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Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Raja Kalayarasan, MS, DNB, MCh, FRCS (Ed), Additional Professor & Head, Department of Surgical Gastroenterology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry 605006, India. kalayarasanraja@yahoo.com

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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

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MINIREVIEWS

Impact of tumour rupture risk on the oncological rationale for the surgical treatment choice of gastrointestinal stromal tumours

Nadia Peparini

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Nadia Peparini, Azienda Sanitaria Locale Roma 6, Ciampino, Rome 00043, Italy

Corresponding author: Nadia Peparini, MD, PhD, Azienda Sanitaria Locale Roma 6, Distretto 3, Via Mario Calò 5, Ciampino, Rome 00043, Italy. nadiapeparini@yahoo.it

Abstract

Tumour rupture of gastrointestinal stromal tumours (GISTs) has been considered to be a remarkable risk factor because of its unfavourable impact on the oncological outcome. Although tumour rupture has not yet been included in the current tumor-node-metastasis classification of GISTs as a prognostic factor, it may change the natural history of a low-risk GIST to a high-risk GIST. Originally, tumour rupture was defined as the spillage or fracture of a tumour into a body cavity, but recently, new definitions have been proposed. These definitions distinguished from the prognostic point of view between the major defects of tumour integrity, which are considered tumour rupture, and the minor defects of tumour integrity, which are not considered tumour rupture. Moreover, it has been demonstrated that the risk of disease recurrence in R1 patients is largely modulated by the presence of tumour rupture. Therefore, after excluding tumour rupture, R1 may not be an unfavourable prognostic factor for GISTs. Additionally, after the standard adjuvant treatment of imatinib for GIST with rupture, a high recurrence rate persists. This review highlights the prognostic value of tumour rupture in GISTs and emphasizes the need to carefully take into account and minimize the risk of tumour rupture when choosing surgical strategies for GISTs.

Key Words: Gastrointestinal stromal tumours; Tumour rupture; Residual tumour; Resection margin; Prognostic factors; Surgical treatment

Core Tip: Tumour rupture is a remarkable risk factor that can change the natural history of low-risk gastrointestinal stromal tumours (GISTs) to a high-risk GIST. This review analyses the concept and prognostic value of tumour rupture in GISTs and highlights the impact of the risk of tumour rupture on the choice of surgical strategy.

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INTRODUCTION

Tumour rupture in gastrointestinal stromal tumours (GISTs) has not been consistently defined in published studies. Although many studies have found an increased risk of recurrence and lower survival rates in patients with tumour rupture, other studies have not found any unfavourable prognostic effect. This is likely due to differences in tumour rupture definitions[1]. Tumour rupture has been considered to be a remarkable (often surgery-related) risk factor that can change the natural history of a low-risk GIST to a high-risk GIST, heavily impacting the long-term outcome[2-5]. However, in addition to tumour rupture, different factors may also impact GIST prognosis. Synchronous GISTs and another primary tumour can significantly increase in the possibility for recurrent disease, resulting in a worse prognosis and a more aggressive course than a single GIST[6].

This review analyses the concept of tumour rupture and its prognostic value in GISTs and highlights the impact of the risk of tumour rupture during surgical treatment for these tumours. Additionally, it emphasize the need to carefully take into account and minimize the risk of tumour rupture when choosing surgical strategies for GISTs.

THE CONCEPT OF TUMOUR RUPTURE IN GISTS

Originally, tumour rupture was defined as the spillage or fracture of a tumour into a body cavity, but recently, new definitions have been proposed. According to these new definitions, the constant factor of all major defects of tumour integrity that qualify for tumour rupture (*i.e.*, tumour fracture and/or tumour spillage in the abdominal cavity, blood-stained ascites, gastrointestinal perforation at the tumour site, microscopic transperitoneal adjacent organ infiltration, piecemeal resection or intralesional dissection, and incisional biopsy)[7,8] is substantial peritoneal exposure to tumour cells. This should be considered a remarkable risk factor because of potential peritoneal contamination. In contrast, minor defects of tumour integrity (such as those caused by core needle biopsy, microscopic peritoneal tumour penetration, iatrogenic superficial tumour capsule laceration or microscopically positive margins) are not considered tumour rupture [7-9].

THE IMPACT OF TUMOUR RUPTURE ON THE PROGNOSIS OF RESECTED GISTS

The impact of R1 resection on the oncological outcome of resectable gastrointestinal stromal tumours is debated. A systematic review and meta-analysis indicated that a microscopically positive margin could significantly impact disease-free survival but had no influence on overall survival. Moreover, adjuvant imatinib treatment could reduce the risk of recurrence for R1 resected primary GISTs[10].

Rutkowski *et al*[11] noted that GIST is a tumour growing under the mucosa and may be often ulcerated. Consequently, the mucosal margin from the gastrointestinal lumen is not clinically meaningful. The authors indicated that the margins of clinical importance that are relevant to assess R status (*i.e.*, R0, R1 or R2) are the peritoneal cavity side, which disruption entails tumour rupture, lateral margins or proximal and distal resection margins of the stomach/intestine wall, whose excision should be verified[11].

However, regarding the residual tumour classification of GISTs, it should be considered that not all tumour ruptures are classified as R1 or R2 resection. Nishida highlighted that peritoneum involvement is unrelated to R status; thus, a GIST disrupted in terms of peritoneal penetration otherwise resected with negative margins is still considered an R0 resection[8]

In their systematic review and meta-analysis, Kong *et al*[12] analysed the impact of R1 resection on the survival outcome of resectable GISTs with and without tumour rupture. They found that when tumour rupture cases were included, R1 resection resulted in a significantly shorter recurrence-free survival or disease-free survival than R0 resection, but the differences in recurrence-free survival and disease-free survival between R0 and R1 resection vanished when tumour rupture cases were excluded[12]. The results of most recent studies suggest that R1 resection does not influence the oncological outcome of resectable GIST compared with R0 resection; consequently, reresection may not be necessary when a positive microscopic margin exists. Moreover, R1 resection would not be considered an indication for adjuvant imatinib treatment in the absence of other high-risk factors as well as tumour rupture[12-17]. However, tumour rupture is significantly associated with the occurrence of R1 resection[12]. Mc Carter and colleagues noted that the significant risk factors associated with a positive microscopic resection margin are tumour size ≥ 10 cm, location and intraperitoneal rupture, and found that the risk of disease recurrence in R1 patients was driven largely by the presence of tumour rupture[18].

TUMOR-NODE-METASTASIS CLASSIFICATION OF GISTS

In the tumor-node-metastasis (TNM) classification of GISTs T (tumour) staging is dependent on the size of the tumour (T1: ≤ 2 cm; T2: > 2 cm and ≤ 5 cm; T3: > 5 and ≤ 10 cm; T4: >10 cm) and not on the depth of local invasion. TNM staging is dependent on the site (gastric and omental GISTs have a better prognosis than small bowel GISTs or other less common intestinal GISTs), size (T), regional lymph node (N) status and mitotic rate (low mitotic rate: 5 or fewer per 50 high power fields; high mitotic rate: over 5 per 50 high power fields).

In contrast to the TNM classification of gastrointestinal carcinomas, in the TNM classification of GISTs: (1) Involvement of the peritoneum is not prognostically graded as an unfavourable T (tumour) factor, *i.e.*, T4a; and (2) after excluding tumour rupture, R1 may not be an unfavourable prognostic factor for GISTs. Moreover, tumour rupture, which may be the true unfavourable prognostic factor instead of R1, has not yet been included in the current TNM Classification of GISTs[19]. From a prognostic point of view macroscopic injuries to the pseudocapsule (which are considered tumour rupture) should be distinguished from microscopic breaks of the pseudocapsule on pathological examination (that are not considered to be tumour rupture)[20]. However, the choice of surgical strategy should consider the unfavourable impact of an eventual tumour rupture on prognosis and the risk of tumour rupture when performing a dissection on the tumour surface (pseudocapsule), *i.e.*, without clearance distance[21].

OPTIONS IN THE SURGICAL TREATMENT OF GISTS

Everett and colleagues emphasised that tumour enucleation is considered insufficient because it may leave behind a tumour-seeded pseudocapsule. Moreover, enucleation is associated with tumour rupture[22] and should not be performed even if it is useful to preserve a vital structure. Interruption of the pseudocapsule or incidental peritumoral disruption can change a curable disease to a poor prognostic tumour. Accurate handling is very important to avoid tumour rupture because GISTs are soft and fragile. This can be a problem in laparoscopic and endoscopic treatment of GIST because of the instrumental manipulation of the tumours. Small low-grade GISTs are often treated by endoscopic resection. However, Song and colleagues argued that in the case of smaller tumours (median tumour size of all patients in their study was 1.5 cm; range 0.3-5 cm), the predictive value of tumour rupture and mitotic index diminished, and the risk of peritoneal metastasis may not be increased, even in tumours ruptured during endoscopic resection[23]. Due to the risks of tumour rupture, tumour remnants, perforation and bleeding, endoscopic resection is not currently recommended as a routine treatment for GISTs of the upper or lower gastrointestinal tract. However, it might be comparable to surgical resection for selected smaller tumours (< 3 cm in size). Surgical resection is still considered the standard treatment for tumours ≥ 2 cm or if the tumour has a high mitotic index or mucosal ulceration[24]. However, a high mitotic index is mostly unknown before resection.

According to the most recent guidelines, the standard treatment for localized GISTs is complete surgical excision of the lesion, with no dissection of clinically negative lymph nodes. The goal is R0 excision, *i.e.*, an excision whose margins are clear of tumour cells at least at the site of origin in the GI tract. In low-risk GISTs located in unfavourable locations, R1 margins can be acceptable, given the lack of evidence that R1 surgery is associated with a worse overall survival.

A laparoscopic/robotic approach is clearly discouraged in patients who have large tumours because of the risk of tumour rupture, which is associated with a very high risk of relapse. For selected patients with small tumours in the upper or lower GI tract, endoscopic excision is an acceptable treatment strategy[25]. Three years of adjuvant imatinib is the standard treatment for resected ruptured GISTs, although the recurrence rate is prominently high[26], and five years of adjuvant imatinib treatment in patients with ruptured GISTs seems to be promising[27,28].

CONCLUSION

In the choice of a surgical strategy for GISTs, key points should be considered. First, R1 resection cannot be a standard treatment for GISTs, and second, the risk of tumour rupture should be carefully evaluated and avoided. According to these key points: (1) Enucleation cannot be considered a standard treatment for GISTs localized in favourable resection sites; (2) laparoscopic/robotic excisions cannot be the standard treatments for large GISTs; and (3) endoscopic treatment cannot be considered a routine procedure for smaller GISTs (Figure 1).

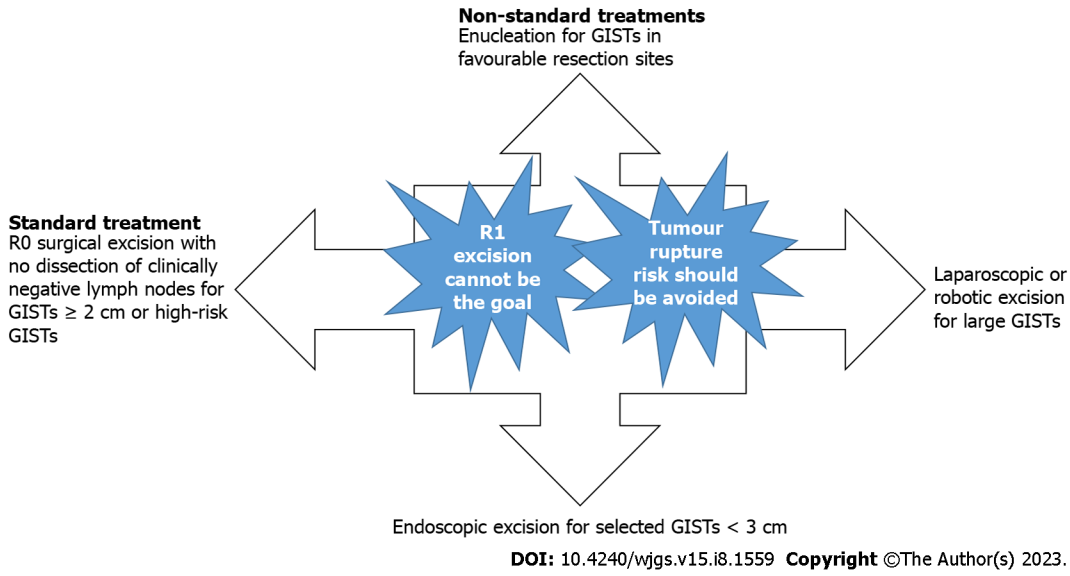

Figure 1 Surgical strategies for gastrointestinal stromal tumours according to key points. GISTs: Gastrointestinal stromal tumours.

FOOTNOTES

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ORCID number: Nadia Peparini 0000-0002-4455-3489.

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Prevention and treatment of hepatic encephalopathy during the perioperative period of transjugular intrahepatic portosystemic shunt

Lan-Jing Wang, Xin Yao, Qi Qi, Jian-Ping Qin

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Lan-Jing Wang, Xin Yao, Qi Qi, Jian-Ping Qin, Department of Gastroenterology, The General Hospital of Western Theater Command, Chengdu 610083, Sichuan Province, China

Corresponding author: Jian-Ping Qin, MD, Chief Physician, Department of Gastroenterology, The General Hospital of Western Theater Command, No. 270 Rongdu Road, Chengdu 610083, Sichuan Province, China. jpqqing@163.com

Abstract

Transjugular intrahepatic portosystemic shunt (TIPS) is an established procedure for treating the complications of portal hypertension in liver cirrhosis. While the pathogenesis of postoperative TIPS-related hepatic encephalopathy (HE) has yet to be fully understood, intraoperative portosystemic shunts may provide a pathological basis for the occurrence of postope-rative HE in patients with liver cirrhosis. Studies at home and abroad have expressed mixed opinions about TIPS-related HE. This study presents a literature review on the risk factors for and prevention and treatment of perioperative TIPS-related HE in patients with liver cirrhosis, aiming to optimize the procedure and reduce the incidence of postope-rative HE.

Key Words: Portosystemic shunt; Transjugular intrahepatic; Hepatic encephalopathy; Liver cirrhosis; Hypertension; Portal; Therapeutics

Core tip: Transjugular intrahepatic portosystemic shunt (TIPS) is a minimally invasive interventional procedure used to treat the complications of portal hypertension in patients with liver cirrhosis of different origins. As the exact pathogenesis of postoperative TIPS-related hepatic encephalopathy (HE) remains unclear, domestic and foreign studies have expressed mixed opinions about TIPS-related HE. This study provides a literature review on the risk factors for and the prevention and treatment of perioperative TIPS-related HE.

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INTRODUCTION

Transjugular intrahepatic portosystemic shunt (TIPS) is a minimally invasive interventional procedure for treating the complications of portal hypertension in liver cirrhosis of various origins. By creating a shunt between the hepatic and portal veins, TIPS is widely used in clinical settings to alleviate variceal bleeding, refractory pleural effusion and ascites, and other complications associated with portal hypertension[1-3]. Hepatic encephalopathy (HE), one of the most common postoperative TIPS-related complications[4], often occurs within the first 1–3 mo after the procedure[5]. With an incidence rate of 25%–50%[6-9], HE has a profound impact on the prognosis and quality of life of patients with liver cirrhosis[10]. According to the "2021 North American Practice-Based Recommendations for Trans-jugular Intrahepatic Portosystemic Shunts in Portal Hypertension"[3], intraoperative embolization of spontaneous portosystemic shunts and the narrowing of the stent diameter may reduce the risk of postoperative TIPS-related HE. The 2019 Clinical Practice Guidelines: Management of TIPS for Portal Hypertension by the Chinese College of Interventionalists (CCI)[11] recommend using stents particularly designed for TIPS to create a shunt from the left branch of the portal vein to reduce the risk of postoperative TIPS-related HE. "The 2023 French Recommendations for the Diagnosis and Management of Hepatic Encephalopathy"[12] viewed that the postoperative use of rifaximin can prevent postoperative TIPS-related HE. Although these recommendations have reached some levels of consensus, some have been debated. This study reviewed the risk factors for and the prevention and treatment of perioperative TIPS-related HE, thereby providing a reference to optimize TIPS and minimize the risk of postoperative HE.

DEFINITION AND CLASSIFICATION OF TIPS-RELATED HE

TIPS-related HE refers to a spectrum of central nervous system dysfunctions caused by metabolic disorders following the creation of a shunt between the portal vein and systemic circulation during TIPS after excluding other known brain diseases[13]. The 11th World Congress of Gastroenterology[14] classified HE into three types (A, B and C) based on etiological factors, with type C being the most common form of HE occurring in patients with chronic liver disease or cirrhosis and a portosystemic shunt. The Practice Parameters Committee of the American College of Gastroenterology[15] further graded HE into 0–4 according to the severity of symptoms based on the widely accepted West Haven Criteria. Seeing the difficulty in distinguishing between grades 0 and 1 in the West Haven Criteria, the International Society for HE and Nitrogen Metabolism[16] introduced an alternative grading system, called the spectrum of neurocognitive impairment in cirrhosis, to differentiate covert HE (CHE) from overt HE (OHE) based on the diagnosis of orientation disorders and asterixis. CHE is defined as a neuropsychiatric disorder without orientation disorders or asterixis in patients with liver cirrhosis. The pathogenesis of postoperative TIPS-related HE is not fully understood. Most patients undergoing TIPS due to portal hypertension have varying degrees of liver dysfunction. This undermines the liver's ability to detoxify ammonia produced by the intestines. Toxins enter the central nervous system through the blood–brain barrier, interfering with brain energy metabolism and eventually causing HE. Natural and artificial shunts play an important role in HE development as they allow toxins in the visceral blood to bypass the liver and enter systemic circulation. Moreover, these shunts can reduce liver perfusion and further exacerbate liver dysfunction. Studies[17-19] have revealed the close associations between the diameter of an intraoperative portosystemic shunt and HE incidence. This may explain the occurrence of postoperative HE in patients with portal hypertension[13]. Nevertheless, HE has other contributory causes, such as liver cell dysfunction, natural collateral circulation, increased production of intestinal neurotoxins, and increased blood–brain barrier permeability[20].

RISK FACTORS FOR POSTOPERATIVE TIPS-RELATED HE

Numerous risk factors are closely associated with the development of HE, which should be carefully considered to optimize preoperative patient selection. A meta-analysis[21] has shown that prior HE is one of the key independent predictors of postoperative TIPS-related HE [odds ratio (OR): 3.07, 95% confidence interval (CI): 1.75–5.40]. The 2020 TIPS guidelines jointly developed by the British Society of Gastroenterology, the British Society of Interventional Radiology, and the British Association for the Study of the Liver (BASL)[22] highlighted that TIPS can aggravate or induce HE; thus, patients should undergo preoperative screening for CHE and OHE before nonemergency TIPS. The latest guidelines for preventing and treating HE[12] and the European Association for the Study of the Liver (EASL) guidelines[10] have suggested that a single episode of OHE is not an absolute contraindication for nonemergency TIPS. Most studies[23-26] have not excluded patients with a history of HE or have merely excluded those with a history of recurrent OHE. As a result, the reported incidence of postoperative TIPS-related HE was not higher than the HE incidence following standard modalities, such as endoscopic treatment plus drug therapy and large-volume paracentesis plus albumin infusion. Many

studies[7,27,28] have addressed the relationship between CHE and an increased risk of postoperative TIPS-related HE. However, no preoperative medication (*e.g.*, lactulose or rifaximin) is recommended for patients diagnosed with CHE and scheduled for TIPS. Therefore, the 2021 North American Practice-Based Recommendations[3] considered whether preoperative medication for CHE and cirrhosis can minimize the risk of OHE after TIPS an emerging research interest. A recent study[29] has indicated that HE is not a contraindication for early TIPS for acute variceal bleeding. Several studies [25,30,31] have suggested that early TIPS does not necessarily entail an increased risk of postoperative HE. Therefore, the 2023 French recommendations[12] state that prior HE is not a contraindication for early TIPS.

The severity of liver disease is closely associated with the occurrence of postoperative TIPS-related HE[21,23,32,33]. The aforementioned meta-analysis[21] has suggested that Child–Turcotte–Pugh class C liver function is the most robust independent predictor of postoperative TIPS-related HE (OR: 4.0, 95%CI: 1.4–11.1). A single-center retrospective study [33] has shown that according to the Model for End-Stage Liver Disease scoring system, > 18 is independently associated with the occurrence of postoperative TIPS-related HE (58% *vs* 37%, $P = 0.009$). Advanced age[33,34], elevated creatinine levels[34], and hyponatremia[35,36] have also been reported to be closely related to the occurrence of postoperative TIPS-related HE. Nutritional status is potentially associated with postoperative TIPS-related HE. The BASL[22] has suggested that cachexia is associated with more postoperative TIPS-related HE. In two recent prospective studies[35,36], sarcopenia has been reported to have a strong association with the occurrence of HE. Nardelli *et al*[36] suggested that sarcopenia is independently associated with the development of postoperative TIPS-related HE (subdistribution hazard ratio: 31.3, 95%CI: 4.5–218.07; $P < 0.001$). They reported that the relationship between sarcopenia and HE contributed to decreased ammonia clearance and highlighted the importance of considering sarcopenia during patient selection for TIPS. Two prospective studies by Tapper *et al*[37,38] have demonstrated a close association between the development of OHE and frailty in patients with cirrhosis, as evaluated by the chair stand, grip strength, and walking speed tests. Ney *et al*[39] have found that based on the Montreal Cognitive Assessment (MoCA) and the Clinical Frailty Scale (CFS), the complex MoCA–CFS scoring system has a predictive value for readmission due to HE within 6 mo postoperatively in liver cirrhosis cases without prior HE. These findings show that in patients with liver cirrhosis, frailty is a risk factor for HE. However, no research has discussed the effect of frailty on the occurrence of postoperative TIPS-related HE. Even if patients were carefully selected by considering all aforementioned factors, there is no guarantee that these patients will not have postoperative TIPS-related HE. The 2021 North American Practice-Based Recommendations[3] consider TIPS unsuitable for patients with cognitive impairment and inadequate family or social support because they are at a higher risk of developing HE after the procedure. In nonspecific cases, informing patients and their families that postoperative HE may unavoidably occur and that they should be aware of possible signs and symptoms to identify the condition as early as possible is necessary for the surgeon and attending physician. According to the risk of postoperative TIPS-related HE, the relative contraindications for nonemergency TIPS are shown in Table 1.

EFFECTS OF PORTAL VEIN BRANCHES ON HE

According to the 2019 CCI Clinical Practice Guidelines[11], establishing a shunt from the left portal vein branch can reduce the incidence of postoperative TIPS-related HE. A study[40] has proposed that the reflux from the splenic and superior mesenteric veins reaches the left and right portal vein branches, respectively, before being thoroughly mixed. Specifically, the blood from the superior mesenteric vein mainly goes to the right branch, whereas that from the splenic vein enters the left branch. Therefore, the blood ammonia level in the systemic circulation after puncturing the left portal vein branch is lower than that of the right branch. In another study[41], based on CO_2 venography, an iodinated contrast was used to replace traditional imaging methods to treat patients with chronic liver disease who underwent percutaneous transhepatic puncture of the portal vein and splenic vein catheterization. The study has reported a difference in the imaging of the blood flow in the left and right portal vein branches by injecting 30 mL of the contrast at a rate of 5 mL/s *via* a mechanical injection system. In 2009, a randomized controlled study[42] assigned 72 patients to two groups and found that the incidence rates of HE and newly occurring HE were both lower when the shunt was established from the left portal vein branch than when the shunt was established from the right branch ($P = 0.036$ and 0.012, respectively). A similar conclusion was reached in a 2014 retrospective study[43]. Based on these findings, some interventional physicians in China now prefer the left portal vein branch when creating a shunt by puncture. However, before the Viatorr stent, particularly designed for TIPS, was released in the Chinese market in October 2015, Fluency covered stents were the most frequently used stents for TIPS. Characterized by strong support and robust axial elastic tension, these stents can malfunction due to occlusion as they are released at a position too low in the hepatic vein, or the portion in the portal vein is too short. With the shunt receiving blood from the main portal vein, whether postoperative HE is associated with the choice of puncture site (at either the left or right portal vein branch) is debatable. Whether there is blood flow into the left and right portal vein branches following the convergence of the splenic and mesenteric blood into the main portal vein in patients with liver-cirrhosis-induced portal hypertension remains controversial[44]. In China, a 2020 study[45] collected data from 120 patients with liver-cirrhosis-induced portal hypertension who underwent TIPS with the Viatorr stent. The study results have shown that in 52 patients, the shunt was created at the left portal vein branch, whereas the remaining 68 patients had a shunt established at the right branch, and the two groups had no significant difference in the incidence of postoperative HE ($\chi^2 = 0.159$, $P = 0.69$). Another domestic study in 2020[46] included 15 patients with hepatitis-B-related cirrhosis and upper gastrointestinal bleeding who underwent TIPS. Blood samples were collected from the left and right branches and the main trunk of the portal vein during the procedure and were found to have similar plasma ammonia levels (left branch: 96.4 ± 17.6 μmol/L, right branch: 113.5 ± 18.4 μmol/L, main trunk: 106.9 ± 38.7 μmol/L; all $P > 0.05$). A recent retrospective cohort study[47] has reported that the incidence of postoperative TIPS-related HE did not

Table 1 Relative contraindications for nonemergency transjugular intrahepatic portosystemic shunt (based on the risk of postoperative-transjugular intrahepatic portosystemic shunt related hepatic encephalopathy)

Relative contraindications for nonemergency transjugular intrahepatic portosystemic shunt
Prior HE episodes
Serious liver dysfunction (Child-Pugh ≥ 12 or MELD ≥ 18)
Advanced age (> 70 yr)
High creatinine (serum creatinine > 1.1 mg/dL)
Cachexia
Cognitive impairment
Lack of social and family support

HE: Hepatic encephalopathy; MELD: Model for End-Stage Liver Disease.

differ between patients with a shunt created at the left portal vein branch and those with a shunt created at the right branch (13% *vs* 24%) (P = 0.177). More multicenter prospective randomized controlled studies are needed to clarify whether the occurrence of postoperative TIPS-related HE is related to the choice of shunting branch.

EFFECTS OF SPONTANEOUS PORTOSYSTEMIC SHUNTS ON HE

As the resistance to the blood flow in the portal vein increases, a compensatory network of blood vessels will take form between the portal vein and systemic circulation to achieve partial diversion of the portal venous flow. As portal hypertension deteriorates, some branches gradually become enlarged, leading to the formation of vascular shunts, termed spontaneous portosystemic shunts (SPSS)[48]. Theoretically, the formation of SPSS and the post-TIPS shunting increase the risk of HE by further diversion of portal blood from the liver. A multicenter study by Laleman *et al*[49] has demonstrated that SPSS occurs in 46%–70% of patients with refractory HE. A large-scale multicenter retrospective study [50] has found that an SPSS with a diameter > 8 mm is associated with an increased risk of OHE and death in patients with liver cirrhosis. Likewise, a recent study[51] has reported that an SPSS with a total cross-sectional area > 83 mm² implies an increased risk of OHE and death in patients with liver cirrhosis. In a comparative analysis of unembolized and embolized SPSS by He *et al*[52], patients with unembolized SPSS are at a higher risk of developing postoperative TIPS-related OHE. In contrast, a meta-analysis[53] has shown that SPSS embolization plus TIPS can reduce the risk of recurrent bleeding compared with TIPS alone, and yet, the two surgical approaches lack significant differences in the incidence of HE. A retrospective study[54] has compared TIPS with and without SPSS embolization and reported no significant difference in the incidence of postoperative TIPS-related HE. The 2021 North American Practice-Based Recommendations [3] has suggested that in patients with refractory pleural effusion and ascites, the embolization of SPSS with a diameter > 6 mm during TIPS can be considered to reduce the risk of postoperative HE. The 2020 TIPS guidelines[22] have recommended the embolization of SPSS when a patient is at a high risk of postoperative TIPS-related HE. However, large-scale, multicenter prospective studies are needed to address whether SPSS should be embolized during TIPS, a much debated question.

