underreporting in clinical practice and cross-sectional designed clinical studies.

The presence of right lower quadrant abdominal pain in acute appendicitis is caused by viscerosomatic (visceromotor, viscerosensory) and somatic (somatosensory and somatomotor) segmental reflexes. This pathophysiologic mechanism differs entirely from the usual initial viscerosensory reflex, where the pain is deep-seated, poorly localized, more widespread, and bilaterally distributed at the T8-T10 dermatomes, primarily at the epigastric and umbilical regions. In cases of early appendicitis where appendiceal distension is abrupt and severe, there may be "spill-over" of visceral to somatic afferent nerve impulses in the dorsal root ganglion, causing efferent activation of alpha-motor neurons and intercostal nerves in the right lower quadrant and abdominal spasm (guarding) in addition to pain at T10-T11 dermatomes (visceromotor and viscerosensory segmental reflexes)[2]. It is recognized that this phenomenon occurs in the absence of involvement of the parietal peritoneum. With rupture of the necrotic appendiceal wall, the inflammatory infiltrate may become localized to the parietal peritoneum on the anterior abdominal wall, most commonly at the site referred to as McBurney point located at the right T11-T12 dermatomes (somatosensory reflexes). Hence, these pathophysiologic processes represent entirely different mechanisms reflecting disease progression, not migration, shifting, or radiation; terms commonly used to describe the sequence of events in acute appendicitis and by which they all represent misnomers[3]. Although not discussed by the authors, McBurney point is the most important sign because it represents the site on the anterior abdominal wall where the pain is greatest and not the location of the appendix[4]. Its presence provides surgeons with reasonable assurance that this finding represents acute appendicitis with peritoneal inflammation.

Murphy syndrome ascribed to John B Murphy (1857-1916) did not involve, as stated by the authors, periumbilical pain radiating to the right iliac fossa associated with nausea or vomiting and fever. Murphy[5] described the symptoms of acute appendicitis in their order of occurrence as: "First, pain in the abdomen, sudden and severe, followed by (second) nausea or vomiting, even within a few hours, most commonly between three and four hours after the onset of pain; third, general abdominal sensitiveness most marked in the right side or more particularly over the appendix; fourth, elevation of temperature, beginning from two to twenty-four hours after the onset of pain"[5] (p.190).

He did not however, specify the specific regions (epigastric and periumbilical) within the abdomen involved. We believe that the sequence of pain initially in the epigastrium and periumbilical regions followed by pain in the right lower quadrant was described by Theodor Kocher (1841-1917), written by Albert Vogel, and attributed to Nikolay Markianovich Volkovitch (1858-1928) and thus named the Kocher-Volkovich sign. According to Vogel[6]: "In our opinion, initial vomiting, and localization of pain in the epigastrium followed by the diffuse spread and gradual fixation in the classical place, McBurney point, occurs because of general peritoneal inflammation. This inflammation should not be confused with the serious type of peritonitis which develops later if the appendix becomes gangrenous or perforates. We can explain the diffuse pain, particularly at the umbilical and epigastric regions, because the appendix is not painful in the first stages of the disease, with the pulling on the peritoneum being the source of pain. Local pain develops if infiltration of the mesentery occurs"[6] (p.2-3).

The findings of "rebound tenderness" performed by Dimitri Sergeevich Shchetkin (1851-1923) in the late 1880s and reported by Jacob Moritz Blumberg (1873-1955) in 1907 (Blumberg-Shchetkin sign) also represents inflammation of the parietal peritoneum. Blumberg[7] described this maneuver in cases of appendicitis: "Very different results occur when pressure is applied compared to when the palpating

hand is raised. In my opinion, it is always necessary to consider these two movements separately based on the type of pain they induce. For example, first, apply pressure on the area of the abdomen to be examined and ask the patient whether it is painful. After listening to the response, suddenly lift the palpating hand and ask the patient whether it was painful when the hand was removed and which of the two types of pain was greatest. (…) I noted an extremely violent pain, causing the patient to momentarily grimace, when the palpating hand was suddenly lifted. During an acute episode, the patient stated with certainty that the pain was greatest when the hand was suddenly lifted compared to when it was pressed. In cases of less severe inflammation involving the peritoneum, the pain when the hand was suddenly lifted was similar to when the hand was pressed. As the healing process progressed, the pain was less when the hand was lifted and finally remained only vaguely present, presumably caused by adhesion, when the hand was lifted. The pain completely disappeared when chronic disease was present (p.1177)[7]. (…) The method can be applied accurately since it is not a matter of assessing the extent of the pain but comparing the intensity of the two pains. This information is reliably conveyed by the patient"[7] (p.1178).

Rovsing sign, initially described Niels Thorkild Rovsing (1862-1927), involves deep palpation at the left lower quadrant with a sliding motion directed proximally at the descending colon towards the splenic flexure. As described by Rovsing[8] in 1907: "I wondered whether I could elicit the typical pain in the right iliac fossa by applying pressure at the left iliac fossa. This involves compressing the descending colon by pushing the fingers of my right hand onto the fingers of the left hand placed flat against the abdomen in the left iliac fossa. Using this method, the hands slide upward toward the left colonic flexure"[8] (p.1258).

Thus, the maneuver involves more than simple palpation of the left iliac fossa as stated by the authors — it causes air within the colon to flow retrograde in response to compression, resulting in distension of the inflamed appendix and activation of a viscerosensory segmental reflex. Rovsing sign is frequently performed incorrectly, explaining the wide sensitivity and specificity reported.

Lastly, the iliopsoas sign described by Vincent Zachary Cope (1881-1974) in 1921 involved the following[9]: "It is well known that if there is an inflamed focus in relation to the psoas muscle the corresponding thigh is often flexed by the patient to relieve the pain. A lesser degree of such contraction (and irritation) can be determined often by making the patient lie on the opposite side and extending the thigh on the affected side to the full extent. Pain will be caused by the maneuver if the psoas is rigid from either reflex or direct irritation"[9] (p.42).

It is recognized that Cope's original description did not involve having the patient flex the thigh against the examiner's hand in the supine position as stated the authors[9,10]. Cope recognized that this test was more likely to be found in cases where the appendix is in a retrocecal position[9,10].

A sensitivity ranging from 0.16-0.27, specificity of 0.86-0.89, positive likelihood ratio 1.49-2.06, and negative likelihood ratio of 0.83-0.94 has been reported for the psoas, obturator, and Rovsing sign in the diagnosis of acute appendicitis[11-15]. These findings show that a positive test suggests the diagnosis of acute appendicitis, but a negative test does not exclude the diagnosis. Hence, these tests increase the likelihood of ruling in acute appendicitis when positive but are less helpful in ruling out disease when negative. Awareness of the differences between the way these signs were originally reported and how they are currently used provides a better understanding of why gaps remain in the existing literature regarding these signs' effectiveness in the clinical diagnosis. It is imperative that the sign is accurately described in the literature and that the examination method is standardized so that surgeons fully understand and appreciate and further study their role in diagnosing acute appendicitis.

FOOTNOTES

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ABOUT COVER

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AIMS AND SCOPE

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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

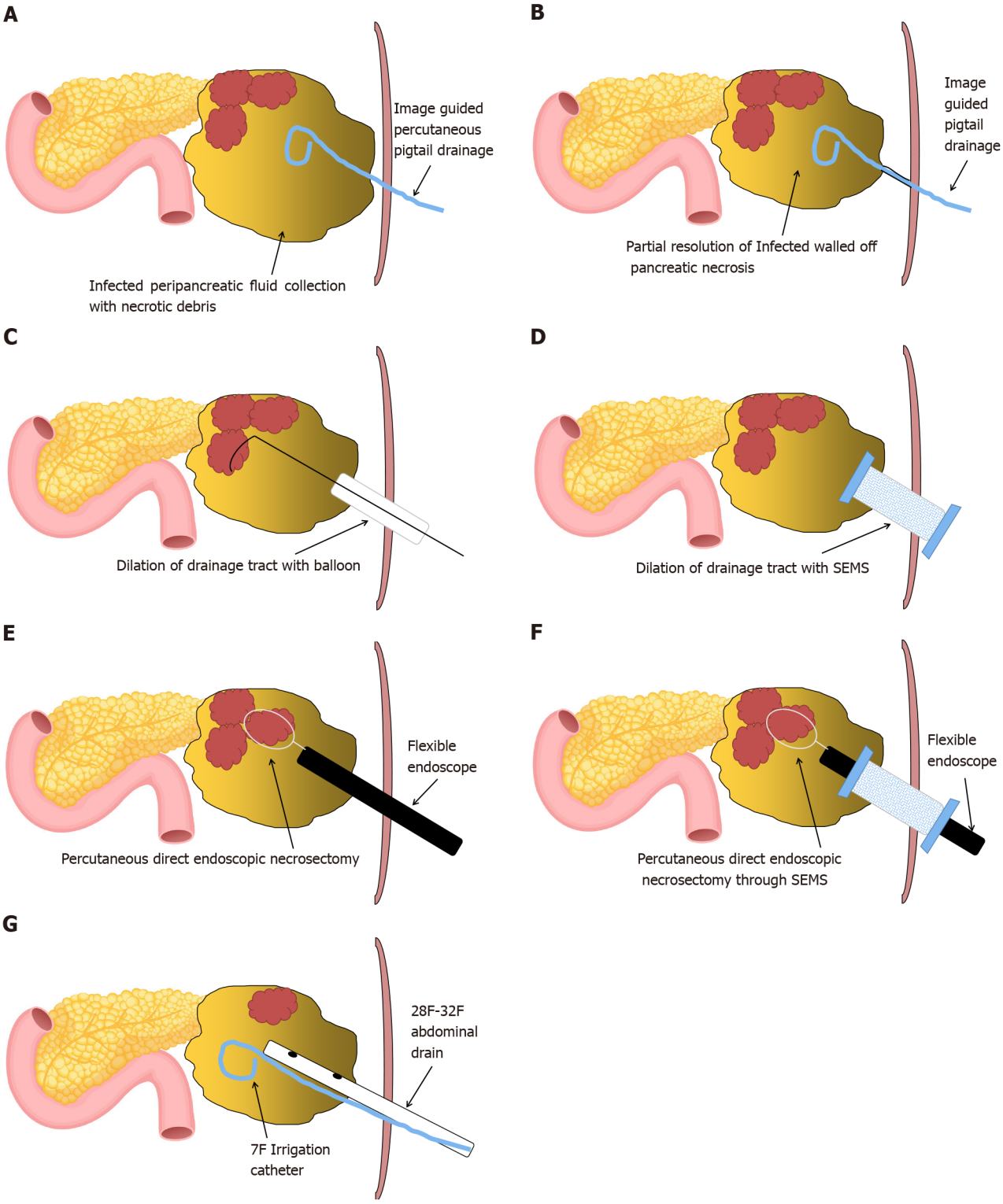

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Figure 1 Schematic representation of steps involved in percutaneous direct endoscopic necrosectomy. A: Image-guided pigtail drainage of infected pancreatic/peripancreatic collection; B: Partial resolution of infected walled off pancreatic necrosis (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.

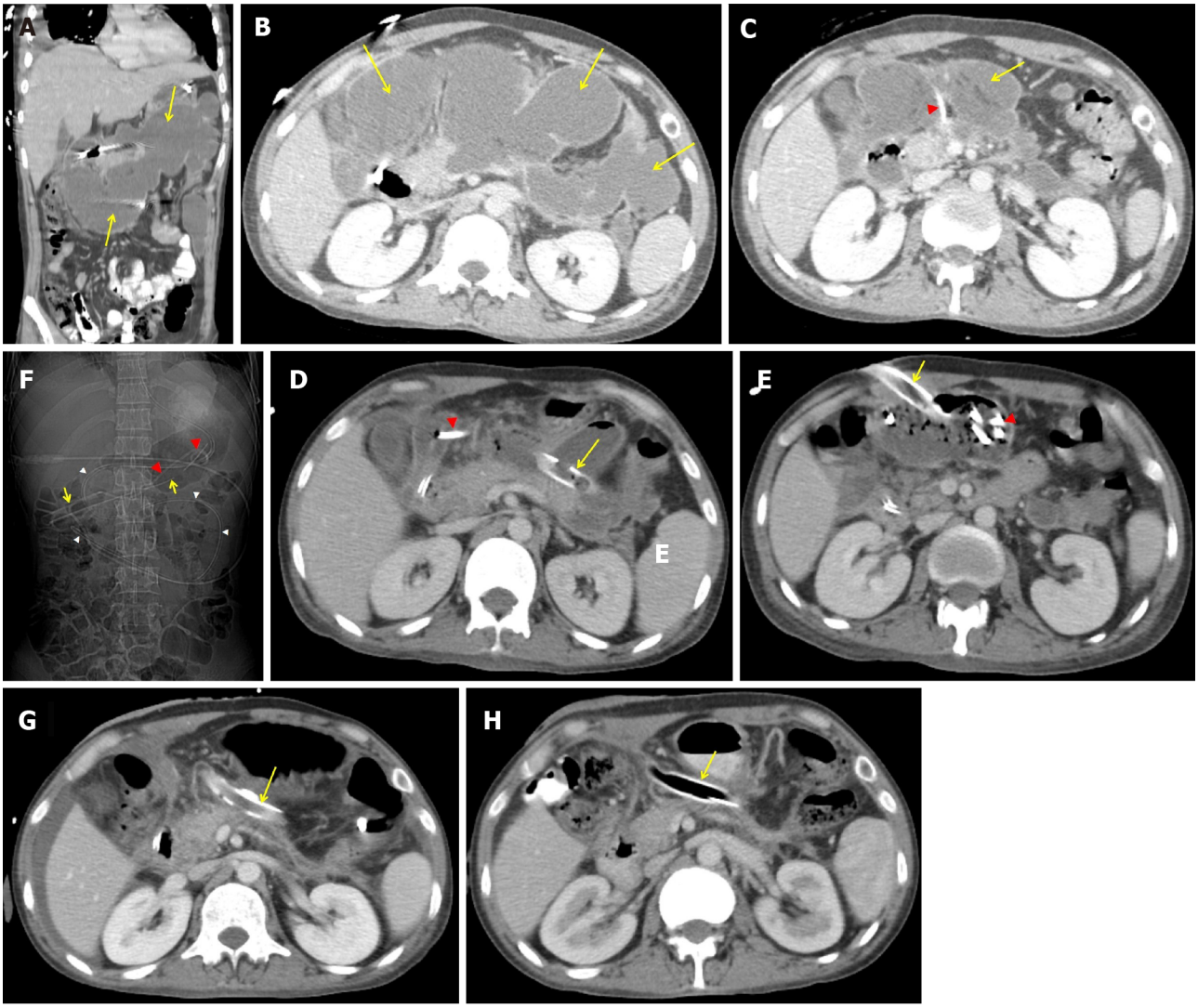

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Figure 2 Abdominal contrast enhanced computerized tomography. A and B: Large, irregular infected pancreatic/peripancreatic collection (PFC) (arrows) in upper abdomen in coronal and transverse sections; C: Partial resolution of PFC (arrow) with a 14 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.

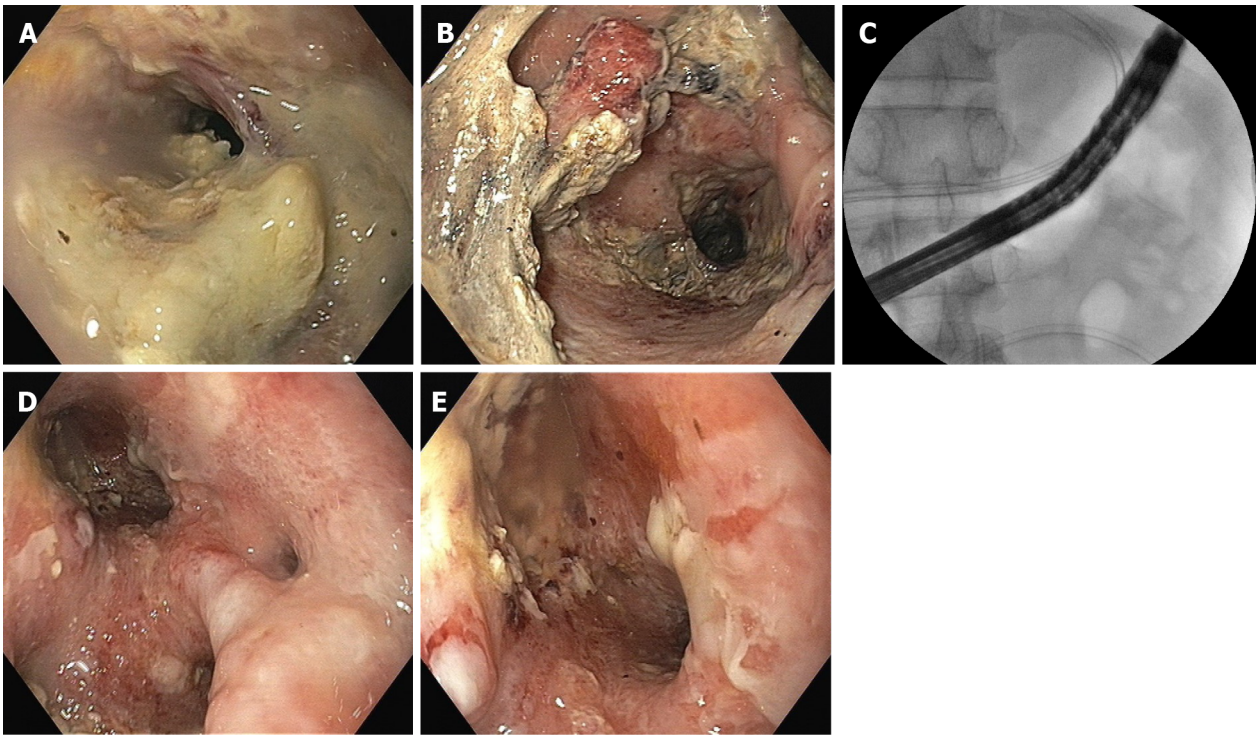

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Figure 3 Percutaneous direct endoscopic necrosectomy. A and B: Infected necrotic debris in walled off pancreatic necrosis (WOPN); C: A flexible upper gastrointestinal scope deep within the WOPN cavity for percutaneous direct endoscopic necrosectomy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

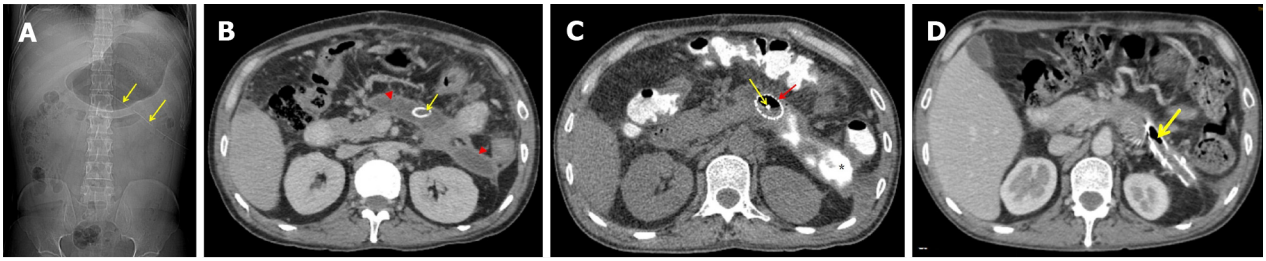

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Figure 4 Abdominal contrast enhanced computerized tomography. A and B: Residual walled off pancreatic necrosis (WOPN) (arrow heads) with post open necrosectomy drain (arrows) *in situ*; C: An esophageal fully covered self-expandable stent (red arrow) 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).

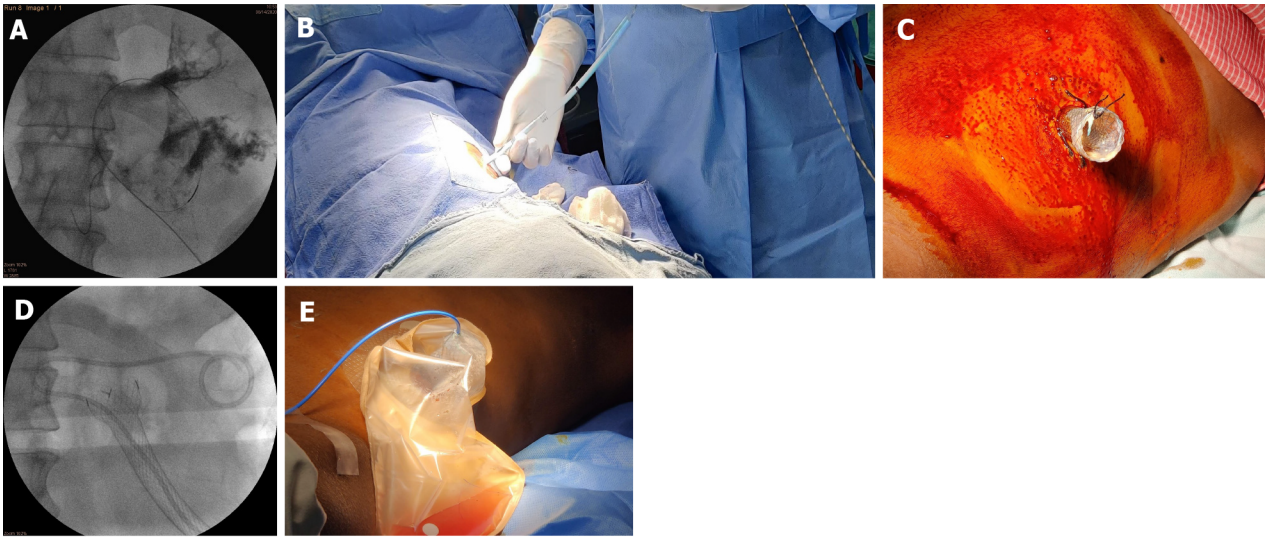

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Figure 5 Drainage tract dilation and placement of a self-expandable metal stent. A: Coiling of the guide-wire along with contrast in walled off pancreatic necrosis (WOPN); B: Dilation of the drainage tract with Amplatz dilators over the guide-wire; 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.

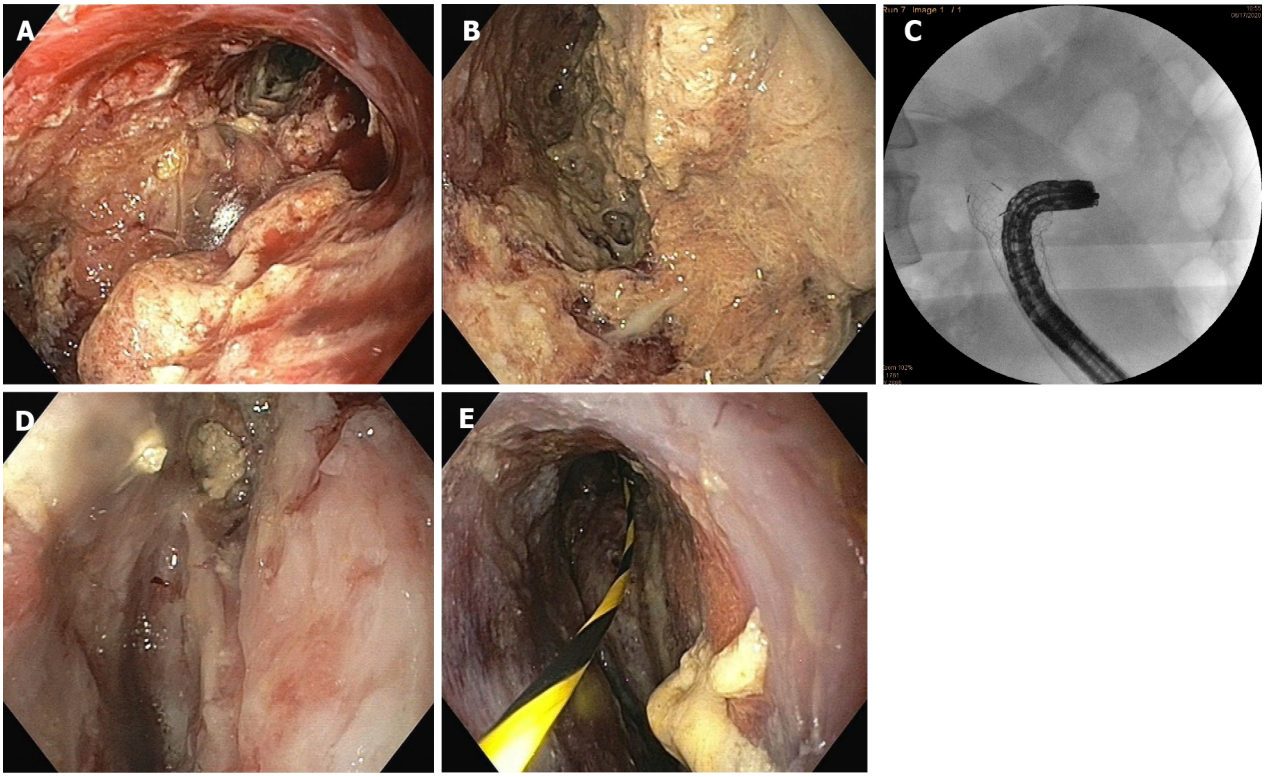

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Figure 6 Percutaneous direct endoscopic necrosectomy. A and B: Infected necrotic debris in walled off pancreatic necrosis (WOPN); C: A flexible endoscope through a fully covered self-expandable metal stent with ability to angulate to reach deep within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

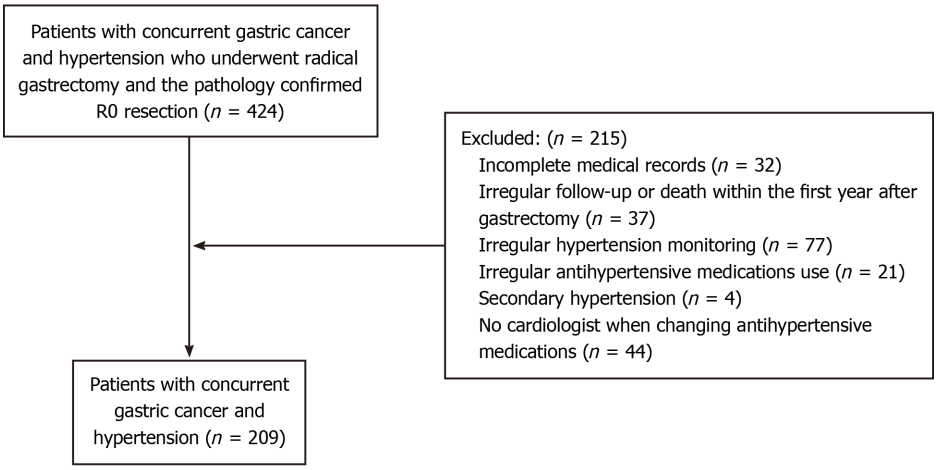

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Figure 1 Inclusion criteria and exclusion criteria of patients with concurrent gastric cancer and hypertension.

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

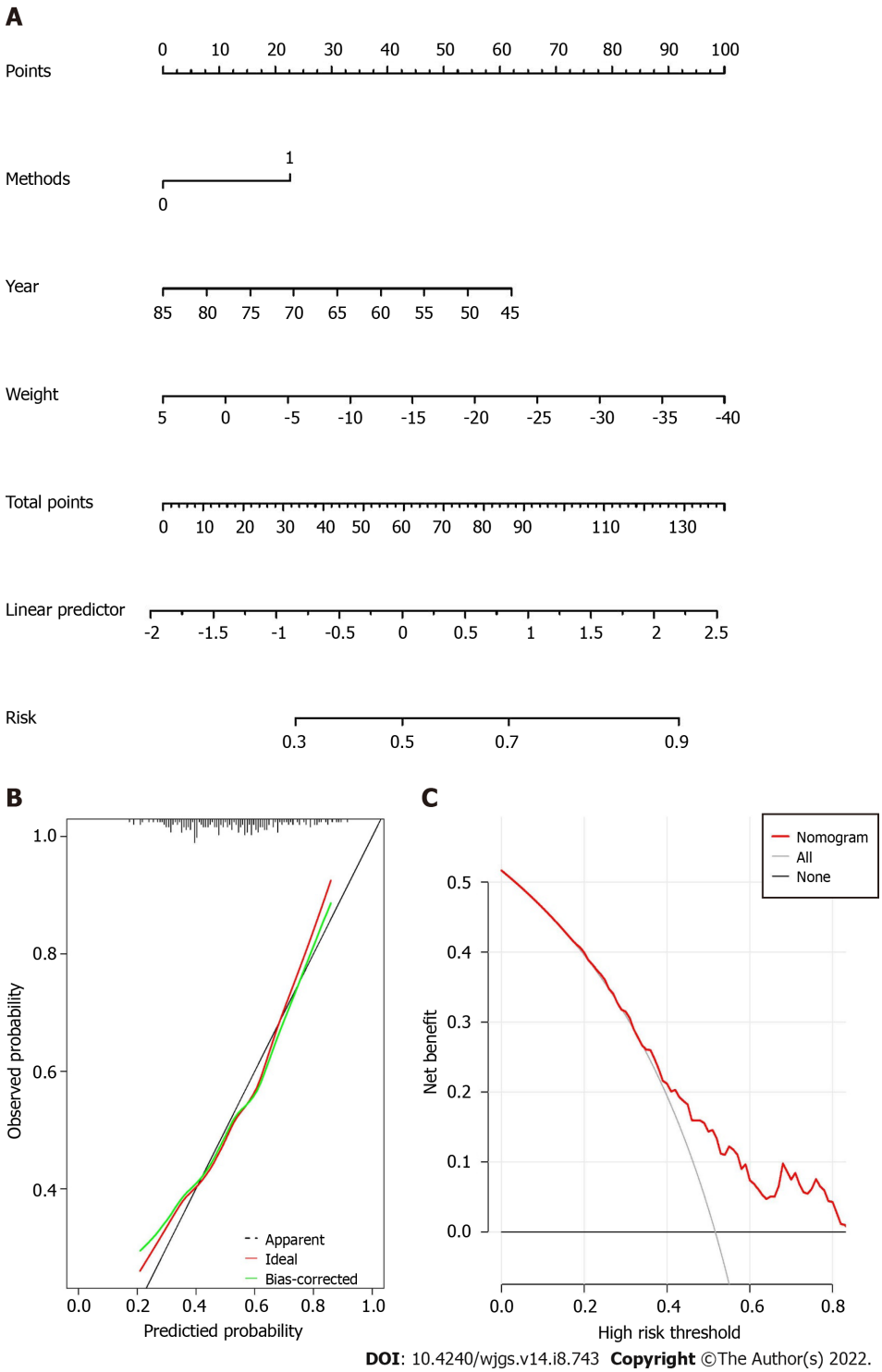

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Figure 2 Predictive model for hypertension remission. A: Nomogram for hypertension remission; B: Calibration curve of the nomogram; C: Decision curve analysis for predicting hypertension remission. TG: Total gastrectomy; SG: Subtotal gastrectomy.

[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

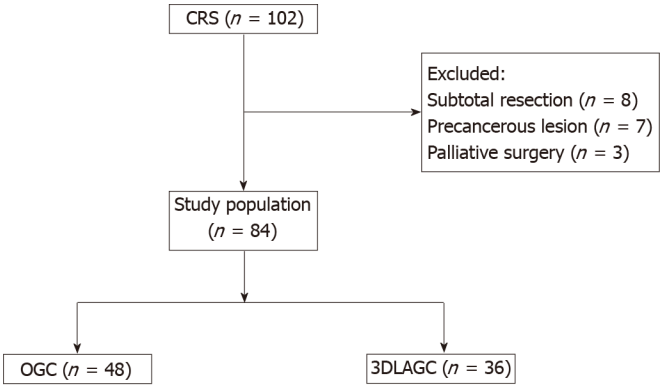

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Figure 1 Flow chart of this study. CRS: Carcinoma in the remnant stomach; OGC: Open gastrectomy for CRS; 3DLAGC: 3D laparoscopic assisted gastrectomy for CRS.

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.

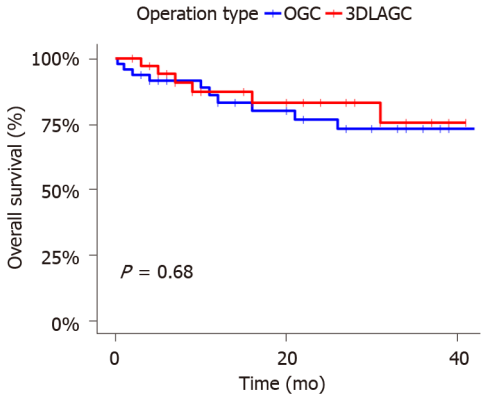

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Figure 2 Kaplan-Meier estimates of overall survival for open gastrectomy for carcinoma in the remnant stomach group and 3D laparoscopic assisted gastrectomy for carcinoma in the remnant stomach group. The 1-yr and 3-yr overall survival (OS) rates for 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-

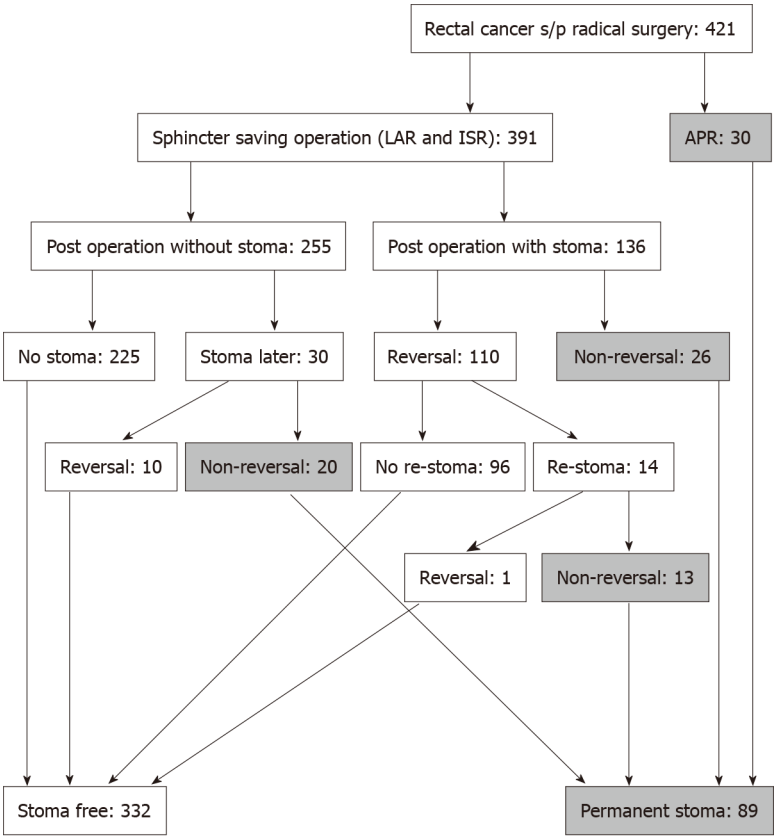

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Figure 1 Study flow chart.

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.

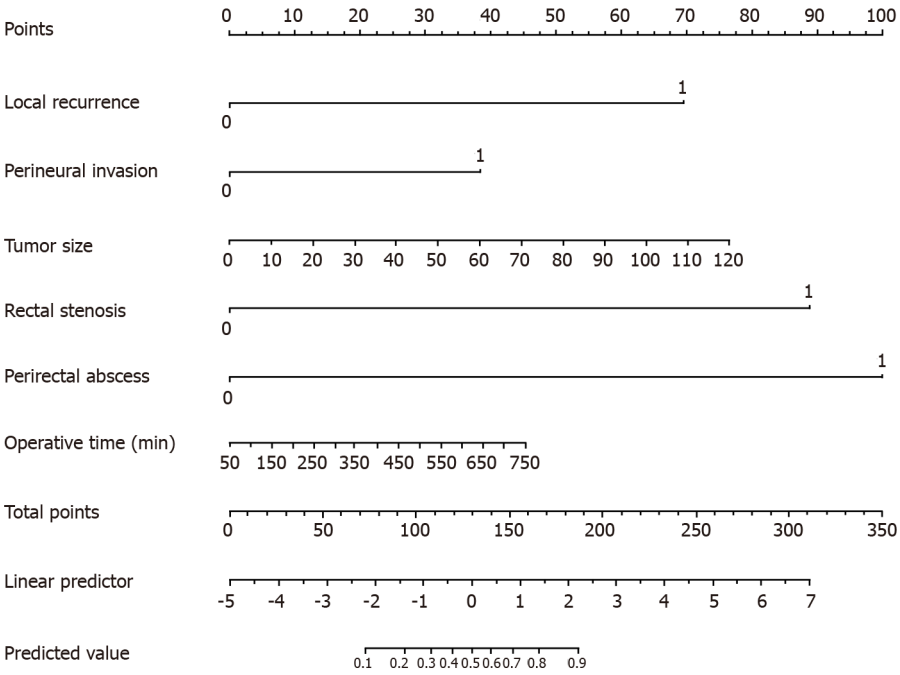

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Figure 2 The established nomogram for predicting permanent stoma was developed by incorporating the following six parameters: Local recurrence, perineural invasion, tumor size (mm), rectal stenosis, perirectal abscess and operative time. First, the 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

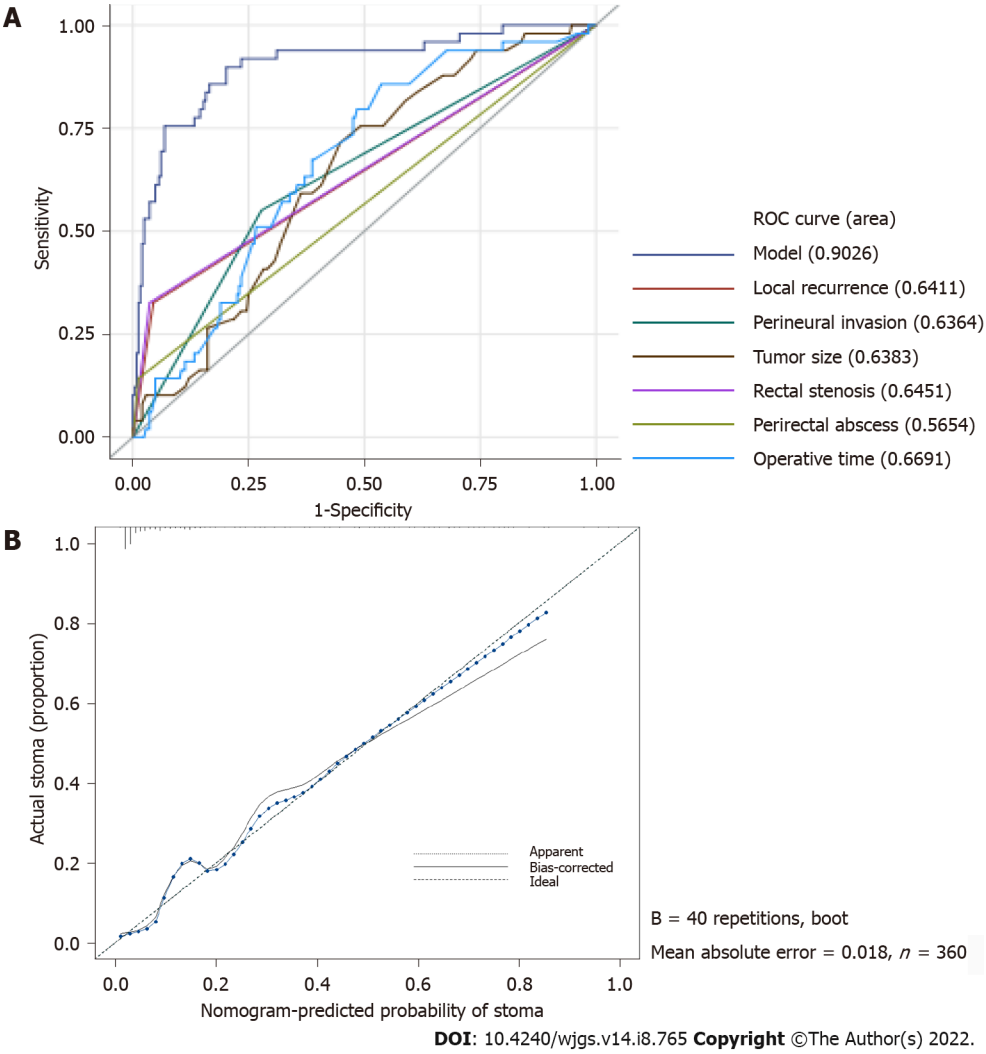

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Figure 3 The nomogram calibration plot demonstrated high reliability. A: The area under the receiver operating characteristic curve for the nomogram was 0.903 (95%CI: 0.851–0.955); B: In the calibration curve, the predicted probability of stoma is 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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Data sharing statement: The original anonymous dataset is available on request from the corresponding authors Li-Jen Kuo, MD (E-mail: kuolijen@gmail.com) and Yen-Kuang Lin, PhD (E-mail: robbinlin@ntsu.edu.tw).

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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

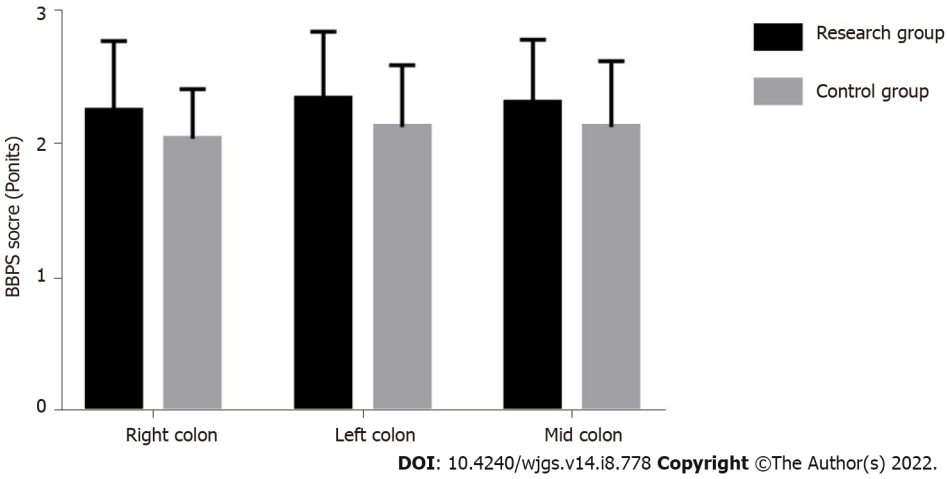

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Figure 1 Histogram of Boston bowel preparation scores of the study group and the control group. BBPS: Boston bowel preparation scores.

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.

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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.

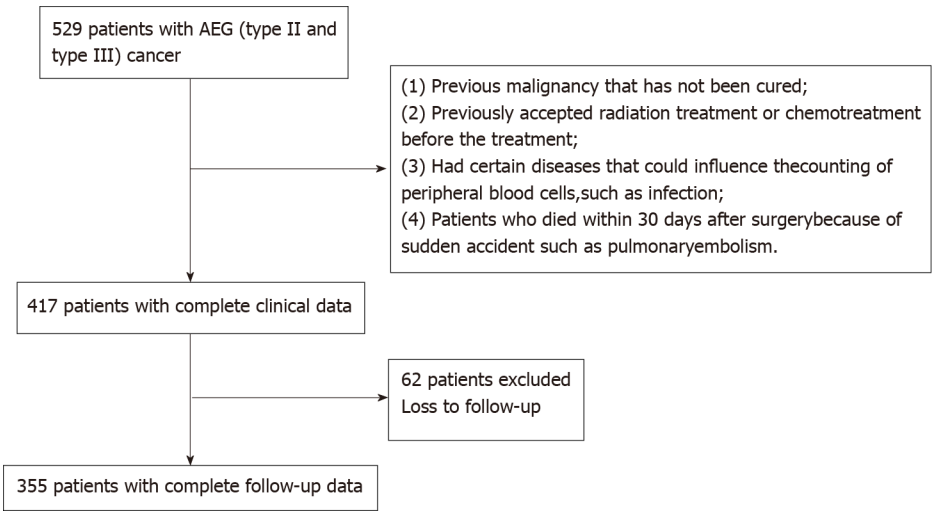

Figure 1 Nomogram for predicting overall survival after curative resection of gastric cancer.

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.

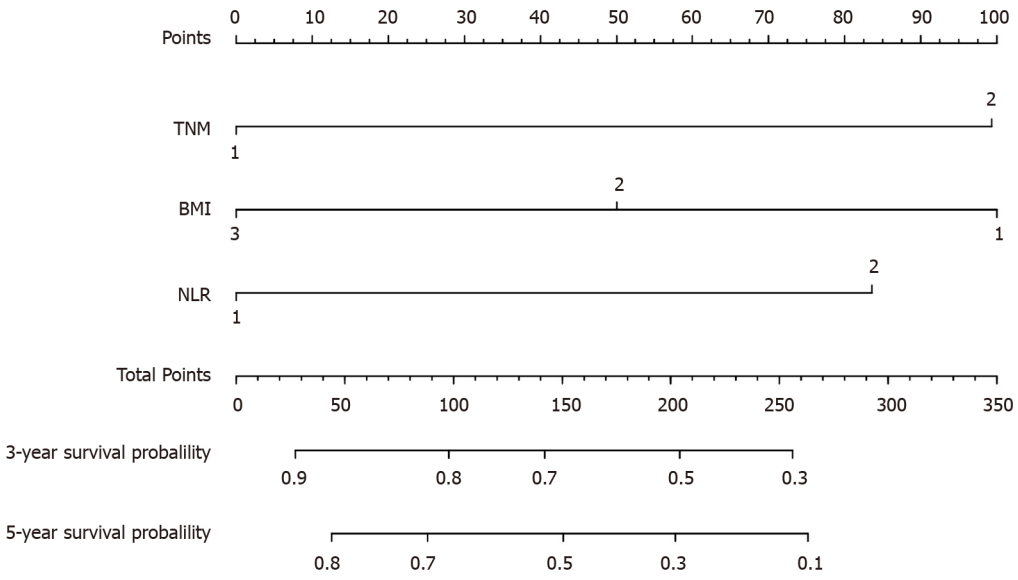

Figure 2 Calibration curves of the prognostic nomogram for 3-year overall survival. TNM: Tumor-node-metastasis; BMI: Body mass index; NLR: Neutrophil-to-lymphocyte ratio.

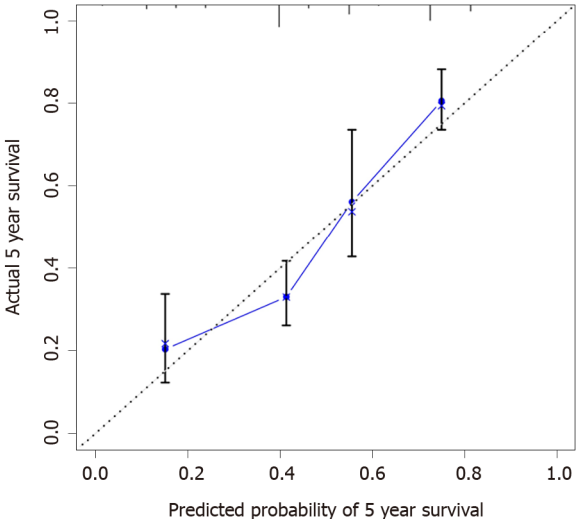

Figure 3 Calibration curves of the prognostic nomogram for 5-year overall survival.

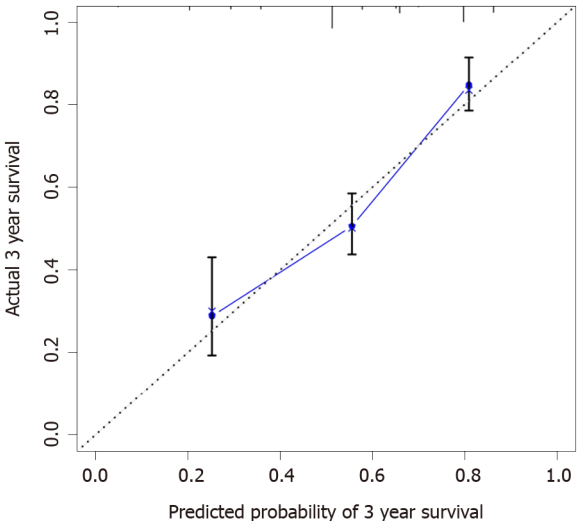

Figure 4 Calibration curves in the testing group for 3-year overall survival.

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.

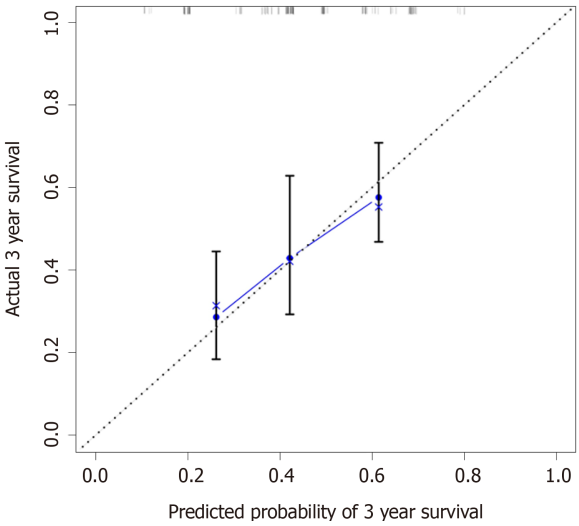

Figure 5 The receiver operating characteristic curves of the prognostic nomogram and tumor-node-metastasis staging for 3-year overall survival.

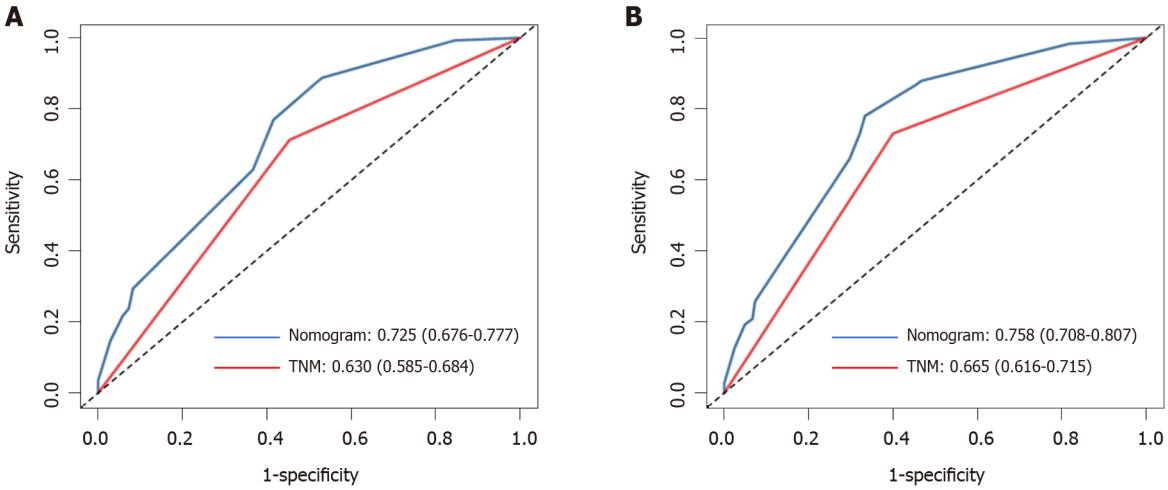

Figure 6 The receiver operating characteristic curves of the prognostic nomogram and tumor-node-metastasis staging for 5-year overall survival.

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.

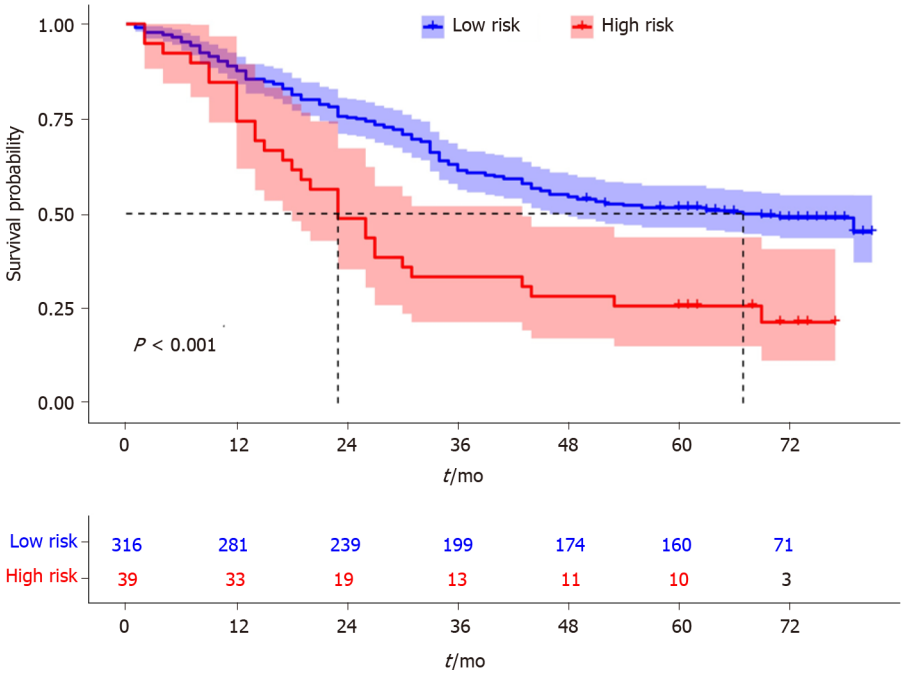

Figure 7 Survival curves stratified by the score calculated by the nomogram (low risk: < 58 and high risk: ≥ 58).

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).

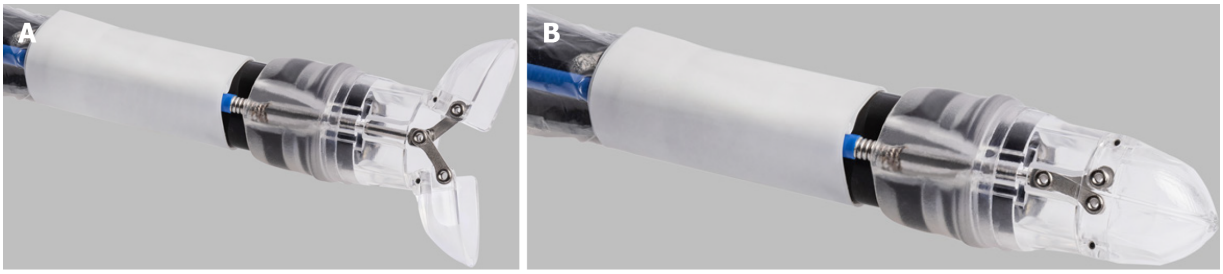

Figure 1 Over-the-scope-grasper attached to an endoscope. A: Open position; B: Closed position. With permission from Ovesco Endoscopy AG, Tübingen, Germany. Available from: http://www.ovesco.com/de.

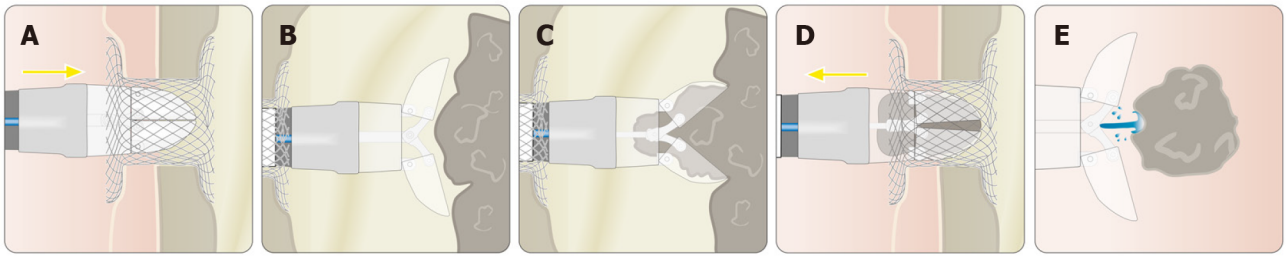

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Figure 2 Application of the over-the-scope-grasper in pancreatic necrosectomy through a lumen apposing metal stent. A: Insertion into the necrotic cavity; B: Opening the device; C: Grasping necrotic tissue; D: Withdrawal from the necrotic cavity; E: 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.

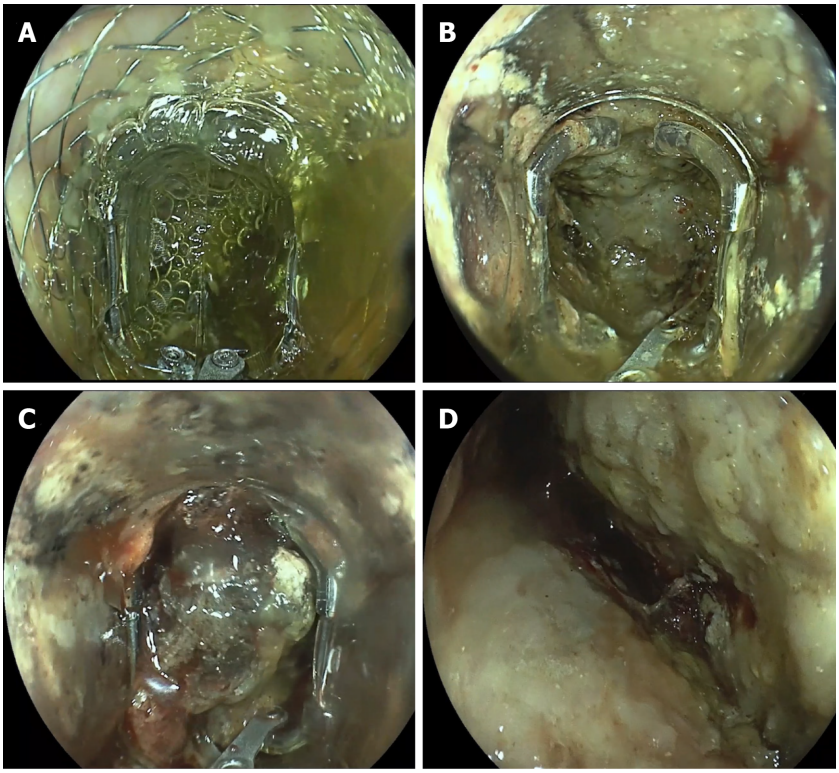

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Figure 3 Pancreatic necrosectomy through a lumen apposing metal stent with the over-the-scope-grasper. A: Insertion through the lumen apposing metal stent; B: Opening the device inside the necrosis; C: Grasping necrotic tissue; D: Cleaned necrotic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

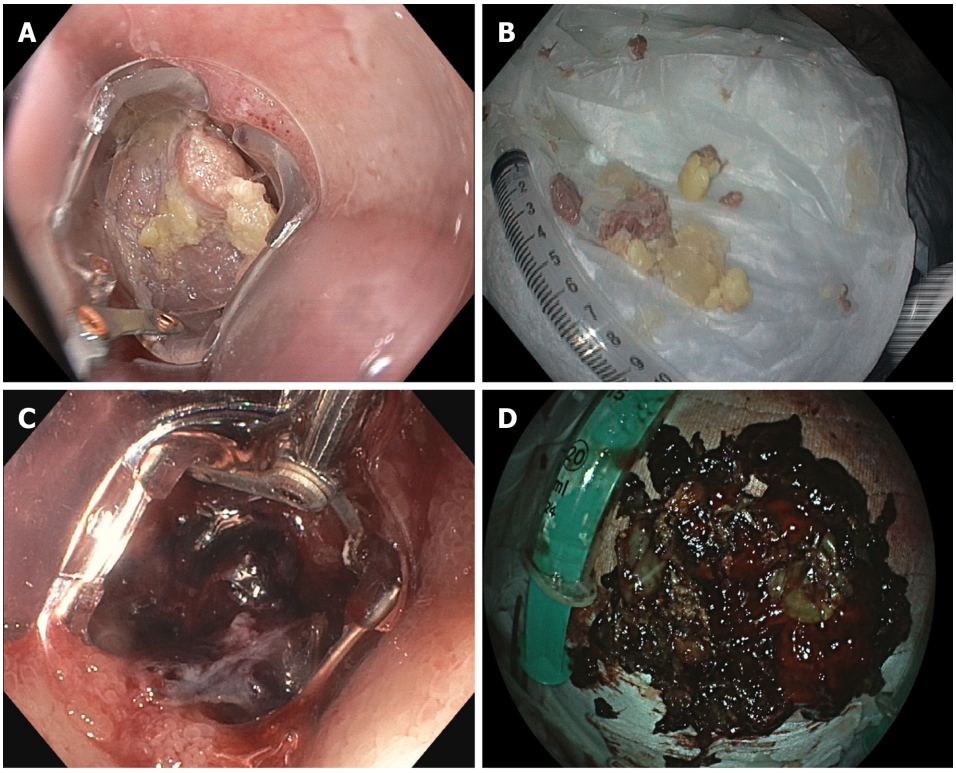

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Figure 4 Removing food bolus and blood clots with the over-the-scope-grasper. A: Grasping a meat chunk in the esophagus; B: Food pieces removed with the new device; C: Grasping a duodenal blood clot; D: Blood clots removed from the stomach with the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

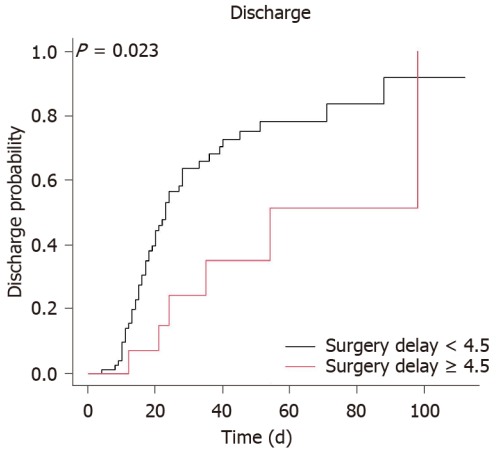

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Figure 1 Kaplan–Meier plot for in-hospital survival with a surgery delay less than or not less than 4.5 d. In patients with a surgery delay < 4.5 d, the 20-d discharge probability was 44.4%, whereas the discharge probability was 50% on day 22. For 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

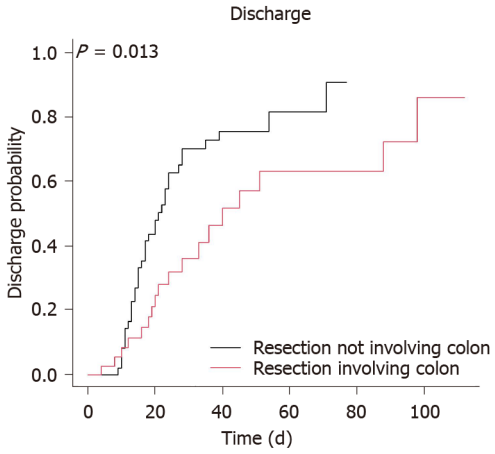

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Figure 2 Kaplan–Meier plot for in-hospital survival with bowel resection involving or not involving the colon. For resection not involving the colon, the 20-d discharge probability was 48.0%, whereas the discharge probability was 50% on day 21. For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

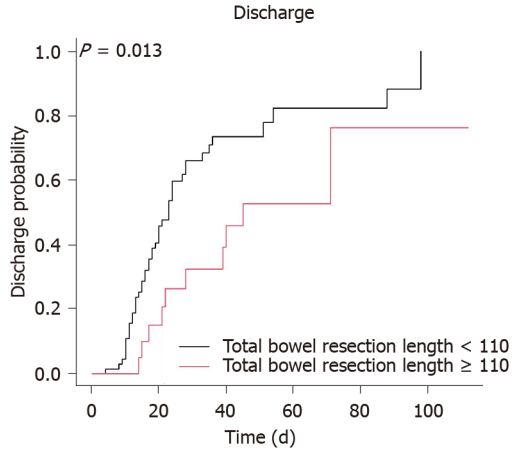

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Figure 3 Kaplan–Meier plot for in-hospital survival with a total bowel resection length less than or not less than 110 cm. In patients with a total bowel resection length < 110 cm, the 20-d discharge probability was 45.8%, whereas the discharge probability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

ACKNOWLEDGEMENTS

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FOOTNOTES

Author contributions: Hsu HH is the guarantor of the integrity of the entire study, designed the study, defined the intellectual content, participated in the literature search, and reviewed the manuscript; Liau SK performed the research, wrote the first draft, and analyzed the data; Lin YJ analyzed the data; Kuo G, Chen CY, Lu YA, Lee CC, Hung CC, and Tian YC participated in the literature search and reviewed the manuscript. All authors read and

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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.

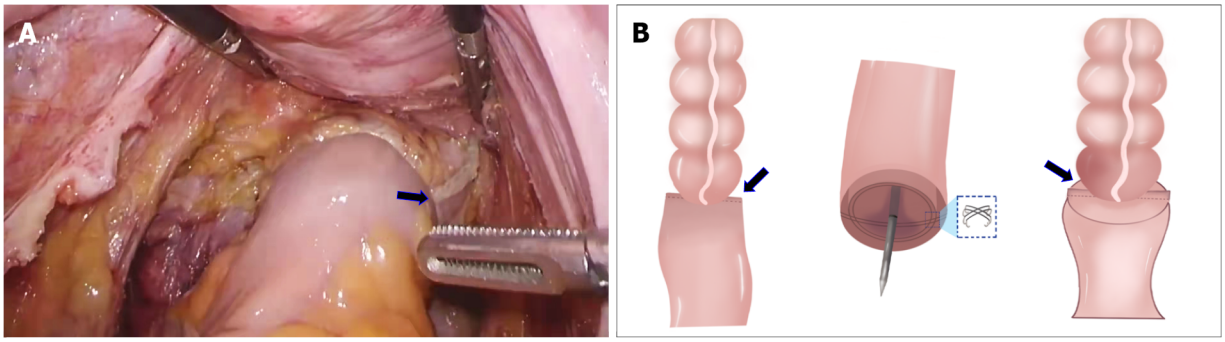

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Figure 1 "Dog ear" structure. A: The intersection of the staple lines (arrow); B: schematic diagram of the intersection of the staple lines (arrow).

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

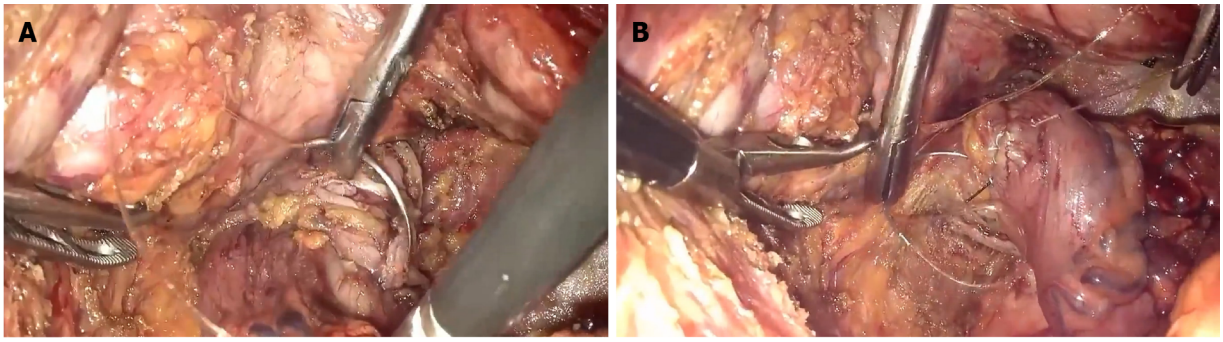

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Figure 2 Continuous suture reinforcement. A: Use of a 3-0 barbed suture at the intersection of the staple lines; B: Completion of the suture on the other side of staple line intersection.

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	

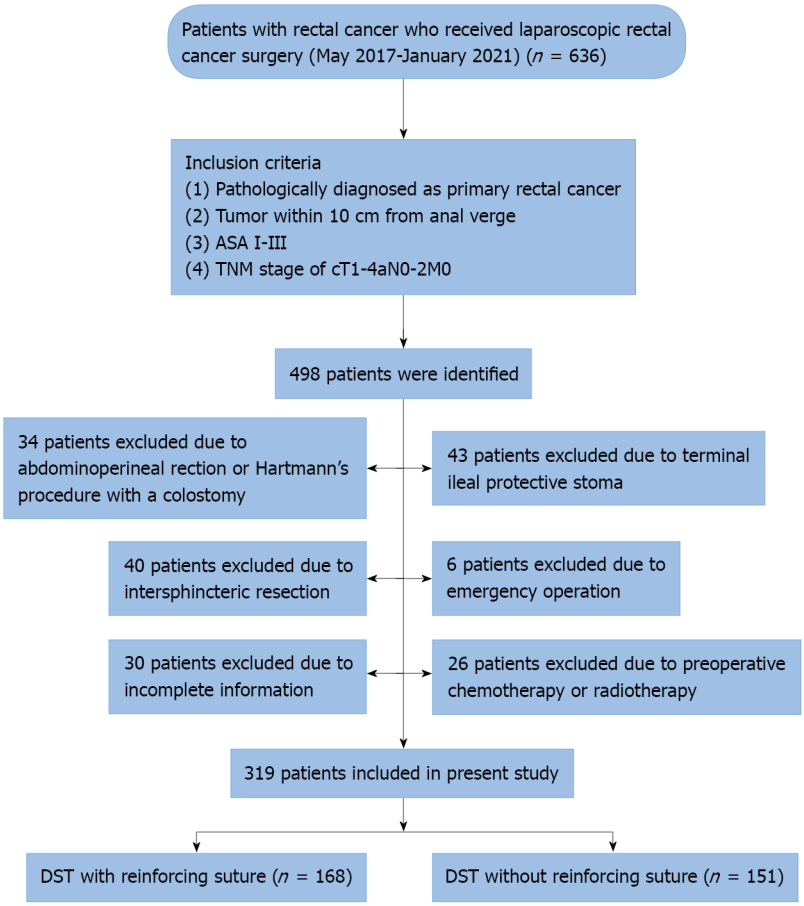

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Figure 3 Consort diagram of patient flow. DST: Double stapling technique; ASA: American Society of Anesthesiologists.

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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ORIGINAL ARTICLE

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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

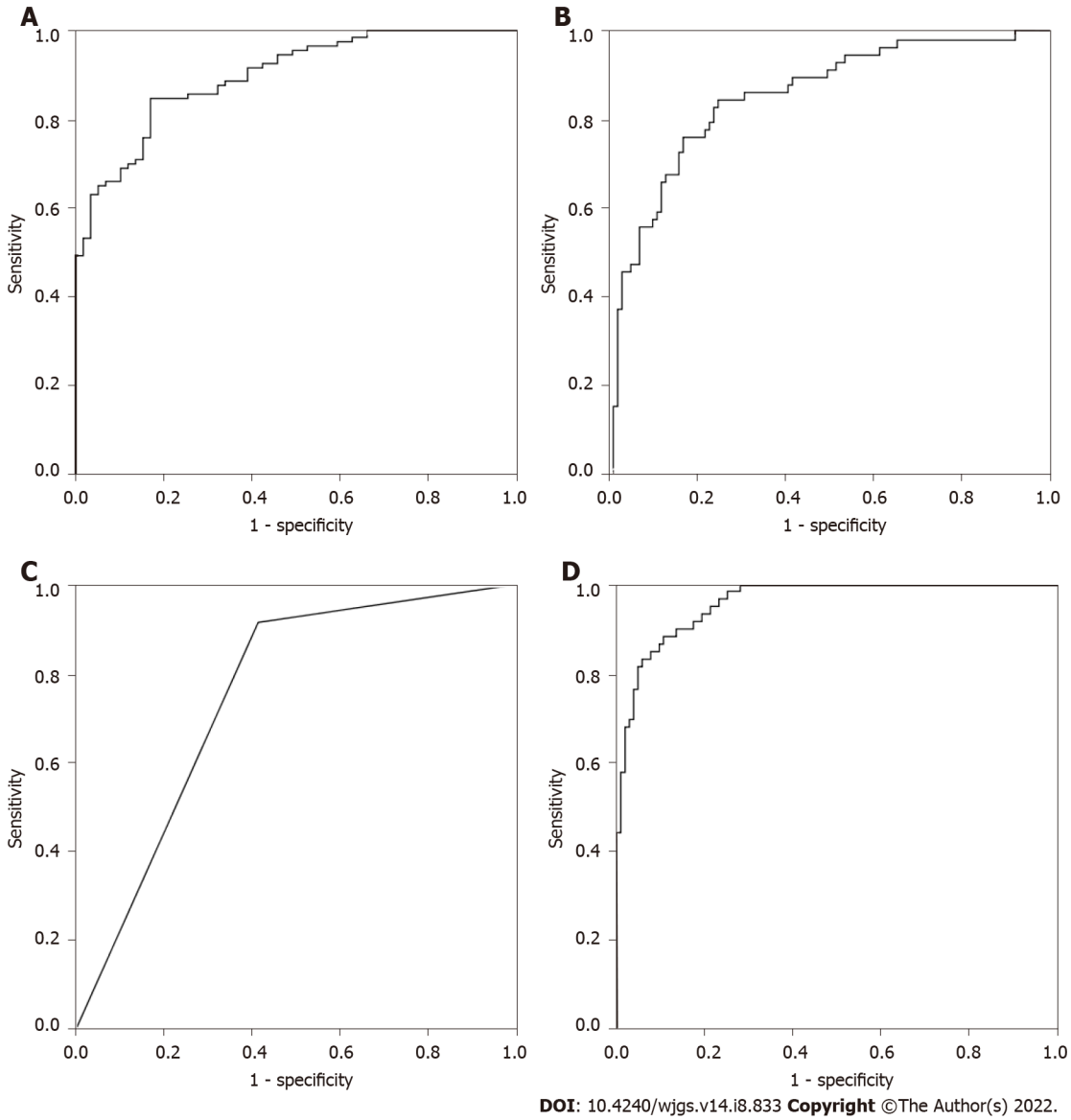

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Figure 1 Diagnostic evaluation of multi-parameter combined auxiliary diagnosis model building. A: Binary logistic regression analysis; B: Discriminant analysis; C: Classification tree analysis; D: Neural network.

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

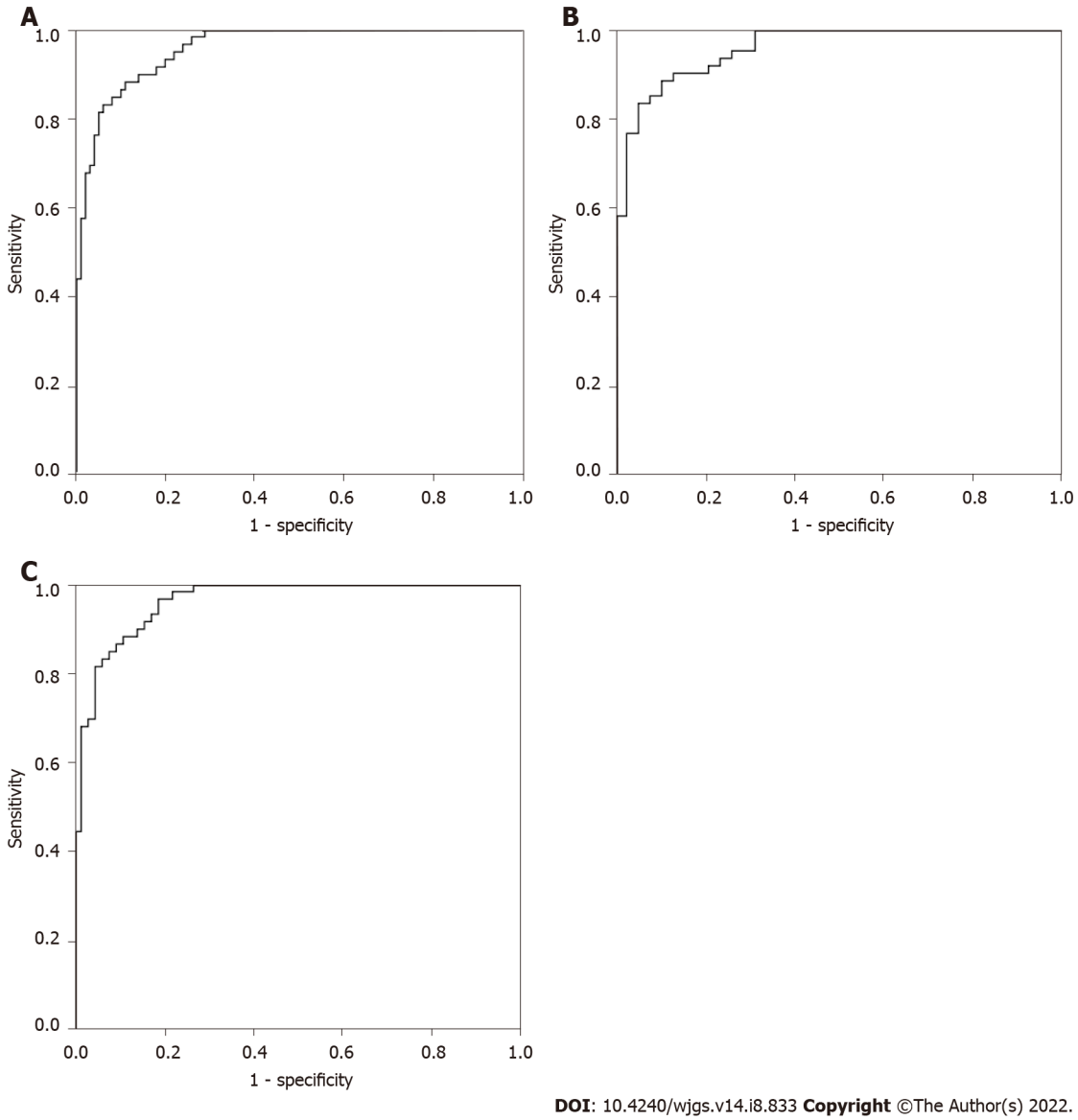

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Figure 2 Diagnostic evaluation of the neural network multi-parameter diagnostic model building. A: Colorectal polyps (CRP) *vs* colorectal cancer (CRC); B: CRP *vs* early stage of CRC; C: CRP *vs* advanced stage of CRC.

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].

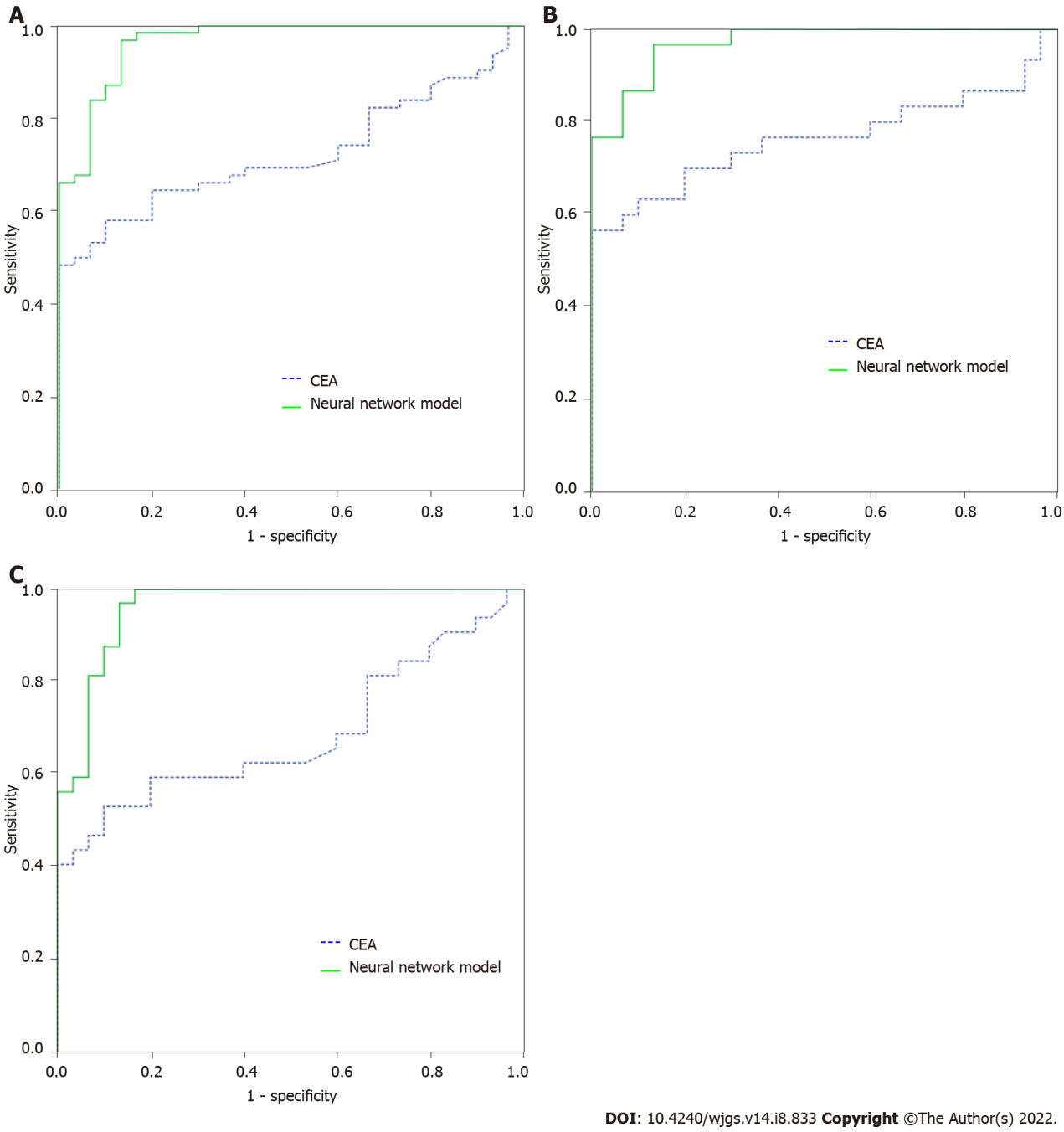

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Figure 3 Diagnostic evaluation of the neural network multi-parameter diagnostic model and carcinoembryonic antigen validation. A: Colorectal polyps (CRP) *vs* colorectal cancer (CRC); B: CRP *vs* early stage of CRC; C: CRP *vs* advanced stage of CRC. 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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Institutional review board statement: The study was reviewed and approved by the Chinese PLA General Hospital Review Board.

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

Conflict-of-interest statement: We declare that we have no financial or personal relationships with other individuals or organizations that can inappropriately influence our work and that there is no professional or other personal interest of any nature in any product, service and/or company that could be construed as influencing the position presented in or the review of the manuscript.

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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

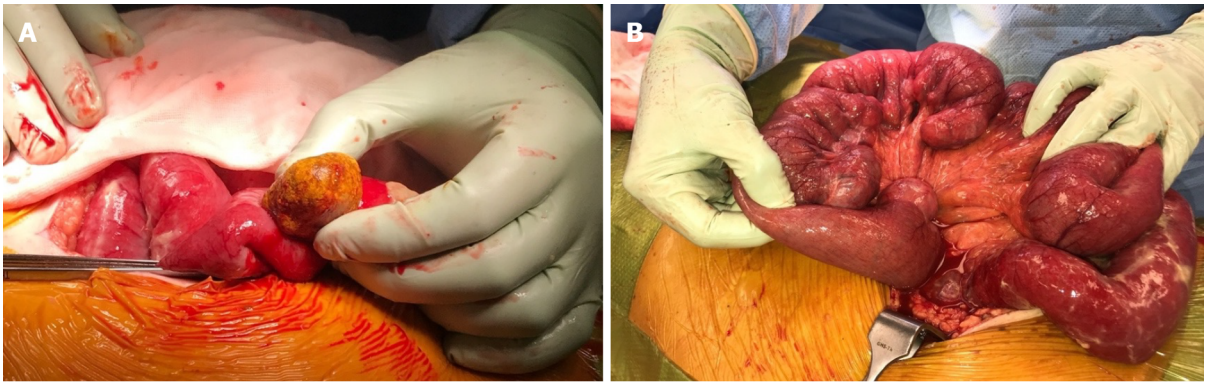

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Figure 1 Intraoperative photographs during the patient's initial laparotomy. A: Offending enterolith removed *via* longitudinal enterotomy; B: Extensive jejunal diverticulosis.

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

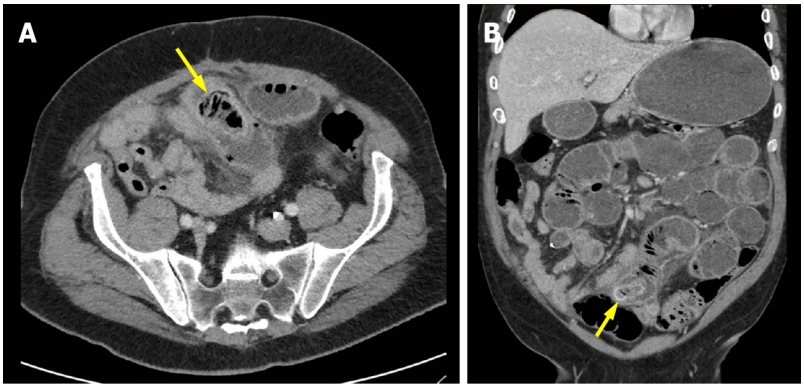

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Figure 2 Obstructing enterolith on computed tomography of abdomen and pelvis. A: Axial image of offending enterolith (yellow arrow); B: Coronal image of offending enterolith (yellow arrow).

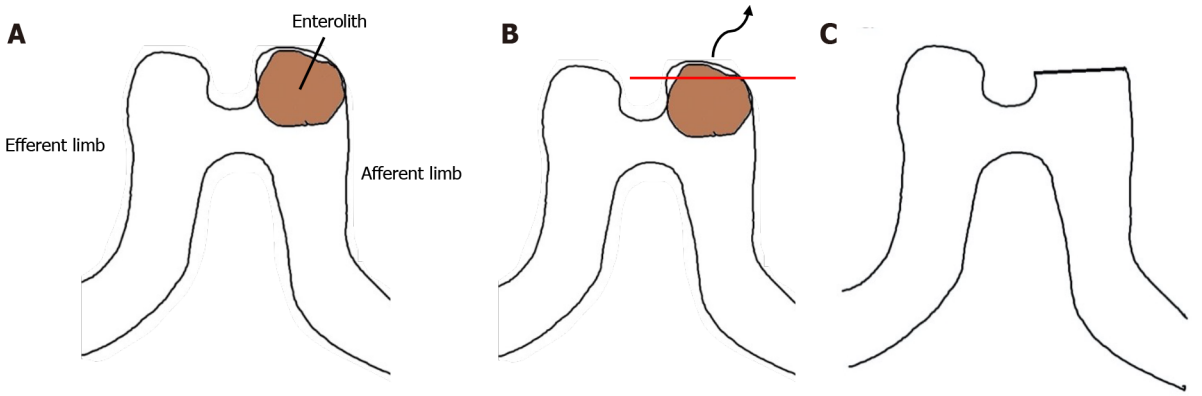

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Figure 3 Animated depiction of intraoperative management of recurrent enterolith impaction. A: Enterolith impaction in blind-ended pouch of previous side-to-side stapled anastomosis; B: Enterotomy at blind-ended pouch with enterolith extraction; C: 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

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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.