EFFECTS OF THE PORTAL VENOUS PRESSURE GRADIENT ON HE AFTER SHUNT PLACEMENT

Studies have shown that a greater decrease in portal venous pressure (PVPG) after TIPS is associated with better outcomes and an increased risk of postoperative TIPS-related HE in patients with liver cirrhosis and complications of portal hypertension[55]. At present, it is believed that PVPG should be reduced to at least 12 mmHg or 50% of the initial baseline level to effectively prevent or treat the complications of portal hypertension[19]. In contrast, some researchers[56] have argued that a decrease in PVPG to below 10 mmHg can significantly increase the incidence of postoperative TIPS-related HE. The 2020 TIPS guidelines[22] have suggested that patients with variceal bleeding are at a higher risk when PVPG is reduced to < 12 mmHg and that a safer option is maintaining PVPG at 20% below baseline. In the face of refractory ascites and other indications, the PVPG level should be managed through individualized assessment of therapeutic effects and the risk of HE. In our recent study[44], a Viatorr stent with 8 mm inner diameter was used for shunting. With all included patients having consistent baseline characteristics, PVPG was reduced to 12 mmHg or below 50% of the initial baseline level. The study results have shown that the incidence of HE differed among patients with liver cirrhosis of different origins, with the incidence of postoperative HE in patients with hepatitis-B-related liver cirrhosis lower than in those with alcoholic or primary biliary cirrhosis. It is believed that the development of HE is somehow associated with post-TIPS liver reserve function, which can be explained by subsequent etiological treatment and patient management in addition to perioperative treatment. There is no clear consensus over the treatment protocol for PVPG in

TIPS. Therefore, the appropriate PVPG level should be determined based on individual conditions, such as the cause of liver cirrhosis and symptoms of portal hypertension, which proposes a direction for future studies.

EFFECTS OF THE CHOICE OF STENT ON HE

A randomized controlled trial[57] has revealed that using a covered stent for TIPS can significantly reduce the risk of malfunction, despite the negligible benefits for HE development and survival. The aforementioned meta-analysis[9] has shown that compared with bare stents, covered stents can improve stent patency and survival; however, these devices have no obvious advantage for minimizing the risk of HE. In a direct comparison between bare and covered stents[8], the study results have shown a lack of significant difference in the incidence of OHE. Therefore, the 2021 North American Practice-Based Recommendations[3] have considered discussing the difference in the incidence of OHE between bare and covered stents. Despite their history, bare stents are virtually obsolete in TIPS because of low survival rates and limited therapeutic effects.

PVPG plays a significant role in the development of postoperative TIPS-related HE, and according to Poiseuille's law ($r = 8L \times \eta/r\ 4$), stent diameter is essentially associated with PVPG[19]. Both the North American and British TIPS guidelines[3,22] have proposed that a smaller stent diameter can reduce the risk of HE but has little effect on reducing PVPG. A prospective, nonrandomized controlled study by Schepis *et al*[58] has shown that as far as covered stents are concerned, a smaller diameter (6–7 mm) can significantly reduce the incidence of HE at 1 year postoperative compared with standard diameters (≥ 8 mm). Several studies[17-19] have reported that the incidence of OHE was significantly lower in patients using an 8-mm-diameter stent than in those using a 10-mm-diameter stent. In the study using a 6-mm-diameter covered stent[59], the efficacy profile was satisfactory, with propranolol compensating for the limited decrease in PVPG and reducing the risk of HE. On this basis, researchers[19] have introduced the use of TIPS-dedicated stents with smaller diameters (6–8 mm) and medication or other treatment methods as combined modalities can effectively treat and prevent the complications of portal hypertension while reducing the risk of HE. Notably, a prospective study on expandable stents[60] has introduced a promising modality of placing an expandable stent into the body during the procedure and adjusting the stent diameter between 8 and 10 mm according to the response to the treatment until satisfactory outcomes are achieved. The study results have shown effective control of variceal bleeding and a reduced risk of HE in patients with portal hypertension following the placement of the expandable stent.

PREVENTION AND TREATMENT OF POSTOPERATIVE TIPS-RELATED HE

While lactulose and rifaximin are recommended medications for HE, their benefits for HE prevention after TIPS remain a controversial and much disputed subject. Two randomized controlled trials[61,62] on secondary prevention of OHE have shown that nonabsorbable disaccharides can significantly reduce the risk of developing recurrent HE. The French guidelines[12] have recommended using lactulose or lactitol as a first-line treatment to prevent recurrent OHE. A randomized controlled trial on bare stents[63] has reported a lack of significant difference in the incidence of postoperative TIPS-related OHE between patients using lactulose, rifaximin and placebo. A large-scale randomized controlled trial[64] in 2021 highlighted that the experimental group using prophylactic rifaximin before TIPS had a lower incidence of postoperative TIPS-related HE than the placebo control group (34% *vs* 53%; OR: 0.48, 95%CI: 0.27–0.87). Based on this study, the latest HE prevention and treatment guidelines[12] have recommended using rifaximin to prevent postoperative TIPS-related HE. Despite the notable findings, this trial has not considered prior OHE because lactulose was merely administered to prevent postoperative TIPS-related HE instead of as preoperative prophylaxis. The latest EASL HE guidelines[10] and the Baveno VII consensus[65] have only recommended the prophylactic use of rifaximin before TIPS in patients with prior HE. A recent prospective study[66] has shown that postoperative infusion of human albumin has no clear association with the incidence of postoperative TIPS-related HE.

Although careful patient selection and perioperative measures can lower the risk of TIPS-related HE, achieving effective management of postoperative TIPS-related HE remains challenging. In addition to standard management and pertinent medication therapy, interventional stent restriction is required in the case of refractory HE. As described by the BASL[22], standard HE management is to correct and restore biochemical parameters to normal levels, withdraw nocturnal sedation, stop using proton pump inhibitors (PPIs), and ensure regular bowel movements using lactulose. The 2021 North American Practice-Based Recommendations[3] have recommended administering lactulose for the first episode of OHE after TIPS and lactulose plus rifaximin for recurrent HE. Several studies[67,68] have shown that decreased tissue zinc levels are observed in patients with liver cirrhosis and are related to the pathogenesis of HE. In contrast, these findings are the opposite of the reported effects of zinc supplementation on HE[69-71]. EASL[10] does not recommend HE management through zinc supplementation. The incidence of refractory HE after TIPS is 3%–8%[72-75]. Although there is no standard definition for refractory HE, the 2021 North American Practice-Based Recommendations[3] have recommended shunt flow restriction if patients with persistent HE do not respond to medication therapy or need readmission due to at least three episodes of HE in the past 3 mo. Most patients show improvement in symptoms through shunt flow restriction[76]; however, they are at risk of the recurrence of complications associated with portal hypertension. In a retrospective study[77], 20 patients with postoperative TIPS-related HE underwent shunt flow restriction (n = 18) or TIPS occlusion (n = 2). Of these patients, HE was responsive in 11 (55%) cases and unresponsive in nine (45%), and the responsive cases showed an improvement in HE grades and did not have refractory ascites or recurrent variceal bleeding. This provides supportive evidence for the safety of shunt flow restriction in treating

Table 2 Modalities for preventing and treating postoperative transjugular intrahepatic portosystemic shunt-related hepatic encephalopathy

Prevention	Treatment
Lactulose	Lactulose
Rifaximin	Rifaximin
Albumin (potential)	Correction of biochemical parameters
	Withdrawal of nocturnal sedation
	Discontinued use of PPIs
	Stent flow restriction
	Liver transplantation

PPIs: Proton pump inhibitors.

postoperative TIPS-related HE, particularly in patients with OHE. However, no response to shunt flow restriction usually indicates a poor prognosis[78]. Finally, liver transplantation remains the last resort for patients with portal hypertension and liver cirrhosis. Modalities for preventing and treating postoperative TIPS-related HE are listed in Table 2.

CONCLUSION

As the TIPS technique and related materials, particularly stents, continue to evolve, the incidence of postoperative TIPS-related HE and related symptoms is expected to decrease. At present, whether the occurrence of postoperative TIPS-related HE is associated with the choice of portal vein branch shunting remains unclear. Given the lack of evidence, the invariable use of the left portal vein branch as the puncture site not only makes the procedure even more challenging but hinders the promotion and application of this technique. Patients with liver cirrhosis largely have widened liver fissures, which could expose the bifurcation of the left portal vein branch and carry an increased risk of intraperitoneal hemorrhage during intraoperative puncture of the left portal vein branch. Currently, it is believed that in patients with liver cirrhosis and portal hypertension, using an 8-mm-inner-diameter stent is associated with satisfactory shunting performance and a significantly reduced incidence of postoperative HE compared with using a 10-mm-inner-diameter product. However, further studies are needed to determine the ideal size of a stent and evaluate the clinical use of the emerging expandable stents with a controllable inner diameter in treating elderly patients with liver cirrhosis and those with poor liver reserve function. Considering the wide spectrum of etiologies causing liver cirrhosis in different countries and regions, it is an intriguing research interest to tailor post-TIPS PVPG management for the Chinese population and develop individualized treatment plans for patients with liver cirrhosis. Proactive etiological treatment can reduce the risk of postoperative TIPS-related HE. In China, post-TIPS etiological treatment has produced favorable outcomes in patients with liver cirrhosis and portal hypertension caused by the most commonly occurring hepatitis B virus[79]. Based on etiological treatment, future studies can hopefully benefit more patients with hepatitis-B-induced liver cirrhosis by achieving recompensated cirrhosis, as defined by the Baveno VII consensus[65]. Considering the complex pathogenesis of HE associated with clinical operations, postoperative patient management, and many other factors, future research requires larger sample sizes and should adopt a multicenter randomized controlled study design.

FOOTNOTES

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Country/Territory of origin: China

ORCID number: Lan-Jing Wang 0000-0003-0804-4828; Xin Yao 0000-0002-9977-6153; Qi Qi 0000-0001-6526-4427; Jian-Ping Qin 0000-0001-7834-8830.

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Dinesh Walia, Anoop Saraya, Deepak Gunjan, Gastroenterology and Human Nutrition Unit, All India Institute of Medical Sciences, New Delhi 110029, India

Corresponding author: Deepak Gunjan, MD, Associate Professor, Gastroenterology and Human Nutrition Unit, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India. drdg_01@rediffmail.com

Abstract

Chronic pancreatitis is a chronic fibro-inflammatory disorder of the pancreas, resulting in recurrent abdominal pain, diabetes mellitus, and malnutrition. It may lead to various other complications such as pseudocyst formation, benign biliary stricture, gastric outlet obstruction; and vascular complications like venous thrombosis, variceal and pseudoaneurysmal bleed. Development of varices is usually due to chronic venous thrombosis with collateral formation and variceal bleeding can easily be tackled by endoscopic therapy. Pseudoaneurysmal bleed can be catastrophic and requires radiological interventions including digital subtraction angiography followed by endovascular obliteration, or sometimes with a percutaneous or an endoscopic ultrasound-guided approach in technically difficult situations. Procedure-related bleed is usually venous and mostly managed conservatively. Procedure-related arterial bleed, however, may require radiological interventions.

Key Words: Chronic pancreatitis; Pseudoaneurysm; Vascular complications; Varices; Venous thrombosis

Core Tip: Patients with chronic pancreatitis (CP) are prone to various venous and arterial complications that may sometimes lead to life-threatening bleed. A prompt approach to such vascular complications includes early identification and appropriate management by various modalities including endovascular, percutaneous, endoscopic ultrasound-guided, or surgical in certain cases. A knowledge of these complications, their presentation, and management are important for improving outcomes in patients with CP.

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INTRODUCTION

Chronic pancreatitis (CP) is a progressive fibro-inflammatory disorder of the pancreas, with irreversible loss of the exocrine and endocrine function[1]. Pain is one of the predominant symptoms of CP[2], however, it may be associated with other local and systemic complications. Local complications include development of pseudocysts (8%-40%)[3-5], benign biliary strictures (3%-23%)[3], pancreatic fistulas (1.5%-3.5%)[3], gastric outlet obstruction (0.5%-13%)[3,5], and inflammatory head mass (1.5%-5.2%)[4,6]. Systemic complications include diabetes mellitus (21%-47%)[4,7], steatorrhea (20%-48%)[4,7], sarcopenia (17%-62%)[8,9], malnutrition (46.4%)[10] and metabolic bone diseases (17%-52%)[5,7]. The prevalence of CP is 36-125 per 100000 population and higher in eastern part of the globe with India having a major fraction of the disease burden[7,11]. The etiologic factors include environmental and genetic. The most common aetiology of CP are alcohol (42%-77%) followed by idiopathic (28%-80%)[7,12].

Vascular complications are associated with both acute pancreatitis (AP) and CP. CP has persistent ongoing inflammation, which leads to diverse vascular complications (Figure 1). It may sometimes present with torrential life-threatening bleed, and hence requires an early recognition and prompt intervention, which is the key for favourable outcomes. In this review, we will summarize the available literature regarding the etiopathogenesis, diagnosis and management of vascular complications in CP and will be broadly divided into venous and arterial sections. This review will mainly focus on venous thrombosis and arterial pseudoaneurysm (PsA), and rare vascular events in CP will not be discussed in detail. We will also outline the approach and management of gastrointestinal (GI) bleed in CP.

TYPES OF VASCULAR COMPLICATIONS IN CP

Different types of vascular complications are described in patients with CP. They are broadly divided into arterial and venous. Venous complications include splanchnic venous thrombosis *i.e.,* thrombosis of splenic, portal and mesenteric veins, either alone or in various combinations and rarely inferior vena cava and renal vein thrombosis[13]. Arterial complications include arterial PsAs, percutaneous drain-related arterial bleeding, rarely aortic PsA[14,15] and arterial thrombosis[16] (Figure 1).

The type and distribution of vascular complications in patients with CP has been described in different studies and a summary of which along with distribution of vascular lesions has been shown in Table 1. The cumulative incidence of vascular events was 3.2% at 5 years and increased to 24.5% at 15 years in a study of 394 patients with CP[17]. The pooled prevalence of splanchnic vein thrombosis was found to be 11.6% in a meta-analysis of 44 studies[18]. Different studies have identified the prevalence of splanchnic vein thrombosis to 3%-41% among patients with CP[17]. The pooled incidence rate of PsA in CP was 0.03% in a meta-analysis of 29 studies[19]. There was heterogeneity among the studies included and differences in results could be explained by small sample sizes, retrospective nature and selection bias (Figure 1).

RISK FACTORS FOR VASCULAR COMPLICATIONS IN CP

Identification of risk factors (Table 1) would allow to risk stratify the patients and take appropriate measures to identify and manage vascular complications. The presence of pseudocyst significantly increases the risk of splanchnic vein thrombosis[17,20-22]. A plausible explanation is that pseudocyst present in the vicinity of splanchnic veins causes local compression and stasis in splanchnic veins that predisposes to thrombosis. Other risk factors identified in different studies are alcohol as the aetiology of CP, history of acute pancreatitis (AP) and diabetes mellitus[17,21,23]. Smoking has been found to be associated with a higher risk of splanchnic vein thrombosis (odds ratio: 3.02) in a study probably due to the endothelial damage and oxidative stress incurred by its metabolites on endothelium[23].

Anand *et al*[21] observed that the risk of venous thrombosis increased with the presence of inflammatory head mass that might cause local compression and inflammation around the splanchnic veins. This study also identified alcohol and pseudocyst as a risk factor for PsA formation[21]. Most of the studies suggested that alcohol and pseudocyst are the common risk factors for the development of vascular complications in a patient with CP. Most of these studies reported risk factors related to the venous thrombosis but failed to identify risk factors for PsA formation.

VENOUS COMPLICATIONS

As discussed above, venous thrombosis is one of the major vascular complications in CP. Thrombosis predominantly

Table 1 Frequency and risk factors of vascular complications in patients with chronic pancreatitis in different studies

Ref.	Number of patients (vascular complications/total CP patients)	Vascular complications	Risk factors
Udd *et al*[81], 2007	33/745 (4.4%)	PsA: 33 (4.4%)	-
Agarwal *et al*[20], 2008	34/157 (21.6%)	Splenic vein thrombosis: 34 (21.6%)	Pseudocyst (OR = 4.01)
Pandey *et al*[23], 2019	37/187 (19.7%)	Splenic vein thrombosis: 37 (19.7%)	Smoking (OR = 3.021). Pseudocyst (OR = 3.743)
Anand *et al*[21], 2020	166/1363 (12.2%)	Venous thrombosis: 132 (9.6%). PsA: 17/166 (1.24%). Both: 17 (1.24%)	Venous thrombosis: Alcohol (OR = 2.1); pseudocyst (OR = 4.6); inflammatory head mass (OR = 3.1). Pseudoaneurysms: Alcohol (OR = 3.49); pseudocyst (OR = 3.2)
Ru *et al*[22], 2020	89/3358 (2.6%)	Splenic vein thrombosis: 89 (2.6%)	Alcohol (OR = 1.28). History of AP (OR = 2.56). Diabetes mellitus (OR = 3.82). Pseudocyst (OR = 8.54)
Vujasinovic *et al*[17], 2021	33/394 (8.37%)	Venous thrombosis: 30 (7.6%). PsA: 3 (0.8%)	Alcohol (HR = 3.56). Pseudocyst (HR = 8.66)

AP: Acute pancreatitis; HR: Hazard ratio; OR: Odds ratio; CP: Chronic pancreatitis; PsA: Pseudoaneurysm.

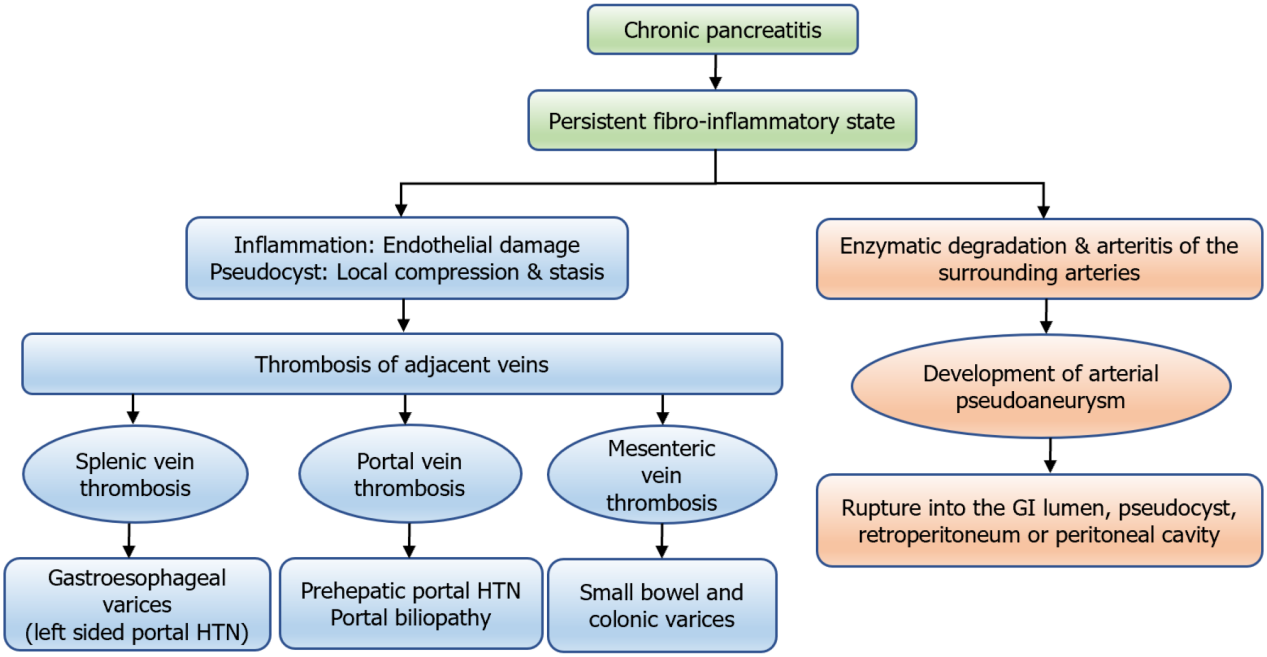

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Figure 1 The types of vascular complications in chronic pancreatitis and their consequences. GI: Gastrointestinal; HTN: Hypertension.

affects the splanchnic veins with variable involvement of splenic, portal, and mesenteric veins.

Pathogenesis

Various proposed mechanisms for splanchnic vein thrombosis include pancreatic inflammation in the vicinity of splanchnic veins causing direct vascular endothelial damage, compression, or pressure from oedematous pancreas or pseudocyst causing venous stasis and hence thrombosis[24]. The persistent release of the inflammatory mediators can activate the coagulation system and may stimulate the formation of platelets and fibrin-rich thrombin. Lastly, certain factors like interleukin-1 (IL-1), IL-6 and tumor necrosis factor-alfa released from the damaged pancreatic tissue into the blood may also trigger a coagulation cascade, leading to endothelial damage and venous thrombosis[25].

Distribution

The extent of thrombosis in splanchnic veins is variable. A meta-analysis including 44 studies showed that the pooled prevalence of splanchnic venous thrombosis was 11.6% [95% confidence interval (CI): 8.5%-15.1%], splenic vein thrombosis was 12.8% (95%CI: 8.7%-17.6%), portal vein thrombosis was 3.5% (95%CI: 2.3%-4.8%), and mesenteric vein thrombosis was 1.2% (95%CI: 0.4%-2.5%) in patients with CP[18]. Another meta-analysis estimated the incidence of

splenic vein thrombosis to be 12.4% among patients with CP[26]. Various studies have shown that splenic vein is most commonly involved due to its anatomical proximity along the posterior surface of pancreas. This is followed by involvement of portal and mesenteric veins to variable extent as depicted in Table 2.

Clinical presentation

Venous thrombosis in the setting of underlying CP may be either asymptomatic and detected incidentally or present as various clinical manifestations as shown in Table 3. Venous thrombosis can be acute or chronic. Acute venous thrombosis is uncommon in CP as compared to AP.

Chronic splanchnic venous thrombosis in CP is associated with formation of collaterals along the splenoportal and gastroepiploic venous systems that may give rise to gastro-esophageal varices. These varices develop due to dilation of the short gastric, gastroepiploic and coronary veins[26]. This phenomenon is referred to as "left sided", "compartmental", "lineal", "splenoportal" or "sinistral'' portal hypertension. The estimated prevalence of gastro-esophageal varices on esophagogastroduodenoscopy (EGD) ranges from 10%-77%[17,21,23,26-28]. The pooled prevalence of gastro-esophageal varices in CP on EGD in a meta-analysis was 53%, 77.3% of which were gastric, however all these studies had significant heterogeneity[26]. Table 3 shows the relative distribution of varices on EGD. Incidentally detected abdominal collaterals on imaging without definitive varices may be present in 30%-83% patients of CP[17,21] (Figure 2).

The clinical presentation as variceal bleed in patients with CP ranges from 3%-20% in different studies[17,20-22]. Bleeding is less frequent in chronic splanchnic venous thrombosis related varices due to development of abundant collaterals with a pooled prevalence of 12.3% in a meta-analysis[20-22,25,26,28-31]. The common presentation of variceal bleed is hematemesis or melena in variable frequency as per different studies[21,23]. Various studies highlighting the prevalence of varices and clinical presentation as bleed have been elaborated in Table 3. Similarly, splenomegaly has been noted in a variable frequency (20%-54%)[17,21,26] in studies as shown in Table 3.

Portal vein thrombosis leads to development of collaterals around the common bile duct (epicholedochal and paracholedochal), which may give rise to benign biliary strictures, predispose to choledocholithiasis and even acute cholangitis[32]. Long standing strictures may eventually lead to secondary sclerosing cholangitis and biliary cirrhosis. The data on the prevalence of portal cavernoma in CP is, however, lacking.

There is wide discrepancy regarding the detection of varices and bleeding manifestations due to variable sample size, retrospective nature of most studies, difference in detection strategies of varices (screening *vs* EGD when symptomatic), and lastly due to the differences in surgical *vs* medical series as methods of detection and management were different among them. Although the presence of varices is higher, but risk of variceal bleed is lower in patients with CP likely due to decompression by the presence of intrabdominal collaterals.

Diagnosis

Venous thrombosis is usually detected on imaging, done for either symptomatic patients or asymptomatic patients undergoing imaging for non-bleed related indications. In the past, angiography was used for diagnosis of splanchnic venous thrombosis, but currently it has limited diagnostic role in this setting[33]. Ultrasound colour doppler is the initial screening modality for detection of splanchnic venous thrombosis[25]. It shows echogenic contents within the vessel lumen along with reduced or absent flow on colour doppler, depending on the degree of occlusion[34]. The visualisation of portal vein is better than splenic and mesenteric veins on ultrasonography. Ultrasound might also show the presence of splenomegaly, collaterals, or portal cavernoma. Ultrasound doppler has a sensitivity of 93% and a specificity of 83% for splenic vein thrombosis[35] and sensitivity and specificity is more than 95% for portal vein thrombosis[34,36]. Endoscopic ultrasound (EUS) has been shown to have a sensitivity of 81%, specificity of 93% and accuracy of 89% for detecting thrombosis in the porto-splanchnic venous system[37].

Contrast-enhanced computed tomography (CECT) (Figure 2) is the investigation of choice for evaluation of extent of splanchnic vein thrombosis and collateral formation, and also gives additional information regarding pancreatic parenchymal or ductal changes, calcification, local complications such as pseudocyst, benign biliary stricture, and to rule out an associated mass, either inflammatory or neoplastic[34,38]. It provides information regarding the degree of occlusion, extent of involvement and ischemic changes in the bowel wall, if any. Venous thrombosis is visible as hypodense non-enhancing contents within the vessels on the portal venous phase with a sensitivity and specificity of more than 90%[39,40] (Figure 2).

Contrast-enhanced magnetic resonance angiography (MRA) may also be used to evaluate the extent of thrombosis with a sensitivity of 100% and specificity of 98%[41]. It shows the clot in the lumen of the veins as isointense material on T1-weighted images and more intense on T2-weighted images[34]. However, its use is limited to indications like evaluation of head mass or biliary obstruction, since CECT has similar sensitivity and specificity for splanchnic venous thrombosis with a short study period, lower cost and easy availability.

Management

Management includes acute management of GI bleed and long-term definitive management. Acute management of GI bleed includes resuscitation by intravenous crystalloids and airway protection, followed by EGD and endotherapy for the variceal and non-variceal sources of bleed. In case of variceal bleed, the endotherapy depends on the source of bleed and involves variceal band ligation or sclerotherapy for esophageal varices or cyanoacrylate glue injection into the gastric varices[42]. EUS-guided coiling with or without glue injection can be used in selected patients where bleeding cannot be controlled by endotherapy (Figure 3B). A recent study showed 100% technical success rate in six patients of CP with splenic vein thrombosis who presented with upper GI bleed from gastric varices using EUS-guided combined coiling and cyanoacrylate glue injection[43].

Table 2 Studies showing the frequency and site of venous thrombosis in chronic pancreatitis

Ref.	Venous thrombosis	Distribution
Bernades *et al*[85], 1992	35/266 (13%)	SVT: 22 (8%)
		PVT: 4% (10%)
		SMVT: 3(1%)
Heider *et al*[28], 2004	Venous thrombosis with chronic pancreatitis: 53	SVT: 34 (64.3%)
		SVT and SMVT: 10 (18.7%)
		SVT and PVT: 3 (5.7%)
		SVT, SMVT and PVT: 6 (11.3%)
Anand *et al*[21], 2020	149/1363 (10.9%)	SVT: 95 (63.8%)
		PVT: 29 (19.4%)
		SVT and PVT: 25 (16.8%)
Vujasinovic *et al*[17], 2021	30/394 (7.6%)	PVT: 2/30 (6.7%)
		SVT: 16/30 (53.3%)
		MVT: 1/30 (3.3%)
		PVT and SVT: 3/30 (10.0%)
		PVT and MVT: 2/30 (6.7%)
		MVT and SVT: 4/30 (13.3%)
		SVT, PVT, and MVT: 2/30 (6.7%)

MVT: Mesenteric vein thrombosis; PVT: Portal vein thrombosis; SVT: Splenic vein thrombosis; SMVT: Superior mesenteric vein thrombosis.

Table 3 Clinical consequences of venous thrombosis in patients with chronic pancreatitis in different studies

Ref.	Varices	Splenomegaly	Clinical presentation
Bernades *et al*[85], 1992 (n = 266)	Esophageal: 2 (5%). Gastric: 4 (10%)	-	Hematemesis: 1. Melena: 1
Sakorafas *et al*[29], 2000 (n = 34)	Gastroesophageal: 12 (35%)	-	Variceal bleed: 6/34 (17.6%)
Heider *et al*[28], 2004 (n = 53)	Overall gastroesophageal varices: 41/53 (77%). On CT: 40/53 (75.4%). On EGD: 11/36 (30.5%). Both CT and EGD: 10/36 (27.7%)	-	Gastric variceal bleed: 2 (4%)
Agarwal *et al*[20], 2008 (n = 34)	Varices: 11 /34. Gastric: 7/11 (64%). Esophageal: 4/11 (36%)	13/34 (38%)	Variceal bleed: 5/34 (15%). Gastric variceal bleed: 3/5 (60%). PHG bleed: 2/5 (40%)
Pandey *et al*[23], 2019 (n = 157)	IGV: 7 (18.9%). GOV: 1 (2.7%)	-	Upper GI bleed: 7 (18.9%). Gastric variceal bleed: 3 (8.1%). Nonvariceal: 4 (10.8%)
Ru *et al*[22], 2020 (n = 3358)	Gastric: 45/89 (50.6%)	50/3358 (1.5%)	Variceal bleed: 17/89 (19.1%). Melena: 13 (76.5%). Hematemesis: 10 (58.8%). Both: 8 (47%)
Anand *et al*[21], 2020 (n = 1363)	43/149 (28.9%)	27/149 (18.1%)	GI bleed: 21/149 (14.1%)
Vujasinovic *et al*[17], 2021 (n = 394)	3/30 (10%)	6/30 (20%)	GI bleed: 0/30. Intraabdominal bleed: 0/30

CT: Computed tomography; EGD: Esophagogastroduodenoscopy; GI: Gastrointestinal; GOV: Gastro-esophageal varices; IGV: Isolated gastric varices; PHG: Portal hypertensive gastropathy.

The definitive management of CP-related venous thrombosis is still a matter of debate. Since most of these patients are asymptomatic and up to 30% have spontaneous venous recanalization[44], the definite role of anticoagulation is not established. There are no well-defined risk factors to predict the group of patients who will have spontaneous recanalization. All patients with CP with venous thrombosis, particularly splenic vein thrombosis, should undergo an EGD to

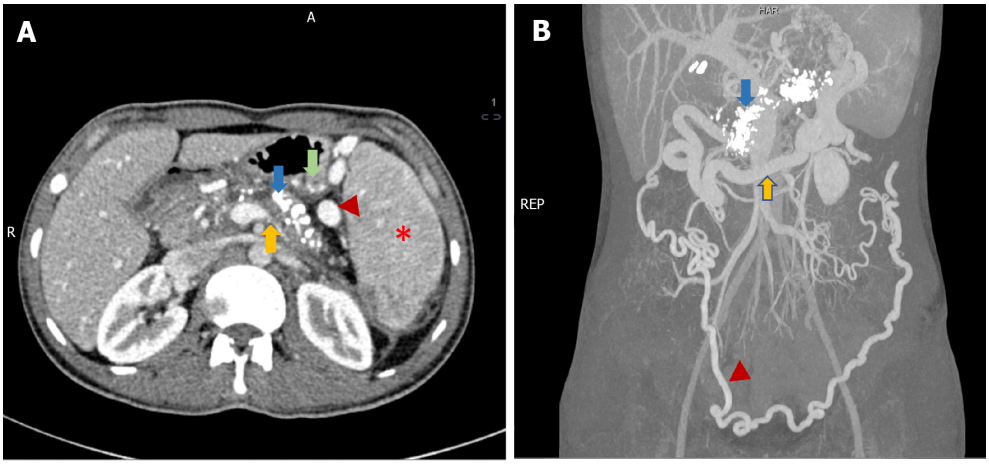

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Figure 2 Radiological features of chronic calcific pancreatitis and its complications including venous thrombosis and collaterals. A: An axial section of contrast-enhanced computed tomography (CECT) showing chronic pancreatitis with calcifications (blue arrow), attenuated splenic vein (yellow arrow), multiple perigastric collaterals (green arrow), gastrosplenic collaterals (red arrowhead) and splenomegaly (red asterisk); B: Coronal section of CECT of the same patient showing extensive pancreatic calcification (blue arrow) with dilated gastroepiploic vein (yellow arrow) and omental collaterals (red arrowhead). Courtesy: Dr Madhusudhan KS, Department of Radiodiagnosis.

identify the presence of varices. The data on the role of anticoagulation including newer oral anticoagulants (NOACs) in venous thrombosis in the setting of CP is scarce as compared to AP, hence, no definite recommendation can be made[24]. Indications of anticoagulation in CP include, the extension of acute thrombus to portal and mesenteric vein, and the development of mesenteric ischemia.

Splenectomy can be considered in some cases with recurrent variceal bleed[29,45]. Some studies suggest that in patients with splenic vein thrombosis, who are undergoing pancreatic surgery, prophylactic splenectomy can be performed simultaneously to decrease the risk of variceal bleed, however it is still a matter of debate[25]. In patients who are not suitable for splenectomy, splenic artery embolization remains an alternate option[46,47]. Therefore, the treatment must be individualised keeping the patient's characteristics and available resources in mind.

For prophylaxis of variceal bleed, beta blockers have been recommended for secondary prophylaxis in extrahepatic portal venous obstruction as extrapolated from data of cirrhotic portal hypertension with no first hand data on their role in CP-related varices[48]. Data on the role of beta blockers for primary prophylaxis is lacking. So, a definite recommendation for beta blockers cannot be made based on available evidence.

ARTERIAL COMPLICATIONS

Arterial complications include formation of PsAs, which may lead to life threating consequences. It may be seen in both AP and CP due to ongoing inflammation. PsA is defined as an encapsulated hematoma communicating with the lumen of the vessel and the outer wall consists of perivascular tissue, fibrosis, or clot making it prone to rupture[24,49].

Pathogenesis

PsA is usually formed as a local complication due to surrounding pancreatic inflammation which causes necrotising arteritis with subsequent erosion of the vessel wall due to enzymatic degradation[49,50]. This leads to weakening and ballooning of the vessel wall resulting in communication with the surrounding fluid collection[51,52]. PsA may also develop in relation to percutaneously placed drains or plastic stents placed for pseudocyst/walled off necrosis drainage due to local irritation and ongoing inflammation due to collection[50,53].

Location

As understood from the pathophysiology, PsA are usually formed adjacent to the site of significant inflammation, in relation to necrotizing pancreatitis in patients with AP and adjacent to pseudocysts in those with CP[54]. A meta-analysis by Sagar *et al*[19] including 29 studies (840 cases of pancreatitis) estimated the pooled incidence of PsA to be 0.05% and 0.03% in AP and CP, respectively. The most commonly involved artery in this meta-analysis was splenic artery (37.7%) followed by gastroduodenal artery (23.6%), pancreaticoduodenal artery (10.6%), hepatic artery (8.3%), left gastric artery (3.3%), superior mesenteric artery (3.3%), colic artery (2%), jejunal arteries (1.1%), coeliac artery (0.6%), and inferior mesenteric arteries (0.2%). The size can be variable and can reach up to 85 mm[55]. The relative distribution of PsA in various studies is elaborated in Table 4.

Clinical presentation

PsAs can be either asymptomatic and detected incidentally while imaging for other indications or may present with

Table 4 Studies showing sites and clinical manifestations of arterial pseudoaneurysms in patients with chronic pancreatitis

Ref.	Vascular complications	PsAs	Site- artery involved	Clinical presentation
Bergert *et al* [86], 2004	36/541	25/36	Splenic: 8/25 (32%). Pancreaticoduodenal (superior or inferior): 7/25 (28%). Gastroduodenal: 4/25 (16%). Superior mesenteric: 2/25 (8%). Jejunal branches: 2/25 (8%). Left gastric: 1/25 (4%). Right colic: 1/25 (4%)	Acute abdominal pain: 12 (48%). Haemorrhagic shock: 10 (40%). Acute upper GI bleed: 9 (36%). Acute lower GI bleed: 3 (12%). Chronic anaemia: 3 (12%). Acute on chronic pancreatitis: 5 (20%)
Udd *et al*[81], 2007	33/745	33	Gastroduodenal/pancreaticoduodenal: 19 (58%). Splenic or its branches: 14 (42%)	Abdominal pain: 22 (66.6%). GI bleed: 17 (51%)
Sethi *et al*[87], 2010	Chronic pancreatitis with PsA: 16	16	Splenic: 7 (43.7%). Hepatic: 3 (18.75%). Gastroduodenal: 2 (12.5%). Right gastric: 2 (12.5%). Left gastric: 1 (6.25%). Pancreaticoduodenal: 1 (6.25%)	Intraabdominal bleed: 2 (13%). GI bleed: 8 (50%). Occult bleed: 10 (63). Pain: 14 (88)
Mallick *et al* [88], 2019	27/380	27	Gastroduodenal: 13 (48.2%). Splenic: 10 (37.1%). Superior mesenteric: 2 (7.4%). Left gastric: 1 (3.7%). Inferior pancreaticoduodenal: 2 (7.4%)	Hematemesis: 6/27 (22.2%). Melena: 17/27 (63.0%). PCD bleed: 1/27 (3.7%)
Zabicki *et al* [55], 2018	Chronic pancreatitis with PsA: 15	15	Splenic: 7/15 (46.7%). Common hepatic: 2/15 (13.3%). Right gastroepiploic: 2/15 (13.3%)	-
Anand *et al*[21], 2020	166/1363 (12.2%)	PsA: 34/1363 (2.5%). PsA alone: 17 (50%). PsA with VT: 17 (50%)	Splenic: 25/33 (75.7%). Gastroduodenal: 6/33 (18.2%). Inferior pancreatico-duodenal: 1/33 (3.0%). Left gastric: 1/33 (3.0%)	GI bleed: 22/34 (64.7%)
Vujasinovic *et al* [17], 2021	33/394	3/394 (0.8%)	Splenic: 2/3 (66.7). Left gastric: 1/3 (33.3)	Incidental finding: 3/3 (100%). Intraabdominal bleeding: 0/3 (0%)
Madhusudhan *et al*[68], 2021	56 patients of chronic pancreatitis	PsA: 61	Splenic: 31/56 (55.3%). Gastroduodenal: 18/56 (32.1%). Inferior pancreaticoduodenal: 1/56 (1.7%). Colic: 1/56 (1.7%). Hepatic: 4/56 (7.1%). Left gastric: 5/56 (8.9%)	Upper GI bleed: 40/56 (71.4%). PCD bleed: 1/56 (1.7%). Pain: 4/56 (7.14%). Incidentally detected on imaging: 11/56 (19.6%)

GI: Gastrointestinal; PCD: Percutaneous drain; VT: Venous thrombosis; PsA: Pseudoaneurysm.

abdominal pain or overt GI bleed. The reported incidence of PsA-related bleed is around 4%-10%[52] with the risk of rupture in up to 50% and mortality after rupture as high as 15%-40% in old surgical series[56-58]. Various studies with reported frequency of clinical presentations with PsAs have been enumerated in Table 4.

Rupture of PsA may be into the GI tract presenting as hematemesis or melena, into abdominal cavity presenting as pain, or features of peritonitis, or retroperitoneum where the main presentation is pain with or without hemodynamic worsening. Less commonly, it may rupture into the pancreatic duct (hemosuccus pancreaticus)[59] or bile duct (hemobilia) resulting in hematemesis or melena[24,60]. Sometimes, the PsA may rupture into a pseudocyst cavity and if the pseudocyst is being drained percutaneously, it may present as bleed in the drainage tube[60].

Most of the studies have investigated the symptomatic luminal gastrointestinal bleed and data on intraabdominal and retroperitoneal bleed is still scant which usually present as worsening abdominal pain with or without hemodynamic instability and hemoglobin drop[24,61]. Retroperitoneal bleed was seen in 2 (5%) of 39 cases presenting with pseudoaneurysmal bleed in a study[62]. Clinical manifestations of a ruptured PsA apart from overt luminal or intra-abdominal bleed include acute worsening of abdominal pain, abdominal distension, or unexplained sudden hemodynamic worsening. The reported frequency of these symptoms as per different studies has been mentioned in Table 4. The bleed resulting due to rupture of PsA can be life threatening if not identified and managed promptly.

Diagnosis

The diagnosis is established by demonstrating a PsA on imaging modalities such as ultrasound doppler, EUS, multidetector CT angiography (CTA), MRA or conventional angiography [digital subtraction angiography (DSA)]. Among these modalities, EUS and DSA are both diagnostic as well as therapeutic, as definitive obliteration can be done in the same setting.

On ultrasonography, a hypoechoic cystic structure may be seen adjacent to a vessel. On doppler imaging, blood flow within that cystic structure has typical turbulent swirling motion known as the "yin-yang sign"[63]. The diagnosis is confirmed by demonstration of a communicating channel (neck) between the cystic structure and the feeding artery with a "to-and-fro" waveform[63]. Thus, doppler increases the detection rate and should always be used to evaluate cystic lesions to avoid confusing PsA with a complex cyst[64]. Doppler can miss small and partially or completely thrombosed PsAs since it may not show characteristic flow patterns[24]. Endosonography (Figures 3C and D) may show similar findings with hypoechoic area adjacent to feeding artery with swirling turbulent blood flow on doppler, the "yin-yang" sign as discussed above[65].

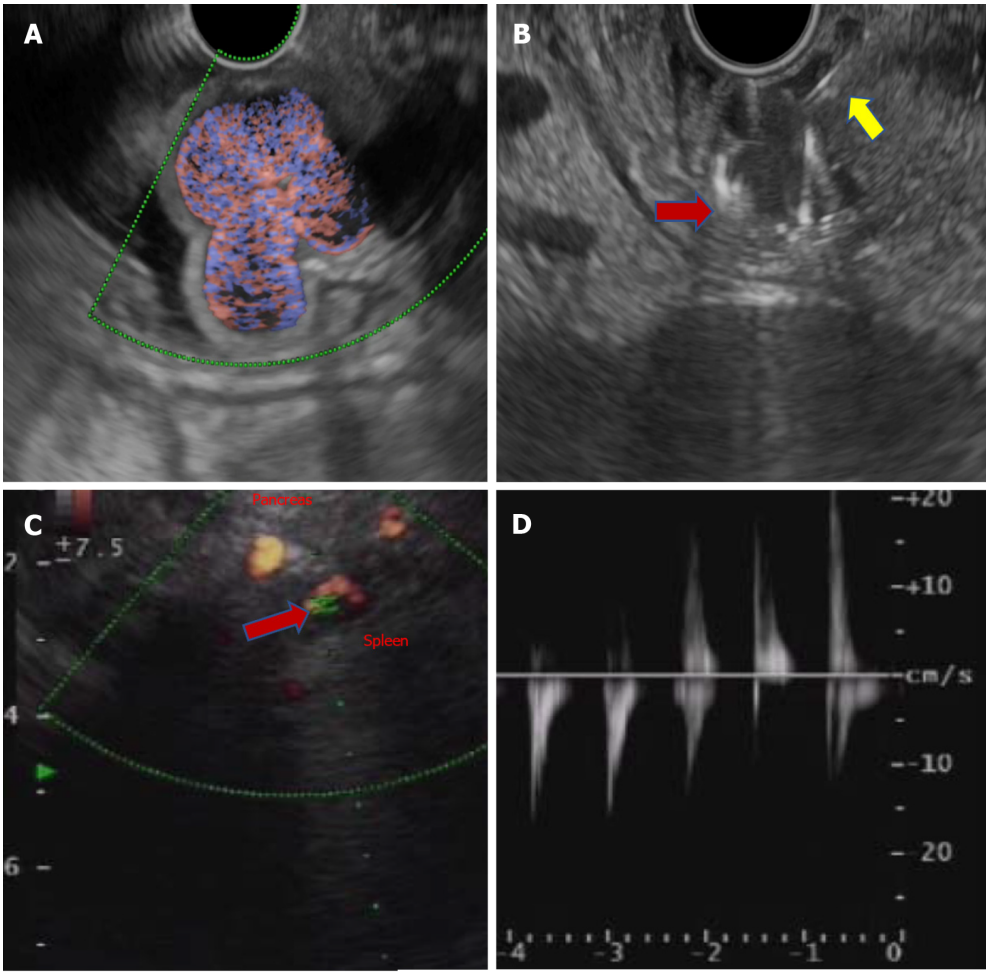

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Figure 3 Endoscopic ultrasound-guided fundal variceal obliteration, and pseudoaneurysm on endoscopic ultrasound. A: Linear endoscopic ultrasound showing the fundal varices on doppler study; B: Linear endoscopic ultrasound guided metal coil (red arrow, hyperechoic curved structure) being pushed into the varices for obliteration after the endoscopic ultrasound needle puncture (yellow arrow, hyperechoic linear structure); C: Linear endoscopic ultrasound showing an arterial pseudoaneurysm (red arrow) on doppler study; D: On power doppler mode Doppler showing an arterial waveform with bidirectional flow, classically labelled as "yin-yang" sign.

CTA is currently the most widely used modality because of its high sensitivity and specificity, easy availability, low cost, user independence and short procedure time (Figures 4A and B). On non-contrast CT, the presence of hyperdense content adjacent to or within a pseudocyst cavity might indicate rupture of PsA[63]. After contrast injection, contrast leak in the collection, or presence of contrast in the cystic structure or communication with the adjacent feeding artery suggests PsA (Figure 4A)[63]. The lumen of PsA may not be completely opacified with contrast owing to thrombosis. CTA has been shown to have a sensitivity and specificity of more than 95% in a study[66]. Three-dimensional reconstruction of CT imaging gives a better idea of anatomy of the PsA and helps in providing a roadmap for further therapeutic interventions (Figure 4B).

MRA is a valuable tool for detection of PsA especially where CT is contraindicated like in contrast allergy, with no radiation risk. It has high sensitivity and specificity for identifying the size, location and feeding artery of PsA, but clinical utility is limited owing to several disadvantages like prolonged procedure time (not feasible in actively bleeding patient), high cost, metal artifacts, patient mobility and limited availability[63].

DSA is the gold standard for diagnosis and treatment (Figure 4C). Major advantages include real time assessment of the PsA, its feeding artery, presence of collateral supply, any active extravasation, determination of neck size, detection of small lesions missed by CT and the potential for therapeutic intervention in the same setting[63]. However, it has some limitations including inaccurate assessment of size of PsA in presence of thrombus, exposure to ionizing radiation, and iodinated contrast-related complications (allergy or nephrotoxicity). DSA may be associated with various procedure-related complications namely development of PsA, hematoma or arteriovenous fistula at the site of puncture, distal embolization and ischemia, arterial spasm, intimal dissection, and vessel thrombosis[67].

Henceforth, approach to diagnosis include assessment of patient related factors, available modalities, and clinical presentation like active bleed with hemodynamic instability which requires an early intervention. The accepted approach for diagnosis of pseudoaneurysmal bleed is CTA followed by DSA and its obliteration.

Pang *et al*[60] described a classification system for peripancreatic PsA from a study which included both pancreatitis-related and postoperative PsAs. The classification system is based on the type of artery involved, its communication with

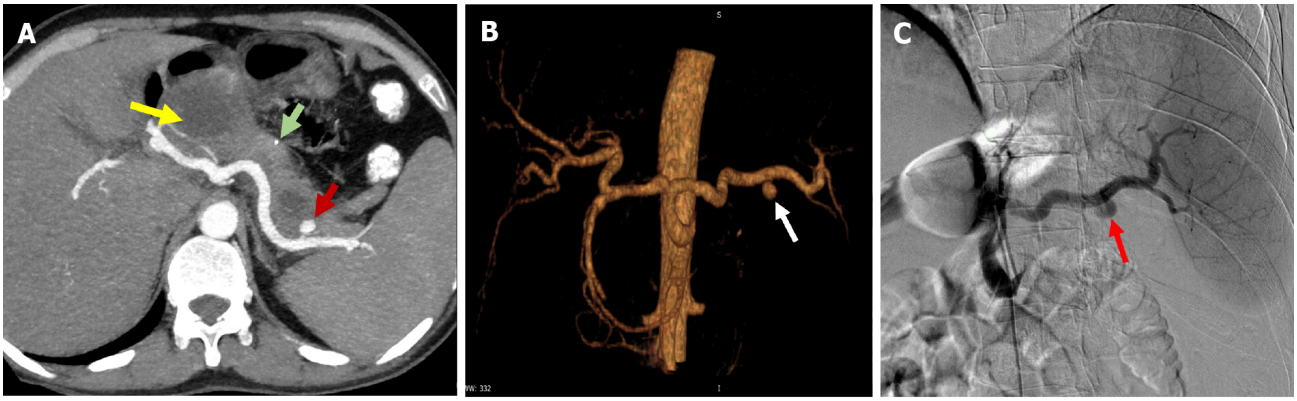

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Figure 4 Arterial pseudoaneurysm in chronic pancreatitis. A: Axial contrast-enhanced computed tomography in a patient of chronic pancreatitis showing a pseudoaneurysm (PsA) (red arrow) arising from splenic artery along with a specks of parenchymal calcification (green arrow) and a pseudocyst (yellow arrow) in the head of pancreas; B: Reconstructed angiographic image of the same patient showing splenic artery PsA (white arrow); C: Digital subtraction angiography of the same patient showing contrast outpouching from the splenic artery suggestive of splenic artery PsA (red arrow) with contrast opacification before endovascular therapy. Courtesy: Dr Madhusudhan KS, Department of Radiodiagnosis.

the GI tract, and exposure to pancreatic juice. This proposed classification system may help in therapeutic decision making, approach to a particular lesion and outcome assessments. However, its external validity is lacking.

Management

As a dictum, all PsAs, including those detected incidentally on imaging done for other indications in CP have to be treated owing to the risk of potential life-threatening bleeding. Various treatment strategies and modalities are available which are employed depending on the mode of presentation. These include endovascular, percutaneous, EUS-guided and surgical treatment[50]. Studies showing various interventions and their outcomes in patients with PsA associated with CP have been enumerated below in Table 5.

Endovascular interventions

It is the mainstay of management of PsAs with high technical (89%-99%) and clinical success rates (74%-88%)[19,68]. The main aim is to exclude the PsA from systemic circulation. This can be achieved either by slowing down the flow of blood within the PsA (using coils, stent grafts), by inducing thrombosis (coils and liquid embolic agents) or by stimulating local inflammation (coils and liquid agents)[69]. Various types of embolic agents available are coils (stainless steel or platinum), n-butyl cyanoacrylate glue, stents (covered or uncovered), gelfoam, thrombin or vascular plugs. They can be used either alone or in combination[63,70,71] (Figure 5).

Metal coils (micro coils) act by slowing down the blood flow by causing mechanical obstruction and inducing thrombosis by their thrombogenic fibres and eliciting local inflammatory reaction. Once inside the PsA, they assume their spiral shape and cause occlusion of the PsA and its neck from main circulation and induce thrombosis. Various coil embolization techniques have been described namely, "sandwich technique"[71] (occlusion of artery proximal and distal to PsA- most commonly used), "sack packing"[72] (occluding the lumen of PsA with microcoils- when the neck is narrow) or proximal embolization[73] (where distal end cannot be cannulated or in case of end arteries). The indications of each technique depend on several factors including the size, location of PsA, nature of feeding artery, collaterals, and size of the neck. A simplified approach to the management of pseudoaneurysmal bleed has been illustrated in Figures 5 and 6. Complications include splenic infarction, splenic abscess formation, coil migration (wide neck), intestinal ischemia and vascular dissection[49] (Figure 5).

N-butyl cyanoacrylate glue is a liquid embolic agent which polymerises to form a hard cast after coming in contact with anions (blood)[69]. Glue is used when the target site is difficult to reach due to a tortuous arterial course, revascularization of PsA post coil embolization, and in patients with coagulation abnormalities, as coils need normal coagulation parameters for thrombosis[70]. It may also be used in combination with coils to provide a scaffolding and to prevent dislodgement of the coils (Figure 5).

Endovascular stent placement with or without coiling may be used in certain situations like PsA with wide neck to prevent coil migration and to preserve the patency of a parent artery[63,74]. Either covered stents alone or uncovered stents along with coiling of sac may be used to obliterate and exclude the PsA, while maintaining adequate flow in the parent artery[75]. This approach is useful where the PsA is located proximally in a large artery like hepatic, proximal splenic or superior mesenteric artery to prevent embolism or ischemia to the major organs[76]. Stent patency rates of about 82% has been reported in a study[76] (Figure 5).