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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

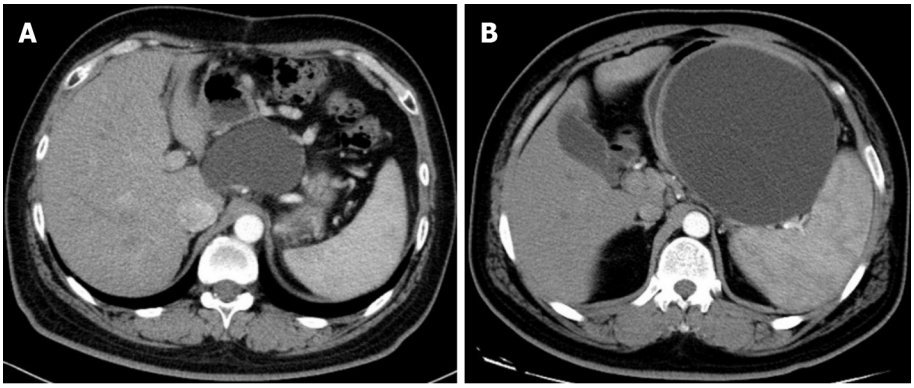

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Figure 1 Preoperative images of contrast-enhanced computed tomography. A: Preoperative contrast-enhanced computed tomography (CECT) image of the first patient showed a cystic lesion in the body of the pancreas, with a size of 7.93 cm × 6.13 cm; B: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

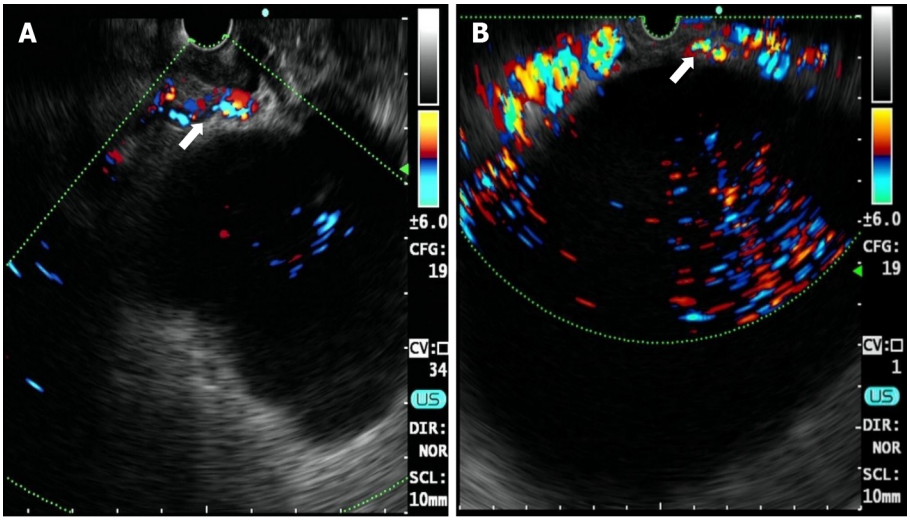

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Figure 2 Multiple vasculature (white arrow) detected by Doppler endoscopic ultrasound. A: Endoscopic ultrasound (EUS) imaging of the first patient; B: EUS imaging of the second patient.

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.

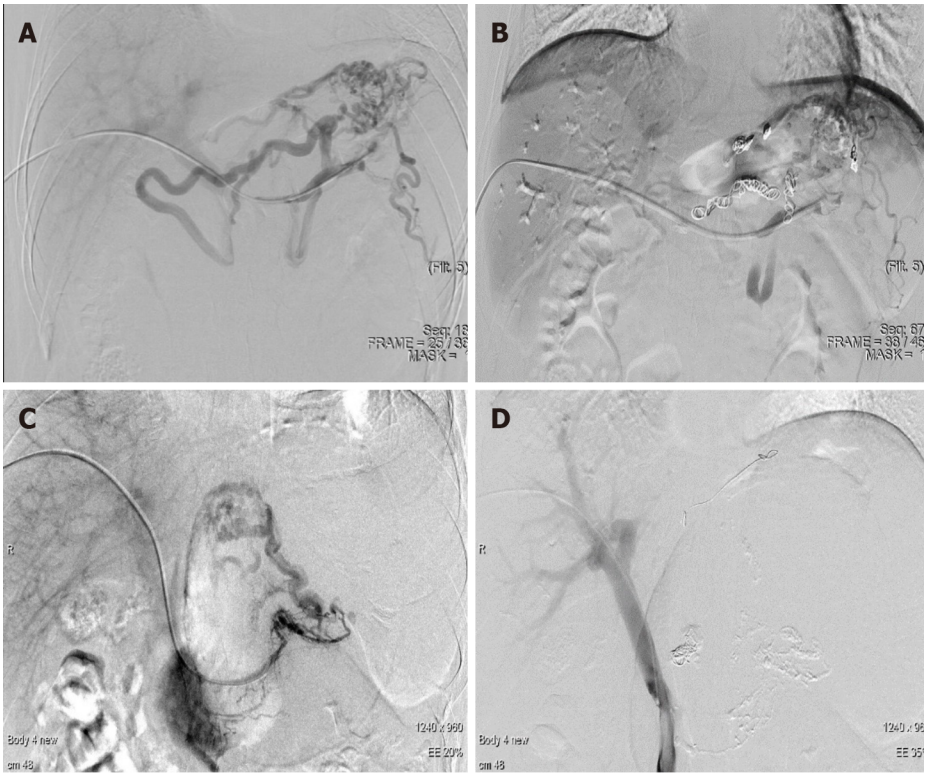

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Figure 3 Typical imaging of interventional radiology. A: Angiogram of the first patient prior to coil embolization; B: Angiogram of the first patient after coil embolization; C: Angiogram of the second patient prior to coil embolization; D: Angiogram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

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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

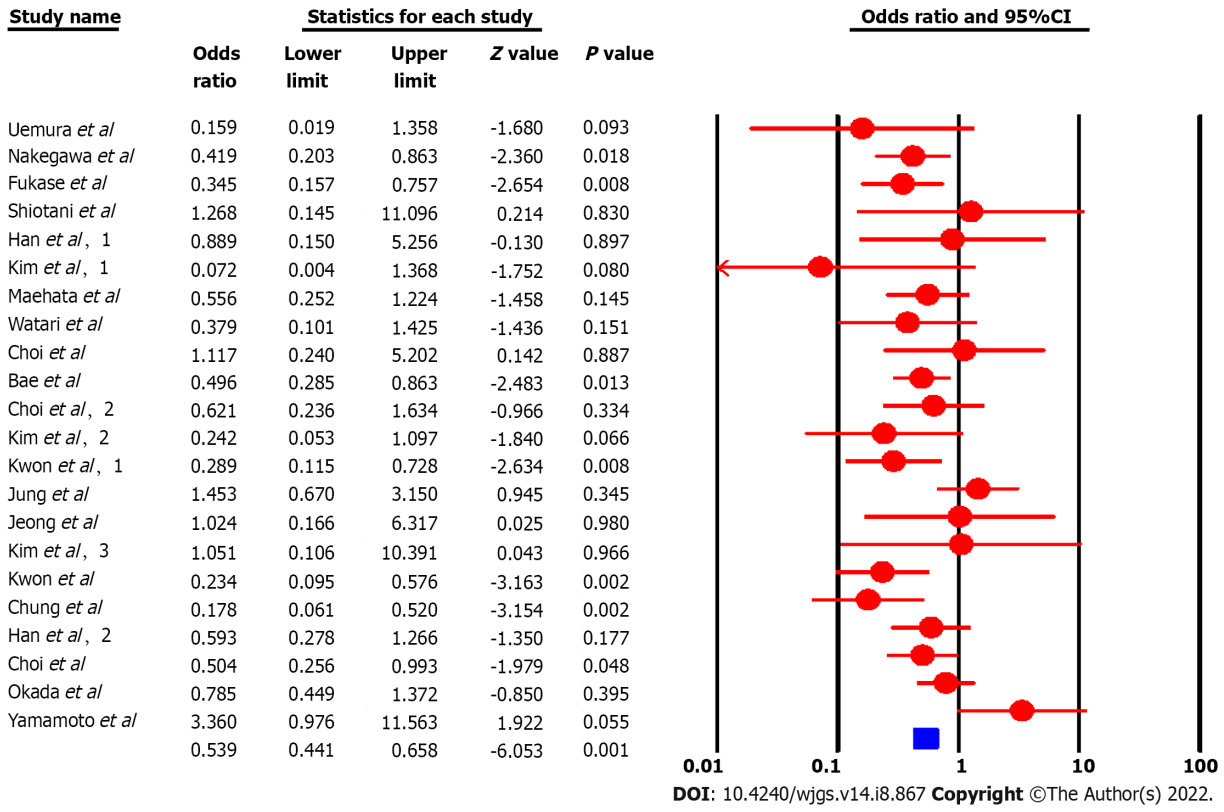

Figure 1 Forest plot for incidence of metachronous gastric cancer between *Helicobacter pylori*-eradicated group and non-eradicated group in 23 studies. 95%CI: 95% confidence interval.

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

Hirokazu Saito, Shuji Tada

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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

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MINIREVIEWS

Oncologic aspects of the decision-making process for surgical approach for colorectal liver metastases progressing during chemotherapy

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Abstract

Colorectal cancer represents the third most diagnosed malignancy in the world. The liver is the main site of metastatic disease, affected in 30% of patients with newly diagnosed disease. Complete resection is considered the only potentially curative treatment for colorectal liver metastasis (CRLM), with a 5-year survival rate ranging from 35% to 58%. However, up to 80% of patients have initially unresectable disease, due to extrahepatic disease or bilobar multiple liver nodules. The availability of increasingly effective systemic chemotherapy has contributed to converting patients with initially unresectable liver metastases to resectable disease, improving long-term outcomes, and accessing tumor biology. In recent years, response to preoperative systemic chemotherapy before liver resection has been established as a major prognostic factor. Some studies have demonstrated that patients with regression of hepatic metastases while on chemotherapy have improved outcomes when compared to patients with stabilization or progression of the disease. Even if disease progression during chemotherapy represents an independent negative prognostic factor, some patients may still benefit from surgery, given the role of this modality as the main treatment with curative intent for patients with CRLM. In selected cases, based on size, the number of lesions, and tumor markers, surgery may be offered despite the less favorable prognosis and as an option for non-chemo responders.

Key Words: Colorectal liver metastases; Oncology; Disease progression; Surgery; Liver

resection; Hepatectomy

Core Tip: The mainstream curative-intent treatment of colorectal liver metastasis (CRLM) is complete surgical resection. Increasingly effective systemic chemotherapy has helped to improve long-term outcomes, downstaging of CRLM, and patient selection for surgery. Disease progression during chemotherapy represents an independent negative prognostic factor. However, in selected cases, based on size, the number of lesions, and tumor markers, surgery may be offered as an option for non-chemo responders. This minireview article aims to explore this open question in the literature using both evidence and meaningful thoughts on this controversial and challenging topic.

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INTRODUCTION

Colorectal cancer (CRC) represents the third most diagnosed malignancy and the second cause of cancer-related death in the world, with an estimated incidence of 1931590 new cases in 2020[1]. Approximately 30% of patients will present metastases at diagnosis, and 10% to 20% of stage 1-3 diseases will progress to local or distant metastases[2]. Half of the patients with metastatic disease will have liver metastases, which are unresectable in up to 80% of cases due to extrahepatic disease or bilobar multiple liver nodules[2].

Patients with initially resectable colorectal liver metastasis (CRLM) but with either high tumor burden or bad prognostic factors usually go to upfront chemotherapy and then surgery. Complete resection is considered the only potentially curative treatment for CRLM, with 5-year survival rates ranging from 35% to 58%[3]. However, part of these patients will progress during pre-operative chemotherapy, and for this group, the role of resection of CRLM remains controversial and with large discrepancies in the literature. This minireview article aims to address oncologic aspects that drive the decision-making process, in a multidisciplinary manner, to offer surgery for patients with CRLM who are progressing during chemotherapy. Despite the scarcity of literature on the subject, we believe that this specific patient population deserves more individualized evaluation because their inherent condition of progression during systemic chemotherapy has kept them from being included in most of the trials with curative-intent treatment.

LIVER RESECTION FOR CRLM

The mainstream curative-intent treatment of CRLM is complete surgical resection. Although metastasectomy has never been tested in a randomized controlled trial, studies have demonstrated long-term survival and cure after this approach[4]. The standard recommended surgical treatment for CRLM is complete macroscopic resection with negative margins (R0 resection). However, complete removal of the macroscopic tumor without safe margins (R1 resection) may be accepted in vascular proximity or multi-nodularity cases. The use of increasingly effective chemotherapy has changed long-term outcomes after R1 resection, with survival similar to that of R0 resection[5].

In 1999, Fong *et al*[6] described the most used Clinical Risk Score (CRS) to predict recurrence after hepatic resection for metastatic CRLM. It was based on five independent prognostic factors: Positive nodal status of the primary tumor, the disease-free interval from identification of the primary tumor to the discovery of liver metastases of < 12 mo, number of metastatic tumors > 1, preoperative carcinoembryonic antigen (CEA) level > 200 ng/mL, and size of the largest tumor > 5 cm. Patients with scores of 0, 1, or 2 had more favorable outcomes compared with scores of 3, 4, or 5[6]. This CRS works as a practical clinical tool helping to select patients for upfront surgery or systemic therapy according to the estimated risks.

Despite the definition of resectability varying from center to center, metastases are usually considered resectable if they can be completely removed (R0 resection) while leaving an adequate functional parenchyma volume[7]. Usually, resectable lesions are those that can be completed removed with a

remnant liver representing at least two contiguous segments, granting the patency of inflow and outflow structures, and sparing at least 20% of total liver volume, for healthy and unexposed livers to chemotherapy, or at least 30% for patients who underwent previous chemotherapy[8]. However, up to 70%-80% of patients with CRLM are not initial candidates for hepatic resection[9].

Several strategies have been introduced to the clinical practice to increase the number of patients eligible for curative hepatic resection, including neoadjuvant chemotherapy, two-stage hepatectomies, and portal vein embolization. In 2004, Adam *et al*[10] reported postoperative 5-year survival of patients submitted to conversion therapy is 33% after rescue surgery[10]. This outcome remains a work in progress and has been increasing with the advent of more modern systemic therapy such as triplet therapies and monoclonal antibodies.

PERIOPERATIVE CHEMOTHERAPY IN INITIALLY RESECTABLE PATIENTS

Despite patients undergoing surgical curative-intent treatment, R0 Liver resection, nearly 50%-65% of patients submitted to surgery will relapse within 5 years[11]. Therefore, the use of perioperative systemic chemotherapy has increased over the last decades as an effort to improve long-term outcomes.

Regardless of being associated with an objective response rate of 50%-65%, the survival benefit of perioperative chemotherapy remains controversial[12]. The EPOC clinical trial randomized patients with initially resectable CRLM into preoperative chemotherapy (FOLFOX4) or surgery alone. While no benefit in overall survival (OS) was demonstrated, preoperative chemotherapy significantly increased progression-free survival (PFS) in eligible patients and those with resected CRLM[13]. Based on those findings, the addition of systemic chemotherapy to surgical resection has become the standard of care for CRLM in many centers.

A comparison between perioperative and postoperative chemotherapy after potentially curative hepatic resection for metastatic CRC was conducted at the Memorial Sloan-Kettering Cancer Center. Both OS and recurrence-free survival (RFS) were similar between the groups when adjusted for clinical-pathological factors and CRSs. Therefore, the authors concluded that the timing of additional chemotherapy for resected CRLM was not associated with outcomes[14].

Corroborating those findings, a systematic review, and meta-analysis of chemotherapy for patients with CRLM who underwent curative hepatic resection showed that regardless of timing and based on nonrandomized and randomized data, patients submitted to hepatic resection for CRLM should receive additional chemotherapy, given that this strategy relative increases RFS and OS in 29 and 23%, respectively[15]. Recently, a randomized controlled trial examining the use of adjuvant chemotherapy (modified infusional fluorouracil, leucovorin, and oxaliplatin-mFOLFOX6) in patients with liver-only metastatic CRC was published. Kanemitsu *et al*[16], after a median follow-up of 59.2 mo, demonstrated that adjuvant chemotherapy improved 5-years disease-free survival when compared to hepatectomy alone (49.8% *vs* 38.7%, CI: 0.41-0.92; $P = 0.006$). No significant differences in 5-year OS were detected, 71.2% (95%CI: 61.7-78.8) with adjuvant chemotherapy and 83.1% (95%CI: 74.9-88.9) with hepatectomy alone. Nonetheless, this trial was not designed to detect a difference in OS as a primary endpoint, and indeed, it has not a long enough follow-up to detect this difference, so improvements in OS could not be demonstrated[16].

The benefit of adding new systemic therapies to improve outcomes in patients with resectable CRLM has been tested. The New EPOC was a phase III trial that included patients with resectable exon-2 RAS wild-type metastatic CRC, randomly assigned to receive perioperative chemotherapy, doublet oxaliplatin-based therapy, with or without cetuximab. The incorporation of cetuximab not only correlated with significantly inferior PFS but also with a trend towards decreased OS. Although the addition of cetuximab to chemotherapy may improve outcomes in patients with initially inoperable metastatic disease, its use preoperatively in resectable patients confers a significant disadvantage and should not be a routine[17].

It seems that chemotherapy should be incorporated into the treatment of resectable CRLM, increasing PFS, and possibly OS. However, the best timing for additional chemotherapy remains unclear. Delivering chemotherapy preoperatively may be used as a means of testing tumor biology in vivo, identifying patients who will benefit most from surgery. Recently, response to neoadjuvant chemotherapy has been established as a major prognostic factor once patients with disease stabilization or progression while on chemotherapy seem to have worse outcomes than responders[18]. Other benefits of initial chemotherapy may be the earlier treatment of micrometastatic disease and cytoreduction of the hepatic disease, facilitating surgical resection. On the other hand, oxaliplatin or irinotecan-based neoadjuvant chemotherapy can increase the rates of perioperative morbidity and cause liver toxicity.

Considering symptomatic synchronous tumors, it is suggested to direct the treatment to the primary tumor first, with resection and/or deviation, followed by systemic chemotherapy. For asymptomatic patients with synchronous tumors and those with metachronous hepatic disease, the timing of additional chemotherapy should be guided by the CRS of recurrence, as proposed by Fong *et al*[6]. For potentially resectable patients with a low risk of recurrence (0-2), initial surgery rather than neoadjuvant

che-motherapy could be chosen, followed by postoperative chemotherapy. For patients with a high risk of recurrence (3-5), neoadjuvant chemotherapy is the preferred approach[3]. Pre-operative che-motherapy, on the other hand, is an important resource for liver parenchyma sparing in patients who require extended hepatectomy, regardless of whether they have a high or low CRS. Perhaps this action prevents postoperative liver dysfunction and increases the chances of a preserved clinical performance when undergoing postoperative chemotherapy or re-hepatectomy when indicated.

PERIOPERATIVE CHEMOTHERAPY IN INITIALLY UNRESECTABLE PATIENTS

For patients with initially unresectable or critically located colorectal liver metastases, upfront chemotherapy represents an appropriate option as conversion therapy. However, the likelihood of downstaging a patient to the point of resectability seems to be below, on the order of 5% to 15%, even in the hands of aggressive surgeons[19].

A regime leading to high response rates and a large tumor shrinkage is recommended. Although there are uncertainties surrounding the best combination to use, it seems that for RAS wild-type disease a cytotoxic doublet in association with an anti-epidermal growth factor receptor (EGFR) offers the best benefit-risk/ratio. For patients with RAS-mutant disease, the preference is for a cytotoxic doublet plus bevacizumab or FOLFOXIRI plus bevacizumab[20].

A meta-analysis assessing the effect of cetuximab and panitumumab in patients with liver-limited initially unresectable CRLM showed that the addition of anti-EGFR increased the R0 resection rate by 60% and reduced the risk of progression by 32%[21]. Considering non-liver limited disease, the CRYSTAL trial demonstrated that FOLFIRI plus anti-EGFR as first-line treatment was beneficial when compared to FOLFIRI alone, especially for the subgroup of wild-type K-RAS[22]. The FOLFIRI plus anti-EGFR *vs* FOLFIRI plus anti-vascular endothelial growth factor (VEGF) for the non-liver limited disease was addressed in the FIRE-3 trial and despite neither difference in objective response nor PFS being identified, FOLFIRI plus anti-EGFR achieve longer OS for patients with wild-type KRAS (33 *vs* 25 mo, P = 0.017)[23,24]. However, in a posthoc analysis of this study population, after a centralized analysis of radiological response, FOLFIRI plus anti-EGFR demonstrated better response outcomes than FOLFIRI plus anti-VGFR[23,24]. Furthermore, Tejpar *et al*[25] investigated the primary tumor locations, whether right-sided (from the appendix to the transverse colon) or left-sided (from the splenic flexure to the rectum), in patients with wild-type RAS from both CRYSTAL and FIRE-3[25]. The data suggested that adding anti-EGFR to patients with wild-type RAS right-sided tumors had no benefit; contrary, the data showed that patients with left-sided tumors had better objective response rates, PFS and OS, which seems to be useful for this subgroup of patients, particularly those with symptomatic primary tumors or high tumor burden of CRLM.

Regarding anti-VGFR action, Xu *et al*[26] demonstrated in a systematic review and metanalysis that Bevacizumab-based combination therapies for patients with advanced mCRC show significant higher objective response rates [risk ratios (RR): 1.40], PFS [hazard ratio (HR): 0.64], and OS (HR: 0.82) values when compared than monotherapy. Regrettably, combined anti-VGEF therapies also increase the risk of grade 3/4 treatment-related toxicity (RR: 1.27) when compared to monotherapy[26]. Among the anti-VEGF combined therapies, capecitabine use is associated with a higher risk of grade 3/4 adverse effects (RR: 1.89 *vs* 1.12) than IFL[26].

EVALUATION OF RESPONSE TO PREOPERATIVE CHEMOTHERAPY

The Response Evaluation Criteria in Solid Tumors is the recommended method of assessing objective response to preoperative chemotherapy in most clinical trials. The total tumor burden is evaluated by selecting up to five target lesions and calculating the average diameter change based on imaging studies. A reduction of at least 30% is classified as a response and an increase of at least 20% as progression[27].

ROLE OF SURGERY IN PATIENTS PROGRESSING WHILE ON CHEMOTHERAPY

The role of surgery in patients with CRLM progressing while on systemic chemotherapy remains controversial. A summary of the major publications addressing this subject is represented in Table 1.

Allen *et al*[28] evaluated patients with synchronous colorectal liver metastases treated between January 1995 and January 2000. Patients who received preoperative chemotherapy, as a group, had similar OS compared to those submitted to surgery upfront. However, the subgroup of patients with diseases that did not progress while on chemotherapy showed significantly improved survival[28].

Similar results were demonstrated by Adam *et al*[29] in a retrospective analysis of 131 patients submitted to liver resection for CRLM after systemic chemotherapy. In this group, patients could

Table 1 Study characteristics according to the type of preoperative chemotherapy, type of response, overall and disease-free survivals of patients who underwent curative-intent treatment hepatectomies for colorectal liver metastases

Ref.	N[1] (total)	N (surgery)	Age[2] (yr)	Median FU (mo)	Preoperative chemotherapy	R0 (%)	Preoperative chemotherapy response (%)	Median OS (mo)	1-yr OS (%)	3-yr OS (%)	5-yr OS (%)	1-yr DFS (%)	3-yr DFS (%)	5-yr DFS (%)
Allen *et al*[28], 2003	106	52	59	30	5-FU	82.6	R: 12 (26); S: 17 (37); P: 17 (37)							RS: 0.87; P: 0.38
Adam *et al* [29], 2004	131	131	59.5 (32-78)	33.1	5-FU/5-FU + Oxaliplatin/5-FU + Irinotecan/5-FU + Oxaliplatin + Irinotecan	90	R: 58 (44); S: 39 (30); P: 34 (36)	O: 30	R: 0.95; S: 0.92; P: 0.63	R: 0.55; S: 0.44; P: 0.12	R: 0.37; S: 0.3; P: 0.08	R: 0.52; S: 0.33; P: 0.23	R: 0.32; S: 0.23 P: 0.07	R: 0.21; S: 0.17; P: 0.38
Neumann *et al* [2], 2009	160	160	R: 59 (35-77); S: 60 (35-73); P: 60 (36-78)	28.8	5-FU/5-FU + Oxaliplatin/5-FU + Irinotecan/5-FU + Oxaliplatin + Irinotecan/5-FU + Oxaliplatin + Irinotecan + antiEGFR or antiVEGF	72.5	R: 44 (27.5); S: 20 (12.5) P: 90 (60)	R: 37.2; S: 44.4; P: 38.1	O: 0.88	O: 0.53	R: 0.34; S: 0.44; P: 0.36			
Gallagher *et al* [30], 2009	111	111	61 (27-85)	63	5-FU/5-FU + Oxaliplatin/5-FU + Irinotecan/Others	84.6	R: 47 (42.3); S: 52 (47); P: 18 (16)	R: 58; S: 65; P: 61			R: 0.5; S: 0.51; P: 0.61			
Tamandl *et al* [18], 2009	244	29	73.1 (70.1-83)	34	5-FU/Capecitabine		R: 13 (44); S: 7 (24) P: 90 (31)				R: 0.64; S: 0.36; P: 0			
de Haas *et al* [35], 2010	119	119	61 (51-71)	34	5-FU/5-FU + Oxaliplatin/5-FU + Irinotecan/Others	59.6	R: 72 (60); S: 28 (24); P: 19 (16)	R: 34; S: 32; P: 20		R: 0.42; S: 0.46; P: 0.36	R: 0.29; S: 0.28; P: 0.07		R: 0.09; S: 0.09; P: 0.07	
Brouquet *et al* [31], 2011	60	60	59 (48-70)	32	5-FU/5-FU + Oxaliplatin/5-FU + Irinotecan/5-FU + Oxaliplatin or Irinotecan + antiEGFR or antiVEGF	80	R: 22 (37); S: 22 (37); P: 16 (27)	R: 41.7; S: 23; P: 15.9	O: 0.83	O: 0.41		O: 0.37	O: 0.11	
Giuliante *et al* [7], 2014	130	113	58.6 (36-81)	19	Oxaliplatin-based/Irinotecan-based/Oxaliplatin + Irinotecan-based/associated antiEGFR/associated antiVEGF	76.1	P: 67 (61.5); R: 36 (32.1); P: 7 (6.35)	O: 43			O: 0.32			
Pugh *et al*[36], 2016	110	63	CA: 65; CC: 64	CA: 14.5; CC: 14.2	CAPOX/Oxaliplatin-MdG/Irinitecan-MdG/CAPOX + Cetuximab/Oxaliplatin-MdG + cetuximab/Irinitecan-MdG + cetuximab	100	O: 63 (100)	CA: 29; CC: 19.9						
Lim *el al*[37], 2016	155	146	65 (33-83)	36	5-FU/Capecitabine/5-FU + Oxaliplatin/5-FU + Irinotecan	85.6	R: 72 (46.5); S: 48 (31); P: 26 (16.8)							
Imai *et al*[38], 2016	846	691	61 (28-89)	44.2	5-FU/5-FU + Oxaliplatin/5-FU + Irinotecan/ + antiEGFR or -antiVEGF or Panitumumab	34.1	RS: 501(72.5); P: 46 (6.6)			O: 64.7	O: 49.6		O: 30.1	O: 19.1
Adam *et al*[9], 2017	6415	6415	G1: 61.6; G2: 61.4	30.1	5-FU + Oxaliplatin/5FU + Irinotecan/5-FU + Oxaliplatin + Irinotecan/5-FU + Oxaliplatin + Irinotecan/ + antiEGFR or -antiVEGF or Panitumumab		R: 4710 (73.4); S: 1289 (20.1); P: 416 (6.5)	G1: 58.9; G2: 58.6		G1: 71; G2: 76	G1: 49; G2: 49		G1: 32; G2: 27	G1: 23; G2: 15
Vigano *et al* [33], 2018	128	128	RS: 61; P: 62	30	5-FU + Oxaliplatin/5FU + Irinotecan/5-FU + Oxaliplatin + Irinotecan/ + antiEGFR or -antiVEGF or		RS: 96 (75); P: 32 (25)			RS: 52.4; P: 0.23			RS: 21.6; P: 6.3	

					Panitumumab				
Ruzzenente *et al*[39], 2019	784	784	59.4 (51.3-67.8)	-	5-FU + Oxaliplatin/5FU + Irinotecan/5-FU + Oxaliplatin + Irinotecan/ + antiEGFR or -antiVEGF or Panitumumab		RS: 405 (51.6); P: 314 (40.1)		RS: 51.6; P: 40.1
Brunsell *et al*[40], 2019	142	142	67 (21-80)	37	5-FU + Oxaliplatin/5FU + Irinotecan/5-FU + Oxaliplatin + Irinotecan/+ antiEGFR or -antiVEGF or Panitumumab	37.8	R: 66 (46.5); S: 63 (44.4); P: 13 (9.1)	R: > 60; S: 47; P: 33	

[1]Total *per* study.

[2]Median (range) or mean plus standard deviation as described by the authors.

FU: Follow-up; 5-FU: 5-fluorouracil; R: Disease response group; S: Stable disease group; P: Progression disease group; RS: Response and stable disease group; O: Overall; OS: Overall Survival; DFS: Disease-Free Survival; MdG: Modified de Gramont; CA: Chemotherapy alone group; CC: Chemotherapy plus cetuximab group; G1: Resection after first-line chemotherapy group; G2: Resection after second-line chemotherapy group.

achieve long-term survival after hepatic resection if the disease was controlled by chemotherapy before surgery. However, tumor progression before the operation conferred a poor outcome, even after potentially curative surgery[29].

Neumann *et al*[2] evaluated 160 patients exposed to preoperative chemotherapy, followed by liver resection for CRLM. Factors associated with poor outcomes were noncurative resection, CEA levels > 200 ng/dL, tumor grading, size of largest tumor > 5cm, and the number of metastases. Controversially, tumor progression while on chemotherapy did not influence long-term survival[2]. Those findings are supported by a retrospective study by Gallagher *et al*[30], that found no difference in survival among the three response groups after chemotherapy[30].

A retrospective analysis of patients with hepatic resection of CRLM following second-line chemotherapy was conducted by Brouquet *et al*[31] The regime proved to be feasible and associated with modest survival benefits, representing a viable option in patients with advanced CRLM[31]. Similarly, Adam *et al*[9] found that selected patients submitted to hepatic resection of CRLM after second-line preoperative chemotherapy could have comparable outcomes to patients resected after first-line chemotherapy. In this scenario, independent predictive factors of worse prognosis were positive primary lymph nodes, extrahepatic disease, tumor progression on second-line therapy, and R2 resection [9].

For patients with extensive bilobar disease, selection based on response to pre-hepatectomy chemotherapy seems to be extremely important before planning a two-stage hepatectomy (TSH). Giuliante *et al*[7] found that tumor progression while on preoperative chemotherapy significantly increased the risk of failure to complete the second stage. However, for patients who completed the TSH, long-term outcomes were similar to those reported for patients following a single-stage hepatectomy[7]. In this context, Jouffret *et al*[32] showed that resectable hepatic disease progression in the future remnant liver after portal vein embolization should not be considered a contraindication for second stage hepatectomy[32]. Vigano *et al*[33] reported a series of 128 patients with disease response or stabilization while on preoperative chemotherapy. Early progression of the disease between the end of chemotherapy and liver resection was reported in approximately 15% of patients and was associated with extremely poor survival[33].

Additionally, caution is necessary for patients in the setting of preoperative use of Anti-VGEF since they have a higher risk of treatment-related complications such as hemorrhage, hypertension, neutropenia, stroke, GI perforation, fistula formation and wound healing complications[34]. Thus, it has been recommended an interval of at least 6 wk between the last dose of bevacizumab and elective surgery to mitigate the risk of complications. Nevertheless, its postoperative use should be delayed at least 6 to 8 wk after surgery[34].

CONCLUSION

Complete surgical resection remains the only potentially curative treatment for colorectal liver metastases. In this context, several strategies have been introduced to the clinical practice to increase the number of patients eligible for curative hepatic resection, including preoperative chemotherapy, portal vein embolization, two-stage hepatectomies, and association of ablative techniques. In recent years, response to preoperative systemic chemotherapy before liver resection has been established as a major prognostic factor. It seems that progression while on chemotherapy confers a worse prognosis than disease response or stabilization[28,29].

Although the role of surgery in patients progressing while on chemotherapy remains controversial, some patients may still benefit from surgery in this scenario, given the role of this modality as the mainstream curative-intent treatment for patients with CRLM. In selected cases, based on size, the number of lesions, and tumor markers, surgery may be offered despite the less favorable prognosis and as an option for non-chemo responders.

FOOTNOTES

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MINIREVIEWS

Research progress on the immune microenvironment of the gallbladder in patients with cholesterol gallstones

Jing-Yi Jiao, Xiao-Jun Zhu, Chun Zhou, Peng Wang

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Abstract

Cholesterol gallstones are very common in hepatobiliary surgery and have been studied to a certain extent by doctors worldwide for decades. However, the mechanism of cholesterol gallstone formation is not fully understood, so there is currently no completely effective drug for the treatment and prevention of cholesterol gallstones. The formation and development of cholesterol gallstones are caused by a variety of genetic and environmental factors, among which genetic susceptibility, intestinal microflora disorders, impaired gallbladder motility, and immune disorders are important in the pathogenesis of cholesterol gallstones. This review focuses on recent advances in these mechanisms. We also discuss some new targets that may be effective in the treatment and prevention of cholesterol gallstones, which may be hot areas in the future.

Key Words: Microflora; Cholesterol gallstones; Gallbladder; Pathogenesis; Immune disorders

Core Tip: Cholesterol gallstone disease is very common. At present, some new progress has been made in the research on the pathogenesis of cholesterol gallstones, and we have also gained a new understanding of this disease. Here, we discuss the latest research progress of genetic susceptibility, intestinal microflora disorders, impaired gallbladder motility, and immune disorders in the formation of cholesterol gallstones and some new drug targets.

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INTRODUCTION

Gallstones occur in about 20% of adults in western countries and are one of the most common diseases of hepatobiliary surgery[1]. In past research studies[2], we found that more than 90% of gallstones are mainly composed of cholesterol, called cholesterol gallstones.

Normally, mixed micelles are composed of cholesterol, phospholipids (mainly phosphatidylcholine), and bile salts in bile. Under the action of mixed micelles, bile is thermodynamically stable and cholesterol does not precipitate. When the cholesterol molecules in bile exceed the maximum limit that the mixed micelles can accommodate, cholesterol is in a supersaturated state and cholesterol is prone to precipitate[3]. The relative saturation of cholesterol in bile varies with the concentration of bile salts and phospholipids[4].

In past studies, we found that risk factors for cholesterol gallstones comprise both unmodifiable and modifiable factors. Non-modifiable factors include age, sex, race, and genetic factors. Modifiable factors include the following: metabolic syndrome features such as diabetes[5], insulin resistance, and obesity [6]; dietary habits such as high-calorie and low-fiber diets[7]; intestinal damage such as colectomy[8]; Crohn's disease; drug factors such as octreotide[9], lipid-lowering drugs, and hormones; and impaired gallbladder motility.

More than 20% of patients with cholesterol gallstones develop symptoms, such as biliary colic, during their lifetime and are at risk of developing cholecystitis, gallbladder cancer[10] and pancreatitis[11]. To date, surgery is the best way to treat cholesterol gallstone patients when they develop these symptoms or complications, but it comes with heavy economic and social burdens[12]. Therefore, it is urgent and important to treat and prevent cholesterol gallstones by studying the pathogenesis of gallstones and taking corresponding intervention measures for specific pathogenic links.

In this review, we focus on the important roles of genetic susceptibility, intestinal microflora disorders, and impaired gallbladder motility. We also discuss some strategies for the treatment and prevention of cholesterol gallstones, which inhibit some of the pathogenic aspects of cholesterol gallstones.

IMMUNE DISORDERS LEAD TO CHOLESTEROL GALLSTONES

Immune disorders play a crucial role in the formation and development of cholesterol gallstones. First, low concentrations of various immunoglobulins including IgA, IgG, and IgM were contained in bile [13]. Among them, IgM is the most effective Ig in promoting the formation of cholesterol gallstones in supersaturated bile, while IgG is less effective and IgA is the least effective[14-16]. In addition, the formation of cholesterol gallstones is closely related to mucin (MUC) gel accumulation in human and animal models, and MUC gel accumulation occurs before cholesterol gallstone formation and is an important cause of cholesterol gallstone formation[17-22]. At the same time, MUC may be positively correlated with the calcification of cholesterol gallstones[23]. Some MUC genes are expressed in human bile duct epithelial cells such as MUC1, MUC2, MUC3, MUC4, MUC5AC, MUC5B, and MUC6[24], and the expression of these MUC genes and the production and secretion of MUC are regulated by inflammatory mediators in the immune system[25-27]. Cholesterol secretion can also be promoted by inflammatory mediators, which promote liver lipid metabolism and secretion, lead to bile cholesterol supersaturation, and promote cholesterol gallstone formation. For example, in mice, the formation of cholesterol gallstones can be promoted by the administration of lipopolysaccharide (LPS) or pro-inflammatory cytokines [interleukin (IL)-1, tumor necrosis factor (TNF)], because these result in elevated serum cholesterol levels and increase the production of 3-hydroxy-3-methylglutarate mono-acyl-coenzyme A reductase (HMG-CoA reductase)[28-30]. In addition, cholesterol catabolism can be inhibited by LPS, which reduces the production of cholesterol 7 alpha-hydroxylase (CYP7A1), CYP7B1, or CYP27A1 protein, leading to bile supersaturation and cholesterol gallstone formation[31,32]. Recent studies have

found that immune factors can also influence the formation of cholesterol gallstones by influencing the movement of gallbladder contraction. Interstitial Cajal-like cells (ICLCs) are widespread in the gallbladder and bile duct and play a significant role in the regulation of gallbladder contractile motion. The density of ICLCs in the gallbladder is significantly reduced in patients with cholelithiasis, suggesting that decreased gallbladder contraction and cholesterol gallstone formation are closely associated with reduced ICLCs. Ursodeoxycholic acid protects ICLCs in the gallbladder from apoptosis by inhibiting the TNF-α/caspase 8/caspase 3 pathway[33], thereby protecting the contractile activity of the gallbladder and ultimately inhibiting the formation of cholesterol gallstones. These objective results indicate that immune disorders play a crucial role in the formation and development of cholesterol gallstones.

The role of adaptive immunity in cholesterol gallstone formation was analyzed by giving *Helicobacter pylori* (*H. pylori*)-infected and uninfected homozygous mice, as well as homozygous immunodeficient Rag mice, a lithogenic diet in a former study. Lymphocyte metastasis studies were also performed to determine which cell subsets are responsible for cholesterol gallstone formation[34]. *H. pylori* usually causes disease by inducing a pro-inflammatory immune response mediated by T-assisted type 1[35,36]. When fed the lithogenic diet for 2 mo, more cholesterol gallstones were found in non-immunodeficient mice than in Rag mice. There was a statistically significant increase in cholesterol gallstone prevalence in *H. pylori*-infected mice compared with uninfected mice. In addition, T lymphocyte transfer to Rag mice significantly increased the prevalence of cholesterol gallstones, while B lymphocyte transfer did not significantly increase cholesterol gallstones. A detailed description of the association between adaptive immunity and cholesterol gallstone formation was provided in this study, which suggested that T cells are an important link in the formation of cholesterol gallstones in mice (Figure 1).

The vital role of neutrophil external traps (NETs) in cholesterol gallstone formation and development was expounded upon in a recent study[37]. By fluorescence microscopy, patchy extracellular DNA (ecDNA), large ecDNA aggregates, and strong neutrophil elastase activity were found in both human and porcine cholesterol gallstones. In previous reports, obesity is related to the release of ecDNA into plasma in mice and humans[38], and ecDNA in peripheral circulation has contact with the risk of metabolic syndrome[39], both of which are risk factors for cholesterol gallstones. Upon contact with neutrophils, cholesterol or calcium crystals are ingested by neutrophils. This process of pinocytosis causes the granular enzymes in lysosomes to leak and bind to the DNA in the cytoplasm, ultimately decondensed chromatin and externalizing to form NETs. Cholesterol crystals and calcium crystals in the bile of the gallbladder are aggregated to form cholesterol gallstones by the "glue" role of NETs. Meanwhile, the formation of NETs is dependent on the activity of peptidyl arginine deiminase type 4 and the production of reactive oxygen species. In addition, this study confirmed that the formation and development of cholesterol gallstones can be effectively reduced by the inhibition of NET formation or neutrophils. The results of this study verify that the formation of NETs is the key link in the formation of cholesterol gallstones caused by the accumulation of crystals in bile, and the formation of neutrophils and NETs may be new targets for the prevention and treatment of cholesterol gallstones (Figure 1).

Together, these findings suggest that immune dysfunction is also an important link in the formation and development of cholesterol gallstones. Targeting immune disorders in the pathogenesis of cholesterol gallstones will be a new hotspot in the treatment and prevention of cholesterol gallstones in the future.

ROLE OF INTESTINAL FLORA DYSREGULATION IN CHOLESTEROL GALLSTONES

Bacteria are present in the bile, cholesterol gallstones, and even gallbladder tissue of patients with cholesterol gallstones[1]; however, the role of these bacteria in cholesterol gallstone formation is not fully understood. A lower incidence of cholesterol gallstones in germ-free mice was found in one of the earliest studies[40]. Another study showed that mice infected with enterohepatic *H. pylori* had an increased risk of cholesterol gallstones[41]. A recent study comparing the biliary microbiota of lithiasis and non-lithiasis groups found that the Alcaligenaceae reached higher relative abundance in lithiasis samples[42]. In this family, *Alcaligenes recti* are reportedly involved in the metabolism of various bile acids. These findings suggest that cholesterol gallstone formation appears to be related to intestinal microbiome dysregulation. With the abundance and diversity of intestinal flora decreased, the number of *Firmicutes* decreased, and the ratio of *Firmicutes* to *Bacteroidetes* decreased in mice with gallstones[43]. In addition, the intestinal bacteria phylum *Proteobacteria* were significantly increased, while *Faecalibacterium*, *Lachnospira*, and *Roseburia* were significantly decreased[44]. The number of Gram-positive fecal anaerobes in the cecum was increased in patients with gallstones compared with those without gallstones, and 7α-dehydroxylation activity was also increased, which seemed to explain the increased concentration of hydrophobic secondary bile acid deoxycholic acid in patients with gallstones[45].

Enrichment of *Desulfovibrionales* has been found in patients with metabolic syndrome and obesity associated with cholesterol gallstones[46], but the specific link between the bacteria and cholesterol gallstones has not been clarified. A recent study found that the abundance of *Desulfovibrionales* in the feces of cholesterol gallstone patients and cholesterol gallstone-susceptible mice was significantly higher

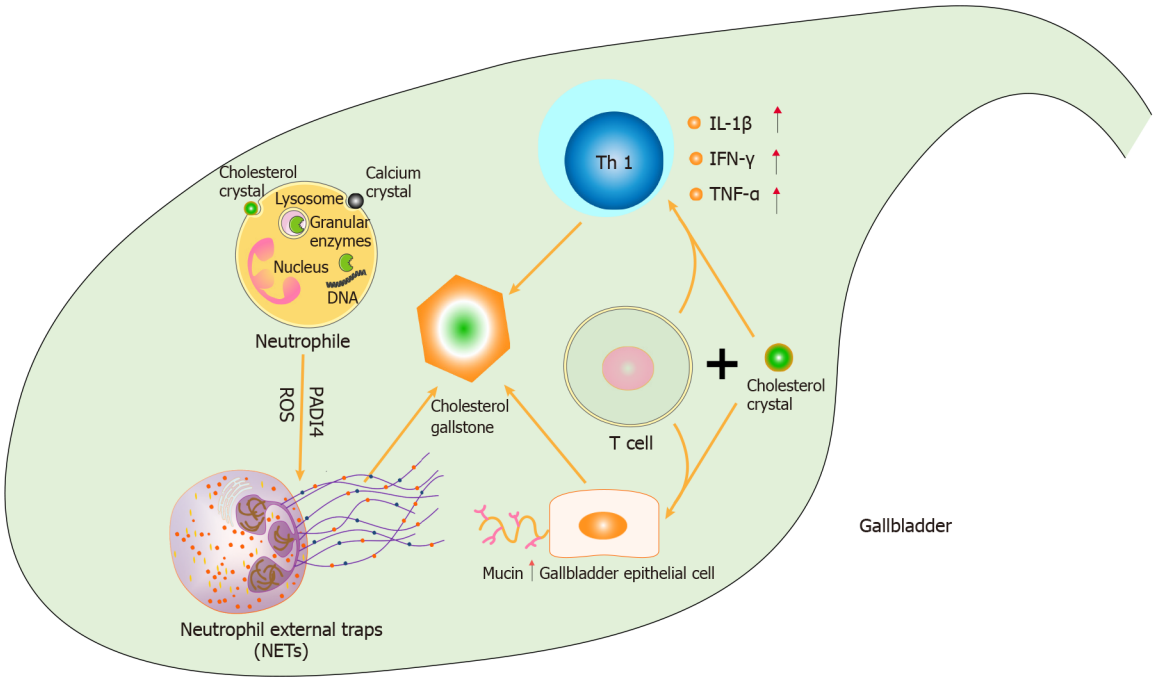

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Figure 1 Role of neutrophils and T cells in cholesterol gallstone formation. In gallbladder bile, cholesterol or calcium crystals are ingested by neutrophils as pinocytosis, inducing leakage of lysosomes and granular enzymes in neutrophils. The intracellular chromatin of neutrophils is decondensed by granular enzymes and externalized to extrachromosomal DNA, resulting in the formation of neutrophil external traps (NETs). Cholesterol crystals and calcium crystals in the bile of the gallbladder are aggregated to form cholesterol gallstones by the "glue" role of NETs. On the other hand, mucin gene expression and mucin gel accumulation in gallbladder epithelial cells can be induced by the joint action of T cells and cholesterol crystals, promoting the formation of cholesterol gallstones. T cells and cholesterol crystals can also induce T helper type 1 cytokines (such as interleukin-1 beta, interferon gamma, tumor necrosis factor-alpha), which cause gallbladder inflammation, gallbladder tissue damage, and gallbladder dysfunction, leading to cholesterol gallstones.

than that in the non-gallstone population, and that the transplantation of intestinal flora from cholesterol gallstone patients into cholesterol gallstone-resistant mice resulted in a statistically significant increase in cholesterol gallstone prevalence[47]. The production of secondary bile acids will be promoted by a large number of *Desulfovibrionales* rich in the cecum, and the hydrophobicity of bile acids will therefore increase, resulting in increased absorption of intestinal cholesterol and easy to cause cholesterol gallstones. In addition, the intestinal lipid absorption process is regulated by CD36. The expression of CD36 can be induced by *Desulfovibrionales*; thus, the intestinal lipid absorption is enhanced, which may also lead to the formation of cholesterol gallstones[48]. On the other hand, hydrogen sulfide, a metabolite of *Desulfovibrionales*, can induce farnesoid X receptor and inhibit the expression of CYP7A1. The expression of cholesterol transporter ATP-binding cassette transporter G5/G8 (ABCG5/ABCG8) in the mouse liver was also induced by *Desulfovibrionales*, which promoted cholesterol secretion in the biliary tract. This study shows that cholesterol gallstone formation is promoted by intestinal *Desulfovibrionales*, which influences bile acid and cholesterol metabolism, further supporting the important role of intestinal microbiome imbalance in cholesterol gallstone formation.

GENETIC SUSCEPTIBILITY TO CHOLESTEROL GALLSTONES

In addition to these two mechanisms, there are other factors that contribute to the formation of cholesterol gallstones, such as genetic factors and gallbladder dyskinesia[49]. Indigenous populations in North and South America are reported to be at highest risk of gallstones in the world. Prevalence rates are lower in Asian populations and lowest in African populations[1]. A study of 43141 twins with gallstone disease in Sweden showed that about 25% of gallstones were caused by a genetic susceptibility [50]. These objective results suggest that gallstone risk and genetic susceptibility are inextricably linked.

Lipid composition in the biliary tract is regulated by complex ATP-binding cassette (ABC) transporters on the hepatocyte canalicular membrane. The transport of bile salts into the biliary tract is carried out by the ABC transporter ABCB11[51]. The transport of phosphatidylcholine into the biliary tract is carried out by the ABC transporter ABCB4[52]. The transport of cholesterol into the biliary tract is carried out by the ABC transporters ABCG5 and ABCG8[53].

Mutations and variants of ABCB4 inhibit the secretion of phospholipids from the liver to the bile ducts, resulting in a decrease or deficiency of phospholipids in bile and the formation of cholesterol gallstones, known as low phospholipid-associated cholelithiasis. A recent study compared the chemical composition of fresh gallbladder bile between ABCB4 knockout and wild-type mice and found cholesterol supersaturation and the presence of cholesterol crystals in gallbladder bile in the former but not in the latter. The results of this study demonstrate the critical role of ABCB4 in phospholipid transport and the important role of ABCB4 mutations in the formation of cholesterol gallstones[54]. A strong association between gallstone disease and ABCG8 was shown in a genome-wide association study (GWAS) involving 280 patients with gallstones and 360 controls in 2007[55]. ABCG8 is responsible for transporting cholesterol into the biliary tract and intestinal lumen, and its association with cholesterol gallstones is attributed to a familiar variant that causes guanine at position 55 to become cytosine, resulting in the replacement of aspartic acid, the amino acid residue at position 19 of the transporter, by histidine (ABCG8D19H, RS11887534). ABCG8D19H constitutes a functional acquisition mutation, which increases the transport activity of ABCG8 by three-fold, increases the hepatic cholesterol discharge into the biliary tract, increases the absolute cholesterol saturation in bile, and ultimately leads to the occurrence of cholesterol gallstones[55-57].

In 2016, four new gallstones susceptibility loci, namely SULT2A1, TM4SF4, GCKR, and CYP7A1, were identified in a large GWAS (there were 8720 gallstones patients and 55152 people who did not have gallstones in the discovery set, and 6489 gallstones patients and 62797 people who did not have gallstones in the validation set), and the association between ABCG8 and gallstones were confirmed [58]. The metabolism of cholesterol into bile acid in the liver is mainly regulated by cholesterol CYP7A1, and its reduced function may lead to the formation and development of cholesterol gallstones by reducing the catabolism of cholesterol into bile acid[59]. The transport of cholesterol from the intestinal lumen into intestinal cells and from bile into liver cells is in the charge of Niemann-Pick C1-like protein 1 (NPC1L1). Reduced activity of the NPC1L1 gene leads to reduced uptake of cholesterol from the lumen to intestinal cells and from bile to liver cells, resulting in increased cholesterol content in the biliary tract, increased absolute cholesterol saturation in the biliary tract, and increased risk of cholesterol gallstone formation[60].

According to a 2019 study, six new gallstone-related or highly related variants were associated with blood cholesterol levels (HNF4A, HNF1A, FUT2, FADS2, MARCH 8, and JMJD1C)[61]. However, the association between these variants and cholesterol gallstone formation and development is unclear. In the future, GWASs will find more new cholesterol-gallstones related variants, and further studies are needed to determine the molecular basis behind these variants[62].

CHOLESTEROL GALLSTONE FORMATION BY IMPAIRED GALLBLADDER MOTILITY

Whatever mechanism causes cholesterol gallstones to form, these processes are slow. Cholesterol gallstones cannot form if the gallbladder is completely emptied several times a day. Therefore, the total or partial extension of bile storage due to impaired gallbladder movement seems to be another important condition for cholesterol gallstone formation. Insufficient gallbladder motility contributes to cholesterol gallstone formation and is impaired under many risk factors for cholesterol gallstone formation, such as pregnant women, obese patients, and their rapid weight loss, diabetes mellitus, and patients receiving total parenteral nutrition[63]. A recent study showed that 78 of 959 patients (8%) who underwent laparoscopic Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy developed symptomatic gallstone disease within 24 mo[64]. In patients without gallstones before RYGB surgery, ursodeoxycholic acid treatment reduced the occurrence of symptomatic gallstone disease compared with placebo[65]. On an empty stomach, bile drained from the liver is stored in the gallbladder. After eating, bile is discharged by the gallbladder into the duodenum and small intestine. The motor function of the smooth muscle of the gallbladder is mainly regulated by cholecystokinin (CCK), a key gastrointestinal hormone. The release of CCK is mainly caused by the stimulation of dietary lipids and proteins. Insufficient gallbladder contraction during fasting is caused by reduced gallbladder stimulation. Patients using the somatostatin analog octreotide may develop cholesterol gallstones because postprandial CCK release and gallbladder contraction was inhibited by octreotide[9]. Injection of CCK in patients receiving total parenteral nutrition, or the addition of dietary fat to promote the release of CCK in the gastrointestinal tract of people who lose weight quickly, enhances the ability of their gallbladder to contract and prevents the formation of cholesterol gallstones[66,67]. Mice with reduced CCK or damaged CCK-1 receptor genes had slower small bowel movement[68,69], suggesting that CCK not only promotes contraction of gallbladder smooth muscle but also speeds up intestinal transport through a CCK-1 receptor signaling cascade. Loss of the CCK-1 receptor gene in mice led to reduced gallbladder contraction and reduced intestinal transport, which in turn led to cholestasis and increased intestinal cholesterol absorption, ultimately increasing the risk of gallstone formation[69]. In addition, ICLCs are widespread in the gallbladder and bile duct and play a significant role in the regulation of gallbladder contractile motion[70,71]. Previous studies have found that the density of ICLCs in the gallbladder is significantly reduced in patients with cholesterol gallstones, suggesting that

decreased gallbladder contraction and cholesterol gallstone formation are closely associated with reduced ICLCs[72-74].

CONCLUSION

Cholesterol gallstones are common in hepatobiliary surgery and their incidence is increasing. At present, surgery is the preferred treatment for symptomatic cholesterol gallstones disease, but there is still a lack of primary prevention drugs for cholesterol gallstones. The pathogenesis of cholesterol gallstones is extremely complex. We identified the modifiable factors in the pathogenesis of cholesterol gallstones through research to provide strategies for the prevention of cholesterol gallstones disease in high-risk groups. At the same time, more emphasis should be placed on the prevention of cholesterol gallstones, which seems to be a better option than cholecystectomy.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Central pancreatectomy for benign or low-grade malignant pancreatic tumors in the neck and body of the pancreas

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Abstract

BACKGROUND

For tumors in the neck and body of the pancreas, distal pancreatectomy (DP) has been the standard surgical procedure for the last few decades and central pancreatectomy (CP) is an alternative surgical option. Whether CP better preserves remnant pancreatic endocrine and exocrine functions after surgery remains a subject of debate.

AIM

To evaluate the safety and efficacy of CP compared with DP for benign or low-grade malignant pancreatic tumors in the neck and body of the pancreas.

METHODS

This retrospective study enrolled 296 patients who underwent CP or DP for benign and low-malignant neoplasms at the same hospital between January 2016

and March 2020. Perioperative outcomes and long-term morbidity of endocrine/exocrine function were prospectively evaluated.

RESULTS

No significant difference was observed in overall morbidity or clinically relevant postoperative pancreatic fistula between the two groups (P = 0.055). Delayed gastric emptying occurred more frequently in the CP group than in the DP group (29.4% *vs* 15.3%; P < 0.005). None of the patients in the CP group had new-onset or aggravated distal metastasis, whereas 40 patients in the DP group had endocrine function deficiency after surgery (P < 0.05). There was no significant difference in the incidence of diarrhea immediately after surgery, but at postoperative 12 mo, a significantly higher number of patients had diarrhea in the DP group than in the CP group (0% *vs* 9.5%; P < 0.05).

CONCLUSION

CP is a generally safe procedure and is better than DP in preserving long-term pancreatic endocrine and exocrine functions. Therefore, CP might be a better option for treating benign or low-grade malignant neoplasms in suitable patients.

Key Words: Central pancreatectomy; Distal pancreatectomy; Endocrine function; Exocrine function; Morbidity

Core Tip: For tumors in the neck and body of the pancreas, distal pancreatectomy (DP) has been the standard surgical procedure for the last few decades, and central pancreatectomy (CP) is an alternative surgical option. It remains unclear whether CP can better preserve remnant pancreatic endocrine and exocrine functions. The results of this retrospective study provide evidence that CP is a generally safe procedure and is better than DP in preserving long-term pancreatic endocrine and exocrine functions.

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INTRODUCTION

With developments in diagnostic imaging systems, the diagnosis and incidence of benign or low-grade malignant pancreatic tumors have increased. For tumors in the neck and body of the pancreas, distal pancreatectomy (DP) has been the standard surgical procedure for the last few decades. DP is usually combined with splenectomy, and excessive pancreatic tissue is resected during the procedure. As a result, DP can lead to pancreatic endocrine or exocrine insufficiency[1,2]. Therefore, it could be beneficial to consider alternative approaches that preserve pancreatic exocrine and endocrine function in patients who require pancreatectomy.

Central pancreatectomy (CP) was first reported by Guillemin and Bessot[3] for the treatment of chronic pancreatitis and pancreatic transection injury, and the modern technique of CP can be attributed to Dagradi and Serio from the Verona group. In the CP procedure, the middle segment of the pancreas is removed and the distal pancreas and spleen are preserved. With this limited resection approach, the normal, uninvolved pancreatic parenchyma can be conserved, and thus, the risk of postoperative exocrine and endocrine dysfunction is reduced[4]. Given its advantages, some surgeons recommend CP as an alternative surgical option for tumors in the body or neck of the pancreas, as it may improve the quality of life of patients by preserving the pancreatic parenchyma and reducing the incidence of pancreatic endocrine and exocrine insufficiency. However, CP involves reconstruction of the digestive tract, and thus may result in a higher risk of postoperative morbidity than DP, especially with regard to the occurrence of postoperative pancreatic fistula (POPF)[5]. Several studies have compared the short- and long-term outcomes of the two procedures, but the efficacy and safety of CP compared to DP are unclear[6]. This study sheds light on this topic by evaluating and comparing the safety and efficacy of CP and DP for the treatment of benign or low-grade malignant pancreatic tumors in the neck and body of the pancreas based on perioperative outcomes and endocrine and exocrine function states.

MATERIALS AND METHODS

Study design and data collection

This study enrolled patients with benign or low-grade malignant neoplasms of the pancreas at the First Affiliated Hospital of Zhejiang University, School of Medicine (Hangzhou, China) between January 2016 and January 2021. The inclusion criteria were as follows: (1) Age of 18-75 years; (2) Eastern Cooperative Oncology Group performance status score of 0-1; (3) Pathological diagnosis of noninvasive intraductal papillary mucinous neoplasm, mucinous cystic neoplasm, serous cystic neoplasm (SCN), solid pseudopapillary neoplasm (SPN), or benign neuroendocrine tumor; and (4) Having received DP (with or without splenectomy) or CP. The exclusion criteria were as follows: (1) Patients with more than one primary pancreatic tumor; (2) Age younger than 18 years or older than 75 years; (3) Pathological diagnosis of invasive carcinoma or other types of lesions; or (4) Having received extra organ resection beyond the standard DP (with or without splenectomy) or CP. Finally, 296 patients were enrolled, of whom 34 underwent elective CP and 262 underwent DP. The study was approved by the institutional review board of the hospital.

Perioperative data and long-term clinical outcomes of endocrine and exocrine function were retrospectively collected and analyzed, including patient characteristics, type of surgery, preoperative radiologic imaging, and preoperative and postoperative laboratory test results. The distance between the tumor and left-side border of the superior mesenteric vein (SMV) was measured based on preoperative computed tomography images.

Postoperative complications

According to the International Study Group on Pancreatic Fistula criteria, POPF was defined as a measurable volume of drainage fluid with an amylase level more than three-times the upper limit of normal after postoperative day 3. Grade B or C of POPF was defined according to the clinical impact of POPF on the patient's postoperative course. Delayed gastric emptying (DGE) has been classified into three grades according to its severity by the International Study Group of Pancreatic Surgery. Only grades B and C correspond to a DGE with clinical impact prolonging overall hospital stay. Postoperative morbidity was also graded according to Clavien-Dindo classification.

Evaluation of endocrine and exocrine functions

Fasting blood glucose was tested routinely in patients after surgery. Short- and long-term endocrine deficiency was defined as deterioration of endocrine function control capacity, as indicated by new-onset diabetes mellitus (DM) after surgery and aggravation of DM (which meant that patients who had been previously diagnosed with and treated for DM required modified treatment after the operation). Exocrine function was evaluated based on the incidence of diarrhea after surgery.

Statistical analyses

Patient characteristics, surgical procedures, perioperative outcomes, endocrine and exocrine functions of the pancreas, and distance between the tumor and left-side border of the SMV were compared using the *t*-test or Wilcoxon signed-rank test for continuous variables and the chi-square test for categorical variables. Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, United States). $P < 0.05$ was considered statistically significant.

RESULTS

Demographic characteristics of the patients

No significant differences were observed between the DP and CP groups regarding sex, age, preoperative body mass index, preoperative hypertension, preoperative DM, or pancreatic tumor size (Table 1). There was a difference in the distance between the tumor and left-side border of the SMV, but it was not significant. With regard to pathologic diagnosis, a higher proportion of patients in the CP group had cystic neoplasms ($n = 31$, 91.2%). Furthermore, the CP group also had a higher incidence of SCNs ($n = 13$, 38.2%) and SPNs ($n = 13$, 38.2%). The incidence of these lesions was similar within the DP group.

Perioperative outcomes

A significant difference in operation time was observed between the CP and DP groups (Table 2), which was significantly longer in the CP group. Laparoscopic surgery was more frequently performed in the DP group than in the CP group [75.8% ($n = 197$) *vs* 26.5% ($n = 9$); $P < 0.005$]. No significant intergroup difference was observed in perioperative blood loss volume. It was reasonable that in the CP group, no patient received splenectomy, whereas in the DP group, 123 patients received DP associated with splenectomy, mainly due to the tissue adhesions or preoperative diagnosis of malignancy.

Table 1 Demographic and clinical characteristics of the patients

	Central pancreatectomy (*n* = 34)	Distal pancreatectomy (*n* = 262)	*P* value
Gender			0.627
Female, *n* (%)	25 (73.5)	182 (69.5)	
Male, *n* (%)	9 (26.5)	80 (30.5)	
Age (x ± s, yr)	48 ± 13	52 ± 15	0.172
BMI (x ± s, kg/m^2)	22.4 ± 3.4	22.8 ± 3.6	0.545
Hypertension, *n* (%)	7 (20.6)	78 (29.8)	0.266
Diabetes, *n* (%)	2 (5.9)	28 (10.7)	0.568
Tumor size (x ± s, cm)	3.2 ± 1.8	3.5 ± 2.1	0.433
Pathology, *n* (%)			< 0.005
SCN	13 (38.2)	48 (18.3)	
IPMN	4 (11.8)	47 (17.6)	
MCN	1 (2.9)	50 (19.1)	
SPN	13 (38.2)	52 (19.8)	
pNET	3 (8.8)	50 (19.1)	
Median distance between the tumor and left-side border of the SMV (mm)	8.9 (10.9)	12.5 (11.4)	0.076

BMI: Body mass index; SCN: Serous cystic neoplasm; IPMN: Intraductal papillary mucinous neoplasm; MCN: Mucinous cystic neoplasm; SPN: Solid pseudopapillary neoplasm; pNET: Pancreatic neuroendocrine tumor; SMV: Superior mesenteric vein.

No significant difference was observed in overall morbidity between the two groups (P = 0.370). Additionally, morbidities in the two groups were all within Clavien-Dindo grade IIIb. Regarding clinically relevant POPF, no significant difference was observed between the two groups. However, the incidence of DGE was significantly higher in the CP than in the DP group [29.4% (n = 10) *vs* 15.3% (n = 41); P < 0.005]. Despite these findings, in the CP group, DGE was classified as grade A in most cases, and none of the patients had grade C DGE. No postoperative bleeding occurred in either group. No significant differences in chyle leakage, wound infection, or other complications were observed. The length of postoperative hospital stay was longer in the CP group, but the difference was not statistically significant (17.0 d *vs* 11.0 d; P = 0.783). No in-hospital mortality was observed in either group, and none of the patients required readmission.

Pancreatic endocrine and exocrine functions

Regarding pancreatic endocrine function, none of the patients had new-onset or aggravated DM in the CP group, whereas 40 patients had endocrine function deficiency after surgery in the DP group (P < 0.05) (Table 3). Regarding exocrine function, only 2 (5.9%) patients had diarrhea immediately after surgery in the CP group, whereas 46 (17.5%) patients in the DP group had diarrhea immediately after surgery; however, the incidence was not significantly different. At 12 mo after surgery, however, the incidence of diarrhea was significantly higher in the DP group than in the CP group [0% (n = 0) *vs* 9.5% (n = 25); P < 0.05]. These findings indicate that the incidence of exocrine function deficiency was significantly higher in the DP group.

DISCUSSION

Our study evaluated and compared the safety and efficacy of CP and DP for benign or low-grade malignant neoplasms in terms of perioperative outcomes and endocrine and exocrine functions. The results showed that CP had similar safety as DP, as the patients who underwent CP did not have more morbidities associated with surgery or more clinically relevant POPF compared to those who underwent DP. Furthermore, although CP was associated with a higher incidence of DGE, it was mild in most patients. Moreover, CP preserved the pancreatic parenchyma, and had significant advantages over DP for preserving pancreatic endocrine and exocrine functions.

Whether CP can preserve the exocrine and endocrine functions of the pancreas remains a subject of debate, even though there is some indication that CP could preserve the pancreatic volume compared

Table 2 Perioperative outcomes of the patients

	Central pancreatectomy (*n* = 34)	Distal pancreatectomy (*n* = 262)	*P* value
Surgery, *n* (%)			< 0.005
Open surgery	25 (73.5)	63 (24.2)	
Laparoscopy	9 (26.5)	197 (75.8)	
Associated splenectomy, *n* (%)	0	123 (46.9)	
Mean operation time (min)	311	244	< 0.05
Mean perioperative blood loss (mL)	159	167	0.525
Overall morbidity, *n* (%)			0.370
I	13 (38.2)	91 (34.0)	
II	11 (32.4)	95 (36.6)	
IIIa	2 (5.9)	17 (6.5)	
IIIb	2 (5.9)	3 (1.1)	
IV	0 (0)	0 (0)	
POPF grade, *n* (%)			0.073
A	15 (44.1)	67 (25.6)	
B	10 (29.4)	85 (32.4)	
C	0 (0)	0 (0)	
Chyle leakage, *n* (%)	1 (2.9)	15 (5.7)	0.926
Delayed gastric emptying, *n* (%)			< 0.05
A	9 (26.5)	38 (14.5)	
B	1 (2.9)	2 (0.8)	
C	0 (0)	1 (0.4)	
Postoperative bleeding	0 (0)	0 (0)	-
Mean postoperative hospital stay (d)	17	11	0.783
In-hospital mortality	0 (0)	0 (0)	-
Readmission within 30 d	0 (0)	0 (0)	-

Data are presented as *n* (%), unless otherwise indicated. POPF: Postoperative pancreatic fistula.

Table 3 Endocrine and exocrine function of the pancreas after surgery

	Central pancreatectomy (*n* = 34)	Distal pancreatectomy (*n* = 262)	*P* value
Endocrine function			
New-onset or aggravated diabetes mellitus, *n* (%)	0 (0)	40 (15.3)	< 0.05
Exocrine function			
Diarrhea immediately after surgery	2 (5.9)	46 (17.6)	0.059
Diarrhea 12 mo after surgery	0 (0)	25 (9.5)	< 0.05

Data are presented as *n* (%).

with DP[5,7-12]. Shin *et al*[13] reported in a randomized controlled study that pancreatic parenchymal atrophy was frequently observed in patients who had clinically relevant POPF, indicating that clinically relevant POPF might reduce pancreatic parenchymal, especially in long-term outcomes. This might explain why some previous studies drew the conclusion that CP could not preserve exocrine and endocrine function, as in those studies, CP was associated with a higher incidence of clinically relevant

POPF than DP[5,7,9].

However, in this study, we found that new-onset or aggravated DM and diarrhea seldom occurred in the CP group compared to the DP group, indicating that exocrine and endocrine functions were indeed preserved with CP. In addition, a previous study compared postoperative body weight change between CP and DP and found that body weight improved within 2 years after CP, indicating that CP is an effective procedure in terms of exocrine function[8]. Thus, the findings to date, including those of the present study, generally indicate that CP is beneficial in terms of preserving pancreatic function. Since CP involves pancreaticojejunostomy and reconstruction of the digestive tract, it is reasonable that it might have a higher incidence of POPF than DP.

In this study, the incidence of diarrhea after surgery was not significantly higher in the DP group immediately after surgery but was significantly higher in the DP group after 12 mo. It is possible that the early preventive use of pancreatin after DP led to underestimation of the perioperative incidence of diarrhea. Several studies have reported that CP is associated with more morbidities (including POPF) than DP[5,7,9]. For example, a retrospective and propensity score-matched study reported that the CP procedure had more morbidities classified as Clavien-Dindo grade IIIa or worse than the DP procedure and required longer hospital stays[9]. However, in this study, the overall morbidities were similar between the two groups and there were no significant differences in the incidence of clinically relevant POPF, the most concerning morbidity. In our center, duct-to-mucosa is the most commonly used method in pancreaticojejunostomy, and this might be the reason why CP does not increase the incidence of clinically relevant POPF.

In most previous studies, open technique is performed in the CP procedure[14], although this does not mean that laparoscopy is not suitable for CP. Over the years, it has been accepted that laparoscopic surgery can be performed safely and effectively by experienced surgeons in suitable patients. Laparoscopic surgery has several apparent advantages over conventional open techniques, such as early postoperative recovery, short hospital stay, and minimally invasive incision[15-17]. In this study, laparoscopic CP was also performed in some patients, and it showed similar safety and efficacy. Therefore, it is likely that laparoscopic CP will be the mainstream choice for the treatment of benign and low-grade malignant pancreatic neck and body tumors in the future.

This study had some limitations. First, this was a retrospective analysis of patients from a single institution, so the results are subject to the biases and limitations inherent to retrospective studies. Additionally, a much lower number of patients underwent CP than DP, so this difference could also have introduced biases. Another limitation is the lack of standard criteria for evaluating exocrine function. In some studies, changes in stool elastase levels before and after surgery are used as an indicator of exocrine function[9], whereas in this study, the incidence of diarrhea was used as an indicator of exocrine function. The incidence of diarrhea caused by exocrine function deficiency may have been overestimated, since diarrhea could also be caused by other factors.

CONCLUSION

In conclusion, we found that CP is a generally safe procedure, and has similar postoperative morbidity to DP. Further, CP is associated with better remnant pancreatic endocrine and exocrine functions after surgery. Therefore, CP might be a better option for the treatment of benign or low-grade malignant neoplasms in suitable patients as it can preserve distal pancreatic volume and improve patients' quality of life.

ARTICLE HIGHLIGHTS

Research background

For tumors in the neck and body of the pancreas, distal pancreatectomy (DP) has been the standard surgical procedure for the last few decades, and central pancreatectomy (CP) is an alternative surgical option.

Research motivation

Whether CP can better preserve remnant pancreatic endocrine and exocrine functions after surgery remains a subject of debate.

Research objectives

This study evaluated the safety and efficacy of CP compared with DP for benign or low-grade malignant pancreatic tumors in the neck and body of the pancreas.

Research methods

This retrospective study enrolled 296 patients who underwent CP or DP for benign and low-malignant neoplasms at the same hospital between January 2016 and March 2020. Perioperative outcomes and long-term morbidity of endocrine/exocrine function were prospectively evaluated.

Research results

No significant difference was observed in overall morbidity or clinically relevant postoperative pancreatic fistula (POPF) between the two groups (P = 0.055). Delayed gastric emptying occurred more frequently in the CP group than in the DP group (29.4% *vs* 15.3%; P < 0.005). None of the patients in the CP group had new-onset or aggravated distal metastasis, whereas 40 patients in the DP group had endocrine function deficiency after surgery (P < 0.05). There was no significant difference in the incidence of diarrhea immediately after surgery, but at postoperative 12 mo, a significantly higher number of patients in the DP group than in the CP group had diarrhea (0% *vs* 9.5%; P < 0.05).

Research conclusions

CP was a generally safe procedure and better than DP in preserving long-term pancreatic endocrine and exocrine functions. Therefore, CP might be a better option for treating benign or low-grade malignant neoplasms in suitable patients.

Research perspectives

The incidence of POPF might affect remnant pancreatic endocrine and exocrine functions after CP. Future prospective studies are needed with more CP cases and laparoscopic CP cases to verify this result. More reliable methods to evaluate pancreatic endocrine and exocrine functions are needed to obtain more accurate results.

FOOTNOTES

Author contributions: Bai XL and Liang TB made equal contributions in conception of the study, and review and finalization of the manuscript; Chen YW, Xu J, Li X, Chen W, Gao SL, Shen Y, Zhang M, Wu J, and Yu J reviewed and collected the data; Chen Y and Xu J analyzed the data; Chen Y wrote the manuscript; and all authors approved the manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Irinotecan- *vs* oxaliplatin-based regimens for neoadjuvant chemotherapy in colorectal liver metastasis patients: A retrospective study

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Abstract

BACKGROUND

Neoadjuvant chemotherapy (NC) improves the survival outcomes of selected patients with colorectal liver metastasis (CRLM). The benefits of irinotecan-based regimens in these patients are still under debate.

AIM

To compare the benefits of irinotecan- and oxaliplatin-based regimens in patients with resectable CRLM.

METHODS

From September 2003 to August 2020, 554 patients received NC and underwent hepatectomy for CRLM. Based on a 1:1 propensity score matching (PSM) model, 175 patients who received irinotecan were matched to 175 patients who received oxaliplatin to obtain two balanced groups regarding demographic, therapeutic, and prognostic characteristics.

RESULTS

Chemotherapy was based on oxaliplatin in 353 (63.7%) patients and irinotecan in 201 (36.3%). After PSM, the 5-year progression-free survival (PFS) and overall survival (OS) rates with irinotecan were 18.0% and 49.7%, respectively, while the 5-year PFS and OS rates with oxaliplatin were 26.0% and 46.8%, respectively. Intraoperative blood loss, operating time, and postoperative complications dif-

fered significantly between the two groups. In the multivariable analysis, carbohydrate antigen 19-9, RAS mutation, response to NC, tumor size > 5 cm, and tumor number > 1 were inde-pendently associated with PFS.

CONCLUSION

In NC in patients with CRLM, irinotecan is similar to oxaliplatin in survival outcomes, but irinotecan is superior regarding operating time, intraoperative blood loss, and postoperative complications.

Key Words: Colorectal cancer; Liver metastasis; Liver resection; Neoadjuvant chemotherapy

Core Tip: This was the first retrospective cohort study to investigate irinotecan-based regimens for neoadjuvant chemotherapy in patients with colorectal liver metastasis (CRLM) in China. It highlighted the benefits of irinotecan and might contribute to modifying the treatment guidelines for CRLM. Chemotherapy was based on oxaliplatin in 353 (63.7%) patients and irinotecan in 201 (36.3%). After propensity score matching, the 5-year progression-free survival (PFS) and overall survival (OS) rates with irinotecan were 18.0% and 49.7%, respectively, while the 5-year PFS and OS rates with oxaliplatin were 26.0% and 46.8%, respectively.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy and the second leading cause of cancer-related mortality[1]. The liver is the most common site of metastatic involvement, and 25%-30% of CRC patients present with metastatic diseases initially. The long-term survival outcome has been significantly improved by radical resection of the primary tumor and metastases. The overall survival (OS) increased from 36% to 58% at 5 years and 23% to 36% at 10 years, respectively[2,3]. Advances in surgical techniques have improved safety dramatically, resulting in perioperative mortality rates < 5%[4].

Currently, the administration of neoadjuvant chemotherapy (NC) in resectable colorectal liver metastasis (CRLM) patients is increasing as it can increase the radical resection rate and treat occult metastases[5]. 5-Fluorouracil (5-Fu) was previously one of the most common anticancer drugs for CRLM. FOLFIRI (irinotecan, 5-Fu, and leucovorin) and FOLFOX (oxaliplatin, 5-Fu, and leucovorin) regimens have been proven more effective. By combining with antibodies targeting epidermal growth factor receptor and vascular endothelial growth factor, a response rate of about 20% observed in the new era of modern chemotherapy has been greatly increased. Nevertheless, it has been shown that systemic chemotherapy for CRLM might cause injury to the nontumoral liver parenchyma. Sinusoidal obstruction syndrome (SOS) has been identified as being a complication to oxaliplatin-based chemotherapy[6]. Steatohepatitis was considered to be associated with irinotecan-based chemotherapy, especially in obese patients[7]. Because of impaired remnant liver function, chemotherapy-induced liver injury is a major cause of morbidity and mortality after hepatic resection.

For resectable CRLM, oxaliplatin-based regimens have been preferred to irinotecan-based regimens as the first-line treatment because of less alopecia and gastrointestinal toxicity[8]. Irinotecan has been administered to patients with resectable CRLM, but supporting evidence is absent, and whether survival outcomes are improved remains under debated. The present study investigated whether irinotecan might improve progression-free survival (PFS) or OS in patients with resectable CRLM.

MATERIALS AND METHODS

Patient eligibility

This study collected the data from CRLM patients who received NC and underwent hepatic resection between September 2003 and August 2020 at the Hepatopancreatobiliary Surgery Department of Peking

University Cancer Hospital. The demographic and clinical data were retrospectively obtained from a prospective patient database. The inclusion criteria were: (1) Evaluated to be resectable by a multidisciplinary team (MDT) that consisted of surgical oncologists, radiologists, and medical oncologists; (2) Received NC and underwent hepatic resection; (3) No other simultaneous malignancies; (4) 19-80 years of age; and (5) Eastern Cooperative Oncology Group performance status < 2. Patients who underwent only ablation or palliative hepatic resection (R2) were excluded. This study was approved by the Ethics Committee of Beijing Cancer Hospital (No. 2021YJZ06-GZ01), and the requirement for informed consent was waived.

Pretreatment evaluation

All patients were evaluated by physical examination, routine hematology, biochemistry analyses, and measurement of levels of tumor markers including carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (Ca19-9) before treatment. According to standard clinical protocols, computed tomography or magnetic resonance imaging of the abdomen and chest was performed for preoperative staging and evaluation of liver metastasis. In addition, positron emission tomography was performed to rule out any extrahepatic metastasis.

Treatment

The NC regimens consisted mainly of 5-Fu, leucovorin, and oxaliplatin, or 5-Fu, leucovorin, and irinotecan, with or without bevacizumab or cetuximab. There were 353 patients who received a regimen based on oxaliplatin and 201 patients who were treated with a regimen based on irinotecan. Based on World Health Organization criteria, the response to NC was classified according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). MDT discussion assessed the treatment response and the possibility of surgery. If the patient presented with disease progression, a new second-line chemotherapy regimen was recommended.

In surgical treatment, the technical criteria for resectability related to the liver remnant after resection were: (1) Preserving two contiguous segments; (2) Preserving adequate vascular inflow, outflow, and biliary drainage; and (3) Preserving adequate future liver remnant volume (30% in normal liver and 40% in patients with preoperative chemotherapy)[9]. Major hepatic resection was defined to be any resection of three or more segments. All the patients underwent hepatic resection and primary tumor resection. All the specimens were examined for pathological diagnosis after surgery.

Statistical analysis

The continuous variables are expressed using median and range, and the categorical variables are expressed as number (n) and frequency (%). The c^2 or Fisher's exact test was used to compare categorical variables between groups, while the Mann-Whitney U test was afforded to compare the continuous variables between groups. Propensity score matching (PSM) was applied to compensate for the biases between the irinotecan and the oxaliplatin groups in the unmatched cohort with a matching ratio of 1:1 by the nearest neighbor method. The caliper value was set at 0.05. The imbalance before and after PSM was assessed by the standardized mean difference. The following variables were included in the PSM model: Age, sex, primary N stage, number of liver metastases, preoperative CEA/Ca19-9, preoperative clinical risk score (CRS) as proposed by Fong *et al*[10], RAS mutation status, cycles of NC, major hepatic resection, intraoperative radiofrequency ablation combined with hepatic resection, adjuvant chemotherapy, and response to NC. Short-term results were compared between the irinotecan and oxaliplatin groups before and after PSM, such as intraoperative blood loss, intraoperative red blood cell (RBC) transfusion, operating time, and Clavien-Dindo grade of general or surgical complications. PFS was defined as the time from treatment to recurrence, disease progression, or death, whichever occurred first[11]. OS was defined as the interval between hepatic resection and the date of death or last follow-up. Kaplan-Meier survival analysis was performed to compare the PFS and OS before and after PSM using the log-rank test. Uni- and multivariable analyses were conducted with Cox proportional hazards model to identify the independent prognostic factors for PFS after PSM. Significance level was set at 0.05, and SPSS version 23 was used for statistical analyses (IBM, Armonk, NY, United States).

RESULTS

Comparison of irinotecan- and oxaliplatin-treated patients before PSM

We enrolled a total of 554 CRLM patients, with 201 in the irinotecan group and 353 in the oxaliplatin group. Primary N stage, timing of liver metastases, biological agent, staged resection, and operating time were significantly different between the two groups ($P < 0.05$) (Table 1).

Long-term outcomes before PSM

The median follow-up was 41 mo. The intrahepatic and extrahepatic recurrence rates were not significantly different between the irinotecan and oxaliplatin groups. There were no significant

Table 1 Demographic and clinical characteristics of patients before propensity score matching

Patient demographic	All patients (*n* = 554)	Irinotecan group (*n* = 201)	Oxaliplatin group (*n* = 353)	*P* value
Age (yr)	57.1 ± 9.5	56.1 ± 9.6	57.7 ± 9.4	0.056
Sex ration (male:female)	193:361	62:139	131:222	0.137
Primary T stage				0.736
T1-2	64	22	42	
T3-4	490	179	311	
Primary N stage				0.036
N0	191	58	133	
N1-2	363	143	220	
Primary tumor location				0.613
Colon	322	114	208	
Rectum	232	87	145	
Primary tumor side				0.839
Right	75	28	47	
Left	479	173	306	
Timing of liver metastasis				< 0.001
Synchronous	482	157	325	
Metachronous	72	44	28	
Tumor number (median)	3 (1-10)	3 (1-9)	3 (1-10)	0.706
Tumor size (mm, mean ± SD)	27.6 ± 18.2	26.78 ± 17.2	29.0 ± 17.8	0.160
Localization of liver metastases				0.250
Unilobar	226	90	176	
Bilobar	288	111	177	
CEA level (ng/mL)	31.44 ± 85.3	24.93 ± 54.1	35.17 ± 98.65	0.175
CA 19-9 level (IU/mL)	215.4 ± 877.9	194.8 ± 232.8	227.4 ± 185.4	0.847
Extrahepatic metastasis				0.572
No	462	170	292	
Yes	92	31	61	
RAS mutation				0.174
Wildtype	332	128	204	
Mutation	222	73	149	
Biological agent				< 0.001
Cetuximab	118	57	61	
Bevacizumab	187	97	90	
No	249	47	202	
Response				0.209
Complete response	5	0	5	
Partial response	217	81	136	
Stable disease	301	112	189	
Progressive disease	31	8	23	
Cycles	4 (1-16)	4 (1-12)	4 (1-16)	0.430
Concomitant ablation therapy	91	39	52	0.154

CRS				
0-2	274	95	179	
3-5	280	106	174	
Resection				0.002
Simultaneous resection	145	41	104	
Staged resection	409	160	249	
Intraoperative blood loss (mL)	213 ± 198	204 ± 172	218 ± 212	0.437
Intraoperative RBC transfusion	24	10	14	0.289
Intraoperative RBC transfusion (U)	2 (1-12)	2 (1-6)	4 (2-12)	0.026
Operating time (min)	199 ± 74	190 ± 72	204 ± 76	0.039
Hepatic resection				0.357
Major resection	123	49	74	
Minor resection	431	152	279	
Margin status				0.308
Positive	72	30	42	
Negative	482	171	311	
Clavien-Dindo classification				0.057
I-II	164	53	111	
II-V	32	7	25	
Adjuvant chemotherapy				0.153
No	132	41	91	
Yes	422	160	262	

PSM: Propensity score matching; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; RBC: Red blood cell; CRS: Clinical risk score.

differences in 1-, 3-, or 5-year PFS and OS rates ($P > 0.05$; Figures 1A and 1B). In the irinotecan group, the median PFS was 14.0 mo and the 5-year PFS was 25.2%. The median OS was 65 mo and 5-year OS rates was 54.0%. In the oxaliplatin group, the median PFS was 12.5 mo and 5-year PFS was 22.0%. The median OS was 46 mo and 5-year OS was 39.8%.

Comparison of irinotecan- and oxaliplatin-treated patients after PSM

After PSM for the significantly different preoperative and prognostic factors between the two groups, 175 patients from the irinotecan group and 175 from the oxaliplatin group were considered for the matched analyses. When the biases associated with the differences in primary N stage, timing of liver metastases, biological agent, staged resection, intraoperative RBC transfusion, and operating time were removed by PSM, differences in intraoperative blood loss, operating time, and postoperative complications were observed (Table 2).

Long-term outcomes after PSM

The median follow-up was 42 mo. The 1-, 3-, and 5-year OS rates were higher in the irinotecan group than in the oxaliplatin group, while the reverse trend was observed for PFS, but the differences were not significant ($P > 0.05$; Figures 1C and 1D). In the irinotecan group, the 5-year PFS and OS rates were 18.0% and 49.7%, respectively, and the median PFS and OS were 13.5 and 49 mo, respectively. In the oxaliplatin group, the 5-year PFS and OS rates were 26.0% and 46.8%, respectively, and the median PFS and OS were 12.0 and 57 mo, respectively.

Building Cox proportional hazards model

Multivariable Cox regression analysis was performed for the PSM cohort. In the univariate analysis, primary tumor location, synchronous liver metastases, tumor size > 5 cm, tumor number > 1, CRS 3-5, concomitant ablation, bilobar distribution, CA 19-9 > 100 U/mL, RAS mutation, and response rate were associated with PFS ($P < 0.05$) (Table 3). In the multivariate analysis, tumor size > 5 cm, tumor number > 1, RAS mutation, CA 19-9 > 100 U/mL, and response rate to NC were independently associated with PFS ($P < 0.05$).

Table 2 Demographic and clinical characteristics of patients after propensity score matching

Patient demographic	All patients (*n* = 350)	Irinotecan group (*n* = 175)	Oxaliplatin group (*n* = 175)	*P* value
Age (yr)	56.0 ± 4.2	56.2 ± 9.6	55.7 ± 10.1	0.632
Sex ration (male:female)	230:120	121:54	109:66	0.177
Primary T stage				0.433
T1-2	47	21	26	
T3-4	303	154	149	
Primary N stage				0.526
N0	104	51	53	
N1-2	246	125	121	
Primary tumor location				0.756
Colon	205	101	104	
Rectum	145	74	71	
Primary tumor side				0.745
Right	48	25	23	
Left	302	150	152	
Timing of liver metastasis				0.077
Synchronous	283	135	148	
Metachronous	67	40	27	
Tumor number (median)	2 (1-25)	2 (1-25)	2 (1-22)	0.422
Tumor size (mm, mean ± SD)	28.8 ± 18.9	29.2 ± 20.3	28.4 ± 17.5	0.681
Localization of liver metastases				0.493
Unilobar	190	98	92	
Bilobar	160	77	83	
CEA level (ng/mL)	27.81 ± 64.87	24.26 ± 55.81	31.36 ± 72.81	0.307
CA 19-9 level (IU/mL)	228.71 ± 203.76	212.92 ± 145.70	244.51 ± 266.39	0.894
Extrahepatic metastasis				0.311
No	293	150	143	
Yes	57	25	32	
RAS mutation				0.912
Wild type	221	111	110	
Mutation	129	64	65	
Biological agent				0.169
Cetuximab	100	53	47	
Bevacizumab	167	88	79	
No	83	34	49	
Response				0.176
Complete response	1	0	1	
Partial response	144	70	74	
Stable disease	183	98	85	
Progressive disease	22	7	15	
Cycles	4 (0-10)	4 (0-10)	4 (0-10)	0.948
Concomitant ablation therapy	66	36	30	0.464

CRS				0.669
0-2	166	81	85	
3-5	184	94	90	
Simultaneous resection	88	39	49	0.443
Staged resection	262	136	126	
Intraoperative blood loss (mL)	222 ± 211	201 ± 181	264 ± 235	0.024
Intraoperative RBC transfusion	15	8	7	0.117
Intraoperative RBC transfusion (U)	2 (1-12)	2 (1-6)	2 (2-6)	0.281
Operation time (min)	198 ± 73	188 ± 73	208 ± 72	0.012
Hepatic resection				0.886
Major resection	90	42	45	
Minor resection	260	133	130	
Margin status				0.367
Positive	32	17	15	
Negative	318	158	160	
Clavien-Dindo classification				0.019
I-II	102	43	59	
III-V	22	7	15	
Adjuvant chemotherapy				0.352
No	132	41	91	
Yes	422	160	262	

PSM: Propensity score matching; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; RBC: Red blood cell; CRS: Clinical risk score.

DISCUSSION

Compared with 5-Fu alone, irinotecan-based preoperative chemotherapy increased the response rates up to 39%[12], and oxaliplatin improved the response rate from 22% to 51%[13]. With newly developed biological agents, further significant benefits were achieved. Almost 60% of populations were evaluated to have tumor response by combining oxaliplatin-based or irinotecan-based chemotherapy with such targeted agents[14]. In the present study, the 5-year PFS and OS rates were 25.2% and 54.0% for the irinotecan group, respectively. In the oxaliplatin group, the 5-year PFS and OS rates were 22.0% and 39.8%, respectively. Our study was the first retrospective cohort analysis to compare the survival outcomes of irinotecan and oxaliplatin in patients with CRLM.

During the past few years, perioperative chemotherapy for CRLM has been developed remarkably. NC is recommended for resectable CRLM patients to increase the possibility of radical resections. It also might crush the occult metastasis in the liver remnant. Moreover, NC could test whether cancer cells are chemosensitive *in situ*. According to the responses mentioned above, physicians might determine the individualized adjuvant chemotherapy regimen and identify patients who would not benefit from immediate hepatic resection because of tumor progression. Nevertheless, it is still controversial whether NC should be applied for all patients with resectable CRLM. It was reported that a significant improvement in PFS was observed for resectable CRLM patients after NC with FOLFOX4 in the EORTC Intergroup Trial 40983. In contrast, 64% of CRLM patients achieved an objective radiological response after NC, and disease-free survival also improved significantly according to a systematic review of 23 studies comprising 3278 patients. In the present study, tumor size > 5 cm, tumor number > 1, RAS mutation, CA 19-9 > 100 U/mL, and response to NC were independent factors for PFS. This was consistent with previous studies. Hepatic resection is considered a standard treatment for CRLM patients, including special populations, such as those treated with hyperthermic intraperitoneal chemotherapy (HIPEC) and pregnant women[15,16]. HIPEC can be administered before or after surgery, and future studies should examine which HIPEC strategy, and combined with which chemotherapy regimen, would achieve better outcomes.

Oxaliplatin- and/or irinotecan-based NC might cause histological damage, vascular lesions, or steatohepatitis although there are conflicting results in the literature[6,7]. Chemotherapy-induced liver injury could reduce the function of the future remnant liver with an increase in postoperative complications

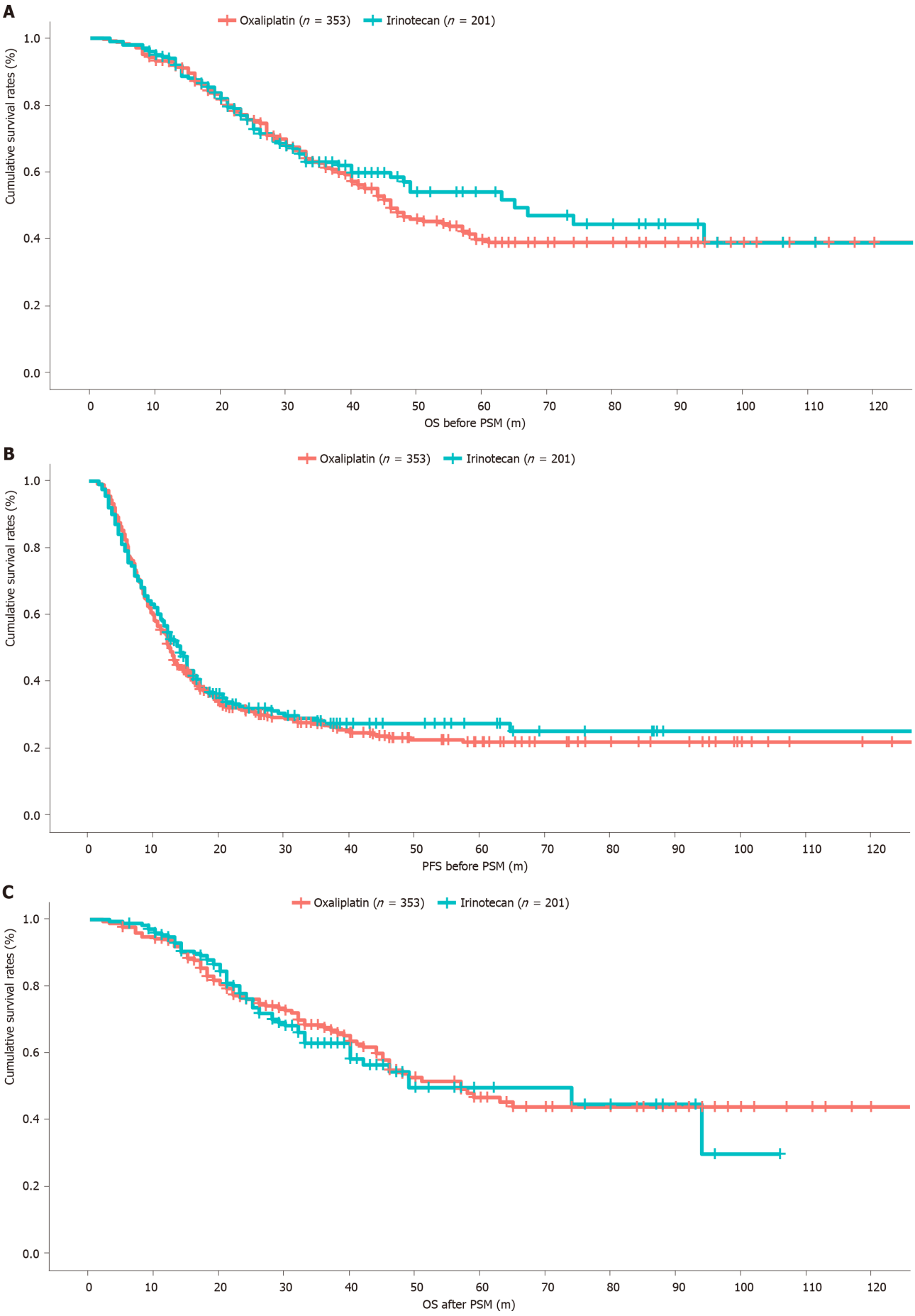
Table 3 Univariable and multivariable analyses of factors associated with progression-free survival

Variable	Univariable analysis			Multivariable analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age, yr						
> 60	Ref					
≤ 60	0.878	0.682-1.131	0.314			
Gender						
Male	Ref					
Female	0.949	0.733-1.230	0.694			
Primary T stage						
1-2	Ref					
3-4	1.183	0.820-1.706	0.369			
Primary N stage						
N0	Ref					
N1-2	1.090	0.952-1.248	0.212			
Location tumor						
Colon	Ref					
Rectum	0.869	0.676-1.116	0.270			
Primary tumor location						
Left	Ref			Ref		
Right	1.508	1.072-2.121	0.018	1.413	0.991-2.015	0.056
Disease-free interval						
> 12 mo	Ref			Ref		
≤ 12 mo	1.487	1.068-2.071	0.019	1.156	0.788-1.696	0.459
CEA						
≤ 200	Ref					
> 200	1.340	0.689-2.607	0.388			
CA 19-9						
≤ 100	Ref			Ref		
> 100	1.528	1.077-2.167	0.017	1.521	1.032-2.241	0.034
Tumor size						
≤ 5 cm	Ref			Ref		
> 5 cm	1.149	1.019-1.554	0.028	1.479	1.062-2.060	0.021
Tumor no.						
≤ 1	Ref			Ref		
> 1	1.702	1.284-2.255	0.000	1.446	1.077-2.146	0.014
CRS						
0-2	Ref			Ref		
3-5	1.665	1.298-2.135	0.000	1.256	0.894-1.765	0.189
RAS status						
Wild	Ref			Ref		
Mutation	1.641	1.276-2.110	0.000	1.468	1.127-1.913	0.004
Extrahepatic metastases						

No	Ref					
Yes	1.081	0.781-1.496	0.638			
Biological agent						
Cetuximab						
Bevacizumab	Ref					
No	1.057	0.910-1.228	0.469			
Response						
Complete response						
Partial response						
Stable disease	Ref			Ref		
Progressive disease	1.564	1.067-2.292	0.022	1.830	1.211-2.764	0.004
Hepatic resection						
Minor	Ref					
Major	0.997	0.753-1.320	0.984			
Concomitant ablation						
No	Ref			Ref		
Yes	1.634	1.195-2.236	0.002	1.002	0.641-1.568	0.992
Stage resection						
No	Ref					
Yes	0.839	0.682-1.033	0.098			
Margin status						
R0	Ref					
R1	0.878	0.581-1.327	0.537			
Distribution						
Unilobar	Ref			Ref		
Bilobar	1.277	1.067-1.528	0.008	1.112	0.875-1.413	0.385
Extrahepatic metastases						
Yes	Ref					
No	1.081	0.781-1.496	0.638			
Adjuvant chemotherapy						
No	Ref					
Yes	0.885	0.654-1.198	0.430			
Clavien-Dino classification						
I-II	Ref					
III-V	1.018	0.833-1.244	0.859			
RBC transfusion						
Yes	Ref					
No	0.857	0.456-1.614	0.634			

PFS: Progression-free survival; HR: Hazard ratio; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; RBC: Red blood cell; CI: Confidence interval; CRS: Clinical risk score.

[17]. Non-parenchymal-sparing strategies have been advocated for radical resection of CRLM and the outcomes associated with these strategies have been reported. Nakano *et al*[17] have reported that major hepatic resection for patients with CRLM with SOS might increase the risk of postoperative complications. Sinusoidal lesions have been associated with an increased blood requirement and higher


A
Oxaliplatin (n = 353)
Irinotecan (n = 201)
Cumulative survival rates (%)
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
70
80
90
100
110
120
OS before PSM (m)
B
Oxaliplatin (n = 353)
Irinotecan (n = 201)
Cumulative survival rates (%)
PFS before PSM (m)
C
Oxaliplatin (n = 353)
Irinotecan (n = 201)
Cumulative survival rates (%)
OS after PSM (m)

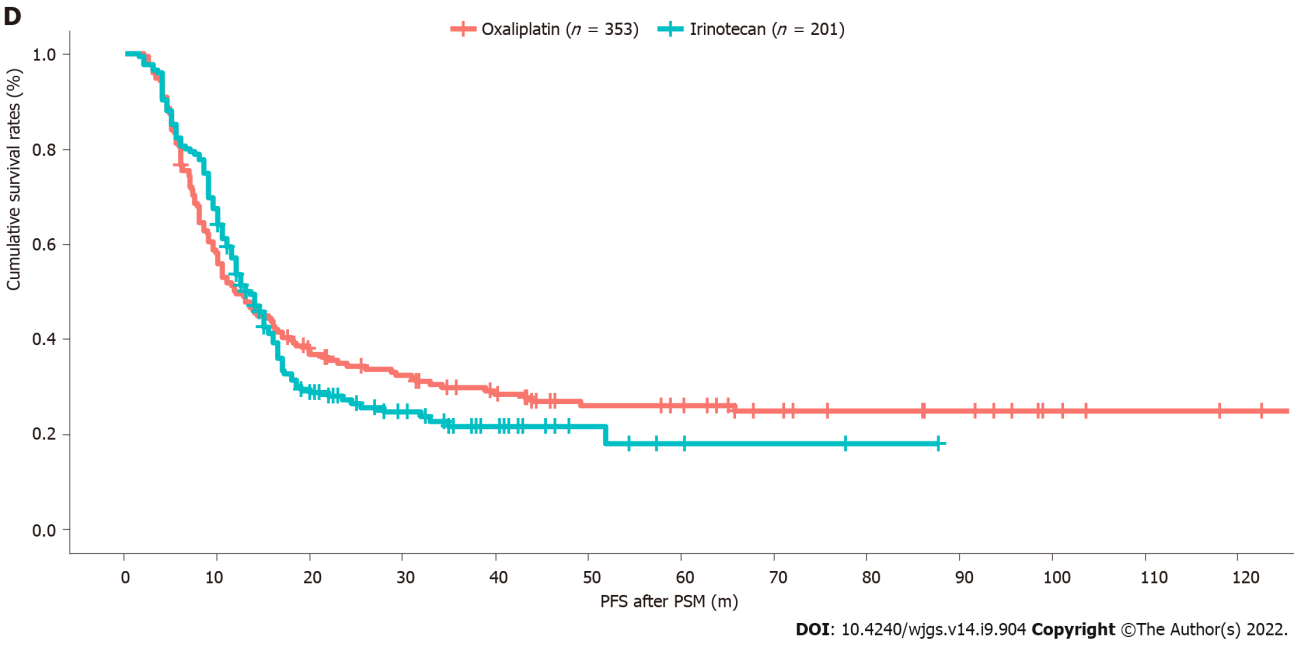


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Figure 1 Overall survival and progression-free survival of patients treated with irinotecan or oxaliplatin before and after propensity score matching. A: Overall survival (OS) of patients treated with irinotecan or oxaliplatin before propensity score matching (PSM) by the Kaplan-Meier method; B: Progression-free survival (PFS) of patients treated with irinotecan or oxaliplatin before PSM by the Kaplan-Meier method; C: OS of patients treated with irinotecan or oxaliplatin after PSM by the Kaplan-Meier method; D: PFS of patients treated with irinotecan or oxaliplatin after PSM by the Kaplan-Meier method. OS: Overall survival; PFS: Progression-free survival; PSM: Propensity score matching.

postoperative liver failure[18,19].

Many studies have attempted to identify predictive factors for chemotherapy-induced liver damage [20]. It is reported that the following could induce SOS: High γ-glutaryl transferase levels, low platelet counts, high aspartate aminotransferase to platelet ratios, and enlarged spleen[21,22]. However, prospective studies are required to confirm the relevance of these factors, and a combination of parameters may provide evidence to establish a diagnosis of SOS preoperatively. Bevacizumab offers an opportunity to prevent SOS and reduces the incidence from 46% to 5% when added to preoperative chemotherapy[23]. It was hypothesized that endothelial cells might secret matrix metalloprotease-9 (MMP-9) and induce SOS in murine models. Bevacizumab might improve SOS by inhibiting vascular endothelial growth factor-dependent induction of MMP-9 and subsequent matrix degradation[24].

The present study had some limitations. First, it was a retrospective cohort study without randomizing for enrolled patients. Second, the included patients were limited after PSM. The sample size should be enlarged in a randomized controlled trial. Third, a validation group would strengthen the present conclusions.

CONCLUSION

In NC for CRLM, irinotecan is similar to oxaliplatin in improving the survival outcomes, but irinotecan is superior in reducing operating time, intraoperative blood loss, and postoperative complications.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) represents an important disease burden worldwide, being the third most common malignancy and the second leading cause of cancer mortality. Many patients are *de novo* metastatic at presentation, and liver metastasis is common in CRC. In selected patients with colorectal liver metastases (CRLM) (*i.e.*, the liver as the only metastatic site), surgery can be performed directly, but some patients with resectable CRLM will require neoadjuvant chemotherapy (NC) to increase the radical resection rate and treat occult metastases. On the other hand, chemotherapy can cause liver injury that will lead to impaired remnant liver function.

Research motivation

For resectable CRLM, oxaliplatin-based regimens have been preferred to irinotecan-based regimens as the first-line treatment because of lower occurrences of alopecia and gastrointestinal toxicity. Irinotecan has been suggested for patients with resectable CRLM, but data for such patients are limited and whether outcomes are improved remains debatable. Therefore, even though NC improves the survival outcomes for selected patients with CRLM, the benefits of irinotecan-based regimens are still under debate.

Research objectives

This study investigated the benefits of irinotecan- *vs* oxaliplatin-based NC regimens in patients with resectable CRLM.

Research methods

At a single hospital in China, 554 patients received NC and underwent hepatectomy for CRLM from September 2003 to August 2020. In order to manage confounding factors, a 1:1 propensity score matching (PSM) was performed. Overall survival (OS), progression-free survival (PFS), intraoperative blood loss, operation time, and postoperative complications were compared between the two groups.

Research results

In the present study, NC regimens were based on oxaliplatin in 353 (63.7%) patients and on irinotecan in 201 (36.3%). Finally, 175 patients who received irinotecan-based NC were matched to 175 who received oxaliplatin-based NC. Hence, the two groups were balanced regarding demographic, therapeutic, and prognostic characteristics. After PSM, the 5-year PFS rates were 18.0% for irinotecan-based NC and 26.0% for oxaliplatin-based NC, while the 5-year OS rates were 49.7% for irinotecan-based NC and 46.8% for oxaliplatin-based NC. Intraoperative blood loss (201 *vs* 264 mL, $P = 0.024$), operation time (188 *vs* 208 min, $P = 0.012$), and postoperative complications (28.6% *vs* 42.3%, $P = 0.019$) all favored the irinotecan-based NC group. In the multivariable analysis, carbohydrate antigen 19-9 [hazard ratio (HR) = 1.52, 95% confidence interval (CI): 1.03-2.24], RAS mutation (HR = 1.47, 95%CI: 1.13-1.91), response to NC (HR = 1.83, 95%CI: 1.21-2.76), tumor size > 5 cm (HR = 1.48, 95%CI: 1.06-2.06), and tumor number > 1 (HR = 1.45, 95%CI: 1.08-2.15) were independently associated with the PFS.

Research conclusions

In patients with CRLM, the PFS and OS are similar between irinotecan- and oxaliplatin-based NC. On the other hand, irinotecan-based NC is superior to oxaliplatin-based NC in terms of shorter operation time, smaller intraoperative blood loss, and fewer postoperative complications.

Research perspectives

This retrospective cohort analysis was the first to compare the OS and PFS of irinotecan-based NC *vs* oxaliplatin-based NC in patients with CRLM. Even though these results can help determine the best options for patients with CRLM, multicenter randomized controlled trials would be required for confirmation. In addition, future studies could examine different dosing strategies in patients with CRLM.

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FOOTNOTES

Author contributions: Liu W designed and performed the research and wrote the paper; Xing BC designed the research and supervised the report; Chen FL designed the research and contributed to the analysis; Wang K, Bao Q, Wang HW, and Jin KM provided clinical advice and reviewed the manuscript; and all authors have read and approved the final version.

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of Helsinki.

Informed consent statement: The present study is a retrospective study, and the requirement for individual consent was waived by the ethics committee.

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ORIGINAL ARTICLE

Retrospective Study

Predictors of difficult endoscopic resection of submucosal tumors originating from the muscularis propria layer at the esophagogastric junction

Yu-Ping Wang, Hong Xu, Jia-Xin Shen, Wen-Ming Liu, Yuan Chu, Ben-Song Duan, Jing-Jing Lian, Hai-Bin Zhang, Li Zhang, Mei-Dong Xu, Jia Cao

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Abstract

BACKGROUND

Endoscopic resection approaches, including endoscopic submucosal dissection (ESD), submucosal tunneling endoscopic resection (STER) and endoscopic full-thickness resection (EFTR), have been widely used for the treatment of submucosal tumors (SMTs) located in the upper gastrointestinal tract. However, compared to SMTs located in the esophagus or stomach, endoscopic resection of SMTs from the esophagogastric junction (EGJ) is much more difficult because of the sharp angle and narrow lumen of the EGJ. SMTs originating from the muscularis propria (MP) in the EGJ, especially those that grow extraluminally and adhere closely to the serosa, make endoscopic resection even more difficult.

AIM

To investigate the predictors of difficult endoscopic resection for SMTs from the MP layer at the EGJ.

METHODS

A total of 90 patients with SMTs from the MP layer at the EGJ were included in the present study. The difficulty of endoscopic resection was defined as a long procedure time, failure of en bloc resection and intraoperative bleeding. Clinicopathological, endoscopic and follow-up data were collected and analyzed.

Statistical analysis of independent risks for piecemeal resection, long operative time, and intraoperative bleeding were assessed using univariate and multivariate analyses.

RESULTS

According to the location and growth pattern of the tumor, 44 patients underwent STER, 14 patients underwent EFTR, and the remaining 32 patients received a standard ESD procedure. The tumor size was 20.0 mm (range 5.0–100.0 mm). Fourty-seven out of 90 lesions (52.2%) were regularly shaped. The overall en bloc resection rate was 84.4%. The operation time was 43 min (range 16–126 min). The intraoperative bleeding rate was 18.9%. There were no adverse events that required therapeutic intervention during or after the procedures. The surgical approach had no significant correlation with en bloc resection, long operative time or intraoperative bleeding. Large tumor size (≥ 30 mm) and irregular tumor shape were independent predictors for piecemeal resection (OR: 7.346, P = 0.032 and OR: 18.004, P = 0.029, respectively), long operative time (≥ 60 min) (OR: 47.330, P = 0.000 and OR: 6.863, P = 0.034, respectively) and intraoperative bleeding (OR: 20.631, P = 0.002 and OR: 19.020, P = 0.021, respectively).

CONCLUSION

Endoscopic resection is an effective treatment for SMTs in the MP layer at the EGJ. Tumors with large size and irregular shape were independent predictors for difficult endoscopic resection.

Key Words: Submucosal tumor; Esophagogastric junction; Muscularis propria; Submucosal tunneling endoscopic resection; Endoscopic submucosal dissection; Endoscopic full-thickness resection

Core Tip: This was the first study to discuss the predictors of difficult endoscopic resection, including various approaches of submucosal tunneling endoscopic resection, endoscopic full-thickness resection and endoscopic submucosal dissection for submucosal tumors originating from the muscularis propria layer at the esophagogastric junction. Our data showed that tumors with greater size and irregular shape were independent predictors of difficult endoscopic resection, which is mainly measured by piecemeal resection, long operative time and intraoperative bleeding.

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INTRODUCTION

Submucosal tumors (SMTs) of the esophagogastric junction (EGJ) are defined as tumors located partially or fully within the area 1 cm proximal to and 2 cm distal to the squamocolumnar junction[1]. Previously, a common view was that periodic endoscopic surveillance was recommended for SMTs smaller than 2.0 cm, which were generally considered benign[2,3], while surgical intervention was the preferred treatment for large lesions. However, some gastrointestinal stromal tumors (GISTs) have malignant potential[4]. The enlargement of the tumor may deprive patients of the opportunity for minimally invasive surgery and place a great psychological burden on patients. Furthermore, surgical resection of the cardia may lead to lifelong gastroesophageal reflux and severely impair the quality of life of patients.

In recent decades, endoscopic therapeutic technology has developed rapidly. Endoscopic resection approaches, including endoscopic submucosal dissection (ESD), submucosal tunneling endoscopic resection (STER) and endoscopic full-thickness resection (EFTR), have been widely used for the treatment of SMTs located in the upper gastrointestinal tract[5-7]. However, compared to SMTs located in the esophagus or stomach, endoscopic resection of SMTs from the EGJ is much more difficult because of the sharp angle and narrow lumen of the EGJ. SMTs originating from the muscularis propria (MP) in the EGJ (especially those that grow extraluminally and adhere closely to the serosa) make endoscopic resection even more difficult, are accompanied by a long operation time, failure of en bloc resection, perforation, and intraoperative and delayed bleeding.

To date, there have been very few reports on the endoscopic excision of SMTs originating from the MP layer at the EGJ by ESD, STER or EFTR[8,9]. Only limited studies have demonstrated the predictors associated with the difficulty of endoscopic resection[10], which is mainly measured by long procedure time, failure of en bloc resection, or intraoperative and postoperative complications, including perforation and bleeding. The aim of the present study was to identify the predictors of technical difficulties during endoscopic resection of SMTs originating from the MP layer at the EGJ.

MATERIALS AND METHODS

Patients

This was a retrospective study including 90 consecutive patients admitted to Endoscopy Center, Shanghai East Hospital, Tongji University School of Medicine between March 2019 and March 2021. Patients who met the following criteria were included: (1) SMTs, which were located at the EGJ, originating from the MP layer as confirmed by endoscopic ultrasonography (EUS) without restriction of extraluminal growth; (2) Tumor size ≤ 100 mm; (3) Age > 18 years, irrespective of gender; and (4) No evidence of lymph node involvement or distant metastasis. Patients with severe cardiopulmonary diseases, with coagulation disorders or were taking drugs to promote bleeding, such as ticlopidine, aspirin or warfarin were excluded. All patients signed informed consent forms. The study protocol was in accordance with the guidelines for clinical research and was approved by the Institutional Review Board and the Ethical Review Committee of the Hospital.

Definitions

Tumors with an oval or globular shape were defined as regularly shaped tumors, while horseshoe-shaped, ginger-shaped, lobulated or polygonal tumors were classified as irregularly shaped tumors. Tumors that were partially located above the anatomic EGJ with the distal edge failing to reach the squamocolumnar junction were considered esophagocardia tumors. The tumor of which the center was within the anatomic EGJ and that straddled the squamocolumnar junction was named the cardia tumor. Tumors that were partially located below the anatomic EGJ with the proximal edge failing to reach the squamocolumnar junction were defined as gastrocardia tumors[11].

En bloc resection is defined as a tumor removed in a single piece, with the capsule intact. Complete resection was defined as a tumor removed with no apparent residual tumor at the resection site (assessed macroscopically by the endoscopist) and with negative margins on pathologic examination. A tumor with an oval or globular shape was defined as a tumor with a regular shape[12]. Procedure time was defined as the time from the beginning of the injection to the withdrawal of the endoscope. Intraoperative bleeding was defined as bleeding that could not be controlled by a single session of hemocoagulation and that required multiple hemoclips for hemocoagulation. No visible bleeding or minor bleeding that stops spontaneously or is easily controlled by a single session of hemocoagulation was classified into the no bleeding group[13].

Endoscopic equipment and accessories

The operation was performed using a single-channel endoscope (GIF-Q260J, Olympus, Tokyo, Japan) and/or a dual-channel endoscope (GIF-2TQ260 M, Olympus). A carbon dioxide insufflator (UCR, Olympus) was used in all procedures. Other equipment and accessories included a high-frequency generator (VIO 200 D, ERBE, Germany), an argon plasma coagulation (APC 2, ERBE), an endoscopic flushing pump (Olympus Medical Systems), a transparent cap (D-201-11804, Olympus Medical Systems), an injection needle (VIN-23, COOK Medical Europe Ltd.), a hook knife (KD-620LR, Olympus Medical Systems), a dual knife (KD-650 L, Olympus Medical Systems), an insulated-tip knife (KD-611 L, IT2, Olympus Medical Systems), sterile hot snare (MTN-PFS-A-28/23, MTN-PFS-E-36/23, Micro-Tech, Nanjing, China), hemostatic clips (ROCC-D-26-195-C, ROCC-F-26-195-C, Micro-Tech, Nanjing, China), and Coagrasper (HBF-23/2000, Micro-Tech, Nanjing, China). A mixed solution of glycerin fructose containing 10% glycerol, 5% fructose, and indigo carmine was used for submucosal injection.

Procedures of endoscopic resection

All patients received general anesthesia with endotracheal intubation. The patient was placed in a left lateral decubitus position. For tumors located in the esophagocardia or cardia region, STER was mainly selected. ESD was chosen for gastrocardia SMTs. EFTR was chosen for tumors with a predominant extraluminal growth patterns located in the gastrocardia region.

Briefly, ESD was performed in a standardized way starting with injection, mucosal incision, and submucosal dissection at the lesion's distal margin[4]. Afterward, the tumor was dissected along the capsule. Any macroscopic vessels on the wound surface were electrically coagulated by argon plasma coagulation to prevent delayed bleeding, and metal clips were used to close the deeply dissected areas if needed. When there was a muscularis defect after ESD, purse-string suturing was performed. The STER procedure includes creation of the submucosal tunnel, resection of the SMT, tumor retrieval, hemostasis

and closure of the tunnel entry site with 4 to 6 metal clips (Figure 1)[14]. EFTR consists of five steps: Marking of the tumor location, submucosal injection, exposure of the lesion, full-thickness resection and purse-string suture with a Nylon loop and metal clips (Figure 2).

Postoperative management

The postoperative observations mainly included complaints of chest or abdominal pain, fever, and gas-related complications such as subcutaneous emphysema, pneumothorax, pneumoperitoneum, and mediastinal emphysema. All patients fasted for one day and were administered proton pump inhibitors and antibiotics. The patients were started on fluid food first and gradually transitioned to a normal diet when there were no abnormal clinical manifestations.

Histopathological assessment

Resected specimens were fixed in 10% formalin for 48 h. Immunohistochemical staining for CD117, CD34, smooth muscle actin, and S-100 markers was used to identify tumor subtypes. The histological type was determined using the 2010 WHO classification of digestive tumors[15].

Follow-up

All patients were followed up with standard endoscopy at 3, 6, and 12 mo during the first year to observe the healing of the wound and to check for residual tumors or recurrence and thereafter annually. For patients with GISTs, a contrast-enhanced computed tomography scan/magnetic resonance imaging every 6 to 12 mo was recommended.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS, version 25.0, Chicago, IL, United States). Continuous variables are presented as medians (ranges), and qualitative data are presented as frequencies. Statistical analysis of independent risks for piecemeal resection, long operative time, and intraoperative bleeding were assessed using univariate and multivariate analyses. The relationship between age and tumor size was analyzed using Pearson correlation analysis. $P < 0.05$ was considered the cutoff value for statistical significance.

RESULTS

Clinical characteristics

Ninety patients with SMTs originating from the MP layer at the EGJ were included in the present study (Table 1). There were 42 males and 48 females, with a mean age of 55.5 years (range 25.0–74.0 years). The tumor size was 20.0 mm (range 5.0–100.0 mm). The tumor size of GISTs was 18.0 mm (range 8.0–34.0 mm). Fourty-seven out of 90 Lesions (52.2%) were regularly shaped, while the remaining lesions (43/90, 47.8%) were irregularly shaped. Of the 90 SMTs, 25 tumors were located in the esophagocardia region, 26 tumors were located in the cardia region, and 39 were defined as gastrocardia tumors. In terms of the growth pattern, 17 tumors were predominantly extraluminal, and 73 were predominantly intracavitary. There was a significant negative correlation between age and tumor size (Figure 3A).

Therapeutic outcomes and complications

In the present study, 44 patients underwent STER, 14 patients underwent EFTR, and the remaining 32 patients received a standard ESD procedure. Tumors larger than 4.0 cm accounted for 31.8%, 7.1% and 9.4% of all tumors in the STER group, EFTR group and ESD group, respectively (Figure 3B). All lesions were successfully removed, and the complete resection rate was 100%. The operation time was 50 min (range 18–126 min) in the STER group, 55 min (range 23–108 min) in the EFTR group and 36 min (range 16–116 min) in the ESD group. Seventy-six out of 90 tumors were en bloc resected, whereas 14 Lesions underwent piecemeal resection. The en bloc resection rates were 77.3%, 92.9% and 90.6% in the STER group, EFTR group and ESD group, respectively. Although the en bloc resection rate in the STER group decreased compared to that in the EFTR group and ESD group, the decrease was not statistically significant. The en bloc resection rate of GIST was 100% (18/18).

Intraoperative bleeding requiring multiple hemoclips and hemocoagulation occurred in 8 (8/44, 18.2%), 3 (3/14, 21.4%) and 6 (6/32, 18.8%) patients in the STER group, EFTR group and ESD group, respectively (Table 2). None of the patients had bleeding greater than 150 mL. No adverse events that required therapeutic intervention occurred during or after the procedures. All defects could be closed completely using metal clips or purse-string suture with a Nylon loop and metal clips if needed. A 20-gauge needle was used to relieve the pneumoperitoneum during EFTR. Two patients had low-grade fever, which was relieved quickly without any treatment during the postoperative period. Mild abdominal pain and chest pain, which spontaneously disappeared 2 days after the procedure, were reported in 2 and 2 patients, respectively. None of the patients presented with delayed bleeding,

Table 1 Clinical characteristics and therapeutic outcomes of 90 patients with submucosal tumors originating from the muscularis propria layer in the esophagogastric junction

Variable	Number
Age, median (range), yr	55.5 (25.0–74.0)
Male/Female, *n* (%)	42/48 (46.7/53.3)
Location, *n* (%)	
Esophagocardia	25 (27.8)
Cardia	26 (28.9)
Gastrocardia	39 (43.3)
Tumor diameter, median (range), mm	20.0 (5.0–100.0)
Shapes of lesion, *n* (%)	
Regular	47 (52.2)
Irregular	43 (47.8)
Growth pattern, *n* (%)	
Predominant extraluminal	17 (18.9)
Predominant intracavitary	73 (81.1)
Surface, *n* (%)	
Smooth	77 (85.6)
Reddish and erosive	13 (14.4)
Surgical approach, *n* (%)	
STER	44 (48.9)
EFTR	14 (15.6)
ESD	32 (35.5)
En bloc resection, *n* (%)	76 (84.4)
Operation time, median (range), min	43 (16–126)
Intraoperative bleeding, *n* (%)	
Bleeding group	17 (18.9)
No bleeding group	73 (81.1)
Histopathology, *n* (%)	
Leiomyoma	71 (78.9)
GIST	18 (20.0)
Schwannoma	1 (1.1)
Follow-up time, median (range), months	16.4 (6.0–26.0)

STER: Submucosal tunneling endoscopic resection; EFTR: Endoscopic full-thickness resection; ESD: Endoscopic submucosal dissection; GIST: Gastrointestinal stromal tumors.

secondary peritoneal or abdominal infections, GI tract leakage, or postoperative stenosis. There were 71 Leiomyomas (78.9%), 1 schwannoma (1.1%), and 18 GISTs (20%, 11 with very low risk, 5 with low risk, 2 with moderate risk) (Table 1).

Resection rate, procedure time and intraoperative bleeding

As shown in Table 3, younger age (< 60 years), tumors with larger size and irregular shape were significant risk factors for piecemeal resection. The piecemeal resection rate in tumors with large size and irregular shape was significantly higher than that in tumors with small size and regular shape. The piecemeal resection rate of tumors in younger patients (< 60 years) was higher than that in older patients (> 60 years). Other clinical characteristics, including sex, tumor location, growth pattern, tumor surface, histopathology and surgical approach, had no significant impact on piecemeal resection.

Table 2 The characteristics of the lesions treated by various methods of endoscopic resection

Variable	STER	EFTR	ESD
Tumor diameter, *n* (%)			
< 30 mm	23 (52.3)	10 (71.4)	23 (71.9)
≥ 30 mm	21 (47.7)	4 (28.6)	9 (28.1)
Location, *n* (%)			
Esophagocardia	19 (43.2)	0 (0.0)	6 (18.8)
Cardia	18 (40.9)	2 (14.3)	6 (18.8)
Gastrocardia	7 (15.9)	12 (85.7)	20 (62.4)
Shapes of lesion, *n* (%)			
Regular	16 (36.4)	11 (78.6)	20 (62.5)
Irregular	28 (63.6)	3 (21.4)	12 (37.5)
Growth pattern, *n* (%)			
Predominant extraluminal	6 (13.6)	11 (78.6)	0 (0.0)
Predominant intracavitary	38 (86.4)	3 (21.4)	32 (100.0)
Histopathology, *n* (%)			
Leiomyoma	42 (95.4)	4 (28.6)	25 (78.1)
GIST	1 (2.3)	10 (71.4)	7 (21.9)
Schwannoma	1 (2.3)	0 (0.00)	0 (0.0)
Operation time, median (range), min	50 (18–126)	55 (23–108)	36 (16–116)
***En bloc* resection, *n* (%)**	34 (77.3)	13 (92.9)	29 (90.6)
Intraoperative bleeding, *n* (%)			
Bleeding group	8 (18.2)	3 (21.4)	6 (18.8)
No bleeding group	36 (81.8)	11 (78.6)	26 (81.3)

STER: Submucosal tunneling endoscopic resection; EFTR: Endoscopic full-thickness resection; ESD: Endoscopic submucosal dissection; GIST: Gastrointestinal stromal tumors.

According to univariate and multivariate analyses, risk factors for a long operative time (≥ 60 min) included the shape and size of the tumor. As shown in Table 3, tumor size in the long operative time group (≥ 60 min) was significantly larger than that in the short operative time group (< 60 min). Moreover, the majority of tumors in the group with a long operative time (≥ 60 min) exhibited an irregular shape, while the tumors in the group with a short operative time (< 60 min) were prone to be regularly shaped.

Similarly, large tumor size and irregular shape were independent risk factors for intraoperative bleeding (Table 3). The occurrence of intraoperative bleeding had no significant correlation with age, sex, tumor location, surgical approach, growth pattern, tumor surface or histopathology.

Follow-up

The overall median follow-up period was 16.4 mo (range 6.0-26.0 mo), and all patients were free from stenosis of the EGJ, residual, local recurrence or distant metastasis during the follow-up period. None of the patients died during the follow-up period.

DISCUSSION

This is the first study discussing the predictors of difficult endoscopic resection, including various approaches of STER, EFTR and ESD, for SMTs originating from the MP layer at the EGJ. Our data showed that tumors with greater size and irregular shape were independent predictors of piecemeal resection, long operative time and intraoperative bleeding.

Table 3 Risk factors associated with piecemeal resection, long operative times (≥ 60 min) and bleeding during the procedure

Variable	*En bloc* resection and piecemeal resection		Operative times ≥ 60 min and < 60 min		Bleeding and no bleeding during the procedure	
	Univariate analysis, OR (95%CI), *P* value	Multivariate analysis, OR (95%CI), *P* value	Univariate analysis, OR (95%CI), *P* value	Multivariate analysis, OR (95%CI), *P* value	Univariate analysis, OR (95%CI), *P* value	Multivariate analysis, OR (95%CI), *P* value
Age, (yr)						
< 60	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
≥ 60	0.095 (0.012–0.763), 0.027	0.082 (0.007–0.929), 0.043	0.648 (0.260–1.614), 0.351	0.896 (0.172–4.677), 0.896	0.828 (0.276–2.485), 0.736	1.226 (0.234–6.419), 0.809
Sex, No.						
Female	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Male	1.171 (0.374–3.665), 0.786	1.807 (0.334–9.776), 0.492	1.111 (0.465–2.655), 0.813	1.089 (0.247–4.799), 0.911	0.760 (0.261–2.215), 0.615	1.101 (0.225–5.380), 0.906
Shape of lesion, No.						
Regular shape	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Irregular shape	19.933 (2.477–160.405), 0.005	18.004 (1.340–241.863), 0.029	9.491 (3.324–27.102), 0.000	6.863 (1.160–40.602), 0.034	12.054 (2.561–56.733), 0.002	19.020 (1.570–230.493), 0.021
Tumor diameter						
< 30 mm	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
≥ 30 mm	14.7270 (3.043–71.279), 0.001	7.346 (1.191–45.323), 0.032	33.150 (9.855–111.510), 0.000	47.330 (8.411–266.322), 0.000	21.316 (4.456–101.977), 0.000	20.631 (3.066–138.803), 0.002
Surgical approach						
STER	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
ESD	0.352 (0.088–1.401), 0.138	0.635 (0.088–4.572), 0.652	0.404 (0.144–1.134), 0.085	1.554 (0.217–11.120), 0.661	1.038 (0.321–3.354), 0.950	2.696 (0.372–19.537), 0.326
EFTR	0.262 (0.030–2.251), 0.222	1.596 (0.039–65.206), 0.805	1.083 (0.321–3.659), 0.897	7.233 (0.335–156.259), 0.207	1.227 (0.277–5.439), 0.787	37.935 (0.849–1694.936), 0.061
Location						
Esophagocardia	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Cardia	0.576 (0.141–2.349), 0.442	0.371 (0.059–2.342), 0.291	1.304 (0.422–4.027), 0.645	0.824 (0.132–5.134), 0.836	0.576 (0.141–2.349), 0.442	0.282 (0.045–1.772), 0.177
Gastrocardia	0.362 (0.091–1.443), 0.150	1.407 (0.115–17.261), 0.789	0.698 (0.239–2.044), 0.512	0.582 (0.051–6.572), 0.661	0.693 (0.203–2.368), 0.558	0.808 (0.055–11.832), 0.876
Growth pattern						
Predominant intracavitary	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Predominant extraluminal	0.288 (0.035–2.373), 0.248	0.272 (0.016–4.484), 0.362	1.932 (0.661–5.649), 0.229	5.522 (0.480–63.514), 0.170	0.516 (0.106–2.505), 0.411	0.086 (0.002–3.016), 0.176
Surface						
Smooth	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Reddish and erosive	1.800 (0.427–7.593), 0.424	0.707 (0.097–5.141), 0.732	1.783 (0.542–5.862), 0.341	1.315 (0.203–8.534), 0.774	2.188 (0.584–8.192), 0.245	2.059 (0.234–18.133), 0.515
Histopathology						
Leiomyoma	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
GIST/Schwannoma	0.248 (0.030–2.027), 0.193	1.513 (0.072–31.658), 0.790	0.849 (0.288–2.508), 0.767	0.632 (0.055–7.297), 0.713	0.763 (0.195–2.988), 0.698	2.037 (0.122–34.081), 0.621

STER: Submucosal tunneling endoscopic resection; EFTR: Endoscopic full-thickness resection; ESD: Endoscopic submucosal dissection; GIST: Gastrointestinal stromal tumors.

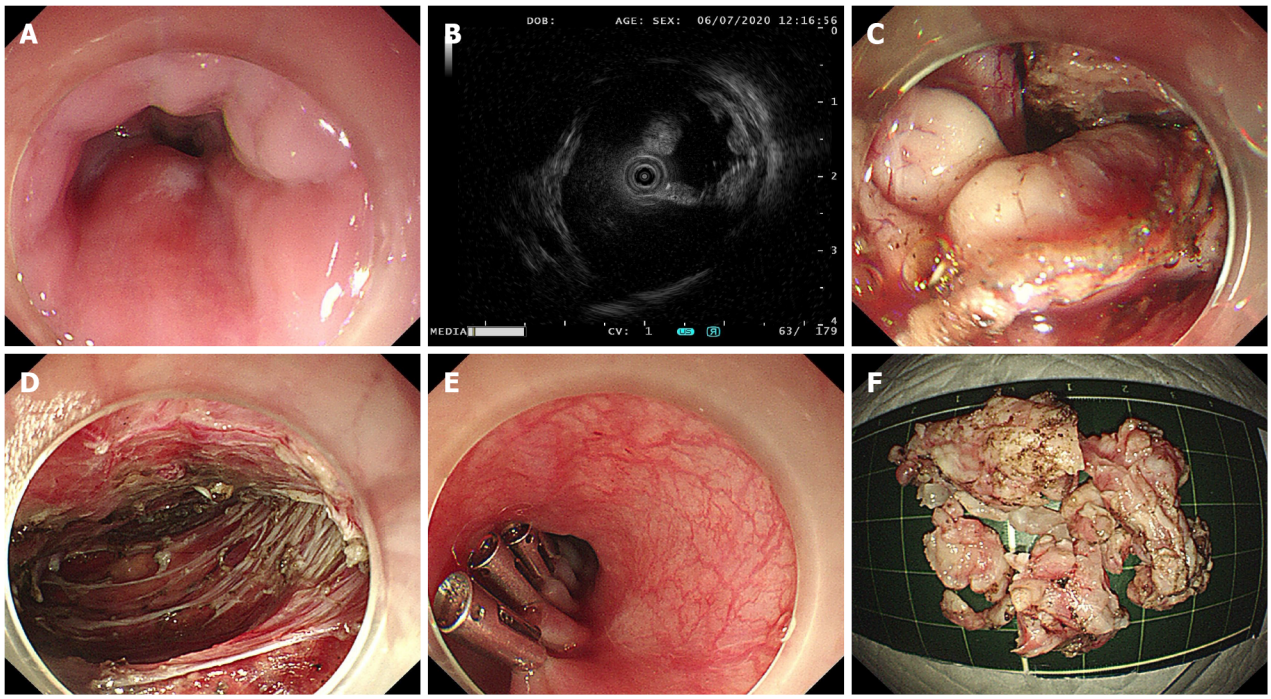

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Figure 1 The procedure of submucosal tunneling endoscopic resection. A: Endoscopic view of the tumor; B: Endoscopic ultrasonography view of the tumor; C: The submucosal tumor exposed using the submucosal tunnel technique; D: Endoscopic view of the submucosal tunnel after the tumor was removed; E: The mucosal entry closed by clips; F: The piecemeal resected tumor.

To date, endoscopic resection has been considered an effective, reliable and safe method to remove SMTs in the deep layer of the EGJ. The difficulty of endoscopic resection is mainly due to the long procedure time, failure of en bloc resection, or intraoperative and postoperative complications. As previously reported, there were no serious complications during the operation, such as major bleeding, perforation or death, indicating that all complications were controllable[9,11,12,16]. In the present study, 90 SMTs that originated from the MP layer at the EGJ were included. The location of SMTs mainly determines which approach of endoscopic resection is chosen to remove the lesion. STER, which was developed by Xu *et al*[14] for the resection of upper gastrointestinal SMTs originating from the MP layer, is the first choice for tumors located in the esophagocardia or cardia region since it has advantages in maintaining the integrity of gastroesophageal mucosa[14]. ESD is an alternative approach for the resection of gastrocardia SMTs for which the submucosal tunnel between the submucosal and MP layers is not always easy to create. EFTR was mainly selected for tumors with a predominant extraluminal growth pattern located in the gastrocardia region.

No major intraoperative or delayed bleeding or perforation occurred during the procedure. No sign of postoperative stenosis was found during the follow-up period. This may be related to the absence of circumferential lesions. There was a circular lesion in the middle of a patient's esophagus at our center. No stenosis occurred after STER resection, but muscularis defects were the reason for the diverticular appearance. Stenosis depends on the area of the mucosal defect after ESD and EFTR resection.

Our data revealed that although there was no significant difference, the operation time in the STER group and EFTR group was increased compared to that in the ESD group. This result may be attributed to the time required for creating the submucosal tunnel between the submucosal and MP layers to expose the lesion in the STER group and for occluding the gastric wall defect by the loop-and-clip closure technique. The overall complete resection rate and en bloc resection rate were 100% and 84.4%, respectively. There was no significant difference in the en bloc resection rate or intraoperative bleeding among the three groups.

We evaluated the predictors of en bloc resection, long operative time and intraoperative bleeding. Tumors with greater size and irregular shape and younger age (< 60 years) were significant risk factors for piecemeal resection. Tumors with greater size and irregular shape were the significant contributors to piecemeal resection. Chen *et al*[12] reported that STER provided a 90.6% en bloc resection rate for upper gastrointestinal SMTs[12]. However, in the present study, the en bloc resection rate in the STER

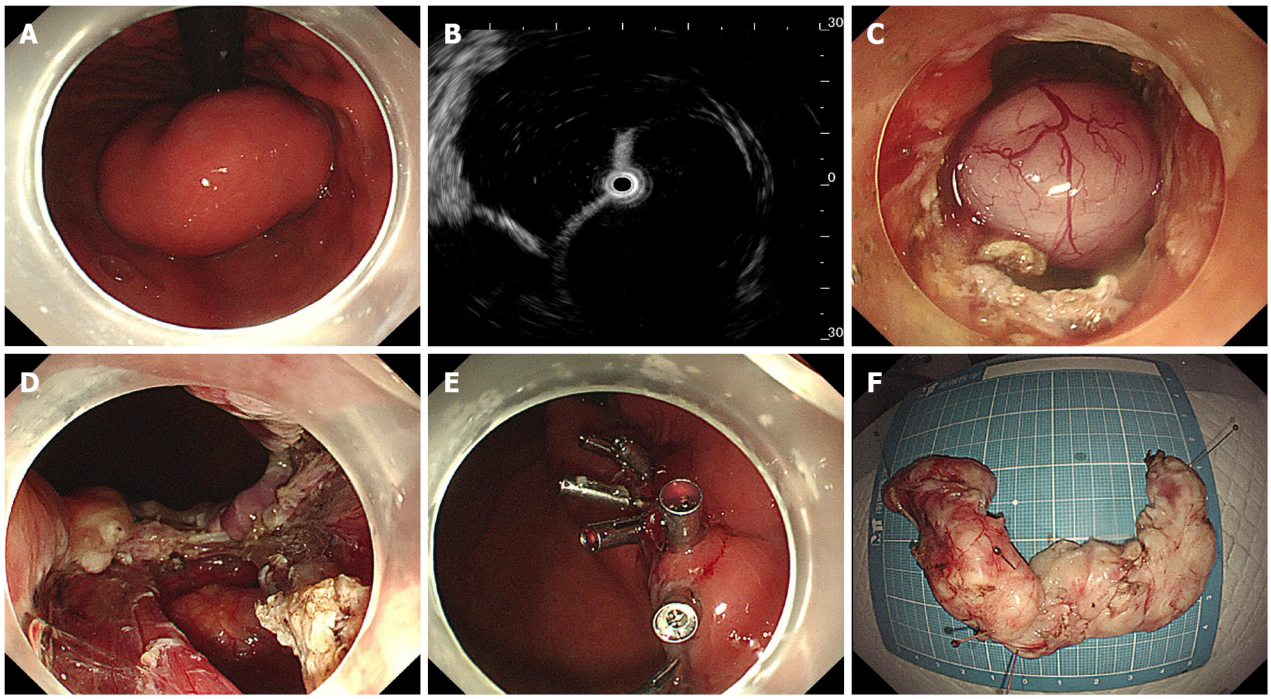

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Figure 2 Case illustration of endoscopic full-thickness resection. A: Endoscopic view of the tumor; B: Endoscopic ultrasonography view of the tumor; C: The submucosal tumor exposed by full-thickness resection; D: The wound surface after removal of the tumor; E: The gastric wall defect was closed with endo-clips; F: The horseshoe-shaped specimen.

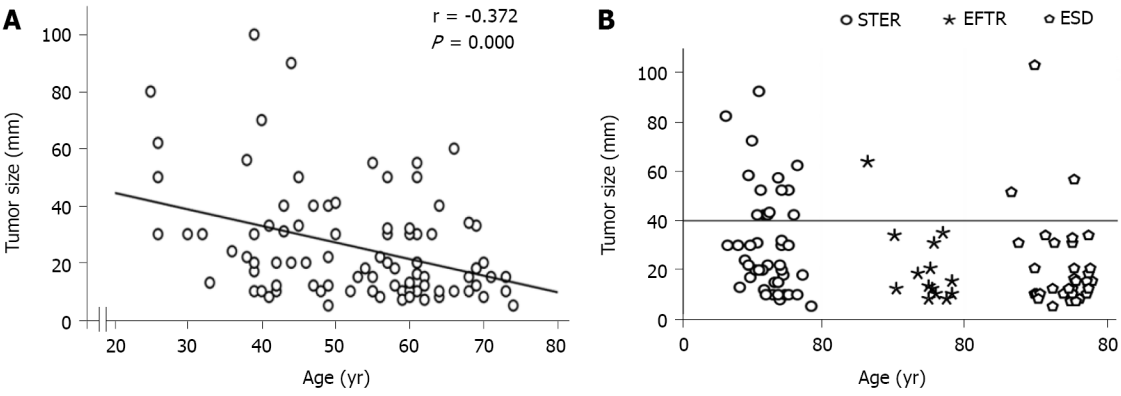

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Figure 3 Tumor size. A: There was a significant negative correlation between age and tumor size; B: Tumor size at different ages in the submucosal tunneling endoscopic resection group, endoscopic full-thickness resection group and endoscopic submucosal dissection group are shown. The circle dots above the horizontal line represent tumors larger than 4 cm. STER: Submucosal tunneling endoscopic resection; EFTR: Endoscopic full-thickness resection; ESD: Endoscopic submucosal dissection.

group was only 77.3%, which is lower than that in the ESD group or EFTR group. In Chen's study, the maximum size of the tumor was 5.0 cm in diameter since they considered that implementation of STER for SMTs with a long diameter ≤ 5.0 cm and a transverse diameter ≤ 3.5 cm could facilitate a high en bloc resection rate[6]. In the present study, the maximum tumor size was 9.0 cm, and tumors larger than 4.0 cm accounted for 31.8% of all tumors in the STER group. Furthermore, the percentage of irregularly shaped tumors in the STER group was 63.6%, which was significantly higher than that in the ESD and EFTR groups. Tumors with large size and irregular shape would be difficult for endoscopists to successfully achieve en bloc resection by STER because of limited space and poor exposure of operative filed in the created submucosal tunnel. In addition, although some large lesions were resected intactly, it was difficult to remove them from the submucosal tunnel due to the high risk of laceration of mucosa at the entrance of the tunnel[14,17]. Importantly, all lesions that received piecemeal resection in the present study were leiomyomas. Similar to previous studies, our data demonstrated that there was no residue or recurrence in lesions that received piecemeal resection during the follow-up period[12,18].

Interestingly, younger age (< 60 years) was one of the independent predictors of piecemeal resection. We considered that the unexpected result was mainly due to the significant negative correlation between tumor size and age.

Similarly, large size and irregular shape were independent predictors for procedures requiring a long operative time (≥ 60 min). A previous study suggested that the maximum size of the lesion removed by STER should be less than 35 mm in diameter, since the large tumor size and narrow lumen in the submucosal tunnel may result in a limited operating field[19]. However, there is a controversial opinion considering that the improvement and maturity of STER technology has made the resection of large tumors feasible. In the present study, the maximum size of the lesion removed successfully by STER was 90 mm, with no recurrence during follow-up. Furthermore, for resection of tumors at the EGJ, it is crucial to inject a small dose of indigo carmine into the submucosa around the tumor location to aid in delineating the submucosal tunnel, and subsequently decreasing the procedure time. The risk of aspiration pneumonia, deep venous thrombosis, and cardiorespiratory distress may increase because of the long procedure time. Thus, it is necessary to fully evaluate the size and shape of the tumor by EUS and radiological examination before the procedure. Tumors with greater size and irregular shape were also independent predictors for intraoperative bleeding. For irregularly shaped large tumors, extra care should be paid to fully expose and pretreat the blood vessels to prevent bleeding.

The current study has several limitations. First, this study is a single-center retrospective study with a relatively small sample size, which may result in the variation between the approach of endoscopic resection and tumor size. Second, the procedures of endoscopic resection were not performed by the same endoscopist. A short follow-up period (range 6–26 mo) is the third limitation. Thus, a prospective, large-scale, randomized controlled study with a long-term follow-up period is necessary in the future to validate the observed results.

CONCLUSION

Endoscopic resection is effective and safe for SMTs in the MP layer at the EGJ. Tumors with large size and irregular shape were independent predictors for piecemeal resection, long operation time and intraoperative bleeding.

ARTICLE HIGHLIGHTS

Research background

Submucosal tumors (SMTs) from the esophagogastric junction (EGJ) are much more difficult to resect because of the sharp angle and narrow lumen of the EGJ. SMTs originating from the muscularis propria (MP) in the EGJ, especially those that grow extraluminally and adhere closely to the serosa, make endoscopic resection even more difficult.

Research motivation

Endoscopic resection approaches, including endoscopic submucosal dissection, submucosal tunneling endoscopic resection and endoscopic full-thickness resection, have been widely used for the treatment of SMTs from the MP layer at the EGJ. Only limited studies have demonstrated the predictors associated with the difficulty of endoscopic resection.

Research objectives

The aim of this study was to investigate the predictors of difficult endoscopic resection for SMTs from the MP layer at the EGJ.

Research methods

A total of 90 patients with SMTs from the MP layer at the EGJ were included in the present study. Difficulty of endoscopic resection is measured by a long procedure time, failure of en bloc resection and intraoperative bleeding. Clinicopathological, endoscopic and follow-up data were collected and analyzed. Statistical analysis of independent risks for piecemeal resection, long operative time, and intraoperative bleeding were assessed using univariate and multivariate analyses.

Research results

No adverse events that required therapeutic intervention occurred during or after the procedures. The surgical approach had no significant correlation with en bloc resection, long operative time or intraoperative bleeding. Large tumor size (≥ 30 mm) and irregular tumor shape were independent predictors for piecemeal resection (OR: 7.346, P = 0.032 and OR: 18.004, P = 0.029, respectively), long operative time (≥ 60 min) (OR: 47.330, P =0.000 and OR: 6.863, P = 0.034, respectively) and intraoperative bleeding (OR:

20.631, $P = 0.002$ and OR: 19.020, $P = 0.021$, respectively).

Research conclusions

Endoscopic resection is an effective treatment for SMTs in the MP layer at the EGJ. Tumors with large size and irregular shape were independent predictors for difficult endoscopic resection.

Research perspectives

The current study may provide a useful reference for operators during endoscopic resection of SMTs originating from the MP layer at the EGJ in the future.

FOOTNOTES

Author contributions: Cao J and Xu MD designed the study; Wang YP, Chu Y, Duan BS, Lian JJ and Zhang HB collected the data; Zhang L performed the pathological diagnosis; Wang YP, Shen JX, Liu WM and Xu H analyzed and interpreted the data; Wang YP drafted the manuscript; Xu H and Cao J were responsible for revising the manuscript for important intellectual content; All authors read and approved the final version.

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ORIGINAL ARTICLE

Retrospective Study

Liver transplantation with simultaneous splenectomy increases risk of cancer development and mortality in hepatocellular carcinoma patients

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Abstract

BACKGROUND

Splenectomy has previously been found to increase the risk of cancer development, including lung, non-melanoma skin cancer, leukemia, lymphoma, Hodgkin's lymphoma, and ovarian cancer. The risk of cancer development in liver transplantation (LT) with simultaneous splenectomy remains unclear.

AIM

To compare hepatocellular carcinoma (HCC) recurrence and *de novo* malignancy between patients undergoing LT with and without simultaneous splenectomy.

METHODS

We retrospectively analyzed the outcomes of 120 patients with HCC within the University of California San Francisco criteria who received LT with (n = 35) and without (n = 85) simultaneous splenectomy in the Tri-Service General Hospital. Univariate and multivariate Cox regression analyses for cancer-free survival and mortality were established. The comparison of the group survival status and group cancer-free status was done by generating Kaplan–Meier survival curves and log-rank tests.

RESULTS

The splenectomy group had more hepatitis C virus infection, lower platelet count, higher -fetoprotein level, and longer operating time. Splenectomy and age were both positive independent factors for prediction of cancer development [hazard ratio (HR): 2.560 and 1.057, respectively, $P < 0.05$]. Splenectomy and hypertension

were positive independent factors for prediction of mortality. (HR: 2.791 and 2.813 respectively, $P < 0.05$). The splenectomy group had a significantly worse cancer-free survival (CFS) and overall survival (OS) curve compared to the non-splenectomy group (5-year CFS rates: 53.4% *vs* 76.5%, $P = 0.003$; 5-year OS rate: 68.1 *vs* 89.3, $P = 0.002$).

CONCLUSION

Our study suggests that simultaneous splenectomy should be avoided as much as possible in HCC patients who have undergone LT.

Key Words: Hepatocellular carcinoma; Liver transplantation; Splenectomy; *De novo* malignancy; Age; Hypertension

Core tip: This retrospective study compared the outcomes of hepatocellular carcinoma (HCC) recurrence and *de novo* malignancy development between HCC patients who underwent liver transplantation (LT) with and without simultaneous splenectomy. Splenectomy leads to a significantly higher risk of cancer development after LT and is a significant risk factor of mortality. Simultaneous splenectomy should be avoided as much as possible.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy in men and the ninth most common in women worldwide[1]. Liver transplantation (LT) is one of the potential curative therapies, according to the Barcelona Clinic Liver Cancer staging classification and treatment schedule[2]. The incidence of recurrent HCC after LT was found to be 7%–25%[3]. Various pre-, intra- and postoperative factors influence the outcomes and disease-free survival (DFS) in patients with HCC after LT[4,5].

The indications for splenectomy are generally divided into traumatic and nontraumatic reasons[6]. Two early studies found an increased risk of cancer after splenectomy, especially in patients with nontraumatic splenectomy[6,7]. The most common post-splenectomy malignancies include lung, nonmelanoma skin cancer, leukemia, lymphoma, Hodgkin's lymphoma, and ovarian cancer[6,7]. A nationwide population-based cohort study published in 2015 revealed that patients undergoing splenectomy were 1.94 times more likely to develop cancer than patients not undergoing splenectomy [8].

There are a number of indications for simultaneous splenectomy in LT recipients, including the prevention of small-for-size syndrome, ABO-incompatible LT (ABO-iLT), or the prevention of thrombocytopenia during therapy for hepatitis C virus (HCV) after LT[9-12]. The purpose of this study was to compare the outcomes of HCC recurrence and *de novo* malignancy development between HCC patients who underwent LT with and without simultaneous splenectomy.

MATERIALS AND METHODS

Patients

Between May 2009 and August 2019, 179 patients with HCC underwent LT and received follow-up management. Among them, 53 patients received simultaneous splenectomy during the LT operation. All patients with HCC met the University of California San Francisco (UCSF) criteria for radiological examinations (a single tumor of ≤ 6.5 cm; a maximum of three tumors with none of them > 4.5 cm; and a cumulative size ≤ 8 cm). The records of these patients were retrospectively reviewed. Fifty-nine patients who had no residual HCCs or who had HCCs without fitting the UCSF criteria on pathological examinations were excluded. Thirty-five of the 120 LT recipients (29.2%) underwent simultaneous splenectomy and were assigned to the splenectomy group. The remaining LT recipients (85/120, 70.8%) did not undergo simultaneous splenectomy and were, thus, assigned to the nonsplenectomy group. The

indications for simultaneous splenectomy in our institution include modulation of portal inflow, thrombocytopenia in recipients with HCV, or ABO-iLT recipients. The reasons for simultaneous splenectomy in the 53 recipients were modulation (22/53, 41.5%), thrombocytopenia in recipients with HCV (25/53, 47.2%), and ABO-iLT (6/53, 11.3%). We recorded the recipient characteristics, including age, sex, underlying liver disease, signs of portal hypertension (ascites, hepatic encephalopathy, bleeding varices), preoperative serum biochemistry results (levels of total bilirubin, creatinine, ammonia, albumin, and glucose), international normalized ratio, blood platelet count, Model for End-stage Liver Disease score (MELD score), α-fetoprotein (AFP), operative factors [surgery types in deceased donor LT including split liver, living donor LT, graft weight, graft-to-recipient weight ratio (GRWR), blood loss, and operating time], and pathological results (tumor size, tumor number, tumor necrosis, and lymphovascular invasion). Neutrophil–lymphocyte ratio was calculated by dividing neutrophil count by lymphocyte count. Platelet–lymphocyte ratio was calculated by dividing platelet count by lymphocyte count.

Post-LT follow-up

Postsurgical follow-up evaluations included monitoring of AFP levels and performing abdominal sonography, computed tomography (CT), or magnetic resonance imaging every 3 mo and chest radiography yearly. Brain CT was performed in patients with worsening headaches or neurological symptoms, and whole-body bone scans were performed in patients with severe bone pain. Positron emission tomography was performed if the AFP levels were elevated, even if the other above-mentioned examinations showed normal findings. Annual chest radiography and stool examination for occult blood were performed to screen for *de novo* lung cancer and gastrointestinal tract malignancy, respectively. Chest CT or lung biopsy was performed if lung nodules were found by chest radiography. Esophagogastroduodenoscopy and colonoscopy were performed if occult blood was detected in the stool. In female participants, annual breast sonography was performed to monitor for *de novo* breast cancer. The time and site of tumor recurrence and patient death were established through follow-up studies. The present study was approved by the institutional review board of Tri-Service General Hospital (IRB No. 2-108-05-127), and informed consent was not required according to the guidance of the Institutional Review Board because this was a retrospective study.

Statistical analysis

Continuous variables were represented as a median with the corresponding range and comparisons between subgroups were performed using the Mann–Whitney *U* test. Categorical variables were expressed as the number (percent) and assessed by Fisher's exact test following Bonferroni correction for comparisons between subgroups. To determine the variables associated with recurrence or death, univariate and multivariate Cox proportional hazard models were established. All factors with $P < 0.1$ in the univariate analysis were entered into a reverse multivariate hazard model. The duration of cancer-free survival (CFS) was calculated from the date of surgery to the date of HCC recurrence, HCC distant metastases, secondary malignancy, or the date of death for patients who died before the end of follow-up. The overall survival (OS) duration was defined as the period between the date of surgery and the date of death. Kaplan–Meier survival curves were generated, and a log-rank test was performed to compare the group survival status. All two-sided statistical analyses were performed using SPSS version 15.0 (SPSS, Chicago, IL, United States). Significance was defined as $P < 0.05$.

RESULTS

Patients' characteristics

A total of 120 HCC patients (89 men and 31 women) with a median age of 57 (37–69) years were included in the analyses. Eighty-five patients did not undergo simultaneous splenectomy, whereas 35 (29.2%) patients did. The average follow-up duration was 55 mo (range 0–128 mo). Patients' characteristics are summarized in Table 1. Age, gender, body mass index, signs of portal hypertension (ascites, hepatic encephalopathy, and varices bleeding), comorbidities (hypertension and diabetes mellitus), preoperative serum tests (white blood count, total bilirubin, creatinine, ammonia, albumin, glucose, INR, and MELD scores), surgical factors (surgical type, graft type, GRWR, and bleeding), and pathology (tumor size, tumor number, tumor necrosis, and lymphovascular invasion) were not significantly different between these two groups (all $P > 0.05$), indicating that the groups has a similar baseline. Nevertheless, patients who underwent simultaneous splenectomy had a lower hepatitis B virus (HBV) infection rate (40% *vs* 77.6%, $P < 0.001$), higher HCV infection rate (65.7% *vs* 25.9%, $P < 0.001$), lower platelet count ($P < 0.003$), higher AFP level ($P = 0.012$), and longer operating time ($P = 0.001$) than patients who did not undergo simultaneous splenectomy.

Outcomes

Upon completion of the analysis, the splenectomy group was found to have a higher proportion of HCC

Table 1 Patients' characteristics

	Nonsplenectomy (*n* = 85)	Splenectomy (*n* = 35)	*P* value
Age (yr), median (range)	57 (37-69)	57 (37-69)	0.667
Gender, *n* (%)			0.107
Male	67 (78.8)	22 (62.9)	
Female	18 (21.2)	13 (37.1)	
BMI, median (range)	24.2 (17.4-43.8)	24.6 (18.4-43.3)	0.707
Underlying liver disease, *n* (%)			
HBV	66 (77.6)	14 (40.0)	< 0.001[a]
HCV	22 (25.9)	23 (65.7)	< 0.001[a]
Alcoholism	13 (15.3)	4 (11.4)	0.775
Signs of portal hypertension, *n* (%)			
Ascites	43 (50.6)	19 (54.3)	0.841
Hepatic encephalopathy	35 (41.2)	13 (37.1)	0.838
Varices bleeding	19 (22.4)	12 (34.3)	0.251
Comorbidity, *n* (%)			
Hypertension	20 (23.5)	9 (25.7)	0.817
Diabetes mellitus	40 (47.1)	11 (31.4)	0.155
Preoperative serum tests, median (range)			
White blood count (/uL)	4600 (1480-11200)	3500 (1350-12200)	0.120
Platelet count (/uL)	80000 (26000-279000)	64000 (27000-155000)	0.003[a]
Neutrophil–lymphocyte ratio	2.44 (0.51-24.18)	3.2 (0.91-21.33)	0.273
Platelet–lymphocyte ratio	78.49 (36.80-284.01)	71.19 (28.53-188.08)	0.386
Total bilirubin (mg/dL)	1.4 (0-38.9)	1.6 (0.4-57.1)	0.984
Creatinine (mg/dL)	0.9 (0.4-10.1)	0.8 (0.5-1.3)	0.578
Ammonia (ug/dL)	99 (0-337)	99 (30-560)	0.737
Albumin (g/dL)	3.2 (1.2-5.3)	3.3 (2.2-5.1)	0.922
Glucose (mg/dL)	115 (0-457)	118 (82-312)	0.956
INR	1.1 (0.9-2.7)	1.2 (0.9-2.1)	0.819
MELD scores	11 (6-32)	11 (6-30)	0.494
AFP (ng/mL)	7.0 (0.5-1190.0)	14.0 (2.0-2170.0)	0.012[a]
Surgical factors			
Surgical type, *n* (%)			0.276
DDLT	26 (30.6)	6 (17.1)	
LDLT	56 (65.9)	28 (80)	
SLT	3 (3.5)	1 (2.9)	
Graft type, *n* (%)			0.120
Whole graft	27 (31.8)	6 (17.1)	
Partial graft	58 (68.2)	29 (82.9)	
GRWR < 0.8	12 (14.1)	6 (17.1)	0.673
Blood loss (mL), median (range)	1600 (200-14400)	1350 (260-11000)	0.519
Operative time (minutes), median (range)	552 (360-1035)	630 (420-870)	0.001[a]
Pathology			

Tumor size (cm)	2.2 (0-6.5)	2.5 (0-6.2)	0.140
Tumor number, *n* (%)			0.404
0 or 1	58 (68.2)	21 (60.0)	
2 or 3	27(31.8)	14 (40.0)	
Tumor necrosis, *n* (%)	49 (58.3)	20 (57.1)	1.000
Lymphovascular invasion, *n* (%)	6 (7.1)	5 (14.3)	0.297
Outcomes			
Hospital stays, median (range) (d)	21 (0-85)	18 (5-116)	0.810
HCC Recurrence, *n* (%)	16 (18.8)	15 (42.9)	0.011[a]
Secondary cancer, *n* (%)	5 (6.4)	0	0.322
Mortality, *n* (%)	9 (10.6)	11 (31.4)	0.013[a]

[a]$P < 0.05$.

BMI: Body mass index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; GRWR: Graft-to-recipient weight ratio; INR: International normalized ratio; MELD: The Model for End-stage Liver Disease; AFP: α-fetoprotein; LT: Liver transplantation; DDLT: Deceased donor liver transplantation; LDLT: Living donor liver transplantation; SLT: Split liver transplantation.

recurrence (42.9% *vs* 18.8%, $P = 0.011$) and mortality (31.4% *vs* 10.6%, $P = 0.013$) compared with that in the nonsplenectomy group (Table 1). Five of the 85 patients (6.4%) in the nonsplenectomy group had *de novo* cancer development. Of five patients with *de novo* cancer development, one each had lung cancer, urothelial carcinoma, squamous cell carcinoma of the tongue, breast cancer, and adenocarcinoma of the esophagus. In the splenectomy group, no *de novo* cancer development was found. However, the length of hospital stay was not significantly different between these two groups ($P > 0.05$, Table 1).

Subsequently, the Cox regression model was used to investigate cancer development and mortality (Tables 2 and 3). In the univariate Cox regression analysis, splenectomy, age and HBV were significantly associated with cancer development (all $P < 0.05$, Table 2), while splenectomy, HBV, HCV and hypertension were associated with mortality (all $P < 0.05$, Table 3). In the multivariate Cox regression analysis, splenectomy [hazard ratio (HR) = 2.560; 95% confidence interval (CI): 1.198–5.471, $P = 0.015$] and age (HR = 1.057, 95%CI: 1.001–1.117, $P = 0.048$) were positive independent factors for prediction of cancer development (Table 2). Splenectomy (HR = 2.791, 95%CI: 1.081–7.206, $P = 0.034$), hypertension (HR = 2.813, 95%CI: 1.111–7.123, $P = 0.029$) and HBV (HR = 4.077, 95%CI: 1.001–16.615, $P = 0.050$) were positive independent factors for prediction of mortality (Table 3). In addition, Kaplan–Meier curve analyses revealed that splenectomy could identify subjects at higher risk for cancer development or mortality (all $P < 0.05$, Figure 1). The cumulative CFS (5-year CFS rates: 76.5% in nonsplenectomy group; 53.4% in splenectomy group) and cumulative OS rates (5-year OS rate: 89.3% in the nonsplenectomy group; 68.1% in the splenectomy group) differed significantly between the two groups.

DISCUSSION

The present study analyzed the outcomes of patients with HCC within the UCSF criteria who underwent LT with and without simultaneous splenectomy. In the past, simultaneous splenectomy was performed in cases of ABO-incompatible living donor LT (ABO-iLDLT) because of immunological concerns, or in patients with HCV for prevention of thrombocytopenia. In recent years, simultaneous splenectomy is performed less due to the advancement of the desensitization protocol in ABO-iLT and the development of direct-acting antiviral agents as anti-HCV therapy. However, inflow modulation was still necessary in many LDLT patients. The topic of simultaneous splenectomy still deserves attention. In our cohort, simultaneous splenectomy was independently correlated with cancer development and OS, suggesting that simultaneous splenectomy should be a factor for concern in patients with HCC who undergo LT.

The increased cancer risk associated with splenectomy was reported in previous clinical studies and in a nationwide Taiwanese population-based cohort study[6-8]. In the Taiwanese study, the HR was 2.06 in the splenectomy cohort[8]. Cancer risk was higher in cases of nontraumatic splenectomy than in traumatic splenectomy, especially in splenectomy cases caused by hematological conditions[6,8]. Splenectomy significantly increases the risk of all malignant neoplasms, especially those of the lung, nonmelanoma skin cancer, leukemia, lymphoma, and Hodgkin's lymphoma[6]. A study published by Linet *et al*[7] revealed a higher incidence of lung and ovarian cancers in patients who underwent splenectomy[7]. Buccal, esophagus, liver, colon, pancreas, lung, prostate, and multiple hematological malignancies were observed in a cohort of cancer-free American veterans after splenectomy[13]. The

Table 2 Cox proportional hazard model for cancer-free survival

	Univariate		Multivariate	
	Hazard ratio (95%CI)	*P* value	Hazard ratio (95%CI)	*P* value
Age	1.055 (1.001, 1.112)	0.047[a]	1.057 (1.001, 1.117)	0.048[a]
Gender/male	1.346 (0.614, 2.950)	0.459	-	
BMI	0.937 (0.850, 1.033)	0.191	-	
HBV	2.070 (1.005, 4.263)	0.048[a]	1.371 (0.632, 2.978)	0.425
HCV	0.687 (0.332-1.423)	0.313	-	
Alcoholism	1.751 (0.532-5.769)	0.357	-	
Diabetes mellitus	1.062 (0.523, 2.157)	0.868	-	
Hypertension	1.704 (0.777, 3.736)	0.183	-	
Tumor size	1.057 (0.817, 1.368)	0.672	-	
Tumor number (2/3 *vs* 0/1)	1.577 (0.777, 3.199)	0.207	-	
Lymphovascular invasion	1.722 (0.600, 4.945)	0.312	-	
Splenectomy	2.754 (1.359, 5.581)	0.005[a]	2.560 (1.198, 5.471)	0.015[a]
PLT	1.000 (1.000, 1.000)	0.579	-	
AFP	1.001 (1.000, 1.002)	0.070	-	

[a]$P < 0.05$.

CI: Confidence interval; BMI: Body mass index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; GRWR: Graft-to-recipient weight ratio; INR: International normalized ratio; MELD: The Model for End-stage Liver Disease; AFP: α-fetoprotein.

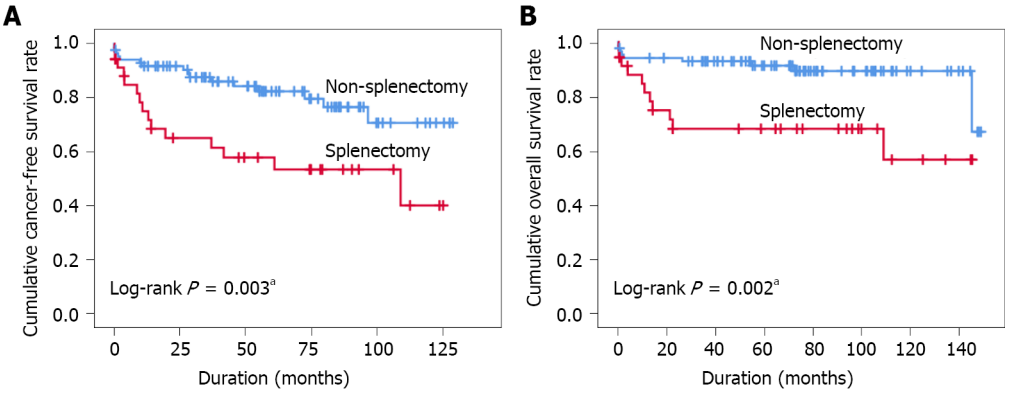

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Figure 1 Kaplan–Meier curves. A: Cancer-free survival in 120 patients. The rates were significantly different between the splenectomy and nonsplenectomy groups ($P = 0.003$); B: Overall survival in 120 patients. The rates were significantly different between the splenectomy and non-splenectomy groups ($P = 0.002$). [a]$P < 0.05$.

previously mentioned Taiwanese study found that the most common cancers after a splenectomy were those of the gastrointestinal tract, head and neck and liver, as well as hematological malignancies[8]. The relationship between splenectomy and cancer has also been proven in animal experiments[14-17]. An early experiment inferred that the ability of the spleen to protect a rat from cancer is due to the preservation of immunological surveillance and not due to the DNA repair mechanism[14]. Splenectomy enhances metastatic ability through the immunological tolerance of regulatory T cells[15]. Splenectomy was also found to enhance tumor growth and peritoneal seeding in an orthotopic syngeneic murine pancreatic cancer mouse model, which is explained by its immunological effects[16, 17].

To the best of our knowledge, there are no studies discussing the oncological effects of simultaneous splenectomy in LT. Therefore, we reviewed the oncological effects of simultaneous splenectomy and hepatectomy in patients with HCC to gain a greater understanding of this relationship. Some studies have found that the results of hepatectomy with simultaneous splenectomy in HCC patients with

Table 3 Cox proportional hazard model for mortality

	Univariate		Multivariate	
	Hazard ratio (95%CI)	*P* value	Hazard ratio (95%CI)	*P* value
Age	1.063 (0.994, 1.136)	0.075	-	
Gender/male	1.424 (0.540, 3.757)	0.475	-	
BMI	0.942 (0.834, 1.063)	0.333	-	
HBV	4.386 (1.719, 11.193)	0.002[a]	4.077 (1.001, 16.615)	0.050
HCV	2.853 (1.145, 7.114)	0.024[a]	0.661 (0.166, 2.640)	0.558
Alcoholism	0.696 (0.161, 3.018)	0.629	-	
Diabetes mellitus	1.640 (0.679, 3.958)	0.271	-	
Hypertension	2.872 (1.142, 7.221)	0.025[a]	2.813 (1.111, 7.123)	0.029[a]
Tumor size	0.944 (0.679, 1.312)	0.732	-	
Tumor number (2-3 *vs* 0-1)	1.911 (0.795, 4.596)	0.148	-	
Lymphovascular invasion	2.054 (0.597, 7.062)	0.254	-	
Splenectomy	3.656 (1.510, 8.848)	0.004[a]	2.791 (1.081, 7.206)	0.034[a]
PLT	1.000 (1.000, 1.000)	0.409	-	
AFP	1.001 (1.000, 1.002)	0.081	-	

[a]$P < 0.05$.

CI: Confidence interval; BMI: Body mass index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; GRWR: Graft-to-recipient weight ratio; INR: International normalized ratio; MELD: The Model for End-stage Liver Disease; AFP: α-fetoprotein.

hypersplenism were positive. Chen *et al*[18] showed that the 5-year DFS rate was significantly higher in patients with HCC who underwent hepatectomy and splenectomy than in those who underwent hepatectomy alone (37% *vs* 27.3%; $P = 0.003$)[18]. Zhang *et al*[19-21] also found that HCC patients with hypersplenism who underwent hepatectomy and simultaneous splenectomy exhibited significantly better DFS and OS rates than those who underwent hepatectomy alone[19-21]. It seems, therefore, that splenectomy benefits surgical management in selected cases of HCC. The role of splenectomy in improving oncological outcomes has also been reported in animal studies[22,23]. Spleen cells release tumor-enhancing factors that promote tumor growth activity *in vivo*[22], and the spleen may also evoke a complex vascular response[23], which suggests that splenectomy could inhibit tumor growth. Besides inhibiting tumor growth, simultaneous splenectomy has been reported to decrease tumor metastasis [24]. However, some papers have put forth opposing views, suggesting that simultaneous splenectomy and hepatectomy did not benefit OS and DFS rates, in comparison to hepatectomy alone[25,26]. The oncological benefits of simultaneous splenectomy in patients with liver cirrhosis are, therefore, still controversial.

The relationship between cancer risk after splenectomy and LT gained little attention in previous clinical studies. Ito *et al*[27] pointed out that simultaneous splenectomy was associated with reoperation due to postoperative hemorrhage, prolonged operating time, increased intraoperative blood loss, and increased incidence of lethal infectious disease[27]. A meta-analysis found that simultaneous splenectomy during LT was associated with prolonged operating time, increased intraoperative blood loss, increased need for intraoperative blood transfusions, and increased incidence of postoperative hemorrhage, thrombosis, infection and mortality[28]. Another study revealed that splenectomy significantly increases the rates of postoperative splenic vein thrombosis and cytomegalovirus infection in LDLT[29]. These three studies suggest that splenectomy has a number of short-term risks and should be performed only in carefully selected patients. Our study shed light on the increased long-term cancer risk after LT, which was associated with simultaneous splenectomy. In brief, LT with simultaneous splenectomy should be avoided as much as possible, whether the risks lie in the short or long term.

The role of age in the oncological outcomes of HCC after LT is still uncertain. There are reports demonstrating that younger patients tend to have more aggressive tumors and a higher risk of recurrence than older patients[30,31]. In the present study, old age was associated with poor outcomes in patients with HCC after LT. A possible explanation is that older patients have been exposed to HBV and HCV infections for a longer period.

Hypertension is the most common cardiovascular complication to occur after LT, with a prevalence reported to be between 40%[32] and 85%[33]. The mechanisms are multifactorial, and hypertension is one of the main risk factors leading to post-transplant mortality[34]. An early diagnosis of hypertension,

as well as implementation of lifestyle changes and antihypertensive medications is essential for increasing the long-term survival of LT patients[35].

The limitations of this study were the patient selection methods and the small sample size. Because of surgical indications for simultaneous splenectomy, more HCV patients underwent simultaneous splenectomy. There may have been biases in terms of patient selection. However, Supplementary Table 1 shows that the HCV subgroup analysis was like that of the whole group. Nevertheless, this study only analyzed patients with HCC within the UCSF criteria and that were confirmed by both radiological and postoperative pathological examinations. The study did not analyze patients who primarily had HCCs outside the UCSF criteria and had successfully treated HCCs to fit the USCF criteria upon radiological examination on the day of LT. The reason for this was that the percentage of tumor necrosis would make it difficult for pathological examination to accurately determine whether patients complied with the UCSF criteria or not. Besides, splenic artery ligation is often considered, instead of splenectomy, for achieving the goal of modulation of portal inflow[36]. The effects of splenic artery ligation, compared to splenectomy, were not discussed in this study.

CONCLUSION

Our study revealed that the patients with HCC who met the UCSF criteria and who underwent LT and simultaneous splenectomy had poorer DFS and OS than patients who did not undergo simultaneous splenectomy. Therefore, simultaneous splenectomy should be avoided in patients with HCC undergoing LT.

ARTICLE HIGHLIGHTS

Research background

Patients undergoing splenectomy were more likely to develop cancer than patients not undergoing splenectomy. There are a number of indications for simultaneous splenectomy in liver transplantation (LT) recipients.

Research motivation

The hypothesis is that simultaneous splenectomy has bad outcomes on cancer and mortality in LT recipients.

Research objectives

The purpose of this study was to compare the outcomes of hepatocellular carcinoma (HCC) recurrence and *de novo* malignancy development between HCC patients who underwent LT with and without simultaneous splenectomy.

Research methods

Of 120 patients with HCC who received LT with (n = 35) and without (n = 85) simultaneous splenectomy were analyzed by Cox regression analysis, Kaplan–Meier survival curves and log-rank tests.

Research results

Splenectomy and age were both positive independent factors for prediction of cancer development. Splenectomy and hypertension were positive independent factors for prediction of mortality. The splenectomy group had a significantly worse cancer-free survival and overall survival curve compared to the nonsplenectomy group.

Research conclusions

Simultaneous splenectomy should be avoided in patients with HCC undergoing LT.

Research perspectives

Splenic artery ligation is often considered, instead of splenectomy, for achieving the goal of modulation of portal inflow. The direction of the future research is the comparison on cancer outcome between splenectomy and splenic artery ligation.

FOOTNOTES

Author contributions: Fan HL participated in data analysis and the writing of the paper; Hsieh CB participated in research design; Kuo SM participated in research design; Chen TW participated in data interpretation and revision of the paper

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ORIGINAL ARTICLE

Retrospective Study

Development of an innovative nomogram of risk factors to predict postoperative recurrence of gastrointestinal stromal tumors

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Abstract

BACKGROUND

There are many staging systems for gastrointestinal stromal tumors (GISTs), and the risk indicators selected are also different; thus, it is not possible to quantify the risk of recurrence among individual patients.

AIM

To develop and internally validate a model to identify the risk factors for GIST recurrence after surgery.

METHODS

The least absolute shrinkage and selection operator (LASSO) regression model was performed to identify the optimum clinical features for the GIST recurrence risk model. Multivariable logistic regression analysis was used to develop a prediction model that incorporated the possible factors selected by the LASSO regression model. The index of concordance (C-index), calibration curve, receiver operating characteristic curve (ROC), and decision curve analysis were used to assess the discrimination, calibration, and clinical usefulness of the predictive model. Internal validation of the clinical predictive capability was also evaluated by bootstrapping validation.

RESULTS

The nomogram included tumor site, lesion size, mitotic rate/50 high power fields, Ki-67 index, intracranial necrosis, and age as predictors. The model presented perfect discrimination with a reliable C-index of 0.836 (95%CI: 0.712-0.960), and a high C-index value of 0.714 was also confirmed by interval validation. The area under the curve value of this prediction nomogram was 0.704, and the ROC result indicated good predictive value. Decision curve analysis showed that the predicting recurrence nomogram was clinically feasible when the recurrence rate exceeded 5% after surgery.

CONCLUSION

This recurrence nomogram combines tumor site, lesion size, mitotic rate, Ki-67 index, intracranial necrosis, and age and can easily predict patient prognosis.