Percutaneous interventions

Percutaneous obliteration of PsA is usually done under ultrasonography or CT guidance (Figure 5). This approach is usually adopted in cases where the PsA cannot be approached endovascularly and is surrounded by a solid organ which

Table 5 Studies showing types of intervention and its outcomes in patients with chronic pancreatitis with pseudoaneurysms

Ref.	Patients	Presentation	Intervention for PsA	Outcomes	Complications
Bergert *et al*[86], 2004	Chronic pancreatitis: 541. Bleed: 36	Acute bleed with haemorrhagic shock: 10/36 (27.7%). GI bleed: 12 (33.3%). Acute severe abdominal pain: 12 (33.3%)	PsA: 25/36 (69.4%). Angioembolization: 9(47%). Surgery: 16 (53%)	Higher rebleeding rate after surgery (25% *vs* 11% after embolization) On follow-up, one patient presented with a left hepatic artery PsA 18 mo post embolization of the gastroduodenal artery	Deaths after surgery: 2. Deaths after embolization: 1 Hospital mortality determinants: Haemorrhagic shock and amount of blood transfusion required
Balachandra *et al*[89], 2005	Total PsA: 214. Spontaneous: 160. Postoperative: 40. CP: 40. Pseudocyst: 135. AP: 39	GI bleed: 147 (69%). Intra-abdominal bleed: 30 (14%)	Angiographic embolization attempted: 115 (66%). Successful: 85 (74%). Surgery: 62 (30%)	Among angiography group: 55 (37%) had subsequent surgery; 94 (63%) underwent embolization. In 30 (48%) of the 62 patients undergoing surgery as first intervention require: Angiography: 21/30; re-operation: 9/30	-
Hsu *et al*[90], 2006	CP with PsA-9	-	Arterial embolization: 5. Surgical intervention: 9	Success rates: Embolization: 20% (1/5). Surgery: 88.9% (8/9)	Mortality: Surgery (0). Post embolization [1 (sepsis)]
Zyromski *et al* [61], 2007	PsA: 24 in pancreatitis. Acute on chronic pancreatitis: 22 (91.6%). Acute pancreatitis: 2 (8.6%). Most common etiology: Alcohol (79%)	GI bleed: 7 (29%). Increasing abdominal pain: 15 (62%)	Coil embolization: 23. Covered stent: 1	Repeat embolization: 1	-
Udd *et al*[81], 2007	Chronic pancreatitis: 745. PsA: 33	GI bleed: 17. Abdominal pain: 22. Bleeding confined to the pseudocyst: 9 (27%). Peritoneal bleed: 5 (15%). Retroperitoneal bleed: 3 (9%)	Angioembolization attempted: 23/33 (70%). Technical failure: 7 cases. Vessel not visualized: 3. Surgery: 4/5 cases with bleeding into the peritoneal cavity	Angioembolization success rate: 22/33 (67%). Re-embolization for recurrent bleed: 3. Success rate: 16/20 (80%) when the pseudocyst in head region and 50% when splenic artery was the source of bleed. Follow-up of surgical cases (14 mo): no rebleed or surgical intervention	4 complications in the embolization procedure: Coil pushed to the MPD: 1 (endoscopically removed); dissection of the bleeding artery: 1; coil pushed into the iliac artery: 1; PsA at inguinal puncture: 1; mortality: 1
Tulsyan *et al* [91], 2007	Visceral aneurysms: 90. PsA: 28	-	Coil embolization: 96%. N-butyl-cyanoacrylate (glue): 19%	Endovascular treatment technically successful: 98%. Secondary interventions for persistent flow: 1. Recurrent bleeding from previously embolized aneurysms: 2	Postembolization syndrome developed: 3 (6%). 30-d mortality: 4 (8.3%)
Kim *et al*[92], 2015	Total cases: 37. Chronic pancreatitis: 31	-	41 procedures. Transcatheter embolization: 39 (95.1%). Stent-grafts: 2	Successful haemostasis: 34 (91.9%). Rebleed: 2 (treated by reintervention)	Focal splenic infarction: 8. Splenic abscess: 3 (2/3 died from sepsis)
Zabicki *et al* [55], 2018	Chronic pancreatitis with PsA: 15	-	Microcoils: 5. Bovine thrombin: 5. Squid embolization: 1. Stent graft: 1. Coil + vascular plug: 1. Thrombin and coil embolization with splenectomy: 1. Squid embolization with splenectomy: 1	Complete exclusion of PsA from systemic circulation: 14/15(93.3%). Reintervention: 1. No recanalization at the follow-up CT after 1 to 3 wk	Splenic ischemia requiring splenectomy: 2 cases. No mortality at 30 d
Mallick *et al* [88], 2019	Chronic pancreatitis: 380	PsA: 27	Endovascular coiling: 13 (48.2%). Endovascular glue: 3 (11.1%). Endovascular coiling + glue: 1 (3.7%). Percutaneous thrombin injection: 8 (29.6%). Conservative management: 1 (3.7%). Surgery: 1 (3.7%)	Technical success of embolization: 17/21 (80.9%). Clinical success of embolization: 16/17 (94.1%). Rebleed: 4 (14.8%)	Major complications of embolization: 1 (3.7%). Death: 1 (3.7%)
Madhusudhan	56 patients of chronic pancre-	Upper GI bleed: 40/56 (71.4%)	Embolization: 59/61 lesions. Technical	Recurrent bleed: 9 (16.1%) (stopped spontaneously in	Major complications: 6 (10.7%). Splenic infarcts:

et al[68], 2021	atitis with 61 PsAs		success rate: 96.7%. Clinical success rate: 83.9% Agents used for obliteration: Coils: 24; glue: 15; coils + glue: 15; gel foam: 2; others: 3	6/7, one expired). 49 patients followed up for a mean duration of 24.1 mo. Late recurrence of bleeding from a different artery- 4 patients (mean duration of 5.4 mo)	2/6. Splenic abscesses: 4/6 Minor complications: Abdominal pain: 5 (8.9%); mortality rate: 1/56 (1.8%)
Dhali *et al*[93], 2022	26 patients with CP with PsA	Upper GI bleed: 25 (96%). Incidental detection: 1 (4%)	Embolization: 11 (42%). Coil embolization: 10 (91%), followed by injection of glue in one patient (9%). Surgery: 20 (77%) including 5 patients after failed embolization	Embolization failed: 3 (27%). Rebleed from embolised PsA: 2 (18%). Over a median follow-up of 24 (6-122) mo, none had rebleed	Embolization-induced complications: 4/11 (36%). Colonic ischemia: 1. Splenic infarct: 1. Splenic abscess: 1. Acute renal failure: 1. The most common postoperative complication was wound infection followed by pancreatic fistula. No procedure-related death

AP: Acute pancreatitis; CP: Chronic pancreatitis; CT: Computed tomography; GI: Gastrointestinal; MPD: Main pancreatic duct; PsA: Pseudoaneurysm.

provides scaffolding[74]. It involves puncturing the PsA under imaging guidance and injection of various embolic agents including thrombin, glue or coils. Various studies have showed technical success rates of 92%-100%[75,77,78]. It may be associated with complications like rupture of PsA, cellulitis, embolic events and incomplete occlusion[63,74] (Figure 5).

EUS-guided interventions

EUS-guided obliteration is used in cases where endovascular approach fails or PsA is not visible on angiography but detected on EUS. EUS-guided obliteration using thrombin, glue or coils can be done to achieve haemostasis[79]. EUS-guided thrombin injection was successful in controlling bleed from splenic and gastroduodenal PsAs in three patients using 300-500 IU with no major complications in a study where endovascular approach was not feasible[56]. EUS-guided glue injection was successful in obliterating a large PsA in left inferior phrenic artery in a case of alcoholic CP after failed embolization and revascularization of PsA after percutaneous thrombin injection[80]. A study of six patients showed complete occlusion of splenic artery PsA using EUS-guided coil and glue injection at 12 wk with no complications[79]. Complications of this approach include bleed from puncture site, embolization to non-target organs or perforation peritonitis[56,79].

Overall, the choice of embolization and the approach depends on a variety of factors[63,74] - the size of PsA and its neck- [choice of coil or glue (narrow neck) or stent (wide neck)]; the nature of feeding artery- end artery or not, abundance of collaterals, accessibility, expandability; location of PsA- landing zone of coils and ease of cannulation; and coagulation parameters of patients- glue is preferable in deranged coagulation parameters.

Surgical management

It is indicated in cases with massive GI bleed and hemodynamic instability or if there is failure of endovascular interventions. The surgical options include direct vessel ligation to pancreatectomy, gastrectomy, or small intestinal resection, depending on the affected vessel and ischemia to the adjacent organs[54,81]. Surgery can be also considered, if a patient has concomitant complications of CP such as pseudocyst, benign biliary strictures, gastric outlet obstruction, painful inflammatory head mass or for pain relief[24,82]. In a nutshell, the optimal management of PsA is by the endovascular approach, however, a different alternative approach can be utilised on an individual patient basis.

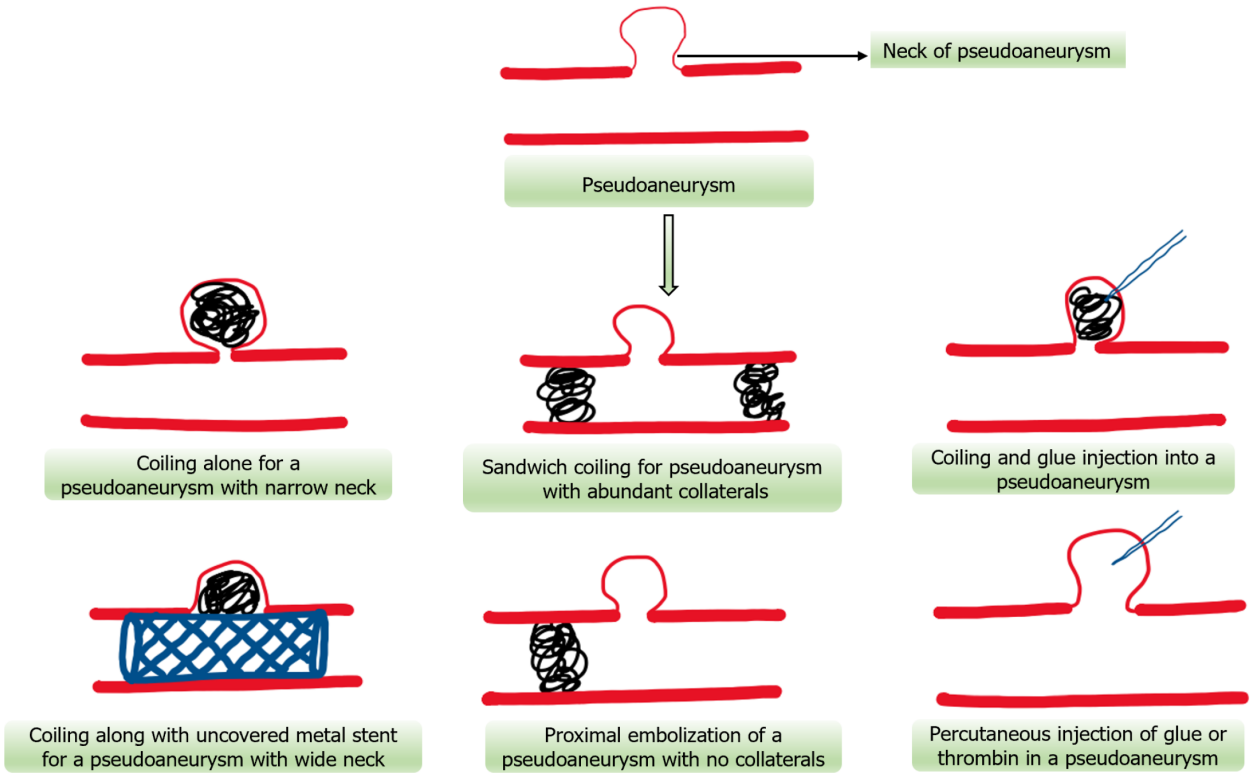

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Figure 5 Schematic representation of various endovascular and percutaneous approaches for pseudoaneurysm obliteration.

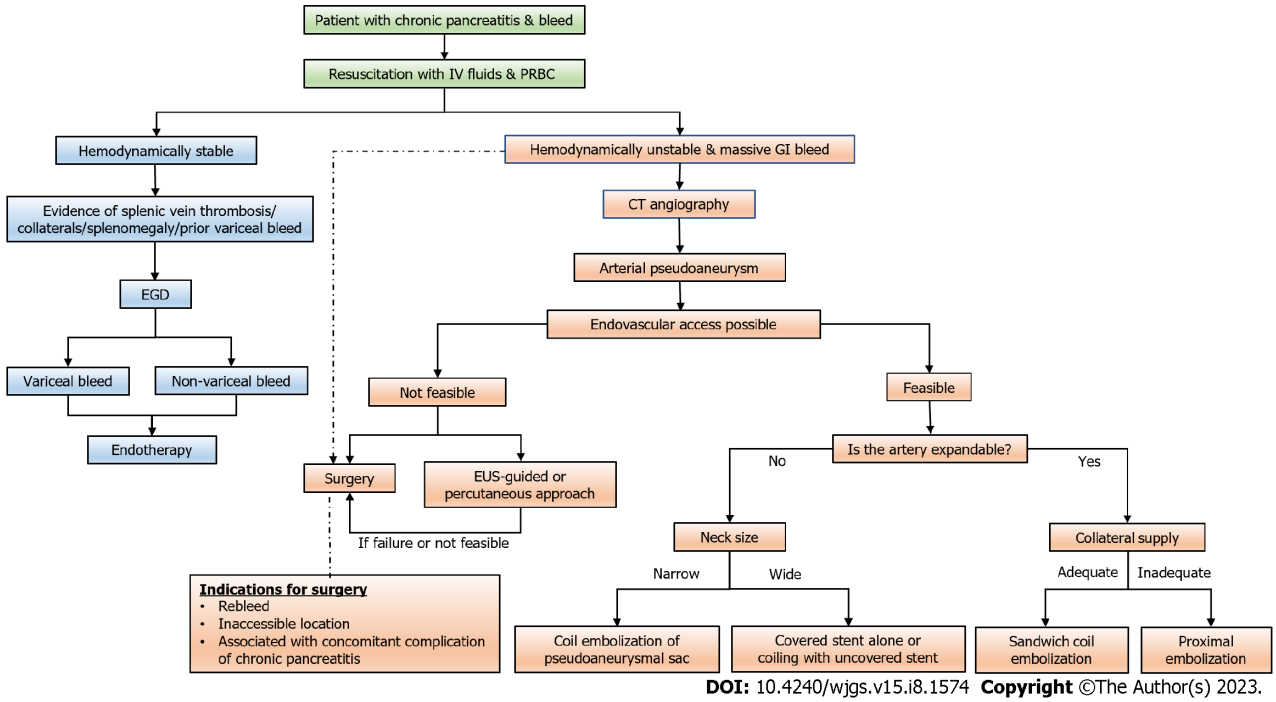

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Figure 6 Flow diagram depicting the approach to a case of gastrointestinal bleeding in patients with chronic pancreatitis (dashed arrow suggests an alternative management strategy). CT: Computed tomography; EGD: Esophagogastroduodenoscopy; GI: Gastrointestinal; PRBC: Packed red blood cell; EUS: Endoscopic ultrasound.

Procedure-related bleeding

Patients with CP usually undergo various diagnostic and therapeutic interventions and some of these patients may develop bleeding as a procedure-related complication. The procedures commonly performed in CP include EUS-guided sampling, cyst aspiration, pseudocyst or ductal drainage, endoscopic retrograde cholangiopancreatography for various

indications and also by percutaneous approach. These procedures may be associated with variable frequencies of risk of bleed[83,84]. Most of these bleeds are self-limiting and controlled endoscopically at the time of the endoscopic procedures, while some patients may require endovascular or surgical interventions, particularly in hemodynamically unstable patients or in cases of failure of endoscopic methods to control the bleed.

If bleed happens after percutaneous intervention, then patient should be observed carefully for haemoglobin drop and hemodynamic instability. If any of these events happen, patient should undergo CTA, followed by approach similar to as discussed earlier.

APPROACH TO GI BLEED IN PATIENT WITH CP

Whenever a patient with known or suspected CP presents with overt GI bleed or acute worsening of abdominal pain with hemodynamic worsening or bleed from percutaneous drain site, the patient should be immediately evaluated for the source and cause of the bleed. Initial management is like any other cause of GI bleed and includes securing two wide bore cannulas, resuscitation with intravenous fluids, airway protection and blood investigations including cross-matching for anticipated requirement of blood transfusion[24,38,50,63,71,74] (Figure 6).

The initial investigation of choice is multidetector CTA owing to its high sensitivity and low acquisition time. If an arterial lesion in the form of PsA is found, further management depends on hemodynamic stability. If a patient is hemodynamically unstable with ongoing bleed and other associated complications, the patient might be considered for upfront surgical intervention. In a hemodynamically stable patient, approach to lesion depends on the factors enumerated above along with the availability of interventional radiological services. The optimal management includes endovascular embolization and obliteration of the lesion. Other options include percutaneous and EUS-guided occlusion which might be considered on a case-to-case basis. In case of high suspicion of arterial bleed and non-identification of definite source of bleed on CTA, a patient can be directly considered for DSA both as a diagnostic and therapeutic option [24,38,50,63,71,74] (Figure 6).

If the imaging shows venous thrombosis with or without splenomegaly or abdominal collaterals, the patient should undergo an EGD for both diagnostic as well as therapeutic options for variceal bleed as described in venous thrombosis section (see above).

In cases of hemosucuss pancreaticus and hemobilia, CTA is used to identify the culprit vessels and further management is similar to what has been described earlier[50,59]. A simplified algorithm to approach a case of GI bleed in CP patient has been shown in Figure 6.

FUTURE DIRECTIONS AND UNRESOLVED ISSUES

So far, we have discussed about what is known about the epidemiology, presentation, and management of vascular complications in patients with CP. There are still many lacunae in the knowledge of these manifestations. Most of these studies are retrospective in nature, so knowing the denominator is difficult. We need a prediction model of factors that might predispose to such complications and in whom a possible role of proactive screening for such vascular lesions might be warranted before they land in life threatening conditions. Another potential area of investigation could be the role of anticoagulation in pancreatitis-related splanchnic venous or arterial thrombosis including NOACs. Another aspect of further investigation could be prospective studies in evaluating the role of endovascular and endosonography-related techniques of managing the PsA exploring the technical and clinical success rates and complications, and in which subgroup of patients which techniques have to be used. Therefore, further investigation into various aspects of pancreatitis-related vascular complications and their management must be explored to optimize patient care.

CONCLUSION

The patients with CP are prone to development of several vascular complications such as vascular thrombosis and PsAs, which sometimes might lead to life threatening consequences. Early identification with a high degree of suspicion and prompt management of these complications has a significant impact on patient outcomes. The management options have evolved over the years from a predominant surgical to a endovascular approach with high technical and clinical success rates. Optimal utilization of these resources can prevent catastrophes and optimise the management of patients with CP.

FOOTNOTES

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Country/Territory of origin: India

ORCID number: Anoop Saraya 0000-0002-3921-6752; Deepak Gunjan 0000-0002-0609-3135.

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MINIREVIEWS

Historical changes in surgical strategy and complication management for hepatic cystic echinococcosis

Ji-De A, Jin-Ping Chai, Sheng-Long Jia, Xiang-Ren A

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Ji-De A, Department of Hepatic Hydatidosis, Qinghai Provincial People's Hospital, Xining 810007, Qinghai Province, China

Jin-Ping Chai, Department of Internal Medicine-Cardiovascular, Qinghai Provincial People's Hospital, Xining 810007, Qinghai Province, China

Sheng-Long Jia, Department of General Surgery, Huangzhong Hospital of Traditional Chinese Medicine, Xining 810007, Qinghai Province, China

Xiang-Ren A, Department of Clinical Laboratory, Qinghai Provincial People's Hospital, Xining 810007, Qinghai Province, China

Corresponding author: Xiang-Ren A, MBBS, Chief Physician, Doctor, Department of Clinical Laboratory, Qinghai Provincial People's Hospital, No. 2 Gonghe Road, Chengdong District, Xining 810007, Qinghai Province, China. xiangrena_001@163.com

Abstract

Echinococcosis is a zoonotic parasitic disease caused by Escherichia larvae. It frequently involves the liver (70%-75%), followed by the lungs (15%-20%), and occasionally the brain, heart, spleen, bone, and other organs. The main pathogenic forms of human echinococcosis currently include cystic echinococcosis (CE) and alveolar echinococcosis (AE). CE is globally distributed, while the distribution of AE is generally restricted to the northern hemisphere. In China, CE accounts for 75% of all echinococcosis cases. With rapid advances in surgical techniques in recent decades, the surgical strategy for CE has changed, especially with the continuous improvement of surgical methods and the expansion of surgical contraindications. To further understand the changes in surgical treatment strategies for hepatic CE, we interpreted and analyzed the existing literature addressing the surgical treatment of hepatic CE both domestically and abroad and briefly summarized them in chronological order. This review aims to provide a deeper understanding of the progress in the surgical treatment of hepatic CE to provide clearer avenues for its clinical diagnosis and treatment.

Key Words: Echinococcosis; Hepatic cystic; Internal capsule; External capsule; Complication; Surgical excision

Core Tip: Many articles have been published on the surgical methods and postoperative complications of hepatic cystic echinococcosis (CE), especially regarding the relationship between surgical methods and patient prognosis. However, few studies have examined the historical changes in surgical methods for hepatic CE. Therefore, this review discusses the main surgical methods and complications in the treatment of hepatic CE over time to provide readers with a deeper understanding of the surgical treatment of this disease.

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INTRODUCTION

Echinococcosis, also known as hydatid disease, is a parasitic disease caused by the echinococcosis tapeworm larvae. The liver is the primary organ involved in echinococcosis, with the brain and other organs occasionally involved[1,2]. To date, at least five species of larvae have been reported to cause echinococcosis, including *Echinococcosis granulosus*, *Echinococcosis multilocularis*, *Echinococcosis oligarthrus*, *Echinococcosis vogeli*, and *Echinococcosis shiquicus*. However, two main pathogens cause echinococcosis in humans: *Echinococcosis granulosus* and *Echinococcosis multilocularis*[3-5]. Cystic echinococcosis (CE), caused by *Echinococcosis granulosus,* is globally distributed, while alveolar echinococcosis (AE), caused by *Echinococcosis multilocularis*, is restricted to the northern hemisphere[6]. The distributions of CE and AE in China are slightly different from the global distribution of echinococcosis, where CE accounts for approximately 75% of all echinococcosis cases[7]. With the rapid advances in surgical techniques in recent decades, the surgical treatment strategy for CE has changed, especially with the continuous improvement of surgical methods and the expansion of surgical contraindications[8]. Original internal capsule excision is a widely used classical procedure because of its safety, practicality, and simplicity. However, owing to the high incidence of postoperative complications, especially residual cavity infection after long-term catheterization, which results in significant physical and psychological trauma, the procedure has been gradually abandoned[9]. Subsequently, various modified methods based on this procedure have evolved, such as internal capsule removal combined with omental tamponade and internal capsule removal combined with external capsule subtotal resection. Although these procedures have addressed many complications caused by partial residual cavity retention, they have not resolved persistent problems associated with internal capsule removal[10]. With the promotion of precision surgery, radical surgical procedures such as external capsule exfoliation and regular or irregular hepatectomy have gradually been accepted by most surgeons in the field[11]. These procedures significantly reduce the incidence of residual cavity complications associated with internal capsule exfoliation. However, radical surgery has stringent requirements for operators and surgical conditions; therefore, it is difficult to popularize this technique. Moreover, forced radical surgery can lead to fatal complications[12,13]. Specialists originally intended to design an individualized surgical plan from the perspective of patient and surgical safety. This article reviews surgical treatment strategies for hepatic CE and the historical evolution of postoperative complications (Table 1).

INITIAL SURGICAL TREATMENT FOR HEPATIC CE

Excision of the internal capsule

A case of successful internal capsule removal for liver CE was first described in 1871[14]. Excision of the internal capsule was the only surgery performed for CE during this period and is still used as a classical surgical approach (Figure 1). Subsequently, some investigators have proposed principles for CE surgery, specifically clearance of the internal capsule, prevention of the extravasation of cyst fluid, elimination of the residual cavity of the external capsule, and prevention of infection[15]. Excision of the internal capsule has the advantages of minimal surgical trauma, safety, and reliability and is a simple operation; however, each procedure has its own drawbacks. Indeed, many common complications can occur after internal capsule removal, such as *in situ* recurrence of the residual cavity, disseminated implantation, biliary fistula, residual cavity infection, and other refractory complications[16]. Some researchers have reported that the recurrence rates of liver CE after internal capsule exocytosis and biliary fistula are as high as 40% and 20%, respectively, and the incidence of residual cavity infection is as high as 65%[17-20]. The main reason for CE recurrence is rupture of the cyst during the operation or failure to completely eliminate the protoscolex when the inner CE cyst is removed, and the protoscolex left in the residual cavity continues to survive and ultimately develops into CE in the outer cavity[21]. The reason for intraperitoneal implantation is that the CE cyst fluid extravasates into the abdomen and pelvis during the operation, contaminating other abdominal organs, and a large number of larvae adhere to the peritoneal surface and survive. The main cause of postoperative biliary fistula is prolonged compression of the bile duct by a CE cyst, leading to intrahepatic bile duct distortion, atrophy, and even distal ischemic necrosis. In addition, owing to the corrosive effect of bile and the dramatic increase in luminal pressure, the external capsule and biliary tract are prone to form internal fistulas. The premise of a postoperative residual cavity infection is the existence of a residual cavity. Some patients experience

Table 1 Main surgical methods for hepatic cystic echinococcosis and their complications in different periods

Period (year)	Surgical methods	Major complications
Initial stage		
1871	Excision of the internal capsule	Recurrence *in situ*, abdominal implantation, biliary fistula, and residual cavity infection
Mature stage		
1965	Complete removal of the external capsule and hepatectomy	Intraoperative hemorrhage, cyst rupture, and liver dysfunction
1985	Percutaneous puncture and catheter drainage	Allergic reaction, abdominal implantation, residual cavity infection, biliary fistula, and recurrence *in situ*
2002	Modified excision of the internal capsule	Abdominal implantation and biliary fistula
2010	Internal capsule removal combined with external capsule subtotal resection	Recurrence *in situ*, disseminated implantation, and biliary fistula
Current stage		
1992	Laparoscopic cyst excision	Intraoperative hemorrhage and cyst rupture
1994	Local ablation	Damage to surrounding tissues and organs. Allergic reaction, cyst rupture, abdominal implantation, and recurrence *in situ*
2002	Liver transplantation	Organ shortage, postoperative complications, and high cost

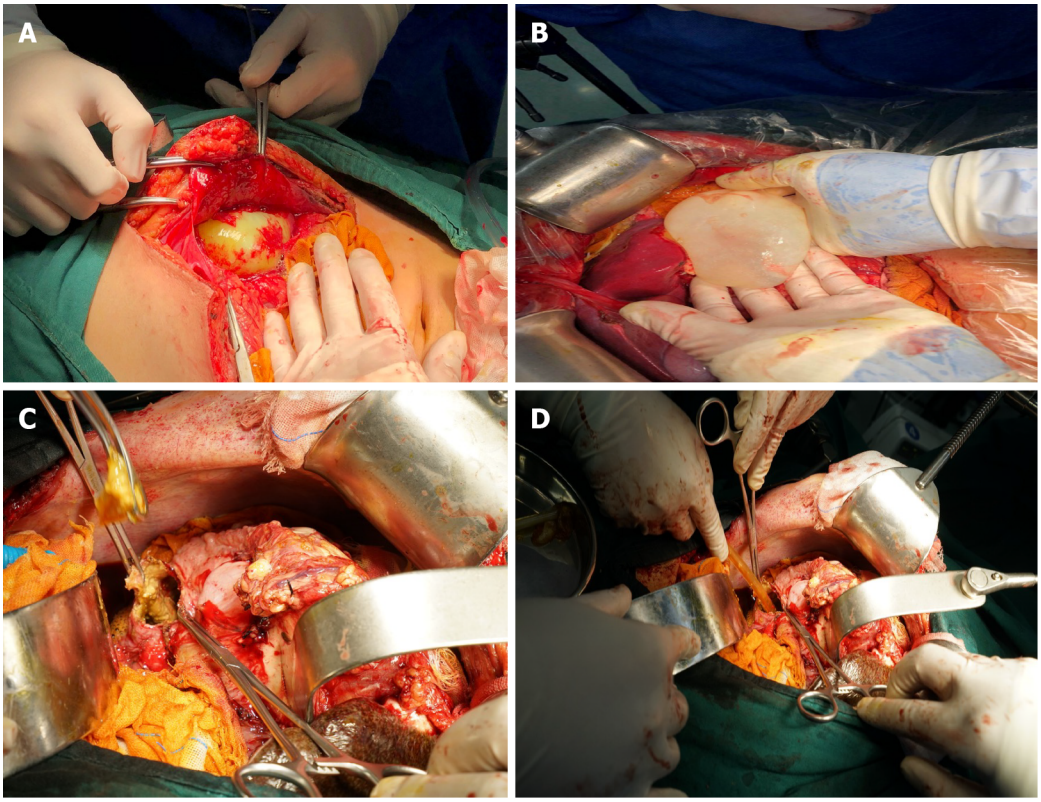

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Figure 1 Excision of the internal capsule. A: After the incision of the peritoneum, the outer capsule of cystic echinococcosis (CE) was ruptured, and the inner capsule was intact; B: The gauze soaked with iodophor was used to isolate the surrounding organs and the intact ascus was removed carefully; C: The CE cyst was large in size and dense in adhesion with the diaphragm. Therefore, we chose to perform the internal capsule enucleation and found an internal fistula in the bile duct of the hydatid cyst, and the contents of the cyst were stained with bile; D: The aspirator aspirated the contents of the capsule, the capsule was repeatedly rinsed with iodophor and wiped with gauze, and a rubber drainage tube was placed.

preoperative cystic cavity infection, or the cyst wall is thick and calcified, and the residual cavity does not heal for a prolonged period. Another major cause of residual cavity infection is the presence of an internal biliary fistula on the cyst wall. When the pressure in the cyst sharply decreases, bile enters the residual cavity from the fistula and causes infection.