Key Words: Gastrointestinal stromal tumors; Recurrence; Clinicopathological; Predictors; Nomogram

Core Tip: This is a retrospective study to explore the risk factors for gastrointestinal stromal tumors recurrence after surgery. The nomogram included tumor site, lesion size, mitotic rate/50 high power fields, Ki-67 index, intracranial necrosis, and age as predictors. The model presented perfect discrimination with a reliable index of concordance (C-index) of 0.836 (95%CI: 0.712-0.960), and a high C-index value of 0.714 was also confirmed by interval validation. The area under the curve value of this prediction nomogram was 0.704, indicating good predictive value. Decision curve analysis showed that the predicting recurrence nomogram was clinically feasible.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) originate from gastrointestinal Cajal cells and are the most common mesenchymal tumors in the gastrointestinal tract, accounting for 1% to 3% of gastrointestinal malignancies[1]. GISTs can occur anywhere in the digestive tract, most commonly in the stomach (50%-60%) and the small intestine (30%-50%)[2]. Surgical resection is the main treatment for GIST. However, even with complete surgical resection, approximately 40% to 50% of patients with high-risk GISTs will have recurrence and metastasis[3]. Therefore, by accurately determining the risk factors for postoperative recurrence, effective preventive measures could be performed, and the prognosis of patients with GIST could be improved.

Clinical characteristics including tumor site, tumor size, and mitotic rate are the most common indicators for analyzing the risk factors for recurrence after surgery for GIST. Some studies also suggest that the systemic inflammatory response plays an important role in the progression and metastasis of tumors[4]. The grade of risk classification after operation for GIST is mainly evaluated by the 2008 modified National Institutes of Health (NIH) risk grading standards[5], the 2020 edition of the World Health Organization soft tissue tumor classification[6], the National Comprehensive Cancer Network guidelines (6th edition, 2019)[7] and the Armed Forces Institute of Pathology criteria[8]. In addition, Joensuu *et al*[9] developed a new contour map to predict the prognosis of patients with GIST by monitoring the follow-up results of more than 2000 patients with GIST. However, the use of a single grading method to predict the probability of postoperative recurrence in patients with GIST has certain limitations, especially for some GIST patients who only evaluate the two key indicators of tumor size and mitotic rate. Therefore, there is currently no consensus on which risk grading system to use. Nomograms have been developed for most malignant tumors[10,11]. The use of nomograms has been compared to many traditional cancer staging systems, and it is proposed as an alternative or even a new standard.

Based on the above factors, a predictive nomogram may provide a more accurate prognostic assessment and basis for postoperative recurrence of GIST. To our knowledge, reports on the establishment of a nomogram for the postoperative recurrence of GIST are rare. Therefore, the aim of this study was to develop an effective and simple predictive tool for the risk assessment of postoperative recurrence after GIST and to evaluate the risk of postoperative recurrence using only

postoperative pathological features and general clinical data.

MATERIALS AND METHODS

Patients

The clinical and pathological data of 130 patients with GIST from January 2010 to January 2017 were retrospectively analyzed. The inclusion criteria were as follows: first, complete surgical resection and postoperative pathology and immunohistochemistry confirmed as GIST; second, complete medical records were available; third, patients presented with no other gastrointestinal malignancies; and fourth, patients reported no history of neoadjuvant targeted therapy. A total of 130 patients were included in the study according to the inclusion criteria. The classification criteria were as follows: the risk of recurrence of primary GIST was divided into 4 groups according to the 2008 NIH risk grading standards [5]: very low risk, low risk, middle risk, and high risk. Tumor size was based on the largest diameter of the lesion. The Ki-67 indicator was divided into two groups: < 5% and ≥ 5%. The mitotic rate/50 high power fields were divided into three groups: ≤ 5, > 5 and ≤ 10, and > 10. The tumors were divided into two groups according to whether there was bleeding or necrosis.

Postoperative survival and follow-up

All cases were followed up mainly by telephone and outpatient and inpatient review after surgery. Recurrence was confirmed by imaging examination (abdominal B-ultrasound, computed tomography or magnetic resonance imaging) and pathological confirmation by biopsy. The last follow-up time was until June 2019, and the endpoint event was recurrence or metastasis of the patient. Recurrence-free survival was defined as the time from the date of surgery to the time of recurrence or metastasis or the last follow-up time.

Statistical analysis

Data processing was performed using R language (version 3.6.0) statistical software. The best predictive risk factors for recurrence were selected from the clinical pathological data of patients with GIST using the least absolute shrinkage and selection operator (LASSO) method suitable for reducing high-dimensional data[12,13]. The process was as follows: select the factor with a nonzero coefficient in the LASSO regression model[14], combine the factors selected in the LASSO regression model, and use multivariate logistic regression analysis to establish the prediction model and obtain the odds ratio value of the corresponding factor, 95%CI and *P* value. Statistical significance levels were relative, variables with a *P* value of < 0.05 were included in the model, and variables associated with disease and treatment factors were also included. All potential predictors have been used to develop predictive models for the risk of GIST recurrence.

Calibration curves were drawn to evaluate the accuracy of the recurrence nomogram. The recognition performance of the recurrence nomogram was quantified by measuring Harrell's index of concordance (C-index). Bootstrap verification (1000 bootstrap resampling) was performed on the recurrence nomogram to determine the relative corrected C-index[15]. Decision curve analysis was performed to quantify the clinical values of the recurrence nomogram by quantifying the net benefit at different threshold probabilities in the GIST cohort[16]. The proportion of all false-positive patients was subtracted from the proportion of true positive patients, and the net benefit was calculated by weighing the relative harm of the intervention with the negative consequences of unnecessary interventions[17].

RESULTS

Patient characteristics

In this study, 130 patients with GIST radical surgery were included, including 101 gastric stromal tumors, 24 small intestinal stromal tumors, and 5 Large intestinal stromal tumors. All patients were divided into a recurrence group (13 cases) and a nonrecurrence group (117 cases) according to the presence or absence of recurrence. The ratio of males to females was close to 1:1. The patients were aged 25-82 years old, and the mean age was 57.0 ± 11.8 years old. All data and proportions of the two groups of patients, including general information and clinicopathological features are shown in Table 1.

Factor selection

Of the 130 patients' general information and clinical pathological features, 9 factors were calculated using the LASSO regression model, and 5 factors with nonzero coefficients were considered potential predictors. These factors included the mitotic rate, Ki-67, intratumoral necrosis, tumor size and tumor site (Figure 1A and B).

Table 1 Differences between the demographic and clinical characteristics of the recurrence and nonrecurrence groups

Demographic characteristics	*n* (%)		
	Recurrence (*n* = 13)	Nonrecurrence (*n* = 117)	Total (*n* = 130)
Age (yr)			
< 60	8 (61.5)	62 (54.0)	70 (53.8)
≥ 60	5 (38.5)	55 (47.0)	60 (46.2)
Sex			
Male	6 (46.2)	61 (52.1)	67 (51.5)
Female	7 (53.8)	56 (47.9)	63 (48.5)
Tumor site			
Stomach	9 (69.2)	92 (78.6)	101 (77.7)
Small intestine	1 (7.7)	23 (19.7)	24 (18.5)
Large intestine	3 (23.1)	2 (1.7)	5 (3.8)
Tumor size			
< 2 cm	2 (15.4)	25 (21.4)	27 (20.8)
≥ 2 and ≤ 5 cm	6 (46.1)	56 (47.9)	62 (47.7)
> 5 and ≤ 10 cm	1 (7.7)	30 (25.6)	31 (23.8)
> 10 cm	4 (30.8)	6 (5.1)	10 (7.7)
NIH risk category			
Very low	3 (23.1)	31 (26.5)	34 (26.2)
Low	2 (15.4)	31 (26.5)	33 (25.4)
Middle	1 (7.7)	27 (23.1)	28 (21.5)
High	7 (53.8)	28 (23.9)	35 (26.9)
Mitotic rate			
≤ 5 cm	7 (53.8)	87 (74.4)	94 (72.3)
> 5 cm and ≤ 10 cm	2 (15.4)	22 (18.8)	24 (18.5)
> 10 cm	4 (30.8)	8 (6.8)	12 (9.2)
Ki-67			
< 5%	4 (30.8)	70 (59.8)	74 (56.9)
≥ 5%	9 (69.2)	47 (40.2)	56 (43.1)
Intratumoral hemorrhage			
Yes	10 (76.9)	100 (85.5)	110 (84.6)
No	3 (23.1)	17 (14.5)	20 (15.4)
Intratumoral necrosis			
Yes	8 (61.5)	99 (84.6)	107 (82.3)
No	5 (38.5)	18 (15.4)	23 (17.7)

NIH: National Institutes of Health.

Development of an individualized prediction model

Multivariate logistic regression analysis was performed on factors with nonzero coefficients in the LASSO regression model. In addition, considering the importance of age in oncology, an additional age factor was added to this analysis is shown in Table 2. Therefore, a total of 6 potential predictors were mitotic rate, Ki 67, intratumoral necrosis, tumor size, tumor site and age. The potential predictive factors are integrated together, and scaled line segments are drawn on the same plane to a certain scale to express the relationship between variables in the predictive model, represented by a nomogram

Table 2 Prediction factors for recurrence of gastrointestinal stromal tumor

Intercept and variable	Prediction model		
	β	Odds ratio (95%CI)	*P* value
Intercept	-3.0092	0.049 (0.006-0.245)	0.001
Mitotic rate	3.2152	24.907 (2.215-707.556)	0.020
Ki-67	0.7514	2.120 (0.340-15.083)	0.425
Intratumoral necrosis	-0.2675	0.765 (0.081-5.421)	0.799
Tumor size	-0.0147	0.985 (0.115-10.405)	0.989
Tumor site	3.4115	30.313 (3.265-405.088)	0.003
Age	0.1048	1.110 (0.228-5.611)	0.895

β: The regression coefficient.

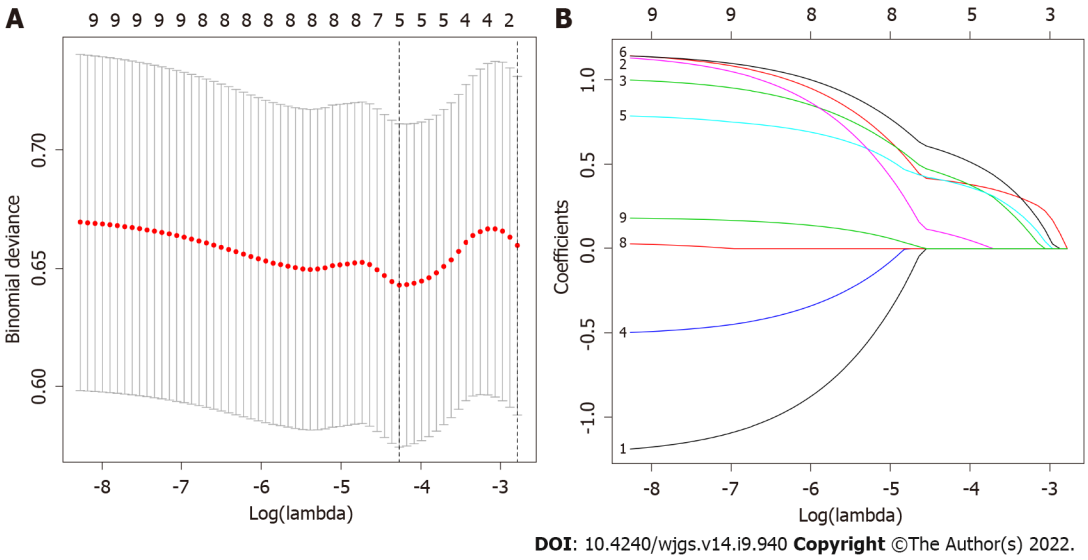

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Figure 1 Clinicopathologic characteristics selection using the least absolute shrinkage and selection operator regression model. A: Optimal parameter (lambda) selection in the least absolute shrinkage and selection operator (LASSO) regression model used five-fold cross-validation *via* minimum criteria. The partial likelihood deviance (binomial deviance) curve was plotted versus log(lambda). Dotted vertical lines were drawn at the optimal values using the minimum criteria and the 1 Standard Error of the minimum criteria; B: LASSO coefficient profiles of the 9 features. A coefficient profile plot was produced against the log(lambda) sequence. A vertical line was drawn at the value selected using five-fold cross-validation, where optimal lambda resulted in five features with nonzero coefficients.

(Figure 2).

Apparent performance of the recurrence risk nomogram in the cohort

The calibration curve of the recurrence risk nomogram used to predict recurrence risk in patients with GIST showed good consistency (Figure 3). The C-index of the predictive nomogram of this cohort was 0.836 (95%CI: 0.712-0.960), and it was confirmed as 0.714 by bootstrapping validation, which indicated that this model had great differentiation. In the recurrence risk nomogram, the apparent performance possessed a good prediction capability.

Clinical use

The decision curve analysis for the GIST recurrence risk nomogram showed that if the threshold probability of a patient and a doctor is > 5 and < 100%, respectively, using this recurrence nomogram to predict recurrence risk adds more benefit than the scheme (Figure 4). As the threshold probability increases, the predictive power will not increase. In this range, according to the risk of recurrence nomogram, the net benefit is comparable to several overlaps.

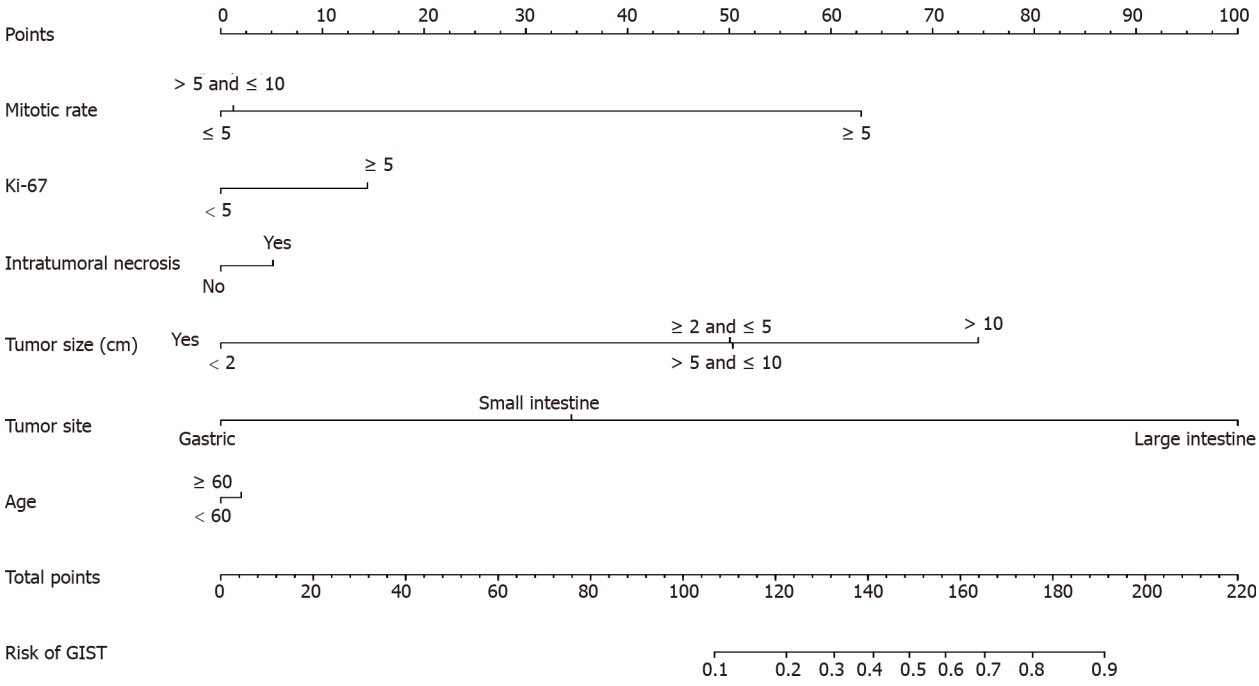

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Figure 2 Developed recurrence nomogram. The recurrence nomogram includes mitotic rate, Ki-67, intratumoral necrosis, tumor size, tumor site and age. GIST: Gastrointestinal stromal tumors.

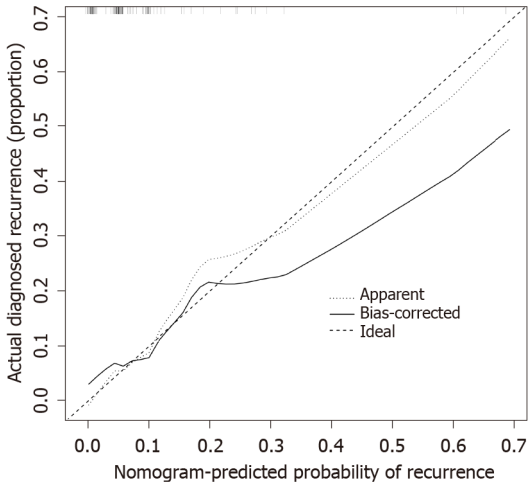

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Figure 3 Calibration curves of the recurrence nomogram prediction. The x-axis represents a possible risk of recurrence of gastrointestinal stromal tumor. The y-axis represents the actual recurrence. Diagonal dotted lines indicate predictions under ideal conditions. The solid line indicates the performance of the nomogram, and the closer it is to the diagonal dotted line, the more predictive the value is.

DISCUSSION

The global incidence of GIST is approximately 11.0-14.5/1 million[18]. Although it is rare compared with other tumors in the digestive tract, China has a large population base, so a considerable number of patients are diagnosed with GISTs every year. In clinical work, an increasing number of patients with GIST have been diagnosed and treated, and the number should not be underestimated. Although the use of small molecule targeted drugs such as imatinib has significantly improved the prognosis of patients with moderate and high-risk GISTs, there is still tumor recurrence or metastasis during or after adjuvant therapy[19]. Therefore, accurate assessment of the factors affecting the recurrence of GIST in patients is essential for guiding the individualized treatment of patients.

Four staging systems are commonly used for GIST. At present, the classification of different staging systems is mainly based on the following three influencing factors: the size of the tumor, the mitotic rate, and the location of the tumor. However, none of these systems were specifically developed for

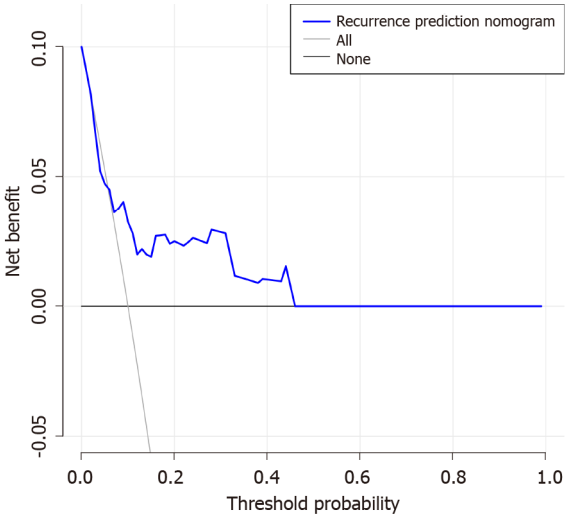

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Figure 4 Decision curve analysis of the recurrence nomogram. The y-axis represents the net benefit. The blue line represents the gastrointestinal stromal tumor (GIST) recurrence risk nomogram. The solid line indicates the hypothesis that all patients have recurrence. The thick solid line indicates the assumption that there is no patient recurrence. The decision curve shows that if the threshold probability is > 5% and < 100%, the recurrence nomogram in the current study can be used to predict the risk of recurrence of GIST and adds more benefit than the intervention-all-patients regimen or the intervention-none regimen.

postoperative prognosis predictions. Similarly, it is not possible to quantify the risk of recurrence among individual patients. Currently, nomograms are widely used in prognostic studies in oncology and medicine. To predict the prognosis of certain cancers, some researchers have developed more accurate scales than conventional staging systems[20,21]. Therefore, the aim of the study was to establish a recurrence risk nomogram for patients with GIST to achieve higher accuracy and predictions that are easier to understand to help better clinical decision-making and maximize patient benefit.

We developed and validated a new predictive tool that uses six easily available variables to predict recurrence risk after radical surgery in patients with GIST. Incorporating general information and risk factors for clinicopathological features into an easy-to-use nomogram can help individualize the prediction of the recurrence of GIST. Nomograms are based on statistical models that use a combination of prognostic variables to determine the likelihood of a particular event and perform well in predicting postoperative recurrence. The predictions are supported by a C-index of 0.836 (95%CI: 0.712-0.960) and a calibration curve. The C-index, an internal verification method, in this study cohort was 0.714, showing good discrimination and calibration ability. Our high C-index in all cohort verifications indicates that this nomogram can be widely and accurately used due to its large sample size. This study provides a relatively accurate predictive tool for postoperative recurrence in patients with GIST. Each postoperative patient was scored according to the nomogram. The higher the score, the higher the probability of postoperative recurrence and the higher the follow-up frequency.

GISTs can occur in any part of the digestive tract or in the omentum, mesentery, peritoneum, and abdominal pelvic cavity, but the stomach (approximately 60%) is the most common, followed by the small intestine (25% to 30%), while a few cases occur in the colorectal (approximately 5%), esophagus and other areas[22]. The results of this group of cases show that the stomach and small intestine are the most common sites of GISTs, similar to previous research reports. Tumors in different parts have large differences in their malignancy and prognosis. For GISTs, the location of tumor growth is also an extremely important prognostic factor. A retrospective study of 332 patients with GIST showed that the tumors with good prognosis were the esophagus, stomach, duodenum, small intestine, parenteral and colorectal[23]. We screened tumor sites for potential predictors of postoperative recurrence using LASSO regression analysis, and further differences in tumor location were found in the multivariate logistic regression analysis ($P < 0.003$). In this study, nomograms showed that tumors in the colorectal region had the highest risk of postoperative recurrence, followed by the small intestine, and finally the stomach region. Studies have shown that the prognosis of gastric stromal tumors is significantly better than that of small intestinal stromal tumors, which is mainly due to the invasive growth of small intestinal stromal tumors, often with early peritoneal metastasis, and the ease with which they rupture; therefore, duodenal stromal tumors should be actively treated as soon as possible[23]. With larger tumors, preoperative treatment should first be considered, and the rate of pancreaticoduodenectomy should be minimized. The degree of malignancy of colorectal stromal tumors is higher than that of small intestine and gastric stromal tumors[24], and the risk of recurrence is the highest. GISTs generally occur most frequently in middle-aged and elderly people, and the most common onset is between 50 and 70 years old[25]. In this study, the mean age was 57.0 ± 11.8 years, and 71.5% of patients were aged 50 years or older. There was no difference based on sex, which was consistent with the above study reports.

At present, the influence of mitotic rate and tumor size on the prognosis of GIST has been generally recognized, and multiple staging systems have been applied to the risk assessment of recurrence after GIST. It has been reported in a study that univariate survival analysis showed that the factors that had a significant impact on prognosis were the primary site of the tumor, tumor diameter and the mitotic rate ($P < 0.05$)[26]. Multivariate survival analysis showed that the mitotic rate is an independent prognostic factor for patients with GIST metastasis or recurrence. Catena *et al*[27] showed that tumor size, mitotic rate, and microscopic resection margins predicted disease-free survival in GIST patients. In general, the larger the tumor size is, the higher the malignant biological behavior, and the relatively poor the prognosis. The prognosis of patients with GIST is closely related to the mitotic rate, and those with a high mitotic rate often show a worse prognosis[28]. The high mitotic rate and larger lesion range in this study significantly increased the risk of recurrence after GIST, consistent with most studies.

In recent years, with the development of immunohistochemistry technology, we often use tumor immunohistochemical markers for tumor prognosis analysis. Ki-67 is a nuclear antigen expressed in proliferating cells, and its antibody marks proliferating cells in the non-G0 phase of the whole cell cycle, so it can be used as a marker of cell proliferation. In breast cancer, Ki-67 positivity has been shown to be negatively correlated with disease-free survival and overall survival[28]. It has been reported[29] that the expression level of Ki-67 is important for judging the malignant degree of GIST. By analyzing the correlation between immunohistochemical markers and prognosis in GIST samples, Kadado *et al*[30] showed that there was a statistically significant difference in the Ki-67 proliferation index between localized GIST and patients with recurrence and metastasis ($P < 0.001$). The nomograms in this study showed that Ki-67 ≥ 5 increased the risk of recurrence after GIST, consistent with the results of the above studies. It is suggested that Ki-67 can be used as an important factor to evaluate the recurrence or metastasis of GIST. In addition, for patients treated with imatinib before surgery, due to tumor liquefaction necrosis, the capsule is prone to spontaneous rupture, resulting in tumor cell dissemination, postoperative recurrence or distant metastasis. The 5-year recurrence-free survival rate of tumor necrosis was significantly lower than that of nonnecrotic rupture ($P < 0.016$), and the risk of death in the former was 2.79-3.03 times that of the latter[28]. Clinically, some patients with GISTs often have necrosis of the lesion at the beginning of diagnosis, which may be associated with metastasis of the abdomen and liver. Distant metastasis is one of the important factors affecting the prognosis of GIST. Patients with distant metastasis or local infiltration metastasis are more aggressive, although the prognosis is still poor after combined resection of the metastatic lesions. This is consistent with the fact that nomogram tumor intratumoral necrosis in this study can increase the risk of recurrence after GIST. Therefore, tumor necrosis may also be an important factor in predicting prognosis.

CONCLUSION

The occurrence, development and prognosis of tumors are the result of a multifactor interaction. It is generally believed that the biological behavior of GIST is the most important factor in determining its prognosis. At present, among the influencing factors of GIST prognosis, it is most common to consider the tumor location, size, and mitotic rate. The prediction model developed in this study also includes Ki-67, tumor intratumoral necrosis and age-related indicators. Comprehensive assessment of patient outcomes will assist in guiding individualized treatment.

ARTICLE HIGHLIGHTS

Research background

There are many staging systems for gastrointestinal stromal tumors (GISTs), and the risk indicators selected are also different; thus, it is not possible to quantify the risk of recurrence among individual patients.

Research motivation

To develop a nomogram of postoperative recurrence risk factors in GIST patients to further guide individualized treatment.

Research objectives

To investigate the risk factors for postoperative recurrence in GIST patients.

Research methods

We retrospectively analyzed the clinical and pathological data of 130 patients with GIST. The least absolute shrinkage and selection operator regression model and multivariable logistic regression analysis were used to develop a prediction model. The index of concordance (C-index), calibration

curve, receiver operating characteristic curve, and decision curve analysis were used to assess the discrimination, calibration, and clinical usefulness of the predictive model.

Research results

The nomogram included tumor site, lesion size, mitotic rate/50 high power fields, Ki-67 index, intracranial necrosis, and age as predictors. The model presented a perfect discrimination with a reliable C-index. The receiver operating characteristic curve indicated a good predictive value. Decision curve analysis showed that the predicting recurrence nomogram was clinically feasible.

Research conclusions

This recurrence nomogram combines tumor site, lesion size, mitotic rate, Ki-67 index, intracranial necrosis, and age and can easily predict patient prognosis.

Research perspectives

We look forward to conducting a multicenter large-sample prospective controlled study in the future to further explore risk factors after GIST surgery, to better guide individualized treatment.

FOOTNOTES

Author contributions: Guan SH is the author of the main idea, conceived and designed the study, collected and analyzed the data, and wrote and revised the manuscript; Wang C conceived and designed the study, collected and analyzed the data and wrote the manuscript; Wang Q and Ma XM participated in drafting and revising the manuscript, and collected the data; Qiao WJ, Li MZ and Lai MG revised the manuscript and analyzed the data. All authors approved the final version of the manuscript.

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Informed consent statement: All patients signed informed consent forms.

Conflict-of-interest statement: Each author in this paper declares no conflict of interest.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

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ORIGINAL ARTICLE

Retrospective Study

Comparison of short-term efficacy between totally laparoscopic gastrectomy and laparoscopic assisted gastrectomy for elderly patients with gastric cancer

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Abstract

BACKGROUND

Totally laparoscopic gastrectomy (TLG) entails both gastrectomy and gastrointestinal reconstruction under laparoscopy. Compared with laparoscopic assisted gastrectomy (LAG), TLG has been demonstrated in many studies to require a smaller surgical incision, result in a faster postoperative recovery and less pain and have comparable long-term efficacy, which has been a research hotspot in recent years. Whether TLG is equally safe and feasible for elderly patients remains unclear.

AIM

To compare the short-term efficacy of and quality of life (QOL) associated with TLG and LAG in elderly gastric cancer (GC) patients.

METHODS

The clinicopathological data of 462 elderly patients aged ≥ 70 years who underwent LAG or TLG (including distal gastrectomy and total gastrectomy) between January 2017 and January 2022 at the Department of General Surgery, First Medical Center, Chinese PLA General Hospital were retrospectively collected. A total of 232 patients were in the LAG group, and 230 patients were in the TLG group. Basic patient information, clinicopathological characteristics, operation information and QOL data were collected to compare efficacy.

RESULTS

Compared with those in the LAG group, intraoperative blood loss in the TLG group was significantly lower ($P < 0.001$), and the time to first flatus and postoperative hospitalization time were significantly shorter (both $P < 0.001$). The overall incidence of postoperative complications in the TLG group was significantly lower than that in the LAG group ($P = 0.01$). Binary logistic regression results indicated that LAG and an operation time > 220 min were independent risk factors for postoperative complications in elderly patients with GC ($P < 0.05$). In terms of QOL, no statistically significant differences in various preoperative indicators were found between the LAG group and the LTG group ($P > 0.05$). Compared with the laparoscopic-assisted total gastrectomy group, patients who received totally laparoscopic total gastrectomy had lower nausea and vomiting scores and higher satisfaction with their body image ($P < 0.05$). Patients who underwent laparoscopic-assisted distal gastrectomy were more satisfied with their body image than patients in the totally laparoscopic distal gastrectomy group ($P < 0.05$).

CONCLUSION

TLG is safe and feasible for elderly patients with GC and has outstanding advantages such as reducing intracorporeal blood loss, promoting postoperative recovery and improving QOL.

Key Words: Totally laparoscopic gastrectomy; Laparoscopic assisted gastrectomy; Gastric cancer; Elderly patients; Efficacy comparison; Quality of life

Core Tip: Compared with laparoscopic assisted gastrectomy (LAG), totally laparoscopic gastrectomy (TLG) has been demonstrated to have many advantages in previous studies. However, whether TLG is safe and feasible for elderly gastric cancer (GC) patients was unclear before our work. In this study, we compared short-term outcomes between TLG and LAG groups and assessed patients' quality of life (QOL) before surgery and 3 mo after surgery. We found that TLG is safe and feasible for elderly patients with GC and has outstanding advantages such as reducing intracorporeal blood loss, promoting postoperative recovery and improving QOL.

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INTRODUCTION

China has a high incidence of gastric cancer (GC), and GC incidence and mortality both rank second among malignant tumors[1], resulting in serious health and medical burdens for Chinese people. Despite slight decreases in GC incidence and mortality with the improvements in diagnosis and treatment, they have gradually increased for elderly patients with GC[2]. Therefore, reasonable treatment regimens still need to be developed for elderly patients with GC.

In 1994, Kitano *et al*[3] carried out the first laparoscopic gastrectomy (LG)[3]. In recent years, an increasing number of multicenter clinical studies have confirmed that LG has comparable surgical safety and long-term prognosis compared to those who received open gastrectomy[4-6]. Therefore, minimally invasive surgery, *i.e.*, laparoscopy, has become an alternative surgical approach for the treatment of GC. Gastrointestinal reconstruction is a key step in LG. With continuous improvements in surgeons' skills and improvements in intracorporeal staplers, totally laparoscopic gastrectomy (TLG) with complete intracorporeal anastomosis has become a research hotspot. Previous studies have shown that compared with laparoscopic assisted gastrectomy (LAG) or open gastrectomy, TLG requires a smaller incision, induces less postoperative pain and improves postoperative quality of life (QOL)[7,8]. These advantages are also shown in patients who have received the neoadjuvant chemotherapy[9].

Because of the advantages of TLG and significant advancement in intracorporeal operation, the number of studies concerning TLG is increasing. A multicenter prospective study focusing on the effects of totally laparoscopic distal gastrectomy (TLDG) or laparoscopic-assisted distal gastrectomy (LADG) on postoperative QOL is being performed in South Korea[10]. However, it is still unclear whether TLG is identically safe and feasible for elderly patients. Therefore, we conducted this study to provide a

proof for the application of TLG for elderly patients by comparing the short-term efficacy and QOL between elderly GC patients who received TLG or LAG.

MATERIALS AND METHODS

Patients

The inclusion criteria were as follows: (1) Age ≥ 70 years; (2) Gastric adenocarcinoma confirmed by preoperative gastroscopic pathology, endoscopic ultrasonography, abdominal computed tomography (CT) or positron emission tomography-CT; and (3) Postoperative pathological staging of Ia-IIIc. The exclusion criteria were as follows: (1) Intraoperative conversion to open surgery for any reason; (2) American Society of Anesthesiologists (ASA) classification > grade III; (3) Gastric stump cancer treated by gastric surgery; (4) Previous proximal gastrectomy; and (5) Absence of clinical and pathological data.

Based on the above criteria, clinical and pathological data were retrospectively collected from 462 elderly GC patients who underwent TLG or LAG at the Department of General Surgery, First Medical Center, Chinese PLA General Hospital between January 2017 and January 2022, including 230 patients in the TLG group and 232 patients in the LAG group. The clinicopathological characteristics of the patients are provided in Table 1. This study meets the requirements of the Declaration of Helsinki and has been approved by the Research Ethics Committee of Chinese PLA General Hospital (Approval Number: S2021-605-01).

Surgical approach

The surgical procedure was performed in accordance with the *Chinese Guidelines for laparoscopic gastrectomy for gastric cancer* (2016 edition). The scope of surgical resection and lymph node dissection was based on the standard criteria established by the *Japanese gastric cancer treatment guidelines 2018* (5th edition)[11]. D2 Lymph node dissection was performed for all patients who underwent distal or total gastrectomy. The intracorporeal gastrointestinal reconstruction procedure in the TLG group was performed in accordance with the *Chinese Expert consensus and surgical operation guidelines for gastrointestinal reconstruction in totally laparoscopic gastrectomy* (2018 edition). After completing intracorporeal reconstruction, a small upper abdominal median incision (length of incision ≤ 7 cm) was made for specimen removal only. After lymph node dissection in the LAG group, the upper abdominal median incision (incision length ≤ 10 cm) was used to remove the specimens, and the extracorporeal gastrointestinal reconstruction was performed. A circular anastomosis was performed at the esophagojejunal anastomotic site in laparoscopic assisted total gastrectomy (LATG). In totally laparoscopic total gastrectomy (TLTG), a linear anastomosis, including overlap or π anastomosis, was performed at the esophagojejunal anastomotic site. The methods for gastrointestinal reconstruction were selected based on the surgeon's preferences and executed in accordance with standardized procedures.

Definition and classification of postoperative complications

The incidence and severity of complications within 30 d after surgery were assessed[12] using the Clavien–Dindo classification. The evaluation criteria mainly included the following: (1) Grade I: Any deviation from the normal postoperative recovery process but without the need for drugs, surgical intervention, endoscopy or interventional therapy; (2) Grade II: A need for drug therapy including blood transfusion, or total parenteral nutrition (except antiemetic, antipyretic, analgesic, diuretic, rehydration and other symptomatic drug therapy); (3) Grade III: Surgical intervention, endoscopy or interventional treatment needed (Grade IIIa, does not require general anesthesia; Grade IIIb, requires general anesthesia); (4) Grade IV: Life-threatening condition with treatment needed in the intensive care unit (Grade IVa, single organ failure; Grade IVb, multiple organ failure); and (5) Grade V: Death. In this study, complications within 30 d after surgery were defined as Clavien–Dindo grade ≥ II, and severe complications within 30 d after surgery were defined as Clavien–Dindo grade ≥ IIIa because of the limitation associated with a retrospective study design.

QOL questionnaire and scoring method

In this study, the Chinese versions of the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30)[13] and QLQ-ST022[14] were used to assess the QOL of patients before and 3 mo after surgery. The EORTC QLQ-C3O is a core scale for all cancer patients, with a total of 30 items. Among them, items 29 and 30 are scored using 7 grade options, which are assigned 1 to 7 points based on the answer options. Other items are scored using 4 grade options, *i.e.*, not at all, a little, quite a bit, and very much, and are assigned 1 to 4 points when scoring. The QLQ-C30 questionnaire is divided into 15 domains, including 5 functional domains (physical, role, cognitive, emotional, and social functioning), 3 symptom domains (fatigue, pain and nausea and vomiting), 1 overall QOL domain and 6 single items (each as a domain). The QLQ-STO22 includes 22 items related to the QOL of GC patients and consists of 9 scales, including dysphagia, pain, reflux, eating restriction, anxiety, dry mouth, taste, body shape and hair loss.

Table 1 Clinical and pathological characteristics of laparoscopic assisted gastrectomy and totally laparoscopic gastrectomy group for elderly patients (mean ± SD)

Characteristics	LAG group (*n* = 232)	TLG group (*n* = 230)	*P* value
Gender			0.472
Male	183	175	
Female	49	55	
Age (yr)	74.62 ± 3.80	74.69 ± 4.10	0.848
BMI (kg/m^2)	23.31 ± 3.08	23.64 ± 3.46	0.285
aCCI score, *n* (%)			0.608
0-4	188	182	
> 4	44	48	
ASA score, *n* (%)			0.426
I	1	1	
II	177	168	
III	54	61	
History of abdominal surgery			0.232
No	189	177	
Yes	43	53	
Tumor resection			0.163
Distal	125	109	
Total	107	121	
Neoadjuvant chemotherapy			0.201
No	223	215	
Yes	9	15	
Tumor diameters (cm) (median, IQR)	4.00 (2.58-6.00)	4.00 (2.65-5.5)	0.230
pT			0.895
T0	2	0	
T1	38	43	
T2	36	37	
T3	116	107	
T4	40	43	
pN			0.544
N0	83	77	
N1	33	33	
N2	49	48	
N3	67	72	
pTNM			0.857
0	2	0	
I	52	60	
II	65	57	
III	113	113	
Nerve invasion			0.249
Yes	71	82	

No	161	148	
Vascular invasion			0.685
Yes	91	86	
No	141	144	
Differentiation			0.945
Well/moderate	151	149	
Poor/undifferentiated	81	81	

LAG: Laparoscopic assisted gastrectomy; TLG: Totally laparoscopic gastrectomy; aCCI: Age-adjusted Charlson Comorbidity Index; BMI: Body mass index; ASA: American Society of Anesthesiologists; SD: Standard deviation; IQR: Interquartile range.

Statistical analysis

SPSS 26.0 statistical software was used for analysis. Normally distributed measurement data are expressed as the mean ± SD. Categorical data are expressed as *n* (%). Data with a skewed distribution are expressed as the median (interquartile range). Binary logistic regression was used to analyze the relationships between postoperative complications and clinical and pathological factors. Factors with $P < 0.20$ in the univariate analysis were included in the multivariate analysis. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical and pathological characteristics

Among the 462 patients, 183 males and 49 females were included in the TLG group, with an average age of 74.69 ± 4.10 years, and 175 males and 55 females were included in the LAG group, with an average age of 74.62 ± 3.80 years. No significant differences in clinical characteristics, such as age, sex, body mass index, age-adjusted Charlson comorbidity index score, ASA score, a history of abdominal surgery and the range of surgical resection, were identified between 2 groups ($P > 0.05$). In terms of pathological characteristics, no significant differences in pathologic T stage, pathologic N stage, pTNM stage, tumor size, nerve invasion, vascular invasion or tumor differentiation were found between the 2 groups, suggesting that the baseline characteristics of the 2 groups were comparable (Table 1).

In the subgroup analysis, we compared the baseline characteristics between the TLTG group and LATG groups and between the TLDG and LADG groups. The results suggested that the tumor diameter in the TLDG group was smaller than that in the LADG group ($P = 0.035$). No significant differences were noted between other clinicopathological indicators ($P > 0.05$, Supplementary Table 1).

Perioperative outcomes and postoperative recovery

The perioperative outcomes are presented in Table 2. Compared with those in the LAG group, intraoperative blood loss in the LTG group was significantly lower [100 (50-100) mL *vs* 100 (50-200) mL] ($P < 0.001$), the time to first flatus was significantly shorter [(3.79 ± 1.15) d *vs* (4.43 ± 1.20) d] ($P < 0.001$), and the postoperative hospitalization time was shorter [7.75 (6.0-9.0) d *vs* 8.0 (7.0-10.0) d] ($P < 0.001$). No significant differences in the operation time, anastomosis methods, numbers of retrieved lymph nodes or R0 resection rates were observed between the 2 groups ($P > 0.05$). In terms of postoperative complications, the overall incidence of postoperative complications in the TLG group was significantly lower than that in the LAG group (16.5% *vs* 26.3%, $P = 0.01$). Additionally, no significant differences in the incidence of anastomotic-related complications (2.6% *vs* 3.4%, $P = 0.599$) or the incidence of severe complications (3.9% *vs* 4.3%, $P = 0.830$) were found between the TLG and LAG groups.

The results of the subgroup analysis indicated that the operation time in the TLDG group was significantly shorter than that in the LADG group [(201.82 ± 45.35) min *vs* (217.88 ± 49.08) min, $P = 0.01$]. In terms of intraoperative blood loss, the time to first flatus, and postoperative hospitalization time, TLG showed significant advantages over LAG in either distal or total gastrectomy (Supplementary Table 2).

We further explored risk factors for postoperative complications (Table 3). Univariate analysis indicated that TLG and LAG were associated with postoperative complications ($P = 0.011$). We included factors with $P < 0.02$ in the multivariate analysis. The results indicated that LAG and an operation time > 220 min were independent risk factors for postoperative complications in elderly patients with GC ($P < 0.05$). For the comparisons between LDG and LTG, the results suggested that a long tumor diameter > 3 cm and an operation time > 220 min were independent risk factors for postoperative complications in the LDG group ($P < 0.05$). No independent risk factors for postoperative complications were observed in the LTG group, as shown in Supplementary Table 3.

Table 2 Perioperative outcomes between laparoscopic assisted gastrectomy and totally laparoscopic gastrectomy group for elderly patients (mean ± SD)

Variable	LAG group (*n* = 232)	TLG group (*n* = 230)	*P* value
Surgical time, min	221.34 ± 54.96	216.48 ± 52.53	0.332
Blood loss, ml (median, IQR)	100.0 (50.0-200.0)	100.0 (50.0-100.0)	0.000
Anastomotic approach			
B1	17	14	
B2 (+Braun)	39	36	
Roux-en-Y	176	180	
Retrieved lymph nodes, *n*	29.32 ± 11.27	30.69 ± 12.65	0.218
Extent of resection			
R0	218	215	
R1/R2	14	15	
Time to first flatus, d	4.43 ± 1.20	3.79 ± 1.15	0.000
Postoperative day, d (median, IQR)	8.0 (7.0-10.0)	7.75 (6.0-9.0)	0.000
Total complication rate (%)	61 (26.3)	38 (16.5)	0.010
Anastomotic-related complication rate (%)	8 (3.4)	6 (2.6)	0.599
Clavien-Dindo classification			
Grade II			
Deep venous thrombosis	1	1	
Lymphatic leakage	1	0	
Gastroplegia	1	2	
Anaphylaxis	1	1	
Ileus	0	1	
Cardiac failure	1	0	
Hypoproteinemia	10	7	
Anemia	12	7	
Cholecystitis	2	0	
Incision infection	2	1	
Atrial fibrillation	4	2	
Pneumonia	8	2	
Anastomotic leakage	5	2	
Anastomotic bleeding	0	2	
Anastomotic stenosis	1	0	
Duodenal trump leakage	2	1	
Grade IIIa			
Deep venous thrombosis	0	0	
Pleural effusion	4	3	
Anastomotic leakage	2	2	
Duodenal trump leakage	1	1	
Abdominal bleeding	0	1	
Grade IV			
Cardiac failure	2	0	

Abdominal bleeding	1	1	
Acute cerebral infarction	0	1	
Severe complication rate (%)	10 (4.3)	9 (3.9)	0.830

Statistically significant *P* values are in bold ($P < 0.05$). LAG: Laparoscopic assisted gastrectomy; TLG: Totally laparoscopic gastrectomy; SD: Standard deviation; IQR: Interquartile range.

For the subgroup analysis based on surgical resection range, patients who underwent TLG had lower risks of postoperative complications in both the LTG (odds ratio (OR) = 0.612; 95% confidence interval (CI): 0.313-1.198) and LDG (OR = 0.619; 95%CI: 0.313-1.224) groups compared with patients who received LAG, although the differences were not statistically significant.

QOL using the EORTC QLQ-C30 and STO-22

We collected preoperative and 3-mo postoperative QOL questionnaire data from the 462 patients and compared changes in QOL between the LAG and LTG groups (Table 4). The results showed no statistically significant differences in symptom indicators, overall health indicators or functional indicators between the LAG and LTG groups before surgery ($P > 0.05$). Postoperative patients in the TLG group reported greater relief from nausea, vomiting and constipation than those in the LAG group. Patients in the TLG group were more satisfied with their body image.

Furthermore, the subgroup analysis (Supplementary Tables 4 and 5) showed that patients in the TLTG group had lower scores in the nausea and vomiting domains than those in the LATG group [0 (0-0) *vs* 0 (0-16.6), $P = 0.016$]. Patients who underwent TLTG were more satisfied with their body image than those who received LAGT [0 (0-0) *vs* 0 (0-33.3)] ($P = 0.027$). Among patients who received distal gastrectomy, the TLDG group showed more satisfaction with their body image than the LADG group [0 (0-0) *vs* 0 (0-33.3)] ($P = 0.002$).

DISCUSSION

The advantages of TLG have been confirmed by many studies. These advantages include less surgical blood loss, faster postoperative recovery of gastrointestinal functions, a shorter postoperative hospital stay, a smaller incision and improved QOL[8,15,16]. However, no studies have evaluated the short-term efficacy of TLG and LAG in elderly patients.

In this study, we found that intraoperative blood loss in the TLG group was lower than that in the LAG group. However, no significant difference in the operation time was found between the 2 groups. In the subgroup analysis, the operation time for the TLDG group was significantly shorter than that for the LADG group, which is similar to previous results[17]. These results indicate that under the limitation of a small abdominal incision, extracorporeal anastomosis may reduce the surgical efficiency, while intracorporeal anastomosis is more convenient and seems to be easier to execute. Elderly patients have an increased risk of surgical complications due to underlying diseases, decreased physical performance and malnutrition. Therefore, choosing a reasonable surgical strategy is very important[18]. Previous results have shown that the incidence of postoperative complications in elderly patients undergoing LG is comparable with that in younger patients, confirming that laparoscopic surgery is a safe method for elderly patients with GC[19,20]. The results from this study indicate that the overall incidence of postoperative complications in the TLG group was significantly lower than that in the LAG group (16.5% *vs* 26.3%, $P = 0.010$) and that the incidence of severe complications was comparable (3.9% *vs* 4.3%, $P = 0.830$). Further analysis revealed that LAG and operation time were independent risk factors for complications in elderly patients. The following reasons may potentially explain these results. For experienced surgeons, anastomosis (especially esophagojejunal anastomosis) under laparoscopy may offer a clearer view and facilitate more precise and accurate manipulation. It may reduce the risk of postoperative complications for patients[21]. Moreover, the longer operation time is mainly due to obesity, advanced tumor stages, intraoperative erroneous injury and difficulties in gastrointestinal reconstruction, which potentially increase the risk of postoperative complications. Based on these results, TLG is a more suitable approach for elderly patients with GC. However, the operation time must be controlled to reduce the occurrence of postoperative complications.

Anastomosis-related complications are crucial indicators when assessing the safety of gastrointestinal reconstruction methods. A meta-analysis of 10 studies by Zhao *et al*[22] showed that the incidence of anastomotic site-related complications after TLTG was similar to that after LATG[22]. Han *et al*[23] demonstrated that the incidence of anastomotic leakage after TLTG was higher than that after LATG. This phenomenon may be due to the difficulty of dissociating the distal esophagus by intracorporeal anastomosis, which increases the risk of anastomotic ischemia[23]. On the other hand, the physician's proficiency in intracorporeal anastomosis is also an important determinant of surgical safety[24]. In the

Table 3 Uni- and multivariate analysis of postoperative complications for elderly patients

Factor	Univariate analysis		*P* value	Multivariate analysis		*P* value
	OR	95%CI		OR	95%CI	
Sex			0.462			
Male	1.000					
Female	1.215	0.724-2.038				
Age (yr)			0.027			0.157
< 75	1.000			1.000		
≥ 75	1.655	1.058-2.587		1.422	0.874-2.313	
BMI (kg/m^2)			0.321			
< 25	1.000					
≥ 25	0.779	0.475-1.276				
Surgical approach			0.011			**0.011**
LAG	1.000			1.000		
TLG	0.555	0.352-0.874		0.539	0.335-0.865	
aCCI score			0.074			0.416
0-4	1.000			1.000		
> 4	1.603	0.952-2.699		1.276	0.709-2.294	
ASA score			0.030			0.069
≤ II	1.000			1.000		
> II	1.713	1.055-2.783		1.626	0.963-2.744	
Tumor resection			0.846			
Distal	1.000					
Total	0.957	0.613-1.493				
Neoadjuvant chemotherapy			0.752			
No	1.000					
Yes	1.165	0.452-3.000				
pTNM stage			0.918			
0-I	1.000					
II	1.072	0.571-2.012				
III	1.124	0.645-1.958				
Tumor diameter (cm)			0.020			0.116
≤ 3	1.000			1.000		
> 3	1.815	1.101-2.995		1.535	0.900-2.618	
Operation time (min)			0.031			**0.039**
≤ 220	1.000			1.000		
> 220	1.636	1.047-2.558		1.671	1.027-2.718	
Estimated blood loss (mL)			0.120			0.895
≤ 200	1.000			1.000		
> 200	1.628	0.880-3.012		1.047	0.530-2.070	
Vascular invasion			0.035			0.223
No	1.000			1.000		
Yes	1.620	1.034-2.538		1.349	0.834-2.185	

Nerve invasion			0.667			
No	1.000					
Yes	0.901	0.559-1.451				
Differentiation			0.760			
Well/moderate	1.000					
Poor/undifferentiated	1.075	0.676-1.708				
R0 resection			0.197			0.263
No	1.000			1.000		
Yes	1.715	0.755-3.895		1.639	0.690-3.892	

Statistically significant *P* values are in bold ($P < 0.05$). LAG: Laparoscopic assisted gastrectomy; TLG: Totally laparoscopic gastrectomy; aCCI: Age-adjusted Charlson Comorbidity Index; BMI: Body mass index; ASA: American Society of Anesthesiologists; OR: Odd ratio.

group of elderly patients, we found no significant differences in the incidence of anastomotic site-related complications (anastomotic leakage, bleeding and stenosis) between the LTG and LAG groups ($P > 0.05$). The results of the subgroup analysis also suggest that intracorporeal anastomosis is as safe as extracorporeal anastomosis for both distal and total gastrectomy and does not significantly increase the risks of anastomotic complications.

When addressing postoperative complications, the impact of surgical methods on the QOL of GC patients has become a key factor for surgeons when selecting an appropriate surgical approach. The EORTC QLQ-C30 and STO-22 questionnaires have been commonly used to assess the QOL of GC patients in recent years[25]. The QOL of patients can be assessed based on overall health, cognition, social interaction and symptoms. Whether TLG can improve the QOL of patients after surgery is still controversial. Park *et al*[7] compared QOL within 1 year after TLTG and LATG, and the results indicated that postoperative dysphagia, pain, eating and odynophagia were significantly improved in the TLTG group compared with the LATG group[7]. Wei *et al*[26] used circular anastomosis and found that postoperative constipation, dysphagia and anastomotic complications were significantly improved in TLTG group patients compared with LATG group patients[26]. In a study by Woo, no significant difference in QOL was found between patients after TLDG and LADG, and various parameters could not reflect subtle differences in surgical invasiveness between TLDG and LADG[27]. Which may be due to the high expectations of changes in QOL in patients undergoing TLDG, potentially affecting their judgment of subjective symptoms[28]. Postoperative QOL changes in elderly patients are different from those in young patients, and the effects on their physical and role functions are more obvious[29]. Physical function significantly varies with age, and changes in the QOL of elderly GC patients after surgery require close attention. Kim *et al*[30] found that in patients who underwent TLG, the postoperative return of bowel movements was slower in elderly patients[30]. In this study, we found no significant difference in preoperative QOL parameters between the TLG group and the LAG group. The 3-mo follow-up results indicated that the scores for nausea, vomiting and constipation in the TLG group were significantly lower than those in the LAG group, which is similar to the results of previous studies. In addition, in terms of body image, patients in the TLG group seemed to be more satisfied with their postoperative body image changes, which may be related to the smaller length of the incision in TLG. The above results suggest that for elderly patients, TLG may be a key factor in improving postoperative QOL.

This study has some limitations. First, this study did not include patients who underwent proximal gastrectomy, mainly because most patients who underwent proximal gastrectomy in our center received extracorporeal anastomosis, and the variety of intracorporeal anastomosis methods may cause potential bias. Second, this study followed up on the QOL of the patients only at 3 mo after surgery, with no complete follow-up for 1 year. Further follow-up is needed to compare the effects of TLG and LAG on the QOL of elderly patients. Third, we retrospectively established the short-term efficacy of TLG for elderly GC patients. Further studies, such as multicenter prospective studies, need to be conducted to evaluate the clinical value of TLG for elderly patients with GC.

In summary, this study found that TLG is safe and feasible for elderly patients with GC. TLG has significant advantages over LAG in terms of intraoperative bleeding, postoperative exsufflation and hospitalization and the overall postoperative complication rate. We found that LAG and an operation time > 220 min were independent risk factors for postoperative complications. Therefore, we recommend that experienced surgeons preferentially choose intracorporeal anastomosis during gastrectomy for elderly GC patients under the premise of ensuring a shorter operation time.

Table 4 Quality of life using European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire and STO-22 questionnaire between laparoscopic assisted gastrectomy and totally laparoscopic gastrectomy group

Factor	Baseline		*P* value	Postoperative 3 mo		*P* value
	LAG group	TLG group		LAG group	TLG group	
QLQ-C30 questionnaire						
Global status	91.6 (91.6-100)	91.6 (91.6-100)	0.096	91.6 (91.6-100)	91.6 (91.6-100)	0.934
Physical functioning	100 (93.3-100)	100 (93.3-100)	0.863	100 (93.3-100)	96.7(93.3-100)	0.777
Role functioning	100 (83.3-100)	100 (83.3-100)	0.269	100 (83.3-100)	83.3 (83.3-100)	0.804
Emotional functioning	91.6 (91.6-100)	91.6 (91.6-100)	0.343	91.6 (91.6-100)	91.6 (91.6-100)	0.880
Cognitive functioning	100 (83.3-100)	100 (83.3-100)	0.962	100 (83.3-100)	100 (83.3-100)	0.925
Social functioning	100 (83.3-100)	100 (83.3-100)	0.853	100 (83.3-100)	100 (83.3-100)	0.925
Fatigue	0 (0-0)	0 (0-0)	0.471	0 (0-0)	0 (0-11)	0.170
Nausea and vomiting	0 (0-0)	0 (0-0)	0.133	0 (0-12.5)	0 (0-0)	0.043
Pain	0 (0-0)	0 (0-0)	0.507	0 (0-0)	0 (0-0)	0.772
Dyspnea	0 (0-0)	0 (0-0)	0.165	0 (0-0)	0 (0-0)	0.880
Insomnia	0 (0-33.3)	0 (0-33.3)	0.428	0 (0-33.3)	0 (0-33.3)	0.984
Appetite loss	0 (0-0)	0 (0-33.3)	0.494	0 (0-33.3)	0 (0-33.3)	0.899
Constipation	0 (0-33.3)	0 (0-33.3)	0.529	33.3 (0-33.3)	0 (0-33.3)	0.024
Diarrhea	0 (0-0)	0 (0-0)	0.122	0 (0-0)	0 (0-0)	0.705
Financial difficulties	0 (0-33.3)	0 (0-33.3)	0.081	0 (0-33.3)	0 (0-33.3)	0.355
STO-22 questionnaire						
Dysphagia	0 (0-0)	0 (0-0)	0.547	0 (0-22)	0 (0-11)	0.169
Pain	0 (0-0)	0 (0-0)	0.793	0 (0-14.6)	0 (0-8.3)	0.389
Reflux	0 (0-11)	0 (0-11)	0.444	0 (0-22)	0 (0-22)	0.548
Eating restrictions	0 (0-0)	0 (0-0)	0.441	0 (0-8.3)	0 (0-8.3)	0.848
Anxiety	0 (0-11)	0 (0-11)	0.952	0 (0-22)	0 (0-22)	0.214
Dry mouth	0 (0-0)	0 (0-0)	0.681	0 (0-0)	0 (0-0)	0.982
Taste	0 (0-0)	0 (0-0)	0.609	0 (0-0)	0 (0-0)	0.858
Body image	0 (0-0)	0 (0-0)	0.573	0 (0-33.3)	0 (0-0)	0.000
Hair loss	0 (0-0)	0 (0-0)	0.442	0 (0-0)	0 (0-0)	0.077

Statistically significant *P* values are in bold ($P < 0.05$). TLG: Totally laparoscopic gastrectomy; LAG: laparoscopic assisted gastrectomy.

CONCLUSION

TLG is safe and feasible for elderly patients with GC and has outstanding advantages in reducing surgical bleeding, promoting postoperative recovery and improving QOL. We recommend that experienced surgeons prioritize TLG as a gastrectomy approach for elderly patients due to the shorter operation time.

ARTICLE HIGHLIGHTS

Research background

The outstanding advantages of totally laparoscopic gastrectomy (TLG) over laparoscopic assisted gastrectomy (LAG) has been proved in many studies.

Research motivation

The safety and reliability of TLG for elderly patients with gastric cancer (GC) remain unclear.

Research objectives

To evaluate the short-term efficiency and quality of life (QOL) of TLG for elderly patients with GC.

Research methods

The clinicopathological data of 462 elderly patients aged ≥ 70 years who underwent LAG or TLG between January 2017 and January 2022 at Department of General Surgery, First Medical Center, PLA General Hospital were retrospectively collected. We compared the perioperative outcomes between TLG and LAG groups, and used univariate and multivariate analysis to figure out the independent risk factors of LG in elderly patients. QOL data before and 3 mo after surgery were collected to evaluate whether TLG is equally safe and feasible in elderly patients.

Research results

The overall incidence of postoperative complications in the TLG group was significantly lower than that in the LAG group (16.5% *vs* 26.3%, $P = 0.01$). Furthermore, there was no significant difference in the incidence of anastomotic site-related complications or the incidence of severe complications between the TLG group and the LAG group ($P = 0.599$, $P = 0.830$). Binary logistic regression results indicated that LAG and operation time > 220 min were independent risk factors for postoperative complications in elderly patients with GC ($P < 0.05$). In terms of QOL, there were no statistically significant differences in various preoperative indicators between the LAG group and the LTG group ($P > 0.05$). Three months after surgery, patients in the TLG group were more satisfied with their body image.

Research conclusions

TLG is safe and feasible for elderly GC patients, especially in reducing surgical bleeding, promoting postoperative recovery and improving QOL.

Research perspectives

In the further study, we will refine the complete one-year follow-up of patients and conduct a multicenter collaborative prospective study to evaluate the clinical value of TLG more thoroughly for elderly patients with GC.

FOOTNOTES

Author contributions: Zhao RY, Li HH and Zhang KC equally contributed to this work; Zhao RY, Li HH, Zhang KC, Cui H, Deng H and Gao JW participated in the patient information collection; Zhao RY, Li HH and Zhang KC cleaned, analyzed the data and wrote the manuscript; Zhao RY, Li HH and Wei B revised the manuscript; Wei B designed and conceived this project; All authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Personal predictive model based on systemic inflammation markers for estimation of postoperative pancreatic fistula following pancreaticoduodenectomy

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Abstract

BACKGROUND

Postoperative pancreatic fistula (PF) is a serious life-threatening complication after pancreaticoduodenectomy (PD). Our research aimed to develop a machine learning (ML)-aided model for PF risk stratification.

AIM

To develop an ML-aided model for PF risk stratification.

METHODS

We retrospectively collected 618 patients who underwent PD from two tertiary medical centers between January 2012 and August 2021. We used an ML algorithm to build predictive models, and subject prediction index, that is, decision curve analysis, area under operating characteristic curve (AUC) and clinical impact curve to assess the predictive efficiency of each model.

RESULTS

A total of 29 variables were used to build the ML predictive model. Among them, the best predictive model was random forest classifier (RFC), the AUC was [0.897, 95% confidence interval (CI): 0.370–1.424], while the AUC of the artificial neural network, eXtreme gradient boosting, support vector machine, and decision tree were between 0.726 (95%CI: 0.191–1.261) and 0.882 (95%CI: 0.321–1.443).

CONCLUSION

Fluctuating serological inflammatory markers and prognostic nutritional index

can be used to predict postoperative PF.

Key Words: Pancreatoduodenectomy; Pancreatic fistula; Machine learning algorithm; Systemic inflammatory biomarker; Risk prediction

Core tip: Our research is based on machine learning (ML) algorithms and integrates the correlation between serum inflammatory factors and high risk of postoperative pancreatic fistula (PF), and constructs early warning models that can predict postoperative PF, and the predictive efficiency of these ML-based models may be at the population-based level. In the future, we expect these findings to expand external research to strengthen valuable supporting information and guide treatment decisions.

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INTRODUCTION

Pancreaticoduodenectomy (PD), also known as a Whipple procedure, is one of the most difficult and complex surgeries that carries a high rate of major complications[1]. Post-operative pancreatic fistula (PF), as one of the most difficult complications after PD, can seriously endanger the lives of patients, so it has become a field of continuous concern for pancreatic surgeons[1,2]. Although the safety of PD has improved significantly in the past three decades[3,4]. Alarmingly, previous prospective studies have reported that postoperative PF occupied an incidence of > 10%[5-7].

In recent years, people have studied different styles of surgery and perioperative attempts to reduce the incidence of postoperative PF. However, regardless of the type of surgery, PF is still the most common fatal complication after pancreatectomy. Understanding the potential complications and early warning of these complications is important for the care of these severe patients.

Previous studies have utilized preoperative radiology and clinical variables combined with specific intraoperative factors to predict the risk of postoperative PF[8-11]. Despite advances in predictive platforms for postoperative PF, they have undergone a constantly changing approach. However, because of its unsatisfactory predictive performance, an improved delivery system is deemed necessary. Therefore, exploring an optimal risk score range model may contribute to eliminating potential life-threatening complications, and stratifying patients with postoperative PF risk, which can be better applied to clinical management.

Nowadays, a series of serum markers suggest that detecting systemic inflammation may be associated with the risk of benign and malignant disease progression[12-14]. At the same time, the systemic reaction stimulated by local inflammation is closely related to the complications after gastrointestinal surgery[15,16]. In addition, machine learning (ML) algorithms have been widely used in the field of medicine. These unceasing new algorithms and iterative analyses might be useful for prognostication in cases and optimize individual treatment decisions[17]. Collectively, this combination has facilitated elevated predictive performance while minimizing the prediction error.

Given this situation, we searched for the help of inflammatory factors and ML-based algorithms to optimize the predictive accuracy for postoperative PF. In this study, we tried to identify alternative predictors independently related to postoperative PF and develop an optimal risk stratification model that can accurately identify high-risk patients with postoperative PF.

MATERIALS AND METHODS

Patients selection

Patients who underwent PD to treat various periampullary tumors from two tertiary medical centers (Jingzhou Hospital and Lu'an Hospital of Anhui Medical University) between January 2012 and August 2021 were retrospectively reviewed. The inclusion criteria were: (1) Resected tumor specimens were confirmed to be malignant by pathological examination; (2) Blood routine examination and liver function examination results were found within 3 d before surgery; and (3) The patient had complete

case data and relevant indicators of imaging, pathology and laboratory examination. The exclusion criteria were: (1) Patients receiving preoperative treatment, such as thermal ablation, neoadjuvant chemotherapy or radiotherapy; (2) Severe respiratory and circulatory diseases; (3) Severe acute cholangitis or infection in other parts of the body before surgery; (4) Metastasis from other parts of the primary tumor or direct invasion of adjacent organs from the primary tumor; and (5) Parathyroid diseases or other factors interfering with abnormal changes of procalcitonin (PCT). This study was a retrospective cohort study, which was approved by the Ethics Committee of Jingzhou Central Hospital (Reference: 2021-JH005) and conformed to the Declaration of Helsinki. Because this study adopted anonymous follow-up, the patients' personal privacy information was strictly confidential. The detailed research flow chart is shown in Figure 1.

Diagnostic criteria for postoperative PF

According to the standards defined by the International Study Group for Pancreatic Fistula (ISGPF) in 2016, that is, drainage flow > 30 mL for ≥ 72 h after an operation, the amylase content of the drainage fluid is measured. If it exceeds ≥ 3 times the upper limit of normal and had a clinical impact (such as abdominal pain or fever) and needed clinical treatment, it is judged that PF has occurred. The grade of PF updated by ISGPF in 2016 removes the diagnosis of grade A PF. The increase in amylase in asymptomatic drainage fluid is considered biochemical leakage, *i.e.*, non-real PF. The occurrence of significant clinical symptoms based on biochemical leakage and the change of treatment strategy (such as puncture and drainage, interventional hemostasis, indwelling abdominal drainage tube for > 3 wk, infection, *etc.*) is defined as grade B PF. If grade B PF needs surgical treatment, or is complicated with organ failure or even death, the grade of PF increases to grade C. Therefore, grades B and C PF are also known as clinical postoperative PF[18,19].

Blood sample collection

We chose to collect 3–5 mL blood samples from each patient on an empty stomach in the morning of 3 d before the operation, and included the latest blood routine and liver function tests in this study. Peripheral venous blood was taken in the morning of d 1, 3 and 5 after the operation, and the changes in C-reactive protein (CRP), serum PCT, and white blood cells were continuously observed.

Data collection and quality assessment

We obtained population baseline data and clinical pathological data from the patients' medical records. For instance, the pancreatic texture was evaluated by the surgeon during the operation (soft 1, hard 0), and the diameter of the main pancreatic was obtained by computed tomography or magnetic resonance imaging before the operation. We also collected routine laboratory measurement results, and when the missing value was ≥ 10% of the bias of the total variable, the variable was directly discarded and not included in the final model variable screening[20]. Finally, a total of 29 variables that met the inclusion criteria were used to build ML-based models.

Construction and verification of ML-based models

At the beginning of building the model, we randomly divided the population data into two parts, namely, the training queue and the verification queue. The training queue was used to construct the predictive model, and the validation queue was used as the internal validation of the model to evaluate the robustness of the model. When screening candidate variables, we adopted the "two-step segmentation evaluation", that is, the principle of random sorting to obtain the intersection[21]. In short, by sorting the intersection of variable sets, the optimal subset modeling was obtained. Finally, these models were evaluated through inspection, discrimination and calibration.

Statistical analysis

As for descriptive variables (*i.e.* continuous or classified variables), the median (interquartile range) or frequency (percentage) were used for statistical analysis. The χ^2 test or Mann–Whitney test was used to calculate the variables between groups to evaluate whether there was a statistical difference. Stepwise regression based on the minimum value of the Akaike information standard was used to select the variables. All data analysis was completed with the help of R language software (version 4.0.4, http://www.r-project.org/). All P values were double tailed, and $P < 0.05$ was statistically significant.

RESULTS

Clinicopathological baseline characteristics of patients

In this study, all patients were randomly divided into a training set (n = 432, 70%) and validation set (n = 186, 30%) *via* the caret package. Seventy-eight (18.06%) and 20 (10.75%) patients developed postoperative PF in the training and validation group, respectively, as shown in Table 1. There were 76 (12.3%) grade B and 22 (3.6%) grace C. One patient died of multiple organ failure due to drug-resistant

Table 1 Baseline demographic and clinicopathological characteristics of patients

Variables	Training set				Testing set			
	Overall (*n* = 432)	Non-POPF (*n* = 354)	POPF (*n* = 78)	*P* value	Overall (*n* = 186)	Non-POPF (*n* = 166)	POPF (*n* = 20)	*P* value
Age, median (IQR)	55.0 (49.0–61.0)	55.0 (49.0–61.0)	53.0 (47.25–61.0)	0.147	55.0 (50.0–60.0)	55.0 (50.0–60.0)	51.50 (45.75–59.50)	0.182
BMI, median (IQR)	23.10 (21.80–24.60)	22.80 (21.50–24.20)	25.0 (23.33–26.92)	< 0.001	22.85 (21.72–24.30)	22.70 (21.52–23.98)	24.35 (22.88–26.13)	< 0.001
Gender (%)								
Male	283 (65.5)	227 (64.1)	56 (71.8)	0.247	127 (68.3)	110 (66.3)	17 (85.0)	0.148
Female	149 (34.5)	127 (35.9)	22 (28.2)		59 (31.7)	56 (33.7)	3 (15.0)	
Smoking (%)								
Yes	198 (45.8)	143 (40.4)	55 (70.5)	< 0.001	89 (47.8)	76 (45.8)	13 (65.0)	0.165
No	234 (54.2)	211 (59.6)	23 (29.5)		97 (52.2)	90 (54.2)	7 (35.0)	
Drinking history (%)								
Yes	129 (29.9)	78 (22.0)	51 (65.4)	< 0.001	54 (29.0)	40 (24.1)	14 (70.0)	< 0.001
No	303 (70.1)	276 (78.0)	27 (34.6)		132 (71.0)	126 (75.9)	6 (30.0)	
Diabetes (%)								
Yes	110 (25.5)	49 (13.8)	61 (78.2)	< 0.001	44 (23.7)	30 (18.1)	14 (70.0)	< 0.001
No	322 (74.5)	305 (86.2)	17 (21.8)		142 (76.3)	136 (81.9)	6 (30.0)	
Hypertension (%)								
Yes	164 (38.0)	129 (36.4)	35 (44.9)	0.208	59 (31.7)	49 (29.5)	10 (50.0)	0.108
No	268 (62.0)	225 (63.6)	43 (55.1)		127 (68.3)	117 (70.5)	10 (50.0)	
Abdominal operation (%)								
Yes	130 (30.1)	103 (29.1)	27 (34.6)	0.409	53 (28.5)	47 (28.3)	6 (30.0)	1
No	302 (69.9)	251 (70.9)	51 (65.4)		133 (71.5)	119 (71.7)	14 (70.0)	
Remnant texture (%)								
Soft	121 (28.0)	62 (17.5)	59 (75.6)	< 0.001	44 (23.7)	27 (16.3)	17 (85.0)	< 0.001
Hard	311 (72.0)	292 (82.5)	19 (24.4)		142 (76.3)	139 (83.7)	3 (15.0)	
Blood transfusion (%)								
Yes	232 (53.7)	188 (53.1)	44 (56.4)	0.686	96 (51.6)	84 (50.6)	12 (60.0)	0.577
No	200 (46.3)	166 (46.9)	34 (43.6)		90 (48.4)	82 (49.4)	8 (40.0)	
Anemia (%)								
Yes	218 (50.5)	179 (50.6)	39 (50.0)	1	84 (45.2)	69 (41.6)	15 (75.0)	0.009
No	214 (49.5)	175 (49.4)	39 (50.0)		102 (54.8)	97 (58.4)	5 (25.0)	
Lesion size (%), cm								
> 3	182 (42.1)	125 (35.3)	57 (73.1)	< 0.001	67 (36.0)	54 (32.5)	13 (65.0)	0.009
≤ 3	250 (57.9)	229 (64.7)	21 (26.9)		119 (64.0)	112 (67.5)	7 (35.0)	
Pancreatic duct diameter (%), mm								
< 3	154 (35.6)	93 (26.3)	61 (78.2)	< 0.001	63 (33.9)	49 (29.5)	14 (70.0)	0.001

≥ 3	278 (64.4)	261 (73.7)	17 (21.8)		123 (66.1)	117 (70.5)	6 (30.0)	
ASA classification (%)								
I + II	231 (53.5)	188 (53.1)	43 (55.1)	0.843	85 (45.7)	78 (47.0)	7 (35.0)	0.436
III + IV	201 (46.5)	166 (46.9)	35 (44.9)		101 (54.3)	88 (53.0)	13 (65.0)	
CRP, median (IQR), mg/L	32.0 (22.0–44.0)	29.0 (21.0–38.0)	88.50 (56.0–120.0)	< 0.001	30.0 (22.0–40.0)	29.0 (21.0–38.0)	84.50 (42.25–109.25)	< 0.001
WBC, median (IQR), 10^9	5.70 (5.30–6.30)	5.70 (5.20–6.20)	6.0 (5.60–6.60)	< 0.001	5.70 (5.20–6.30)	5.60 (5.20–6.20)	6.40 (5.52–6.82)	0.002
PCT, median (IQR), μg/L	0.54 (0.37–0.68)	0.49 (0.34–0.61)	1.06 (0.78–1.21)	< 0.001	0.52 (0.37–0.67)	0.49 (0.35–0.63)	0.84 (0.68–1.09)	< 0.001
AGR, median (IQR)	1.50 (1.30–1.60)	1.50 (1.40–1.60)	1.35 (1.20–1.40)	< 0.001	1.50 (1.30–1.60)	1.50 (1.40–1.60)	1.35 (1.17–1.52)	0.003
PNI, median (IQR)	49.60 (48.10–51.23)	49.90 (48.32–51.60)	48.60 (47.35–49.60)	< 0.001	50.10 (48.40–51.48)	50.30 (48.42–51.60)	49.30 (46.85–50.37)	0.02
Neutrophil count, median (IQR), 10^9	4.02 (3.49–4.59)	4.18 (3.70–4.68)	3.36 (3.03–3.74)	< 0.001	3.94 (3.51–4.54)	4.03 (3.57–4.57)	3.46 (3.11–3.76)	< 0.001
Lymphocyte count, median (IQR), 10^9	1.64 (1.51–1.78)	1.63 (1.50–1.76)	1.79 (1.60–1.94)	< 0.001	1.64 (1.53–1.76)	1.63 (1.52–1.73)	1.83 (1.69–1.98)	< 0.001
Platelet count, median (IQR), 10^9	230.0 (208.0–252.0)	236.0 (213.0–255.0)	206.0 (185.25–229.75)	< 0.001	229.0 (206.0–253.75)	232.0 (208.25–257.75)	200.0 (182.50–225.0)	< 0.001
Monocyte count, median (IQR), 10^9	0.52 (0.45–0.60)	0.55 (0.47–0.62)	0.44 (0.39–0.49)	< 0.001	0.53 (0.46–0.61)	0.54 (0.47–0.62)	0.48 (0.42–0.52)	0.003
Hemoglobin, median (IQR), g/L	132.0 (124.0–139.0)	130.0 (121.25–138.0)	138.0 (133.0–142.75)	< 0.001	132.0 (126.0–140.0)	132.0 (126.0–139.75)	134.50 (130.0–141.0)	0.026
NLR, median (IQR)	2.0 (1.70–2.30)	1.90 (1.70–2.20)	2.70 (2.22–3.10)	< 0.001	2.0 (1.70–2.30)	1.90 (1.60–2.20)	2.80 (2.42–3.05)	< 0.001
NAR, median (IQR)	0.08 (0.07–0.09)	0.08 (0.07–0.09)	0.60 (0.30–0.88)	< 0.001	0.08 (0.07–0.09)	0.08 (0.07–0.09)	0.65 (0.38–0.80)	< 0.001
PLR, median (IQR)	136.20 (116.68–157.43)	143.85 (123.23–161.70)	113.15 (102.58–128.0)	< 0.001	136.45 (120.62–155.80)	141.0 (121.22–159.78)	120.15 (104.78–128.57)	< 0.001
LMR, median (IQR)	3.40 (2.90–3.80)	3.30 (2.80–3.70)	3.90 (3.52–4.70)	< 0.001	3.50 (3.0–3.80)	3.40 (2.90–3.70)	4.15 (3.75–4.48)	< 0.001
HALP, median (IQR)	53.95 (51.08–56.50)	52.90 (50.50–55.20)	72.75 (69.32–75.25)	< 0.001	52.45 (50.40–55.18)	51.95 (50.10–54.30)	70.10 (68.18–72.62]	< 0.001

POPF: Postoperative pancreatic fistula; IQR: Inter-quartile range; BMI: Body mass index; ASA: American Society of Anesthesiologists; CRP: C-reactive protein; WBC: White blood cell; PCT: Procalcitonin; AGR: Albumin-to-globulin ratio; PNI: Prognostic nutrition index; NLR: Neutrophil-to-lymphocyte ratio; NAR: Neutrophil-to-albumin ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; HALP: Hemoglobin level × albumin level × lymphocyte count/platelet count ratio.

bacterial infection; five underwent reoperation because of continuous blood drainage *via* the drainage tube, which was confirmed to be abdominal bleeding caused by intraoperative PF; and two were transferred to intensive care.

Selection of candidate variables

Feature selection is a universal problem in ML[22]. We performed an iterative analysis of 29 potential candidate variables, and the correlation matrix showed that there was a significant correlation between postoperative PF and inflammatory factors and some clinical variables (Figure 2A), including CRP, PCT, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and hemoglobin level × albumin level × lymphocyte count/platelet count ratio (HALP). As shown in Figure 2B, HALP, PCT, neutrophil-to-albumin ratio (NAR), PLR and PNI were the top important predictors. Meanwhile, the seven top-ranked predictors were HALP, remnant texture, PCT, NAR, PLR, PNI, and body mass index (BMI).

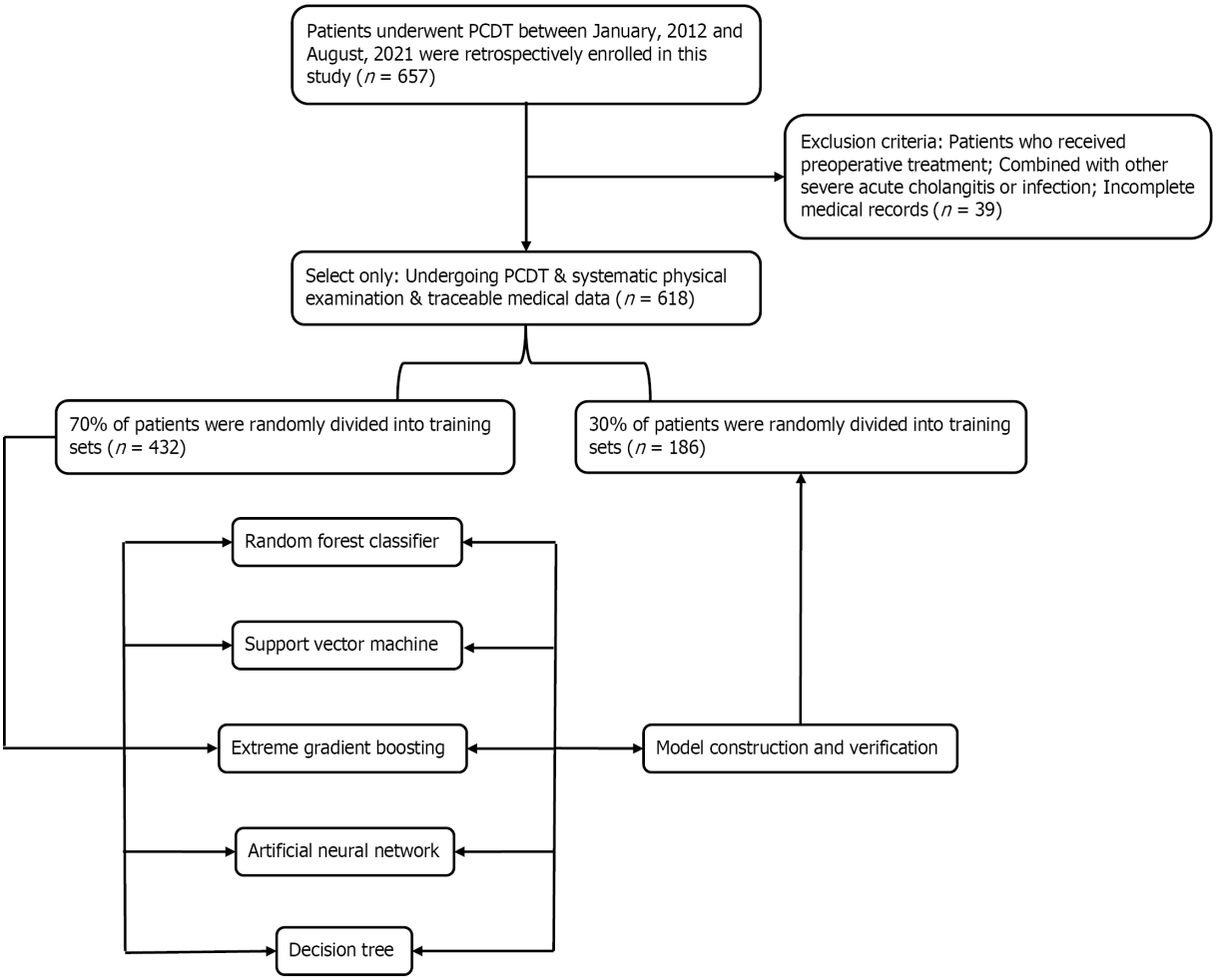

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Figure 1 The flow chart. PD: Pancreatoduodenectomy.

Construction of PF predictive model based on ML algorithm

In the training queue, each patient could use positive or negative training and output the final judgment results. For example, a random forest classifier (RFC) algorithm could be used to effectively navigate the free parameter space to obtain a robust model (Figure 3A). The variable Gini index in the RFC model is shown in Supplementary Table 1. In addition, data mining through the decision tree (DT) model was useful, as shown in Figure 3B, among the candidate variables related to inflammatory factors, PCT and BMI also played an important role in DT as branch weight, which could be used as an important predictor of postoperative PF. The artificial neural network (ANN) model also showed relatively robust predictive performance, but slightly lower than that of RFC (Figure 4). We also constructed nomographs, which depended on the parameters obtained by LR, as shown in Supplementary Table 2. Compared with traditional predictive models, inflammatory factors also accounted for an important proportion.

Comparison between ML-based models

To explore the effectiveness of five supervised learning models for postoperative PF evaluation, we used decision curve analysis (DCA) for evaluation, which was consistent with the results of the included candidate variables. Even if different predictive models included the same variables, there were certain differences in their predictive effectiveness, as shown in Figure 5. In addition, as shown in Table 2, the predictive efficiency of RFC was the best [0.897, 95% confidence interval (CI): 0.370–1.424] compared with the other four predictive models, followed by ANN (0.882, 95%CI: 0.321–1.443), DT (0.807, 95%CI: 0.250–1.364), extreme gradient boosting (XGboost) (0.793, 95%CI: 0.270–1.316), and support vector machine (SVM) (0.726, 95%CI: 0.191–1.261). In conclusion, the iterative algorithm analysis using supervised learning, RFC and ANN, as well as DT (ML-aided decision support) models were properly used to guide postoperative PF prediction.

Table 2 The operating characteristic curve analyses for each machine learning-based model

Model	AUC		No. of candidate variables
	Mean	95%CI	
RFC	0.897	0.370–1.424	7
SVM	0.726	0.191–1.261	8
DT	0.807	0.250–1.364	8
ANN	0.882	0.321–1.443	7
XGboost	0.793	0.270–1.316	9

95%CI: 95% confidence interval; RFC: Random forest classifier; SVM: Support vector machine; DT: Decision tree; ANN: Artificial neutral network; XGboost: Extreme gradient boosting; AUC: Area under curve.

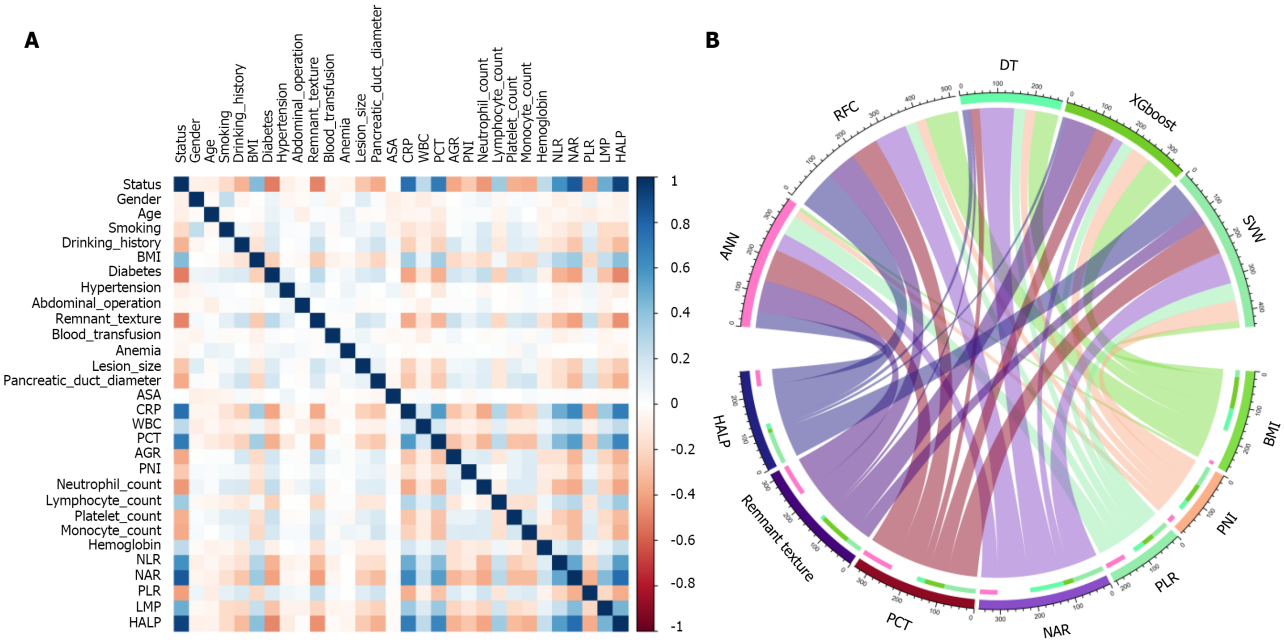

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Figure 2 Variable filtering and weight allocation. A: Correlation matrix analysis; B: Weight distribution of the candidate variables. BMI: Body mass index; ASA: American Society of Anesthesiologists; CRP: C-reactive protein; WBC: White blood cell; PCT: Procalcitonin; AGR: Albumin-to-globulin ratio; PNI: Prognostic nutrition index; NLR: Neutrophil-to-lymphocyte ratio; NAR: Neutrophil-to-albumin ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; HALP: Hemoglobin level × albumin level × lymphocyte count/platelet count ratio; RFC: Random forest classifier; SVM: Support vector machine; DT: Decision tree; ANN: Artificial neural network; XGboost: Extreme gradient boosting.

Internal validation of the optimal postoperative PF predictive model

We evaluated the clinical predictive efficiency of the optimal prediction model (RFC), as shown in Supplementary Figure 1. RFC can be used to achieve accurate stratification of patients' postoperative PF *via* clinical impact curve (CIC). In general, RFC performed best in the construction of prediction models by fusing inflammatory markers.

DISCUSSION

Our study revealed two major findings. First, accurate risk stratification of postoperative PF in patients who received PD, which mainly depended on the added value of systemic inflammation markers. Second, the ML-based predictive model is better than the traditional predictive algorithm model, which is suitable for identifying whether patients have postoperative PF.