MATURE STAGE OF SURGICAL TREATMENT FOR HEPATIC CE

Percutaneous puncture and catheter drainage of CE cysts

Advances and developments in modern medical science have led to a more comprehensive and in-depth understanding of CE, especially when a breakthrough was achieved in the puncture treatment of CE, in which the puncture diagnosis and treatment were no longer considered a "taboo". In 1985, Livraghi *et al*[22] performed an ultrasound-guided diagnostic puncture for hepatic CE. In the same year, Mueller first reported the success of fine-needle puncture in the treatment of human hepatic CE[23]. In 1990, researchers reported ultrasound-guided puncture sclerotherapy for hepatic CE cysts in a large number of patients. This procedure is mainly aimed at patients with simple cyst-type CE who cannot tolerate surgery or for whom the effect of albendazole is not ideal. It has the advantages of less trauma, safety, effectiveness, low cost, and a short hospital stay[24]. Investigators domestically and abroad have reported that percutaneous tube puncture under ultrasound guidance combined with albendazole for the treatment of CE achieved curative effects similar to those of surgery[25]. Ultrasound-guided percutaneous puncture combined with drug therapy for CE is mainly used for cases of liver and abdominal wall adhesions caused by multiple operations and is a simple and less invasive method. Thousands of cases have been reported, both domestically and internationally. The rate of anaphylaxis and shock of puncture and extravasation of cyst fluid leading to CE implantation and dissemination is not higher than that of traditional surgical methods; as such, it is included in the World Health Organization (WHO) guidelines for the diagnosis and treatment of CE. However, some studies have reported that puncture treatment for CE is also associated with problems, including allergic reactions and cholangiosclerosis caused by head-extinguishing agents such as ethanol and formalin, residual cavity infection, biliary fistula, and recurrence *in situ*[26]. Some investigators have reported a complication rate of approximately 17%, a CE cyst infection rate of 2.6%, and an *in situ* recurrence rate as high as 40%[27-29]. To address this problem, researchers designed a special puncture instrument. Puncture and aspiration of the sac contents have been reported to have positive effects. However, the complication rate remained high after follow-up; therefore, this procedure was abandoned in China[30].

Modified excision of the internal capsule

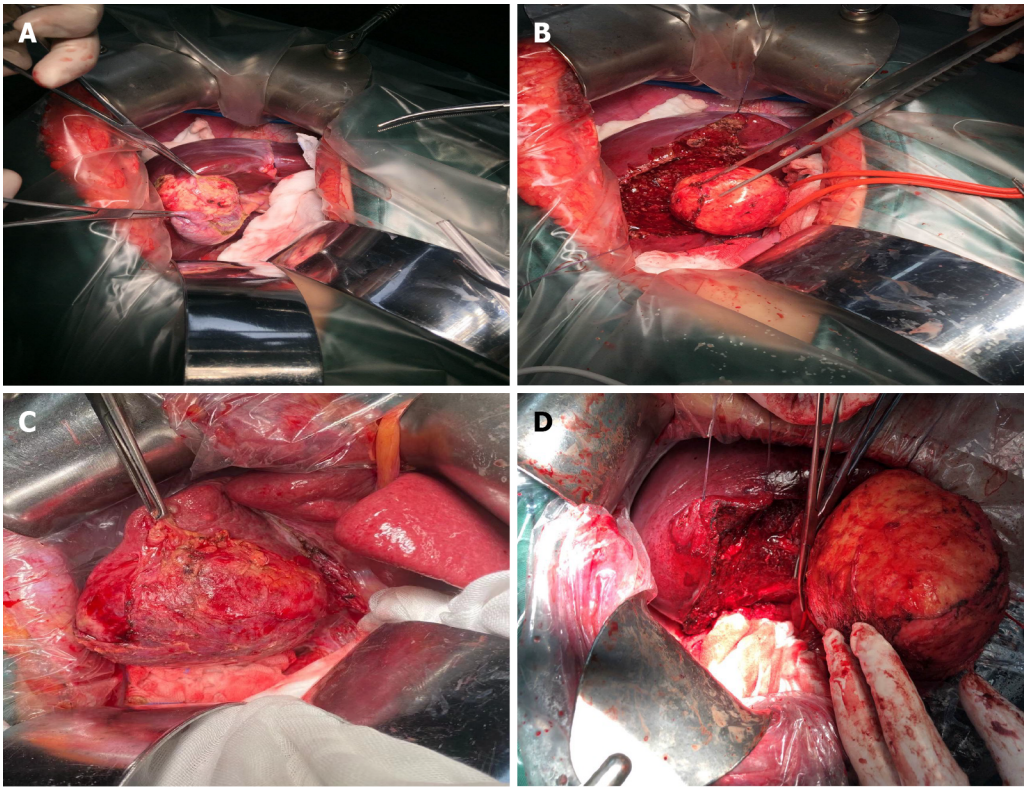
At the beginning of the 20th century, Wen Hao first proposed modified enucleation of the internal capsule for the treatment of hepatic CE. The goal of this operation is to further reduce the incidence of high residual cavity complications after traditional internal capsule removal. A further improved surgical method is performed based on traditional internal capsule removal[31] to completely remove the internal capsule, remove the external capsule as far as possible, convert the large residual cavity into a small residual cavity, suture and repair the biliary fistula, manage the residual cavity with omental tamponade, which can reduce CE recurrence, abdominal spread, and the occurrence of refractory biliary fistula and residual cavity fluid infection. This surgery is suitable for patients with multiple cysts in whom the external capsule cannot be completely removed. Studies have reported that the incidence rates of biliary fistula and residual cavity infections were 17.56% and 2.70%, respectively. There were no recurrences or deaths, and the cure rate was reported to be 100%[10].

Total cystectomy

In 1965, French researchers proposed the concept of radical surgery for the complete removal of the CE external capsule. Peng *et al*[32,33] reported, for the first time in 1999, the complete excision of a hepatic CE cyst inside the outer membrane, which was based on the liver resection technique, combined with experience in the surgical treatment of hepatic CE. The main technical point and radical purpose of this procedure are to completely remove the CE cyst along the potential gap between the external capsule of the CE and the normal liver tissue (Figure 2). Compared with traditional internal capsule extraction, this operation significantly reduces postoperative bile leakage, residual cavity infection, and recurrence. It is an ideal new surgical method for radical treatment, which has been recognized by the WHO and gradually popularized [34,35]. This procedure is suitable for patients with single or external cysts that can be completely resected. Complete excision of the external capsule can completely remove the lesion; however, this operation requires a high degree of knowledge and proficient surgical skills of the surgeon. Otherwise, the cyst could easily rupture during surgery, resulting in serious intraoperative complications. Some studies have reported that the incidence of biliary fistula complications after complete exfoliation of the external capsule is 2.34%, and the incidence of postoperative liver dysfunction is 3.03%. No cases of postoperative recurrence, residual cavity infection, implantation spread, or death occurred, and the cure rate was 100%[36]. However, owing to the expansive growth of CE cysts, some important vessels in the liver are compressed, deformed, and/or displaced, and an internal fistula may form. Although there is a potential gap between the external capsule and normal liver tissue, these vessels and bile ducts are likely to be destroyed during the removal of the external capsule. Furthermore, intraoperative hemorrhage is significantly increased compared with the removal of the internal capsule and subtotal removal of the external capsule[37,38].

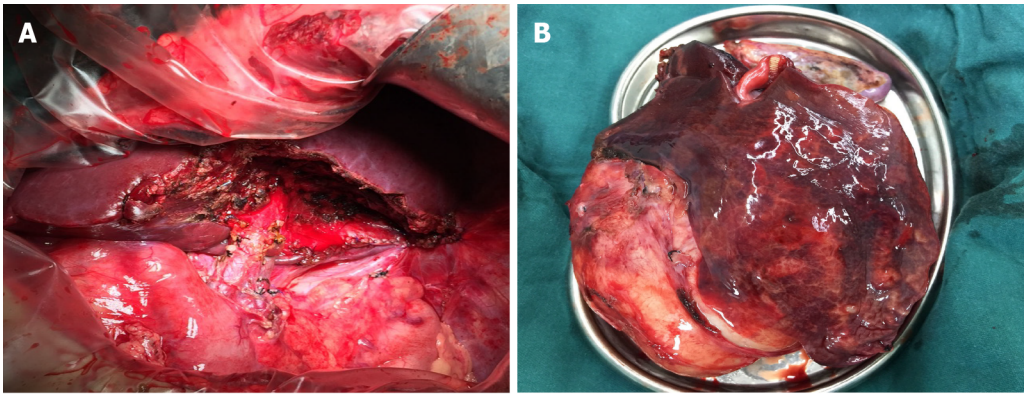
Partial hepatectomy

In 2007, researchers reported that partial hepatectomy was used in France to treat hepatic CE as early as 1965[37]. With advances in liver surgery, hepatectomy has become one of the main radical treatments for hepatic CE[39]. Birnbaum *et al* [40] proposed that active hepatectomy has advantages over conservative internal capsule removal in the treatment of CE. However, not all CE cases should be treated by liver resection because regular liver resection removes part of the normal liver tissue at the same time as the resection of the lesion, especially when the residual liver volume is small; therefore, hepatectomy should be more conservative (Figure 3). This procedure is mainly suitable for patients with multiple and/or large lesions, thick and calcified CE cyst walls, or complications due to intracystic infection[32,41].



DOI: 10.4240/wjgs.v15.i8.1591

Figure 2 Total cystectomy. A: The cystic echinococcosis (CE) cyst was located behind the gallbladder, and the lesion size was small; B: The gallbladder and CE cyst were completely removed; C: CE cyst was located in the S5 and S6 segments of the liver, with a certain distance from the first and second hilum hepatitis; D: The CE cyst was completely removed along the edge of the external capsule, and the remaining liver section was definitely hemostatic.



DOI: 10.4240/wjgs.v15.i8.1591

Figure 3 Partial hepatectomy. A: Cystic echinococcosis (CE) occupied the entire S3 segment of the liver, so segmentectomy was performed; B: Some liver tissue was observed on the surface of CE.

Internal capsule removal combined with external capsule subtotal resection

In 2010, researchers described the treatment of hepatic CE using internal capsule removal combined with subtotal resection[42]. This procedure combines the advantages of traditional endocystectomy and complete removal of the external capsule, particularly in patients with complex CE or in whom total cystectomy is difficult. Moreover, patients with CE cysts near the main hilar vessels and biliary tract achieved satisfactory results. The primary technical aspects include conventional internal capsule extraction followed by external capsule stripping along the potential gap of the CE external capsule, which maximally preserves the normal liver parenchyma and protects the surrounding hepatic duct system. Simultaneously, separation in this space also reduces bleeding without blocking blood flow into the liver, leaving a residue in the outer capsule wall near important blood vessels and the hilus. It aims to remove the outer capsule wall to the greatest extent possible, reduce the residual cavity volume, or eliminate the residual cavity, thereby significantly reducing postoperative residual cavity infections and biliary fistula complications. However, Zhang *et al*[43] found that, although subtotal external capsule resection removes part of the external capsule, it does not avoid the risk of a residual

internal capsule. For example, during surgery, the internal capsule is routinely removed, and there is the possibility of dissemination and implantation of the cephalic segment during the removal of the internal capsule. In addition, compared with internal capsule resection, subtotal external capsule resection also requires the removal of part of the external capsule, which prolongs the operation and increases the surgical risk and incidence of postoperative complications.

CURRENT STATUS OF SURGICAL TREATMENT FOR HEPATIC CE

Laparoscopic CE cyst excision

With advances and developments in minimally invasive techniques, particularly laparoscopic surgery, to a higher level, the indications for surgery continue to expand and extend to the treatment of various diseases. The first case of laparoscopic liver CE internal capsule excision was reported[44]. In the ensuing ten years, several liver surgery centers in China have successively performed total laparoscopic complete cystectomies and laparoscopic hepatectomies to treat hepatic CE. Furthermore, laparoscopic hepatectomy is safe, reliable, minimally invasive, and has a rapid postoperative recovery [45,46]. However, the technical requirements for laparoscopic hepatectomy are high, the technological maturity curve is long, and cases must be carefully selected. The procedure needs to be performed in experienced endoscopic centers; therefore, it is difficult to promote wide-range adoption and a low recurrence rate in the short term. Moreover, surgical indications should be strictly controlled, such as those without a history of abdominal surgery, and cases with CE cysts located in the superficial part of the liver, and clear exposure of the surgical field[47]. Additionally, the three principles of CE surgery should be strictly observed during the procedure: No cystic fluid overflow, a fully inactivated original segment, and field isolation and protection. Attention should be paid to inactivating the extravasated cystic fluid to prevent infection and implant recurrence; therefore, the choice of indication must be emphasized.

Local ablation therapy for CE

With the popularization of minimally invasive concepts in recent years, local lesion ablation, a newly emerging minimally invasive technique, has been recognized by the medical community for the treatment of diseases, especially small lesions [48]. After more than 20 years of development, many domestic and foreign echinococcosis diagnosis and treatment centers have attempted to apply this technology to the treatment of CE or AE because of its simplicity, minimal trauma, low incidence of postoperative complications, and rapid recovery[49-52]. The echinococcosis diagnosis and treatment center of Qinghai Provincial People's Hospital successfully performed radiofrequency ablation for liver CE disease in more than 40 cases. In addition, we found that patients with a smaller hepatic echinococcosis diameter had a shorter operative duration, less postoperative liver damage, and faster recovery of liver function. The operative duration for a single lesion is shorter than that for multiple lesions, the postoperative liver damage is less severe, and the short term clinical effect is good. Radiofrequency ablation has the advantages of being a simple operation that results in less trauma, rapid patient recovery, and fewer complications, and it can, to a certain extent, reduce the economic burden on patients. In addition, in patients with advanced age, poor pulmonary function, or cirrhosis who do not meet the indications for surgery or cannot undergo surgery, it can replace part of the traditional open surgery. However, there are also many uncertain factors in radiofrequency ablation, such as the severity of damage to the surrounding tissues and organs, which cannot be verified. Therefore, to reduce the damage to organs, tissues, and cells caused by radiofrequency ablation puncture, it is necessary to strictly observe operative specifications, accurate preoperative positioning, and careful intraoperative ultrasound guidance, and control the temperature and ablation time during radiofrequency ablation. Reducing the number of ablation attempts with a radiofrequency needle, repeated irregular insertion of the radiofrequency needle, and avoiding careless operations can effectively reduce damage to intrahepatic bile ducts, tissues, and cells.

Liver transplantation for hepatic CE

Hepatic CE lesions compress the second hilum, resulting in severe liver congestion. Traditional treatments cannot effectively improve liver function, hypersplenism, and portal hypertension or relieve abdominal fluid[9]. Allograft liver transplantation is performed when there is a risk of liver failure after autologous transplantation. However, liver transplantation has some shortcomings, such as organ shortage, postoperative complications, and high costs. Therefore, liver transplantation in patients with hepatic CE is rarely reported globally, and there are no records of liver and biliary disease treatment centers in the authors' location.

Continuous improvements in interventional therapeutic technologies, such as laparoscopy, and their application in clinical practice have ushered in significant changes and breakthroughs in the diagnosis, treatment, and postoperative management of hepatic CE. The boundary between minimally invasive and traditional surgeries is constantly being broken, especially as laparoscopic surgery progresses to higher levels. The application of imaging techniques, such as computed tomography angiography, magnetic resonance cholangiopancreatography, and three-dimensional reconstruction, can reveal the relationship between CE lesions, liver vessels, and the biliary tract and provide detailed preoperative imaging for precision surgery for CE. Despite these remarkable achievements, problems persist in the diagnosis and treatment of hepatic CE. Accurate surgical prediction, postoperative evaluation, and the diagnosis and treatment of postoperative complications require further investigation.

MANAGEMENT OF COMPLICATIONS

Albendazole should be administered for a prolonged period after CE recurrence. Reoperation should be considered for patients with poor drug efficacy to prolong and improve their quality of life. Among patients who experience a postoperative biliary fistula, only unobstructed drainage is needed if the size of the biliary fistula is small. If stubborn biliary leakage occurs, which requires long-term catheterization or repeated debridement, and the liver is severely damaged, partial hepatectomy or reoperation can be performed. The leak is sutured, and biliary duct decompression or endoscopic duodenal papillary incision is made for biliary duct decompression, and the biliary leak can be closed by itself [21]. For patients with postoperative residual cavity infection, the first step is smooth drainage, followed by reasonable use of antibiotics to control the infection. If the infection persists, repeat surgical debridement or resection of the part of the liver with bile leakage should be considered to achieve recovery. To prevent recurrence *in situ* or peritoneal implantation, intraoperative protection and isolation measures should be taken, such as using hypertonic saline or iodophor gauze to isolate the tissues and organs around the lesion during the operation, regularly taking albendazole after the operation, and follow-up work to achieve early detection and treatment as far as possible.

CONCLUSION

Compared with 200 years ago, there is a deeper understanding of the pathogenesis of CE, and medical diagnosis and treatment technologies have improved dramatically. However, key treatment principles for hepatic CE remain unchanged. Complete resection of the lesion and prevention of CE recurrence and implantation are lifelong pursuits of CE specialists. However, our team believes that because we cannot guarantee the integrity of the cyst, we should shift the focus of treatment to prevent the inactivation of the head segment, such as pre-inactivation of the head segment and solidification of the cyst fluid, which can not only reduce the implantation and recurrence rates of CE but also improve the safety of surgery. We hope that there will be qualitative breakthroughs in the surgical treatment of hepatic CE.

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FOOTNOTES

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Country/Territory of origin: China

ORCID number: Ji-De A 0000-0003-4478-1972; Jin-Ping Chai 0000-0001-8873-1323; Xiang-Ren A 0000-0002-0305-996X.

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ORIGINAL ARTICLE

Basic Study

High spindle and kinetochore-associated complex subunit-3 expression predicts poor prognosis and correlates with adverse immune infiltration in hepatocellular carcinoma

Lin-Lin Zheng, Ya-Ru Wang, Zhen-Rong Liu, Zhi-Hao Wang, Chang-Cheng Tao, Yong-Gang Xiao, Kai Zhang, An-Ke Wu, Hai-Yang Li, Jian-Xiong Wu, Ting Xiao, Wei-Qi Rong

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Lin-Lin Zheng, Chang-Cheng Tao, An-Ke Wu, Hai-Yang Li, Jian-Xiong Wu, Wei-Qi Rong, Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Ya-Ru Wang, Zhen-Rong Liu, Ting Xiao, State Key Laboratory of Molecular Oncology, Department of Etiology and Carcinogenesis, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Zhi-Hao Wang, Department of Hepatobiliary Hernia Surgery, Liaocheng Dongcangfu People's Hospital, Liaocheng 252000, Shandong Province, China

Yong-Gang Xiao, The Second Ward of Hepatobiliary Surgery, Qianxinan People's Hospital, Xingyi 562400, Guizhou Province, China

Kai Zhang, Department of Interventional Therapy, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin 300000, China

Corresponding author: Wei-Qi Rong, MD, Professor, Surgeon, Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17 Panjiayuan South Lane, Beijing 100021, China. dr_rongweiqi@163.com

Abstract

BACKGROUND

Spindle and kinetochore-associated complex subunit 3 (SKA3) is a malignancy-associated gene that plays a critical role in the regulation of chromosome separation and cell division. However, the molecular mechanism through which SKA3 regulates tumor cell proliferation in hepatocellular carcinoma (HCC) has not been fully elucidated.

AIM

To investigate the molecular mechanisms underlying the role of SKA3 in HCC.

METHODS
SKA3 expression, clinicopathological, and survival analyses were performed using multiple public database platforms, and the results were verified by Western blot and immunohistochemistry staining using collected clinical samples. Functional enrichment analyses were performed to evaluate the biological functions and molecular mechanisms of SKA3 in HCC. Furthermore, the Tumor Immune Estimation Resource and single-sample Gene Set Enrichment Analysis (ssGSEA) algorithms were utilized to investigate the abundance of tumor-infiltrating immune cells in HCC. The response to chemotherapeutic drugs was evaluated by the R package "pRRophetic".

RESULTS
We found that upregulated SKA3 expression was significantly correlated with poor prognosis in patients with HCC. Multivariable Cox regression analysis indicated that SKA3 was an independent risk factor for survival. GSEA revealed that SKA3 expression may facilitate proliferation and migratory processes by regulating the cell cycle and DNA repair. Moreover, patients with high SKA3 expression had significantly decreased ratios of CD8+ T cells, natural killer cells, and dendritic cells. Drug sensitivity analysis showed that the high SKA3 group was more sensitive to sorafenib, sunitinib, paclitaxel, doxorubicin, gemcitabine, and vx-680.

CONCLUSION
High SKA3 expression led to poor prognosis in patients with HCC by enhancing HCC proliferation and repressing immune cell infiltration surrounding HCC. SKA3 may be used as a biomarker for poor prognosis and as a therapeutic target in HCC.

Key Words: Spindle and kinetochore-associated protein 3; Hepatocellular carcinoma; Prognosis; Immune infiltration cells

Core Tip: In this research, we used biological methods and bioinformatics analyses to explore the mechanisms underlying hepatocellular carcinoma (HCC) progression. We revealed that upregulated spindle and kinetochore-associated complex subunit 3 (SKA3) was substantially correlated with a poor prognosis in patients with HCC. SKA3 expression may facilitate proliferation and migratory processes by regulating the cell cycle and DNA repair. Patients in the high SKA3 expression group had significantly decreased ratios of CD8+ T cells, natural killer cells, and dendritic cells. Our study suggested that high SKA3 expression led to poor prognosis in patients with HCC by enhancing HCC proliferation and repressing immune cell infiltration surrounding HCC. Therefore, SKA3 could serve as a potential biomarker and therapeutic target for HCC.

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INTRODUCTION

Primary liver cancer (PLC) is the sixth most common cancer and the third leading cause of cancer-related death worldwide. In China, PLC is the fifth most common cancer and the second leading cause of cancer death[1]. Hepatocellular carcinoma (HCC) is the most common pathological type, accounting for almost 90% of PLC[2]. A growing body of evidence has linked chronic hepatitis virus infection (hepatitis B virus, hepatitis C virus), alcoholic hepatitis, aflatoxin exposure and metabolic syndrome to an increased risk of HCC occurrence[3-5]. Due to the nonspecific early symptoms of HCC, more than half of HCC patients are diagnosed in the middle or advanced stages, thus the five-year survival rate of HCC patients is approximately 5%-30%[6]. In recent years, several serum biomarkers have been proposed for HCC screening and early diagnosis, including alpha fetoprotein (AFP), des-gamma-carboxy prothrombin, and glypican-3. Nevertheless, the sensitivity and specificity remain unsatisfactory[7]. Thus, an exploration of the new prognostic biomarkers for the early prediction and prognosis evaluation of prognosis in HCC is urgently needed.

The spindle and kinetochore-associated (SKA) complex, composed of the SKA complex subunit 1, SKA complex subunit 2, and SKA complex subunit 3 (SKA3) proteins, plays a significant role in kinetochore-microtubule attachment and chromosome movement, ensuring correct chromosome segregation and normal progression in mitosis[8]. SKA3 is an essential component of the SKA complex, located on chromosome 13q12.11, which functions to stabilize the kinetochore-microtubule interaction in mitosis[9]. SKA3 phosphorylated by cyclin-dependent kinase (CDK) 1 binds to NDC80 and recruits the SKA complex to the centromere, which promotes the mitotic process and thereby regulates cell proliferation and apoptosis[10,11]. Growing evidence supports that the overexpression of SKA3 is implicated in the occurrence and

development of various malignant tumors, including laryngeal cancer[12], cervical cancer[13], colorectal cancer[14], breast cancer[15], and lung adenocarcinoma[16]. Previous studies reported that overexpressed SKA3 interacts with polo-like kinase 1, activates the protein kinase B (AKT) signaling pathway, and selectively upregulates the expression of the glycolytic enzymes hexokinase 2, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 and pyruvate dehydrogenase kinase 1 to promote glycolysis in laryngeal cancer cells, thereby promoting malignant proliferation. Moreover, SKA3 overexpression could promote the proliferation and metastasis of cervical cancer and lung adenocarcinoma through the phosphatidylinositiol 3-kinase/AKT pathway[13,16]. In addition, overexpression of SKA3 has been associated with tumor progression and poor prognosis in patients with colorectal cancer[14] and breast cancer[15]. The above findings demonstrate that SKA3 plays a crucial role in promoting the proliferation and migration of tumors. However, the mechanism of SKA3 in HCC has not been fully elucidated.

This study aimed to investigate the relationship between SKA3 expression and clinicopathological features, enrichment analysis, immune infiltration, immune checkpoints, and drug sensitivity in HCC, which may contribute to our understanding of the molecular mechanisms of SKA3 in HCC.

MATERIALS AND METHODS

Pathological sample collection

Thirteen pairs of HCC tissues and corresponding normal tissues were collected from patients undergoing surgery at the Peking Union Medical College Hospital of the Chinese Academy of Medical Sciences from October 2019 to December 2019 and were used for Western blot (WB) analysis. This study was approved by the Ethics Committee of the Peking Union Medical College Hospital. Fifty-six paraffin-embedded HCC tissue samples were used for immunohistochemical staining, which was provided by the hospital. The samples were collected from December 2008 to October 2012. This study was performed in accordance with the principles of the Declaration of Helsinki.

Bioinformatics analysis by public databases

The Tumor Immune Estimation Resource (TIMER) (https://cistrome.shinyapps.io/timer/) is a public database containing 10897 samples across 32 cancer types from The Cancer Genome Atlas (TCGA) database[17]. A pancancer study of SKA3 expression was performed using the TIMER database. The TCGA (https://cancergenome.nih.gov/) is a large-scale Cancer Genome Project database that provides clinical and pathological information on 33 cancers[18]. Gene expression data and corresponding clinical information of 424 samples, namely, 374 tumors and 50 normal samples were collected from TCGA database. The HCC patients were divided into high- and low-expression groups according to the median SKA3 Level. Clinical characteristics of the HCC patients were summarized in Table 1. The Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo) contains high-throughput gene expression data from research institutions worldwide[19]. Gene expression profiles of the GSE62232 and GSE121248 datasets were downloaded from the GEO database. The TIMER, TCGA and GEO databases are publicly available and did not require the ethics committee's approval.