Several risk factors leading to such complications have been reported in the relevant literature, including pancreas texture, BMI, intraoperative blood loss, blood transfusion, and operating time[9,23, 24]. We summarize updated literature on predicting postoperative PF, in combination with various

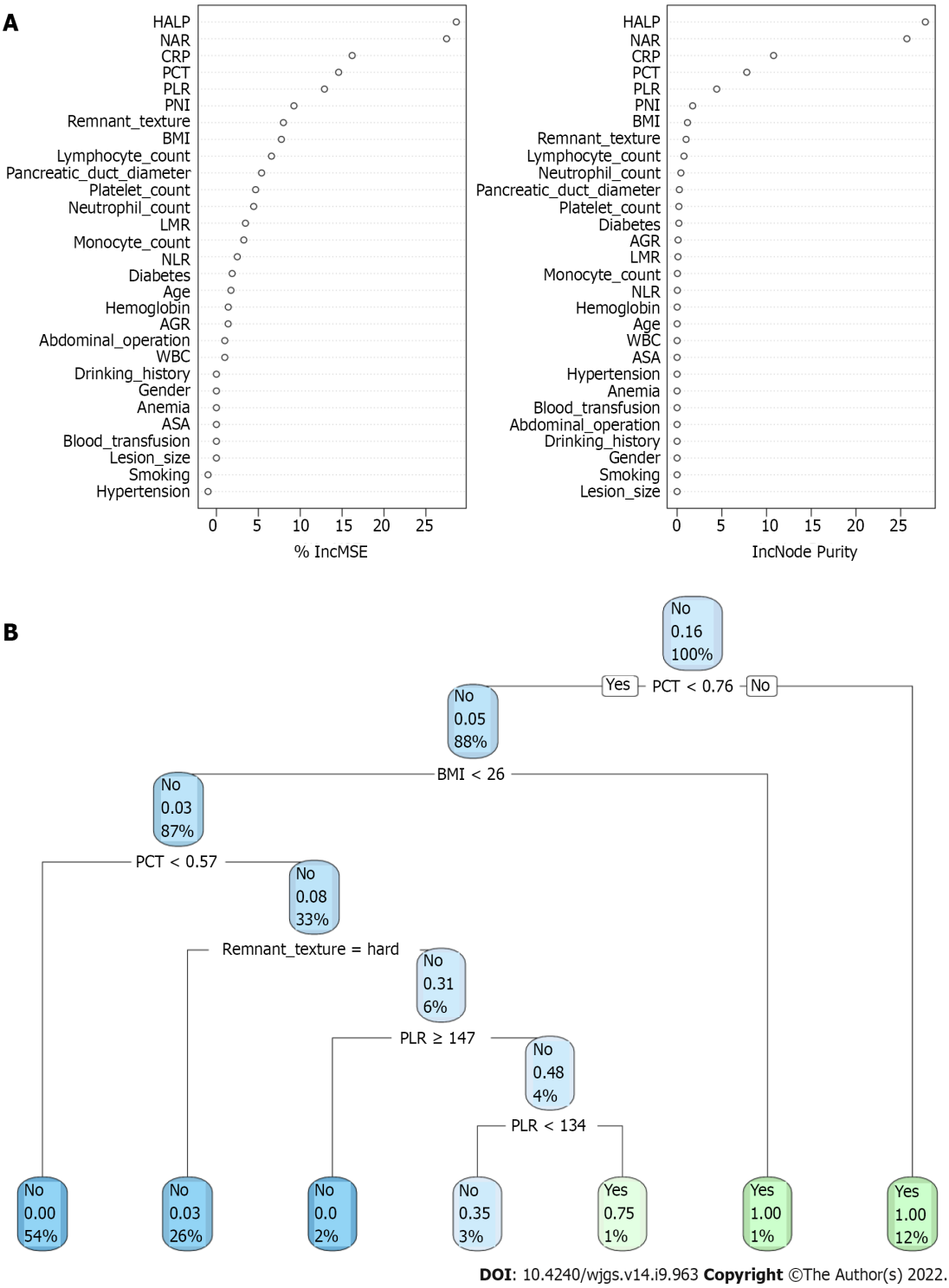

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Figure 3 Visualization of predictive model based on machine learning algorithm. A: Random forest classifier model; B: Decision tree (DT) model. The candidate factors associated with postoperative pancreatic fistula were ordered *via* RFC algorithm (A) and (B) prediction node and weight were allocated *via* DT algorithm. BMI: Body mass index; ASA: American Society of Anesthesiologists; CRP: C-reactive protein; WBC: White blood cell; PCT: Procalcitonin; AGR: Albumin-to-globulin ratio; PNI: Prognostic nutrition index; NLR: Neutrophil-to-lymphocyte ratio; NAR: Neutrophil-to-albumin ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; HALP: Hemoglobin level × albumin level × lymphocyte count/platelet count ratio; RFC: Random forest classifier; SVM: Support vector machine; DT: Decision tree; ANN: Artificial neural network.

candidate predictive markers in Supplementary Table 3. Guo *et al*[25] reported that the texture of pancreas, size of the main pancreatic duct, portal vein invasion and confirmed pathology are the risk factors of postoperative PF. Tajima *et al*[26] summarized that preoperative imaging evaluation of pancreatic pathologies would be also beneficial for stratifying. Not surprisingly, systemic inflammatory markers such as neutrophils, lymphocytes, platelets, CRP, albumin, and biomarkers may help predict postoperative PF. The systemic response to postoperative local inflammatory stimulation is tightly

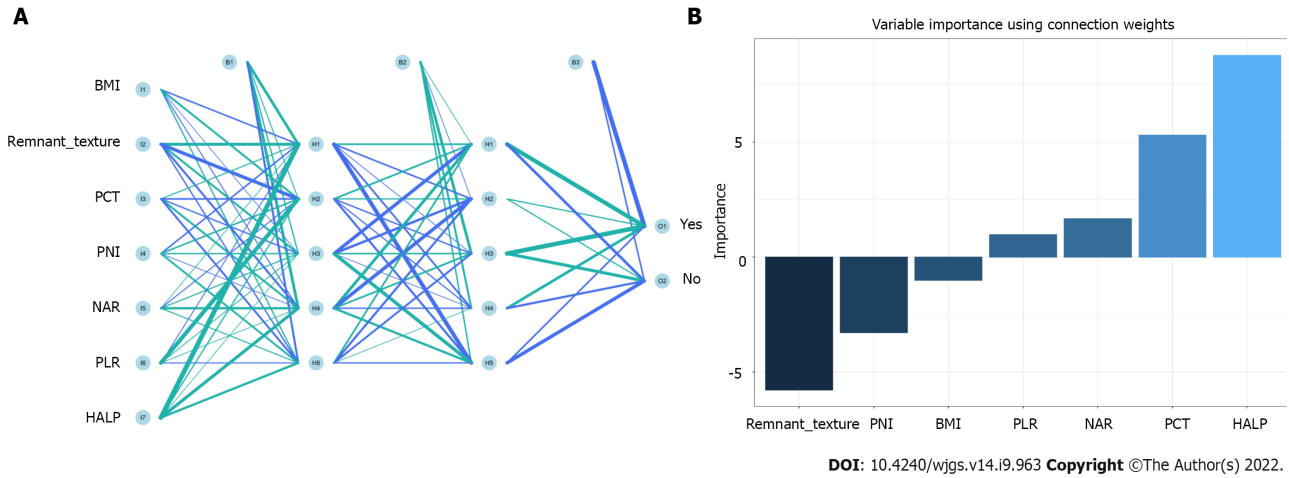

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Figure 4 Visualization of predictive model based on artificial neural network algorithm. A: Artificial neural network model; B: Variable importance using connection weight. BMI: Body mass index; PCT: Procalcitonin; PNI: Prognostic nutrition index; NAR: Neutrophil-to-albumin ratio; PLR: Platelet-to-lymphocyte ratio; HALP: Hemoglobin level × albumin level × lymphocyte count/platelet count ratio.

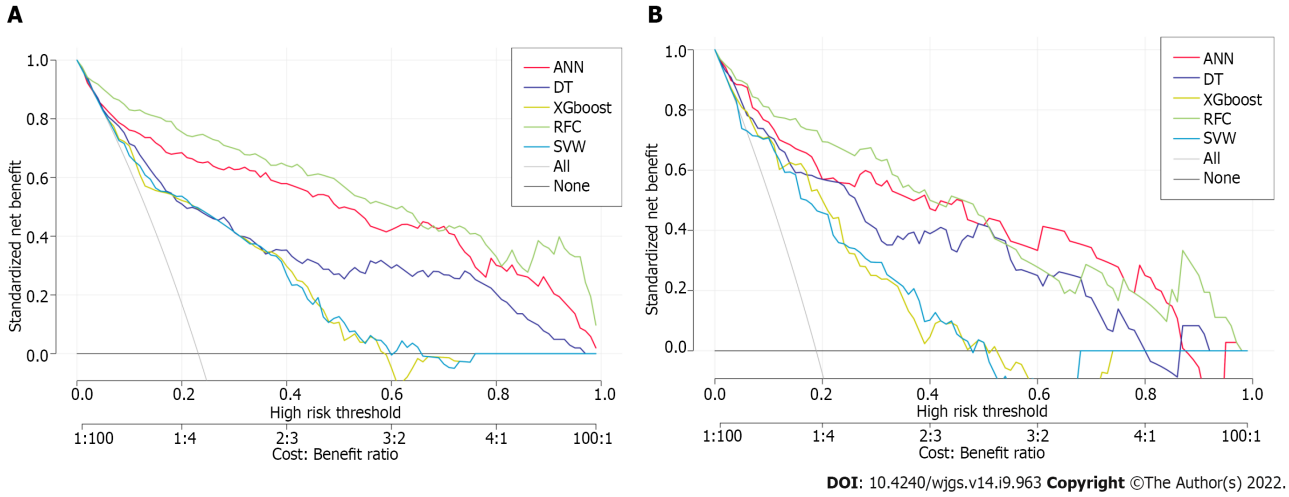

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Figure 5 Efficiency evaluation of machine learning-based prediction model. A: Decision curve analysis (DCA) of training set; B: DCA of testing set. SVM: Support vector machine; DT: Decision tree; ANN: Artificial neural network; RFC: Random forest classifier; XGboost: Extreme gradient boosting.

related to the complications after gastrointestinal surgery[27]. Gasteiger *et al*[15] reported that postoperative pancreatitis and inflammatory reaction are the main determinants of postoperative PF [15]. Intriguingly, our calculated risk factors for postoperative PF and inflammatory factors accounted for an irreplaceable weight in the predictive model.

In this study, an attempt was made to improve early postoperative risk stratification by combining local pancreatic residual inflammatory status and systemic response. We found that abnormal HALP, PCT, NAR, PLR and PNI showed reliable predictive value for postoperative PF. Previous studies have confirmed that neutrophils, as the source of vascular endothelial growth factor and tissue inhibitor protease, can promote tumor infiltration and distant metastasis[28-30]. Additionally, the number of lymphocytes in cancer patients changes frequently, which seriously affects the prognosis and survival rate[31,32]. As noted above, it appears that inflammatory factors were highly related to the presence of postoperative PF. Combined with these findings, our analysis showed that systemic inflammatory markers are of value in predicting postoperative PF.

Our ML-based model was based on clinical parameters and laboratory test results, which were consistent with previous research results. Clinical indicators including preoperative serum albumin, lipase level, and amount of intraoperative fluid infusion were independent risk factors of postoperative PF[23,24,33]. Therefore, we further analyzed the accuracy of the predictive model constructed between clinical parameters and systemic inflammatory markers based on an ML-based algorithm. Not surprisingly, we found that systemic inflammatory markers accounted for a high weight in each model. Among these predictive models, RFC allowed the calculation of risk level based on candidate variables, so the best predictive efficiency was obtained. It is not surprising that RFC adopted the resampling

technique of bootstrapping to repeatedly focus on the "bagging" procedure[34]. To detect the discrimination of the ML-based model, the DCA and CIC methods were used to evaluate the predictive performance, and the results were consistent with the expected goal. Taken together, our model may apply to patients who intended to receive PD, especially to help surgeons decide whether to prevent postoperative PF after surgery.

Despite several strengths, there were some noteworthy limitations to this study. First, patients included were from two tertiary referral hospitals, which may have resulted in selection bias. Second, although we have established a perfect predictive model through an ML-based algorithm, our model still needs to be confirmed in other hospital settings. Although we adopted internal data cross-validation, we still need more external data to verify its feasibility in the future. Third, we only adopted simple data obtained from classification, missing clinical data were not considered throughout the study. Hence, incorporating specific new technologies such as immunodiagnostic biomarkers may help to improve the accuracy of predictive models.

CONCLUSION

Our results provide new insights into candidate predictive markers associated with high risk of PF. With the help of HALP, NAR, CRP, PCT and PLR, we developed ML-based predictive models, and the performance of these unsupervised integrated models was superior to that of traditional predictive models. We expect these findings to extend research to strengthen clinical decision-making and guide treatment.

ARTICLE HIGHLIGHTS

Research background

We provide insights into the candidate predictive markers associated with a high risk of postoperative pancreatic fistula (PF) *via* serum inflammatory secretion. With the help of hemoglobin level × albumin level × lymphocyte count/platelet count ratio, neutrophil-to-albumin ratio, C-reactive protein, procalcitonin and platelet-to-lymphocyte ratio, we develop machine learning (ML)-based predictive models, and the predictive performance of these unsupervised integrated models was superior to that of traditional predictive models. We expect these findings to extend research to strengthen clinical decision-making and guide treatment.

Research motivation

Fluctuating serological inflammation markers and prognostic nutritional index can be detected in the early postoperative period, and clinically well established to predict postoperative PF; in particular, random forest classifier (RFC) performed best, which can guide optimal treatment, clinical management and prevent or mitigate adverse consequences.

Research objectives

A total of 29 variables were used to build the ML predictive model. Among them, the best predictive model was RFC, the area under the curve (AUC) was [0.897, 95% confidence interval (CI): 0.370–1.424], while the AUC of the artificial neural network, eXtreme gradient boosting, support vector machine, and decision tree were between 0.726 (95%CI: 0.191–1.261) and 0.882 (95%CI: 0.321–1.443).

Research methods

As for descriptive variables (*i.e.*, continuous or classified variables), the median (interquartile range) or frequency (percentage) were used for statistics in this study. The χ^2 test or Mann–Whitney test was used to calculate the variables between groups to evaluate whether there was a statistical difference. Stepwise regression based on the minimum value of the Akaike information standard was used to select the variables. All data analysis was completed with the help of R language software (version 4.0.4, http://www.r-project.org/). All P values were double tailed, and $P < 0.05$ was statistically significant.

Research results

A total of 29 variables were used to build the ML predictive model. Among them, the best predictive model was RFC, the area under the curve (AUC) was [0.897, 95% confidence interval (CI): 0.370–1.424], while the AUC of the artificial neural network, eXtreme gradient boosting, support vector machine, and decision tree were between 0.726 (95%CI: 0.191–1.261) and 0.882 (95%CI: 0.321–1.443).

Research conclusions

Fluctuating serological inflammatory markers and prognostic nutritional index (PNI) can be detected in

the early postoperative period, which has been clinically proved to predict postoperative PF. In particular, RFC performed best, which can guide optimal treatment, clinical management, and prevent or mitigate adverse consequences.

Research perspectives

PD, also known as a Whipple procedure, is one of the most difficult and complex surgeries that carries a high rate of major complications. Postoperative PF, as one of the most difficult complications after PD, can seriously endanger the lives of patients, so it has become an area of continuous concern for pancreatic surgeons. Although the safety of PD has improved significantly in the past three decades, previous prospective studies have reported that postoperative PF has an incidence of > 10%. Understanding the potential complications and early warning of these complications is important for the care of these patients.

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FOOTNOTES

Author contributions: Long ZD, Lu C, Xia XG, Chen B, Xing ZX, Bie L, Zhou P, Ma ZL, and Wang R designed the research study; Long ZD, Lu C, Xia XG, and Chen B performed the research; Xia XG, Chen B, and Xing ZX contributed new reagents and analytic tools; Long ZD, Lu C, Xia XG, Chen B, Xing ZX, Bie L, Zhou P, Ma ZL, and Wang R analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

Institutional review board statement: This retrospective study was following the declaration of Helsinki, and was ethically reviewed and approved by the Institutional Ethics Committee of Jingzhou Hospital, No. 2021-JH005.

Informed consent statement: Since the patient information contained in this study was anonymous, written informed consent was not obtained from all participants.

Conflict-of-interest statement: All authors declare that there is no conflict of interest.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

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ORIGINAL ARTICLE

Retrospective Study

Feasible management of median arcuate ligament syndrome in orthotopic liver transplantation recipients

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Abstract

BACKGROUND

In orthotopic liver transplantation (OLT) recipients, median arcuate ligament syndrome (MALS) is considered a risk factor for hepatic arterial thrombosis (HAT), which is dreadful for OLT recipients. Different alternative surgical procedures have been proposed to overcome the impact of MALS on transplantation, but clinical evidence is still scarce.

AIM

To evaluate the feasible surgical management of MALS to reduce complications in OLT patients.

METHODS

Data for 288 consecutive patients who underwent OLT at The First Hospital of Jilin University between January 2017 and July 2020 were retrospectively reviewed. The surgical management of median arcuate ligament (MAL) and modifications to the arterial anastomosis were recorded. The perioperative and long-term prognosis of MALS recipients were noted. Detailed preoperative and postoperative data of patients were analyzed in a descriptive manner.

RESULTS

Eight patients with MALS were included in this study. The first patient with MALS received no intervention during the primary surgery and developed postoperative HAT. Salvage liver transplantation with MAL division was successfully performed. Gastroduodenal artery (GDA) preservation with splenic artery ligation was performed on three patients, only GDA preservation was performed on two patients, and no intervention was performed on two patients. No patient developed HAT after surgery and postoperative recovery was

satisfactory.

CONCLUSION
The preservation of collateral circulation between the superior mesenteric artery and celiac trunk *via* the GDA with or without splenic artery ligation is a safe and feasible alternative to MAL division.

Key Words: Orthotopic liver transplantation; Median arcuate ligament syndrome; Surgical complications; Surgical management; Hepatic artery thrombosis

Core Tip: This retrospective single-center study analyzed diagnosis, surgical procedure and outcome of 8 patients with median arcuate ligament syndrome (MALS). In eight patients with MALS, orthotopic liver transplantation without median arcuate ligament (MAL) division and celiac trunk-aorta bypass ensured adequate hepatic arterial blood flow. No new onset hepatic arterial thrombosis was observed. The study suggests that without intraoperative MAL release, one cannot ensure adequate hepatic artery flow and prevent hepatic arterial thrombosis.

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INTRODUCTION

Orthotopic liver transplantation (OLT) is the most effective treatment for end-stage liver disease[1]. Although the operative technique for OLT has been standardized, postoperative hepatic arterial thrombosis (HAT) remains a rare but dreadful complication[2-4]. Previous studies have demonstrated that factors associated with HAT include anastomotic stenosis, anastomosis inversion, arterial tortuosity, acute cellular rejection, transfusion and other rare factors. Median arcuate ligament syndrome (MALS) is one of the rare causes of HAT[5-7]. MALS refers to an extrinsic compression of the celiac axis caused by the fibrous ligament known as the MAL and periaortic ganglionic tissue[8]. The condition was first reported as a post-mortem finding by Lipshutz[9] in 1917. Harjola[10] and Dunbar *et al*[11] successfully performed median arcuate ligament (MAL) release operations in 1963 and 1965, respectively. MALS can reduce the hepatic blood flow velocity from 425 cm/s to 200 cm/s[12]. This indicates that MALS can disrupt the hepatic artery hemodynamics, which is considered a high-risk factor for HAT in OLT recipients[12,13]. Thus, timely recognition and management of MALS is of major importance for transplant surgeons. Different surgical procedures have been proposed to overcome the impact of MALS on transplantation, but clinical evidence is still scarce with regard to the surgical treatment of MALS. In this retrospective study, we evaluated the surgical management of MALS to reduce complications in OLT patients.

MATERIALS AND METHODS

Patients

The data for 288 consecutive patients who underwent OLT at The First Hospital of Jilin University between January 2017 and July 2020 were retrospectively reviewed. All patients received liver grafts from cardiac death donors. Patients without adequate preoperative images as well as those who received simultaneous liver-kidney transplantation and pediatric liver transplantations were excluded. The collected data included preoperative data on celiac truck stenosis and MALS, surgical procedures for MALS as well as postoperative short- and long-term follow-up details. The investigators obtained approval from the Ethics Committee of The First Hospital of Jilin University. All patients provided written informed consent for the procedures.

Preoperative computed tomographic angiography

All OLT recipients underwent preoperative computed tomographic angiography (CTA) (Figure 1). End-inspiratory arterial phase, end-expiratory portal venous phase and sagittal arterial reconstruction were

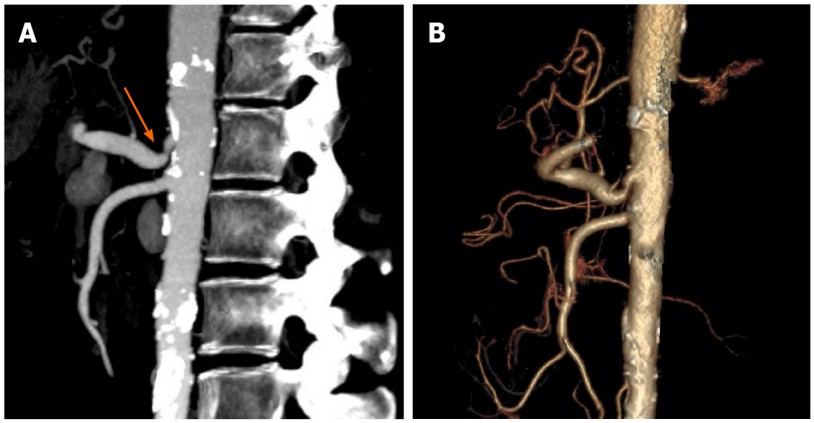

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Figure 1 Computed tomography images of orthotopic liver transplantation recipients with median arcuate syndrome in the sagittal plane.
A: Patient with median arcuate ligament syndrome showing stenosis of the celiac trunk due to compression by the median arcuate ligament and the post-stenotic dilation (arrow); B: Abundant collateral circulation between the superior mesenteric artery and the celiac trunk (arrow).

examined. Vascular abnormalities were evaluated by a senior staff radiologist and the transplant surgeon to determine the operative approach. According to stenosis rate, length of stenosis and distance from aorta, Sugae *et al*[14] classified MALS to three types. The rate of type A stenosis should be less than 50%, its length should be less than 3 mm, and its position should be more than 5 mm from the aorta. The rate of type B stenosis should be between 50 and 80 percent, its length should be between 3 and 8 mm, and its position should be greater than 5 mm from the aorta. The rate of type C stenosis should exceed 80%, its length should exceed 8 mm, and its position should be less than 5 mm from the aorta. MALS was defined based on extrinsic compression on the celiac trunk due to MAL, post-stenotic dilatation, and patients diagnosed with MALS should exhibit at least one or more of the following symptoms postprandial pain, weight loss and small meals as described previously[8,15].

Surgical management of MALS

OLT recipients with suspected or confirmed MALS on pre-operative imaging underwent detailed evaluation of the collateral circulation between the superior mesenteric artery and the celiac trunk based on the pre-operative imaging and intraoperative findings. Gastroduodenal arteries (GDAs) with abundant collateral branches were clamped to determine whether the hepatic arterial flow or pulse was reduced. If clamping decreased the hepatic arterial flow, then the GDA and collateral branches were preserved. The hepatic artery/splenic artery patch from the donor and right/left hepatic artery patch from the recipient were used for branch patch anastomosis (Figure 2). If hepatic arterial flow was not affected by GDA clamping, the hepatic artery/GDA patch from the recipient and hepatic artery/splenic artery patch from the donor was used for branch patch anastomosis as a standard arterial revascularization method (Figure 3). After the anastomosis, the intrahepatic arterial blood flow was evaluated using Doppler ultrasound. If the blood flow was not satisfactory (hepatic arterial blood flow rate < 50 cm/s), after assessing the potential for splenic artery steal syndrome, the splenic artery was ligated and the hepatic arterial flow and pulse was tested again. Surgical division of MAL or celiac trunk-aorta bypass was performed when the hepatic arterial flow remained poor despite all the above measures.

Postoperatively, Doppler ultrasound was used periodically: every 12 h during the first week, twice per week until discharged, and once a week for 3 mo to monitor hepatic artery anastomosis. If Doppler ultrasound revealed any abnormal findings, such as HAT as defined by resistive index (RI) < 0.5 and hepatic artery blood flow < 39 cm/s[16] combined with elevated liver enzymes and bilirubin suggestive of hepatocellular injury, CTA was performed immediately to determine the status of hepatic artery anastomosis and initiate the timely salvage of the liver graft if required.

If there were no other signs, the patients received standard prophylaxis of thromboembolism for 6 wk post-OLT and no anticoagulant therapy was used.

RESULTS

Patient characteristics and perioperative outcomes

Among 288 patients who received OLT, eight were diagnosed with MALS (Figure 1). The mean recipient age was 59 years. There were four men and four women. The warm ischemia time for the liver graft ranged from 12 s to 41 s and the cold ischemia time ranged from 452 min to 632 min. The median follow-up was 20 mo. Other patient characteristics are presented in Table 1. The surgical details for the

Table 1 Characteristics and prognoses of patients with median arcuate ligament syndrome who received orthotopic liver transplantation

Characteristics and prognoses	1	2	3	4	5	6	7	8
Age, donor/recipient	55/52	54/53	67/66	45/48	62/63	52/62	56/38	50/63
Sex, donor/recipient	F/F	M/F	M/M	F/M	M/M	M/F	M/M	M/F
BMI, donor/recipient	20/19	22/22	22/23	21/19	23/20	26/21	22/20	25/21
Donor cause of death	CVA	CVA	Trauma	CVA	Trauma	CVA	CVA	Trauma
The primary disease	PBC	AIH	AIH	Viral	Viral	Viral	Viral	HCC
MALS type	B	B	B	C	A	B	A	A
Cold ischemic time in min	608	348	461	582	586	510	550	458
Warm ischemic time in s	19	15	41	29	12	26	15	16
Intraoperative blood loss in mL	1800	1500	2850	3000	7000	300	1000	2000
Intra-operative red blood cell transfusions in U	4	20	10.5	22	27	9	8	16.5
Intra-operative fresh frozen plasma transfusions in mL	1000	2350	1200	950	3600	960	420	960
Operation time in min	485	580	526	538	632	556	560	452
Intraoperative hepatic arterial blood flow rate in cm/s	NA	80	90	50	60	65	50	53
Hepatic arterial blood flow rate on discharge in cm/s	80	85	102	64	65	70	60	68
Hospital stay in d	17	28	39	18	21	17	17	15

AIH: Autoimmune hepatitis; BMI: Body mass index; CVA: Cerebrovascular accident; F: Female; HCC: Hepatocellular carcinoma; M: Male; NA: Not available; PBC: Primary biliary cirrhosis.

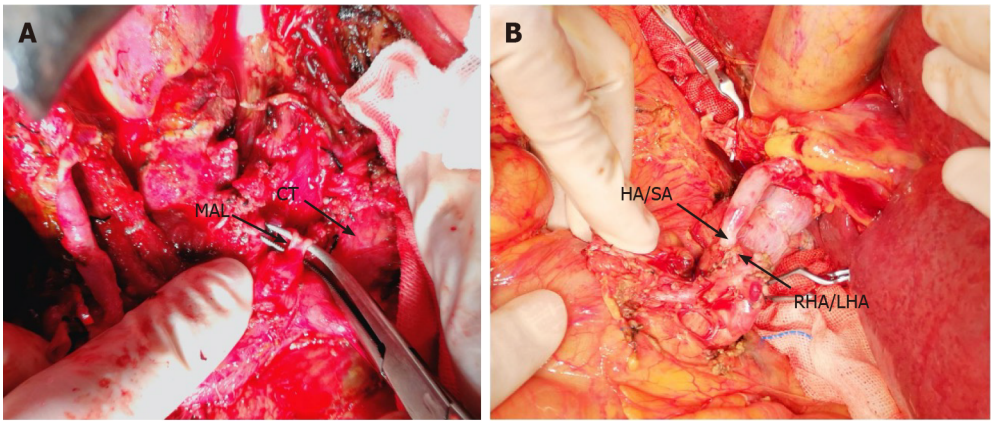

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Figure 2 Intraoperative photograph. A: Median arcuate ligament division; B: The hepatic artery/splenic artery patch from the donor and the right/left hepatic artery patch from the recipient were used for branch patch anastomosis with preservation of the gastroduodenal artery. MAL: Median arcuate ligament; CT: Computed tomography; HA/SA: Hepatic artery/splenic artery; RHA/LHA: Right/left hepatic artery.

recipients with MALS are shown in Table 2.

For the first patient, due to a lack of knowledge about MALS, no intervention for celiac trunk stenosis caused by MAL was performed during the first operation and standard revascularization was performed. On the ninth postoperative day, the total and direct bilirubin reached 210 mmol/L and 130 mmol/L, respectively. Markers of hepatocellular injury increased (alanine aminotransferase 337.5 U/L, aspartate aminotransferase 88.9 U/L). The hepatic flow rate decreased to 10 cm/s and the resistive index dropped to 0.4, suggestive of HAT. On exploratory laparotomy, there was extensive thrombosis in the hepatic artery around the anastomosis. Thrombectomy was performed and hepatic arterial blood flow was restored after re-anastomosis. However, there was no intrahepatic blood flow on Doppler ultrasound, probably due to intrahepatic arterial thrombosis. Thrombolytic therapy with alteplase was

Table 2 Details about hepatic arterial reconstruction

No.	Donor arterial patch	Recipient arterial patch	Ligament lysis	GDA preservation	Splenic artery ligation
1	Celiac truck	Hepatic/gastroduodenal artery patch	Yes	No	No
2	Hepatic/splenic artery patch	Right/left hepatic artery patch	No	Yes	Yes
3	Common hepatic artery	Right/left hepatic artery patch	No	Yes	Yes
4	Hepatic/splenic artery patch	Right/left hepatic artery patch	No	Yes	Yes
5	Common Hepatic artery	Right/left hepatic artery patch	No	Yes	No
6	(1) Gastroduodenal artery; (2) common hepatic artery	(1) Right hepatic artery from the superior mesenteric artery; (2) proper hepatic artery	No	Yes	No
7	Hepatic/splenic artery patch	Hepatic/gastroduodenal artery patch	No	No	No
8	Hepatic/splenic artery patch	Hepatic/gastroduodenal artery patch	No	No	No

GDA: Gastroduodenal artery.

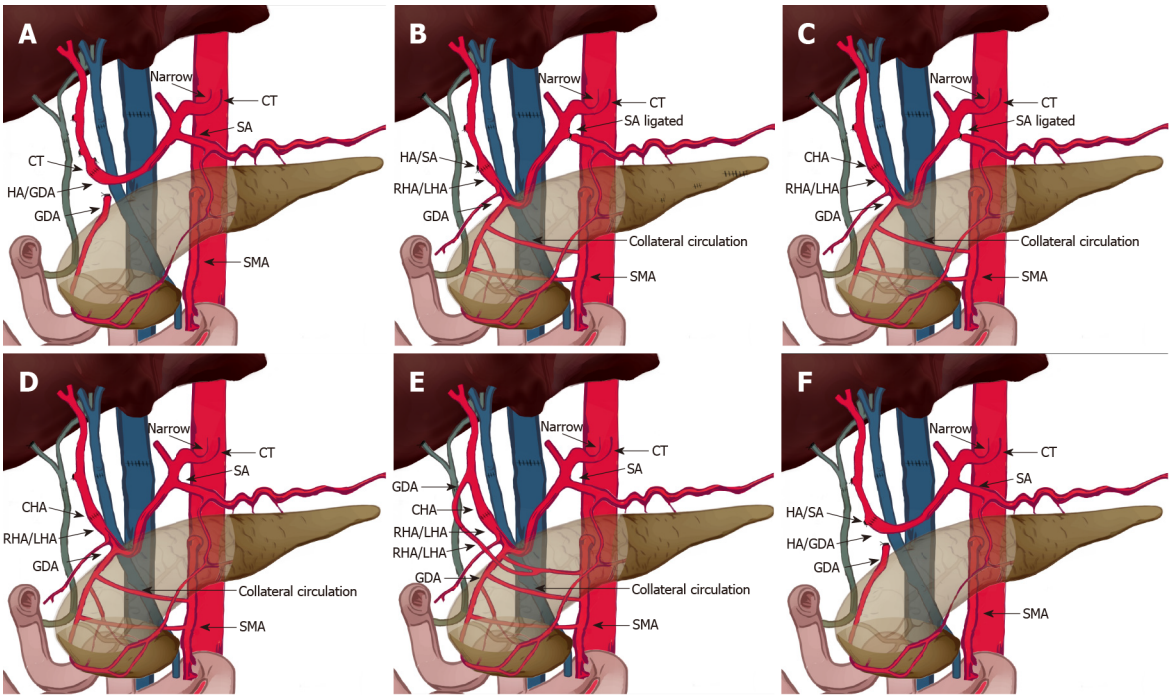

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Figure 3 Schematic diagram showing different types of patch anastomoses performed in this study. A: Donor: celiac trunk; recipient: hepatic/gastroduodenal artery (GDA) patch. Median arcuate ligament (MAL) was divided. Splenic artery was not ligated; B: Donor: hepatic/splenic artery (HA/SA) patch; recipient: right/left hepatic artery (RHA/LHA) patch; MAL was not divided. GDA was preserved. Splenic artery was ligated; C: Donor: common hepatic artery (CHA); recipient: RHA/LHA patch; MAL was not divided. GDA was preserved. Splenic artery was ligated; D: Donor: CHA; recipient: RHA/LHA patch; MAL was not divided. GDA was preserved. Splenic artery was not ligated; E: Donor: (1) GDA; and (2) CHA; recipient: (1) aberrant right hepatic artery; and (2) right/left hepatic artery patch; MAL was not divided. GDA was preserved. Splenic artery was not ligated; F: Donor: HA/SA patch; recipient: hepatic/GDA patch; MAL was not divided. Splenic artery was not ligated. MAL: Median arcuate ligament; CT: Computed tomography; HA/SA: Hepatic artery/splenic artery; RHA/LHA: Right/left hepatic artery; GDA: Gastroduodenal artery; SMA: Superior mesenteric artery; CHA: Common hepatic artery.

given but failed to restore the intrahepatic blood flow. Six hours later, salvage liver transplantation was performed and the MAL was divided (Figure 2A and 3A, Table 1 and 2). Postoperatively, the hepatic blood flow rate increased to 70-87 cm/s.

The remaining six patients had normal preoperative hepatic arterial flow. Four patients had abundant collateral circulation between the superior mesenteric artery and the celiac trunk *via* GDA (Figure 1B), thus GDA was preserved and the hepatic artery/splenic artery patch from the donor and right/left hepatic artery patch from the recipient were used for branch patch anastomosis (Figure 2B).

In three patients, low hepatic arterial flow rate was detected using Doppler ultrasound during the operation with patent anastomosis. Consequently, splenic artery steal syndrome was evaluated when RI was greater than 0.8 and hepatic artery blood flow was less than 35 cm/s[17]. Hepatic artery blood flow returned to normal after splenic artery ligation, and no HAT occurred after surgery (Figures 3B-D).

Another patient with aberrant right hepatic artery received two anastomoses. The first anastomosis was performed between the recipient right hepatic artery from the superior mesenteric artery and the donor GDA. The second anastomosis was done between the recipient's proper hepatic artery and the donor common hepatic artery (Figure 3E).

Two patients received standard arterial revascularization without preservation of the GDA or splenic artery ligation (Figure 3F).

The seven MALS patients without MAL division had satisfactory hepatic arterial blood flow after the operation. All eight patients had adequate hepatic arterial blood flow at discharge, as presented in Table 1.

Long-term outcomes of patients with MALS

The median follow-up was 19 mo (range: 10-29 mo). All the patients are alive. Among these eight patients, seven of them are healthy without complications. One patient developed biliary stricture 2 mo after surgery, which was successfully managed with endoscopic retrograde cholangiography and biliary stenting.

DISCUSSION

In MALS, the coeliac artery gets compressed by the MAL, leading to reduced blood flow in the hepatic artery[12,13,18-20]. Because the blood flow in the hepatic artery is significantly reduced, it predisposes the patients to HAT after OLT, which leads to graft failure in 50% of cases and re-transplantation[2,21-24]. MALS patients with normal hemodynamics usually have no or little clinical symptoms before OLT. However, in the postoperative phase after OLT, patients may develop severe hemodynamic restrictions in hepatic arterial flow, which increases the risk of HAT[25]. Hence, an appropriate preoperative surgical plan should be developed for OLT patients with MALS. The reported incidence of MALS after liver transplantation varies from 2% to 12%[21,26,27]. The low incidence of MALS in previous reports may be due to insufficient awareness of this disease and limited diagnostic methods. Currently, the extensive application of contrast enhance computed tomographic (CECT) has improved the diagnostic rate of MALS.

Recurrent post-prandial epigastric pain, weight loss, nausea or vomiting and abdominal pain after exercise is common symptoms of MALS. Eight patients in this study had a history of epigastric pain and weight loss, but these symptoms were attributed to chronic hepatitis and decompensated liver cirrhosis. Therefore, the diagnosis of MALS is partly clinical and mainly based on radiology. Celiac axis stenosis caused by MAL appears similar to a hook on CECT during sagittal reconstruction[28]. Abundant collateral branches, post-stenotic dilation and thickening of the MAL can also help in the diagnosis of MALS. Angiography used to be a routine test for detecting aberrant arterial vessels but is now used selectively for suspected cases in arterial dynamic studies[21,28]. Gruber *et al*[29] found that the combination of a maximum end-expiratory velocity over 350 cm/s in the celiac trunk and a deflection angle higher than 50°, detected using functional ultrasound, was a reliable diagnostic method for MALS. At our center, we routinely perform CTA on OLT patients to detect vascular variations and MALS.

Sugae *et al*[14] classified MALS into three types according to the stenosis rate, length of stenosis, distance from the aorta and collateral pathways. According to the different types, it has been suggested that type A MALS should not be manipulated, while type B and type C usually require surgery to maintain the blood supply of the hepatic artery.

Cassar *et al*[24] reported the fourth type in which coeliac artery compression from MAL is at the origin of splenic artery and surgical intervention is required to restore hepatic artery flow during liver transplantation. These suggestions are all based on maintaining the hepatic blood to the liver graft, as it is sensitive to hemodynamic changes. Therefore, whether an intervention should be performed for type A needs to be determined carefully. If MAL-related compression is mild with adequate pre- or intraoperative arterial blood flow, surgical division of MAL is not necessary. However, the perioperative hepatic artery flow is determined by various factors, making it difficult to determine whether the blood flow is adequate[8]. Golse *et al*[30] used intraoperative contrast-enhanced Doppler ultrasonography to determine the hepatic blood flow in OLT patients. In their reports, MALS patients who required further treatment and six patients with weak arterial flow without intervention underwent MAL division and the incidence of postoperative vascular complications was significantly reduced. In this study, we determined the hepatic blood flow based on the pulse in the hepatic artery and arterial blood flow rate measured using intraoperative Doppler ultrasonography after anastomosis. In MALS patients, postoperative Doppler ultrasound was used routinely to determine hepatic arterial blood flow.

Currently, there is no consensus on the treatment of MALS in patients who undergo liver transplantation. The various methods reported in the literature are as follows: (1) Endovascular interven-

tional therapy; (2) MLA division to release the extrinsic compression on the celiac axis; (3) Anastomosis of the graft's celiac artery to the recipient's aorta; and (4) Use of gastroduodenal branch-patch anastomosis without MAL division[21].

With the continuous advancements in endovascular interventional therapy, some OLT recipients with MAL have been treated with interventional therapy postoperatively to restore the hepatic blood flow [31,32]. However, the preoperative use of stenting remains controversial, as persistent external compression from the MAL carries a higher risk[21,33].

Recent studies have suggested that regular vascular reconstruction after surgical division of MAL in liver transplant recipients with MALS is safe and effective[13,34]. Czigany *et al*[21] reported a 7-year retrospective study of 34 MALS patients, in which 26 patients received MAL division and four patients required aorto-hepatic conduit construction. Twenty-six patients who underwent surgical division of MAL or alternative reconstruction had no postoperative complications. Three patients with MALS who did not receive any intervention for MALS developed severe vascular complications and one of them required re-transplantation. In their study, preoperative assessment of vascular aberrations and different surgical approaches were planned before the surgery which led to a relatively low HAT rate.

MAL division is a standard treatment for MALS. However, OLT recipients with MALS usually have gastroesophageal varices and extensive collateral vessels between the celiac trunk and superior mesenteric artery, which increases the risk of bleeding during MAL division. The most common collateral circulation is the superior mesenteric artery-pancreaticoduodenal artery-GDA-hepatic artery network. This collateral circulation helps in maintaining hepatic arterial flow in MALS patients after liver transplantation, even without MAL division. Lubrano *et al*[27] reported that one out of 10 patients with MALS underwent MAL division while six patients underwent standard hepatic arterial reconstruction without the division of MAL. None of the 10 patients experienced postoperative vascular complications. In this study, one patient with MALS received standard hepatic arterial reconstruction with GDA ligation. The patient developed HAT during the postoperative period and required a salvage liver transplantation with MAL division. The remaining seven MALS patients were diagnosed with MALS before surgery and had adequate hepatic blood flow preoperatively, determined with Doppler ultrasound. Thus MAL was not divided irrespective of the type. Five patients were found to have abundant collateral circulation between the superior mesenteric artery and the celiac trunk before surgery; therefore, the GDA was preserved intraoperatively. The other two patients had no obvious collateral circulation. Consequently, the GDA was clamped and hepatic arterial blood flow was assessed. Since there was adequate hepatic blood flow despite GDA clamping, GDA ligation with standard hepatic arterial anastomosis was performed. All seven patients had good postoperative hepatic blood flow without HAT. Hence, we believe that in OLT recipients with MALS, preservation of the collateral circulation without MAL division is a safe and feasible procedure. The procedure has fewer complications and makes surgery easier. In addition to collateral preservation, the splenic artery can be ligated if necessary. Additionally, we used the left and right hepatic artery bifurcations to enlarge the anastomosis. If the hepatic artery blood flow is still unsatisfactory with the above measures, the division of MAL may be considered. Hepatic artery-abdominal aorta bypass is the most difficult surgical procedure and can be used as a last resort.

This study has certain limitations. First, this study was a single-center retrospective study. Second, the number of patients was limited. Hence, future studies with larger sample sizes are needed to verify the findings of this study.

CONCLUSION

Preoperative diagnosis of MALS in OLT recipients is important to prevent HAT. Preservation of collateral circulation with or without splenic artery ligation is an easier surgical technique with shorter operation time and a lower risk of intraoperative complications compared to MAL division and celiac trunk-aorta bypass to ensure adequate hepatic arterial blood flow.

ARTICLE HIGHLIGHTS

Research background

In orthotopic liver transplantation (OLT) recipients, median arcuate ligament syndrome (MALS) is regarded as a risk factor for hepatic artery thrombosis (HAT), a devastating complication of OLT. To counteract the influence of MALS on transplantation, a variety of different surgical methods have been proposed, but clinical evidence is still lacking.

Research motivation

To increase the survival rate of MALS patients who receive OLT and decrease postoperative complications.

Research objectives
To evaluate the efficacy of surgical treatment for MALS to reduce complications in OLT patients in order to improve patient survival and decrease the incidence of postoperative complications.

Research methods
A total of 288 consecutive OLT patients at The First Hospital of Jilin University were retrospectively evaluated. Median arcuate ligament (MAL) surgical treatment and arterial anastomosis modification were recorded. Perioperative and long-term MALS prognoses were noted.

Research results
In this investigation, eight patients with MALS were enrolled. The first patient with MALS did not get any intervention during the main operation, and afterward developed HAT. Successful salvage liver transplantation with MAL division was accomplished. Gastroduodenal artery (GDA) preservation with splenic artery ligation was performed on three patients, GDA preservation alone was performed on two patients, and no intervention were performed on two patients. After surgery, no patient got HAT and healing was acceptable.

Research conclusions
The preservation of collateral circulation between the superior mesenteric artery and celiac trunk *via* the GDA, with or without ligation of the splenic artery, provides a safe and practicable alternative to MAL division.

Research perspectives
To provide surgeons with effective and feasible surgical options when they need to perform OLT in MALS patients.

FOOTNOTES

Author contributions: Li SX and Fan YH contributed equally to this work; Li SX wrote the original draft of the manuscript; Fan YH was responsible for the revision and editing of the manuscript; Tian GY was responsible for data curation and software; LV GY was responsible for supervision and methodology; All authors issued final approval for the version submitted.

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ORIGINAL ARTICLE

Retrospective Study

Study of preoperative diagnostic modalities in Chinese patients with superficial esophageal squamous cell carcinoma

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Abstract

BACKGROUND

Endoscopic ultrasonography (EUS) and magnifying endoscopy (ME) reliably determine indications for endoscopic resection in patients with superficial esophageal squamous cell carcinoma (SESCC). ME is widely accepted for predicting the invasion depth of superficial esophageal cancer with satisfying accuracy. However, the addition of EUS is controversial.

AIM

To evaluate the diagnostic efficiency of ME *vs* EUS for invasion depth prediction and investigate the influencing factors in patients with SESCC to determine the best diagnostic model in China.

METHODS

We retrospectively analyzed patients with suspected SESCC who completed both ME and EUS and then underwent endoscopic or surgical resection at Sun Yat-Sen University Cancer Center between January 2018 and December 2021. We evaluated and compared the diagnostic efficiency of EUS and ME according to histological results, and investigated the influencing factors.

RESULTS

We included 152 lesions from 144 patients in this study. The diagnostic accuracies of ME and EUS in differentiating invasion depth were not significantly different (73.0% and 66.4%, $P = 0.24$); both demonstrated moderate consistency with the pathological results (ME: kappa = 0.58, 95% confidence interval [CI]: 0.48-0.68, $P < 0.01$; EUS: kappa = 0.46, 95%CI: 0.34-0.57, $P < 0.01$). ME was significantly more accurate in the diagnosis of high-grade intraepithelial (HGIN) or carcinoma *in situ* (odds ratio [OR] = 3.62, 95%CI: 1.43-9.16, $P = 0.007$) subgroups. Using a miniature probe rather than conventional EUS can improve the accuracy of lesion depth determination (82.3% *vs* 49.3%, $P < 0.01$). Less than a quarter of circumferential occupation and application of a miniature probe were independent risk factors for the accuracy of tumor invasion depth as assessed by EUS (< 1/4 circumferential occupation: OR = 3.07, 95%CI: 1.04-9.10; application of a miniature probe: OR = 5.28, 95%CI: 2.41-11.59, $P < 0.01$). Of the 41 lesions (41/152, 27.0%) that were misdiagnosed by ME, 24 were corrected by EUS (24/41, 58.5%).

CONCLUSION

Preoperative diagnosis of SESCC should be conducted endoscopically using white light and magnification. In China, EUS can be added after obtaining patient consent. Use of a high-frequency miniature probe or miniature probe combined with conventional EUS is preferable.

Key Words: Superficial esophageal squamous cell carcinoma; Endoscopic ultrasound; Magnifying endoscopy; Endoscopic resection; Japan Esophageal Society classification

Core Tip: Endoscopic ultrasonography (EUS) and magnifying endoscopy (ME) reliably determine indications for endoscopic resection in patients with superficial esophageal squamous cell carcinoma (SESCC). ME is a widely accepted method for predicting the invasion depth. However, the addition of EUS is controversial. We retrospectively analyzed Chinese patients with suspected SESCC who completed both ME and EUS and underwent resection at our facility. We found that EUS and ME demonstrated comparable accuracy and EUS can compensate for deficiencies inherent to ME in some cases. The miniature probe was best suited for detecting early-stage lesions. These findings may further improve diagnostic accuracy.

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INTRODUCTION

Esophageal cancer is the leading malignancy in China, with national morbidity and mortality rankings of third and fourth, respectively, among all malignancies[1]. In China, esophageal squamous cell carcinoma accounts for 90% of esophageal carcinomas[2].

Due to its mild and atypical clinical manifestations, most patients with esophageal carcinoma are diagnosed with advanced-stage disease. This results in a poor prognosis, reduced treatment effectiveness, and low quality of life. This situation underscores the need for better methods for detecting and treating esophageal squamous cell carcinoma during the early disease stages.

Superficial esophageal squamous cell carcinoma (SESCC), considered early-stage cancer, is defined as a tumor confined within the mucosa and submucosa layers of the esophagus, regardless of lymph node metastasis[3]. There are several treatment options for SESCC including traditional surgery or endoscopic resection (ER). Compared to surgery, ER can be curative and less invasive, is generally well tolerated, and is associated with fewer postoperative complications[4]. Identifying patients with SESCC who are ER candidates is, therefore, critical. ER is indicated based on the tumor infiltration depth because the risk of lymph node metastasis increases with the depth of invasion. Lesions confined to the epithelium/lamina propria mucosa (EP/LPM) are rarely accompanied by lymph node metastasis (0-3.3%)[5-7]; in these cases, ER may be curative[8]. Despite their association with an elevated risk of lymph node metastasis, lesions confined to the muscularis mucosa/superficial submucosa (MM/SM1) are also suitable for ER, potentially followed by additional treatments[4,8]. Lesions deeper than the SM1

are contraindicated for ER because of the high rate of lymph node and distant metastases (> 20%)[5-7, 9]; surgery is recommended for these lesions[8].

Accurate determination of tumor infiltration depth before resection is important. To estimate the lesion invasion depth, conventional endoscopy combined with magnification (ME) and endoscopic ultrasound (EUS) are considered the best approaches[10-12]. Currently, ME is more widely accepted than EUS for predicting the invasion depth of SESCC with satisfying accuracy, but the addition of EUS is controversial[13-15].

The endoscopists, access environment, and medical policies differ markedly between China and foreign countries. Chinese physicians require a preoperative diagnosis model that maximizes patient benefit. We, therefore, sought to evaluate the diagnostic efficiency of ME *vs* EUS for invasion depth prediction, to determine the most suitable preoperative diagnostic modality for Chinese patients with SESCC.

MATERIALS AND METHODS

Patients and lesions

We retrospectively analyzed patients with suspected SESCC who underwent examination, including both ME and EUS, and then underwent surgery or ER at Sun Yat-Sen University Cancer Center between January 2018 and December 2021. We included patients with suspected SESCC following white light imaging (WLI) screening or other modalities. All patients were pathologically diagnosed with atypical esophageal hyperplasia or SESCC. We excluded patients who received chemotherapy or radiotherapy as an initial treatment after diagnosis and those who were suspected of having lymph node or organ metastases by imaging. The institutional review board of Sun Yat-Sen University Cancer Center approved this study.

Resected complete specimens obtained during surgery or ER were processed and diagnosed by our Center's pathology department. According to the Paris Endoscopic Classification of Superficial Neoplastic Lesions[16] and the 11th Edition of the Japanese Classification of Esophageal Cancers[3], in the esophageal mucosa (T1a), lesion involvement included the epithelium (EP) (including high-grade intraepithelial neoplasia (HGIN) and carcinoma *in situ)*, the lamina propria mucosa (LPM), and the muscularis mucosa (MM). Submucosal (SM, T1b) lesions were divided into SM1, SM2, and SM3. These lesion layers featured equivalent thickness and were ordered from shallower (SM1) to deeper (SM3). Since the submucosal thickness remained unknown in endoscopically resected specimens, lesions involving the submucosa to 200 μm or less from the MM were classified as T1b-SM1. Those deeper than 200 μm were considered T1b-SM2/SM3. Thus, in our study, lesion invasion depths were categorized pathologically as pEP/LPM, pMM/SM1, and pSM2/SM3.

Examination procedure

The examination procedure was identical to that used in our daily practice. All lesions included were initially examined by conventional endoscopy with WLI. Suspicious lesions were further assessed using magnifying endoscopy with narrow-band or blue laser imaging (ME-NBI/BLI) using a GIF-H260Z (Olympus Corporation, Tokyo, Japan) or EG-L590ZW gastroscope (Fujifilm Corporation, Tokyo, Japan). EUS followed, utilizing 7.5MHz, 10MHz, or 12MHz radical scanning probes (SU 9000, EG-530UR2, Fujifilm; EU-ME2, Olympus) or a 20-MHz miniature probe (UM-DP20-25R, Olympus). Six certified and experienced endoscopists at our center performed all these examinations. The involved endoscopists were divided into junior and senior groups according to their seniority. The senior endoscopist was defined as having a title of Associate Professor or higher with at least 12 years of experience in endoscopy. The junior endoscopist is defined as having a title of Attending Physician or above, with more than 6 years of experience in endoscopy. Residents and trainees did not participate in this study. Each patient's ME-NBI/BLI and EUS were conducted on the same day. The endoscopic findings were later extracted from the electronic medical record.

ME, combined with image-enhanced endoscopy, NBI, or BLI, allows visualization of micro-vessels on the esophageal surface. Intra-papillary capillary loops (IPCL) are basic microvasculature units on the squamous mucosal surface. IPCL forms are used to characterize lesions and predict invasion depth for SESCC. We applied the Japan Esophageal Society (JES) classification scheme, which integrates previous Inoue and Arima classification schemes, presently in widespread clinical use[7,17]. Here, micro-vessels observed by ME were divided into type A and type B. Type A vessels were non-cancerous lesions; type B vessels were abnormal micro-vessels characterized by dilatation, meandering, caliber change, and uneven morphology. These abnormal features were suggestive of cancerous lesions and include three subtypes: B1 (vessels with loop-like formations), B2 (without loops but appearing stretched and markedly elongated), and B3 (highly dilated vessels with calibers more than three times those of B2 vessels). To predict invasion depth, type B1, B2, and B3 vessels corresponded with depths of EP/LPM, MM/SM1, and SM2/SM3, respectively. The subclassification of type B vessels was based upon the indication for ER: Lesions with B1 were absolutely indicated, B2 vessels were relatively indicated, and B3 vessels were contraindicated.

During EUS, a cross-sectional image of the esophageal wall structure was obtained and divided into five layers using a 7.5 MHz radical conventional probe[18]. When using a high-frequency (≥ 20 mHz) miniature probe, the canal wall was depicted as a nine-layer structure if the distance between the probe and mucosa was appropriate. Specifically, the mucosa and submucosa were sonographically divided into an additional four layers. The first and second layers corresponded to the EP/LPM, the third layer to the MM, and the fourth layer to the SM. Specifically, lesions confined to the first and second layers were categorized as EP/LPM; lesions involving the third layer were MM/SM1; lesions that invaded the fourth layer were SM2/SM3. Esophageal cancer usually appears as a hypoechoic lesion that disrupts the normal structure of the esophageal wall, forming images with defects, irregularities, and interruptions.

Statistical analysis

The diagnostic efficiencies of EUS and ME-NBI/BLI for determining exact invasion depth were evaluated by sensitivity, specificity, and accuracy. A paired χ^2 test (McNamar's) was used to assess their differences. P values < 0.05 were considered statistically significant. We applied Cohen's kappa to evaluate the consistency of EUS and ME-NBI/BLI with the final pathological result for determining the depth of tumor infiltration[19,20]. The accuracy of ME-NBI/BLI or EUS concerning the clinicopathologic features was assessed using the χ^2 test or Fisher's exact test. Multivariate logistic regression analysis was performed to identify variables that significantly influenced the performance of ME-NBI/BLI or EUS. SPSS version 25 for Windows software (IBM Inc, Armonk, United States) was used for statistical analyses.

RESULTS

Clinicopathological features of patients and lesions

Of the 146 patients who met our enrollment criterion, two were excluded from the analyses. One was because of hemorrhage during ER, which was later converted to surgical resection; this resulted in an incomplete pathological specimen. Another patient was excluded because we could not obtain a clear view during ME-NBI, preventing micro-vessel characterization.

Ultimately 152 lesions in 144 patients were included in this study. Of these, 108 were male (75%), and 36 were female (25%), with a mean age of 61.3 ± 7.5 years. Most tumors were located in the middle thoracic esophagus (82/152, 53.9%), and the main macroscopic type was flat (90/152, 59.2%). The mean tumor size was 22.9 mm (range 5-60 mm). The average time interval between examinations and resection treatment was 18 d (1-82 d). As for treatment selection, 71 lesions were treated by ER, and 81 were treated by surgery. Pathologically, 78 lesions (51.3%) were diagnosed as pEP/LPM lesions, 28 (22.4%) as pMM/SM1, and 46 (30.3%) as pT1b-SM2/SM3. Detailed clinicopathological features of the patients and lesions are shown in Table 1.

Diagnostic efficiency of ME-NBI/BLI and EUS in estimating invasion depth

The relationships between ME-NBI/BLI or EUS diagnosis and the final pathological result after treatment are listed in Table 2 and Figures 1-3. The overall accuracy of ME-NBI/BLI, based upon the JES classification for determining invasion depth, was 73.0% (111/152), moderately consistent with the pathological results (kappa = 0.58, 95% confidence interval [CI]: 0.48-0.68, P < 0.01). The overall accuracy of EUS for determining invasion depth was 66.4% (101/152), also moderately consistent with the pathological results (kappa = 0.46, CI: 0.34-0.57, P < 0.01).

We also compared the diagnostic efficiency of ME-NBI/BLI and EUS for determining the invasion layer according to the indication for ER (Table 3). There was no significant difference in overall accuracy between ME-NBI/BLI and EUS (73.0% *vs* 66.4%, P = 0.24). For pEP/LPM lesions, ME-NBI/BLI had a higher sensitivity, specificity, and accuracy than EUS (sensitivity 84.6% *vs* 73.1%; specificity 91.9% *vs* 81.1%; accuracy 88.2% *vs* 77.0%), with a significant difference in accuracy (P < 0.01). For pMM/SM1 lesions, ME-NBI/BLI was more sensitive, and EUS had a better specificity (sensitivity 92.9% *vs* 35.7%; specificity 73.4% *vs* 91.1%; P < 0.01 for both); the two techniques demonstrated equivalent accuracy (77.0% *vs* 80.9%, P = 0.51). For pSM2/SM3, ME-NBI/BLI was more specific and EUS was more sensitive (sensitivity 41.3% *vs* 73.9%, P < 0.01; specificity 98.1% *vs* 75.4%, P < 0.01); the techniques had equivalent accuracy (80.9% *vs* 75.0%, P = 0.22). Lastly, of the 41 lesions (41/152, 27.0%) misdiagnosed by ME-NBI/BLI, 24 were corrected by EUS (24/41, 58.5%).

Clinicopathological factors that influence diagnostic accuracy

For ME-NBI/BLI, diagnostic accuracy did not vary significantly according to the tumor location, macroscopic type, circumferential occupation, tumor size, or endoscopist grade (Table 4). The accuracy of ME-NBI/BLI increased significantly for HGIN or carcinoma *in situ* subgroups (P = 0.03). During the multivariate analysis, HGIN and carcinoma *in situ* were independent risk factors for the accuracy of tumor invasion depth, as assessed by ME-NBI/BLI (odds ratio [OR] = 3.62, 95%CI: 1.43-9.16, P = 0.007).

Table 1 Clinicopathological features of patients and lesions

Variable	152 lesions in 144 patients
Sex, *n* (%)	
Male	108 (75.0)
Female	36 (25.0)
Age, average ± SD, yr	61.3 ± 7.5
Location, *n* (%)	
Cervical esophagus	2 (1.3)
Upper thoracic esophagus	13 (8.6)
Middle thoracic esophagus	82 (53.9)
Lower thoracic esophagus	55 (36.2)
Macroscopic type, *n* (%)	
Elevated	60 (39.5)
Flat	90 (59.2)
Depressed	2 (1.3)
Mean tumor size, range, mm	22.9 (5-60)
Circumferential occupation, *n* (%)	
< 1/4	38 (25)
1/4-1/2	51 (33.6)
1/2-3/4	37 (24.3)
≥ 3/4	26 (17.1)
Time interval between examination and resection, d, range	18 (1-82)
Treatment, *n* (%)	
Endoscopic resection	71 (46.7)
Surgery	81 (53.3)
Differentiation degree, *n* (%)	
HGIN or carcinoma *in situ*	60 (39.5)
Poor	13 (8.6)
Moderate	72 (47.4)
Good	7 (4.6)
Depth according to pathological diagnosis, *n* (%)	
EP/LPM	78 (51.3)
MM/SM1	28 (22.4)
SM2/SM3	46 (30.3)

SD: Standard deviation; HGIN: High-grade intraepithelial neoplasia; EP: Epithelium; LPM: Lamina propria mucosa; MM: Muscularis mucosa; SM: Submucosa.

As for EUS, the overall diagnostic accuracy did not vary significantly according to the tumor location, macroscopic type, differentiation degree, and endoscopist grade (Table 4). Increased circumferential occupation and tumors larger than 3 cm were mostly associated with decreased accuracy (P = 0.06 and P = 0.05, respectively). Using a miniature probe instead of conventional EUS improved accuracy (82.3% *vs* 49.3%, P < 0.01). In the multivariate analysis, less than a quarter of circumferential occupation and application of a miniature probe were independent risk factors for the accuracy of tumor invasion depth, as assessed by EUS (< 1/4 circumferential occupation: OR = 3.07, 95%CI: 1.04-9.10; application of a miniature probe: OR = 5.28, 95%CI: 2.41-11.59, P < 0.01).

Table 2 Relationship between magnifying endoscopy or endoscopic ultrasound diagnosis and final pathological results

	Depth according to pathological results			
	EP/LPM (*n* = 78)	MM/SM1 (*n* = 28)	SM2/SM3 (*n* = 46)	Total
ME-NBI/BLI				
B1	66	1	5	72
B2	11	26	22	59
B3	1	1	19	21
EUS				
EP/LPM	57	4	10	71
MM/SM1	9	10	2	21
SM2/SM3	12	14	34	60

ME: Magnifying endoscopy; NBI: Narrow-band imaging; BLI: Blue laser imaging; EUS: Endoscopy ultrasonography; HGIN: High-grade intraepithelial neoplasia; EP: Epithelium; LPM: Lamina propria mucosa; MM: Muscularis mucosa; SM: Submucosa.

Table 3 Diagnostic efficiency of magnifying endoscope or endoscopic ultrasound in dividing specific invasion layer

	EP/LPM			MM/SM1			SM2/SM3		
	ME, %	EUS, %	*P* value	ME, %	EUS, %	*P* value	ME, %	EUS, %	*P* value
Sensitivity	84.60	73.10	0.08	92.90%	35.7	< 0.01	41.30	73.90	< 0.01
Specificity	91.90	81.10	0.06	73.40%	91.10	< 0.01	98.10	75.40	< 0.01
Accuracy	88.20	77.00	< 0.01	77.00%	80.90	0.51	80.90	75.00	0.22

ME: Magnifying endoscopy; EUS: Endoscopy ultrasonography; EP: Epithelium; LPM: Lamina propria mucosa; MM: Muscularis mucosa; SM: Submucosa.

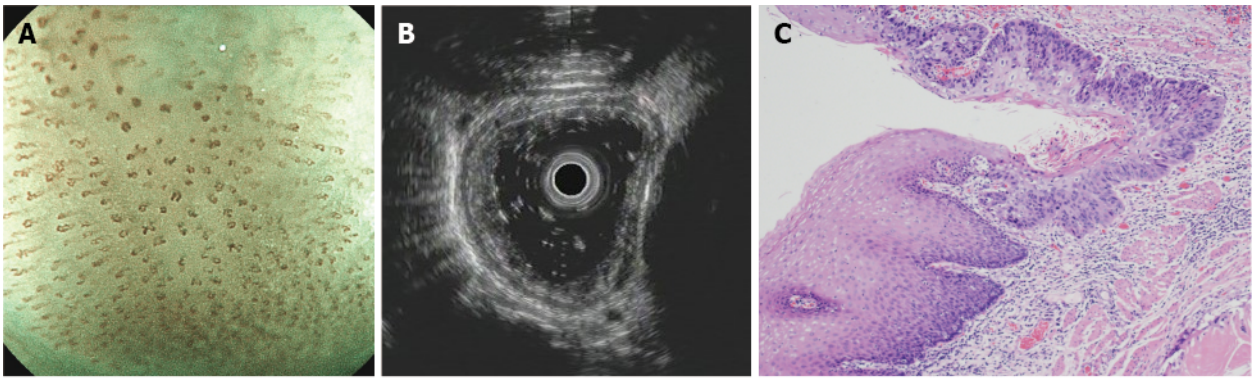

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Figure 1 A typical case of carcinoma *in situ*. A: ME-BLI image shows micro-vessels with a loop-like formation (type B1); B: Ultrasonography image shows hypoechoic thickening confined to the first two layers; C: Hematoxylin-eosin staining (× 40) of an endoscopic resection specimen shows that the squamous cell carcinoma is limited to the epithelium, without invasion.

DISCUSSION

In daily practice, SESCC invasion depth can be diagnosed by observing the micro-vessels using ME-NBI/BLI and is unaffected by biopsy, inflammation, *etc*. However, sometimes visualization is impeded. In contrast, EUS can image deeper lesions and collect vital information that differs from that obtainable by ME. The objective of this study was to evaluate the diagnostic efficiency of ME-NBI/BLI *vs* EUS for diagnosing invasion depth in patients with SESCC based on the indication for ER. We also investigated influencing factors to determine the best model for use during preoperative diagnosis in Chinese patients with SESCC.

Table 4 Diagnostic accuracy of magnifying endoscopy or endoscopic ultrasound according to clinicopathological features

Features	ME-NBI/BLI		EUS	
	Accurately assessed lesions (%)	*P* value	Accurately assessed lesions (%)	*P* value
Location of esophagus				
Cervical	2/2 (100)	0.69	1/2 (50.0)	0.17
Upper thoracic	11/13 (84.6)		9/13 (69.2)	
Middle thoracic	60/82 (73.2)		60/82 (73.2)	
Lower thoracic	38/55 (69.1)		31/55 (56.4)	
Macroscopic type				
Elevated	43/60 (71.1)	0.60	40/60 (66.7)	1.00
Flat	67/90 (74.4)		60/90 (66.7)	
Depressed	1/2 (50.0)		1/2 (50.0)	
Circumferential occupation				
< 1/4	26/38 (68.4)	0.38	31/38 (81.6)	0.06
1/4-1/2	35/51 (68.6)		34/51 (66.7)	
1/2-3/4	31/37 (83.3)		23/37 (62.2)	
≥ 3/4	19/26 (73.1)		13/26 (50.0)	
Tumor size				
≤ 3 cm	87/121 (71.4)	0.54	85/121 (70.2%)	0.05
> 3 cm	24/31 (77.4)		16/31 (51.6)	
Differentiation degree				
HGIN or carcinoma *in situ*	51/60 (85.0)	0.03	43/60 (71.7)	0.54
Good	5/7 (71.4)		4/7 (57.1)	
Moderate	48/72 (66.7)		47/72 (65.3)	
Poor	7/13 (53.8)		7/13 (53.8)	
Endoscopist grade				
Junior	33/41 (80.5)	0.21	23/41 (56.1)	0.10
Senior	78/111 (70.3)		78/111 (70.3)	
EUS probe				
Conventional EUS			36/73 (49.3)	< 0.01
Miniature probe			65/79 (82.3)	

ME: Magnifying endoscopy; NBI: Narrow-band imaging; BLI: Blue laser imaging; EUS: Endoscopy ultrasonography; HGIN: High-grade intraepithelial neoplasia; EP: Epithelium; LPM: Lamina propria mucosa; MM: Muscularis mucosa; SM: Submucosa.

We applied accuracy, sensitivity, and specificity to evaluate diagnostic efficiency. Of these parameters, accuracy is widely used because it combines sensitivity and specificity. We found no significant differences in the diagnostic accuracy of ME-NBI/BLI and EUS for determining invasion depth (73% *vs* 66.4%, $P = 0.24$), and both demonstrated moderate consistency with pathological findings (ME-NBI/BLI: kappa=0.58; EUS: kappa = 0.46). However, both had advantages and limitations for differentiating distinct invasion layers.

We grouped patients according to the indications for ER to optimize clinical decision-making for patients. ME-NBI/BLI presented better diagnostic efficiency than EUS in the prediction of pEP/LPM layer. In addition, tumors confined to EP—including HGIN and carcinoma *in situ*—were more accurately assessed by ME-NBI/BLI than other subgroups (OR = 3.62, 95%CI: 1.43-0.16, $P = 0.007$). Thus, ME-NBI/BLI performed better than EUS for distinguishing EP/LPM invasion; this finding was consistent with current clinical practice and previous research[7,21,22].

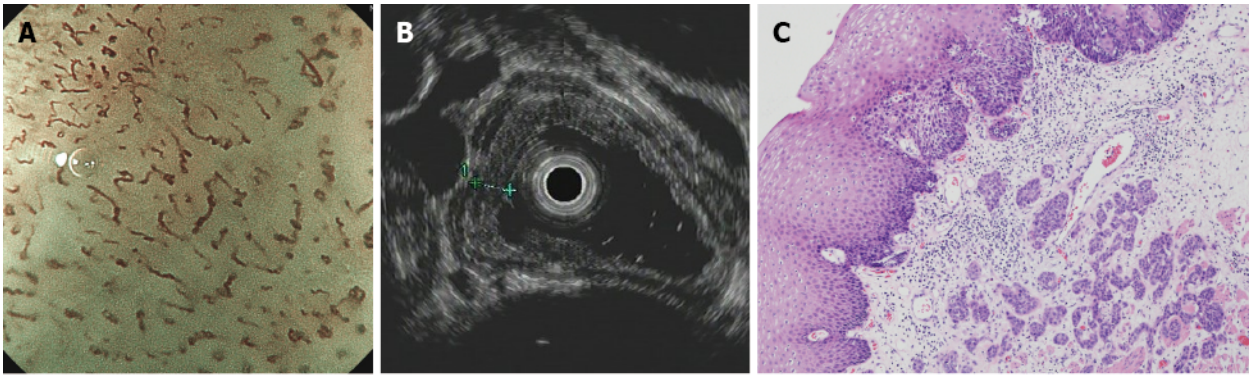

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Figure 2 A typical muscularis mucosal lesion. A: ME-BLI image shows type B2 vessels without loop-like formations but with a stretched and markedly elongated transformation; B: Ultrasonography image shows a hypoechoic lesion invading the third layer with continuous submucosa; C: Hematoxylin-eosin staining (× 40) of a surgical specimen shows a moderately differentiated squamous cell carcinoma invading the muscularis mucosa.

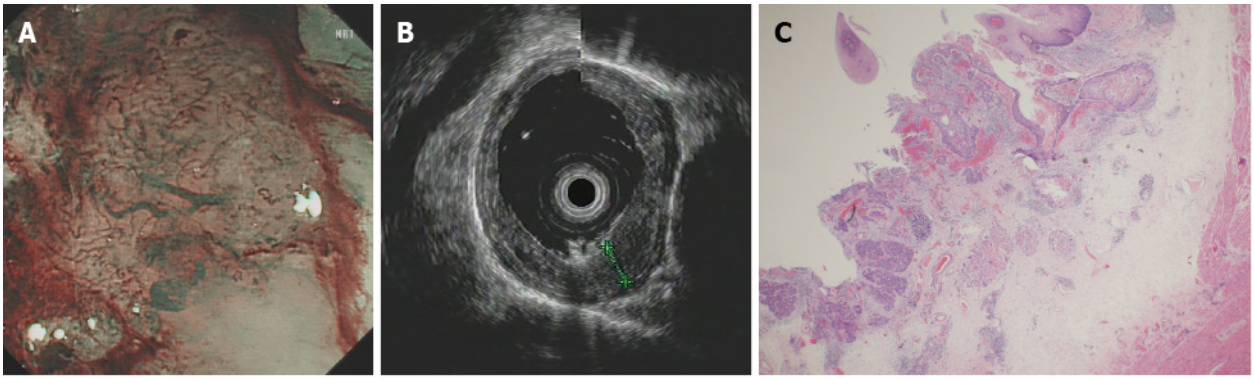

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Figure 3 A typical submucosal lesion. A: ME-NBI image shows micro-vessels dilated more than three times that of B2 vessels (type B3); B: Ultrasonography image shows a hypoechoic lesion invading the fourth layer; C: Hematoxylin-eosin staining (× 20) of a surgical specimen shows a moderately differentiated squamous cell carcinoma infiltrated to the middle third of the submucosa without muscularis propria involvement.

For pT1b-SM2/SM3 lesions, B3 vessels were highly specific for diagnosis (98.1%) but less sensitive (41.3%), consistent with previous reports. Type B3 vessels were negative for 43.1% of the pT1b-SM2/SM3[23]; however, according to our data, EUS can compensate for this deficiency with a significantly higher specificity than ME-NBI/BLI (EUS 73.9% *vs* NBI 41.3%, $P < 0.01$). Therefore, EUS can be a useful supplementary tool to determine if a lesion has invaded the submucosa. Combining ME-NBI/BLI and EUS enables the most comprehensive assessment of lesion infiltration depth.

Considering the lesser diagnostic accuracy for B2 and B3 vessels (77.0% and 80.9%, respectively), the criteria for B2 and B3 vessel characteristics required further refinement[24,25] to improve the accuracy of JES classification. However, this violated the original intention of the JES classification to simplify the items set by previous Inoue and Arima classifications[17], thus increasing the difficulty of memorization and impeding widespread use. Therefore, we tried to find a model of preoperative diagnosis. Surprisingly, we found that when patients were misdiagnosed by ME-NBI/BLI, EUS often determined the correct invasion depth (24/41, 58.5%). These findings may assist clinicians with treatment decision-making and maximize the benefit to the patient.

In our study, EUS was performed using either a miniature probe or conventional EUS. Some lesions were visualized using both probe types according to different detection purposes. Except for depth prediction, EUS can determine the presence of malignant regional lymph nodes with better sensitivity than CT and PET-CT[26], and can sample the suspected lymph nodes to gain pathological confirmation. We compared the accuracy of conventional EUS and the miniature probe for determining lesion infiltration depth. The miniature probe was significantly more accurate than conventional EUS (82.3% *vs* 49.3%, $P < 0.01$). This finding answers questions unanswered by previous data and is consistent with previous study findings[11,27,28]. Because of higher frequencies, the miniature probe can clearly visualize esophageal wall structures. However, as frequency increases, the detection range becomes shallower and more limited, potentially preventing comprehensive exploration of large lesions[29]. Therefore, the miniature probe seems more suitable for small, superficial, and early-stage lesions[27].

This conclusion was further confirmed by our findings. We observed that increased circumferential occupation (P = 0.06) and larger (P = 0.05) tumors were less accurately assessed using EUS. In our clinical practice, we mainly use miniature probes to determine the infiltration depth of early-stage lesions. Conventional EUS is typically used to detect the apparent advanced-stage lesions and determine the presence of lymph nodes or adjacent organ metastases.

Compared with foreign peers, most Chinese endoscopists in tertiary hospitals are proficient in ME-NBI/BLI and EUS. From our data, the diagnostic capacities of junior and senior endoscopists in our center were comparable, and the difference was not significant (ME-NBI/BLI, P = 0.21; EUS, P = 0.10). Additionally, in China, the cost of EUS examinations–including general gastroscopy–is around 150 dollars, much lower than that of developed countries, such as Europe, America, Japan, *etc.* Due to affordability, EUS does not post a substantial financial burden on Chinese patients.

Our findings should be considered within the context of specific limitations. First, all patients were initially examined using ME-NBI/BLI, then EUS. There may be an ordering effect, with ME-NBI/BLI affecting the prediction obtained using EUS. Future studies should alter the order of EUS and ME-NBI/BLI to control for a potential order effect. Second, this was a retrospective study of extracting patients' medical records at a single cancer center in China. As such, selection bias could not be denied. Future prospective multi-center nationwide double-blinded trials are needed to evaluate the clinical validity of EUS and ME-NBI/BLI in patients with SESCC.

CONCLUSION

We recommend that preoperative diagnosis of SESCC be conducted based on the finding of WLI and ME-NBI/BLI. EUS can be added after patient consent in China, preferably utilizing a high-frequency miniature probe or miniature probe combined with conventional radical EUS.

ARTICLE HIGHLIGHTS

Research background

Early-stage detection and treatment of esophageal carcinoma can typically optimize prognosis. Compared with traditional surgery, endoscopic resection is a less invasive and potentially curative treatment for early-stage esophageal cancer. Identification of patients that are candidates for endoscopic resection is crucial. Endoscopic ultrasonography (EUS) and magnifying endoscopy (ME) reliably determine indications for endoscopic resection in patients with superficial esophageal squamous cell carcinoma (SESCC). ME is a widely accepted method for predicting the invasion depth of superficial esophageal cancer with satisfying accuracy. However, the addition of EUS is controversial.

Research motivation

To evaluate the diagnostic efficiency of ME *vs* EUS for invasion depth prediction, and investigate the influencing factors.

Research objectives

To determine the most suitable preoperative diagnostic modality for Chinese patients with SESCC.

Research methods

We retrospectively analyzed patients with suspected SESCC who completed both ME and EUS and then underwent endoscopic or surgical resection at Sun Yat-Sen University Cancer Center between January 2018 and December 2021. We evaluated and compared the diagnostic efficiency of EUS and ME according to histological results, and investigated the influencing factors.

Research results

EUS and ME demonstrated comparable accuracy for determining the depth of invasion of early-stage esophageal cancers, and EUS can compensate for deficiencies inherent to NBI in some cases. The miniature probe was best suited for detecting early-stage lesions

Research conclusions

Preoperative diagnosis of SESCC should be conducted endoscopically using white light and magnification. In China, EUS can be added after obtaining patient consent. Use of a high-frequency miniature probe or miniature probe combined with conventional EUS is preferable.

Research perspectives

Future studies are required to explore how to combine the findings of ME and EUS to make a compre-

hensive preoperative evaluation, instead of solely depending on the experience of endoscopists.

FOOTNOTES

Author contributions: Zeng Y designed and performed the study and wrote the manuscript; Sun Y and Huang C contributed to the conception of the study; Tan W and Luo G helped perform the analysis with constructive discussions; Luo S and Zhou B collected the data;

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ORIGINAL ARTICLE

Observational Study

Oesophageal cancer metastases: An observational study of a more aggressive approach

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Abstract

BACKGROUND

The prognosis for oesophageal carcinoma is poor, but once distant metastases emerge the prognosis is considered hopeless. There is no consistent protocol for the early identification and aggressive management of metastases.

AIM

To examine the outcome of a policy of active postoperative surveillance with aggressive treatment of confirmed metastases.

METHODS

A prospectively maintained database of 205 patients diagnosed with oesophageal carcinoma between 1998 and 2019 and treated with curative intent was interrogated for patients with metastases, either at diagnosis or on follow-up surveillance and treated for cure. This cohort was compared with incomplete clinical responders to neoadjuvant chemoradiotherapy (nCRT) who subsequently underwent surgery on their primary tumour. Overall survival was estimated using the Kaplan-Meier method, and the log-rank test was used to compare survival differences between groups.

RESULTS

Of 205 patients, 11 (5.4%) had metastases treated for cure (82% male; median age 60 years; 9 adenocarcinoma and 2 squamous cell carcinomas). All had undergone neoadjuvant chemotherapy or chemoradiotherapy, followed by surgery in all but 1 case. Of the 11 patients, 4 had metastatic disease at diagnosis, of whom 3 were successfully downstaged with nCRT before definitive surgery; 2 of these 4 also developed oligometastatic recurrence and were treated with curative intent. Following definitive treatment, 7 had treatment for metachronous oligometastatic disease; 5 of whom underwent metastasectomy (adrenal × 2; lung × 2; liver × 1). The median overall survival was 10.9 years [95% confidence interval (CI): 0.7-21.0 years], which was statistically significantly longer than incomplete clinical responders undergoing surgery on the primary tumour without metastatic intervention [n = 62; median overall survival = 1.9 (95%CI: 1.1-2.7; P = 0.012]. The cumulative proportion surviving 1, 3, and 5 years was 100%, 91%, and 61%, respectively compared to 71%, 36%, and 25% for incomplete clinical responders undergoing surgery on the primary tumour who did not undergo treatment for metastatic disease.

CONCLUSION

Metastatic oesophageal cancer represents a unique challenge, but aggressive treatment can be rewarded with impressive survival data. In view of recent advances in targeted therapies, intensive follow-up may yield a greater number of patients with curative potential and thus improved long-term survival.

Key Words: Oesophageal metastases; Oligometastases; Active surveillance; Treatment for cure; Metastasectomy; Survival

Core Tip: Modern imaging technologies can detect oligometastatic oesophageal cancer earlier than ever before, and targeted multimodal therapies, combined with innovative surgery, increases the potential for cure. Unfortunately, current guidelines do not reflect these advances and all too often consign patients to palliation. This approach is incongruous with other oligometastatic cancers such as colorectal cancer. Based on the survival outcomes of patients with oligometastatic disease treated for cure at our institution we advocate for more intensive surveillance strategies for earlier identification of patients with curative potential to improve overall long-term survival.

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INTRODUCTION

Oesophageal cancer is an aggressive disease that presents insidiously, disseminates early, and spreads rapidly in most patients. It remains a leading cause of death from cancer worldwide and fewer than 5%-12% will survive 5 years[1,2]. At least 40% of patients present with distant metastasis at initial diagnosis [3], and only 5% of these patients will be alive at 5 years[4]. Even when presenting with early disease, 29%-54% of patients undergoing surgical resection with curative intent will develop locoregional or distant recurrence[5-7]. Of patients with a ypT0N0M0 tumour at resection following neoadjuvant chemoradiotherapy (nCRT), up to 17% will succumb to distant metastases[8-10]. Because of these poor survival outcomes, the role of intensive surveillance post-oesophagectomy and treatment of metastatic disease remains controversial.

The management of oesophageal cancer has undergone major advances over the past 30 years. Specifically, both neoadjuvant chemotherapy and nCRT have been shown to increase survival over surgery alone[11-13]. While neoadjuvant chemotherapy has achieved this increase by targeting occult micrometastases[14], combined CRT has increased survival by both targeting micrometastases and sterilizing locoregional disease, thus up to 50% of patients with squamous cell carcinoma (SCC) and up to 25% of patients with adenocarcinoma (AC) undergoing CRT have a complete pathological response in the resected specimen, depending on the regimen and the disease stage[11,12].

Nevertheless, metastatic oesophageal cancer remains a challenge. Oligometastases are defined as a state of limited metastatic disease characterized by fewer than five metastases[5,15]. Synchronous oligometastases may be detected at the time of diagnosis of the primary cancer, while metachronous

oligometastases are those detected during follow-up[5,16]. Metastasectomy is well-established in the treatment of certain oligometastatic cancers, such as colorectal cancer, where partial hepatectomy and pulmonary resection are well established[5]. Both the United Kingdom's National Institute for Health and Clinical Excellence and the United States' National Comprehensive Cancer Network recommend surveillance strategies to identify recurrence as well as liver and pulmonary metastasectomy where possible[17,18]. In contrast, the National Institute for Health and Clinical Excellence recommends neither routine clinical follow-up nor radiological follow-up be offered to patients who have no symptoms or evidence of residual disease after treatment for oesophagogastric cancer with curative intent for the detection of recurrent disease[19]. The National Comprehensive Cancer Network reco-mmends clinical follow-up alone for asymptomatic patients and palliation alone for patients who develop metastatic recurrence[20].

Over the past decades, efforts have focused on the molecular and biological alterations that lead to oesophageal cancer, specifically the influence of angiogenesis on micrometastatic tumour growth[21,22]. This has resulted in the development of novel molecularly targeted agents that target a variety of relevant pathways, such as vascular endothelial growth factor, cyclooxygenase-2, epidermal growth factor receptor, and mammalian target of rapamycin[23] as well as targeted radiotherapy in the form of stereotactic radiotherapy[24]. Leading the way are HER-2 inhibitors for the treatment of HER-2 expressing metastatic ACs[23]. It is intuitive that aggressive treatment of oligometastatic disease would improve disease control and provide a survival benefit for patients with recurrent cancer detected at its earliest stage. The purpose of this study was to examine survival outcomes in patients who underwent active surveillance and targeted therapy at our institution for their oligometastatic disease.

MATERIALS AND METHODS

Study design and patients

We conducted a retrospective review of a prospectively maintained database of all patients diagnosed with oesophageal carcinoma and treated with curative intent between 1998 and 2019 at Connolly Hospital Blanchardstown, Dublin, Ireland. Patients were treated with either CRT alone, or CRT followed by surgery, or surgery alone.

Patient management and follow-up

Over a 21-year period, 205 patients with oesophageal carcinoma underwent curative management. Following discharge, patients were followed up in the clinic every 3 mo for the first 3 years with esophagogastroduodenoscopy performed every 3 mo and computed tomography (CT) performed every 6 mo. Between 3 years and 5 years they were followed up in the clinic every 6 mo with esophagogastroduodenoscopy every 6 mo and CT scanning performed annually. After 5 years patients were followed up annually with endoscopy and a clinic visit (which was on the same day for patients who had to travel from a distance). In addition, patients had access to their oncology coordinator and were encouraged to call at any time with any concern. On receipt of a call, the coordinator would offer them a clinic visit or an esophagogastroduodenoscopy (or other imaging) depending on their symptoms or concerns.

Patient database

A patient database was maintained over the study period, both by nursing and clinical staff. This was scrutinized for patients with synchronous and metachronous oligometastases. Only patients who underwent curative treatment of oligometastatic disease were included in this study. A second group of patients (with non-metastatic disease) who had an incomplete clinical response to nCRT and subsequently underwent surgery on the primary tumour were identified for comparison of survival outcomes.

Of 205 patients treated with curative intent, 62 had an incomplete response to nCRT for non-metastatic oesophageal cancer and subsequently underwent surgery, and 11 had oligometastases treated for cure. The medical and electronic records of the oligometastatic cohort treated for cure were reviewed for demographic, clinical, and histopathologic variables. Notably, staging of the primary oesophageal cancer was prospectively assigned according to the TNM classification of the American Joint Committee for Cancer Staging, initially the 6th edition and then the 7th following its publication. Each case was assessed with respect to the use of neoadjuvant therapy, history of oesophagectomy, and timing of metastasis. Further details regarding the site and treatment of metastasis were included. Survival data was included for analysis and comparison.

Ethical approval

As this was a retrospective audit ethical approval was not required, but audit approval was sought and granted by the Connolly Hospital Ethics Committee.

Statistical analysis

The statistical analysis of this study was performed by biostatistician Mary Dunne from St Luke's Radiation Oncology Network, Dublin D06 HH36, Ireland. Overall survival was estimated using the Kaplan-Meier method and was defined as the duration from the date of diagnosis until death from any cause or last follow-up at study endpoint on February 26, 2020. The log-rank test was used to compare survival differences between groups (assessed for significance at the 0.05 level). Statistical analysis was performed using IBM SPSS Statistics 25 (Chicago, IL, United States).

RESULTS

Clinical characteristics of patients

Of the 205 patients, 11 (5.4%) patients diagnosed with oesophageal carcinoma [146 (71.0%) male; 135 (65.9%) AC; 68 (33.2%) SCC; 2 adenosquamous)] between 1998 and 2019 and treated with curative intent had metastases treated for cure. Of these, 4 had synchronous oligometastatic oesophageal cancer, 2 of which also had treatment for cure for oligometastatic recurrence. A further 7 had metachronous oligometastatic oesophageal cancer only. The median age of patients with synchronous metastasis was 65 years (range: 53-71 years; AC 75%) and in patients with metachronous carcinoma was 57 years (range: 36-72 years; AC 86%) (Table 1). The majority of both cohorts were male (75% and 86%, respectively).

Treatment of synchronous oligometastatic oesophageal cancer

The 4 patients that had metastatic disease at presentation were treated with nCRT, 3 of whom underwent subsequent oesophagectomy and achieved a margin free R0 resection and 1 of whom declined surgery following a clinical complete response to nCRT (Table 1). Two of these patients subsequently presented with metachronous metastases, which were also treated for cure (Table 2).

Patient 1 had locally advanced SCC at diagnosis (T4N1M1). Despite a complete clinical response to definitive CRT, routine surveillance positron emission tomography–CT (PET-CT) almost 12 mo later (11.5 mo) revealed fluorodeoxyglucose (FDG) avid lung lesions bilaterally. These were subsequently treated with stereotactic radiotherapy. The patient survived for 3 years post metastatic recurrence (36.4 mo). Patient 2 had a 12 mm short-axis FDG-positive lymph node lying immediately to the right of the coeliac axis on staging PET-CT (AC, T3N2M1). The patient was treated with nCRT and radical oesophagogastrectomy for a poorly differentiated junctional/cardia AC (ypT2bN1Mx). Almost 18 mo later (17.9 mo) a radiological work-up for a pulmonary embolus revealed a 1.9 cm left para-aortic node with FDG uptake on PET-CT, which was subsequently treated with chemotherapy (Table 2). Follow-up CT showed a reduction in tumour size and subsequent surveillance with endoscopy and CT revealed stable disease with no evidence of recurrence. The patient was alive and well at the conclusion of this study, 83.3 mo after his initial diagnosis (65.4 mo post-recurrence).

Two further patients (Patient 3 and Patient 4) had treatment for cure of synchronous oligometastatic disease only (Tables 1 and 2). Patient 3 had liver metastasis on staging PET-CT (AC, T3N1M1). Restaging CT post nCRT was negative for liver metastasis, and the patient subsequently underwent oesophagectomy (ypT3N0M0). Patient 4 had a 1 cm FDG avid right supraclavicular node on staging PET-CT (AC, T3N2M0) and underwent nCRT and subsequent oesophagectomy for a moderate to poorly differentiated AC at the oesophagogastric junction (ypT2N0Mx). The patient was alive and well at the conclusion of this study, 8.5 years after his initial diagnosis (102.8 mo).

Treatment of metachronous oligometastatic oesophageal cancer

The remaining 7 patients did not have clinical evidence of metastatic oesophageal cancer at diagnosis. These patients had mostly T3 disease with or without nodal involvement (Table 1; Patient 5-11). All underwent nCRT or neoadjuvant chemotherapy followed by surgery for their primary cancer. Of this cohort (n = 7), 3 developed pulmonary recurrence, 2 adrenal, 1 liver, and 1 patient had biopsy proven retroperitoneal nodal recurrence. All 7 patients underwent targeted treatment for metastatic recurrence with intent to cure, the details of which are summarized in Table 2. The median time from diagnosis to recurrence was 19.2 mo (range: 15.7-33.0 mo), and the median survival post recurrence was 97.4 mo [95% confidence interval (CI): 0-204 mo). The median overall survival (MOS) was 130 mo (95%CI: 3-258 mo), or the MOS was 10.9 years (95%CI: 0.2-21.5 years).

Survival outcomes

The MOS of the 11 patients who underwent curative treatment for synchronous or metachronous metastatic disease or both was 10.9 years (95%CI: 0.7-21) which was statistically significantly longer than patients with an incomplete clinical response following nCRT undergoing surgery [n = 62; MOS = 1.9 years (95%CI: 1.1-2.7); P = 0.012] (Figure 1). Of note, the latter did not undergo curative treatment for any future proven or probable metastatic recurrence. The cumulative proportion of patients with metastatic disease treated for cure surviving 1, 3, and 5 years was 100%, 91%, and 61%, respectively,

Table 1 Clinical characteristics of patients

Patient	Age in yr	Sex	Primary tumour location	Histologic type of tumour	Differentiation	Clinical stage of primary tumour	Neoadjuvant therapy	Oesophagectomy	ypTNM
Synchronous and Metachronous Oligometastatic Disease									
1[1]	62	Female	Upper third	SCC	Moderate	T4N1M1	Walsh Regimen[17]	No	NA
2[2]	53	Male	OGJ	AC	Poor	T3N2M1	Walsh Regimen + CROSS	Yes	T2bN1Mx
Synchronous Oligometastatic Disease Only									
3	71	Male	Lower third/OGJ	AC	Poor	T3N1M1	Carbo5FU; 60Gy	Yes	T3N0M0
4	68	Male	OGJ	AC	Moderate-poor	T3N2M0	Walsh Regimen	Yes	T2N0Mx
Metachronous Oligometastatic Disease Only									
5	56	Male	Middle/lower third	SCC	Moderate	T3N2M0	Walsh Regimen	Yes	T2N1Mx
6	36	Male	Lower	AC	Moderate	T3N1M0	CROSS	Yes	T3N0Mx
7[3]	72	Female	OGJ	AC	Moderate	T3N0M0	CROSS	Yes	T2N0
8	70	Male	OGJ	AC	Poor	Nodal disease/Stage IIIA	MAGIC	Yes	T2N1Mx
9	48	Male	Lower third	AC	Poor	Stage IIB	Walsh Regimen	Yes	T1N0Mx
10[4]	57	Male	Lower third	AC	Poor	T3N0M0	CROSS	Yes	T2N0M0
11	60	Male	OGJ	AC	Poor	T3N0M0	CROSS	Yes	T0N0Mx

[1]Patient 1 had a complete clinical response.
[2]Patient 2 received six cycles of cisplatin and fluorouracil, followed by six cycles of paclitaxel and carboplatin.
[3]Patient 7 underwent salvage surgery after surveillance Positron-emission tomography suggested residual disease despite initial complete clinical response to neoadjuvant chemoradiotherapy.
[4]Patient 10 was diagnosed with a synchronous primary renal cell carcinoma, which was discovered incidentally during staging for his oesophageal cancer. He was referred to a urology service in another hospital and treated with radiofrequency ablation.
ypTNM: Pathologic staging after neoadjuvant therapy; Walsh Regimen[17]: Cisplatin/5-fluorouracil, 40 Gy concurrent radiotherapy; CROSS: The Dutch Chemoradiotherapy for Oesophageal Cancer Followed by Surgery study–weekly carboplatin and paclitaxel with concurrent radiotherapy; Carbo5FU: Carboplatin/5-fluorouracil; MAGIC: Epirubicin, cisplatin, and fluorouracil; NA: Not applicable; OGJ: Oesophagogastric junction; AC: Adenocarcinoma; SCC: Squamous cell carcinoma.

with 6 patients still alive at the end of the study period, compared to 71%, 36%, and 25% for incomplete clinical responders without metastatic disease undergoing surgery on the primary tumour.

Patients that underwent surgical resection for their recurrence (n = 5) had a MOS of 10.9 years (95%CI: 0.6-21.2) from date of diagnosis, 8.1 years (95%CI: 0-16.8 years) post recurrence, and a 5-year survival of 80% from the date of diagnosis.

DISCUSSION

Patients with metastatic oesophageal cancer present a unique challenge. Although solitary metastases of oesophageal cancer are uncommon[25], the evolution of imaging will ensure ever-earlier detection, which challenges oncologists and surgeons to detect and deal with them. Treatment of oligometastatic oesophageal cancer is controversial, and to date formal guidelines are lacking. There are no large randomized multicenter trials, and thus case series, such as ours, remain an important source of information for clinicians managing these challenging patients.

Those patients treated surgically for recurrence in our study had a MOS of 10.9 years, or 130.3 mo and a 5-year survival of 80%. Depypere *et al*[26] conducted a large retrospective study comparing different treatment options for different subtypes of recurrence following curative resection, including single solid organ metastasis and single metastasis at another location. Of 1754 patients that had curative resection, 43.7% had recurrence, 14.4% of whom had clinical solitary solid organ recurrence (liver, lung, brain, or adrenal)[26]. Only 20 patients (1.14%) had their recurrence resected with or without systemic

Table 2 Treatment of synchronous and metachronous oligometastatic oesophageal carcinoma

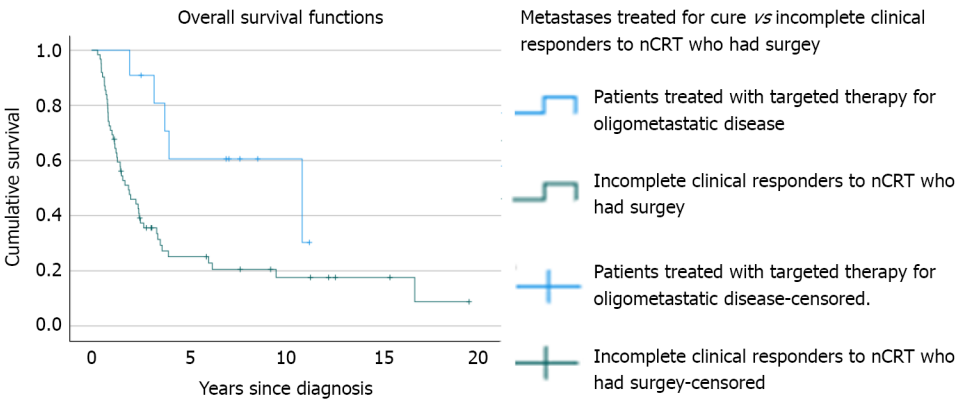
Patient	Synchronous metastases	Type	Treatment	Metachronous metastases	Type	Time to recurrence in mo	Treatment	Survival post recurrence in mo	Alive at study endpoint	Overall survival in mo
1	Yes	Locally advanced[1]	Walsh regimen	Yes	Lung	11.5	Stereotactic radiotherapy	36.4	No	47.9
2	Yes	Coeliac axis	Walsh regimen + CROSS + radial gastrectomy	Yes	Left para-aortic nodes	17.9	Chemotherapy (Epirubicin, Oxaliplatin + Capecitabine)	65.4	Yes	83.3
3	Yes	Liver	Carbo5FU; 60 Gy + oesophagectomy	No	NA	NA	NA	NA	No	23.6
4	Yes	Locally advanced[2]	Walsh regimen + oesophagectomy	No	NA	NA	NA	NA	Yes	102.8
5	No	NA	NA	Yes	Lung	32.9	Left upper lobectomy (VATS)	97.4	No	130.3
6	No	NA	NA	Yes	Lung	16.7	Chemotherapy (*carbo/taxol* + *FOLFOX)*	21.9	No	38.6
7	No	NA	NA	Yes	Lung	19.2	Wedge resection (VATS)	26.1	No	45.3
8	No	NA	NA	Yes	Adrenal	29.7	Adrenalectomy	62.1	Yes	91.8
9	No	NA	NA	Yes	Adrenal	15.9	Adrenalectomy + chemotherapy *(irinotecan)*	118.9	Yes	134.8
10	No	NA	NA	Yes	Liver	33.0	Resection + chemotherapy	51.9	Yes	84.9
11	No	NA	NA	Yes	Paraaortic + Retroperitoneal	15.7	Chemotherapy *(FOLFOX)*	14.9	Yes	30.6

[1]Right innominate artery and pars membrane of the trachea with a right 1 cm subcarinal adenopathy and left 5 mm paratracheal node on staging whole-body positron emission tomography-computed tomography (squamous cell carcinoma, T4N1M1).
[2]1 cm fluorodeoxyglucose avid right supraclavicular node on staging positron emission tomography-computed tomography.
NA: Not applicable; VATS: Video-assisted thoracoscopic surgery; FOLFOX: Folinic acid, fluorouracil, oxaliplatin; CROSS: The Dutch Chemoradiotherapy for Oesophageal Cancer Followed by Surgery study–weekly carboplatin and paclitaxel with concurrent radiotherapy; Carbo5FU: Carboplatin/5-fluorouracil.

therapy and had a significantly better median and 5-year survival than 63 non-surgically treated patients [54.8 mo (5-year survival 43.9%) *vs* 11.6 mo (5-year survival 4.6%)][25,26]. Arguably, those suitable for resection self-select, but the survival statistics for metastatic resection in a disease as aggressive as oesophageal cancer are impressive.

The patients in our study who underwent adrenalectomy were alive at 62.1 and 118.9 mo post recurrence. The oesophagus is the third most frequent site of origin of adrenal metastasis[27], and there are only a few reports of adrenalectomy for recurrence with survival ranging from 28 mo to over 5 years [27-30]. These findings confirm that adrenalectomy for isolated adrenal metastases from oesophageal carcinoma is worthwhile. A disease-free interval of over 6 mo and an AC subtype are reported as predictors of improved survival and should be considered in patient selection[31,32]. As adrenal metastases are clinically silent, intensive surveillance imaging is indicated if they are to be identified early enough for curative resection.

The remaining patients who underwent metastasectomy in our case series had either lung or liver metastases. All had metachronous oligometastases, had received nCRT, and had undergone resection of their primary tumour. Those who underwent pulmonary metastasectomy lived for 26.1 and 97.4 mo post recurrence, while the patient who underwent liver metastasectomy was alive and disease-free at 51.9 mo post recurrence. While hepatectomy and pulmonary resection are universally recommended for colorectal cancer metastases[17,18], they are not recommended for oesophageal cancer[19,20]. A nationwide study by Seesing *et al*[33] of the Dutch national registry for histopathology and cyto-



	Censored	Deaths	Total	Number at risk at each time point			
				5 yr	10 yr	15 yr	20 yr
Patients treated with targeted therapy for oligometastatic disease	6	5	11	6	2	0	0
Patients who had an incomplete clinical response to nCRT and underwent subsequent oesophagectomy	14	48	62	12	6	3	0

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Figure 1 Survival plots for patients undergoing treatment of oligometastatic disease for cure *vs* patients with an incomplete clinical response to neoadjuvant chemoradiotherapy who underwent subsequent oesophagectomy. nCRT: Neoadjuvant chemoradiotherapy.

pathology identified 32057 patients who underwent resection for gastro-oesophageal cancer between 1991 and 2016 and reported that 34 (0.11%) underwent resection for pulmonary (n = 15) or hepatic (n = 19) metastases across 21 hospitals and had an overall 5-year survival of 53% and 31%, respectively[33]. Liu *et al*[34] reported that 26 SCC patients with solitary hepatic metastasis, who underwent liver resection, had 1- and 2-year survival rates of 50.8% and 21.2%, respectively, which was significantly higher than the 31.0% and 7.1% survival rates for the 43 non-surgically treated patients[34].

Oesophageal cancer patients very frequently present with metastases, which almost inevitably consigns them to palliative management. Until recently primary cancer resection in these circumstances was rarely considered. Of the 4 patients who presented with metastatic oesophageal cancer in our case series, 3 underwent surgery to the primary cancer. All 3 had nCRT and all achieved an R0 resection, with a cumulative proportion surviving 2 years of 67%. Zhang *et al*[35] analysed a large population-based cohort of 4367 metastatic oesophageal cancer patients (M1b-stage) from the SEER database[35] and found a significant survival benefit for surgery for the primary tumour with a median survival for the surgery group of 14 mo compared with 9 mo for the no surgery AC group, and a similar significant survival advantage for surgery (11 mo) compared with the no surgery SCC group (7 mo)[35]. Of note, patients who had not received neoadjuvant chemotherapy failed to benefit from resection for either tumour subtype[35]. Thus, when combined with neoadjuvant chemotherapy, surgery for the primary tumour is associated with improved survival in a select group of patients with metastatic oesophageal cancer[35].

Three of the patients in our series received chemotherapy alone for recurrent oligometastatic oesophageal cancer (patients 2, 6, and 11). Although chemotherapy is commonly considered as merely palliative in recurrent metastatic cancer, it also has the potential to cure[36]. Taxanes as single agents have a slightly higher response rate in patients with AC (34%) than in patients with SCC (28%), resulting in an overall survival rate of 13.2 mo[37]. Parry *et al*[38] reported complete tumour regression in 2 patients after chemotherapy alone, with both patients alive at last follow-up (35 and 112 mo)[38]. Developments in proton beam therapy and stereotactic ablative radiation increases its conformality and reduces radiation toxicity[39]. Sachdeva *et al*[40] recently reported on the use of external beam radiotherapy for the treatment of oligometastatic sacral metastases in a 46-year-old male with a rare case of primary oesophageal lymphoma[40]. Moreover, 1-year and 2-year progression-free survival and overall survival rates have been reported at 62% and 48% and 90% and 72%, respectively, following stereotactic ablative therapy for pulmonary metastases[41].

With few predictive factors for survival of metastatic oesophageal cancer in the literature[42], it is unclear which patients or which tumour characteristics predict the best survival outcomes. The current approach to metastatic disease all too often consigns the patient to palliative care and a dismal outcome.

We have previously reported that bone marrow positivity for micrometastases at the time of oesophagectomy is a predictor of increased risk of cancer-related death and can identify patients requiring intensive surveillance for early detection of metastases with intent to treat[43]. Our current findings suggest that a more optimistic approach can be rewarded with impressive survival data. It is intuitive that aggressive treatment can improve survival, but it implies a need for more intensive surveillance strategies, especially in the first 3 years post-resection, to identify salvageable patients and consider curative intent. In an era of molecularly targeted agents, the identification of such patients is more important than ever as identified by the CheckMate 557 trial where the addition of nivolumab for patients with residual disease following CRT provided a median disease-free survival of 22.4 mo *vs* 11.0 mo in the placebo arm, which was significant[44].

The obvious limitation of our study is the small sample size of patients with metastatic oesophageal cancer treated for cure. Moreover, the survival data reported in our study reflects a policy of aggressive treatment of confirmed limited metastases only. Such patients self-select, and our survival data cannot be applied to all patients with metastatic oesophageal cancer.

CONCLUSION

In conclusion, as advances in imaging facilitate earlier metastatic disease detection and advances in multimodal and targeted treatments improve survival outcomes, surveillance strategies must be intensified to diagnose metastatic disease earlier in the recurrence process to institute medical or surgical measures with a greater possibility of success. Future studies are needed to prospectively identify the rate of oligometastatic recurrence in oesophageal carcinoma in the context of today's imaging technologies to update surveillance and treatment guidelines in line with those for cancers of the lower gastrointestinal tract.

ARTICLE HIGHLIGHTS

Research background

The prognosis of metastatic oesophageal cancer is poor. The rate of oligometastatic oesophageal cancer is not well established nor is the survival benefit of intervention. As a result, current guidelines advocate against a proactive approach, which is incongruent with other oligometastatic cancers such as colorectal cancer. Based on a policy of active postoperative surveillance and survival outcomes of patients with oligometastatic disease treated with curative intent at our institution, we advocate for more intensive surveillance strategies to identify patients with curative potential early and thus improve long-term survival.

Research motivation

To evaluate the impact of a policy of active surveillance and aggressive management of confirmed metastases on long-term survival.

Research objectives

To examine survival outcomes in patients who underwent active surveillance and targeted therapy of their oligometastatic disease, either at diagnosis or on follow-up surveillance, at our institution. When compared to incomplete clinical responders to neoadjuvant chemoradiotherapy (nCRT) for non-metastatic oesophageal cancer who underwent surgery on their primary tumour, the median overall survival of the oligometastatic cohort was statistically significantly longer. These findings suggest that aggressive treatment of confirmed metastases can be rewarded with impressive survival data and that a more proactive approach to oesophageal oligometastases should be considered.

Research methods

A prospectively maintained database of patients diagnosed with oesophageal carcinoma and treated with curative intent in a single institution was interrogated for patients with metastases, either at diagnosis or on follow-up surveillance, and treated for cure. This cohort was compared with incomplete clinical responders to nCRT who subsequently underwent surgery on their primary tumour. Overall survival was estimated using the Kaplan-Meier method, and the log-rank test was used to compare survival differences between groups.

Research results

The overall survival of patients with oligometastatic disease who were treated for cure at our institution is impressive and statistically significantly longer than incomplete clinical responders without metastatic disease who subsequently underwent surgery on their primary tumour. These results suggest

that intensive follow-up and aggressive management of confirmed metastases may improve long-term survival. Further studies are needed to prospectively identify the rate of oligometastatic recurrence in oesophageal carcinoma and evaluate the cost-benefit ratio of a policy of active surveillance and aggressive management of confirmed oligometastatic disease.

Research conclusions

In view of recent diagnostic and therapeutic advances, intensive follow-up and aggressive treatment of confirmed metastases may improve long-term survival in patients with oligometastatic oesophageal carcinoma.

Research perspectives

Further research should prospectively establish the rate of oligometastatic recurrence in oesophageal carcinoma to evaluate the cost-benefit ratio of active surveillance and aggressive management and inform future clinical guidelines.

FOOTNOTES

Author contributions: Walsh TN was the guarantor, designed the study, participated in the acquisition of data, and revised and edited the article critically; Pickett L acquired, analysed, and interpreted the data and drafted the initial manuscript; Dunne M statistically analysed the data and edited the manuscript; Monaghan O, Grogan L, and Breathnach O reviewed the article and made critical revisions related to important intellectual content.

Institutional review board statement: The study was reviewed and approved by the Connolly Hospital Institutional Review Board.

Informed consent statement: As this was a retrospective audit and many patients were not alive at the commencement of this study, written informed consent was not feasible/obtained. This was an observational study, and no patient received treatment as part of the study. Furthermore, we have not included any identifiable patient information in our manuscript. Verbal consent, although not required, was obtained where appropriate/feasible.

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

Data sharing statement: The statistical analysis and dataset are available from the corresponding author at lianne.pickett@ucdconnect.ie. As this was a retrospective audit consent was not routinely obtained but the presented data are anonymized, and risk of identification is low.

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ORIGINAL ARTICLE

Observational Study

Change of tumor-infiltrating lymphocyte of associating liver partition and portal vein ligation for staged hepatectomy for hepatocellular carcinoma

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Abstract

BACKGROUND

The role of tumor-infiltrating lymphocytes (TILs) in the growth and progression of hepatocellular carcinoma (HCC) has attracted widespread attention.

AIM

To evaluate the feasibility of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) for massive HCC by exploring the role of TIL in the tumor microenvironment.

METHODS

Fifteen massive HCC patients who underwent ALPPS treatment and 46 who underwent hemi-hepatectomy were selected for this study. Propensity score matching was utilized to match patients in ALPPS and hemi-hepatectomy groups (1:1). Quantitative analysis of TILs in tumor and adjacent tissues between the two groups was performed by immunofluorescence staining and further analyses with oncological characteristics. In the meantime, trends of TILs in peripheral blood

were compared between the two groups during the perioperative period.

RESULTS

Continuous measurement of tumor volume and necrosis volume showed that the proportion of tumor necrosis volume on the seventh day after stage-I ALPPS was significantly higher than the pre-operative value (P = 0.024). In the preoperative period of stage-I ALPPS, the proportion of tumor necrosis volume in the high CD8$^+$ T cell infiltration group was significantly higher than that in the low group (P = 0.048).

CONCLUSION

TIL infiltration level maintained a dynamic balance during the preoperative period of ALPPS. Compared with right hemi-hepatectomy, the ALPPS procedure does not cause severe immunosuppression with the decrease in TIL infiltration and pathological changes in immune components of peripheral blood. Our results suggested that ALPPS is safe and feasible for treating massive HCC from the perspective of immunology. In addition, high CD8$^+$T cell infiltration is associated with increasing tumor necrosis in the perioperative period of ALPPS.

Key Words: Associating liver partition and portal vein ligation for staged hepatectomy; Tumor-infiltrating lymphocytes; Multiplexed immunohistochemistry; Tumor necrosis

Core Tip: This study was conducted to evaluate the feasibility of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) for massive hepatocellular carcinoma by exploring the role of tumor-infiltrating lymphocyte (TIL) subpopulations in the tumor microenvironment. The ALPPS procedure did not cause severe immunosuppression due to reduced TIL infiltration and pathological alterations in peripheral blood immune components. In addition, high perioperative CD8$^+$T cell infiltration with ALPPS was associated with increased tumor necrosis.

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INTRODUCTION

Primary liver cancer is a common digestive system malignancy, with around 906000 new cases and 830000 deaths occurring globally, with the incidence rate and mortality rate increasing yearly. More than 75% of cases of primary liver cancer are hepatocellular carcinoma (HCC)[1]. According to the newly released diagnosis and treatment guidelines, surgery is the primary choice of radical resection of HCC tumors and the principal treatment strategy for prolonging the survival time of patients with HCC [2,3].

In March 2012, Schnitzbauer *et al*[4] were the first to report associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), an innovative hepatectomy, publicly. ALPPS can block part of the blood flow supplying the tumor and completely block the possible collateral circulation between the two hepatic lobes. Thus, ALPPS can effectively stimulate liver hyperplasia and create more favorable conditions for the second-stage surgical resection of the tumor. With the gradual maturity and improvement in ALPPS technology, the clinical application of ALPPS has gone through an early transition, and the incidence of complications and mortality has been gradually reduced. In HCC patients who have undergone rigorous screening for ALPPS treatment, these risks are comparable to those of traditional hepatectomy and portal vein embolization + hepatectomy, which leads to an increase in the resection rate of massive HCC[5]. As a new method of liver surgery, ALPPS is a promising approach to treating HCC patients.

Tumor-infiltrating lymphocytes (TILs) migrate to the tumor microenvironment (TME) after leaving the peripheral blood circulation system, which involve T and B lymphocytes and natural killer (NK) cells. TILs are an integral part of the TME, and their role in HCC tumor growth and progression has attracted widespread attention. Recent studies have focused on the relationship between TILs and the prognosis of liver cancer patients. Anantha *et al*[6] reported for the first time that various immunological components of the future liver remnant (FLR) did not change during the perioperative period of ALPPS.

This shows that FLR proliferates rapidly and relatively expands the formation of various immune cells and components to maintain immune functions. However, in the perioperative period of ALPPS, patients need to withstand two surgical insults. The impact of subsequent stress or inflammatory response on the changes and effects of immune cells residing or recruited in the TME is still unclear. More specifically, to understand whether ALPPS could be used as a viable alternative to traditional hepatectomy techniques, it is necessary to study the potential mechanism of ALPPS complications and the changes and effects of tumor-infiltrating immune cells or components. Here, we investigated the effect of ALPPS surgery on TIL subsets, analyzed the changes in the immune microenvironment of tumor cells during the two-stage ALPPS surgery, and finally evaluated the safety and effectiveness of ALPPS as an alternative to traditional hemi-hepatectomy for the treatment of massive HCC.

MATERIALS AND METHODS

Study design

All subjects were HCC cases from the Department of Hepatobiliary Surgery of a single center from August 2018 to August 2019. Surgical resection was performed in all cases, with the types of tumors confirmed by postoperative pathological examination. These data have been uploaded to the International ALPPS Registry (www.alpps.net). This study followed the declaration of Helsinki and was approved by the ethics committee of the center. Patients were not required to give informed consent for the study because the clinical data were obtained retrospectively after each patient agreed to treatment by written consent.

Patient criteria

The following inclusion criteria were used for the selection of patients: (1) Patients with an FLR/standard liver volume (SLV) ratio < 30%-50% and who have received stage-I ALPPS treatment; (2) Child-Pugh classification A or B; and (3) All subjects were confirmed to be HCC patients by surgery and pathology. The following exclusion criteria were used for rejecting the patients: (1) Incomplete clinical data or histological specimens; (2) Patients without stage-II ALPPS treatment; and (3) Patients undergoing left hemi-hepatectomy.

Multiple immunofluorescence staining

Each specimen was numbered according to the chronological order of the included cases and the site of collection, and hematoxylin-eosin-stained sections of HCC tissues kept in the case specimen library were retrieved. After the pathologists read the slides, paraffin specimens with typical HCC characteristics of cancerous and paracancerous tissues were selected. The screened tissues were then arranged on empty white wax blocks in a certain order using a tissue microarray spotter with the assistance of a pathology technician, and the tissue chip was obtained by serially slicing the wax blocks through a slicer, in which each core spot represented a pathological specimen. The prepared tissue chips were placed in slide boxes and refrigerated at 4 °C for storage. Tissue chips were subjected to antigen repair after dewaxing and dehydration. Subsequently, 3% H_2O_2 was added dropwise to block endogenous peroxidase. Primary antibodies (Abcam, United States) were added and kept at 4 °C overnight. Secondary antibodies were added dropwise at room temperature for 50 min, and then horseradish peroxidase reagent was added dropwise. CD4, CD56, CD3, CD20, CD8, and Foxp3 were stained with different colors of fluorescent dyes. DAPI (Sigma-Aldrich, Germany) was used to stain the nucleus. Dimethyl sulfoxide (1 mL) was added to the tissue chip at room temperature for 5 min, and the slide was covered. Complete images were acquired with the Mantra system (PerkinElmer, Waltham, Massachusetts, United States) to collect multispectral images. The inform image analysis software was used to quantify the amount of fluorescence excitation for each core site and for each fluorophore. The positive expression rate of cells in each sample was calculated as number of positive cells/total number of nucleated cells.

Surgical technique

During stage-I ALPPS, the surgeon first opened the abdominal cavity to exclude extrahepatic metastatic tissues. The right portal vein branch would be ligated in the absence of any metastasis. Intra-operative ultrasound-guided anterior hepatic transection was conducted along the middle hepatic vein, and the blood flow of the hepatic artery was preserved. The interval between stage I and stage II of ALPPS depended on the patient's condition and increased FLR. During stage-II ALPPS, right hepatectomy or enlarged right hepatectomy was performed[7].

Propensity score matching

To add to the control analysis, patients in the ALPPS group were matched 1:1 with those in the right hemicolectomy group using the propensity score matching (PSM) module built into the SPSS 22.0 software. The independent variables of tumor size and number, alpha-fetoprotein (AFP) level, Child-

Pugh score, presence of large vessel cancer thrombi, and presence of distant metastases were used as covariate matching items. Age, gender, body mass index, liver cancer end-stage score, and Barcelona clinic liver cancer (BCLC) staging system were used as balanced matches. The caliper value was set to 0.1.

Volume measurement of the liver and tumor

The liver volume was analyzed using IQQA-3D Liver (EDDA Technology, United States) combined with patient imaging data[8]. SLV was calculated using the Chinese adult standard liver volume estimation formula[9]. FLR/SLV ratio before surgery was used to determine whether FLR was sufficient. The increase in FLR volume confirmed the stage-I ALPPS and stage-II ALPPS. The following conditions were considered acceptable for stage-II ALPPS: (1) FLR/SLV ratio ≥ 50% suggested severe fibrosis or cirrhosis; (2) FLR/SLV ratio ≥ 40% suggested the presence of mild/moderate fibrosis; and (3) FLR/SLV ≥ 30% suggested the absence of liver fibrosis or cirrhosis[10]. A complete tumor image was drawn, and the tumor volume was calculated[11]. The tumor necrosis volume was also calculated. The percentage of tumor necrosis volume was then calculated as tumor necrosis volume/tumor volume × 100%. The tumor size and necrotic volume were analyzed before ALPPS and 3 d and 7 d after stage-I ALPPS.

Follow-up

The patients were followed regularly for 3 mo after discharge and every 3 to 6 mo after that, mainly involving imaging examination (ultrasound, computed tomography, and magnetic resonance imaging), liver function inspection, and AFP level test. After analysis, the overall survival rate of each patient was calculated, with the survival time defined as the time from treatment operation to death. The final events of overall survival included extrahepatic or intrahepatic metastasis, recurrence, and death after primary resection.

Statistical analysis

The data were analyzed and processed with IBM SPSS22.0. The normally distributed measurement data are expressed as the mean ± SD, and the count data are defined as quantity (%). The student's *t*-test was conducted to compare the measurement data between two paired groups. Comparison of counting data was made between two groups using the chi-square test or Fisher's exact test, and the R × C chi-square test was used for comparison among groups. Repeated measurement data were compared by repeated measurement analysis of variance. Kaplan-Meier method was used for survival analysis and fitting survival curves. The Log-rank test was used to compare the differences in survival curves among different groups. $P < 0.05$ was considered statistically significant.

RESULTS

Matching results between the two groups

The clinical data of 90 patients undergoing hepatectomy in a single center were collected. Fifteen HCC patients treated by ALPPS and 46 patients by right hemi-hepatectomy were included for analysis (Figure 1). A 1:1 match was performed between the ALPPS group and the right hemi-hepatectomy group using the PSM module. After matching, the variables such as age, sex, body mass index, liver cancer end-stage score, BCLC stage, tumor size and number, AFP level, Child-Pugh score, presence of macrovascular tumor thrombus, and distant metastasis were found to be similar between the two groups ($P > 0.05$, Table 1). In addition, the average FLR/SLV ratio of the ALPPS group measured before the operation was 36.9% (range, 21.6%-45.4%), and the FLR/SLV value of the right hemi-hepatectomy group was 58.9% (range, 35.3%-77.3%).

Intraoperative and postoperative survey of patients in the two groups

The average operation time of stage-I ALPPS, stage-II ALPPS, and right hemi-hepatectomy was 342 min (range, 229-459 min), 293 min (range, 167-400 min), and 338 (range, 140-515) min, respectively, while the mean intraoperative bleeding volume was 230 (range, 100-500) mL, 619 mL (range, 200-1800 mL), and 344 (range, 190-638) mL, respectively. There was no allogeneic blood transfusion in stage-I ALPPS, while four cases in stage-II ALPPS required allogeneic blood transfusion and one case received leukocyte-depleted red blood cell suspension 2 U after right hemi-hepatectomy. All surgical margins were resected with R0. The median interval between the first stage of ALPPS and the second one was 15 d (range, 9-27 d).

No ALPPS group patients experienced postoperative bile leakage, while two right hemi-hepatectomy group patients underwent postoperative bile leakage. By the Clavien-Dino criteria[12], for stage-I ALPPS, the number of patients with grade I, grade II, and grade III postoperative complications was 13, 1, and 1, respectively. For stage-II ALPPS, the number of patients with grade I, grade II, grade III, and grade IV postoperative complications was 8, 4, 2, and 1, respectively. Whereas, for right hemi-

Table 1 Propensity score matching results of associating liver partition and portal vein ligation for staged hepatectomy group and right hemi-hepatectomy group

Variable	Before matching			After matching		
	ALPPS (15 cases)	Hepatectomy (46 cases)	*P* valve	ALPPS (15 cases)	Hepatectomy (15 cases)	*P* valve
Age (yr)	45.1 ± 11.4	49.4 ± 9.6	0.157	45.1 ± 11.4	49.5 ± 9.9	0.276
Sex (%)			0.795			0.543
Female	2 (13.3%)	5 (10.9%)		2 (13.3%)	1 (6.7%)	
Male	13 (86.7%)	41 (89.1%)		13 (86.7%)	14 (93.3%)	
BMI	22.4 ± 3.2	22.8 ± 3.1	0.644	22.4 ± 3.2	23.0 ± 3.4	0.608
HCC end-stage score	5.8 ± 2.3	5.4 ± 2.6	0.626	5.8 ± 2.3	6.1 ± 3.7	0.815
BCLC stage			0.775			0.915
A	3 (20.0%)	13 (28.3%)		3 (20.0%)	3 (20.0%)	
B	5 (33.3%)	12 (26.0%)		5 (33.3%)	4 (26.7%)	
C	7 (46.7%)	21 (45.7%)		7 (46.7%)	8 (53.3%)	
AFP (%)			0.031			1.000
≥ 400 ng/mL	11 (73.3%)	19 (41.3%)		11 (73.3%)	11 (73.3%)	
< 400ng/mL	4 (26.7%)	27 (58.7%)		4 (26.7%)	4 (26.7%)	
Child-Pugh class (%)			0.984			1.000
A	14 (93.3%)	43 (93.5%)		14 (93.3%)	14 (93.3%)	
B	1 (6.7%)	3 (6.5%)		1 (6.7%)	1 (6.7%)	
Tumor number (%)			0.125			1.000
1	10 (66.7%)	39 (84.8%)		10 (66.7%)	10 (66.67%)	
> 1	5 (33.3%)	7 (15.2%)		5 (33.3%)	5 (33.33%)	
Tumor size (cm)	10.7 ± 4.5	7.7 ± 4.8	0.033	10.7 ± 4.5	9.0 ± 4.9	0.332
Vascular invasion (%)			0.952			0.705
Yes	6 (40.0%)	18 (39.1%)		6 (40.0%)	5 (33.3%)	
No	9 (60.0%)	28 (60.9%)		9 (60.0%)	10 (66.6%)	
Extrahepatic metastasis (%)			1.000			1.000
Yes	0 (0%)	1 (2.2%)		0 (0%)	0 (0%)	
No	15 (100%)	45 (97.8%)		15 (100%)	15 (100%)	

ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; BMI: Body mass index; HCC: Hepatocellular carcinoma; BCLC: Barcelona Clinic Liver Cancer; AFP: Alpha-fetoprotein.

hepatectomy, the number of patients with grade I, grade II, grade III, and grade IV postoperative complications was 9, 4, 1, and 1, respectively. All other complications were cured, except that a stage-II ALPPS patient rated as grade IV due to postoperative liver failure and a right hepatectomy patient with respiratory failure rated as grade IV died during the perioperative period.

The 15 cases of ALPPS patients underwent postoperative liver failure classification by the International Study Group of Liver Surgery standards[13]. After stage-I ALPPS, four were graded as A, 10 as B, and 1 as C and after stage-II ALPPS, 4 were graded as A, 9 as B, and 2 as C. For the right hepatectomy group, the number of cases graded as A, B, and C was 6, 8, and 1, respectively. One patient of the ALPPS group died on the 32nd d after the second stage, while one of the right hepatectomy group died on the 28th d after the operation (Table 2).

Expression of TILs in HCC microenvironment

TILs are an important component of the TME involved in the local immune response, and their degree of infiltration greatly affects tumor growth and progression. In order to determine the infiltration degree

Table 2 Intraoperative and postoperative conditions of patients in associating liver partition and portal vein ligation for staged hepatectomy group and right hemi-hepatectomy group

	ALPPS		Hepatectomy
	Stage-I ALPPS	Stage-II ALPPS	
Surgery time (min)	342 (229-459)	293 (167-400)	338 (140-515)
Intraoperative blood loss (mL)	230 (100-500)	619 (200-1800)	344 (190-638)
Postoperative bile leakage (yes/no)	0/15	0/15	2/13
Postoperative complications, Clavien-Dino (I/II/III/IV)	13/1/1/0	8/4/2/1	9/4/1/1
Classification of postoperative liver failure, ISGLS (A/B/C)	4/10/1	4/9/2	6/8/1
90 d survival after operation (death/alive)	0/15	1/14	1/14

ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; ISGLS: International Study Group of Liver Surgery.

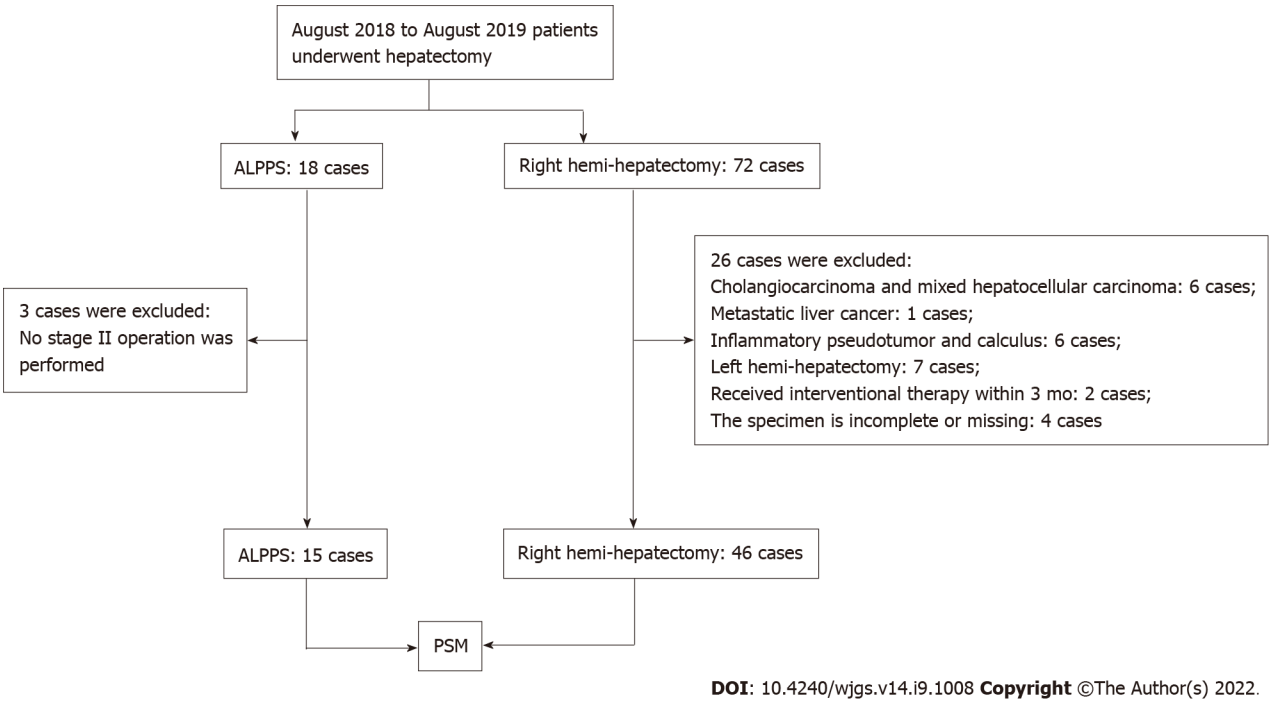

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Figure 1 Flow chart of patient selection. Fifteen hepatocellular carcinoma patients treated by associating liver partition and portal vein ligation for staged hepatectomy and 46 patients by right hemi-hepatectomy were included for analysis. ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; PSM: Propensity score matching.

and trend change of TILs in the HCC microenvironment, we took tissues from 15 cases of ALPPS and 15 matched patients with right hepatectomy. Cancerous tissues and para-cancerous tissues were used to make tissue microarrays. The specific marker molecules of lymphocyte subsets in the TME underwent polychromatic immunohistochemical staining. The results showed that the infiltration pattern of TILs in cancer tissues was significantly different from that in para-cancerous tissues. The infiltration of TILs in cancer tissues was irregular and diffusely distributed. Whereas, in para-cancerous tissues, TILs were mainly concentrated in the connective tissues of the interlobular portal area, often accompanied by three kinds of ducts: Interlobular artery, interlobular vein, and interlobular bile duct (Figure 2).

The quantitative analysis showed the number of target cells and the total number of all nucleated cells. The positive expression levels of six TIL subsets of T cells, $CD8^+$ T cells, $CD4^+$ T cells, Treg cells, B cells, and NK cells in the same spatial tissues were calculated. Furthermore, the TILs of the right hemi-hepatectomy group, ALPPS group (including stages I and II), and cancer or para-cancerous tissues were compared and analyzed (Figure 3). The results showed that the positive expression level of Treg cells in the cancer tissues was significantly higher than that of the adjacent tissues (P = 0.043, Tables 3-6).

Table 3 Comparison of positive expression rates of tumor-infiltrating lymphocyte subpopulations in tumor tissues in stage-I associating liver partition and portal vein ligation for staged hepatectomy, stage-II associating liver partition and portal vein ligation for staged hepatectomy, and right hemi-hepatectomy groups

	ALPPS		Hepatectomy	Variance analysis	
	Stage-I ALPPS	Stage-II ALPPS		*F* valve	*P* valve
Total T cells (%)	3.3 ± 2.9	3.1 ± 2.0	2.8 ± 1.8	0.188	0.829
CD4+ T cells (%)	1.0 ± 0.9	1.2 ± 1.1	0.9 ± 0.5	0.458	0.635
CD8+ T cells (%)	0.8 ± 0.7	1.0 ± 0.9	0.6 ± 0.4	0.546	0.583
Treg cells (‰)	0.2 ± 0.1	0.2 ± 0.2	0.3 ± 0.1	0.166	0.848
B cells (%)	1.7 ± 1.3	1.3 ± 0.7	2.1 ± 0.8	0.726	0.490
NK cells (%)	0.7 ± 0.2	0.4 ± 0.2	0.7 ± 0.2	0.664	0.520

NK: Natural killer; ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy.

Table 4 Comparison of positive expression rates of tumor-infiltrating lymphocyte subpopulations in adjacent tissues in stage-I associating liver partition and portal vein ligation for staged hepatectomy, stage-II associating liver partition and portal vein ligation for staged hepatectomy, and right hemi-hepatectomy groups

	ALPPS			Variance analysis	
	Stage-I ALPPS	Stage-II ALPPS	Hepatectomy	*F* valve	*P* valve
Total T cells (%)	2.0 ± 0.6	1.9 ± 0.9	1.8 ± 1.3	0.129	0.879
CD4+ T cells (%)	0.8 ± 0.3	0.9 ± 0.3	0.9 ± 0.7	0.258	0.774
CD8+ T cells (%)	0.8 ± 0.3	1.0 ± 0.5	1.0 ± 0.7	0.510	0.604
Treg cells (‰)	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.292	0.748
B cells (%)	2.0 ± 1.2	1.8 ± 0.8	1.7 ± 0.5	0.269	0.765
NK cells (%)	0.7 ± 0.7	0.6 ± 0.5	0.8 ± 0.7	0.550	0.581

NK: Natural killer; ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy.

Table 5 Comparison of tumor-infiltrating lymphocyte subpopulations between tumor and adjacent tissues in associating liver partition and portal vein ligation for staged hepatectomy group

	Stage-I ALPPS			Stage-II ALPPS		
	Tumor	Adjacent	*P* valve	Tumor	Adjacent	*P* valve
Total T cells (%)	3.3 ± 2.9	2.0 ± 0.6	0.116	3.1 ± 2.0	1.9 ± 0.9	0.056
CD4+ T cells (%)	1.0 ± 0.9	0.8 ± 0.3	0.403	1.2 ± 1.1	0.9 ± 0.3	0.278
CD8+ T cells (%)	0.8 ± 0.7	0.8 ± 0.3	0.902	1.0 ± 0.9	1.0 ± 0.5	0.792
Treg cells (‰)	0.2 ± 0.1	0.0 ± 0.1	0.056	0.2 ± 0.2	0.0 ± 0.0	0.156
B cells (%)	1.7 ± 1.3	2.0 ± 1.2	0.515	1.3 ± 0.7	1.8 ± 0.8	0.085
NK cells (%)	0.7 ± 0.2	0.7 ± 0.7	0.985	0.4 ± 0.2	0.6 ± 0.5	0.403

NK: Natural killer; ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy.

Perioperative tumor necrosis in stage-I ALPPS and its relationship with TILs

The proportion of tumor necrosis volume was calculated by analyzing the tumor volume and tumor necrosis volume in the perioperative period of stage-I ALPPS (Figure 4). The results showed that the proportion of tumor necrotic volume on the seventh day after stage-I ALPPS was significantly higher than before the operation (P = 0.024, Figure 5). In order to further clarify the relationship between tumor

Table 6 Comparison of tumor-infiltrating lymphocyte subpopulations between tumor and adjacent tissues in right hemi-hepatectomy group

	Right hemi-hepatectomy		
	Tumor tissues	Adjacent tissues	*P* valve
Total T cells (%)	2.8 ± 1.8	1.8 ± 1.3	0.105
CD4+ T cells (%)	0.9 ± 0.5	0.9 ± 0.7	0.840
CD8+ T cells (%)	0.6 ± 0.4	1.0 ± 0.7	0.101
Treg cells (‰)	0.3 ± 0.1	0.0 ± 0.0	0.043
B cells (%)	2.1 ± 0.8	1.7 ± 0.5	0.645
NK cells (%)	0.7 ± 0.2	0.8 ± 0.7	0.678

NK: Natural killer.

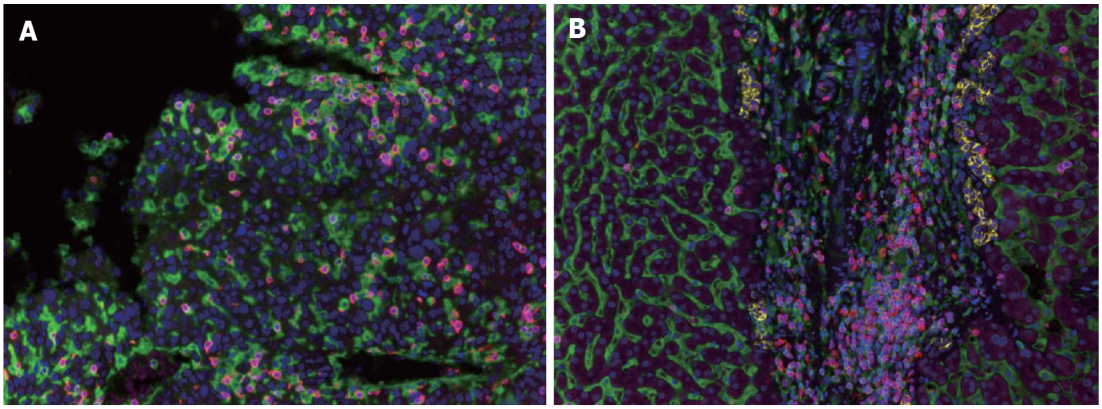

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Figure 2 Expression of tumor-infiltrating lymphocytes in the hepatocellular carcinoma tumor microenvironment. A: Immunohistochemistry image showing the distribution and expression of tumor-infiltrating lymphocyte subpopulations in tumor tissues; B: Immunohistochemistry image showing the distribution and expression of tumor-infiltrating lymphocyte subpopulations in adjacent tissues.

necrosis and TILs in the perioperative period of stage-I ALPPS, the median positive expression level of the six TIL subgroups in stage-I ALPPS cancer tissues was used as the cut-off point. The HCC patients receiving ALPPS treatment were divided into a high-infiltration group and a low-infiltration group. We then compared the difference in the proportion of tumor necrosis volume between the two groups. The results showed that the proportion of tumor necrosis volume in the high $CD8^+$ T cell infiltration group was significantly higher than that in the low $CD8^+$ T cell infiltration group (P = 0.048, Figure 6).

Comparison between immune components in peripheral blood of right hemi-hepatectomy, stage-I ALPPS, and stage-II ALPPS patients

Pairwise comparisons of immune components of peripheral blood were measured between the right hemi-hepatectomy group, stage-I ALPPS group, and stage-II ALPPS group. We found that the components of the complement system, C1q and C3 in peripheral blood in stage-I ALPPS, were significantly higher than those in stage II (C1q: P = 0.007; C3: P = 0.047, Figure 7). In addition, interleukin (IL)-6 levels in the stage-I ALPPS and stage-II ALPPS increased significantly and reached a peak value on the first day after surgery, and then decreased rapidly but were significantly higher than the preoperative level ($P1$ = 0.000, $P2$ = 0.002). NK cells in stage-I and stage-II ALPPS temporarily increased on the first day after surgery and gradually decreased on the second day after surgery to figures lower than the preoperative level (Figure 8). There was no significant difference in other remaining peripheral blood indicators among the groups (P > 0.05, Figure 9, Tables 7-9).

Follow-up results

The ALPPS and right hemi-hepatectomy group patients were followed after the surgery. As of May 20, 2020, the median follow-up time of ALPPS group patients and that of right hemi-hepatectomy group patients were 472 d (279-607 d) and 449 d (267-740 d), respectively. There was no significant difference in follow-up time between the two groups (P = 0.528). The survival rate of the ALPPS group and that of

Table 7 Comparison of immunological data during stage-I associating liver partition and portal vein ligation for staged hepatectomy

Item	Preoperative	Stage-I ALPPS				*F* value	*P* value
		POD1	POD3	POD5	POD7		
T lymphocyte count (cells/μL)	1331.5 ± 600.0	472.8 ± 289.9	682.0 ± 346.9	837.9 ± 383.6	1012.5 ± 444.2	10.095	0.001
Total T lymphocyte percentage (%)	67.8 ± 8.7	59.6 ± 8.5	68.4 ± 12.3	70.5 ± 11.7	68.9 ± 10.3	6.717	0.000
CD4+ T lymphocytes (cells/μL)	806.3 ± 428.2	241.1 ± 202.2	412.3 ± 224.7	520.1 ± 255.1	608.0 ± 266.1	9.049	0.002
CD8+ T lymphocyte (cells/μL)	438.2 ± 194.2	187.6 ± 96.6	238.9 ± 141.0	277.4 ± 143.5	361.2 ± 201.6	11.294	0.001
Natural killer cells (%)	16.5 ± 7.8	27.2 ± 8.6	10.8 ± 6.9	11.0 ± 3.7	11.2 ± 3.7	17.341	0.000
IgA (g/L)	3.11 ± 1.28	2.63 ± 1.64	1.87 ± 0.77	2.08 ± 0.79	2.69 ± 1.24	10.025	0.001
IgG (g/L)	15.11 ± 3.70	10.52 ± 2.89	8.70 ± 2.72	8.89 ± 2.69	9.82 ± 2.70	62.360	0.000
IgM (g/L)	1.27 ± 0.68	0.89 ± 0.40	0.71 ± 0.39	0.82 ± 0.38	1.08 ± 0.53	6.114	0.008
Complement C1q (mg/L)	194.5 ± 28.7	168.9 ± 44.2	140.4 ± 39.6	157.7 ± 45.9	159.17 ± 55.3	6.726	0.000
Complement C3 (g/L)	1.18 ± 0.19	0.87 ± 0.15	0.79 ± 0.19	0.87 ± 0.21	0.91 ± 0.26	44.808	0.000
Complement C4 (g/L)	0.40 ± 0.18	0.26 ± 0.12	0.23 ± 0.11	0.25 ± 0.12	0.28 ± 0.15	8.731	0.002
Interleukin-6 (g/L)	10.7 ± 17.0	177.4 ± 121.6	84.0 ± 62.3	52.6 ± 40.9	41.2 ± 35.1	7.877	0.003
CD19 expression rate (%)	10.5 ± 4.0	9.6 ± 5.62	12.1 ± 5.6	12.7 ± 5.2	13.3 ± 6.1	1.866	0.129

ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; POD: Postoperative day; Ig: Immunoglobulin.

Table 8 Comparison of immunological data during stage-II associating liver partition and portal vein ligation for staged hepatectomy

Item	Preoperative	Stage-II ALPPS				*F* value	*P* value
		POD1	POD3	POD5	POD7		
T lymphocyte count (cells/μL)	1414.4 ± 634.0	455.9 ± 255.4	716.3 ± 311.3	796.3 ± 282.8	913.4 ± 387.1	17.626	0.000
Total T lymphocyte percentage (%)	67.8 ± 8.7	63.7 ± 9.2	72.3 ± 7.5	74.8 ± 6.4	73.6 ± 7.2	8.288	0.000
CD4+ T lymphocytes (cells/μL)	806.3 ± 428.2	246.4 ± 168.2	375.9 ± 170.1	493.9 ± 196.7	537.9 ± 231.3	7.925	0.003
CD8+ T lymphocytes (cells/μL)	438.2 ± 194.2	168.5 ± 89.4	290.3 ± 184.7	291.9 ± 159.0	356.1 ± 210.8	8.775	0.000
Natural killer cells (%)	16.5 ± 7.8	23.0 ± 7.1	12.7 ± 4.6	8.7 ± 4.8	10.2 ± 3.2	15.615	0.000
IgA (g/L)	3.11 ± 1.28	2.37 ± 1.88	2.31 ± 1.41	2.59 ± 1.30	3.40 ± 1.66	8.900	0.002
IgG (g/L)	15.11 ± 3.70	8.71 ± 2.10	8.11 ± 1.90	8.53 ± 1.66	9.68 ± 2.26	12.604	0.000
IgM (g/L)	1.27 ± 0.68	0.70 ± 0.37	0.67 ± 0.28	0.70 ± 0.36	0.83 ± 0.37	1.277	0.001
Complement C1q (mg/L)	194.5 ± 28.7	140.8 ± 33.8	111.1 ± 39.1	118.5 ± 41.3	124.2 ± 42.1	14.422	0.000
Complement C3 (g/L)	1.18 ± 0.19	0.72 ± 0.27	0.54 ± 0.20	0.58 ± 0.20	0.62 ± 0.18	24.345	0.000
Complement C4 (g/L)	0.40 ± 0.18	0.22 ± 0.16	0.15 ± 0.12	0.15 ± 0.14	0.17 ± 0.16	15.305	0.000
Interleukin-6 (pg/mL)	10.7 ± 17.0	210.3 ± 160.9	62.6 ± 27.6	37.1 ± 19.7	41.6 ± 61.3	12.206	0.000
CD19 expression rate (%)	10.5 ± 4.0	9.4 ± 5.1	10.2 ± 4.1	11.2 ± 5.8	11.0 ± 5.6	0.522	0.720

ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; POD: Postoperative day; Ig: Immunoglobulin.

the right hemi-hepatectomy group showed no significant difference (Figure 10, log-rank test $P = 0.733$). During the 90-d follow-up, one person died after stage-II ALPPS, and one died after hemi-hepatectomy; the mortality rate in each group was 6.67% (1/15).

DISCUSSION

As a planned step-by-step hepatectomy, ALPPS involves strict requirements for liver anatomy, degree

Table 9 Comparison of immunological data during conventional hepatectomy

Item	Preoperative	Conventional hepatectomy				*F* value	*P* value
		POD1	POD3	POD5	POD7		
T lymphocyte count (cells/μL)	1194.7 ± 305.4	447.1 ± 240.9	808.8 ± 313.7	835.7 ± 323.7	1032.7 ± 323.6	123.342	0.000
Total T lymphocyte percentage (%)	71.2 ± 5.2	58.9 ± 14.5	65.9 ± 11.7	72.3 ± 9.1	72.8 ± 7.7	17.676	0.000
CD4+ T lymphocytes (cells/μL)	761.1 ± 146.6	244.1 ± 113.9	515.9 ± 155.1	520.7 ± 168.7	644.8 ± 149.1	198.675	0.000
CD8+T lymphocytes (cells/μL)	379.9 ± 119.0	147.9 ± 98.5	226.8 ± 104.5	253.0 ± 110.4	331.8 ± 120.9	106.219	0.000
Natural killer cells (%)	17.9 ± 4.7	25.8 ± 8.4	14.1 ± 3.0	12.9 ± 4.6	13.8 ± 3.8	12.893	0.000
IgA (g/L)	2.67 ± 1.49	2.23 ± 1.34	2.11 ± 1.32	2.44 ± 1.50	2.82 ± 1.60	19.117	0.000
IgG (g/L)	11.78 ± 5.58	8.14 ± 3.97	7.89 ± 3.98	8.09 ± 4.05	8.55 ± 3.95	35.249	0.000
IgM (g/L)	0.91 ± 0.39	0.54 ± 0.31	0.63 ± 0.26	0.66 ± 0.27	0.82 ± 0.30	24.051	0.000
Complement C1q (mg/L)	174.6 ± 51.3	142.8 ± 49.9	121.9 ± 46.9	125.1 ± 52.1	132.2 ± 47.0	39.750	0.000
Complement C3 (g/L)	1.11 ± 0.45	0.84 ± 0.41	0.74 ± 0.37	0.70 ± 0.36	0.73 ± 0.37	31.517	0.000
Complement C4 (g/L)	0.32 ± 0.13	0.24 ± 0.11	0.21 ± 0.11	0.22 ± 0.11	0.24 ± 0.12	37.071	0.000
Interleukin-6 (pg/mL)	16.3 ± 17.7	171.6 ± 119.2	73.3 ± 46.3	43.5 ± 28.8	44.1 ± 31.1	8.981	0.002
CD19 expression rate (%)	13.04 ± 2.21	9.93 ± 3.05	10.68 ± 3.40	12.81 ± 4.37	14.03 ± 3.62	11.115	0.000

ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; POD: Postoperative day; Ig: Immunoglobulin.

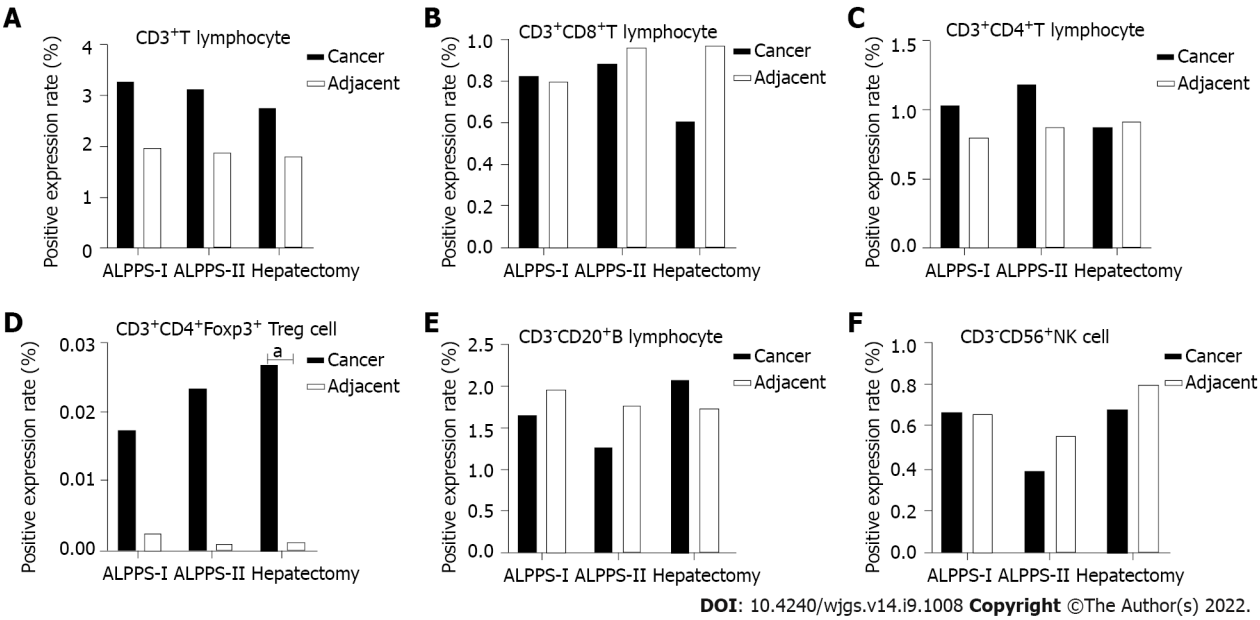

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Figure 3 Expression of each subpopulation of tumor-infiltrating lymphocytes in the associating liver partition and portal vein ligation for staged hepatectomy group (stage I and stage II) and right hemi-hepatectomy group. A: Positive expression level of $CD3^+$ T cells; B: Positive expression level of $CD3^+CD4^+$ T cells; C: Positive expression level of $CD3^+CD8^+$ T cells; D: Positive expression level of $CD3^+CD4^+Foxp3^+$ Treg cells; E: Positive expression level of $CD3^-CD20^+$ B cells; F: Positive expression level of $CD3^-CD56^+$ natural killer cells in different groups and tissues. $^aP < 0.05$.

of FLR hyperplasia, liver volume evaluation, and patient screening. Stage-I ALPPS separates the left hepatic lobe and the right one and ligates the right hepatic vein, resulting in an inflammatory reaction, hypoxia, tumor necrosis, and other factors, thus leading to a unique and complex immune microenvironment of tumor cells. Therefore, it is necessary to understand such immunological effects of the unique TME formed during HCC treatment by ALPPS from an immunological perspective as anti-tumor effect or tumor-induced immunosuppression. HCC treatment by ALPPS, the subsequent recruitment and change of TILs in the TME, and its effect on the tumor are still not completely understood. To verify the safety of ALPPS in treating massive HCC, more in-depth research on TILs in the TME is needed.

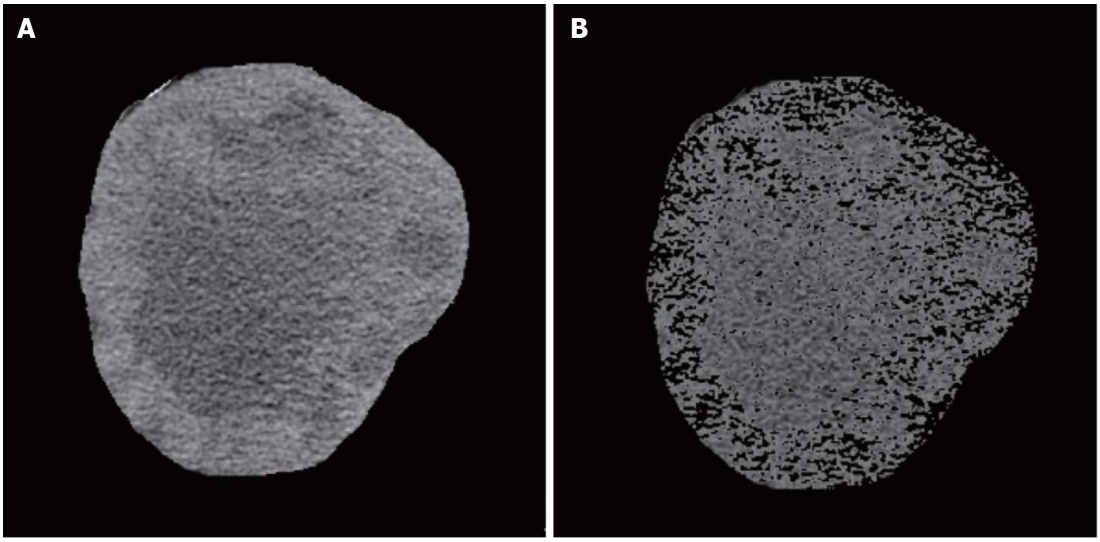

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Figure 4 Diagrammatic representation of tumor volume and tumor necrosis volume measurement. A: Tumor tissue; B: Component of tumor necrosis.

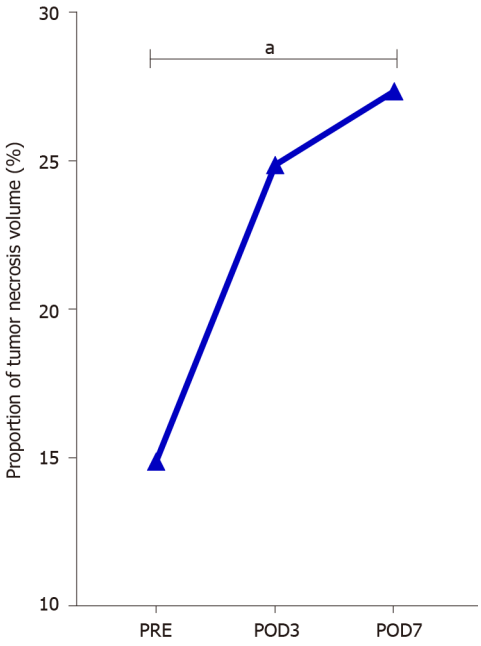

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Figure 5 Change in the proportion of tumor necrosis volume in stage-I associating liver partition and portal vein ligation for staged hepatectomy. The proportion of tumor necrotic volume on the seventh day after stage-I associating liver partition and portal vein ligation for staged hepatectomy was significantly higher than that before the operation. POD: Postoperative day. $^{a}P < 0.05$.

In order to determine the perioperative changes of TILs in patients with massive HCC in the right lobe treated by ALPPS and its effect on the tumor, we used PSM analysis on 15 HCC patients treated by ALPPS and 15 HCC patients treated by right hemi-hepatectomy. The results showed that all clinical baseline and tumor nature trends of the two groups were similar. The PSM method was used to reduce the selection deviation and baseline difference to make the sample data of the two groups more comparable[14]. Meanwhile, cancer and para-cancerous histopathological specimens of the right hemi-hepatectomy group and the ALPPS group were collected. The positive expression levels of TIL subsets were detected by polychromatic immunohistochemical staining. The results showed no significant differences in the six main TIL subsets between the ALPPS and right hepatectomy groups or between the cancerous and adjacent tissues in the same group. Especially during the "isolated" period of tumor-bearing right hepatic lobe between stage-I ALPPS and stage-II ALPPS, the positive expression levels of TIL subsets did not change significantly. It indicated that the degree of TIL infiltration in the TME has

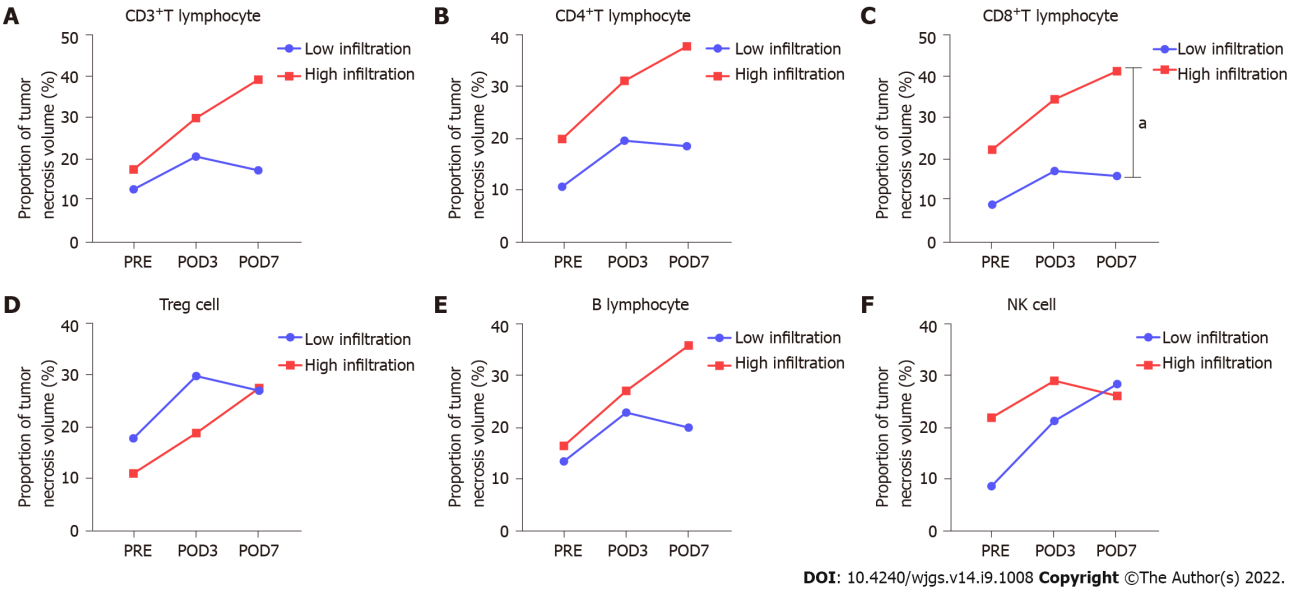

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Figure 6 Relationship between the proportion of tumor necrosis volume and tumor-infiltrating lymphocyte subpopulations in perioperative period of stage-I associating liver partition and portal vein ligation for staged hepatectomy. A: Proportion of tumor necrosis volume between high- and low- infiltration groups divided based on the positive expression level of CD3$^+$ T cells; B: Proportion of tumor necrosis volume between high- and low- infiltration groups divided based on the positive expression level of CD4$^+$ T cells; C: Proportion of tumor necrosis volume between high- and low- infiltration groups divided based on the positive expression level of CD8$^+$ T cells; D: Proportion of tumor necrosis volume between high- and low- infiltration groups divided based on the positive expression level of Treg cells; E: Proportion of tumor necrosis volume between high- and low- infiltration groups divided based on the positive expression level of B cells; F: Proportion of tumor necrosis volume between high- and low- infiltration groups divided based on positive expression level of natural killer cells. $^aP < 0.05$.

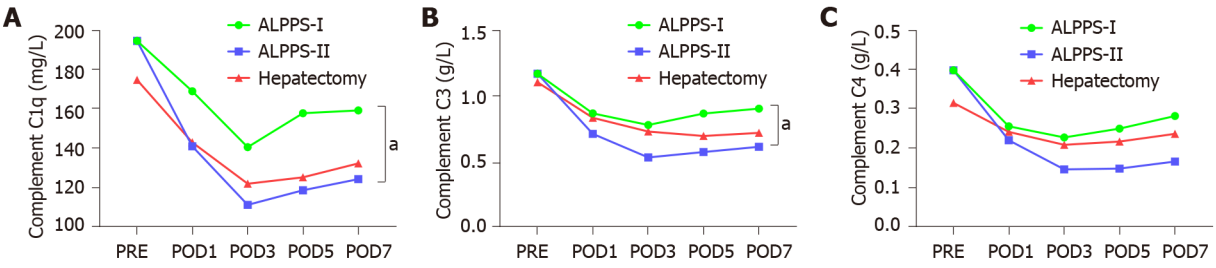

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Figure 7 Changes in peripheral blood complement concentrations after stage-I and II associating liver partition and portal vein ligation for staged hepatectomy and right hemi-hepatectomy. C1q and C3 in peripheral blood in stage-I associating liver partition and portal vein ligation for staged hepatectomy, were significantly higher than those in stage II. A: C1q; B: C3; C: C4. POD: Postoperative day; ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy.

not changed due to the traumatic stress of ALPPS surgery and the persistence of stage-I ALPPS to II tumors, which provides a basis for the operation of tumor local immune function and the body's resistance to tumor invasion. Previous studies have shown that the decrease in the invasion of TILs could promote tumor immune escape and malignant progression and limit the effect of immunotherapy, leading to a poor prognosis. In contrast, the increase in the infiltration degree of TILs produces the opposite result[15-17].

This study showed that the level of TIL infiltration during the perioperative period of ALPPS maintains a dynamic balance, suggesting that there is no adverse effect on TIL infiltration due to the surgical methods of ALPPS. To further verify the correlation between TILs and HCC, we measured the tumor volume and tumor necrotic volume before stage-I ALPPS operation and 3 d and 7 d after the stage-I ALPPS operation. We further calculated the ratio of tumor necrotic volume to tumor volume. We found an increase in tumor necrosis volume proportion, gradually from stage I to stage II of ALPPS, which might be caused by ligation of the right hepatic vein during ALPPS operation[18,19].

TILs play a central role in tumor local immune response, and their infiltration levels largely determine the severity of immune response. This is the main reason for using TILs to evaluate the intensity of immune response induced by ALPPS in this study. T cells not only mediate cellular immune response but also participate in humoral immune response induced by thymus-dependent antigen. CD8$^+$ T cells, also known as cytotoxic T cells, are the primary effector cells of the immune system against

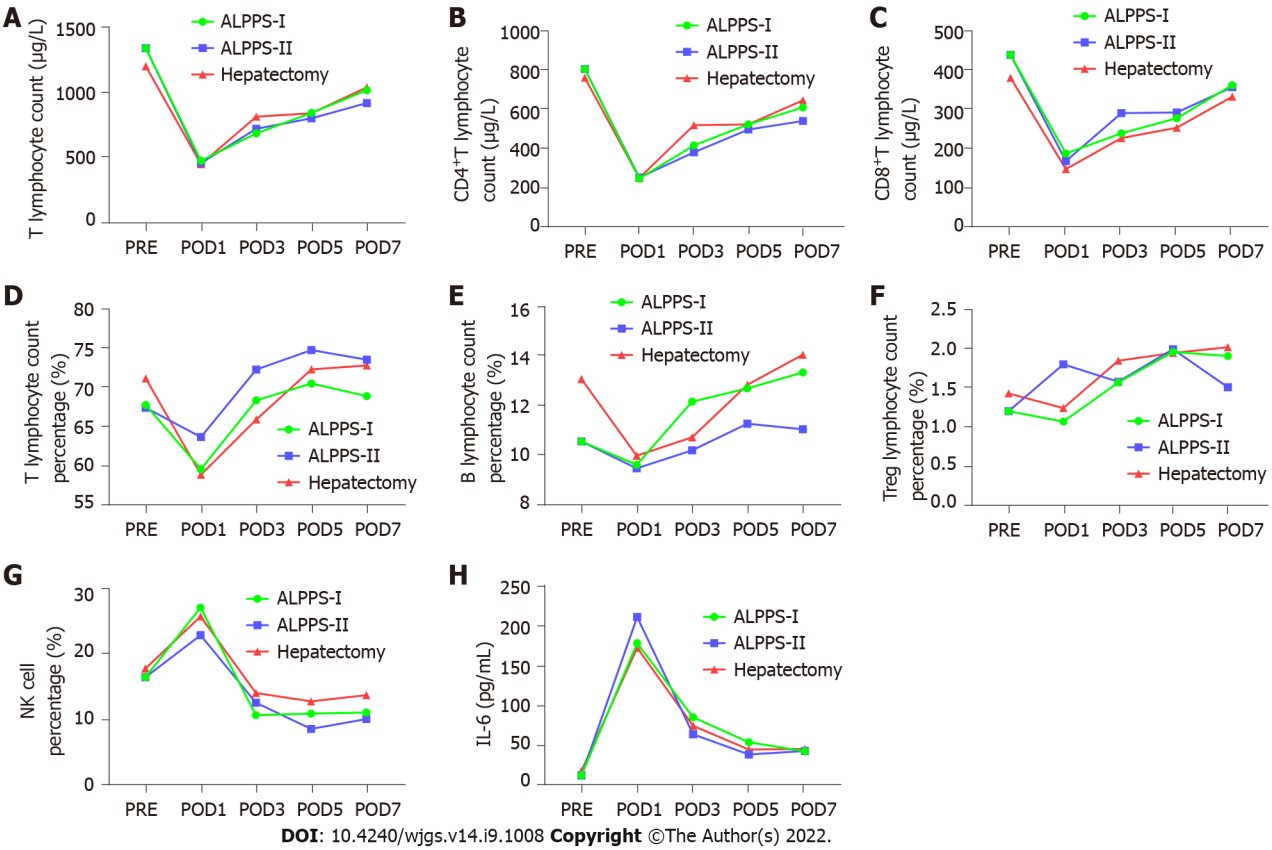

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Figure 8 Changes in peripheral blood lymphocyte subpopulations after stage-I and II associating liver partition and portal vein ligation for staged hepatectomy and right hemi-hepatectomy. Interleukin-6 levels in stage-I associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) and stage-II ALPPS increased significantly and reached a peak value on the first day after surgery. Natural killer cells in stage-I and stage-II ALPPS temporarily increased on the first day after surgery and gradually decreased on the second day after surgery to figures lower than the preoperative level. A: T lymphocyte count (/μL); B: CD4$^+$ T lymphocyte count (/μL); C: CD8$^+$ T lymphocyte count (/μL); D: T lymphocyte percentage (%); E: B lymphocyte percentage (%); F: Treg lymphocyte percentage (%); G: Natural killer cells percentage (%); H: Interleukin-6 (pg/mL). NK: Natural killer; IL: Interleukin; POD: Postoperative day; ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy.

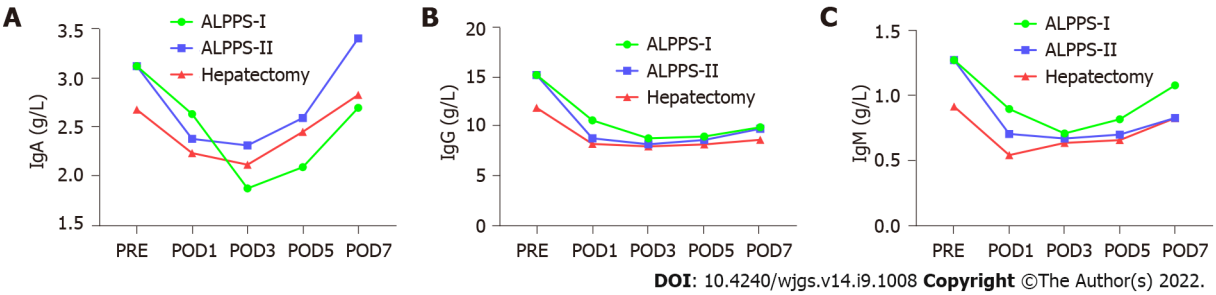

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Figure 9 Changes in peripheral blood immunoglobulins after stage-I and II associating liver partition and portal vein ligation for staged hepatectomy and right hemi-hepatectomy. A: Immunoglobulin (Ig)A (g/L); B: IgG (g/L); C: IgM (g/L). Ig: Immunoglobulin; POD: Postoperative day; ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy.

tumors. They can kill tumor cells efficiently through the perforin-granzyme pathway, Fas-FasL pathway, and tumor necrosis factor (TNF)-TNF receptor pathway[20,21]. Studies have shown that the local low level of CD8$^+$ T cell infiltration makes the tumor grow and progress more rapidly. Here, we found a correlation between the infiltration level of CD8$^+$ T cells and the degree of tumor necrosis. The proportion of tumor necrotic volume in the perioperative stage-I ALPPS gradually increased with time. Moreover, the proportion of tumor necrotic volume in the high CD8$^+$ T cell infiltration group was significantly higher than that in the low infiltration group. Based on the fact that there was no difference in the expression levels of CD8$^+$ T cells between the cancer tissues of the ALPPS group and the right hepatectomy group, it can be inferred that after stage-I ALPPS, the right lobe of the tumor-bearing liver is segregated and the right hepatic vein is ligated, while CD8$^+$ T cells can still effectively infiltrate the

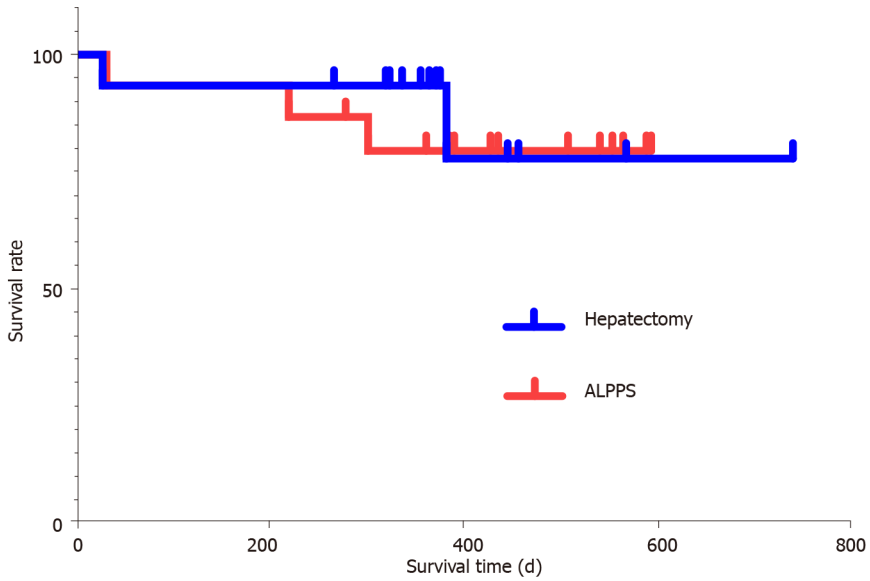

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Figure 10 Comparison of survival rate between associating liver partition and portal vein ligation for staged hepatectomy group and right hemi-hepatectomy group. The survival rate showed no significant difference between the two groups. ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy.

TME, thus exerting cytotoxicity to kill tumor cells. This result also proves that $CD8^+$ T cells do not reduce their infiltration degree due to the ALPPS operation and maintain the stability of the immune system's killing function.

Components of the peripheral blood circulatory system, including T cells, B cells, Treg cells, NK cells, IL-6, complement components (C1q, C3, and C4), and immunoglobulins (IgA, IgG, and IgM) can comprehensively reflect the immune function of the body. NK cells are the primary killer cells in innate immunity and can produce cytotoxic effects on tumor cells[20]. Among the peripheral blood immune indicators tested, NK cells temporarily increased on the first day after stage-I and stage-II ALPPS. They then gradually decreased to a lower level than the preoperative one. This trend may be related to the inhibitory effect of Treg cells on NK cells. One study has shown that higher serum IL-6 levels are associated with an increased risk of adverse HCC[22]. In this study, IL-6 in stage-I and II ALPPS increased significantly on the first postoperative day, and reached a peak. However, their levels were consistently higher than the preoperative levels. The levels after Stage-I and II ALPPS were significantly higher than that before surgery ($P1 = 0.000$, $P2 = 0.002$). This phenomenon might be related to the "waterfall" inflammation and persistent inflammation stimulus caused by surgical strikes. It is reported that the serum complement C1q increases significantly in the occurrence and development of nonalcoholic fatty liver[23]. In addition, complement C3 is involved in the occurrence and development of alcoholic hepatitis, thus inducing liver cancer[24]. In our study, the contents of complement C1q and C3 in peripheral blood after tumor removal in stage-II ALPPS were significantly lower than those in stage-I ALPPS. Finally, there was no significant change in serum IgA, IgG, or IgM levels between stage-I and stage-II ALPPS, indicating that the two-stage surgery performed by ALPPS did not cause excessive physiological stress or inflammation. In summary, comparing the changing trend of peripheral blood immune components in different groups showed that the traumatic stress and inflammatory reaction caused by right hepatectomy and ALPPS are similar. The ALPPS procedure did not cause more severe immunosuppression due to the "radical" surgical strategy, which is consistent with previously reported results[25].

In the past few decades, researchers have gained a deeper understanding of the importance of the TME in the occurrence, development, invasion, and metastasis of HCC[26]. The dynamic changes of the TME significantly affect the tumor biological characteristics of HCC. The TME is thought to have an active interaction with tumors, not just the passive structural support for tumor growth or survival. Therefore, more researchers are actively studying to understand the TME and its interaction with HCC cells. Because each component of the TME plays a complex role and influences one another, targeting a specific component of the TME is usually of little effect. It can be seen that a better understanding of the biological effects and molecular interactions between each component of the TME and tumor cells is crucial for understanding the mechanism and development of tumorigenesis.

In 1988, Rosenberg *et al*[27] invented the TIL therapy. Lymphocytes were isolated and extracted from the patient's body, amplified *in vitro*, and then infused back into the patient's body, opening up a new avenue in the field of tumor treatment. After years of continuous development and improvement, various new therapies based on TIL therapies have come out, such as chimeric antigen receptor T cell

immunotherapy (CAR-T) and T cell receptor chimeric T cell immunotherapy (T cell receptor-modified T cell immunotherapy, TCR-T)[28-30]. CAR-T and TCR-T cells are T cells that have been directionally modified and screened by genetic engineering technology, which strengthens the ability to recognize tumor cells or tumor-associated antigens. They can change the local immune suppression microenvironment induced by tumors and reverse tumor immunity tolerance status, showing good safety and effectiveness in treating various cancers. CAR-T therapy has a significant effect on hematological tumors [31,32], and TCR-T therapy has achieved good results in melanoma[33], multiple myeloma[34], lung cancer[35], and ovarian cancer[36]. The two therapies still face many challenges in treating solid tumors, such as low and uneven treatment response rates, local immunosuppressive effects of the TME, and lack of high-efficiency molecular targets[37,38]. However, the global R&D boom has continued, and several studies on TIL treatment of tumors have entered the clinical trial stage. Given the critical role of TILs in tumor local immunity, various new types of "TIL therapies" have developed rapidly, and significant breakthroughs have been continuously made in the field of tumor treatment. As an essential branch of tumor immunotherapy, TIL therapy is one of the indispensable directions for future medical development. The global multi-center and multi-organization collaboration can promote the standardization of ALPPS surgery and large-scale data statistics. Therefore, it is necessary to deeply understand the trend of TIL changes caused by ALPPS surgery.