WB

The total protein from the HCC tissues was extracted with radioimmunoprecipitation assay lysis buffer, and the protein was quantitated with a bicinchoninic acid protein assay kit. Then, the protein was separated by 10% SDS-polyacrylamide gel electrophoresis and transferred to a polyvinylidene difluoride (PVDF) membrane. The PVDF membranes were incubated in 5% nonfat milk powder diluted in Tris-buffered saline Tween (TBST) at room temperature for 2 h. After washing three times with TBST, the membranes were incubated with SKA3 antibodies (1:1000 dilution) overnight at 4 °C. The next day, the membranes were washed three times with TBST and incubated with the secondary antibody diluted in blocking solution for 1-2 h at room temperature. The membranes were washed three times with TBST. An appropriate volume of developer solution was evenly applied to the PVDF membrane, which was developed with a fluorescence imaging system.

Immunohistochemistry

We performed immunohistochemistry staining on 56 paraffin-embedded HCC tissues, and SKA3 antibody was purchased from Thermo Fisher (PA5-58722). The samples were mixed with SKA3 primary antibodies, incubated overnight at 4 °C, deparaffinized, hydrated, and blocked. The immunohistochemistry (IHC) staining results were analyzed and scored by two pathologists who were blinded to the sample origins. The staining intensity (0, no staining; 1+, weak staining; 2+, moderate staining; 3+, strong staining) and percentage of positive cells (0: < 5%; 1: 5%-25%, 2: 26%-50%; 3: 51%-75%; 4: > 75%) were evaluated using a semiquantitative scoring system. The staining intensity and positive cells were rated as follows: 0 was negative (-), 1-4 was weakly positive (+), 5-8 was moderately positive (++), and 9-12 was strongly positive (+++).

Construction of the nomogram

A nomogram is a reliable statistical predictive tool that estimates individualized risk[20]. Based on the SKA3 expression and clinicopathological features, we constructed a prognostic model to predict the overall survival (OS) of HCC patients. Model performance was quantified by discrimination and calibration[21]. The discriminative ability of the nomogram was assessed by the C-index, which ranged from 0.5 (no discrimination) to 1 (perfect discrimination). The calibration

Table 1 Clinical characteristics of hepatocellular carcinoma patients in The Cancer Genome Atlas database, *n* (%)

Characteristic	Low expression of SKA3	High expression of SKA3	*P* value
	n = 187	*n* = 187	
Age			0.034
≤ 60	78 (44.1)	99 (55.9)	
> 60	109 (55.6)	87 (44.4)	
Sex			0.269
Female	55 (45.5)	66 (54.5)	
Male	132 (52.2)	121 (47.8)	
Race			0.008
Asian	65 (40.6)	95 (59.4)	
Black or African American	9 (52.9)	8 (47.1)	
White	106 (57.3)	79 (42.7)	
T stage			0.031
T1	105 (57.4)	78 (42.6)	
T2	41 (43.2)	54 (56.8)	
T3	33 (41.2)	47 (58.8)	
T4	5 (38.5)	8 (61.5)	
N stage			1.000
N0	119 (46.9)	135 (53.1)	
N1	2 (50)	2 (50)	
M stage			0.355
M0	128 (47.8)	140 (52.2)	
M1	3 (75)	1 (25)	
AFP (ng/mL)			< 0.001
≤ 400	124 (57.7)	91 (42.3)	
> 400	17 (26.2)	48 (73.8)	
Child-Pugh grade			0.813
A	118 (53.9)	101 (46.1)	
B	10 (47.6)	11 (52.4)	
C	1 (100)	0 (0)	
Pathologic stage			0.024
Stage I	98 (56.6)	75 (43.4)	
Stage II	39 (44.8)	48 (55.2)	
Stage III	34 (40)	51 (60)	
Stage IV	4 (80)	1 (20)	
Vascular invasion			0.121
No	115 (55.3)	93 (44.7)	
Yes	50 (45.5)	60 (54.5)	

HCC: Hepatocellular carcinoma; SKA3: Spindle and kinetochore-associated complex subunit 3; AFP: Alpha fetoprotein.

curve was used to compare the actual risk and predicted risk. A value of $P < 0.05$ was considered statistically significant.

Enrichment analysis

Gene Set Enrichment Analysis (GSEA) is a computational method for determining whether a predefined set of genes is statistically significant in two biological states[22]. GSEA was performed to identify signaling pathways involved in SKA3-mediated effects by using the R package ClusterProfiler[23]. The reference gene set in this study was c2.cp.v7.2.symbols.gmt. The normalized enrichment score was calculated for each gene set. A false discovery rate < 0.25 and adjusted *P* value < 0.05 were used to identify positive significantly enriched pathways[24,25].

Immune cell infiltration and immune checkpoint analysis

To evaluate the potential relationships between SKA3 expression and tumor-infiltrating immune cells (TIICs) in the microenvironment, the TCGA database was used to quantify the level of immune cell infiltration *via* the TIMER database and single-sample GSEA (ssGSEA) algorithm[26]. Subsequently, a heatmap showed the correlation of 24 types of immune cells. Additionally, we explored the correlation between SKA3 expression and immune checkpoints [programmed cell death protein 1 (PDCD-1), cytotoxic T lymphocyte antigen 4 (CTLA-4)] with Spearman's correlation test. A value of $P < 0.05$ was considered statistically significant.

Drug sensitivity analysis

The Genomics of Drug Sensitivity in Cancer (GDSC) (https://www.cancerrxgene.org/) is the largest publicly available pharmacogenomics database[27,28], and we predicted each sample's chemotherapeutic response to sorafenib, sunitinib, paclitaxel, doxorubicin, VX-680, and gemcitabine by the R package "pRRophetic". Ridge regression was used to calculate the half-maximal inhibitory concentration (IC50). A value of $P < 0.05$ was considered statistically significant.

Statistical analysis

Statistical analysis was performed with R (http://www.Rproject.org). The expression of SKA3 in HCC tissues and normal tissues was assessed by the Wilcoxon rank-sum test and Wilcoxon signed-rank test. Kruskal-Wallis and Wilcoxon rank-sum tests were used to evaluate the relationship between SKA3 expression and clinicopathological features. Receiver operating characteristic (ROC) analysis was performed to assess the diagnostic value of SKA3 in HCC using the pROC package. The link between SKA3 expression and prognosis was investigated using Kaplan-Meier survival analysis. In all tests, a value of $P < 0.05$ was considered statistically significant.

RESULTS

High expression of SKA3 in HCC

We found that SKA3 expression was significantly increased in various malignant tumors, including liver hepatocellular carcinoma, cervical cancer, and colorectal cancer (Figure 1A). TCGA, GSE62232, and GSE121248 revealed that SKA3 expression was increased in HCC tumor tissues compared to that in matched normal tissues (Figure 1B-E). In addition, the WB results were consistent with the above results (Figure 1F and G). We also obtained RNA-sequencing data and clinical prognostic information resources of 374 HCC patients from the TCGA database (Table 1). The relationship between SKA3 expression and clinicopathological features was explored, and the results showed that SKA3 expression was significantly correlated with the pathological stage (Stage I and Stage III, $P < 0.01$, Figure 2A), T stage (T1 and T2, $P < 0.05$; T1 and T3, $P < 0.01$; Figure 2B), AFP level ($P < 0.001$, Figure 2C) and vascular invasion ($P < 0.05$, Figure 2D). The area under the curves of SKA3 expression and the AFP level were 0.973 and 0.720, respectively, suggesting that SKA3 expression had a strong diagnostic ability for HCC (Figure 2E and F). In conclusion, SKA3 expression, mRNA expression and protein expression were significantly higher in HCC tissues.

High SKA3 expression indicated a poor survival outcome in HCC

Kaplan-Meier survival analysis was performed to investigate the relationship between SKA3 expression and prognosis, and the results revealed that patients with high SKA3 expression had a poor OS and progression-free interval ($P = 0.004$, Figure 3A; $P = 0.001$, Figure 3B). Furthermore, we included the TNM stage, pathological status, vascular invasion, and AFP levels in the subgroup Kaplan-Meier analysis. The subgroup analysis indicated that the high SKA3 expression group had poorer OS in the T stage (T1 and T2 and T3, $P = 0.009$, Figure 3C), N stage (N0, $P < 0.001$, Figure 3D) and M stage (M0, $P < 0.001$, Figure 3E). The above results showed that the expression level of SKA3 could be used to predict the prognosis of HCC patients with different TNM stages. To further verify the relationship between SKA3 expression and the prognosis of HCC patients, we performed IHC staining on 56 paraffin-embedded HCC tissues and found that high SKA3 expression was associated with poor OS ($P = 0.246$, Figure 3F). In summary, SKA3 overexpression indicated a poor prognosis for HCC.

Construction of the nomogram

We performed univariable and multivariable Cox regression analyses to evaluate the relationship between SKA3 expression, clinicopathological features, and OS. Univariate Cox regression revealed that the pathological status (Stage III and Stage IV, $P < 0.001$), T stage (T3 and T4, $P < 0.001$), M stage (M1, $P = 0.017$) and high SKA3 expression ($P = 0.004$) were risk factors (Figure 4A) (all $P < 0.05$). Multivariate Cox analysis further confirmed that high SKA3 expression could serve as an independent risk factor ($P = 0.003$, Figure 4B). To provide clinicians with a quantitative method for predicting the prognosis of patients, a nomogram based on SKA3 expression and clinicopathological features was constructed

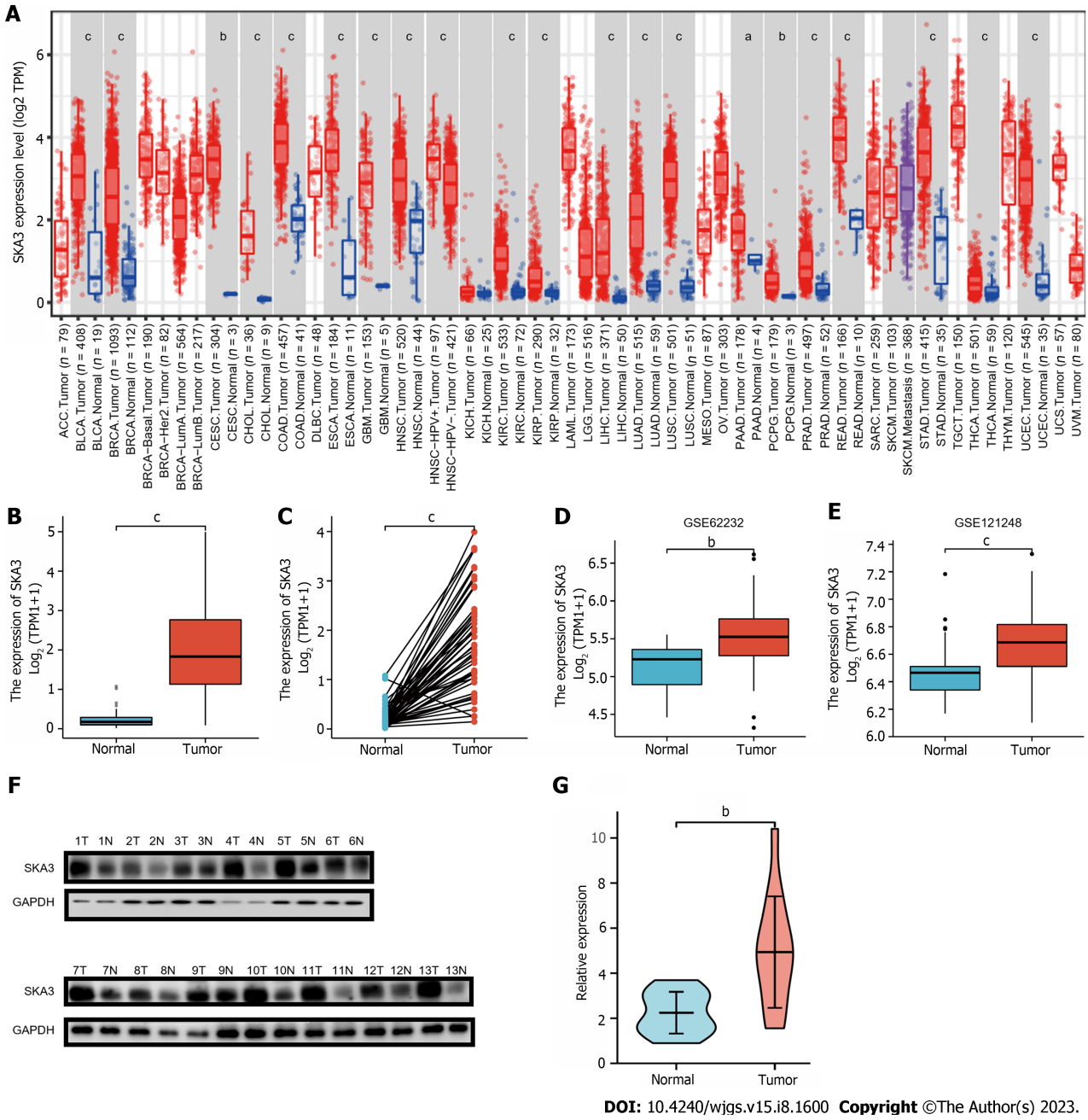

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Figure 1 Spindle and kinetochore-associated complex subunit 3 expression levels in cancers. A: Expression levels of spindle and kinetochore-associated complex subunit 3 (SKA3) in different cancers according to the Tumor Immune Estimation Resource database; B and C: Expression levels of SKA3 in hepatocellular carcinoma (HCC) tissues and normal tissues in The Cancer Genome Atlas database; B: Unmatched tissues; C: Matched tissues; D-G: Validation of high SKA3 expression in HCC using an external database and clinical specimens; D and E: GSE62232 and GSE121248 datasets; F: Western blot; G: The relative expression of SKA3 protein was analyzed by ImageJ software. SKA3: Spindle and kinetochore-associated complex subunit 3; HCC: Hepatocellular carcinoma. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$.

(Figure 4C). Each patient was assigned a total score from the nomogram, and patients with higher scores had a poor prognosis. The C-index and calibration plot were constructed to estimate the accuracy of the prognostic model. The results showed that the C-index was 0.661, and the calibration curve had good agreement between the actual and predicted probability (Figure 4D). The nomogram was a reliable prognostic tool for predicting OS in HCC patients.

GSEA identifies SKA3-related signaling pathways

GSEA was performed to identify the biological signaling pathways associated with SKA3 expression in HCC. Functional enrichment analysis indicated that DNA repair and the cell cycle checkpoints, mitotic G1 phase and G1-S transition, S phase, G2-M checkpoints, M phase, mitotic spindle checkpoint, regulation of tumor protein 53 (TP53) activity, and cell cycle were enriched in the high SKA3 expression group (Figure 5) (all *P*.adj < 0.05). In addition, we analyzed the correlation between SKA3 expression and cell cycle-related molecules and found that SKA3 expression was positively correlated with the expression of CDK1, CDK2, CDK4, cell division cycle 6 (CDC6), cell division cycle 20 (CDC20), cell

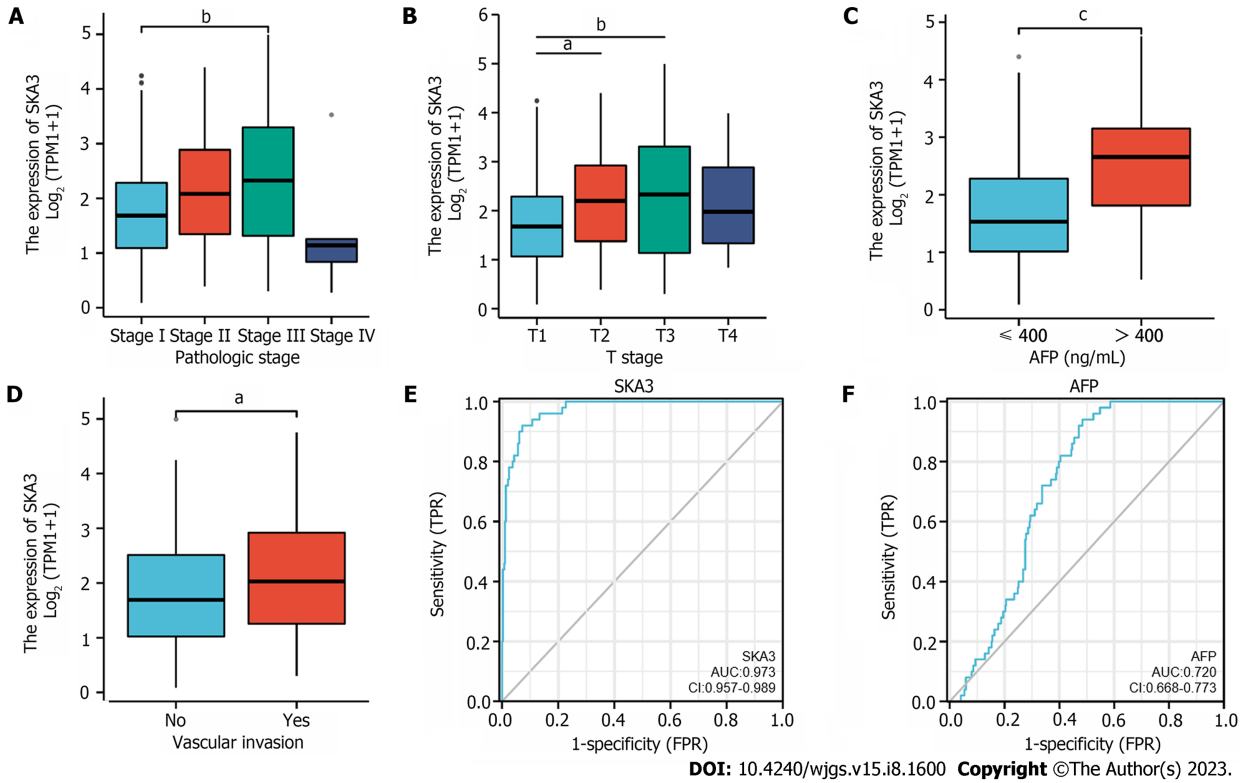

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Figure 2 Relationship between spindle and kinetochore-associated complex subunit 3 expression and clinicopathological features. A: Pathologic stage; B: T stage; C: Alpha fetoprotein (AFP) level; D: Vascular invasion; E and F: Receiver operating characteristic curve of spindle and kinetochore-associated complex subunit 3 expression (E) and AFP level (F) in hepatocellular carcinoma. SKA3: Spindle and kinetochore-associated complex subunit 3; AFP: Alpha fetoprotein; AUC: Area under the curves. [a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$.

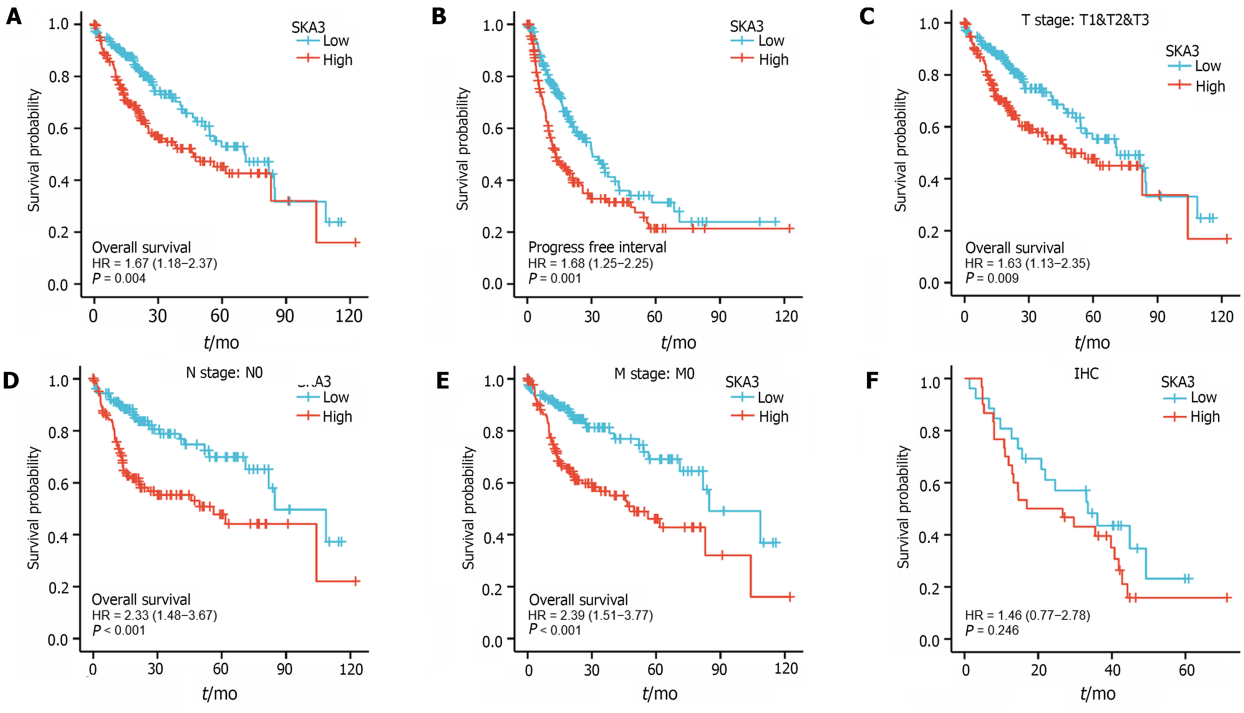

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Figure 3 Kaplan Meier survival curves of hepatocellular carcinoma patients in the spindle and kinetochore-associated complex subunit 3 high- and low-expression groups. A: Overall survival (OS); B: Progression-free interval; C-E: OS for subgroup analysis based on T stage (C), N stage (D), and M stage (E); F: Immunohistochemistry staining results showing that high spindle and kinetochore-associated complex subunit 3 expression was associated with poor prognosis in hepatocellular carcinoma patients. SKA3: Spindle and kinetochore-associated complex subunit 3; HR: Hazard ratio; IHC: Immunohistochemistry.

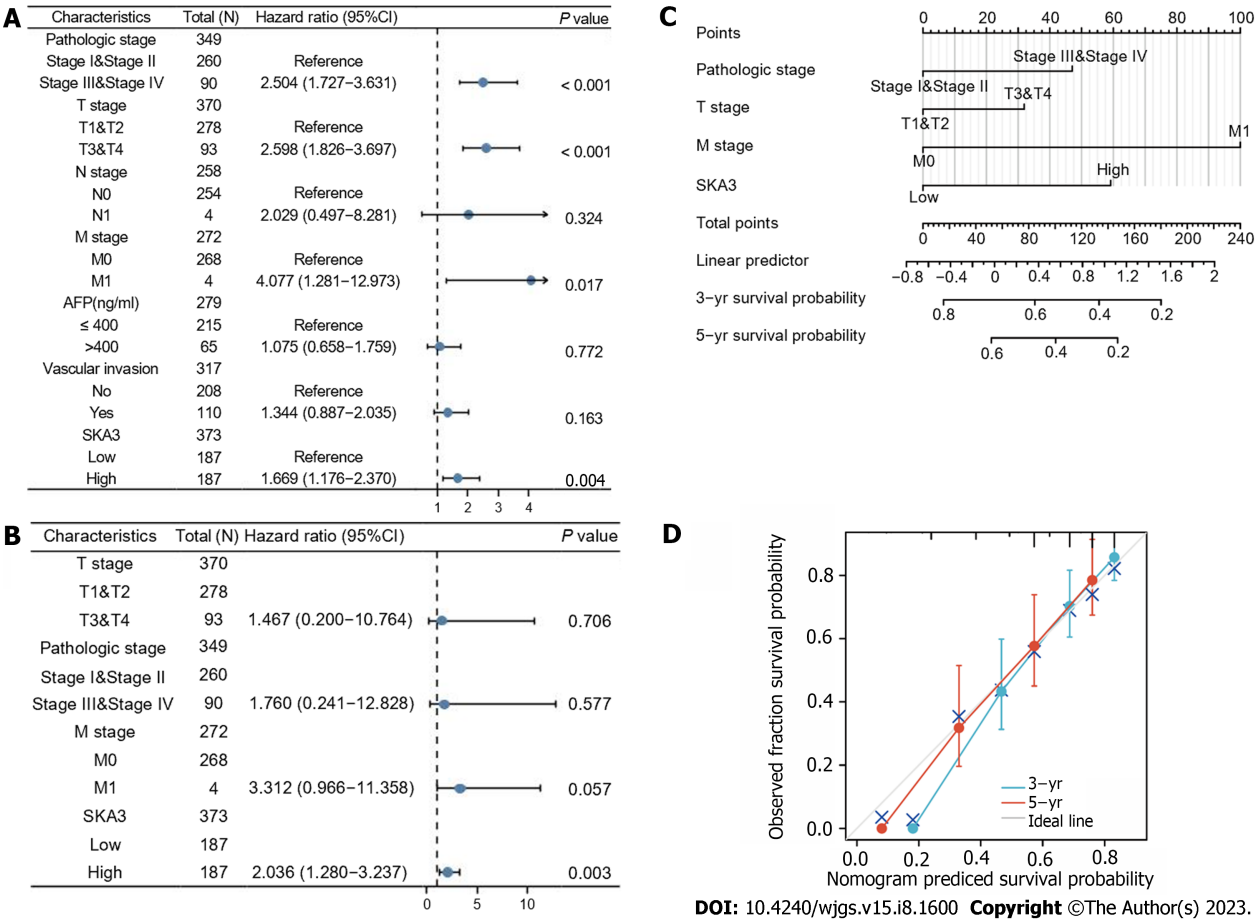

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Figure 4 Construction of the nomogram. A and B: Forest plot revealing the univariate and multivariate Cox analyses of overall survival (OS)-related variables; C: The nomogram incorporating the pathological stage, T stage, M stage and spindle and kinetochore-associated complex subunit 3 expression was identified as a predictor of the 3-, and 5-yr OS probabilities of hepatocellular carcinoma patients; D: Calibration curves of 3-, and 5-yr of OS. SKA3: Spindle and kinetochore-associated complex subunit 3; AFP: Alpha fetoprotein.

division cycle 25A (CDC25A), E2F transcription factor 1 (E2F1), cyclin A2 (CCNA2), and cyclin E2 (CCNE2) (Figure 6) (all $P < 0.001$). SKA3 may promote HCC cell proliferation by regulating the cell cycle. In summary, the above findings revealed that SKA3 expression may be closely involved in proliferation-related processes *via* the cell cycle, DNA repair, and the TP53 pathway.

SKA3 expression was involved in immune infiltration in HCC

The TIMER database showed that SKA3 was significantly related to the infiltration levels of B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells (Figure 7A) (all $P < 0.05$). Furthermore, we used the ssGSEA algorithm to quantify the level of immune cell infiltration in the high- and low-expression groups of SKA3, and the results demonstrated that the CD8+ T cells, natural killer (NK) cells, and DCs had lower infiltration levels in the high SKA3 expression group (Figure 7B). A heatmap was applied to evaluate the relationship between 24 immune cells, which revealed that the ratios of different TIIC subpopulations were moderately to strongly correlated (Figure 7C). In addition, we also analyzed the correlation between SKA3 expression and immune checkpoints and found that SKA3 expression was positively correlated with PDCD-1 and CTLA-4 (Figure 7D). Our results indicated that the high SKA3 expression group had lower antitumor immune cells.