From an immunological perspective, this study describes the change in the trend of the TME during the perioperative period of ALPPS. We demonstrate that ALPPS is safe and feasible for massive HCC in the right lobe of the liver. However, this study is a single-center study, with a limited number of patients and clinical data, thus, more in-depth discussion on the conclusions is required.

CONCLUSION

The level of TIL infiltration can maintain a dynamic balance during the perioperative period of ALPPS, which is the basis for the normal tumor local immune response. Compared with the right hepatectomy, ALPPS does not cause a decrease in TIL infiltration and the pathological changes of immune components in peripheral blood, thus resulting in severe immunosuppression. After stage-I ALPPS, $CD8^+$ T cells effectively infiltrate into the TME and play a cytotoxic role in killing tumor cells. Our results suggest that the infiltration of high $CD8^+$ T cells is related to the increase in tumor necrosis.

ARTICLE HIGHLIGHTS

Research background

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is an innovative approach to hepatectomy. The surgical trauma experienced by ALPPS is relatively high. In addition, stage-I ALPPS separates the right and left liver lobes and ligates the right hepatic vein, which causes inflammatory reactions, hypoxia, and tumor necrosis, resulting in a unique and complex immune microenvironment for tumor cells.

Research motivation

The trends and effects of tumor-infiltrating lymphocytes (TIL) residing or recruited in the tumor microenvironment (TME) are still unexplored in studies on ALPPS for hepatocellular carcinoma (HCC).

Research objectives

From an immunological perspective, the immunological effects exerted by the unique TME formed during the treatment of HCC by ALPPS, such as anti-tumor effects or tumor-induced immunosuppression, were investigated to further evaluate the safety and efficacy of ALPPS in treating massive HCC and conduct an in-depth study of TILs in the TME.

Research methods

Patients of the ALPPS and hemi-hepatectomy groups were screened using propensity score matching. Immunofluorescence staining was performed to detect and quantify TILs in tumors and adjacent tissues in these two groups of patients. Trends in TILs in peripheral blood during the perioperative period were compared between the two groups.

Research results

The proportion of tumor necrosis volume at postoperative day 7 after stage-I ALPPS was significantly higher than the pre-operative value (P = 0.024). The proportion of tumor necrosis volume was significantly higher in the high $CD8^+$ T-cell infiltrated group than in the low group before surgery for stage-I ALPPS (P = 0.048).

Research conclusions

From an immunological point of view, ALPPS is safe and feasible for treating right lobe massive HCC. The level of TIL infiltration during the perioperative period is dynamically balanced, and the ALPPS procedure itself does not lead to severe immunosuppression due to reduced TIL infiltration and pathological changes in peripheral blood immune components.

Research perspectives

Many studies on TIL therapy for tumors have entered clinical trials. As an important branch of tumor immunotherapy, TIL therapy is one of the potential directions for the future development of medicine.

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FOOTNOTES

Author contributions: Wang W and Deng ZF contributed equally to this work; Wang W, Deng ZF, Wang JL, Xu BH, Zhu H, Guo Y, and Wen Z designed the research study; Wang W, Deng ZF, Wang JL, Bao L, and Zhang L performed the research; Bao L, Zhang L, Xu BH, Zhu H, Guo Y, and Wen Z contributed reagents and analytic tools; Wang W, Deng ZF, and Wen Z analyzed the data; Wang W and Deng ZF wrote the manuscript; and all authors have read and approved the final manuscript.

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

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

Data sharing statement: The data presented in this study are available upon request to the corresponding author.

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Blood index panel for gastric cancer detection

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Abstract

BACKGROUND

Gastric cancer is a common malignant tumor. Early detection and diagnosis are crucial for the prevention and treatment of gastric cancer.

AIM

To develop a blood index panel that may improve the diagnostic value for discriminating gastric cancer and gastric polyps.

METHODS

Thirteen tumor-related detection indices, 38 clinical biochemical indices and 10 cytokine indices were examined in 139 gastric cancer patients and 40 gastric polyp patients to build the model. An additional 68 gastric cancer patients and 22 gastric polyp patients were enrolled for validation. After area under the curve evaluation and univariate and multivariate analyses.

RESULTS

Five tumor-related detection indices, 12 clinical biochemical indices and 1 cytokine index showed significant differences between the gastric cancer and gastric polyp groups. Carbohydrate antigen (CA) 724, phosphorus (P) and ischemia-modified albumin (IMA) were included in the blood index panel, and the area under the curve (AUC) of the index panel was 0.829 (0.754, 0.905). After validation, the AUC was 0.811 (0.700, 0.923). Compared to the conventional index

CA724, the blood index panel showed significantly increased diagnostic value.

CONCLUSION
We developed an index model that included CA724, P and IMA to discriminate the gastric cancer and gastric polyp groups, which may be a potential diagnostic method for clinical practice.

Key Words: Gastric cancer; Gastric polyp; Blood; Index; Panel

Core Tip: Early diagnosis and early treatment of gastric cancer is the key to improving the survival and cure rates of patients. Therefore, early detection and diagnosis are crucial for the prevention and treatment of gastric cancer. In this study, the we aimed to evaluate the diagnostic value of the blood index panel for gastric cancer.

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INTRODUCTION

Gastric cancer is a common malignant tumor that endangers human health, and it ranks second only to lung cancer in the number of deaths resulting from various malignant tumors[1]. The occurrence and development of gastric cancer is a multistage process involving changes at the gene and molecular levels. There is a period of precancerous lesions in the early stage of gastric cancer, and most of the precancerous lesions remain unchanged, while some develop into cancer[2]. The Correa cascade is a generally recognized model of gastric cancer, which is superficial gastritis-atrophic gastritis-intestinal metaplasia-dysplasia-gastric cancer. In recent years, the incidence of gastrointestinal malignant tumors in China has increased significantly[3]. Because most gastrointestinal malignant tumors have no obvious symptoms during the early stage, they cannot be detected quickly. The postoperative survival rate of malignant tumors is very low[4]. Early diagnosis and early treatment of gastric cancer is the key to improving the survival and cure rates of patients. Therefore, early detection and diagnosis are crucial for the prevention and treatment of gastric cancer[5].

With further research, finding a simple, fast and easy dynamic observation method that can screen high-risk groups of gastric cancer (such as patients with atypical hyperplasia) would be beneficial for early diagnosis, and serum biomarkers (tumor markers, combined screening of cytokines and biochemical indicators) may be new targets for the early diagnosis of gastric cancer. Tumor markers reflect the occurrence and development of tumors and the degree of activation or inactivation of tumor-related genes. Since these substances are secreted by tumor cells and released into the blood and body fluids during tumor proliferation, they can be used to indicate the presence of tumors[6,7]. An ideal tumor marker has the characteristics of high sensitivity and high specificity, is present in body fluids, especially blood, and is easy to detect. In recent years, due to the rapid development of molecular biology, markers related to gastric cancer have been continuously discovered. The cell surface structural antigen carcinoembryonic antigen (CEA) is a tumor-associated antigen that can be extracted from embryonic tissue and detected in a variety of body fluids. As one of the most common tumor markers, it is widely used as a diagnostic and monitoring index for various gastrointestinal tumors (especially gastric adenocarcinoma)[8-10]. Carbohydrate antigen (CA) 724 is a high molecular weight glycoprotein and one of the best tumor markers for the diagnosis of gastric cancer. CA724 is highly specific for gastric cancer and has good application value in digestive system malignant tumors[10-12]. In addition, cytokines also play important roles in the initiation and treatment of cancer. Cytokines produced by tumor cells or the tumor stroma can stimulate the survival, proliferation, and metastasis of cancer cells. These factors were demonstrated to be potential biomarkers for various cancers[13-15].

In our study, we examined 13 tumor-related indices, 38 clinical biochemical indices and 10 cytokines in gastric cancer and gastric polyp patients and aimed to develop an index panel that can improve the diagnostic value of discriminating gastric cancer and gastric polyp patients. This panel may become a detection method for clinical practice.

MATERIALS AND METHODS

Study subjects

Signed informed consent was obtained, and this study was approved by the Ethics Committee of the First Center of Chinese PLA General Hospital. A total of 269 serum samples were collected from patients with gastric cancer and gastric polyps who were admitted to the First Center of Chinese PLA General Hospital. The inclusion criteria for gastric cancer and gastric polyps were as follows: (1) Primary; (2) Confirmed by pathological diagnosis; (3) No radiotherapy or chemotherapy before surgery; (4) Preoperative diagnosis with more than two imaging results; and (5) Complete medical records and follow-up data. The exclusion criteria were as follows: (1) Received radiotherapy, chemotherapy, and immunotherapy; (2) Immune system diseases; (3) Chronic wasting diseases and infectious diseases; and (4) Other types of malignant tumors. A total of 139 gastric cancer patients and 40 gastric polyp patients were enrolled for model building. An additional 68 gastric cancer patients and 22 gastric polyp patients were enrolled for validation. The two groups were age- and sex-matched. Three milliliters of fasting venous blood was collected from the subjects, incubated for 30 min, and centrifuged at 3500 r/min for 7 min to separate the serum, and the specimens without hemolysis or chyle were qualified and stored at -80 °C.

Tumor-related and clinical biochemical index detection

The 13 tumor-related indices included 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 indices 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-glutamyltransferase (GGT), glucose (GLu), urea nitrogen (UN), creatinine (Cr), uric acid (UA), cholesterol (CHO), triglyceride (TG), creatine kinase (CK), lactate dehydrogenase (LDH), isoenzyme of creatine kinase (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).

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 detection kits, standards and controls were purchased from Roche Diagnostics Ltd. ApoA1, ApoB, CYS, Lp (a), and CKMB detection kits, standards and quality controls were purchased from Beijing Leadman Biochemical Co., Ltd. SCC, PG I and PG II assay kits, standards and controls were purchased from Abbott Laboratories. TBA and HCY detection kits, standards and quality controls were purchased from Beijing Jiuqiang Biotechnology Co., Ltd. TB and DB detection kits, standards and controls were purchased from Hitachi Japan. IMA test kits, standards and quality controls were purchased from Changsha Yikang Technology Development Co., Ltd. SA detection kits, standards and quality controls were purchased from Zhejiang Dongou Diagnostics Products Co., Ltd. SOD detection kits, standards and quality controls were purchased from Fujian Fuyuan Biotechnology Co., Ltd. The serum was collected from the -80 °C serum specimen bank, and after being thawed, 500-1000 μL was dispensed into a centrifuge tube and assigned a new number. The Modular 7600 automatic biochemical analyzer, Roche E170 immunoassay analyzer and Architect i2000 immunoassay system were used to complete quality control and calibrations before the assays. After analysis, the experimental data from each instrument were exported for statistical analysis.

Cytokine detection

The 10 cytokines included granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-γ (IFNγ), interleukin-1β (IL-1β), IL-2, IL-4, IL-6, IL-8, IL-10, monocyte chemoattractant protein (MCP-1), and tumor necrosis factor α (TNFα) and were analyzed by a Luminex Instrument Model 200 Liquid Core Analyzer according to the instructions of the Human Cytokine/Chemokine Detection Kit. All reagents were equilibrated to room temperature (20 °C-25 °C) before the test. A schematic diagram of sample loading in a 96-well plate was drawn on paper (standards, 0, 3.2, 16, 80, 400, 2000, and 10000 ng/mL, QC I, QC II, sample), and duplicate wells were recommended. Then, 200 μL of assay buffer was added to each reaction well, which was sealed and shaken on a horizontal shaking instrument for 10 min (room temperature, 20 °C-25 °C). The excess assay buffer was blotted from the bottom with filter paper or paper towels. Then, 25 μL of analysis buffer was added to the background standard well, 25 μL of buffer was added to each sample well, 25 μL of each standard or quality control was added to the corresponding reaction well, and 25 μL of the appropriate matrix diluent was added to the background wells, standard wells, and quality control wells. When the analyte was serum or plasma, the serum matrix provided by the kit was used. When the analyte was tissue culture fluid or other supernatant, the corresponding medium was used as a diluent. A total of 25 μL of sample was added to the appropriate reaction well, the microspheres were mixed, and 25 μL of the mixed microspheres was added to each

well. The wells were covered with parafilm and aluminum foil and incubated at room temperature (20 °C-25 °C) on a horizontal shaker for 1 h (when the test substance was serum or plasma, overnight incubation at 4 °C can improve the sensitivity). Then, the liquid was gently aspirated, the wells were washed with wash solution (200 μL/well) twice, the liquid was aspirated, and the washing solution at the bottom of the reaction plate was dried with filter paper or paper towel. The detection antibody was added (25 μL/well), and the plates were covered with parafilm and aluminum foil, shaken on a horizontal shaker and incubated at room temperature for 30 min. Streptavidin-PE (25 μL/well) was added, and the plates were covered with parafilm and aluminum foil, shaken on a horizontal shaker and incubated at room temperature for 30 min. Then, the liquid was gently aspirated, the wells were washed with wash solution (200 μL/well) twice, the liquid was aspirated, and the washing solution at the bottom of the reaction plate was blotted with filter paper or paper towel. Sheath fluid (100 μL/well) was added. The plates were covered with aluminum foil and shaken on a horizontal shaker for 5 min to resuspend the microspheres. The microspheres were read on a Luminex instrument, and the results were calculated.

Statistical analysis

SPSS 22.0 was used in this study. Measurement data are expressed as the median (25%, 75%). If the data were normally distributed, they were compared by two independent samples t tests. If not, they were compared by the rank sum test. The area under the curve (AUC) was used to evaluate the diagnostic value. Univariate and multivariate analyses were used to analyze the Exp (B) of the indices. Logistic regression analysis was used to build the index model. *Z* scores were used to compare the AUCs of the two groups.

RESULTS

Comparison of the tumor-related detection indices between the gastric cancer and gastric polyp groups

As shown in Table 1, 13 tumor-related detection indices, including CEA, AFP, CA125, CA199, CA153, CA724, CY211, Ferr, NSE, SCC, PG I/II, PG II, and PG I, were compared between the gastric cancer and gastric polyp groups. Among the 13 tumor-related detection indices, CEA (P = 0.014), CA125 (P = 0.033), CA199 (P = 0.017), CA724 (P = 0.007) and PG I/II (P = 0.008) showed significant differences between the two groups, and the other 8 tumor-related detection indices (AFP, CA153, CY211, Ferr, NSE, SCC, PG II, and PG I) showed no significant differences.

Comparison of the clinical biochemical indices of the gastric cancer and gastric polyp groups

As shown in Table 2, 38 clinical biochemical indices, including 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, LP (a), HDL, LDL, ApoA1, ApoB, CYS, SA, HCY, CRP, AMY, LPS, SOD and IMA, were compared between the gastric cancer and gastric polyp groups. ALB (P = 0.007), CHO (P = 0.035), TG (P = 0.017), Ca (P = 0.025), P (P = 0.008), Cl (P = 0.008), HDL (P = 0.004), LDL (P = 0.010), ApoA1 (P = 0.001), ApoB (P = 0.021), SOD (P = 0.001) and IMA (P = 0.001) showed significant differences between the two groups. The other 26 tumor-related detection indices, including ALT, AST, TP, TB, DB, TBA, ALP, GGT, GLu, UN, Cr, UA, CK, LDH, CKMB, Mg, K, Na, CO_2, LP (a), CYS, SA, HCY, CRP, AMY and LPS, showed no significant differences.

Comparison of the cytokine indices in the gastric cancer and gastric polyp groups

As shown in Table 3, 10 tumor-related detection indices, including GM-CSF, IFNγ, IL-10, IL-1β, IL-2, IL-4, IL-6, IL-8, MCP-1, and TNFα, were compared between the gastric cancer and gastric polyp groups. Because IL-2 and IL-4 were lower than the detection limit in most samples, these two cytokine indices were deleted. After analysis, only TNFα (P = 0.001) showed a significant difference between the two groups, and the other 7 tumor-related detection indices, including GM-CSF, IFNγ, IL-10, IL-1β, IL-6, IL-8, and MCP-1, showed no significant differences.

Diagnostic value evaluation of a single differential index for discriminating the gastric cancer and gastric polyp groups

After comparing the tumor-related, clinical biochemical and cytokine indices between the gastric cancer and gastric polyp groups, the diagnostic value of the differential indices for discriminating between the gastric cancer and gastric polyp groups was evaluated. As shown in Table 4, the differential indices of CEA (P = 0.014), CA125 (P = 0.033), CA199 (P = 0.017), CA724 (P = 0.007), PG I/II (P = 0.008), ALB (P = 0.007), CHO (P = 0.035), TG (P = 0.017), Ca (P = 0.025), P (P = 0.008), Cl (P = 0.008), HDL (P = 0.004), LDL (P = 0.010), ApoA1 (P = 0.001), ApoB (P = 0.021), SOD (P = 0.001), IMA (P = 0.001) and TNFα (P = 0.001) were evaluated by the area under the curve. Only CA199 and CHO showed no significant differences. CEA, CA125, CA724, PG I/II, ALB, TG, Ca, P, Cl, HDL, LDL, ApoA1, ApoB, SOD, IMA and TNFα

Table 1 Comparison of tumor related detection index between gastric cancer and gastric polyp group

Indicator	Gastric polyp (*n* = 40)	Gastric cancer (*n* = 139)	*P* value
CEA	1.16 (1.55, 2.11)	1.11 (2.33, 5.11)	0.014
AFP	1.64 (2.63, 3.62)	1.43 (2.24, 3.23)	0.499
CA125	6.86 (9.91, 14.81)	8.56 (13.73, 24.39)	0.033
CA199	4.8 (7.74, 13.91)	5.07 (10.52, 29.36)	0.017
CA153	6.53 (9.3, 12.54)	6.42 (9.03, 13.15)	0.268
CA724	0.84 (1.34, 3.68)	1.43 (3.33, 11)	0.007
CY211	1.32 (1.67, 2.35)	1.7 (2.47, 4.46)	0.390
Ferr	63.86 (144.35, 268.48)	26.19 (79.3, 174.4)	0.176
NSE	8.39 (10.06, 11.87)	7.55 (9.27, 11.57)	0.732
SCC	0.43 (0.7, 1.08)	0.5 (0.7, 1)	0.247
PG1/2	1.3 (4.31, 6.26)	0.67 (2.98, 4.26)	0.008
PG2	7.65 (13.9, 29.68)	9.9 (19.3, 32.4)	0.199
PG1	12.83 (58.5, 115.93)	20.3 (53.8, 82)	0.255

CEA: Carcinoembryonic antigen; AFP: Alpha fetoprotein; CA125: Carbohydrate antigen 125; CY211: Cytokeratin 211; Ferr: Ferritin; NSE: Neuron-specific enolase; SCC: Squamous cell carcinoma; PG: Pepsinogen.

showed significant differences. The AUC of the best indicator, IMA, was 0.790 (0.705, 0.875). The *P* value was < 0.001. The AUC of the conventional index CA724 was 0.702 (0.614, 0.789). The *P* value was <0.001.

Univariate and multivariate analysis of the differential index between gastric cancer and gastric polyp groups

After the diagnostic value evaluation of a single differential index for discriminating the gastric cancer and gastric polyp groups was performed, 16 indices, including CEA, CA125, CA724, PG I/II, ALB, TG, Ca, P, Cl, HDL, LDL, ApoA1, ApoB, SOD, IMA and TNFα, were further analyzed by univariate and multivariate analysis. As shown in Table 5, after the univariate analysis, the 3 indices Exp (B), CA724 (*P* = 0.03), P (*P* = 0.03) and IMA (*P* = 0.03) showed significant differences. The other indices (CEA, CA125, PG I/II, ALB, TG, Ca, Cl, HDL, LDL, ApoA1, ApoB, SOD and TNFα) showed no significant differences. Then, the 3 indices that showed significant differences were further analyzed by multivariate analysis. The Exp (B) of CA724, P and IMA was 1.17 (1.02, 1.34), 0.13 (0.03, 0.58), and 0.85 (0.78, 0.92), respectively.

Diagnostic value evaluation of the index panel for differentiating the gastric cancer and gastric polyp groups

CA724, P and IMA were analyzed by logistic regression analysis to build a diagnostic index panel to differentiate the gastric cancer and gastric polyp groups. As shown in Figure 1A, for discriminating 139 gastric cancer and 40 gastric polyp patients, the AUC index panel was 0.829 (0.754, 0.905), and the conventional index CA724 was 0.704 (0.617, 0.791). The AUC of the index panel showed a significant increase compared to CA724 by z score statistics. After building the index model, as shown in Figure 1B, samples from independent individuals, including 68 gastric cancer patients and 22 gastric polyp patients, were used to validate the model. The AUC of the index panel and CA724 was 0.811 (0.700, 0.923), and that of the conventional index CA724 was 0.779 (0.668, 0.890).

DISCUSSION

The pepsinogen PG is a protein polypeptide chain composed of 375 amino acids, which can be divided into two categories according to biochemical and immunological properties: PG I and PG II. PG I is mainly synthesized by chief cells and cervical mucous cells, while PG II can be synthesized by gastric antrum mucous cells and proximal duodenal Brunner glands, in addition to chief cells and cervical mucous cells[16]. Synthesized PG I and PG II are mainly secreted into the gastric cavity, but a zymogen level of approximately 5% can be reversed and diffuse into the blood, which allows it to be detected in the blood. Studies have shown that the level of PG I can reflect the secretory function of gastric glands to a certain extent, and its level is positively correlated with the maximum secretion of gastric acid but

Table 2 Comparison of clinical biochemical index gastric cancer and gastric polyp group

Indicator	Gastric polyp (*n* = 40)	Gastric cancer (*n* = 139)	*P* value
ALT	11.73 (15.75, 19.35)	10.7 (13.2, 18.3)	0.322
AST	13.93 (17.85, 20.45)	13.1 (15.6, 18.6)	0.252
TP	64.73 (69.4, 72.3)	61.9 (66.2, 69.4)	0.095
ALB	38.9 (41.5, 43.8)	36.5 (38.9, 41)	0.007
TB	8.75 (11.8, 14.95)	6.8 (9.4, 13.7)	0.116
DB	2.33 (3.65, 4.7)	2.4 (3.3, 4.9)	0.248
TBA	2.65 (4.4, 5.98)	2.6 (3.9, 7.4)	0.622
ALP	44.65 (66.85, 77.48)	56.2 (65.2, 81.9)	0.076
GGT	13.13 (16.05, 27.43)	13.3 (16.5, 24)	0.773
GLu	4.74 (5.27, 5.6)	4.72 (5, 5.49)	0.627
UN	4.37 (5.22, 6.49)	4.5 (5.21, 6.23)	0.812
Cr	58.83 (65.3, 75.15)	57.5 (68.2, 77.8)	0.838
UA	261.1 (301.15, 371.9)	228.4 (278.1, 330.5)	0.117
CHO	3.99 (4.34, 5.18)	3.56 (4.16, 4.68)	0.035
TG	1.2 (1.46, 1.81)	0.98 (1.25, 1.48)	0.017
CK	37.68 (55.9, 82.83)	38.6 (56.8, 76.1)	0.740
LDH	139.65 (153.85, 174.43)	118.1 (138, 158.9)	0.792
CKMB	3.15 (6.7, 10.73)	2.4 (6.2, 9.3)	0.357
Ca	2.16 (2.26, 2.34)	2.13 (2.19, 2.26)	0.025
P	1.31 (1.53, 1.81)	1.2 (1.36, 1.51)	0.008
Mg	0.82 (0.87, 0.94)	0.79 (0.85, 0.94)	0.188
K	3.76 (4.05, 4.41)	3.79 (3.99, 4.29)	0.319
Na	141.23 (143.7, 146.35)	141.3 (143.1, 144.5)	0.579
Cl	104.6 (106.6, 108.38)	103.3 (105.3, 106.9)	0.008
CO2	19.75 (22.15, 26.55)	22.3 (24.9, 27.3)	0.281
LP (a)	6.14 (17.34, 35.2)	9.51 (14.82, 26.13)	0.582
HDL	0.95 (1.12, 1.38)	0.83 (1.03, 1.15)	0.004
LDL	2.33 (2.77, 3.34)	1.98 (2.4, 2.93)	0.010
ApoA1	1.08 (1.32, 1.59)	0.96 (1.11, 1.24)	0.001
ApoB	0.7 (0.84, 1.04)	0.66 (0.77, 0.9)	0.021
CYS	0.91 (1, 1.17)	0.84 (0.96, 1.09)	0.816
SA	53.85 (61.4, 65.38)	55.8 (64.5, 70.6)	0.179
HCY	9.85 (13.47, 16.5)	10.63 (13.62, 17.74)	0.414
CRP	0.43 (0.9, 3.78)	0.7 (1.9, 5.4)	0.702
AMY	47.2 (56.9, 77.23)	40.9 (54.8, 68.1)	0.433
LPS	28.25 (34.85, 44.13)	28.2 (35.7, 44.5)	0.291
SOD	141.33 (164.3, 189.5)	108.3 (127.4, 157.4)	0.001
IMA	62.73 (66, 69.35)	56 (60.2, 63.6)	0.001

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-glutamyltransferase; Glu: Glucose; UN: Urea nitrogen; Cr: Creatinine; UA: Uric acid; CHO: Cholesterol; TG: Triglyceride; CK: Creatine kinase; LDH: Lactate dehydrogenase; CKMB: Isoenzyme of creatine kinase; 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.

Table 3 Comparison of cytokine index gastric cancer and gastric polyp group

Indicator	Gastric polyp (*n* = 40)	Gastric cancer (*n* = 139)	*P* value
GM-CSF	1.24 (2.7, 6.27)	0.01 (0.53, 2.32)	0.640
IFNγ	0.08 (0.25, 1.08)	0.01 (0, 0.82)	0.585
IL-10	2.14 (3.39, 5.24)	1.63 (4.06, 9.34)	0.326
IL-1β	0.02 (0.31, 1.14)	0.01 (0.08, 0.94)	0.905
IL-6	0.34 (0.94, 2.58)	0.1 (1.98, 7.16)	0.483
IL-8	23.73 (51.11, 112.94)	39.4 (62.55, 138.23)	0.697
MCP-1	321.54 (429.78, 594.82)	310.31 (448.27, 612.02)	0.993
TNFα	5.53 (7.09, 8.72)	5.7 (9.87, 16.6)	0.001

GM-CSF: Granulocyte-macrophage colony-stimulating factor; IFNγ: Interferon-γ; IL: Interleukin; MCP-1: Monocyte chemoattractant protein; TNFα: Tumor necrosis factor α.

Table 4 Diagnostic value evaluation of single differential index for discriminating the gastric cancer and gastric polyp group

Indicator	AUC	*P* value	Lower	Upper
CEA	0.627	0.014	0.543	0.712
CA125	0.637	0.008	0.546	0.729
CA199	0.592	0.078	0.500	0.683
CA724	0.702	< 0.001	0.614	0.789
PG1/2	0.628	0.014	0.517	0.738
ALB	0.687	< 0.001	0.585	0.788
CHO	0.599	0.057	0.499	0.700
TG	0.655	0.003	0.561	0.748
Ca	0.640	0.007	0.534	0.746
P	0.668	0.001	0.566	0.769
Cl	0.635	0.009	0.537	0.733
HDL	0.648	0.004	0.551	0.746
LDL	0.633	0.010	0.532	0.735
ApoA1	0.702	0.000	0.602	0.802
ApoB	0.609	0.036	0.505	0.714
SOD	0.755	< 0.001	0.676	0.834
IMA	0.790	< 0.001	0.705	0.875
TNFα	0.656	0.003	0.575	0d.736

CEA: Carcinoembryonic antigen; CA125: Carbohydrate antigen 125; PG: Pepsinogen; ALB: Albumin; CHO: Cholesterol; TG: Triglyceride; Ca: Calcium; P: Phosphorus; Cl: Chlorine; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; ApoA1: Apolipoprotein A1; SOD: Superoxide dismutase; IMA: Ischemia-modified albumin; TNFα: Tumor necrosis factor α.

Table 5 Univariate and multivariate analysis of the differential index between gastric cancer and gastric polyp groups

Indicator	Univariate analysis					Multivariate analysis				
	Wals	*P* value	Exp (B)	Lower	Upper	Wals	*P* value	Exp (B)	Lower	Upper
CEA	1.02	0.31	1.04	0.97	1.11					
CA125	1.53	0.22	0.99	0.98	1.01					
CA724	4.50	0.03	1.18	1.01	1.38	5.21	0.02	1.17	1.02	1.34
PG12	0.96	0.33	0.91	0.75	1.10					
ALB	0.01	0.93	0.99	0.85	1.16					
TG	0.79	0.37	0.64	0.23	1.72					
Ca	0.01	0.91	0.84	0.04	19.42					
P	4.45	0.03	0.15	0.03	0.88	7.05	0.01	0.13	0.03	0.58
Cl	2.73	0.10	0.85	0.71	1.03					
HDL	0.34	0.56	2.09	0.17	25.09					
LDL	0.10	0.76	0.84	0.27	2.60					
ApoA1	2.42	0.12	0.09	0.00	1.86					
ApoB	0.39	0.53	4.36	0.04	45.13					
SOD	1.22	0.27	0.99	0.98	1.00					
IMA	4.50	0.03	0.89	0.79	0.99	14.77	< 0.001	0.85	0.78	0.92
TNFα	3.07	0.08	1.08	0.99	1.19					

CEA: Carcinoembryonic antigen; CA125: Carbohydrate antigen 125; PG: Pepsinogen; ALB: Albumin; CHO: Cholesterol; TG: Triglyceride; Ca: Calcium; P: Phosphorus; Cl: Chlorine; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; ApoA1: Apolipoprotein A1; SOD: Superoxide dismutase; IMA: Ischemia-modified albumin; TNFα: Tumor necrosis factor α.

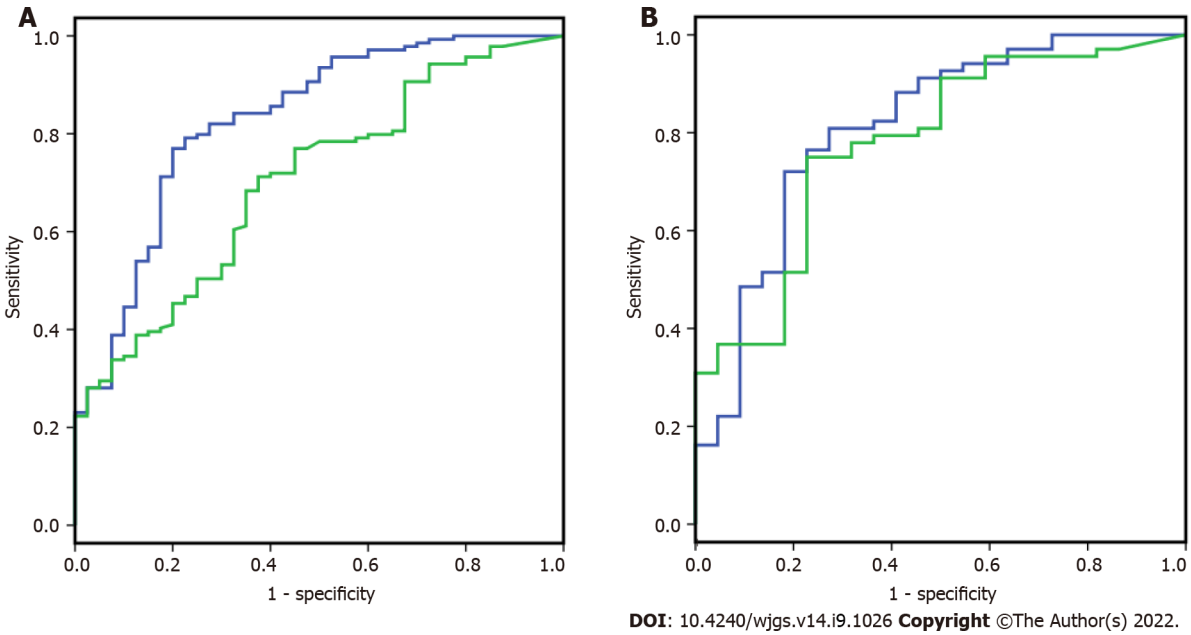

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Figure 1 Diagnostic value evaluation of index panel for discriminating the gastric cancer and gastric polyp group. A: Training model; B: Validation model. Blue line represents index model. Green line represents carbohydrate antigen 724.

negatively correlated with the degree of gastric body inflammation and atrophy[17]. An increase in the level of PG II suggests an inflammatory response in the gastric mucosa, while a decrease in the level of PG I suggests atrophy of the gastric corpus[13]. When the gastric mucosa atrophies and develops severe injury, the number of gastric glands and fundic glands will decrease or be replaced by pyloric glands,

and the pyloric glands lack gastric chief cells and cervical mucous cells, which will lead to a decreases in the level of PG I and the ratio of PG I/II[18]. In our study, the result was 1.3 (4.31, 6.26) in the gastric polyp group and 0.67 (2.98, 4.26) in the gastric cancer group. The AUC was 0.628, which has certain clinical significance in the early diagnosis of gastric cancer.

Cytokines are important in the diagnosis of gastric cancer. Cytokines are small molecular proteins secreted by cells in response to various stimuli that can exert biological effects by binding to specific receptors on target cells[19]. Cytokine production and cellular immune function are important in the occurrence and development of tumors and have certain diagnostic and prognostic value in gastric diseases[20]. The occurrence and development of gastric cancer are biological processes involving multiple stages and multiple factors. A large number of studies have shown that activated inflammatory factors are involved in the occurrence and development of gastric cancer. The immune function of cells is closely related to the occurrence and development of tumors. These inflammatory factors, as multifunctional cytokines, can not only directly damage tumor cells but are also important mediators by which monocytes kill tumor cells[20,21]. Studying the relationship between cytokines and gastric cancer provides a new direction for exploring the pathological mechanism of gastric cancer and provides a theoretical basis for the clinical development of more effective diagnosis and treatment. Studies have confirmed that tumor patients typically have immune function defects, especially cellular immune dysfunction[22]. TNFα is an important mediator of the inflammatory response and a series of pathophysiological processes in vivo. The dysregulation of cytokines and their receptors is closely related to the occurrence and development of tumors[23]. TNFα is known for its ability to significantly induce hemorrhagic necrosis of tumors in mice and is a multifunctional cytokine produced by macrophages and activated T cells. The functions of TNFα mainly include inducing an acute albumin response, activating neutrophils and lymphocytes, regulating the metabolic activity of tissues, and promoting the release of other cytokines[24]. Studies have shown that TNFα can not only kill a variety of tumor cells and enhance antitumor effects but also promote the growth and metastasis of certain tumors. When the concentration is appropriate, TNFα can cause tumor tissue hypoxia and vascular damage around the tumor and promote the cytotoxic effects of NK cells and macrophages, thereby enhancing immunity and inhibiting tumor growth. When TNFα is abnormally elevated in the body, the immune system is disturbed, causing systemic cytotoxicity, and tumor cells evade immune surveillance and continue to grow[25]. TNFα can promote the production of more TNFα in thymic cancer cells cultured in vitro. Tumor cells themselves can also promote the production of TNFα by myeloid cells by secreting versican, and TNFα can promote the accumulation of myeloid cells with a vascular endothelial phenotype to the tumor site, promote the formation of blood vessels, and then promote tumor growth and transfer[26]. In our study, compared to that in the gastric polyp group, the level of TNFα was significantly increased in the gastric cancer group. As an important inflammatory regulator, TNFα may play a role in tumor-associated inflammatory processes, increasing the risk of inflammation-induced tumors.

There are still some limitations in this study. First, the detection indices were only examined in the gastric polyp and gastric cancer groups, and a healthy control group was not evaluated. Second, the stage of gastric cancer was not evaluated and should be evaluated in future studies. Third, the sample size of the gastric polyp group was relatively small, which may cause bias in this study.

CONCLUSION

In summary, we developed an index model that included CA724, P and IMA to distinguish between gastric cancer and gastric polyps. After validation, when compared to the conventional index CA724, the panel showed improvements in detecting gastric cancer and may be a potential discriminating method for use in clinical practice.

ARTICLE HIGHLIGHTS

Research background

Early detection and diagnosis are crucial for the prevention and treatment of gastric cancer in clinical practice.

Research motivation

Blood index panels have been shown to improve the diagnostic value in many studies compared with single indices.

Research objectives

We aimed to develop a blood index panel that can improve the diagnostic value for discriminating gastric cancer and gastric polyps.

Research methods

Tumor-related detection indices, clinical biochemical indices and cytokine indices were analyzed in samples from 139 gastric cancer patients and 40 gastric polyp patients for model building. An additional 68 gastric cancer patients and 22 gastric polyp patients were enrolled for validation.

Research results

Carbohydrate antigen (CA) 724, phosphorus (P) and ischemia-modified albumin were included in the blood index panel, and the area under the curve (AUC) index of the panel was 0.829 (0.754, 0.905). After validation, the AUC index was 0.811 (0.700, 0.923). Compared to the conventional CA724 used in the training and validation, the AUC index was 0.704 (0.617, 0.791) and 0.779 (0.668, 0.890). The blood index panel showed significantly increased diagnostic value.

Research conclusions

We have developed a potential method for differentiating gastric cancer and gastric polyps based on a blood index panel. this tool may be helpful in clinical practice.

Research perspectives

A healthy control group and stage of gastric cancer should be evaluated in future studies, and a larger sample size should be used.

FOOTNOTES

Author contributions: Guo GH and Jiang T designed the study; Guo GH and Zhang PJ performed the research; Guo GH and Xie YB analyzed the date; Guo GH wrote the paper; Jiang T and Zhang PJ revised the manuscript for final submission; Guo GH and Xie YB contributed equally to this study; Zhang PJ and Jiang T are the co-corresponding authors; and all authors have read and agreed to the published version of the manuscript.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Effect of cardiac output - guided hemodynamic management on acute lung injury in pediatric living donor liver transplantation

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Abstract

BACKGROUND

Acute lung injury (ALI) after liver transplantation (LT) may lead to acute respiratory distress syndrome, which is associated with adverse postoperative outcomes, such as prolonged hospital stay, high morbidity, and mortality. Therefore, it is vital to maintain hemodynamic stability and optimize fluid management. However, few studies have reported cardiac output-guided (CO-G) management in pediatric LT.

AIM

To investigate the effect of CO-G hemodynamic management on early post-operative ALI and hemodynamic stability during pediatric living donor LT.

METHODS

A total of 130 pediatric patients scheduled for elective living donor LT were enrolled as study participants and were assigned to the control group (65 cases) and CO-G group (65 cases). In the CO-G group, CO was considered the target for hemodynamic management. In the control group, hemodynamic management was based on usual perioperative care guided by central venous pressure, continuous invasive arterial pressure, urinary volume, *etc.* The primary outcome was early postoperative ALI. Secondary outcomes included other early post-operative pulmonary complications, readmission to the intense care unit (ICU) for pulmonary complications, ICU stay, hospital stay, and in-hospital mortality.

RESULTS

The incidence of early postoperative ALI was 27.7% in the CO-G group, which was significantly lower than that in the control group (44.6%) ($P < 0.05$). During the surgery, the incidence of postreperfusion syndrome was lower in the CO-G group ($P < 0.05$). The level of intraoperative positive fluid transfusions was lower and the rate of dobutamine use before portal vein opening was higher, while the usage and dosage of epinephrine during portal vein opening and vasoactive

inotropic score after portal vein opening were lower in the CO-G group ($P < 0.05$). Compared to the control group, serum inflammatory factors (interleukin-6 and tumor necrosis factor-α), cardiac troponin I, and N-terminal pro-brain natriuretic peptide were lower in the CO-G group after the operation ($P < 0.05$).

CONCLUSION

CO-G hemodynamic management in pediatric living-donor LT decreases the incidence of early postoperative ALI due to hemodynamic stability through optimized fluid management and appropriate administration of vasopressors and inotropes.

Key Words: Cardiac output; Hemodynamic management; Child; Liver transplantation; Acute lung injury; Reperfusion injury

Core Tip: This is the first randomized controlled trial to evaluate the effect of cardiac output (CO)-guided hemodynamic therapy in pediatric liver recipients. In this study, hemodynamic parameters, including CO, stroke volume index, stroke volume variation, and the maximum increase in the speed of intraventricular pressure (dp/dt_{max}) obtained through the pressure recording analytical method monitoring were used to guide intraoperative hemodynamic management. The incidence of postoperative acute liver injury was significantly lower in the interventional group. Moreover, the inflammatory factors (interleukin-6 and tumor necrosis factor-α), cardiac troponin I, and N-terminal pro-brain natriuretic peptide levels decreased faster in the intervention group.

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INTRODUCTION

Pediatric liver transplantation (LT) is a life-saving procedure for children with end-stage liver disease caused by biliary atresia or progressive familial intrahepatic cholestasis[1]. The number of LTs performed globally has been reported to be 4-9 per million people < 18 years, with a 10-year survival rate of > 80%[1-3]. The incidence of post-LT acute lung injury (ALI) has been reported to vary between 34.2% and 77.8%[4,5]. ALI may lead to acute respiratory distress syndrome (ARDS), which is associated with adverse postoperative outcomes, such as prolonged hospital stay, high morbidity, and mortality [6]. ARDS is often caused by hemodynamic instability during surgery, which results in liver hypoperfusion and ischemia-reperfusion injury, exaggerating the inflammatory process[7]. Additionally, hemodynamic instability accompanied by excessive administration of fluids and blood products leads to fluid imbalance during LT. Clinical studies have demonstrated that intraoperative fluid overload is the primary risk factor for postoperative pulmonary complications (PPCs)[8]. Effective fluid management strategies can reduce the occurrence of PPCs[9].

In the early stages after LT, ALI may prolong the intubation time and increase the risk of systemic infectious complications. Prolonged mechanical ventilation due to refractory respiratory failure is an extremely morbid event and a marker of poor recipient recovery that predisposes a recipient to long-term ventilator dependency and predicts further complications. Several factors are involved in the onset of postoperative ALI, among which intraoperative hemodynamic instability and fluid overload are the most important[10].

Pediatric patients with poor oxygen reserve capacity are vulnerable to ischemia and hypoxia, leading to ALI. Therefore, it is vital to maintain hemodynamic stability and optimize fluid management. A study on pediatric kidney transplantation showed that the use of the cardiac output-guided (CO-G) algorithm led to excellent renal results, with a trend toward less fluids in favor of norepinephrine[11]. However, few studies have reported CO-G management in pediatric LT. CO monitoring is extremely difficult and limited due to the anatomical characteristics and biomaterial technology in pediatric liver transplant patients. The pressure recording analytical method (PRAM) is a minimally invasive hemodynamic monitoring method that calculates hemodynamic parameters, with the advantages of being invasive, not requiring calibration, and suitable for pediatric patients weighing < 20 kg compared to other devices[12]. In this study, a randomized controlled trial was designed to evaluate the effect of

CO-G algorithm management on reducing ALI events after pediatric LT and intraoperative hemodynamic stability with PRAM.

MATERIALS AND METHODS

Participants

This was a randomized controlled trial conducted at Tianjin First Central Hospital. This study was approved by the Ethics Committee of Tianjin First Center Hospital in China (Approval Number: 2019N180KY), and written informed consent was obtained from eligible guardians. The clinical trial registration number is ChiCTR1900026016. The inclusion criteria were as follows: (1) Pediatric liver recipients 5-24 mo of age; (2) American Society of Anesthesiologists physical status III or IV; and (3) Living donation. The exclusion criteria were as follows: (1) Contraindications to arterial puncture and cannulation; (2) Preoperative incomplete data; (3) Preoperative severe cardiac, renal, and other viral organ failure before LT; and (4) Sepsis and/or pulmonary complications, including pneumonia, atelectasis, pulmonary edema, pleural effusion, and ARDS within 2 wk before surgery. Every case of transplantation passed the ethical review and approval of the Tianjin First Center Hospital.

Anesthesia and surgery

Patients enrolled in this study were routinely monitored for heart rate (HR), non-invasive blood pressure, pulse oximetry, and electrocardiography. Anesthesia was induced using scopolamine (0.01 mg/kg), midazolam (0.15 mg/kg), etomidate (0.15 mg/kg), fentanyl (2-5 μg/kg), and vecuronium (0.2 mg/kg) to maintain analgesia, muscle relaxation, and sedation. After intubation, mechanical ventilation was performed with a fraction of inspired oxygen (FiO_2) of 50%-60%, tidal volume of 8-10 mL/kg, respiratory rate of 20-28/min, an inspiration-to-expiration ratio of (1.0:1.5)-2.0 min, an inspiration-to-expiration ratio of (1.0:1.5)-2.0, and a postapneic end-tidal carbon dioxide pressure of 30-35 mmHg (1 mmHg = 0.133 kPa). Anesthesia maintenance included intravenous infusion of propofol (9-15 mg/kg/h), intermittent intravenous fentanyl (1-3 μg/kg), and intravenous infusion of atracurium besylate (1-2 μg/kg/h).

The operative procedure was performed using both the caval replacement and piggyback techniques. Reperfusion of the liver graft started with opening of the portal vein, followed by opening of the artery. After arterial reperfusion, the bile duct was connected to the recipient's bile duct (choledocho-choledochostomy) or to a small bowel loop (hepaticojejunostomy). A back table biopsy of the donor liver was performed before implantation.

Hemodynamic instrumentation and design

The central venous pressure (CVP) was monitored continuously with a three-lumen central venous catheter placed using ultrasound-guided right internal jugular vein puncture and arterial pressure was monitored invasively in both groups using a catheter placed in the radial artery. The mean arterial blood pressure (MAP), HR, cardiac index (CI), stroke volume index (SVI), stroke volume variation (SVV), and left ventricular contractility index, which is the maximum increase in the speed of intraventricular pressure (dp/dt_{max}), were continuously monitored through PRAM (Most Care monitoring system; Vytech Healthcare, Padova, Italy) *via* a pressure catheter (Pulsion Medical Systems, Munich, Germany) in the CO-G group.

Hemodynamic management included fluid transfusion and use of vasopressors and/or inotropes: (1) Fluid management protocol: In the control group, fluid management was implemented mainly according to CVP, urine volume, bleeding, *etc.* CVP was maintained at a level of 6-12 mmHg, and the urine volume at ≥ 20 mL/h. If the urine volume was < 20 mL/h and/or CVP < 6 mmHg, 4% albumin or crystalloid was infused to expand the volume; if the urine volume was < 20 mL/h and/or CVP > 12 mmHg, 0.5 g/kg furosemide was also administered to decrease fluid load. In the CO-G group, fluid was infused at a rate of 10 mL/kg/h to maintain SVV at 12%-15%. If SVV was > 12%, 4% albumin or crystalloid was administered in combination with CI, SVI, and other parameters; and (2) Vasopressor and/or inotrope protocol: In the control group, if MAP was < 50 mmHg, norepinephrine or dopamine was pumped intravenously, and if MAP fell rapidly below 30 mmHg after the opening of the portal vein, rehydration and/or epinephrine of 1-5 mg/kg was administrated. In the CO-G group, the administration of vasopressors and/or inotropes according to the CO and other hemodynamic parameters is illustrated in the PRAM diagram (Figure 1). Other management: Albumin and blood products were infused to maintain the blood volume and hemoglobin level at ≥ 8 g/L. The electrolyte and acid-base balance were maintained within the normal range during surgery and were kept warm.

Blood assays

Venous blood (3 mL) was collected from the right internal jugular catheter and placed into vacuum tubes containing sodium heparin. Blood samples were collected at four time points: Immediately before the induction of general anesthesia (baseline, T_0), at the end of surgery (T_1), 1 d after surgery (T_2), and 3

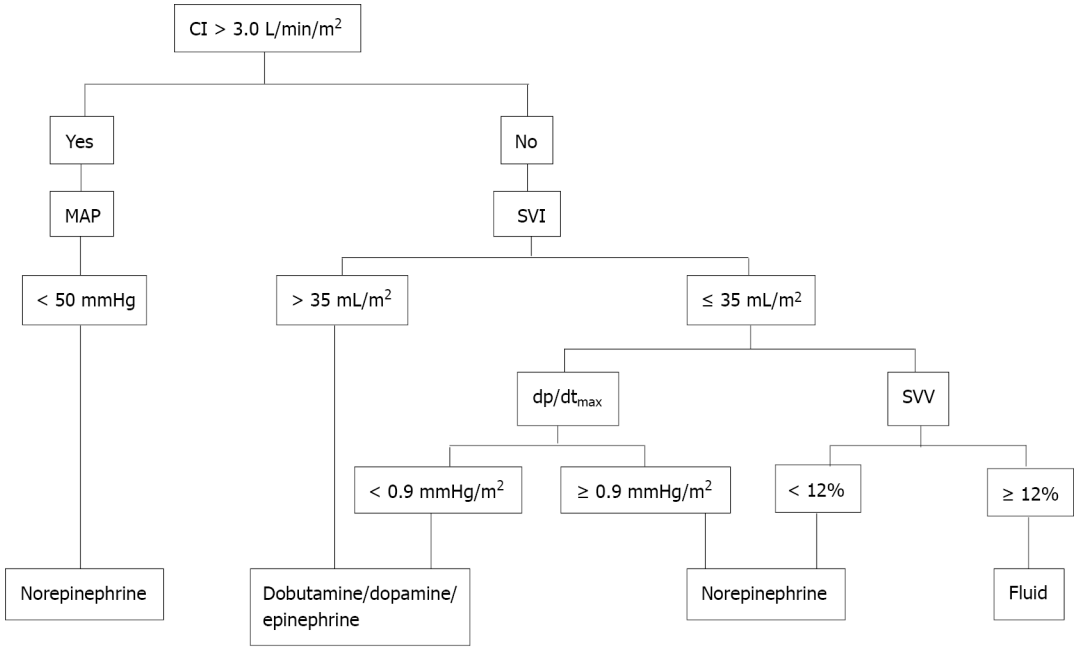

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Figure 1 Pressure recording analytical method. CI: Cardiac index; MAP: Mean arterial blood pressure; SVI: Stroke volume index; SVV: Stroke volume variation.

d after surgery (T_3). The samples were then placed in dry tubes and centrifuged. The serum was removed and stored at -80 °C until analysis. The levels of serum inflammatory factors interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), cardiac troponin I (cTnI), and N-terminal pro-brain natriuretic peptide precursor (NT-pro-BNP) were analyzed at four time points. Wuhan Huamei Biological Technology Company (Wuhan, China) was used to construct the reaction standard curves. The protein levels were calculated by comparing the optical density values of the samples with the standard curve.

Data collection

The following patients and preoperative variables were assessed: Patient characteristics, including age, weight, pediatric end-stage liver disease, and graft characteristics, including graft mass, graft-to-recipient body weight ratio, cold ischemia time of the graft, and preoperative laboratory test results. The intraoperative hemodynamic parameters included baseline values, the maximum and minimum values of HR, MAP, CVP, and the incidence of postreperfusion syndrome (PRS, defined as a sudden drop in MAP of ≥ 30% within 1-5 min of reperfusion)[13], and hemodynamic management, including transfusion of red blood cells, fresh frozen plasma, and fluids (colloids and crystalloids), usage of vasopressor or inotrope agents, and vasoactive drug score (VIS) [VIS = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 10000 × vasopressin dose (μg/kg/min) + 100 × norepinephrine dose (μg/kg/h) + 100 × milrinone dose (μg/kg/min)][14]. The postoperative variables included the occurrence of ALI and pulmonary complications in the first week after surgery, duration of mechanical ventilation, intense care unit (ICU) stay, incidence of readmission to the ICU for pulmonary complications, hospital stay, and in-hospital mortality.

Relevant definitions

ALI was defined according to the following criteria[15]: (1) Acute onset; (2) PaO_2/FiO_2 < 300; (3) Pulmonary artery wedge pressure < 18 mmHg without clinical evidence of left atrial hypertension; and (4) Bilateral infiltrates on chest radiography.

Study outcomes

The primary outcome was early postoperative ALI. The secondary outcomes included early PPCs, ICU stay, readmission to the ICU for pulmonary complications, hospital stay, in-hospital mortality, and intraoperative hemodynamic stability.

Sample size, randomization, and blinding

Sample size: The incidence of ALI in children after LT in the control and intervention groups was 50% and 25%, respectively, based on previous reports[3,4]. The α-error was set to 0.05, β-error to 80%, and the ratio to 1:1. PASS 15 (NCSS, LLC. Kaysville, UT, United States) was used to calculate the sample size, and the results showed that at least 58 patients should be included per group, with an expected

dropout rate of 10%.

Randomization and blinding: Pediatric patients were randomly assigned to the CO-G hemodynamic therapy algorithm (CO-G group) and the control group by a computer-generated random number system and individually sealed in envelopes. One investigator created computer-generated randomization codes and enrolled participants in accordance with the approved study protocol (ChiCTR1900026016), one investigator created computer-generated randomization codes and enrolled the participants. The participants were assigned to different groups based on the codes, which were kept in sequentially numbered opaque envelopes. After anesthetic induction, the envelopes were opened by another investigator, who was an anesthesiologist conducting CO-G hemodynamic management during the LT. An additional third investigator measured the primary and secondary outcomes in a blinded manner. The surgeons were blinded to the group allocation.

Statistical analysis

Outcome analyses were performed using SPSS software package (SPSS; IBM. Corp., Armonk, NY, United States). The Kolmogorov-Smirnov test was used to analyze the distribution of the data. The results are presented as the mean (SD), median (second quartile, third quartile), or number of patients. The patient characteristics and perioperative variables were compared using an independent *t*-test or Fisher's exact test, as appropriate. Changes in the above variables in the group over time were analyzed using repeated ANOVA, followed by an appropriate *post hoc* test. Categorical data were compared using the chi-squared test or Fisher's exact method. The results were evaluated within a 95% reliability index ($P < 0.05$).

RESULTS

Baseline patient characteristics and intraoperative data

A total of 148 patients were screened from December 2019 to October 2020, and 130 patients were enrolled and analyzed in this study. Among whom, 65 patients were randomly allocated to the CO-G group and 65 to the control group (Figure 2, Table 1). The patient characteristics were similar between the study groups (Table 1).

Primary outcome

The incidence of early postoperative ALI was 27.7% in the CO-G group, which was lower than that in the control group (44.6%) ($P < 0.05$) (Table 2). There were no significant differences in other pulmonary complications and ICU stay, readmission to the ICU for pulmonary complications, hospital stay, and in-hospital mortality (Table 2).

Intraoperative hemodynamic changes

Compared to the control group, intraoperative fluid transfusion (865.5 ± 153.1 mL *vs* 1222.7 ± 381.9 mL, $P < 0.001$), and positive fluid balance (598.8 ± 320.7 mL *vs* 1021.4 ± 467.9 mL, $P < 0.001$) were lower in the CO-G group. The utilization of dobutamine before portal vein opening was higher, whereas the usage and dosage of epinephrine during portal vein opening and VIS after portal vein opening [2 (2-3) *vs* 3 (2-7), $P < 0.05$] were lower in the CO-G group. The peak value of CVP was lower (9.46 ± 1.66 mmHg *vs* 11.64 ± 2.1 mmHg, $P < 0.001$) while the bottom value of MAP was higher (43.3 ± 7.4 mmHg *vs* 34.9 ± 5.5 mmHg, $P < 0.001$) in CO-G group. The incidence of PRS in the CO-G group was lower than that in the control group (33.8% *vs* 53.8%, $P = 0.022$) (Table 3).

Differences in inflammatory factors

In both groups, the levels of inflammatory factors (IL-6 and TNF-α) and cTnI increased during the operation, decreased gradually during the following 3 d postoperatively, and returned to preoperative levels (Table 4). The NT-proBNP levels showed the same trend (Table 4). For group comparisons, at T1 and T2, the values of IL-6, TNF-α, and cTnI were significantly lower in the CO-G group (Table 4). At T1, T2, and T3, the NT-proBNP levels were significantly lower in the CO-G group (Table 4).

DISCUSSION

To the best of our knowledge, this is the first randomized controlled trial to evaluate the effect of CO-guided hemodynamic therapy in pediatric liver recipients. In this study, hemodynamic parameters, including CO, SVV, SVI, and dp/dt_{max}, obtained through PRAM monitoring were used to guide intraoperative hemodynamic management. The incidence of postoperative ALI was significantly lower in the interventional group than in the control group. Moreover, the inflammatory factors of IL-6, TNF-α, and cTnI decreased faster in the intervention group than in the control group.

Table 1 Patient demographic and perioperative data

Variables	Control group (*n* = 65)	CO-G group (*n* = 65)	*P* value
Age, mo	7.5 (5.9, 9.6)	7.0 (6.0, 8.5)	0.390
Gender (boy/girl), *n*	31/34	33/32	0.726
Weight of receptor, kg	7.5 (6.5, 9.0)	7.4 (6.5, 8.0)	0.383
Mass of graft, g	220.5 ± 40.7	218.8 ± 39.5	0.736
GRWR, %	3.10 ± 0.76	3.03 ± 0.76	0.631
Pretransplant PELD score	16.5 ± 3.2	17.2 ± 3.5	0.549
Pretransplant INR, IU	1.77 ± 0.86	1.91 ± 0.67	0.300
Pretransplant PTA, %	57.5 ± 20.7	51.4 ± 20.2	0.095
Pretransplant PT, s	20.2 ± 9.9	21.5 ± 8.7	0.454
Pretransplant WBC, 10^9/L	13.3 ± 6.3	12.2 ± 5.6	0.331
Pretransplant hemoglobin, g/L	90.4 ± 13.6	86.8 ± 12.8	0.116
Pretransplant platelets, 10^{12}/L	194.3 ± 87.0	207.3 ± 72.1	0.355
Pretransplant albumin, g/L	34.1 ± 4.4	35.6 ± 5.9	0.088
Pretransplant total bilirubin, μmol/L	271.6 ± 128.3	282.9 ± 122.4	0.607
Pretransplant creatinine, μmol/L	12.7 ± 3.5	11.8 ± 3.0	0.099
Graft cold ischemia time, min	65.9 ± 25.7	60.2 ± 14.8	0.081
Anhepatic time, min	44.4 ± 11.5	47.1 ± 15.8	0.267
Operation time, min	545.0 ± 44.9	559.5 ± 49.6	0.083
Mechanical ventilation after operation, h	3.00 (2.25, 4.50)	2.75 (2.00, 3.88)	0.789

Data are expressed as number (%), mean ± SD, or median (interquartile range), as appropriate. CO-G: Cardiac output-guided; GRWR: Graft-to-recipient body weight ratio; PELD: Pediatric end-stage liver disease; INR: International Normalized Ratio; PTA: Prothrombin activity; PT: Prothrombin time; WBC: White blood cell.

Effects on ALI

The incidence of ALI in the control group was 44.6%, which was close to that used in the sample size calculation (50%). These results are similar to those of previous studies. Hong *et al*[4] reported that the rate of ALI was 34.6% in adult LT, while Yao *et al*[5] showed that the incidence of ALI in a rat LT model was 77.8%. CO-G interventions significantly decreased ALI occurrence after pediatric LT. This might be due to more stable hemodynamic parameters, which can mitigate ischemia-reperfusion injury, as well as optimized vasopressor use and fluid management in the CO-G group.

Effects on inflammatory factors

Inflammatory lung liver interactions, and the activation of nuclear factor-kappa B in particular, may be implicated in the pathogenesis of permeability-type pulmonary edema[16]. It is well accepted known that the inflammatory response is involved in the progression of ALI and that cytokines, such as TNF-α, IL-1β, and IL-6, play important roles in the massive inflammatory response that is a hallmark feature of ALI[17]. In contrast, IL-4 and IL-10 seem to exert protective roles[18].

Therefore, in the present study, we selected TNF-α and IL-6, which are typical factors that reflect inflammation and oxidative stress in the lungs. The results showed that the inflammatory factors mentioned above were elevated from the end of the operation and returned to preoperative levels 3 d after surgery. Compared with the control group, TNF-α and IL-6 levels were significantly lower from the end of the operation to 1 d after surgery in the CO-G group, indicating that CO-G hemodynamic therapy can attenuate lung inflammation during LT.

Effects on hemodynamic stability

Several triggering conditions, including bleeding, blood transfusion, and ischemia-reperfusion, can exaggerate the inflammatory process of ALI. Among them, liver ischemia-reperfusion may be the most notable factor. The greatest hemodynamic disturbance in LT is defined as PRS, which occurs during reperfusion of the donated liver after unclamping of the portal vein. PRS is characterized by marked decreases of > 30% in MAP lasting > 1 min within 5 min after reperfusion and occurring with an

Table 2 Results for primary outcome and secondary outcomes

	Control group (*n* = 65)	CO-G group (*n* = 65)	*P* value
Primary outcomes			
ALI, *n* (%)	29 (44.6)	18 (27.7)	0.045
Others			
Pneumonia, *n* (%)	12 (18.5)	8 (12.3)	0.634
Atelectasis, *n* (%)	18 (27.7)	12 (18.5)	0.687
ARDS, *n* (%)	6 (9.2)	4 (6.2)	0.742
Refractory heart failure, *n* (%)	3 (4.6)	1 (1.5)	0.612
Readmission to ICU for pulmonary complications, *n* (%)	3 (4.6)	2 (3.1)	1.000
ICU stay, d	2 (2, 3)	2 (2, 3)	0.200
Hospital stay, d	28 (22, 39)	27 (20, 37)	0.450
In-hospital mortality, *n* (%)	2 (3.1)	0	0.476

Data are expressed as number (%), mean ± SD, or median (interquartile range), as appropriate. CO-G: Cardiac output-guided; ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit.

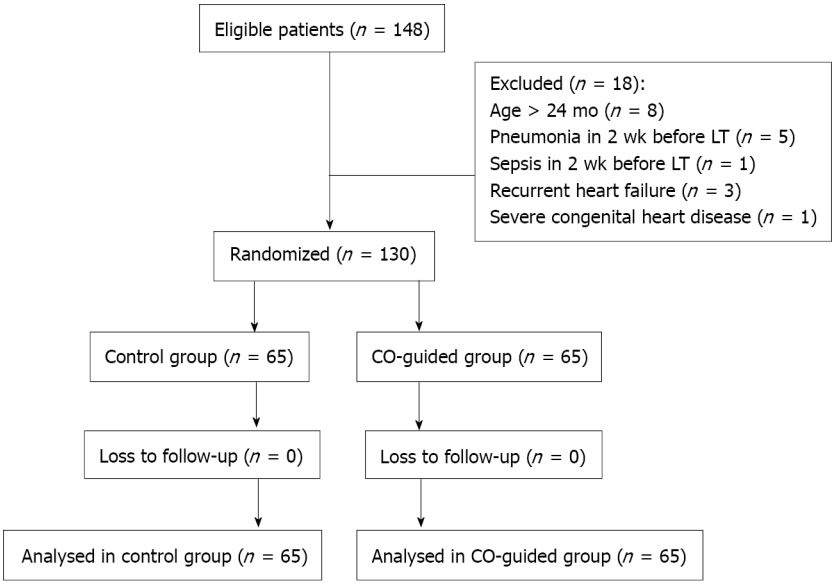

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Figure 2 Trial profile. CO: Cardiac output; LT: Liver transplantation.

incidence of 12.1%-42%[19]. A dramatic drop in blood pressure and myocardial inhibition are manifestations, but are also risk factors for PRS[20]. It is noteworthy that the intraoperative stabilization of arterial pressure through the preventive use of vasopressors during the reperfusion phase is capable of decreasing the incidence of PRS[21]. In our study, the incidence of PRS in the CO-G group was lower than that in the control group, which was attributed to the appropriate cardiotonic and optimized vasopressor by the continuous monitoring of CO.

In our study, the use of dobutamine before portal vein opening was higher than that in the control group, whereas the usage and dosage of epinephrine during portal vein opening and VIS after portal vein opening were lower in the CO-G group. CO-G hemodynamic therapy can reduce hemodynamic fluctuations and prevent the occurrence of PRS by continuously monitoring the intraoperative CO, which can consistently summarize cardiac function, and aid to the appropriate administration of vasopressors and inotropes.

Effects on myocardial injury

Myocardial injury commonly occurs in LT[22], which leads to arrhythmias and myocardial depression,

Table 3 Hemodynamic parameters and hemodynamic management

	Control group (*n* = 65)	CO-G group (*n* = 65)	*P* value
Preoperative hemodynamic parameters			
HR, bpm/min	110 ± 12	108 ± 11	0.325
MAP, mmHg	60.3 ± 8.0	61.6 ± 9.5	0.382
CVP, cmH_2O	6.08 ± 1.37	5.79 ± 1.44	0.241
Intraoperative hemodynamic parameters			
HR_H, bpm/min	123 ± 15	125 ± 18	0.317
HR_L, bpm/min	82 ± 8	86 ± 8	0.003
MAP_H, mmHg	72.3 ± 8.8	71.7 ± 10.4	0.531
MAP_L, mmHg	34.9 ± 5.5	43.3 ± 7.4	< 0.001
CVP_H, cmH_2O	11.64 ± 2.1	9.46 ± 1.66	< 0.001
CVP_L, cmH_2O	4.17 ± 1.49	3.55 ± 1.34	0.013
Intraoperative hemodynamic events			
PRS, *n* (%)	35 (53.8)	22 (33.8)	0.022
Malignant ventricular arrhythmia, *n* (%)	3 (5)	2 (3.1)	1.000
Cardiac arrest, *n* (%)	1 (1.5)	0	1.000
Intraoperative hemodynamic management			
Intraoperative blood transfusions, U	2.5 (2, 3)	2.0 (1.5, 2.5)	0.821
Intraoperative frozen plasma transfusions, mL	0 (0, 200)	0 (0, 110)	0.751
Intraoperative fluid transfusions, mL	1222.7 ± 381.9	865.5 ± 153.1	< 0.001
Intraoperative bleeding volume, mL	300 (200, 500)	300 (200, 400)	0.543
Intraoperative urinary volume, mL	300 (277.5, 400)	400 (200, 510)	0.416
Positive fluid balance, mL	1021.4 ± 467.9	598.8 ± 320.7	< 0.001
VIS before portal vein opening	2 (2, 5)	3 (2, 6.25)	0.565
During portal vein opening			
Bolus injection of epinephrine, *n* (%)	30 (46.2)	18 (27.7)	0.029
Bolus dosage of epinephrine, μg	3 (2, 5)	2.5 (1.75, 4.25)	0.030
VIS after portal vein opening	3 (2, 7)	2 (2, 3)	0.049

Data are expressed as number (%), mean ± SD, or median (interquartile range), as appropriate. CO-G: Cardiac output-guided; HR: Heart rate; MAP: Mean arterial blood pressure; CVP: Central venous pressure; HR_H: Intraoperative maximum heart rate; HR_L: Intraoperative minimum heart rate; MAP_H: Intraoperative maximum mean arterial blood pressure; MAP_L: Intraoperative minimum mean arterial blood pressure; CVP_H: Intraoperative maximum central venous pressure; CVP_L: Intraoperative minimum central venous pressure; PRS: Postreperfusion syndrome; VIS: Vasoactive inotropic score.

severely affecting circulatory stability and aggravating ischemia-reperfusion injury. cTnI is currently recognized as a sensitive and specific gold standard for reflecting the degree of myocardial injury, and mildly elevated cTnI levels (≥ 0.04 ng/mL) are strongly associated with postoperative mortality[23]. Sheng *et al*[24] demonstrated that intraoperative cTnI elevation (≥ 0.07 ng/mL) was a significant prognostic risk factor in ALI after pediatric living-donor LT for children with biliary atresia. NT-proBNP is an early and reliable predictor of myocardial dysfunction onset[25]. BNP levels positively correlated with left ventricular systolic function and required inotropic support[26].

In our study, we analyzed cTnI and NT-pro-BNP levels to identify myocardial injury and cardiac dysfunction. The results showed that cTnI and NT-pro-BNP levels were elevated from the end of the operation and returned to preoperative levels 3 d after surgery. NT-pro-BNP level was lower at 3 d after surgery than at the preoperative level. Compared to the control group, the values of cTnI were significantly lower at the end of surgery and 1 d after surgery in the CO-G group. In the CO-G group, the NT-pro-BNP values from the end of surgery to 3 d after surgery were all lower than those in the control group, indicating that CO-G hemodynamic therapy can attenuate myocardial injury and cardiac

Table 4 Changes in serum interleukin-6, tumor necrosis factor-α, troponin I, and N-terminal pro-brain natriuretic peptide levels at every time point

		IL-6 (pg/mL)	TNF-α (pg/mL)	cTnI (ug/L)	NT-proBNP (ng/L)
Control group (n = 65)	T_0	78.9 ± 23.2	87.5 ± 25.6	0.032 ± 0.015	556.6 ± 251.2
	T_1	170.4 ± 42.3[b]	175.3 ± 43.1[b]	0.383 ± 0.166[b]	1012.4 ± 568.8[b]
	T_2	126.2 ± 33.6[b]	129.5 ± 35.2[b]	0.182 ± 0.067[b]	866.0 ± 283.6[b]
	T_3	80.7 ± 23.2	92.8 ± 26.8	0.030 ± 0.011	667.4 ± 247.7
CO-G group (n = 65)	T_0	80.6 ± 22.5	83.2 ± 23.8	0.029 ± 0.012	562.2 ± 195.8
	T_1	145.5 ± 34.5[a,b]	156.7 ± 36.1[a,b]	0.255 ± 0.128[a,b]	876.7 ± 268.2[a,b]
	T_2	108.6 ± 24.9[a,b]	115.5 ± 25.6[a,b]	0.116 ± 0.070[a,b]	594.0 ± 163.3[a,b]
	T_3	78.6 ± 21.9	86.2 ± 22.6	0.028 ± 0.011	462.6 ± 154.5[a,b]

[a]P < 0.05, compared with control group.
[b]P < 0.05, compared with T_0.
Data are expressed as number (%) or mean ± SD. T_0 before induction of general anesthesia, T_1 at the end of surgery, T_2 1 d after surgery, T_3 3 d after surgery. CO-G: Cardiac output-guided; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; cTnI: Cardiac troponin I; NT-pro-BNP: N-terminal pro-brain natriuretic peptide.

volume load, which could be helpful in circulatory stability and attenuation of pulmonary edema.

Optimizing fluid management

Intraoperative fluid overload can exacerbate pulmonary edema and heart failure, thereby increasing the duration of postoperative mechanical ventilation, pulmonary infection, and mortality. Previous intraoperative volume management is often achieved through empirical rehydration and CVP-directed management; CVP is a pressure-based index that cannot accurately reflect volume status, and CVP-directed fluid management can result in volume overload[27,28]. Compared to pressure-monitoring metrics, volume-monitoring metrics better reflect volume status to guide hemodynamic management, and SVV < 12% and PPV < 13% are more accurate in predicting fluid responsiveness[29]. Shin *et al*[30] showed that the sensitivity of SVV for monitoring blood volume changes during the neohepatic period of LT was 89%, with a specificity of 80%, which was significantly better than that of CVP. In addition, studies have shown that CO-G fluid management reduces postoperative complications by 20% to 30% compared with any infusion strategy[31]. In this study, CO-directed fluid management combined with SVI and SVV showed that intraoperative fluid transfusion and maximum CVP were significantly lower in the CO-G group than in the control group. The incidence of postoperative ALI was also significantly lower, suggesting that CO-G hemodynamic management can reduce fluid overload, decrease the occurrence of pulmonary edema, stabilize cardiopulmonary function, control CVP, and reduce the occurrence of ALI.

Limitations

As this was a single center study, a multicenter study with other monitoring indicators is needed for further analysis.

CONCLUSION

CO-G hemodynamic management in pediatric living donor LT can decrease the incidence of early postoperative ALI due to hemodynamic stability through optimized fluid management and appropriate administration of vasopressors and inotropes achieved by continuous monitoring of CO.

ARTICLE HIGHLIGHTS

Research background

Acute lung injury (ALI) post-liver transplantation (LT) may lead to acute respiratory distress syndrome, which is associated with adverse postoperative outcomes, such as prolonged hospital stay, high morbidity, and mortality. Therefore, it is vital to maintain hemodynamic stability and optimize fluid management. However, few studies have reported cardiac output-guided (CO-G) management in

pediatric LT.

Research motivation

In this study, a randomized controlled trial was designed to evaluate the effect of CO-G algorithm management on reducing ALI events after pediatric LT and intraoperative hemodynamic stability with pressure recording analytical method (PRAM).

Research objectives

To investigate the effect of CO-G hemodynamic management in pediatric living donor LT on early postoperative ALI and its influence on hemodynamic stability during surgery.

Research methods

A total of 130 pediatricians scheduled for elective living donor LT were enrolled as study participants and were assigned to the control group (65 cases) and CO-G group (65 cases). In the CO-G group, CO was considered the target for hemodynamic management. In the control group, hemodynamic management was based on usual perioperative care guided by central venous pressure, continuous invasive arterial pressure, urinary volume, *etc*. The primary outcome was early postoperative ALI. Secondary outcomes included other early postoperative pulmonary complications, readmission to the intense care unit (ICU) for pulmonary complications, ICU stay, hospital stay, and in-hospital mortality.

Research results

The incidence of early postoperative ALI was 27.7% in the CO-G group, which was significantly lower than that in the control group (44.6%) ($P < 0.05$). During the surgery, the incidence of postreperfusion syndrome was lower in the CO-G group ($P < 0.05$). The level of intraoperative positive fluid transfusions was lower and the rate of dobutamine use before portal vein opening was higher, while the usage and dosage of epinephrine when portal vein opening and vasoactive inotropic score after portal vein opening were lower in the CO-G group ($P < 0.05$). Compared to the control group, the serum inflammatory factors interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), cardiac troponin I (cTnI), and N-terminal-pro hormone BNP in the CO-G group were lower after the operation ($P < 0.05$).

Research conclusions

CO-G hemodynamic management in pediatric living-donor LT decreased the incidence of early postoperative ALI, which is considered to benefit from hemodynamic stability through optimized fluid management and appropriate administration of vasopressors and inotropes by continuous monitoring of CO.

Research perspectives

This is the first randomized controlled trial to evaluate the effect of CO-G hemodynamic therapy in pediatric liver recipients. In this study, hemodynamic parameters, including CO, stroke volume index, stroke volume variation, and the maximum increase in the speed of intraventricular pressure (dp/dt_{max}), obtained through the PRAM monitoring were used to guide intraoperative hemodynamic management. The incidence of postoperative ALI was significantly lower in the interventional group. Moreover, the inflammatory factors of IL-6, TNF-α, cTnI, decreased faster in the intervention group.

FOOTNOTES

Author contributions: Dou XJ contributed to acquisition of data, data analysis, and wrote the manuscript; Yu WL provided substantial contribution to the conception and design of the study and corrected the manuscript; Wang QP, Liu WH, Weng YQ, and Sun Y collected the data.

Institutional review board statement: This study was approved by the Ethics Committee of Tianjin First Center Hospital in China (Approval Number: 2019N180KY).

Clinical trial registration statement: The clinical trial registration number is ChiCTR1900026016.

Informed consent statement: Informed consent was obtained from eligible guardians.

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SYSTEMATIC REVIEWS

Minimally invasive endoscopic repair of rectovaginal fistula

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Abstract

BACKGROUND

Surgical techniques for repair of rectovaginal fistula (RVF) have been continually developed, but the ideal procedure remains unclear. Endoscopic repair is a novel and minimally invasive technique for RVF repair with increasing reporting.

AIM

To review the current applications and preliminary outcomes of this technique for RVF repair, aiming to give surgeons an alternative in clinical practice.

METHODS

Available articles were searched according to the search strategy. And the sample size, fistula etiology, fistula type, endoscopic repair approaches, operative time and hospital stay, follow-up period, complication and life quality assessment were selected for recording and further analysis.

RESULTS

A total of 11 articles were eventually identified, involving 71 patients with RVFs who had undergone endoscopic repair. The principal causes of RVFs were surgery (n = 51, 71.8%), followed by obstetrics (n = 7, 9.8%), inflammatory bowel disease (n = 5, 7.0%), congenital (n = 3, 4.2%), trauma (n = 2, 2.8%), radiation (n = 1, 1.4%), and in two patients, the cause was unclear. Most fistulas were in a mid or low position. Several endoscopic repair methods were included, namely transanal endoscopic microsurgery, endoscopic clipping, and endoscopic stenting. Most patients underwent > 1-year follow-up, and the success rate was 40%-93%, and all cases reported successful closure. Few complications were mentioned, while postoperative quality of life assessment was only mentioned in one study.

CONCLUSION

In conclusion, endoscopic repair of RVF is novel, minimally invasive and promising with acceptable preliminary effectiveness. Given its unique advantages, endoscopic repair can be an alternative technique for surgeons.

Key Words: Endoscopic repair; Minimal-invasive technique; Rectovaginal fistula

Core Tip: The current status of minimally invasive endoscopic repair for rectovaginal fistulas (RVFs) was reviewed. This is the first review to explore the current application status and evaluate the preliminary outcomes. Endoscopic repair is recommended as a novel and promising technique for RVF and warrants consideration by surgeons. The disappointing quality of published studies on surgical treatment of RVF is discussed, along with the possible role of endoscopic repair in improving the situation.

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INTRODUCTION

Rectovaginal fistula (RVF), a type of chronic gastrointestinal fistula, refers to an abnormal epithelialized-lined connection between the rectum and the vagina, presenting with symptoms including uncontrollable passage of gas and/or fecal discharge from the vagina[1]. Even though it is benign, the distressing and persistent symptoms interfere with daily activities and sexual life, and have a long-term potential detrimental impact on psychological health[2,3]. Obstetric trauma is the primary etiological factor for RVF, but it can also be acquired from local abscess, pelvic floor or rectal surgery, trauma, or radiotherapy[3-5]. Chronic inflammatory bowel disease (most commonly Crohn's disease) is the second most common etiology with rates varying between 6% and 23%[6]. It is reported that RVF occurs in up to 10% of women diagnosed with Crohn's disease[7,8]. Congenital RVF is rare, usually coexists with anal malformation, and can be treated by anal reconstruction at a young age[9].

Standard classification of RVF will benefit to the choice of treatment approach and the comparison of treatment outcomes between studies, and help develop an algorithm for repair. However, there is no generally accepted classification of RVF. Currently, the classification of "simple/complex" or "low/middle/high" according to location, size, and etiology of RVF is most used[10,11]. With the development of diagnostic and therapeutic techniques, the imaging results, endoscopic exploration and gradually defined local anatomical structure will promote a classification consensus[12,13]. The anatomical features are always the principle of classification, which makes it necessary to achieve a more detailed and precise anatomical recognition[14].

Various medical and surgical treatments have been applied for RVF, but treatment is still a challenge for doctors due to the high recurrence rate. Nonoperative methods are recommended for the treatment of fresh and slight symptomatic fistula. Surgical repair is essential, once it occurs and persists[15]. There is still no standard surgical repair technique worldwide for RVF and no evidence can suggest one surgical technique over another since the release of the procedural guidelines in Europe.

Multiple surgical repair techniques, including fistulectomy, advancement flap, muscle transposition, closure with biomaterials, endoscopic repair and transabdominal approaches[16], have been gradually reported in the literature. Fistulectomy is not technically demanding, whose main step is to remove the fistula tract, together with the surrounding scarred and sclerotic tissue. It may fail due to incomplete removal and excessive tissue tension of tissue suture for large excision, and is therefore, mostly used to repair small and simple RVFs[17,18]. Advancement flaps are performed by raising either the rectal mucosa (transrectal) or vaginal mucosa (transvaginal) to cover the fistula tract. Transrectal advancement flap is more commonly adopted compared to the transvaginal approach, and the repair is performed from the high pressure of the rectum side, and has an actual success rate of 50%-70%[1,4]. Even though some studies have recommended transrectal advancement flap as the first-line treatment for low RVFs, it is not as effective as expected if the periorificial tissue is chronically inflamed, or when the fistula is large in diameter and causes anal stenosis[19]. Reconstruction by Martius flap, gracilis muscle flap or bulbocavernosus muscle transposition can be used to introduce healthy vascularized tissues, which has achieved a certain effect for recurrent, Crohn's-disease-related and radiation-related RVFs, with reported overall success rates ranging from 25% to 100%[20,21]. However, given the aggressive incision, tissue damage, prolonged hospital stay and protective stoma diversion routinely required, this technique is demanding and not easily accepted by patients[22,23]. Biomaterials and endoscopic repair are novel and less invasive techniques and constant attempts have been made to apply them for RVF repair. However, given the limited number of publications available, there are currently no relevant recommendations. Transabdominal approaches are recommended for high RVFs resulting from

complications of colorectal anastomosis, and laparoscopic repair has been frequently adopted[15,24]. In clinical practice, protective stoma diversion is generally applied for the treatment of RVF, whereas absence of any reliable efficacy assessment for RVF makes it remain controversial. Theoretically, diversion stoma may help control the symptoms by fecal diversion and support healing of the fistula and surgical success[25]. Corte *et al*[26] claimed that a temporary diversion stoma could significantly improve the success rate of repair. However, Lambertz *et al*[27] found no connection between diversion stoma creation and rate of recurrence, which was supported by other authors[28,29]. Some studies have shown that radiation- and Chron's-disease-related RVFs are indications for diversion stoma[30,31], and stating that once the diversion stoma is made, large invasion, distressing conditions and potential complications can occur[32]. Although the techniques for RVF repair have been developing, the etiology, classification, surrounding tissue condition, prior treatment procedures and the surgeon's preference are always the basis for determining the approach. In addition, individualized, precise, and less-invasive surgical techniques for RVFs repair are gradually being recommended[13,33].

All the surgical interventions performed *via* an endoscope or in the endoscopy unit can be classified as endoscopic repair, which is a novel and minimally invasive surgical technique for RVF. Several endoscopic repair approaches have been applied and reported for RVF surgical treatment. Transanal endoscopic microsurgery (TEMS) is an endoscopic technique performed entirely through the anus and rectum, which was originally developed in the 1980s to treat lower rectal adenomas[34] (Figure 1). Vávra *et al*[35] reported the first case of RVF treatment using TEMS in 2006, which is one of the most reported endoscopic approaches for RVF. Several minimally invasive endoscopic approaches such as the through-the-scope clip (TTSC), over-the-scope clip proctology system (OTSC) and endoscopic stenting have successively proven their role in RVF repair. After more than a decade of development, endoscopic repair for RVF has been continuously advanced and more advantages have been unveiled. Endoscopic repair for RVF is novel but limited by the information available. Therefore, a review of studies on minimally invasive endoscopic repair for RVF was carried out to assess the preliminary outcomes and introduce several endoscopic approaches for RVF surgical repair to surgeons, thereby contributing to developing a more individualized, precise, and less-invasive treatment plan appropriate for each patient.

MATERIALS AND METHODS

A search was performed to identify the existing literature available in PubMed and EMBASE databases in December 2021, without timeframe limitations (Figure 2). The following keywords, including "rectovaginal fistula," "rectovaginal," "fistula," "endoscope", "endoscopic," and "endoscopy", were used for searching. Given that there were only around 184 articles available, every single article was reviewed at the beginning. Exclusion criteria included irrelevancy, not English language, guidelines, or reviews. Articles published by the same author were found a duplication in the inclusion of patients, and the study with the longest follow-up was included. Three independent reviewers extracted and summarized data from the included articles and conducted qualitative assessment in accordance with the Oxford Centre for Evidence-Based Medicine 2011 Level of evidence[36]. All disagreements were settled by consensus. In addition, we conducted a research using Reference Citation Analysis (https://www.referencecitationanalysis.com/) and cited the relevant references.

RESULTS

A total of 11 articles were eventually identified according to the search strategy. Data were extracted by the reviewers and eventually reported using summary statistics, as shown in Table 1. The limited number of available articles and the low evidence of all studies made the primary outcome not sufficiently satisfactory. Besides, there were not enough eligible articles to perform a meta-analysis. In terms of the type of study, case reports seemed to be preferred for this novel technique, and the number of patients in each retrospective study was limited. The etiology was classified as: related to surgery (n = 51) such as rectal surgery, pelvic surgery and the colorectal anastomosis, *etc*., with 22 patients undergoing rectal surgery with a history of radiotherapy; and directly caused by radiotherapy (n = 1), inflammatory bowel diseases (n = 5) including Crohn's disease and ulcerative colitis; congenital (n = 3), obstetric injury (n = 7), trauma (n = 2), with the etiology unclear in two patients. Most fistulas were situated in the middle or low. Most of the patients had undergone previous repairs, even on multiple occasions. Fecal diversion was chosen as part of surgical treatment in some patients. Psychological components regarded as important as the success rate were rarely reported[19,37], with improved sexual function after repair mentioned in only one paper.

Table 2 summarized the details and preliminary outcomes of endoscopic repair of RVFs. A total of 38 patients underwent the conventional surgical procedure with a transrectal endoscopic device, when the layered suture was closed for 24, and mucosal advancement flap was for 14 patients. Endoscopic clip was another commonly used approach for RVF repair, and 18 patients who were treated using this

Table 1 Extract data of studies included

Number	Ref.	Type of study and evidence level	No. of patient(s)	Age of patients (yr)	Fistula etiology	Fistula type	No. of patients with previous repair	Diversion stoma	Life quality assessment (yes or no)
1	D'Ambrosio *et al*[41], 2012	Retrospective, level IV	13	44 (range, 25-70)	Surgery (n = 12); Radiation (n = 1)	Mid-low	13	Yes, 13 patients	No
2	Lamazza *et al* [54], 2016	Retrospective, level IV	15	58 (rang, 36-77)	Surgery with radiation (n = 15)	Mid-low	4	Yes, 4 patients	No
3	van Vledder *et al*[56], 2016	Retrospective, level IV	5	40 (range, 35-73)	Surgery (n = 5)	Mid-low	0	Yes, 3 patients	No
4	Yuan *et al* [42], 2019	Retrospective, level IV	17	46 (range, 10-76)	Surgery (n = 11); Congenital (n = 3); Obstetric (n = 2); IBDs (n = 1)	Mid-low	6	Yes, 9 patients	No
5	Tong *et al* [50], 2019	Prospective, level IV	16	40.1 (range, 27-56)	Surgery with radiation (n = 6); Obstetric (n = 5); IBDs (n = 3); Unclear (n = 2)	Mid-low	13	Yes, 11 patients	No
6	Shibata *et al* [57], 1999	Case report, level IV	1	71	Surgery	Low	0	No	No
7	Darwood *et al* [58], 2008	Case report, level IV	1	71	Surgery with radiation (n = 1)	Unclear	0	Yes	No
8	John *et al*[45], 2008	Case report, level IV	1	77	Infection (n = 1)	Mid	0	No	No
9	Vavra *et al* [59], 2009	Case report, level IV	1	53	Trauma (n = 1)	Mid	0	Yes	Yes
10	Chen *et al* [43], 2016	Case report, level IV	1	22	Trauma (n = 1)	Mid	2	Yes	No
11	Matano *et al* [48], 2019	Case report, level IV	1	71	Surgery (n = 1)	Mid	Multiple times	Yes	No

technique benefited from TTSC (n = 2) and OTSC (n = 16). One retrospective study reported endoscopic repair with placement of a self-expandable metal stent (n = 15). Several other endoscopic repair approaches for RVF such as endoscopic plugs, endoscopic injection and endoscopic–laparoscopic combined approach were noted, which were removed due to no complete references. Operating time and hospital stay were the desired outcomes, but not frequently reported. Most patients underwent > 1 year of follow-up. All case reports reported successful outcomes, but the success rates were different (40%-93%) in retrospective case series. More than half the studies reported no severe complications, and a few reported some minor postoperative complications, such as hematoma or abscess of rectovaginal septum (n = 2), moderate sphincter hypotonia (n = 1), pain (n = 5), minimal vaginal flatus (n = 1).