Relationship between SKA3 expression and drug sensitivity

According to the predicted IC50 values, there was a statistically significant difference in the response to anticancer drugs between the high- and low-SKA3 groups. Patients in the high SKA3 group were more sensitive to sorafenib, sunitinib, paclitaxel, doxorubicin, gemcitabine, and vx-680 (Figure 8).

DISCUSSION

Given the high morbidity and mortality of HCC, a large proportion of patients with HCC are diagnosed at an advanced stage with poor clinical outcomes, mainly due to tumor metastasis and tumor recurrence[29]. Therefore, identifying genes

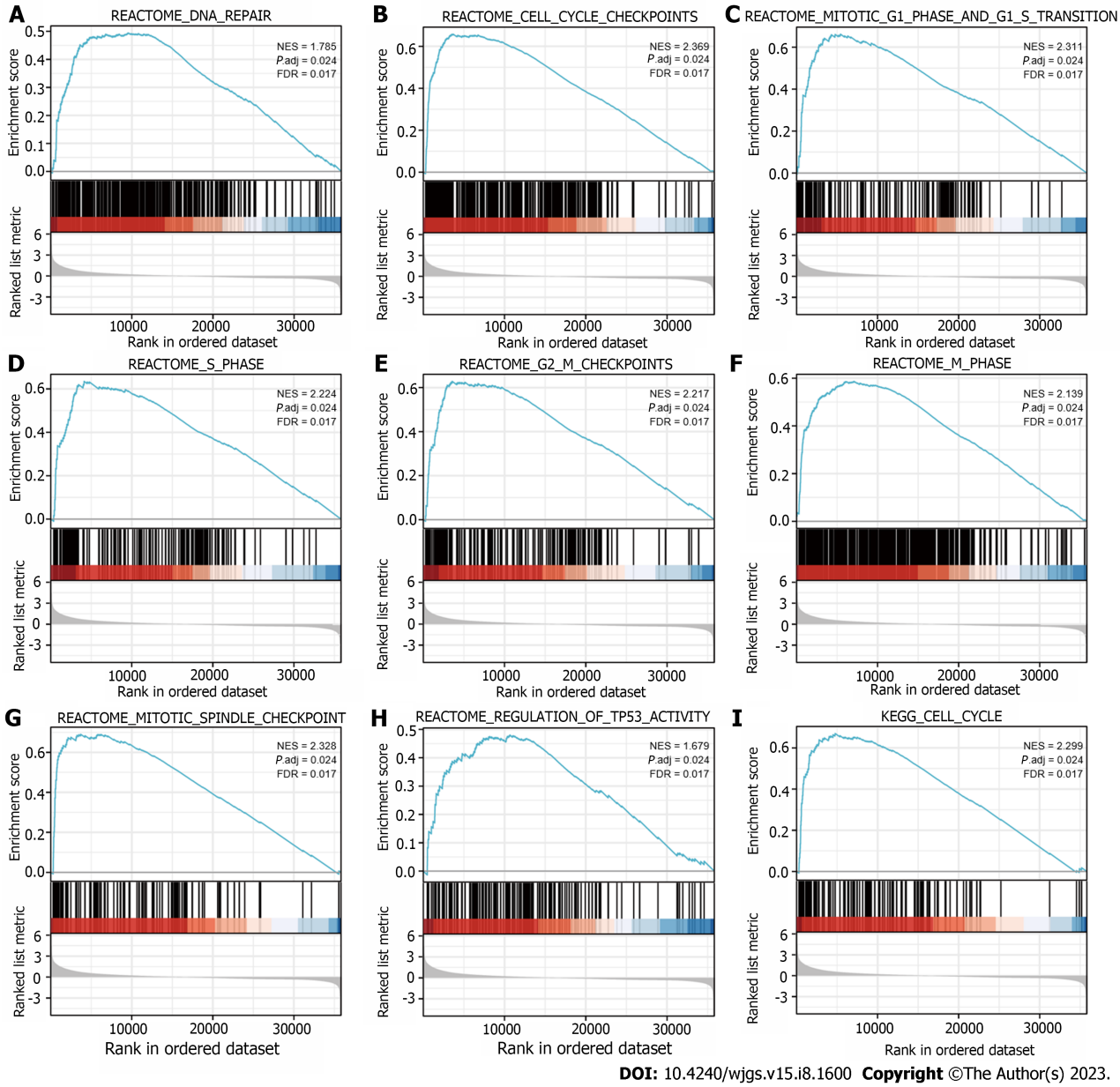

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Figure 5 Analysis of spindle and kinetochore-associated complex subunit 3-related biological pathways by Gene Set Enrichment Analysis. A: DNA repair; B: Cell cycle checkpoints; C: Mitotic G1 phase and G1-S transition; D: S phase; E: G2-M checkpoints; F: M phase; G: Mitotic spindle checkpoint; H: Regulation of TP53 activity; I: Cell cycle. SKA3: Spindle and kinetochore-associated complex subunit 3; GSEA: Gene Set Enrichment Analysis.

that are dysregulated during tumor growth may potentially help improve prognosis and therapy options.

SKA3 encodes a component of the SKA complex that regulates microtubule attachment to kinetochores during mitosis. The encoded protein localizes to the outer kinetochore and is required for normal chromosome segregation and cell division[30]. SKA3 drives cell cycle progression and is frequently overexpressed in various tumors, which is closely associated with tumorigenesis and development. However, the mechanism of SKA3 expression in HCC has not been elucidated in detail. In this study, we identified that SKA3 expression was significantly upregulated and associated with poor prognosis in patients with HCC in public databases and those with collected clinical samples. Multivariate analysis showed that high SKA3 expression could be an independent risk factor for poor prognosis in HCC patients. In addition, a nomogram was constructed based on clinicopathological features and SKA3 expression to predict the prognosis in patients with HCC. The above findings suggested that upregulated SKA3 was substantially correlated with poor prognosis in patients with HCC.

The most basic biological feature of malignant tumors is the uncontrolled proliferation of tumor cells, and dysregulation of the cell cycle is a hallmark feature of uncontrolled cell proliferation[31]. Studies have demonstrated that the transition from the G1 phase to the actively cycling S/G2/M phases is controlled by sequential activation of cyclin-CDK complexes. Cell cycle progression from the G1 to S phase is guided by CDK4, CDK6, and CDK2, followed by the phosphorylation and inactivation of pRB and release of E2F transcription factors[32,33]. Hou *et al*[34] found that the overexpression of SKA3 could alleviate apoptosis and promote proliferation of HCC cells, which may be related to inhibiting the phosphorylation of p53 by interaction with CDK2[34]. The p53 gene is a tumor suppressor gene that plays

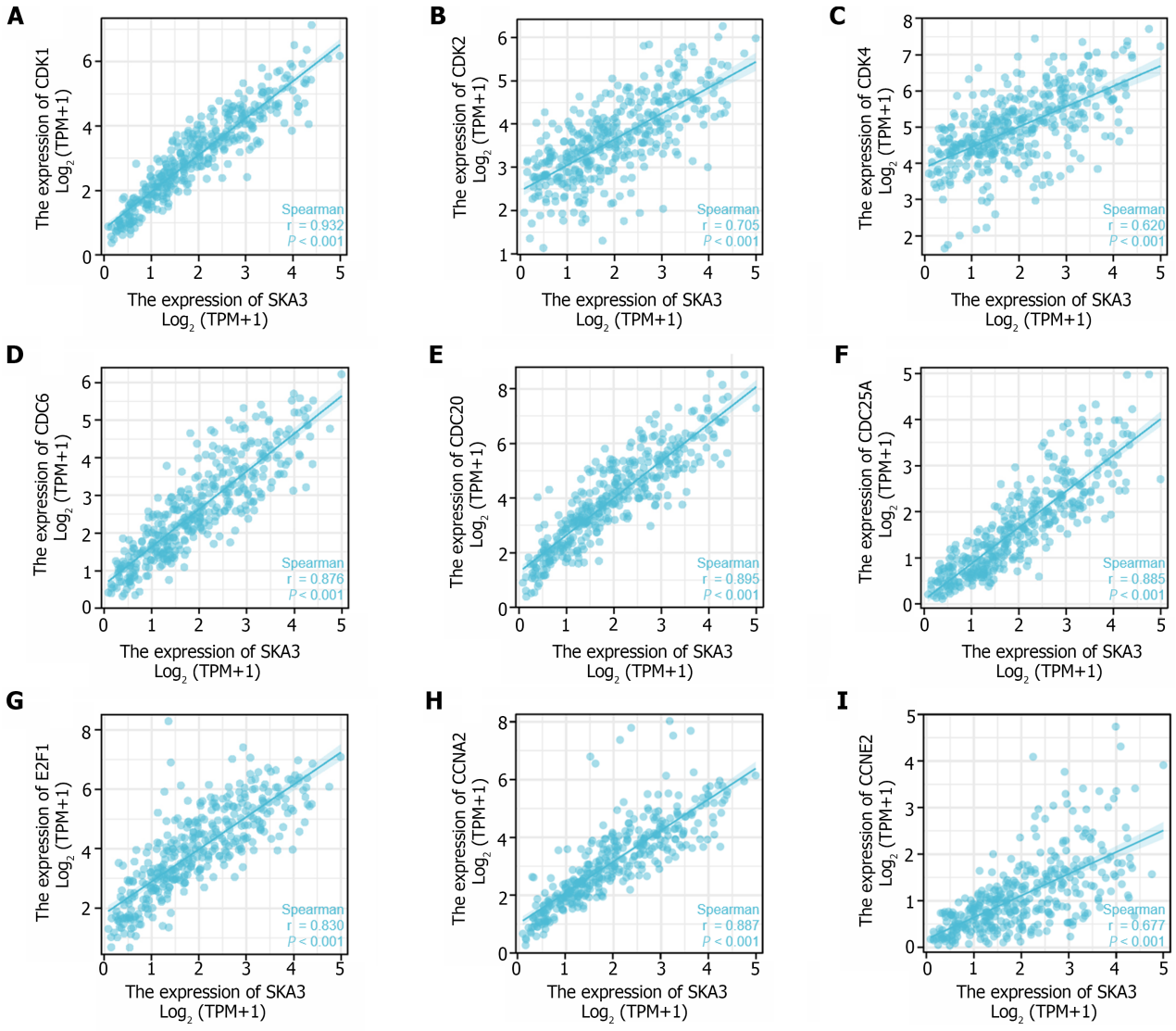

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Figure 6 Correlation of spindle and kinetochore-associated complex subunit 3 expression with cell cycle-related molecules. A: Cyclin-dependent kinase 1; B: Cyclin-dependent kinase 2; C: Cyclin-dependent kinase 4; D: Cell division cycle 6; E: Cell division cycle 20; F: Cell division cycle 25A; G: E2F transcription factor 1; H: Cyclin A2; I: Cyclin E2. SKA3: Spindle and kinetochore-associated complex subunit 3; CDK1: Cyclin-dependent kinase 1; CDK2: Cyclin-dependent kinase 2; CDK4: Cyclin-dependent kinase 4; CDC6: Cell division cycle 6; CDC20: Cell division cycle 20; CDC25A: Cell division cycle 25A; E2F1: E2F transcription factor 1; CCNA2: Cyclin A2; CCNE2: Cyclin E2.

an important role in regulating the cell cycle, DNA damage repair and immunity[35]. Mutant p53 can act as a transcription factor to regulate the expression of downstream target genes, leading to tumorigenesis. Our research found that the high SKA3 expression group was significantly enriched in DNA repair and the cell cycle checkpoints, mitotic G1 phase and G1-S transition, S phase, G2-M checkpoints, M phase, mitotic spindle checkpoint, regulation of TP53 activity, and cell cycle. Furthermore, SKA3 was positively correlated with the expression of CDK1, CDK2, CDK4, CDC6, CDC20, CDC25A, E2F1, CCNE2 and CCNA2 (all $P < 0.05$). SKA3 expression promoted HCC proliferation, which may be related to the uncontrolled cell cycle, constant division and proliferation.

The tumor microenvironment (TME), consisting of tumor cells, immune cells, and extracellular matrix, is inextricably linked with the development, invasion, and metastasis of tumors. Previous research has proven that a high infiltration of CD8+ T cells in malignant tumors indicates a favorable prognosis[36,37]. Low NK cell activity is associated with an increased risk of carcinogenesis, suggesting its role in the natural immunological host defense mechanisms against cancer [38]. Patients with a high number of DC cell infiltrations had a better prognosis in various solid tumors, such as lung, gastric, and colorectal carcinoma[39]. Interestingly, patients with high SKA3 expression displayed low infiltration levels of CD8+ T cells, NK cells, and DCs, indicating that high SKA3 expression may suppress antitumor-related innate immunity and adaptive immunity in the TME, based on the results from TIMER and ssGSEA. In addition, immune checkpoint inhibitors (ICISs) are an emerging tumor immunotherapy strategy that can improve the prognosis of cancer patients. PDCD-1 and CTLA-4 are common response biomarkers to ICISs. The results showed that SKA3 expression was positively correlated with PDCD-1 and CTLA-4 Levels ($P < 0.05$). SKA3 may upregulate the expression level of related immunosuppressive molecules (PDCD-1 and CTLA-4), resulting in immune escape. The above results revealed that SKA3

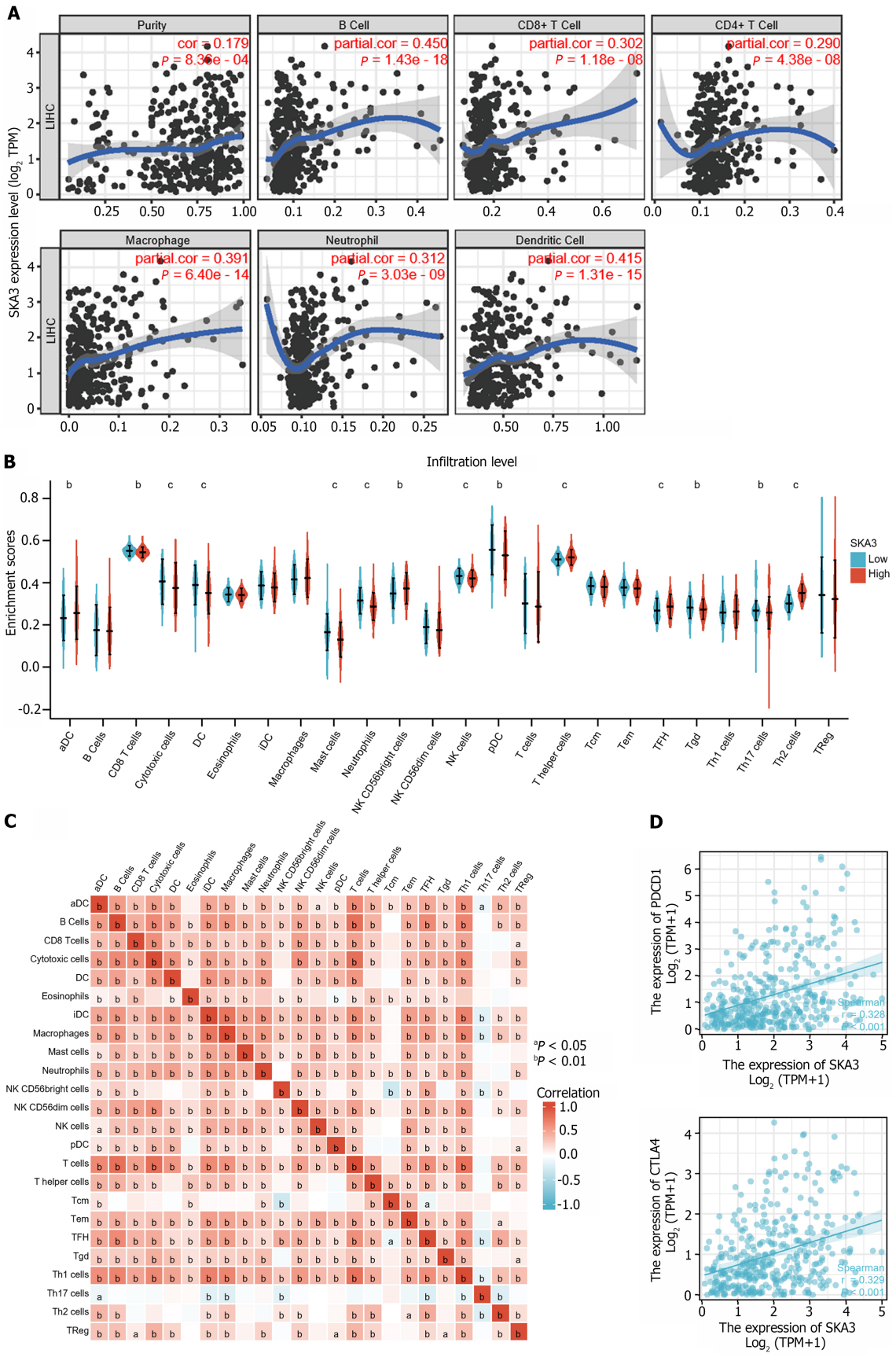

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Figure 7 Association between the spindle and kinetochore-associated complex subunit 3 expression level and immune microenvironment factors in hepatocellular carcinoma. A: Correlation analysis between spindle and kinetochore-associated complex subunit 3 (SKA3) expression and the infiltration levels of 7 tumor-infiltrating immune cells as assessed *via* the Tumor Immune Estimation Resource database; B: Proportions of 24 types of infiltrating immune cells in the groups with low and high expression of SKA3 determined by single-sample Gene Set Enrichment Analysis; C: Correlation

heatmap of the 24 immune cell types; D: Scatter plot. The fitted line showed the relationship between SKA3 expression and immune checkpoint inhibitors (programmed cell death protein 1, cytotoxic T lymphocyte antigen 4). SKA3: Spindle and kinetochore-associated complex subunit 3; HCC: Hepatocellular carcinoma; TIICs: Tumor-infiltrating immune cells; PDCD-1: Programmed cell death protein 1; CTLA-4: Cytotoxic T lymphocyte antigen 4. [a]*P* < 0.05, [b]*P* < 0.01, [c]*P* < 0.001.

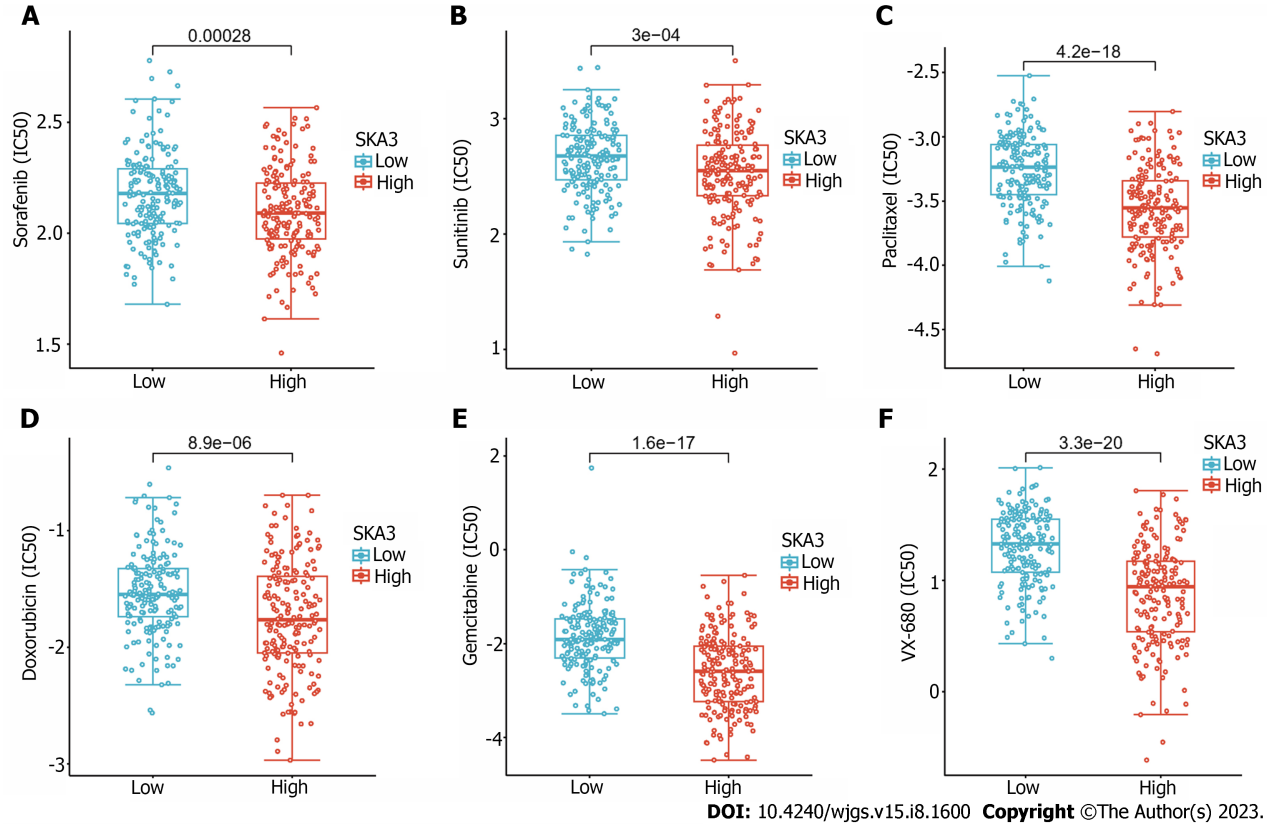

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Figure 8 Half maximal inhibitory concentration of six commonly used chemotherapeutic drugs in groups with high and low expression of spindle and kinetochore-associated complex subunit 3. A: Sorafenib; B: Sunitinib; C: Paclitaxel; D: Doxorubicin; E: Gemcitabine; F: Vx-680. IC50: Half maximal inhibitory concentration; SKA3: Spindle and kinetochore-associated complex subunit 3.

may affect patient prognosis by regulating immune infiltration and ICI response in HCC.

For most patients with advanced HCC, chemotherapy remains the main therapeutic strategy, and first-line agents such as sorafenib have improved the prognosis of patients[40]. To investigate the roles of SKA3 on the sensitivity of chemotherapeutics drugs, we also revealed the sensitivity of six commonly used drugs in HCC with high and low SKA3 expression based on the GDSC database. Our results indicated that patients in the high SKA3 group were more sensitive to sorafenib, sunitinib, paclitaxel, doxorubicin, gemcitabine, and vx-680. SKA3 may be a promising predictive marker for therapy in HCC.

However, our research also had certain limitations. First, the sample size should be further expanded to increase the credibility of the results. Furthermore, animal experiments are needed to clarify the biological mechanism of SKA3 expression in HCC.

CONCLUSION

Upregulation of SKA3 expression led to poor prognosis in patients with HCC by enhancing HCC proliferation and repressing immune cell infiltration surrounding HCC. SKA3 has the potential to be a potential prognostic biomarker for HCC.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC) is a malignant tumor with high morbidity and high mortality. Therefore, there is an urgent need to explore biomarkers for the early diagnosis, prognostic assessment and treatment of HCC in the clinic.

Research motivation
Spindle and kinetochore-associated protein 3 (SKA3) is a malignancy-related gene, and plays an important role in promoting the proliferation and migration of tumors. Studies have reported that SKA3 overexpression is significantly associated with poor prognosis in various malignant tumors. However, the mechanism of SKA3 in HCC has not been fully elucidated.

Research objectives
This study aimed to explore the molecular mechanisms of SKA3 in HCC.

Research methods
SKA3 expression, clinicopathological characteristics, and survival analysis were performed using the Tumor Immune Estimation Resource (TIMER), The Cancer Genome Atlas and Gene Expression Omnibus databases, and the results were further verified with collected clinical samples by western blot and immunohistochemistry staining. Gene Set Enrichment Analysis (GSEA) was performed to evaluate the biological functions and molecular mechanisms of SKA3 in HCC. In addition, we utilized the TIMER and single-sample GSEA algorithms to estimate the abundances of tumor-infiltrating immune cells in HCC. The R package "pRRophetic" was applied to predict chemotherapeutic response in HCC patients.

Research results
SKA3 was significantly upregulated in HCC, and upregulated SKA3 expression correlated with poor prognosis in HCC patients. Multivariable COX regression analysis indicated that SKA3 was an independent risk factor for overall survival. GSEA revealed that SKA3 may be involved in proliferation-related processes by regulating cell cycle and DNA repair. In addition, there were lower levels of infiltrating CD8+ T cells, natural killer cells, and dendritic cells in the high SKA3 expression group. Drug sensitivity analysis showed that patients with high SKA3 expression were more sensitive to sorafenib, sunitinib, paclitaxel, doxorubicin, gemcitabine, and vx-680.

Research conclusions
High SKA3 expression was associated with poor prognosis and decreased immune cell infiltration in HCC.

Research perspectives
SKA3 may be a biomarker of poor prognosis and a therapeutic target in HCC.

FOOTNOTES

Author contributions: Zheng LL wrote the manuscript; Wang YR, Liu ZR, Wang ZH, Tao CC, Xiao YG, Zhang K, Wu AK and Li HY contributed to the design of and critically reviewed and revised the manuscript; Wu JX, Xiao T and Rong WQ revised the draft; all authors reviewed and approved the final version.

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Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

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Country/Territory of origin: China

ORCID number: Lin-Lin Zheng 0000-0001-7274-3872; Chang-Cheng Tao 0000-0002-1082-2572; An-Ke Wu 0000-0003-3316-2930; Jian-Xiong Wu 0000-0002-7274-3917; Wei-Qi Rong 0000-0002-1127-1709.

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ORIGINAL ARTICLE

Case Control Study

Post-transplant biliary complications using liver grafts from deceased donors older than 70 years: Retrospective case-control study

Carlos Jimenez-Romero, Iago Justo-Alonso, Pilar del Pozo-Elso, Alberto Marcacuzco-Quinto, Cristina Martín-Arriscado-Arroba, Alejandro Manrique-Municio, Jorge Calvo-Pulido, Alvaro García-Sesma, Ricardo San Román, Oscar Caso-Maestro

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Carlos Jimenez-Romero, Iago Justo-Alonso, Pilar del Pozo-Elso, Alberto Marcacuzco-Quinto, Alejandro Manrique-Municio, Jorge Calvo-Pulido, Alvaro García-Sesma, Oscar Caso-Maestro, Unit of HPB Surgery and Abdominal Organs Transplantation, `12 de Octubre´ University Hospital, Madrid 28041, Spain

Cristina Martín-Arriscado-Arroba, Clinical Research Unit (I+12), `12 de Octubre´ University Hospital, Madrid 28041, Spain

Ricardo San Román, Department of Radiology, `12 de Octubre´ University Hospital, Madrid 28041, Spain

Corresponding author: Oscar Caso-Maestro, MD, PhD, Associate Professor, Surgeon, Unit of HBP Surgery and Abdominal Organs Transplantation, '12 de Octubre' University Hospital, Av. Córdoba s/n, Madrid 28041, Spain. oscarcasomaestro@hotmail.com

Abstract

BACKGROUND

The shortage of liver grafts and subsequent waitlist mortality led us to expand the donor pool using liver grafts from older donors.

AIM

To determine the incidence, outcomes, and risk factors for biliary complications (BC) in liver transplantation (LT) using liver grafts from donors aged > 70 years.