Minimally invasive endoscopic repair

TEMS: Minimally invasive techniques have been one of the major advancements in surgery in the last few decades, and are also one of the future trends. Such a technique has been almost routinely performed in colorectal resection irrespective of underlying diseases[38]. With the development of surgical instruments, endoscopic surgery is considered a feasible and minimally invasive approach that can facilitate better exposure, direct visualization and precise operation, with an increasing number of surgeons choosing it[39]. TEMS, as a platform for natural orifice transluminal endoscopic surgery, has developed into a well-established method of accurate resection of specimens from the rectum under binocular vision after the initial application for rectal cancer, and has also been adopted as an operative intervention in an extended setting for RVF[40]. After the first case of TEMS for RVF repair reported in 2006[35], the first retrospective review with 13 patients who had undergone layered sutures *via* this repair technique was published in 2012, with a closure rate of 93%[41]. In the present review, more than half of patients (n = 38) underwent conventional surgical repair procedures with transanal endoscopic devices, with a success rate of 40%-93%. The latest study reported a closure rate of 82% of mid-low RVF TEMS with layered sutures and mucosal advancement flaps[42]. Another three cases all reported successful closure. The superior 3D exposure and direct vision were the greatest advantages of TEMS. Under good visualization, comprehensive procedures exploring the anatomical structural relationship

Table 2 Details and results of the endoscopic repair approaches for rectovaginal fistulas

Number	Endoscopic repair	Operative time (min) and hospital-stay (d)	Follow-up (mo)	Results[a]	Complication
1	TEMS + fistulectomy + suturing (n = 13)	130 min (range, 90-150 min); 5 d (range, 3-8 d)	25	93% closed	Hematoma of the septum (n = 1); Abscess of the septum (n = 1); Moderate sphincter hypotonia (n = 1)
2	Endoscopic stenting (n = 15)	Unclear; Unclear	22 (range, 4-39)	80% closed	Pain (n = 1); Too uncomfortable to tolerate the stent (n = 1)
3	TEMS + fistulectomy + suturing (n = 4); TEMS + RAF (n = 1)	Unclear; Unclear	5 (range, 1-68)	40% closed	No complication
4	TEMS + VAF (n = 6); TEMS exploration + VAF (n = 6); TEMS + transvaginal suturing (n = 3); TES exploration + transvaginal suturing (n = 2)	75 min (range, 60-120 min); 8.29 d (range, 2-24 d)	8 (range, 2-24)	82.4% closed	No complication
5	OTSCs (n = 16)	Unclear; Unclear	10.2 (range, 8-36)	43.7% closed	Pain (n = 4); Spontaneous clip detachment (n = 1)
6	Endoscopic injection of fibrin glue (n = 1)	Few min; 0 d	12	Closed successfully	No complication
7	TEMS + RAF (n = 1)	Unclear; 2 d	6	Closed successfully	No complication
8	TTSCs (n = 1)	Unclear; Unclear	12	Closed successfully	Minimal flatus from vaginal (n = 1)
9	TEMS + suturing (n = 1)	125 min; 7d	12	Closed successfully	No complication
10	TEMS + stratified suturing (n = 1)	40 min; 2 d	12	Closed successfully	No complication
11	TTSCs (n = 1)	Unclear; Unclear	13	Closed successfully	No complication

[a]Success rate (%) for retrospective or prospective studies, closed successfully or unsuccessfully for case reports.

TEMS: Transanal endoscopic microsurgery; OTSC: Over-the-scope clip; TTSC: Through-the-scope clip; RAF: Rectal advancement flap; VAF: Vaginal advancement flap.

could be provided preoperatively and intraoperatively. The conventional invasive procedure could be performed more accurately with TEMS equipment, and ensure complete removal of the surrounding scarred or granulomatous tissues, but without significant loss of normal tissue. Therefore, there was a greater certainty of adequate blood supply to the tissue overlaps and/or flaps owing to the fresh tissue with the healthy margins[42]. In addition, the smaller tissue defect and good control of suture tightness enable free-tension repair[43], and make up for the shortcomings of conventional local repair that cannot completely remove surrounding tissue and is subject to insufficient blood supply and prompt healing. Using a natural endoluminal approach with endoscopy, precise operation and visualization can greatly reduce the invasiveness of conventional surgery with less intraoperative bleeding, shorter operating time and hospital stay, and fewer postoperative complications.

Endoscopic clipping: Endoscopic clipping is another technology using endoclips to completely close gastrointestinal leaks and fistulas, initially applied for iatrogenic gastric perforation in 1993[44]. John *et al*[45] reported the first successful closure of an RVF with TTSCs, which was also applied for repair of refractory RVF[33]; Ortiz-Moyano *et al*[46] described a combined approach using TTSCs and tissue adhesive that improved the rate of technical success in the endoscopic clips treatment of RVFs, since clips not only worked in opposing the margins, but acted as a scaffold for the glue. OTSCs for the gastrointestinal tract had greater force and a consistently high mean rate of procedural success of 80%-100%, and a durable clinical success rate of 57%-100%, and was preferred over TTSCs for closure of gastrointestinal fistulas[47]. Regarding colon perforation, small perforations (< 10 mm) could be successfully closed with TTSCs, whereas larger perforations could be successfully closed with OTSCs [48]. The first RVF closure using the OTSC proctology system was performed by Prosst *et al*[49] in 2015. One prospective study in 2019[50] presented the first evaluation of the therapeutic effects and safety of the application of OTSCs in complex RVFs, with a success rate of 43.7%, which was as high as that for gastrointestinal fistulas and convincing for complicated ones. Endoscopic clipping is a minimally invasive technique that involves transrectal placement of endoclips for RVF closure to avoid tissue incision, sphincter damage and intraoperative bleeding[49]. It is considered suitable for small fistulas,

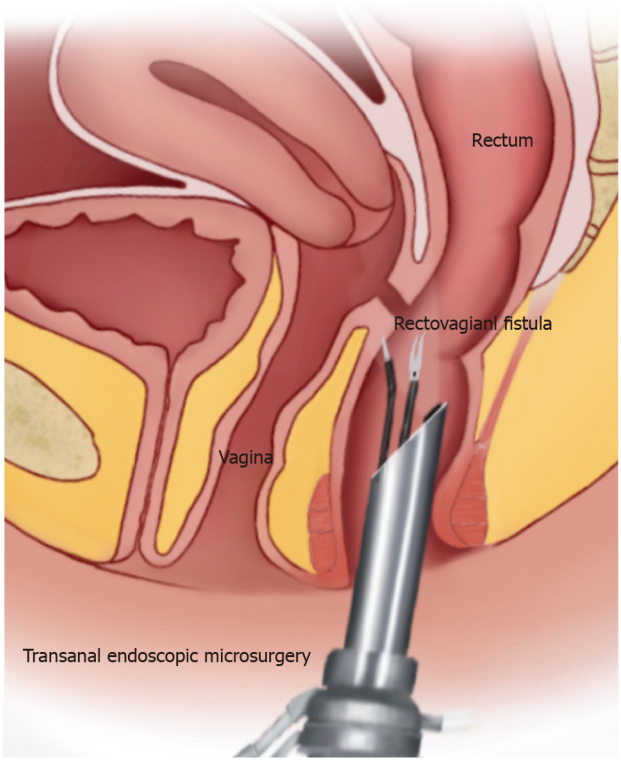

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Figure 1 Transanal endoscopic microsurgery for rectovaginal fistula repair.

and is even recommended to repair high-level fistulas[45,48]. Given limited data and obtained evidence, the role of endoscopic clips in RVF repair remains to be further investigated.

Endoscopic stenting: Endoscopic stenting involves placement of a self-expandable metal stent into the gastrointestinal tract to treat the defects, especially anastomotic leaks or perforation of the upper gastrointestinal tract[51]. Endoscopic placement of the self-expandable metal stent to treat RVFs after colorectal resection for cancer was a useful alternative to divert colostomy for the palliation of malignant rectal obstruction[52]. The team presented the two series outcomes with a success rate of 83% (5 of 6 patients)[53] and 80% (12 of 15 patients)[54], and the fistula size decreased significantly in all remaining patients, indicating that endoscopic placement of self-expandable metal stents may be a valid adjunctive treatment of RVF after colorectal resection for cancer. However, the favorable results may have been due to the low number of patients and selection bias. In the selected cases, the endoscopic placement of the self-expandable metal stent for RVF repair showed that the endoscopic stenting allowed a fast and proper closure of the fistula in a minimally invasive endoscopic way, with minor discomfort for patients and early discharge. A clear indication and results are still required for further in-depth study.

DISCUSSION

Surgical outcomes of RVF repair are mostly measured by the rates of closure and reoperation[37]. The successful closure rates for RVF surgical repair vary in the literature[55]. A similar variation in success rate (20%-93%) was found in this study using different etiologies and endoscopic approaches. We acknowledge that the varying rate of successful closure, limited number of publications available on this novel technique, and the low quality of included studies were limitations of the present review. In addition, the indications for endoscopic repair for RVF are not clear due to the lack of high-quality clinical studies. From a review of the included literature, endoscopic repair for RVF seems to be more commonly used in the treatment of low- and mid-level fistulas. However, it is also used for high-level fistulas with small openings, because transabdominal surgery is an invasive approach for small fistulas; therefore, endoscopic repair is considered a viable minimally invasive approach[48]. Moreover, endoscopic repair is a promising option for primary repair of RVF, and can be recommended for treatment of recurrent fistulas as well[50]. Regarding endoscopic repair is performed locally, it is not suitable for refractory RVFs with large openings and excessive tissue defects. Nevertheless, the minimally invasive endoscopic approach for RVF repair is a promising choice, and more surgical methods could be developed based on the endoscopic technique. As the research progresses, more

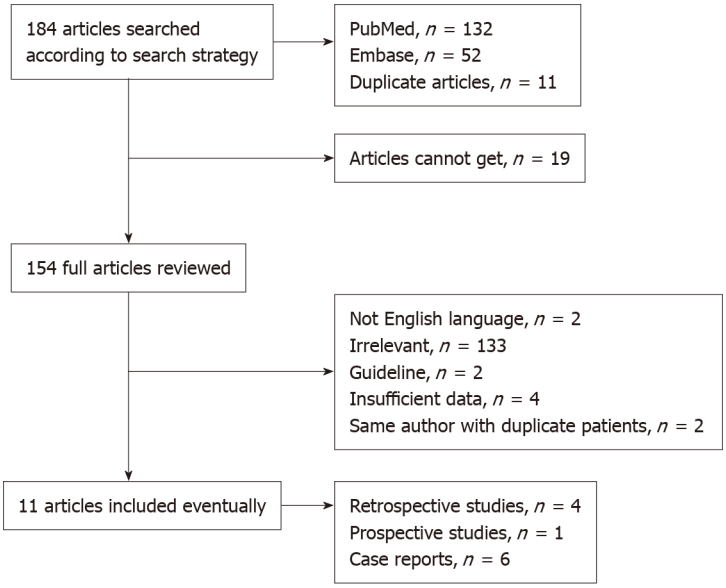

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Figure 2 The search strategy.

indications should be unveiled as well.

A 2014 systematic review claimed that the reason for difficulties in formulating a conclusion about the best surgical technique for RVF repair was the disappointing quality of existing literature surrounding different surgical techniques and outcomes for RVF repair[16]. Such a result not only persisted in the present review, but also in some related to single surgical approaches[8,20]. On the one hand, the limited number of samples and the heterogeneity of etiologies and local conditions made it hard to design large studies. RVF is a benign and chronic disease without a high incidence, but subject to variable and complex causes. There is no doubt that compared to the sample iatrogenic etiologies, IBDs-or radiation-related RVF would make difference in the local condition and the selection of surgical techniques. Therefore, retrospective studies were reviewed carefully to ensure the study sample size and homogeneity. With the continuous advancement of endoscopic techniques, different surgical procedures can be applied and standardized, which may improve the homogeneity of the surgical devices and contribute to designing large studies. On the other hand, in terms of the precise anatomical relationship of the fistula defect and the surrounding tissue, the lack of consensus on classification of RVFs makes it difficult to compare different surgical techniques. It is therefore proposed that further revisions are needed to guide the choice of newly developed treatment approaches[19]. Additionally, some authors claimed that a precise preoperative anatomical relationship assessment allowed better classification of fistulas and comparisons among different techniques[14]. It is believed that diagnostic imaging and endoscopic exploration could play a role in clarifying and developing anatomical relationship standards.

CONCLUSION

Endoscopic repair for RVFs is novel, effective and promising. A precise operation under good visualization through a natural lumen can reduce the invasiveness of conventional procedures. Some endoscopic surgical modes such as clipping and stenting mentioned in this review could even close the fistula without incision, less intraoperative bleeding, fewer complications, and shorter operating time and hospital stay. Surgeons could clarify the anatomical relationship of the fistula and surrounding tissue by endoscopic preoperative exploration and provide patients with a more appropriate treatment approach. However, endoscopic surgical repair for RVFs is technically demanding with a long learning curve and requires sufficient professional experience. Therefore, it is advocated to be performed by professional colorectal surgeons in highly specialized centers. Besides, larger high-quality studies and longer follow-up studies are necessary to unveil the clear indication and advantages of this novel minimally invasive endoscopic technique for RVF repair.

ARTICLE HIGHLIGHTS

Research background

Rectovaginal fistula (RVF) is abnormal connection between the rectum and vagina. Surgical repair is essential, once it occurs and persists. Surgical techniques for repair of rectovaginal fistula have been continually developed, but the ideal procedure remains unclear. Endoscopic repair is a novel and minimally invasive technique for RVF repair with increasing reporting.

Research motivation

To review the current literature of endoscopic repair of RVF and highlight the novel and minimally invasive technique for RVF repair to surgeons.

Research objectives

To evaluate the preliminary outcomes of this technique for RVF repair and analyze the indication and technical superiority.

Research methods

We searched PubMed and EMBASE databases for available studies. Data were extracted and qualitative assessment was conducted.

Research results

The endoscopic repair of RVF is in constant development, including several available approaches. The preliminary effectiveness of endoscopic technique for RVF repair is acceptable.

Research conclusions

Endoscopic repair for RVF is novel, effective and promising with acceptable preliminary effectiveness. In this manuscript, we have provided a detailed review of literatures, summarized its indications and unique technical advantages and made suggestions for its application and future development.

Research perspectives

Endoscopic repair for RVF is effective and safe according to preliminary outcomes. It is a promising technique for the treatment of rectovaginal fistulas and provides a minimally invasive technique selection for surgeons to treat rectovaginal fistulas.

FOOTNOTES

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META-ANALYSIS

Laparoscopic appendectomy, stump closure and endoloops: A meta-analysis

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Abstract

BACKGROUND

Acute appendicitis (AA) is one of the main indications for urgent surgery. Laparoscopic appendectomy (LA) has shown advantages in terms of clinical results and cost-effectiveness, even if there is still controversy about different devices to utilize, especially with regards to the endoloop (EL) *vs* endostapler (ES) when it comes to stump closure.

AIM

To compare safety and cost-effectiveness of EL *vs* ES.

METHODS

From a prospectively maintained database, data of 996 consecutive patients treated by LA with a 3 years-follow up in the department of Emergency General Surgery - St Orsola University Hospital, Bologna (Italy) were retrieved. A meta-analysis was performed in terms of surgical complications, in comparison to the

international literature published from 1995 to 2021.

RESULTS
The meta-analysis showed no evidence regarding wound infections, abdominal abscesses, and total post-operative complications, in terms of superiority of a surgical technique for the stump closure in LA.

CONCLUSION
Even when AA is complicated, the routine use of EL is safe in most patients.

Key Words: Acute appendicitis; Laparoscopic appendectomy; Endoloops; Stapler; Post-operative complications

Core Tip: Stump closure in the acute appendectomy setting could be performed *via* endoloop (EL) or endostapler use. The present meta-analysis assesses the experience of 996 patients consecutively treated in the department of Emergency General Surgery - St Orsola University Hospital, Bologna (Italy) and the evidence published in literature, confirming there is no superiority of a surgical method on how to perform the stump closure, with regards to wound infections, abdominal abscess, and total post-operative complications. Even when acute appendicitis is complicated, the routine use of EL is safe in most patients.

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INTRODUCTION

Acute appendicitis (AA) is one of the most frequent causes of acute abdominal pain and access to emergency care department. The lifetime chance of developing AA is lower in women, and the risk of being subject to surgery is higher in males[1], representing in fact one of the main indications for an urgent operation. Surgery is generally performed *via* a laparoscopic approach, and given the high volume of AA procedures worldwide, it represents a training operation as well[2].

Laparoscopic appendectomy (LA)[3,4] is demonstrated to be superior in terms of clinical results[5-9] and cost-effectiveness[10-14], even if there is still controversy[15-19] about the use of different devices during the operation[20-24]. Currently, it is still debated the use of endostapler (ES) *vs* endoloop (EL) in appendiceal stump closure[25-28]. The routine use of EL is safe in most patients affected by AA, also when it is complicated[29-32], representing a cost-effective device when taking into consideration the additional costs of potential post-operative complications, too[33-37]. We have previously shown money saving as well as the safety of the routine use of ELs[38]. The aim of this study is to meta-analyze the international literature, to compare the outcome of the patients laparoscopically treated in Bologna *via* EL to the data from the international literature.

MATERIALS AND METHODS

Between November 2011 and January 2018, a total of 1045 LAs were performed in the department of Emergency General Surgery - St Orsola University Hospital, Bologna (Italy). Patients who undergone LA until January 2018 were identified retrospectively from a prospectively maintained database, so that a 3-year follow-up was achieved[39,40]. All grades of post-operative complications were collected and examined. Institutional review board for this study was not required, as this is a meta-analysis of already previous published data. At Bologna centre, patients were initially evaluated by a general surgeon, then underwent laboratory tests, and Alvarado or appendicitis inflammatory response (AIR) score (Table 1) were calculated in females and in males respectively[41,42].

Surgery

Surgical procedures were performed by attendants or supervised trainees. Written informed consent

Table 1 Alvarado and appendicitis inflammatory response score

	Alvarado score	AIR score
Likely appendicitis	7-10	9-12
Probably appendicitis	5-6	5-8
Unlikely appendicitis	0-4	0-4

AIR: Appendicitis inflammatory response.

was signed by all the patients before the procedures. Antibiotic prophylaxis was always administered. A supraumbilical 12 mm-Hasson trocar with an open approach was adopted to induce pneumoperitoneum and initiate laparoscopy. Then, 2 other operative trocars were placed in the left flank (10 mm) and suprapubic position (5 mm), with identification of the appendix, cut and coagulation of the mesoappendix.

EL or ES use

The choice of EL *vs* ES to close the base of the appendiceal stump was made by the operating surgeon, after evaluating the inflammatory infiltration of the appendicular base[43]. If an EL was used, the appendicular stump was cut 3-5 mm away from cecum. The surgical specimen was then removed in an endobag through the 12 mm trocar.

Bologna cohort

Patients were divided in two groups (EL and ES) and in three categories (edematous, phlegmonous and gangrenous appendicitis) based on the severity of the histological examination. Cases requiring conversion to open appendectomy were excluded, while 996 LA (95.3%) were included in the meta-analysis.

Meta-analysis

A meta-analysis was performed in terms of surgical complications, comparing the clinical data of the EL group (821 patients) to the international literature retrieved by Pubmed (Figure 1), according to the PRISMA principles[44].

Inclusion and exclusion criteria

Manuscripts were excluded from the analysis if they dealt with pediatric patients (< 15 years of age) or were published before 1995.

Statistical analysis

Data were collected and analyzed with MedCalc software. Statistical expertise was available to the authors. MedCalc 13.0.6.0 (MedCalc Software bvba, Østend, Belgium) was used for the meta-analysis. MedCalc uses a Freeman-Tukey transformation (arcsine square root transformation) to calculate the weighted summary proportion under the fixed and random effects model. The program lists the proportions (expressed as a percentage), with their 95% confidence interval (CI), found in the individual studies included in the meta-analysis. The heterogeneity was evaluated by means of statistics Cohran's Q and I2. The results of the different studies, with 95%CI, and the pooled proportions with 95%CI are shown in a forest plot. Bias was detected using a funnel plot. Publication bias results in asymmetry of the funnel plot. $P < 0.05$ was considered statistically significant.

RESULTS

Meta-analysis of clinical outcome in EL patients and comparative results

The sample of our study consisted of all our patients treated with EL for a total of eight hundred twenty-one patients (Table 2), corresponding to the 78.5% of all LAs. Post-operative complications in this group of interest were collected (Table 3) and reported according to the Clavien-Dindo classification [45,46] (Table 4). These data were then compared to those retrieved from the manuscripts finally considered in the analysis[9,19,26,29-31,47] (Table 5), in fact other four papers that were initially assessed and that were from the last 3 years[48-51], were not included, because of the lack of information and partial numbers and percentages of patients with wound infections, abdominal abscesses and total post-operative complications.

Table 2 Groups and categories of severity of Bologna patients

	EL (*n* = 821)	ES (*n* = 175)	*P* values
Age (yr)	35 (14-94) ± 18	36 (14-91) ± 17	0.50
Male:Female	425:396	111:64	< 0.05
BMI	23.85 (14-44) ± 4.4	24 (17-42) ± 4.5	0.68
CV comorbidities	7.6%	24%	< 0.05
Other comorbidities	13.9%	31.4%	< 0.05
Edematous AA	251	5	0.18
Phlegmonous AA	410	59	0.05
Gangrenous AA	160	111	0.05

EL: Endoloop; ES: Endostapler; BMI: Body mass index; CV: Cardiovascular; AA: Acute appendicitis.

Table 3 Post-operative complications in Bologna endoloop group

	EL (*n* = 821)
Wound infections	2 (0.3%)
Abdominal abscesses	12 (1.5%)
Post-op complications IIIa/IIIb Clavien-Dindo	17 (2%)
Total post-op complications	35 (4.3%)

EL: Endoloop.

Table 4 Post-operative complications in Bologna 996 laparoscopic appendectomy patients

Clavien-Dindo	Number of patients (% of total cohort)
I	3 (0.3)
II	24 (2.4)
IIIa	7 (0.7)
IIIb	16 (1.6)
IVa	0 (0)
IVb	0 (0)
V	0 (0)
Total	50 (5)

Examination of the seven papers involved in the meta-analysis[9,19,26,29-31,47] showed that only Beldi *et al*[26] were in favor of application of an ES for transection and closure of the appendiceal stump in patients with AA. In their report it lowered the risk of postoperative intra-abdominal surgical-site infection and the need for readmission to hospital. All the other 6 papers didn't find a statistically significant difference for intra or postsurgical complications, length of stay (LOS), wound infections, and abdominal abscesses among different groups of patients. Sahm *et al*[29] and Van Rossem *et al*[30] clearly stated that infectious complication rate is not influenced by the type of appendicular stump closure, either if performed by EL or ES, and routine stump closure using an EL is an easy, safe, and cost-effective procedure. Finally, it is important to mention the retrospective cohort study conducted by Swank *et al*[31] that compares the two strategies for closure of the appendiceal stump. The routine use of the ES showed no clinical advantages over the use of ELs.

Statistical data and results showed that our experience followed the trend of the evidence in literature in terms of wound infections (Figure 2 and Table 6), abdominal abscesses (Figure 3 and Table 7) and total post-operative complications (Figure 4 and Table 8). The meta-analysis proved a wide heterogeneity among analyzed groups, as the funnel plots and the forest plots confirmed. Tables 6-8 report

Table 5 Complete data to meta-analyse

Ref.	Number of patients (% of EL)	Wound infection	Abdominal abscesses	Post-op complications
Bologna experience	821 (78.5)	2 (0.3%)	12 (1.5%)	26 (3.2%)
Ortega *et al*[9], 1995	89	4 (4.5%)	4 (4.5%)	14 (15.7%)
Sadat-Safavi *et al*[19], 2016	38 (50)	1 (2.6%)	0 (0%)	0 (0%)
Beldi *et al*[26], 2006	2565 (39.5)	12 (0.5%)	41 (1.6%)	37 (1.4%)
Sahm *et al*[29], 2011	1670 (97.3)	34 (2%)	27 (1.6%)	48 (2.9%)
Van Rossem *et al*[30], 2017	1050 (76.7)	16 (1.5%)	48 (4.5%)	20 (1.9%)
Swank *et al*[31], 2014	465 (44.9)	7 (1.5%)	20 (4.3%)	14 (3.1%)
Klima *et al*[47], 1998	100	3 (3%)	4 (4%)	4 (4%)

EL: Endoloop.

Table 6 Wound infection: Data standard deviation in the meta-analysis

Ref.	Standard deviation	Proportion (%)	95%CI
Our experience	821	0.244	0.0295-0.877
Van Rossem *et al*[30], 2017	1050	1.524	0.873-2.463
Sadat-Safavi *et al*[19], 2016	38	2.632	0.0666-13.810
Swank *et al*[31], 2014	465	1.505	0.607-3.077
Sahm *et al*[29], 2011	1670	2.036	1.414-2.833
Beldi *et al*[26], 2006	2565	0.468	0.242-0.816
Klima *et al*[47], 1998	100	3.000	0.623-8.518
Ortega *et al*[9], 1995	89	4.494	1.238-11.109
Total (fixed effects)	6798	1.064	0.834-1.337
Total (random effects)	6798	1.496	0.759-2.475

CI: Confidence interval.

data related to the standard deviation of wound infection, abdominal abscesses, and post-operative complications, respectively. Figures 2A, 3A and 4A are Funnel Plots showing an asymmetrical distribution of the articles (*dot*) among both sides indicating that bias can be present. In Figures 2A and 4A, few papers are near the middle solid line, indicating the overall effect from the meta-analysis, possibly in relation to the limited size of the samples. Figures 2B, 3B and 4B Forrest Plots prove there is no statistically significant result in favor of ES or EL for the overall incidence of wound infections, abdominal abscess, or post-operative complications.

DISCUSSION

Appendectomy is one of the most performed emergency surgery procedures. The laparoscopic approach is recognized and recommended internationally, but a matter of debate during the operation is the choice of the different available devices to close the appendicular stump, in consideration of the possible consequent leak leading to infection and postoperative complications.

Already previously[38], we evidenced that the routine use of EL is safe in most patients affected by AA, including cases with signs of complications. Furthermore, it is a cost-effective device, even when possible additional costs secondary to the occurrence of adverse events in the post-operative course are included. Conversely, Lasek *et al*[48] assessed *via* a multicenter observational study the stump closure only in patients affected by complicated AA. Their results highlighted some clinical benefits of ES use, but EL was superior in terms of overall morbidity and LOS, with no statistically significant difference in major complication rates and postoperative intra-abdominal abscess formation.

Table 7 Abdominal abscess: Data standard deviation in the meta-analysis

Ref.	Standard deviation	Proportion (%)	95%CI
Our experience	821	1.462	0.757-2.539
Van Rossem *et al*[30], 2017	1050	4.571	3.390-6.016
Sadat-Safavi *et al*[19], 2016	38	0.000	0.000-9.251
Swank *et al*[31], 2014	465	4.301	2.647-6.565
Sahm *et al*[29], 2011	1670	1.617	1.068-2.344
Beldi *et al*[26], 2006	2565	1.598	1.149-2.162
Klima *et al*[47], 1998	100	4.000	1.100-9.926
Ortega *et al*[9], 1995	89	4.494	1.238-11.109
Total (fixed effects)	6798	2.206	1.870-2.583
Total (random effects)	6798	2.699	1.697-3.924

CI: Confidence interval.

Table 8 Post-operative complications: Data standard deviation in the meta-analysis

Ref.	Standard deviation	Proportion (%)	95%CI
Our experience	821	3.167	2.079-4.606
Van Rossem *et al*[30], 2017	1050	1.905	1.167-2.926
Sadat-Safavi *et al*[19], 2016	38	0.000	0.000-9.251
Swank *et al*[31], 2014	465	3.011	1.656-5.000
Sahm *et al*[29], 2011	1670	2.874	2.127-3.793
Beldi *et al*[26], 2006	2565	1.442	1.018-1.983
Klima *et al*[47], 1998	100	4.000	1.100-9.926
Ortega *et al*[9], 1995	89	15.730	8.875-24.982
Total (fixed effects)	6798	2.304	1.961-2.689
Total (random effects)	6798	3.089	1.979-4.437

CI: Confidence interval.

In literature, two papers systematically analyzed the techniques for appendiceal stump closure during LA[49,50]. Ceresoli *et al*[49] meta-analysed randomized trials and cohort studies comparing ES with endoscopic loop ties for the closure of the appendicular stump in LA, including pediatric patients and complicated AA, such as gangrenous/necrotic appendix or the perforated ones. In their analysis, ES was associated with a similar intra-abdominal abscess rate, but a lower incidence of wound infection, while LOS, readmission and reoperation rates were similar. In a subgroup analysis ES significantly reduced the wound infection rate in pediatric patients, while no difference in the main outcomes was observed in patients with complicated AA.

Makaram *et al*[50] performed a systematic review evaluating all methods of stump closure (ELs, polymeric endoclips, metallic endoclips, endosuture and ES). In this study[50], no difference in complication rate, LOS or cost was found. According to their analysis, endoclips provide the most time-efficient method of closure, although not statistically significant; closure by endosuture, represents the cheapest method, but it is hindered by a high complication rate. Current evidence suggests endosuture should then be avoided. ESs appear very safe and effective for stump closure, however they seem to be associated with high postoperative complication rates; furthermore, the consequent cost limits their use to the most severe cases of appendicitis, while instead EL provides a valuable alternative for closure, with a risk of intraoperative complications of 4.61%.

Another recent retrospective cohort study[51], whose subject was to determine the safety and efficiency of the use of EL and ES in complicated and uncomplicated AA, concluded that the systematic use of EL could reduce costs in uncomplicated appendicitis, while in complicated cases both options

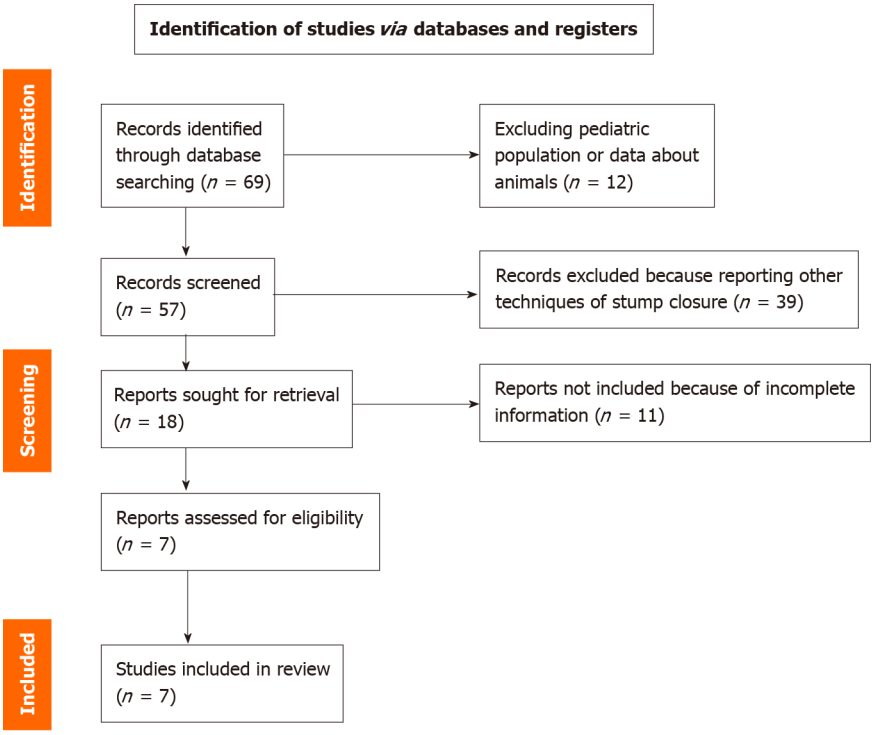

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Figure 1 PRISMA diagram.

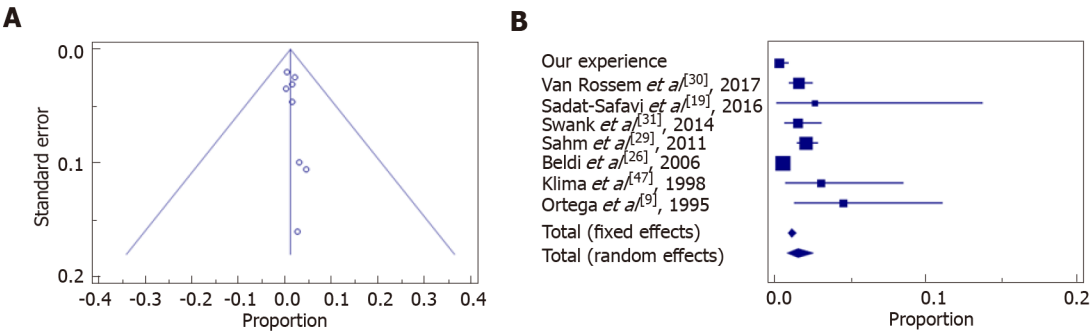

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Figure 2 Wound infection Funnel plot. A: Asymmetrical distribution among both sides indicates that bias can be present; B: The confidence interval (diamond) confirms there is no statistically significant result.

(loop and stapler) are valid. Also a prospective randomized clinical trial[52] and a retrospective study [53] recently analyzed the technical aspects of appendix stump closure: Ihnát *et al*[52] reported similar postoperative morbidity and safety following the use of EL, ES or hem-o-lok and even White *et al*[53] demonstrated non univocal superiority of one technique over the others, too.

Another point indeed to be considered is LA availability together with the fact that the different devices rely upon the resources of the hospital and the country where surgery is performed, pending possible spending reviews carried out by the government. It has been demonstrated that LA is performed more frequently in high-income countries in comparison to low-income countries (67.7% *vs* 8.1%), with better postoperative outcomes[54]. The difference in the costs of the used surgical devices (above all stapler) represented a principal determinant for the overall economic impact of the surgical procedure in some recent reports[33,36,38,50,51], to highlight how important is the cost-effectiveness in the measured outcomes. The medium saving reported in the present paper is relevant, varying from around approximately 300 € to more than 500 € just for the device, which then must be multiplied for the many LA conducted worldwide; further cost-analysis including operative time and LOS could reach major savings.

Our study presents some limitations: The design is a retrospective analysis to investigate the safety of ELs, then the results are pooled with other reports; the comparison between studies is difficult due to heterogenous patient selection and outcomes measured. However, EL seems to have the potential for

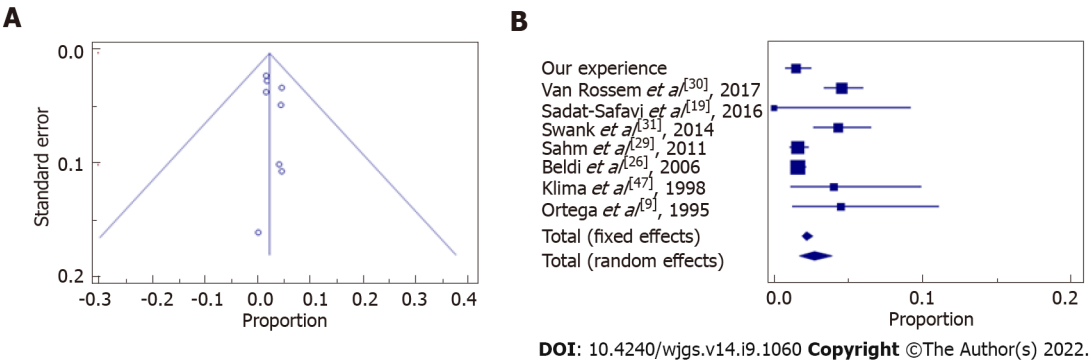

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Figure 3 Abdominal abscess Funnel plot. A: With asymmetrical distribution among both sides, indicating that bias can be present; B: The confidence interval (diamond) confirms there is no statistically significant result favoring endoloop or endostapler.

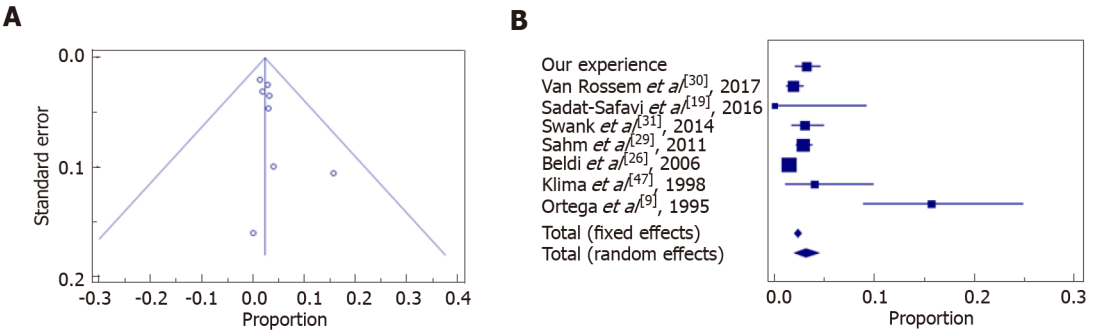

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Figure 4 Post-operative complications Funnel plot. A: Asymmetrical distribution among both sides indicates that bias can be present; B: The confidence interval (diamond) confirms there is not statistically significant difference between endoloop *vs* endostapler.

being a safe and cost-effective device.

CONCLUSION

In conclusion, there is no evidence clearly illustrating a superior surgical method for performing stump closure in LA. Given that comparison between studies is difficult due to heterogeneous patient selection and measured outcomes, our meta-analysis shows that the data of our sample, related to wound infections, post-operative abdominal abscesses, and total post-operative complications, mirror current literature trend. The routine use of EL is safe in most patients affected by AA, even when complicated, and these findings could have above all more relevance in lower resource environments that may not have easy access to ES. Prospective studies are needed to analyze a greater number of patients and taking into account an accurate grading system for AA severity such as Disease Severity Score[55], Alvarado Score[41], AIR Score[42] or imaging severity scoring, such as the CT-Determined Severity Score[56]. Their aim should be first to stratify preoperatively the grade of AA and secondly to observe differences in postoperative complications. Finally, studies aiming at an accurate cost analysis are required, ideally in the form of randomized controlled trials comparing EL to polymeric clips, as both techniques are safe and effective, with favorable outcomes[50,52].

ARTICLE HIGHLIGHTS

Research background

Laparoscopic appendectomy (LA) has shown advantages in terms of clinical results and cost-effectiveness, even if there is still controversy about which surgical device should be preferred to perform it.

Research motivation

To evaluate the safety cost-effectiveness of surgical devices in LA stump closure.

Research objectives
Incidence of wound infections, abdominal abscesses and total post-operative complications according to the Dindo-Clavien classification in LA stump closure with endoloop (EL) or endostapler.

Research methods
A meta-analysis was performed in terms of surgical complications, comparing the clinical data of the EL group (821 patients) to the international literature retrieved by Pubmed, according to the PRISMA principles.

Research results
There is no superiority of one or another technique in terms of surgical complications for LA stump closure.

Research conclusions
Routine use of EL is safe in most patients affected by acute appendectomy, even when complicated.

Research perspectives
Studies of EL performing accurate cost analysis are required, in addition to randomized controlled trials comparing this method to polymeric clips, as both techniques have been proved to have to be safe and effective with favorable outcomes.

FOOTNOTES

Author contributions: Zorzetti L and Bellini MI wrote and revised the article; Lauro A, Dalla Via B, Cervellera M, Tonini V, Sorrenti S, Cirocchi R and D'Andrea V designed the research study; Vaccari S, Zorzetti N, Lauro A, and Bellini MI performed the research; and all authors have read and approve the final manuscript.

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CASE REPORT

Retrorectal mucinous adenocarcinoma arising from a tailgut cyst: A case report and review of literature

Yan-Shuai Wang, Qing-Yun Guo, Fang-Hong Zheng, Zi-Wei Huang, Jia-Lang Yan, Fu-Xiang Fan, Tian Liu, Shun-Xian Ji, Xiao-Feng Zhao, Yi-Xiong Zheng

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Abstract

BACKGROUND

Tailgut cysts are defined as congenital cysts that develop in the rectosacral space from the residue of the primitive tail. As a congenital disease, caudal cysts are very rare, and their canceration is even rarer, which makes the disease prone to misdiagnosis and delayed treatment. We describe a case of caudal cyst with adenocarcinogenesis and summarize in detail the characteristics of cases with analytical value reported since 1990.

CASE SUMMARY

A 35-year-old woman found a mass in her lower abdomen 2 mo ago. She was asymptomatic at that time and was not treated because of the coronavirus disease 2019 pandemic. Two weeks ago, the patient developed abdominal distension and right waist discomfort and came to our hospital. Except for the high level of serum carcinoembryonic antigen, the medical history and laboratory tests were not remarkable. Magnetic resonance imaging showed a well-defined, slightly lobulated cystic-solid mass with a straight diameter of approximately 10 cm × 9 cm in the presacral space, slightly high signal intensity on T2-weighted imaging, and moderate signal intensity on T1-weighted imaging. The mass was completely removed by laparoscopic surgery. Histopathological examination showed that the lesion was an intestinal mucinous adenocarcinoma, and the multidisciplinary

team decided to implement postoperative chemotherapy. The patient recovered well, the tumor marker levels returned to normal, and tumor-free survival has been achieved thus far.

CONCLUSION
The case and literature summary can help clinicians and researchers develop appropriate examination and therapeutic methods for diagnosis and treatment of this rare disease.

Key Words: Tailgut cysts; Adenocarcinoma; Magnetic resonance imaging; Retrorectal disease; Preoperative biopsy; Case report

Core Tip: Tailgut cysts (TGCs) are rare congenital cysts of the retrorectal space. We report a case of TGC with adenocarcinogenesis and review the literature on caudal cyst adenocarcinogenesis. Magnetic resonance imaging is the most valuable tool for diagnosis and differential diagnosis, and preoperative biopsy is not worth advocating. Early MDT plays an important role in the accurate diagnosis and selection of the most appropriate personalized treatment. Complete resection of TGCs is the key to avoiding postoperative recurrence. We recommend MDT with complete surgical resection as the core and discuss the advantages and disadvantages of various diagnostic and treatment strategies.

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INTRODUCTION

Tailgut cysts (TGCs) are congenital cysts that develop in the retrorectal-presacral space from the remnants of the primitive embryonic hindgut[1,2]. These rare cysts are more common in women. Patients may present with lower abdominal pain and perianal lesions. Due to the risk of complications, such as recurrent perianal suppuration and malignant changes, surgical treatment is necessary. TGCs with malignant transformation are extremely rare[3]. The types of malignant transformation include adenocarcinoma, neuroendocrine tumor, and carcinoid. Most of these tumors are more inert than other epithelial malignant tumors; however, a small number of them are aggressive and resistant to treatment. Adenocarcinoma caused by TGCs is very rare, with only 28 cases with clinical details having been reported in the medical literature since 1990. In this paper, we report a new case and summarize the clinical and pathological features of adenocarcinoma from TGCs with a literature review. The reported cases were retrieved from the PubMed and *Reference Citation Analysis* (https://www.referencecitation-analysis.com/) database, and case summary information was carefully extracted from each article searched by PubMed (Table 1). To the best of our knowledge, a summary of adenocarcinogenesis of TGCs has not been reported before. Here, we focus on the regular characteristics of malignant transformation of TGCs to facilitate clinical diagnosis and treatment.

CASE PRESENTATION

Chief complaints

A 35-year-old Chinese woman complained of a lower abdominal mass for 2 mo and abdominal distension for 2 wk.

History of present illness

The patient accidentally found a mass in her lower abdomen in May 2020 with no related clinical symptoms. She delayed hospitalization for 2 mo due to the coronavirus disease 2019 pandemic. Two months later, due to abdominal distension and right waist discomfort, the patient went to the gynecology clinic to seek medical help. Since the onset of the disease, the patient has had no dysuria or menstrual changes.

Table 1 Summary of disease information on adenocarcinogenesis of tailgut cysts published from 1990-2021

Case	Ref.	Sex	Age	Clinical symptoms	Duration	Size (mm)	MRI/CT	Biopsy	Invasion	Position S4+/S3-	CEA/CA199	Surgery planning
1	Baverez *et al*[19], 2021	F	57	Perianal suppuration	5 yr	55	+/+	+	Anal canal and perianal skin	-	30/UN	Abdominoperineal resection
2	Wang *et al*[3], 2020	F	50	Irregular defecation	2 wk	90 × 80	+/+	-	-	-	79.89/57.60	Trans-sacrococcygeal approach
3	Rachel *et al*[20], 2019	F	73	Anal abscess and associated fistula	40 yr	56 × 46	+/+	+	Anal canal and perianal skin	-	UN	Trans-sacrococcygeal approach
4	Martins *et al*[4], 2020	F	54	Pelvic and perineal pain	1-2 mo	50 × 35	+/+	+	Sacrum	-	UN	Trans-sacrococcygeal approach
5	Li *et al*[21], 2019	M	33	-	-	80 × 59	+/-	-	-	-	26.97/106.50	Trans-sacrococcygeal approach
6	Şahin *et al*[22], 2020	F	55	Swelling of the buttocks	6 mo	21 × 16	+/-	-	-	-	-/204	Trans-sacrococcygeal approach
7	Almeida Costa and Rio [23], 2018	F	53	Defecation and lower abdominal pain	UN	UN	+/+	-	Sacrum	+	UN	Trans-sacrococcygeal approach
8	Zhao *et al*[11], 2015	F	44	Pelvic and perineal pain	6 mo	100	-/+	+	Rectum and surrounding	+	+/UN	Partial resection and drainage of the pelvic tumor
9	Chhabra *et al*[8], 2013	F	56	Hematuria	1 yr	46 × 37	-/+	+	-	-	-/UN	Trans-sacrococcygeal approach
10	Jarboui *et al*[24], 2008	F	49	Pelvic and perineal pain	6 mo	150	-/+	-	-	+	UN	Laparotomy
11	Tampi *et al*[2], 2007	F	57	Low backache	6 mo	120 × 100 × 80	-/+	-	Liver	+	-/-	Laparotomy
12	Andea and Klimstra[25], 2005	F	47	Gluteal pain	3 mo	40 × 40	UN/UN	-	-	UN	-/UN	UN
13	Cho *et al*[26], 2005	F	40	Perianal pain	1 mo	100 × 80 × 70	+/	+	Sacrum	-	159/2270	Abdominoperineal resection and partial sacrectomy
14	Kanthan *et al*[12], 2004	F	76	Perianal pain	UN	65 × 45 × 35	-/+	+	-	-	UN	Trans-sacrococcygeal approach
15	Moreira *et al*[13], 2001 (case-1)	F	64	Constipation and frequent urination	2 mo	120 × 100	+/UN	-	-	UN	UN	UN
16	Moreira *et al*[13], 2001 (case-2)	F	68	Rectal "fullness"	2 yr	180 × 40	+/+	-	-	UN	UN	UN
17	Schwarz *et al*[14], 2000	M	47	Bilateral flank pain, constipation	3 mo	160	-/+	-	-	-	46/-	Abdominoperineal resection and partial sacrectomy
18	Prasad *et al*[27], 2000	F	36	-	UN	95 × 92 × 88	+/+	UN	-	UN	UN	UN
19	Sauer *et al*[28], 2000	F	58	Recurrent perianal fistulas	17	55 × 40 × 35	+/+	-	-	+	6.7/42	Laparotomy
20	Graadt van Roggen *et al*	F	43	-	-	130	+/-	-	UN	+	+/UN	UN

	[7], 1999											
21	Maruyama *et al*[29], 1998	F	66	Perianal pain	6 mo	100 × 90	+/+	-	-		3.8/-	Trans-sacrococcygeal approach
22	Lim *et al*[10], 1998	F	40	Urinary frequency and constipation	8 mo	250 × 100 × 100	+/-	-	-	UN	-/-	Laparotomy
23	Yamaguchi *et al*[30], 2001	M	32	Anal fistula	4 yr	UN	+/+	-	Rectum	UN	UN	Pelvic evisceration
24	Liessi *et al*[31], 1995	M	50	UN	UN	UN	+/+	UN	Sacrum	UN	UN	Trans-sacrococcygeal approach

CT: Computed tomography; MRI: Magnetic resonance imaging; F: Female; M: Male; CEA: Carcinoembryonic antigen.

History of past illness

The patient's past medical history included a loop electrosurgical excision procedure for cervical erosion 10 years ago.

Personal and family history

No family history was identified.

Physical examination

Physical examination showed that the patient's abdomen was flat and soft, with no abnormal bulge, tenderness, or rebound pain. A cystic-solid mass of approximately 10 cm, which was painless and could not be pushed, was palpated slightly higher than the pubic bone. Gynecological bimanual examination showed no abnormalities of the vagina, cervix, or uterus.

Laboratory examinations

Laboratory studies were normal except for an elevation in serum carcinoembryonic antigen (CEA) to 132.69 ng/mL.

Imaging examinations

Gynecological B-mode ultrasonography examination showed that there was a cystic-solid mass close to the surface of the right ovary, mainly cystic, and the sound difference of the internal diaphragm was noisy. The appearance of thick and intense light spots followed by sound shadows, as well as a small blood flow signal in the solid part, allowed us to calculate a resistance index of 0.55. Computed tomography (CT) showed a cystic mass in the posterior rectal pelvis, extending to the level of the sacral promontory but not reaching the bony components of the sacrum or coccyx. The size of the mass was approximately 10 cm × 9 cm, and it showed polycystic changes with a septum and calcification. Contrast-enhanced CT indicated that the septum of the mass could be enhanced. Magnetic resonance imaging (MRI) showed a mass of abnormal signal on the right side of the pelvis measuring approximately 10 cm × 7 cm. Its borders were clear, with mixed high signal on T2-weighted imaging (T2WI) and localized lamellar low signal within. The right adnexal region was a cystic abnormal signal focus with a moderate signal on T1-weighted imaging (T1WI) and a slightly high signal on T2WI, with

nodular ring reinforcement on an enhanced scan. No enlarged lymph nodes or abnormal masses were seen in the pelvis. There was also no abnormal signal in the pelvic wall tissue (Figure 1).

FINAL DIAGNOSIS

Histopathology revealed that the lesion was an intestinal mucinous adenocarcinoma, and the malignant transformation of an embryonic residual enterogenous cyst was considered. The results of pathological sections showed fibrous tissue with a cystic lining; the lesion was rich in cellular mucus and infiltrating the columnar epithelium, and it also showed high-grade atypical cell hyperplasia and mitotic activity. Morphologically, this was consistent with mucinous adenocarcinoma, intestinal type. Immunopathology showed that cytokeratin 20 (CK) 20, CK7, CDX2, and STATB2 were positive (Figure 2). After joint consultation with the Department of Pathology of University of California, Los Angeles, we diagnosed the patient with a TGC with adenocarcinogenesis.

TREATMENT

After a multidisciplinary consultation and evaluation, laparoscopic surgery was performed under general anesthesia on July 14, 2020. During the operation, there was no obvious free fluid in the pelvis and no obvious abnormalities in the uterus, fallopian tubes, or ovaries.

An enlarged cyst, swollen and measuring approximately 10 cm × 9 cm, was found behind the peritoneum in front of the sacrum near the right iliac vessel. Hyperplastic vessels were visible on the smooth surface of the swelling, the ureter was observed to pass through the surface, and the iliac vessels were visible below it, with no adhesion to the surrounding tissues of S2-S4.

The operation was performed by an experienced general surgeon and a gynecologist. With the help of laparoscopy, we successfully removed the cyst completely. After the cyst was removed from the abdominal cavity, we opened the cyst and found that its inner wall was rough; moreover, we found multiple tissue calcifications. The intraoperative frozen pathological results showed a retroperitoneal benign cyst and cyst wall fibrosis and calcification. After flushing the abdominal cavity and retroperitoneal space with distilled water, no residual cysts or enlarged lymph nodes were found, and the peritoneum was closed by suture (Figure 3).

OUTCOME AND FOLLOW-UP

The patient received six cycles of capecitabine and oxaliplatin (CapeOX) chemotherapy, and there were no grade 3-4 side effects during this treatment. After treatment, her CEA level decreased progressively and ultimately fell within the normal range, and no metastatic focus was found on CT. The patient received therapy with high compliance, expressed satisfaction with her recovery, and has been tumor-free for more than 18 mo.

DISCUSSION

TGCs are considered to be congenital cysts that develop in the rectosacral space from the residue of the primitive tail[1,2]. This incomplete degeneration of the extension of the tail from the posterior intestine of the embryo usually occurs at the 8th week of the embryonic stage[4]. The rectosacral space is a potential space located in the deep part of the pelvis, with the posterior rectal fascia in the front and the presacral fascia (Waldeyer fascia) in the back; this space extends upward to the peritoneum and downward to the level of the rectosacral fascia and perineal muscle[5]. The boundaries on both sides are roughly outlined by the ureter, iliac vessels, and sacral nerve roots[6]. This area includes the confluence of the embryonic hindgut, pelvis, and neuroectoderm, and consequently, there are many different tissue types that can lead to retrorectal tumors. Retrorectal tumors can be divided into congenital, inflammatory, neurogenic, and osteogenic tumors. Cystic congenital lesions consist of epidermoid cysts, dermoid cysts, TGCs, enterogenous cysts, teratomas, and teratocarcinomas[7]. Such lesions affect people of all ages from birth to adulthood and are more common in women. Sometimes, patients may have space-occupying symptoms due to the enlargement of deep pelvic masses[1,3]. Clinical manifestations are usually nonspecific, with half of the patients experiencing pain, perianal lesions, changes in defecation habits, dysuria, and neurological symptoms of the lower extremities and perineum[8]. Among congenital cystic lesions, the incidence of TGCs is relatively high, but the incidence of canceration is very rare.

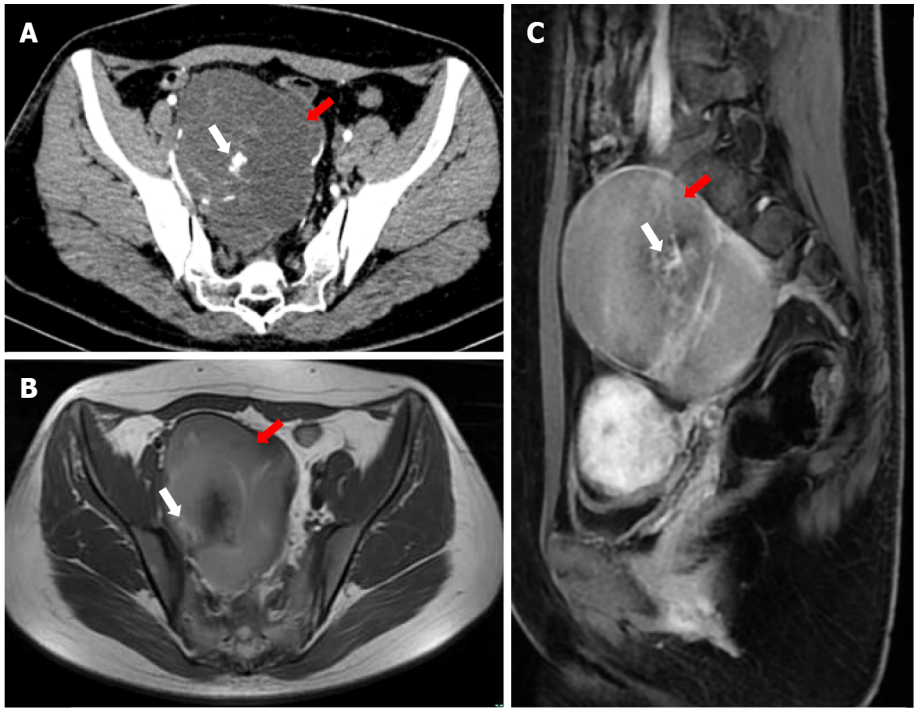

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Figure 1 Imaging examination. A: Computed tomography showed a low-density mass (red arrow) of approximately 10 cm × 9 cm in the pelvis, with cordlike separation and unclear boundaries with the posterior wall and lateral wall. Inhomogeneous enhancement and high-density areas (white arrow) were seen; B and C: Magnetic resonance imaging showed a mass (red arrow) of abnormal signal intensity on the right side of the pelvic cavity, whereas the boundary was still clear. T1-weighted imaging showed a slightly high signal intensity, T2-weighted imaging showed a mixed high signal intensity, and the septal changes in the enhanced scan showed obvious enhancement (white arrow).

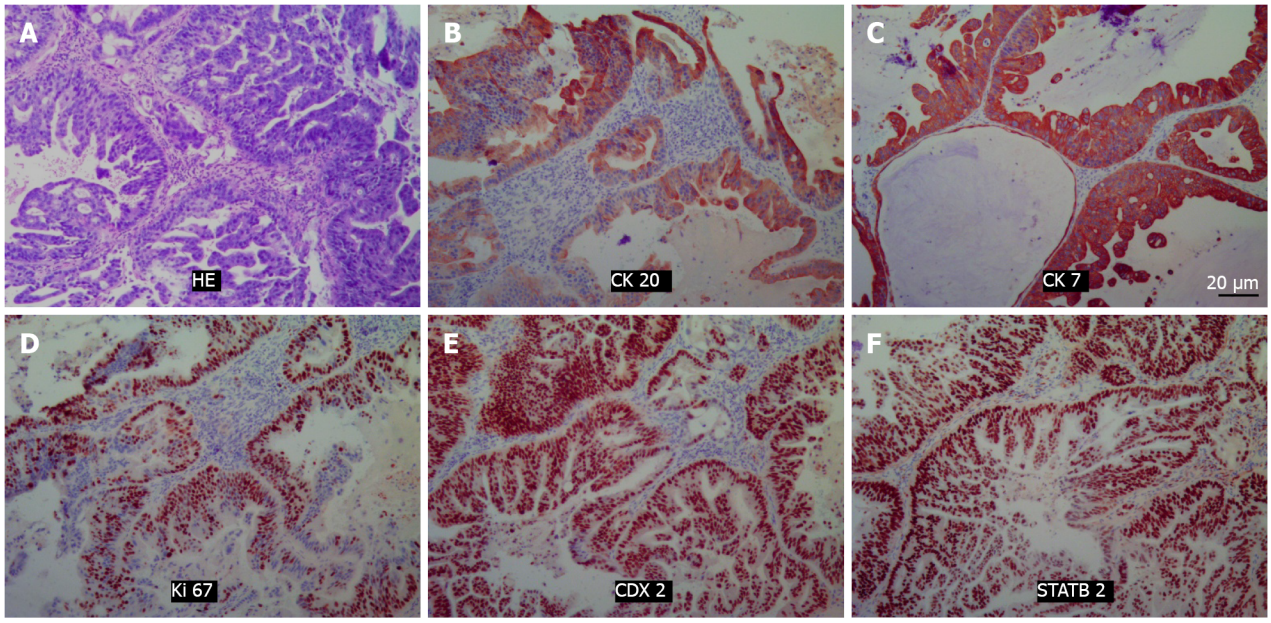

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Figure 2 Hematoxylin-eosin staining and immunohistochemical pictures. Positivity for cytokeratin 20, cytokeratin 7, Ki67, CDX2, and STATB2 was noted. A: Hematoxylin-eosin staining; B: CK20; C: CK7; D: Ki67; E: CDX2; F: STATB2. HE: Hematoxylin-eosin; CK20: Cytokeratin 20; CK7: Cytokeratin 7.

The malignant transformation of TGCs into reported tumors includes adenocarcinoma, carcinoid, neuroendocrine carcinoma, endometrioid carcinoma, adenosquamous carcinoma, squamous cell carcinoma, and sarcoma[2]. Most of them are endocrine tumors and adenocarcinomas, while others, such as carcinoids, are rare. At present, approximately 28 cases of TGC adenocarcinoma have been reported, of which 24 with relatively complete data were retrieved. We describe a new case of TGC with

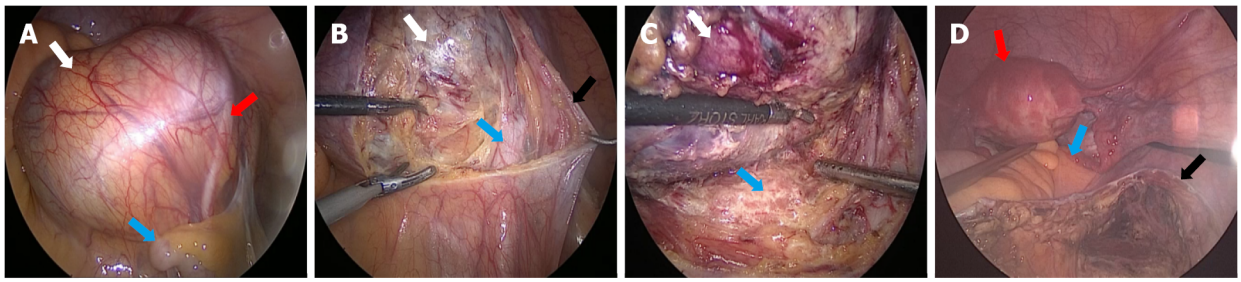

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Figure 3 Surgical pictures. A: Gross view of the mass (white arrow) under laparoscopy. The sigmoid colon (blue arrow) and ureter (red arrow) can be seen; B: Opening of the retroperitoneum (black arrow) and exposure of the mass (white arrow) and external iliac artery (blue arrow); C: Careful separation of the mass (white arrow) from the presacral tissue (blue arrow); D: The operative field after the tumor was removed, and the uterus (red arrow), rectum (blue arrow), and retroperitoneum (black arrow) can be seen.

mucinous cystadenocarcinoma and review the literature reports of TGCs with adenocarcinogenesis to provide a reference for diagnosis and treatment.

We summarize cases of TGC adenocarcinoma reported from 1990 to 2021, as the diagnostic and therapeutic approach is of limited interest due to the low prevalence and accuracy of diagnostic tools such as MRI and CT prior to 1990.

First, we sorted out the historical process of a complete understanding of TGCs. Cancerous TGC was first reported in 1932, and Ballantyne reported the first case of adenocarcinoma with TGCs. That patient developed local recurrence, lung metastasis, and inguinal lymph node metastasis and died 8 mo after cyst resection. Subsequently, doctors began to pay attention to and share the diagnosis and treatment of this rare disease. Through the review of articles related to TGCs, we found that there were two related landmark systematic retrospective studies. The first one was conducted in 1987 when Hjermstad and Helwig[1] evaluated all the pathological specimens of posterior rectal cysts diagnosed by the Institute of Pathology of the Armed Forces of the United States during a period of 35 years, and 53 cases of "tailgut cysts" were selected[1]. Their screening criteria were that the cysts must be partially covered by a columnar or transitional epithelium, but there must be no myenteric plexus or serosa, nor can there be a complete muscular layer. Hjermstad and Helwig's study defined the pathological criteria for the diagnosis of TGCs, allowing doctors to unify the definition of the disease[1]. The second was a retrospective analysis of the clinical and pathological data of patients who underwent colectomy at Mayo Clinic in 2008, conducted by Mathis *et al*[9]. A total of 31 patients were diagnosed, including 28 females, with an average age of 52 years. The median diameter of the cyst was 4.4 cm. There were four patients with malignant transformation, comprising three cases of adenocarcinoma and one case of carcinoid, and the 5-year survival rate was 83%. The work of Mathis *et al*[9] provides a single-center clinical experiential basis for the treatment and prognosis of TGCs. At present, with the progress of medical technology, the surgical methods and chemotherapy schemes have changed, but their principle of complete resection of the tumor remains unaddressed.

The summary of cases of TGCs with adenocarcinogenesis showed that most of the patients were middle-aged adults with a female–male ratio of 10:1, which was much higher than the ratio of 3-4:1 in previous articles on caudal cysts. The clinical manifestations of TGCs are varied and nonspecific. However, by summarizing the cases of caudal cysts with adenocarcinoma, we found that half of the patients complained of an abdominal mass and pain, perianal disease, and changes in stool habits and stool characteristics, while other patients did not have any symptoms. TGC is a rare congenital retrorectal disease in which the residue of the fetal retroanal intestine grows in the retrorectal space. It should be noted that this gap is a potential space, and the mass has considerable room for growth. This can explain the late onset of the disease, and TGC canceration occurs during this process. It is suggested that TGCs should be regarded as a precancerous lesion to explain this phenomenon. More than half of the patients were diagnosed with TGCs within 1 year after the onset of symptoms, and most of them exhibited retrorectal masses by imaging examinations such as CT and MRI. Compared with CT, MRI has the ability of multiplanar imaging and better tissue contrast in presacral masses[10]. MR has more advantages in differential diagnosis. Regarding the differential diagnosis of presacral masses, anal gland cysts, repeated cysts, teratomas, epidermoid cyst chordomas, abscesses, metastatic tumors, and neurofibromas should be considered. Fat content on fat-saturated images indicates dermoid cysts[1]. In presacral cystic masses, epidermoid cysts, dermoid cysts, rectal repeated cysts, and meningoceles are usually monocular. Rectal repetitive cysts, which are located in front of the rectum, often communicate with the rectal cavity. In contrast, TGCs are usually polycystic and can be characterized by large cysts with small peripheral cysts. This polycystic change is very important. Regarding the MRI features of TGCs, low signal intensity is usually shown on T1WI, and high signal intensity is shown on T2WI. However, the internal signal intensity of T1WI and T2WI indicates the protein concentration in the lesion, which increases with age, and the cysts show high signal intensity on T1WI. However, the

consistent feature is that most of the dominant cysts on T2-weighted sequences are hyperintense relative to the pelvic muscles. In addition, we are more concerned about the accuracy of MRI in predicting the nature of tumors. Cystic tumors with smooth, well-defined boundaries and no infiltrative or gadolinium enhancement are generally considered to be benign, whereas cysts with thickened and irregularly enhancing cyst wall boundaries, which may even be surrounded by inflammatory changes, are usually malignant.

MRI is the most valuable tool to meet the needs of diagnosis and differential diagnosis, to help improve preoperative assessments, to estimate the extent of the disease and malignant risk, and to determine the most appropriate treatment strategy. The effect of CT is not as accurate as that of MRI[3]. By pooling the literature, it was found that half of the cases had calcification and that the presence or absence of calcification was not of significant value in the diagnosis of benign or malignant lesions. Enhanced MRI and PET may be good examination methods for the diagnosis of malignant transformation and metastasis of TGCs, which is worth exploring in the future.

Preoperative biopsy of TGCs is considered unnecessary because it cannot confirm or even misconfirm the diagnosis of adenocarcinogenesis or tumor differentiation of TGCs[8]. Some authors believe that in the case of heterogeneous masses with elevated CEA, direct surgery should be performed without biopsy. However, in our statistical table, we can see that among three patients with benign lesions diagnosed by preoperative biopsy, one had a high CEA level (case 8)[11], one had a normal CEA level (case 9)[8], and one had an unknown CEA level (case 14)[12], but postoperative pathology confirmed adenocarcinoma. Therefore, biopsy can provide very limited help in diagnosing heterogeneous masses with normal CEA. Preoperative biopsies may pose major risks, such as malignant cell spillage or needle implantation. After such a biopsy, it is necessary to consider removing the tissue around the needle track during the operation, but in many cases, this is not easy to do. When we make the surgical plan, regardless of the biopsy results, we need to assume that this is a malignant lesion and adhere to the principle of complete resection. The accuracy of preoperative biopsy is in doubt, and this procedure may bring the risk of metastasis and increase the difficulty of operation. However, for patients who are unable or difficult to surgically remove the tumor, it is indeed a good method to determine the nature of the tumor through the pathological results of the biopsy and then perform surgical treatment after neoadjuvant chemotherapy.

Because cases of adenocarcinogenesis of TGCs are very rare, there are no guidelines to follow in the treatment of retrorectal tumors. In view of the strong positive expression of p53 and Ki-67 and the negative expression of p21 in the dysplastic epithelium of tailgut adenocarcinoma, it is speculated that the occurrence order of dysplasia and carcinoma is similar to that of colonic adenocarcinoma[13]. At present, the treatment mainly draws lessons from the clinical treatment guidelines for rectal adenocarcinoma, including European ESMO guidelines and American NCCN guidelines. It is suggested that multidisciplinary treatment should be adopted. Considering the postoperative pathological report and high CEA level, the present patient chose surgery and chemotherapy. The key to such operations is to remove the cyst wall completely. There are three common surgical approaches, namely, the anterior approach (abdomen), posterior approach (perineal approach), and combined abdominal perineal approach[4,14]. MRI will help to determine the margin of resection and identify the relationship between the tumor and the sacral level. For instance, if the tumor is below the middle of S3, the perineal approach can be considered[15]. All tumors extending above S4 usually require an abdominal or combined approach. For small lesions, the surgeon can also use a transvaginal approach. If malignant lesions are confirmed or suspected, the tumor tissue can be cleared more thoroughly *via* the combined abdominal perineal approach. Minimally invasive surgery has great advantages in the fine separation of anatomical hierarchy and reduction of complications[16,17]. In view of the leakage of the cancer and the large mass, it is recommended to use an endobag in the extraction of the specimen through a small incision in the abdominal wall. If there is no R0 resection or residual cyst wall and invasion of the tissue around the tumor leads to postoperative recurrence, comprehensive treatment schemes such as cytoreductive surgery, radiotherapy, chemotherapy, interventional therapy, and molecular targeted drug therapy are recommended. Considering that a small amount of leakage of TGC fluid during the operation might occur and that the postoperative pathology showed mucinous adenocarcinoma with high CEA, we chose to use CapeOX treatment to prevent recurrence. The reason for choosing CapeOX treatment is that it is feasible and widely used in malignant tumors of the digestive tract; the other reason is that the incidence of serious side effects of this regimen is low. In summary, complete resection of TGC masses during surgery is the key to avoiding postoperative recurrence and obtaining long-term survival for patients without metastasis[18].

CONCLUSION

Adenocarcinoma of TGCs is a very rare disease, and complete resection is still the gold standard. We do not recommend preoperative biopsies. Early MDT plays a significant role in the accurate diagnosis and selection of the most appropriate personalized treatment.

FOOTNOTES

Author contributions: Wang YS and Guo QY contributed to the conceptualization; Zheng FH, Huang ZW, and Yan JL contributed to the literature search and data analysis; Wang YS wrote the original draft; Fan FX, Liu T, and Ji SX reviewed and edited the manuscript; Zheng YX and Zhao XF supervised the manuscript.

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LETTER TO THE EDITOR

Successful treatment of acute symptomatic extensive portal venous system thrombosis by 7-day systemic thrombolysis

Fang-Bo Gao, Le Wang, Wen-Xiu Zhang, Xiao-Dong Shao, Xiao-Zhong Guo, Xing-Shun Qi

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Abstract

Acute portal venous system thrombosis (PVST) can cause acute mesenteric ischemia and even intestinal infarction, which are potentially fatal, and requires recanalization in a timely fashion. Herein, we report a 56-year-old man with acute non-cirrhotic symptomatic extensive PVST who achieved portal vein recanalization after systemic thrombolysis combined with anticoagulation. Initially, anticoagulation with enoxaparin sodium for 4 d was ineffective, and then systemic thrombolysis for 7 d was added. After that, his abdominal pain completely disappeared, and portal vein system vessels became gradually patent. Long-term anticoagulation therapy was maintained. In conclusion, 7-d systemic thrombolysis may be an effective and safe choice of treatment for acute symptomatic extensive PVST which does not respond to anticoagulation therapy.

Key Words: Portal vein; Mesenteric vein; Thrombosis; Thrombolysis; Anticoagulation; Deep vein thrombosis

Core Tip: The present case suggests that systemic thrombolysis should be safe and effective for acute extensive portal venous system thrombosis, if it is unresponsive to anticoagulation.

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TO THE EDITOR

Acute portal venous system thrombosis (PVST) is potentially life-threatening and can achieve a good response to agitation thrombolysis combined with catheter-directed thrombolysis[1]. However, it should be acknowledged that systemic thrombolysis, a more convenient treatment approach, has been rarely attempted for the treatment of acute PVST in clinical practice due to its potential bleeding risk. Herein, we report a case of acute symptomatic extensive PVST successfully treated by systemic thrombolysis combined with anticoagulation to strengthen our confidence in its clinical efficacy and safety.

A 56-year-old man with a history of hepatitis B virus infection was admitted to the Department of Gastroenterology due to aggravating severe epigastric pain for nearly half a month. He had no other obvious medical history. On physical examinations, his abdomen was soft without abdominal tenderness, rebound, or tension. On day 1 of admission, laboratory tests were performed (Table 1). Contrast-enhanced computed tomography (CT) showed no contrast agent filling within all vessels of the portal venous system, including the main portal vein (MPV), right portal vein (RPV), left portal vein (LPV), confluence of the superior mesenteric vein (SMV) and splenic vein (SV), SMV, and SV (Figure 1A), suggesting a diagnosis of occlusive PVST. Thus, subcutaneous injection of enoxaparin sodium was immediately initiated at a dose of 5000 IU (62.5 IU/kg) twice daily. On day 5, his abdominal pain was not relieved. Anti-Xa level was 0.05 IU/mL (reference range: 0-0.1 IU/mL). Contrast-enhanced CT showed no significant improvement of PVST (Figure 1B). Thus, systemic thrombolysis was recommended. After obtaining this patient and his relatives' informed consent, intravenous injection of urokinase at a dose of 300000 IU twice daily was added on subcutaneous injection of enoxaparin sodium at a dose of 5000 IU twice daily. On day 10, this patient's abdominal pain improved significantly. Contrast-enhanced CT showed that MPV, LPV, and RPV thromboses were partially recanalized (Figure 1C). On day 12, urokinase was discontinued. No bleeding event occurred during the period of systemic thrombolysis. On day 17, his abdominal pain completely disappeared. Then, he was discharged. Enoxaparin sodium was replaced with oral rivaroxaban 20 mg once daily. After 5-mo anticoagulation with rivaroxaban, contrast-enhanced CT showed that the SMV and SV became patent and fine collateral vessels developed around the RPV without signs of esophageal varices (Figure 1D). Laboratory tests were performed again (Table 1). At the time of writing this paper, rivaroxaban is still continued.

Anticoagulation is the preferred choice of treatment for acute PVST[2], but 18% of patients still develop transmural intestinal necrosis after anticoagulation therapy, and 25%-50% will develop prehepatic portal hypertension[3,4]. Patients with acute PVST who do not respond to anticoagulation therapy may benefit from thrombolytic therapy[5]. However, thrombolytic therapy has a higher risk of bleeding, including upper gastrointestinal bleeding, abdominal bleeding, and epistaxis. Notably, the current evidence on systemic thrombolytic therapy for PVST is scare. In a retrospective cohort study[6], 33 patients with acute PVST were treated with intravenous injection of 750000 IU/d streptokinase or 100-150 mg/6-12 h recombinant tissue-type plasminogen activator (rt-PA) for 2-3 d, followed with heparin infusion, and then received oral anticoagulants for 12 mo after discharge. Thrombosis recanalization was achieved in 23 patients. In a prospective cohort study[7], nine cirrhotic patients with recent PVST received continuous intravenous infusion of rt-PA at a dose of 0.25 mg/kg/d combined with subcutaneous injection of low molecular weight heparin for a maximum duration of 7 d. Thrombosis recanalization was achieved in eight patients. Besides, a stepwise thrombolysis regimen for PVST should be considered. In a study by Benmassaoud *et al*[8], 22 non-cirrhotic patients with acute PVST received systemic thrombolysis, of whom eight achieved portal vein recanalization, and the remaining 14 did not have any improvement of thrombosis or abdominal pain and were then treated with transjugular intrahepatic portosystemic shunt (TIPS) or local thrombolysis. Finally, the overall rate of portal vein recanalization was 86.4%. Notably, local thrombolysis and TIPS were employed in the study by Benmassaoud *et al*[8], but they are more invasive and technically complicated as compared to systemic thrombolysis. In our case, initial anticoagulation was less effective, and thus systemic thrombolysis was given. The symptoms improved significantly after thrombolysis, which avoided further vascular interventional procedures, and even surgery for intestinal infarction and necrosis[9].

Acute PVST is often defined if PVST develops 1-3 wk since the onset of symptoms. Accordingly, our case should be diagnosed with acute PVST. Notably, the timing of antithrombotic therapy for acute PVST is very important. A shorter interval from the diagnosis of PVST to initiation of antithrombotic therapy indicates a higher probability of thrombus recanalization[10]. In our case, the interval was

Table 1 Laboratory tests in this patient

Laboratory tests	Reference range	Before antithrombotic treatment	After 7-d thrombolysis	After 5-mo oral anticoagulants
White blood cell count (10^9/L)	3.5-9.5	9.70	5.20	6.7
Hemoglobin (g/L)	130-175	143	119	164
Platelet count (10^9/L)	125-350	230	242	123
Total bilirubin (μmol/L)	5.1-22.2	16.70	8.1	13.9
Aspartate aminotransferase (U/L)	15-40	17.60	16.29	18.65
Alanine aminotransferase (U/L)	9-50	20.39	20	21.99
International normalized ratio	0.9-1.2	1.19	1.15	0.99
Prothrombin time (s)	11.0-13.7	14.80	14.4	13.1
Activated partial thromboplastin time (s)	31.5-43.5	32.30	38.9	34.6
D-dimer (mg/L)	0-0.55	7.71	4.77	0.27
Antithrombin III (%)	80-120	48	-	55
Fibrinogen (g/L)	2.0-4.0	3.09	4.87	3.09
Protein C (%)	70-140	-	-	89.3
Protein S (%)	75-130	-	-	90.4

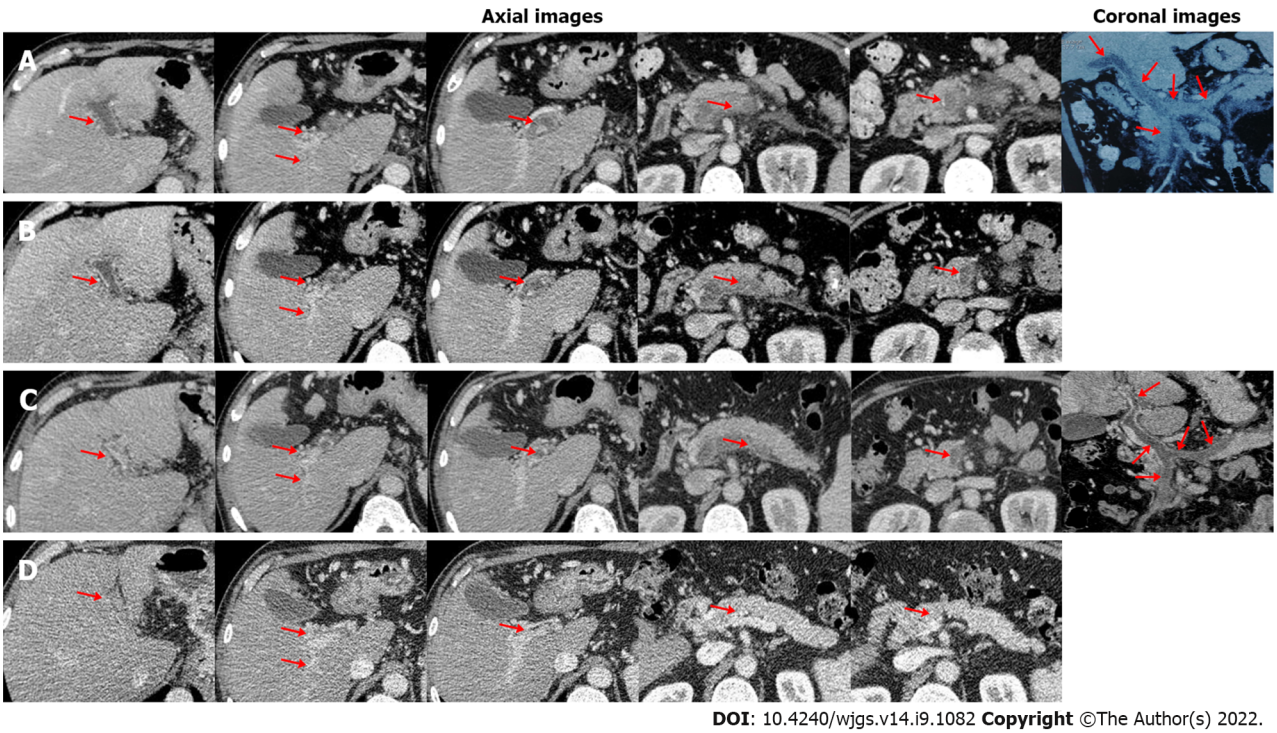

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Figure 1 Axial and coronal computed tomography images in this patient. A: On day 1 of admission, computed tomography (CT) images demonstrated occlusive thrombosis within the main portal vein (MPV), left portal vein (LPV), right portal vein (RPV), confluence of the superior mesenteric vein (SMV) and splenic vein (SV), SMV, and SV, with fine collaterals around the hilum (red arrow); B: On day 5, CT images demonstrated partially recanalized LPV and RPV (red arrow); C: On day 10, CT images demonstrated partially recanalized MPV, LPV, and RPV (red arrow); D: After 5-mo anticoagulation with rivaroxaban, CT images demonstrated completely recanalized SMV and SV (red arrow).

relatively long, which potentially compromised the efficacy of anticoagulation and forced the use of systemic thrombolysis.

In conclusion, systemic thrombolysis should be considered in the cases where anticoagulant therapy fails and interventional therapy is neither available nor feasible. The timing of systemic thrombolytic

therapy and the dose of thrombolytic drugs should be further explored.

FOOTNOTES

Author contributions: Qi XS conceived this manuscript; Zhang WX, Guo XZ, and Qi XS treated this case; Gao FB, Wang L, and Qi XS followed this case; Gao FB and Qi XS drafted the manuscript; Gao FB, Wang L, Zhang WX, Shao XD, Guo XZ, and Qi XS revised the manuscript; all authors have made an intellectual contribution to the manuscript and approved the submission.

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LETTER TO THE EDITOR

Prediction factors for ischemia of closed-loop small intestinal obstruction

Efstathios Theodoros Pavlidis, Theodoros Efstathios Pavlidis

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Abstract

A closed-loop type of intestinal obstruction leads to ischemic necrosis. There have been indicators that may predict ischemia and its severity, such as biomarkers and computed tomography scans. In addition to the usual inflammation markers, such as white blood count-neutrophil count and c-reactive protein (CRP), the most accurate predictors that have been proposed are the CRP-to-albumin ratio, the neutrophil/lymphocyte ratio and the platelet/lymphocyte ratio. Endothelin 1 is another promising biomarker of ischemia that must be assessed in daily clinical practice. Advanced age and frailty status were assessed as predictors of mortality. A timely operative procedure without any delay ensures a better outcome.

Key Words: Acute abdomen; Obstructive ileus; Bowel ischemia; Closed loop; Predictive factors; Inflammatory markers

Core Tip: Early recognition of closed loops is important to interrupt ongoing ischemia by prompt surgical intervention, especially for older age patients. In such a case, we achieve avoidance of bowel necrosis and enterectomy as well as septic complications, which ultimately resulted in an improved outcome. Endothelin 1, c-reactive protein and leukocyte-neutrophil count must be more often used in daily practice as a severity marker of small bowel ischemia.

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TO THE EDITOR

It was very interesting to read the recent paper by Toneman *et al*[1]. We were pleased and enlightened by their excellent work. This retrospective trial included 148 patients who underwent surgery for suspected closed-loop small bowel obstruction; the sample size was adequate. After assessing several parameters, the authors concluded that older age and an American Society of Anesthesiologists score ≥ 3 were prediction factors of irreversible ischemia. We completely agree with their conclusions because their conclusions are reasonable in that both conditions are associated with an increased risk of reduced tissue blood supply. Thus, the manifestation and progression of intestinal ischemia is faster. Early surgical operation prevents necrosis that leads to bowel perforation causing severe peritonitis and subsequent severe sepsis. The topic is very interesting, and it prompts certain thoughts and observations.

Intestinal obstruction is a common clinical occurrence in the acute surgical setting, with an incidence ranging from 12% to 16%, and is a causative factor for morbidity and mortality worldwide (2%-8%). The most common causes of obstructive ileus of the small intestine are adhesions (60%-70%) and hernia incarceration (20%). The obstruction may be complete, partial, incarcerated or closed-loop type. Questions, such as whether there is an obstruction, where is it located, what is the cause, whether there is ischemia and which are the management choices? In addition to patient history, clinical examination, laboratory tests and plain abdominal radiogram, computed tomography (CT) is the gold standard, with a sensitivity and specificity up to 95%. CT findings include intestinal wall thickening (> 3 mm) and abnormal enhancement, edema of the mesentery, fluid in the mesentery and/or peritoneal cavity, dilatation of veins, a closed-loop obstruction or volvulus, and in advanced cases, intraperitoneal gas, mesenteric or even portal venous gas[2].

The term closed loop means obstruction of two parts of the intestinal loop at the same point, including the mesentery. The mucosa continues to produce secretions, causing distention and wall edema, followed by blood supply disturbances and ischemia. It is crucial to assess bowel viability during the operation. A pink, edematous and thickened bowel is at low risk for ischemia. Violaceous or cyanotic serosa should be kept warm and observed for 15 to 20 min. If perfusion is not improved and viability remains questionable, Doppler ultrasound or a fluorescein dye should be used to evaluate the blood supply[3].

There has been no preoperative finding of an ideal biomarker for predicting the outcome. C-reactive protein (CRP) is a useful biomarker that may predict the clinical course[4,5]. Levels higher than 50 mg/L indicate moderate inflammation and levels above 150 mg/L indicate potential necrosis. Nevertheless, clinicians should obtain CT scans of obstructive ileus; in such cases, imaging should be performed immediately without delay. However, the ratio of CRP to albumin (CRP/Alb) is the most accurate indicator for predicting the severity of inflammation and the outcome, as recently reported. Values of CRP/Alb > 1.32 have a sensitivity of 94% and specificity of 70% for intestinal ischemia[6]. Other markers, including L-lactate, D-dimers, white blood count, neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR), have no particular prognostic value[4,5,7]. Otherwise, in another study, NLR > 4.5 and PLR > 157 were independent predictors of outcome[8]. The univariate analysis showed that leukocyte and neutrophil counts were predictors of mortality, and the multivariate analysis showed that age was a predictor of mortality[7].

Endothelin 1 (ET-1) is a vasoconstrictive peptide derived from vessel endothelium that has been used as a biomarker of ischemic damage severity in experimental models[9-11] but also occasionally in clinical studies, in which it is increased in mesenteric ischemia[12,13]. ET-1 and CRP must be more often assessed in daily practice as markers of small bowel ischemia.

Other experimental biomarkers of ischemia include tumor necrosis factor-alpha, P-selectin, antithrombin III, and intracellular adhesion molecule-1[9]. Research is focused on these biomarkers and may indicate a future perspective. Treatment to avoid both an unnecessary operation and a missed diagnosis of bowel ischemia must be carefully decided. A prediction model has been introduced for the latter, indicating surgical management instead of conservative management. Surgical management is indicated for CT findings, including intraperitoneal free fluid, mesenteric edema and lack of small bowel feces signs, and a history of vomiting[14]. In conclusion, a closed-loop small intestinal obstruction must be excluded in the initial stage of an investigation. Acute phase proteins and cooperation between surgeons and radiologists is important, since a prompt operation ensures a better outcome.

FOOTNOTES

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