METHODS

Between January 1994 and December 31, 2019, 297 LTs were performed using donors older than 70 years. After excluding 47 LT for several reasons, we divided 250 LTs into two groups, namely post-LT BC (n = 21) and without BC (n = 229). This retrospective case-control study compared both groups.

RESULTS

Choledocho-choledochostomy without T-tube was the most frequent technique (76.2% in the BC group *vs* 92.6% in the non-BC group). Twenty-one patients (8.4%) developed BC (13 anastomotic strictures, 7 biliary leakages, and 1 non-

anastomotic biliary stricture). Nine patients underwent percutaneous balloon dilation and nine required a Roux-en-Y hepaticojejunostomy because of dilation failure. The incidence of post-LT complications (graft dysfunction, rejection, renal failure, and non-BC reoperations) was similar in both groups. There were no significant differences in the patient and graft survival between the groups. Moreover, only three deaths were attributed to BC. While female donors were protective factors for BC, donor cardiac arrest was a risk factor.

CONCLUSION

The incidence of BC was relatively low on using liver grafts > 70 years. It could be managed in most cases by percutaneous dilation or Roux-en-Y hepaticojejunostomy, without significant differences in the patient or graft survival between the groups.

Key Words: Older liver; Liver transplant; Biliary complications; Biliary strictures; Septuagenarian donors; Octogenarian donors

Core Tip: The shortage of liver grafts and subsequent waitlist mortality led us to expand the donor pool using liver grafts from older donors. Some authors have proposed a higher incidence of biliary complications (BC) using advanced age donors. In our experience, the incidence of BC was low on using liver grafts > 70 year (8.4%). Patient and graft survival were similar to patients without biliary complications and most of them could be managed by percutaneous dilation or Roux-en-Y hepaticojejunostomy.

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INTRODUCTION

Excellent outcomes obtained with liver transplantation (LT) have led to an increasing number of candidates on the waiting list. However, the number of liver grafts remains stable. The historical liver shortage and subsequent waiting list mortality (5.2% in 2019)[1] led us to expand the donor pool using livers from extended-criteria donors, such as those with split-liver, living-related, and donor after circulatory death (DCD)[2]. However, our group principally increased the progressive utilization of livers from older donors, without an age limit, a practice already initiated in 1996[3].

There is controversial because some series have reported a significantly worse patient and graft survival[4,5] using older livers from deceased donors *vs* other reports defending the use of septuagenarian[6-11] and octogenarian liver grafts for non-hepatitis C virus (HCV) diseases[6,8,9,12-15]. A recent study from the Scientific Registry of Transplant Recipients has demonstrated that the use of liver grafts ≥ 70 years provide substantial long-term survival benefits, compared to waiting for a better organ offer[16]. In contrast, several series using older livers from donors after brain death (DBD) have demonstrated significantly higher incidence of post-LT biliary complications (BC) than the use of younger livers[11,17-21], considering BC is a major source of morbi-mortality and costs[21-23]. There are no studies analyzing the incidence and outcomes of BC in patients older and younger than 70 years. There is only a recent meta-analysis that did not find significant differences in BC between recipients of liver grafts ≥ 70 years and those of grafts < 70 years[24].

Thus, the aim of the present study is to analyze specifically the incidence, outcomes, and risk factors of BC in patients who underwent LT using liver grafts from donors older than 70 years.

MATERIALS AND METHODS

Study population and design

Between April 1986 and December 2019, 2057 LTs were performed at our hospital. Between January 1994 and December 31, 2019, 297 LTs were performed using livers older than 70 years. In order to achieve a more homogeneous study population, and avoid confounder factors we excluded 47 LTs because of the following reasons: re-transplantation (11 patients), acute liver failure (9 patients), donation after circulatory death (3 patients), simultaneous liver kidney (1 patient), primary non-function (7 patients), and hepatic artery thrombosis (HAT) (16 patients). Thus, our sample comprised 250 LTs divided into two groups as follows: patients who developed post-LT BC (n = 21) and those without BC (n = 229) (Figure 1).

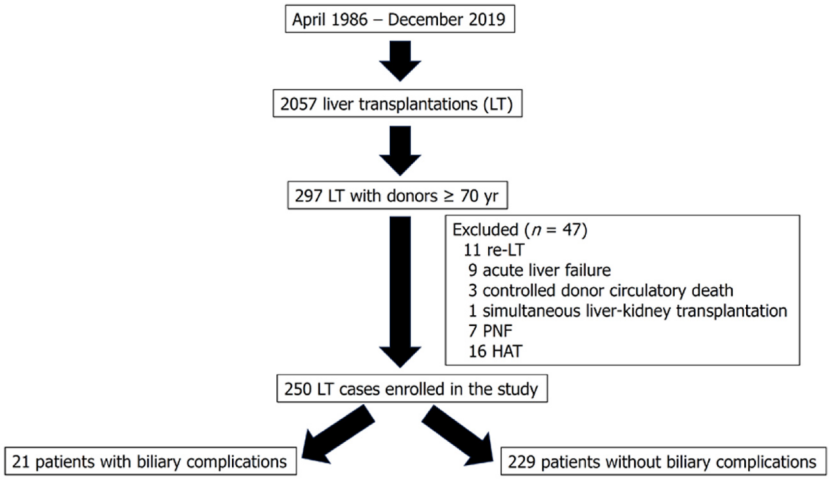

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Figure 1 Flowchart for patient selection. HAT: Hepatic artery thrombosis; PNF: Primary non- function; LT: Liver transplantation.

A retrospective case-control study was carried out comparing both groups and following the STROBE guidelines for reporting observational studies[25].

This study was terminated on June 31, 2021, with a minimal follow-up period of 18 mo after LT. Patients were not required to give informed consent to the study because the analysis used anonymous data that was collected after each patient agreed to treatment by written consent. This study was approved by our Institutional Review Board, and it was conducted and reported according to the declaration of Helsinki. All data generated or analyzed during this study are available upon request.

Donor evaluation and transplant technique

General criteria for the acceptance of liver grafts older than 70 years for LT at our department were the following: good pre-procurement hemodynamic stability avoiding severe hypotension episodes or the use of high doses of vasopressors, bilirubin < 2.5 mg/dL, transaminases < 150 IU/L, intensive care unit (ICU) stay < 4 d, soft graft consistency, liver biopsy displaying the absence of hepatitis or fibrosis or macro-steatosis up to 25%, and cold ischemia time (CIT) usually not exceeding 9 h. The presence of atheroma at the bifurcation of the common hepatic artery or gastroduodenal artery was a contraindication for the use of older livers. All liver grafts were biopsied at the beginning of the procurement. Dual aortic and portal vein flush was performed using Belzer or Celsior (since 2008 to present) preservation solutions. Donor procurement was performed according to standard techniques, except for donors displaying hemodynamic instability. A rapid procurement technique was carried out in such cases. The gallbladder and biliary tract were flushed with cold saline solution at the beginning of procurement.

Recipient hepatectomy was performed using the vena cava-sparing technique (piggy-back). Portal reperfusion was performed initially, followed by arterial anastomosis and subsequent arterial reperfusion. The vascularization of the donor and recipient choledochus was carefully preserved. Biliary reconstruction was usually performed by an end-to-end choledocho-choledochostomy, without a T-tube, using interrupted sutures of polyglyconate 5-6/0. A T-tube was only placed in cases of extremely small bile ducts, diameter discrepancy between both the donor and recipient bile ducts, or intraoperative difficulties. A cholangiography through a T-tube was usually performed on postoperative day 7, closing the tube at 5-8 d thereafter. Three months after LT, a second cholangiography through the T-tube was repeated, being then removed if there were not abnormal radiological findings. Similarly, Roux-en-Y hepaticojejunostomy (RYHJ) was only indicated inpatients with a diameter extreme discrepancy between both donor and recipient bile ducts or in case of recipients with biliary disease or prior RYHJ.

Donor and recipient characteristics

The following donor variables were evaluated: Demographics, ICU stay, the cause of death, medical history, cardiac arrest, hemodynamic instability, norepinephrine use, laboratory values (serum glucose, creatinine and sodium, liver function, and coagulation parameters), the presence of micro- and/or macro-steatosis, CIT, warm ischemia time (WIT), and preservation solutions. Moreover, the following pre-LT recipient data were assessed: demographics, LT indication, the presence of hepatocellular carcinoma (HCC), pre-LT transarterial chemoembolization (TACE), model for end-stage liver disease (MELD), MELD- Na, D-MELD scores, United Network for Organ Sharing (UNOS) status, medical history, major abdominal operations, and laboratory values (serum glucose, creatinine, albumin, liver function, and hematological parameters).

Perioperative variables, morbi/mortality, and patient and graft survival

The following perioperative variables were analyzed: Biliary reconstruction techniques, intraoperative transfusion, and base immunosuppression. Post-LT complications, such as early allograft dysfunction (EAD), acute renal failure, non-surgical related infections, acute rejection, HCV and HCC recurrence, non-biliary related reoperations, re-transplantation,

ICU and hospital stay, patientfollow-up, overall mortality rate and causes, and patient and graft survival were also analyzed.

Definitions

Non-anastomotic biliary stricture (NABS) or ischemic-type biliary lesion was defined as any stricture, dilation, or irregularity of the intra- or extra-hepatic bile ducts, with a patent hepatic artery. In contrast, anastomotic biliary stricture (ABS) was defined as a lesion localized within the biliary anastomosis[19]. Anastomotic biliary leakage (ABL) was defined as the presence of bile leak through abdominal drainage oran intra-abdominal biliary collection requiring radiological or surgical drainage.

Biliary strictures were diagnosed based on the clinical symptoms and cholestasis laboratory pattern, confirmed at the first era by ultrasound, CT scan and percutaneous transhepatic cholangiography (PTC). From 2005, a magnetic resonance imaging cholangiography (MRIC) was used for stricture confirmation. PTC was used for biliary stricture delineation and subsequent balloon dilation therapy. RYHJ was performed only after an interventional radiology failure.

EAD was defined according to Olthoff *et al*[26]. Post-LT acute renal failure was defined as a > 0.5% increase in the serum creatinine level or > 50% over the baseline value[27]. Acute and chronic rejection and HCV recurrence were confirmed by biopsy.

Immunosuppression

The immunosuppressive regimen consisted of cyclosporine or tacrolimus and prednisone. Mycophenolate mofetil or mammalian target of rapamycin inhibitors were introduced when appropriate, and tacrolimus was reduced. Steroids were usually discontinued between 3-6 mo.

Statistical analysis

The statistical review of the study was performed by a biomedical statistician. Continuous variables were expressed as mean ± SD and as median and interquartile range, according to the Kolmogorov-Smirnov test results. Qualitative variables were expressed as absolute frequencies (*n*) and relative frequencies (%). The chi-square test and Fisher's exact test were performed to compare the qualitative variables. In contrast, the continuous variables were compared using the *t* -test. Non-parametrictests were conducted when appropriate. The graft and patient survival rates were estimated using the Kaplan-Meier method. Donor and recipient variables ($P < 0.10$) from the univariate analysis were subsequently investigated in a multivariate analysis to assess their eventual effect on the development of BC. The results were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). A *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics, version 27 (SPSS Inc., Chicago, IL, United States).

RESULTS

Donor and recipient characteristics

A total of 250 patients underwent LT using liver grafts from donors aged ≥ 70 years (175 and 75 patients were septuagenarians and older than 80 years, respectively). The overall incidence of BC in this series was 8.4%. If we divide the patients who underwent LT into two eras, donor age was similar (76.1 years in the first era *vs* 77.6 years in the second era; $P = 0.073$), and no significant differences were found ($P = 0.551$) regarding the rate of BC: 6.6% (4 cases) in the first era (61 LT performed between January 1994 and December 2004), and 9% (17 cases) in the second era (189 LT performed between January 2005 and December 2019).

The mean donor age was similar between the groups (BC and non-BC), and women were significantly less frequent in the BC group ($P = 0.017$). Moreover, we did not find differences in obesity, body mass index, ICU stay, and causes of donor death, and cerebrovascular disease was the most frequent cause of death. There were also no differences in hypertension, diabetes, hemodynamic instability, and norepinephrine use. The incidence of cardiac arrest was significantly higher in the BC group than that in the non-BC group (19% *vs* 5.7%; $P = 0.043$). Donor laboratory values were similar, except for a lower platelet count in the BC group ($P = 0.016$).

There were no significant differences in the rates of micro-steatosis and macro-steatosis, and the mean CIT and WIT values were similar too (Table 1).

The median recipient age was equal in both groups, and there were no significant differences in LT indications. Pre-LT TACE as a bridging therapy in patients with HCC, MELD scores, and UNOS status demonstrated similar frequencies. Medical history, such as hypertension, diabetes, and pre-LT major abdominal operations were more frequent in the BC group, but the difference was statistically in significant. While the median values of total bilirubin were significantly lower ($P = 0.036$) in the BC group, the prothrombin rate was significantly higher ($P = 0.030$) (Table 2).

Perioperative characteristics and morbi/mortality

We observed a statistically significant difference in biliary tract reconstruction techniques between the groups ($P = 0.013$). Choledocho-choledochostomy without a T-tube was the most frequent technique (76.2% cases in the BC group *vs* 86.9% cases in the non-BC group), but the frequency of choledocho-choledochostomy with a T-tube and RYHJ was higher in the BC group.

Post-LT complications, such as EAD, acute renal failure, acute rejection, and non-biliary related reoperations, were similar between the groups. The rate of non-surgical related infections was higher, but statistically insignificant in the BC

Table 1 Donor characteristics

	BC (*n* = 21)	Non-BC (*n* = 229)	*P* value
Age (yr)	77.5 ± 5.8	77.2 ± 5.2	0.757
Sex (female), *n* (%)	7 (33.3)	138 (60.3)	0.017
BMI (kg/m^2)	26.1 ± 5.1	27.4 ± 4.7	0.366
Obesity (BMI ≥ 30), *n* (%)	5 (23.8)	57 (25.2)	0.409
ICU stay (h)	34 ± 24	24 ± 24	0.964
Cause of death, *n* (%)			
Cerebrovascular	14 (66.7)	183 (79.9)	0.773
Head trauma	5 (23.8)	36 (15.7)	
Other	2 (9.5)	10 (4.4)	
Hypertension, *n* (%)	13 (61.9)	131 (57.2)	0.677
Diabetes, *n* (%)	5 (23.8)	47 (20.5)	0.452
Cardiac arrest, *n* (%)	4 (19.0)	13 (5.7)	0.043
Hemodynamic instability, *n* (%)	9 (42.9)	67 (29.3)	0.195
Norepinephrine use, *n* (%)	15 (71.4)	163 (71.2)	0.981
Laboratory values			
Serum glucose (mg/dL)	158 ± 42	174 ± 70	0.378
Serum creatinine (mg/dL)	0.9 ± 0.5	0.8 ± 0.4	0.148
Serum sodium (mEq/L)	145 ± 7	146 ± 8	0.402
AST (IU/L)	23 ± 17	28 ± 19	0.191
ALT (IU/L)	22 ± 19	26 ± 22	0.444
GGT (IU/L)	24 ± 49	21 ± 35	0.447
Platelets/m^3	134 ± 84	172 ± 86	0.016
Prothrombin rate (%)	77 ± 16	72 ± 23	0.426
Partial thromboplastin time (s)	30 ± 6	30.5 ± 7.3	0.495
Steatosis (biopsy findings) , *n* (%)			
Microsteatosis	6 (28.6)	39 (17.0)	0.509
Mild macrosteatosis	4 (19.0)	61 (26.6)	
Moderate macrosteatosis	0	8 (3.5)	
Cold ischemia time (min)	442 ± 225	429 ± 235	0.783
Warm ischemia time (min)	55 ± 15	55 ± 15	0.486
Preservation solution, *n* (%)			
Celsior	18 (85.7)	189 (82.5)	0.496
Belzer	3 (14.3)	40 (17.5)	

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; GGT: Gamma-glutamyl transpeptidase.

group (28.6% *vs* 13.1%; *P* = 0.062). Other complications, such as HCV and HCC recurrence rates, did not differ significantly. None of the patients who developed BC underwentre-transplantation. The median follow-up period of the BC group was lower than that of the non-BC group, but differences were not statistically significant (46 ± 56 mo *vs* 72 ± 95 mo; *P* = 0.099). Overall mortality was lower but no significant in the BC group (28.6% *vs* 38.9%; *P* = 0.352). Infections were the main cause of the death in the BC group and cardiovascular disease and malignancies were the main cause of death in the non-BV group (*P* = 0.041) (Table 3).

Table 2 Pre-liver transplantation recipient characteristics

Variables	BC (*n* = 21)	Non-BC (*n* = 229)	*P* value
Age (yr)	59 ± 10	59 ± 12	0.767
Sex (female)	3 (14.3)	53 (23.1)	0.264
LT indications, *n* (%)			
Alcohol	11 (52.4)	97 (42.4)	0.705
HCV	7 (33.3)	80 (34.9)	0.883
HBV	0	27 (11.8)	0.081
Biliary related	1 (4.8)	5 (2.2)	0.413
Other	2 (9.5)	20 (8.7)	0.244
HCC, *n* (%)	7 (43.8)	70 (30.6)	0.793
Pre-LT TACE, *n* (%)	3 (42.9)	31 (44.3)	0.631
MELD	11 ± 7	13 ± 7	0.334
MELD-Na	11 ± 8	13 ± 8	0.189
D-MELD	810 ± 526	996 ± 510	0.360
UNOS status, *n* (%)			
Home	19 (90.5)	212 (93.4)	0.343
Hospital	1 (4.8)	13 (5.7)	
ICU	1 (4.8)	2 (5.2)	
Medical history, *n* (%)			
Hypertension	6 (28.6)	46 (20.1)	0.254
Diabetes	6 (28.6)	44 (19.2)	0.223
Pre-LT major abdominal operations	5 (23.8)	23 (10)	0.069
Laboratory values, *n* (%)			
Serum glucose (mg/dL)	130 ± 56	128 ± 63	0.801
Serum creatinine (mg/dL)	1.1 ± 0.8	1 ± 0.6	0.823
Serum albumin (g/dL)	3.6 ± 0.6	3.4 ± 0.6	0.203
AST (IU/L)	53 ± 42	54 ± 56	0.836
ALT (IU/L)	33 (33)	33 ± 36	0.955
GGT (IU/L)	57 ± 129	61 ± 70	0.645
Total bilirubin (mg/dL)	1.1 ± 0.9	1.7 ±2	0.036
Leukocytes/mm^3	4483 ± 2819	5356 ± 3110	0.063
Hemoglobin (g/100 mL)	12.6 ± 4.4)	12.3 ± 3.1	0.986
Platelets × 10^3/mm^3	100.7 ± 75.6	94.2 ± 50.2	0.496
Prothrombin rate (%)	70.6 ± 22.2	65 ± 18.3	0.030
aPTT (s)	34.9 ± 5.3	36.4 ± 8.1	0.272

BC: Biliary complications; ALT: Alanine aminotransferase; aPTT: Activated partial thromboplastin time; AST: Aspartate aminotransferase; D-MELD: Donor model for end-stage liver disease; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; ICU: Intensive care unit; LT: Liver transplantation; MELD: Model for end-stage liver disease; TACE: Transarterial chemoembolization; UNOS: United Network for Organ Sharing.

Patient and graft survival

There were no significant differences in the patient and graft survival between the recipients of donors aged ≥ 70 years who developed BC *vs* non-BC recipients. The 1-, 3-, and 5-year patient survival rates in the BC group were 81.0%, 81.0%, and 67.5%, respectively, *vs* 86.9%, 80.2%, and 72.5%, respectively, in the non-BC group (P = 0.954; Figure 2A). The 1-, 3-, and 5-year graft survival rates in the BC group were 81.0%, 81.0%, and 67.5%, respectively, *vs* 86.0%, 78.8%, and 71.1%,

Table 3 Perioperative variables and morbidity/mortality

Variables	BC (*n* = 21)	Non-BC (*n* = 229)	*P* value
Biliary reconstruction, *n* (%)			
Chol-Chol-without T-tube	16 (76.2)	212 (86.9)	0.013
Chol-Chol-with T-tube	3 (14.3)	11 (4.8)	
RYHJ	2 (9.5)	6 (2.6)	
Transfusion (units)			
Packed red blood cells	7 ± 10	5 ± 8	0.147
Fresh frozen plasma	9 ± 12	10 ± 10	0.647
Platelets	1 ± 1	1 ± 3	0.100
Initial immunosuppression, *n* (%)			
Tacrolimus + steroids	20 (95.2)	199 (86.9)	0.231
Cyclosporine + steroids	1 (4.8)	30 (9.8)	
Early allograft dysfunction	4 (19.0)	32 (14.0)	0.357
Acute renal failure	5 (23.8)	54 (13.1)	0.581
Non-surgical related infections	6 (28.6)	30 (13.1)	0.062
Acute rejection	6 (28.6)	54 (23.6)	0.608
HCV recurrence	1 (4.8)	43 (18.8)	0.085
HCC recurrence	0	9 (3.9)	0.446
Non-biliary related reoperation	1 (4.8)	12 (5.2)	0.701
Re-transplantation	0	6 (2.8)	0.643
ICU stay (d)	4 ± 5	4 ± 4	0.559
Hospital stay (d)	15 ± 13	12 ± 10	0.326
Patient follow-up (mo)	46 ± 56	72 ± 95	0.099
Overall mortality rate, *n* (%)	6 (28.6)	89 (38.9)	0.352
Causes of death, *n* (%)			
Cardiovascular disease	1 (4.8)	20 (8.7)	0.041
Infections	4 (19.0)	12 (5.2)	
Malignancies	1 (4.8)	23 (10)	
HCV recurrence	0	13 (5.7)	
Other	0	21 (9.3)	

BC: Biliary complications; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; ICU: Intensive care unit; RYHJ: Roux-en-Y hepaticojejunostomy.

respectively, in the non-BC group (P = 0.909; Figure 2B).

Univariate and multivariate analysis of predictors of BC

In the univariate analysis, donor variables, such as female donors (OR: 0.33; 95%CI: 0.13-0.85, P = 0.021), cardiac arrest (OR: 3.91; 95%CI: 1.14-13.30, P = 0.029), and platelet count (OR: 1.00; 95%CI: 1.00-1.00, P = 0.031) displayed statistically significant differences. In the multivariate analysis, while female donors (OR: 0.27; 95%CI: 0.08-0.90, P = 0.033) was a protective factor for BC, donor cardiac arrest (OR: 7.66; 95%CI: 1.52-38.61, P = 0.013) was a risk factor (Table 4).

Diagnosis, management, and outcomes of patients with BC

The incidence of BC in 175 recipients of septuagenarian liver grafts and 75 recipients of octogenarian liver grafts was 7.4% and 10.7%, respectively (P = 0.398). The initial techniques of biliary reconstruction were choledocho-choledochostomy without a T-tube, with a T-tube, and RYHJ in 16 patients, 3 patients, and 2 patients, respectively. MRIC was used in nine patients to confirm ABS following an ultrasound. While 15 (71.4%) patients were diagnosed with BC within the first year of LT (eight ABS and seven ABL), 6 (28.6%) patients were diagnosed after the first year (five ABS and one mild NABS

Table 4 Univariate and multivariate analysis of predictors of biliary complications

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Donor variables				
Age (per year)	1.01 (0.93-1.10)	0.755	-	-
Sex (female)	0.33 (0.13-0.85)	0.021	0.27 (0.08-0.90)	0.033
Obesity (BMI ≥ 30) (Y/N)	1.26 (0.44-3.64)	0.661	-	-
Cause of death				
Cardiovascular *vs* trauma	0.55 (0.18-1.62)	0.143	-	-
Other causes *vs* trauma	1.44 (0.24-8.56)	0.420		
Cardiac arrest (Y/N)	3.91 (1.14-13.30)	0.029	7.66 (1.52-38.61)	0.013
Donor hypertension (Y/N)	1.21 (0.48-3.04)	0.677	-	-
Donor diabetes (Y/N)	1.21 (0.42-3.47)	0.722	-	-
Platelets/mm^3 (per unit)	1.00 (1.00-1.00)	0.031	1.00 (1.00-1.00)	0.141
Cold ischemia time (per min)	0.99 (0.99-1.00)	0.685	-	-
Recipient variables				
Age (per year)	1.01 (0.96-1.06)	0.620	-	-
Sex (female)	0.55 (0.15-1.95)	0.357	-	-
Recipient hypertension (Y/N)	1.59 (0.58-4.32)	0.362	-	-
Recipient diabetes (Y/N)	1.68 (0.61-4.58)	0.309	-	-
HCC (Y/N)	1.13 (0.43-2.93)	0.792	-	-
MELD (per unit)	0.96 (0.88-1.05)	0.481	-	-
Total bilirubin (per unit)	0.63 (0.40-1.02)	0.160	-	-
Leukocytes/mm^3 (per unit)	1.00 (1.00-1.00)	0.221	-	-
Prothrombin rate (%) (per unit)	1.01 (0.99-1.04)	0.195	-	-
PRBC transfusion (per unit)	1.02 (0.97-1.06)	0.332	-	-
Pre-LT major abdominal operations (Y/N)	2.80 (0.93-8.35)	0.064	3.08 (0.83-11.33)	0.090
Biliary reconstruction				
Chol-Chol-with T-tube	3.61 (0.91-14.27)	0.486	-	-
RYHJ	4.41 (0.82-23-67)	0.342		

BMI: Body mass index; HCC: Hepatocellular carcinoma; LT: Liver transplantation; MELD: Model for end-stage liver disease; PRBC: Packed red blood cells; RYHJ: Roux-en-Y hepaticojejunostomy.

without any therapeutic requirement).

Of the 7 patients with ABL, 3 (42.8%) patients closed spontaneously, and 4 (57.2%) patients required reoperation (two were treated by a leakage repair, one underwent RYHJ, and the remaining patient with a prior RYHJ underwent several surgeries because of multiple biliary complications). Nine (69.2%) of the 13 patients with ABS underwent PTC balloon dilation (range: 1-6 times), and 4 patients underwent RYHJ. In addition, 4 patients also required a RYHJ procedure due to failure of prior PTC balloon dilation. During follow-up, 6 patients died among those who developed BC (5 among the recipients of septuagenarian donors, and 1 among recipients of octogenarian donors). However, only three (14.3%) ofthese deaths were related to BC (two in recipients of septuagenarian donors, and one in a recipient of an octogenarian donor) (Table 5).

DISCUSSION

Before the introduction of direct-acting antivirals (DAAs), the use of older livers in patients with HCV was associated with a significantly lower patient and graft survival owing to HCV recurrence[28]. However, on excluding recipients with

Table 5 Diagnosis, management, and outcomes of patients with biliary complications post-liver transplantation with grafts older than 70 years

Cases	Donor age (yr)	Recipient age (yr)	LT indication	Biliary anastomosis technique	BC type	Diagnosis	Time from LT to BC	PTB dilation (times)	Reoperation: surgical procedure	Current status (causes of death)
Donors aged 70-79 yr (13/175, 7.4%)										
1	M (70)	M (49)	Alcohol	Chol-chol-T tube	ABL	US	7 d	-	-	Deceased (57 m): CV disease
2	M (73)	M (50)	Alcohol	Chol-chol-T tube	ABS	US, CT scan	12 m	1	-	Deceased (88 m): tumor
3	M (76)	M (50)	Alcohol	Chol-chol	ABL	US, CT scan	10 d	-	Roux-en-Y HJ	Deceased (1 m): BC-infection
4	M (72)	M (61)	HCV	Roux-en-Y HJ	ABS	US	1 m	1	-	Deceased (3 m): aspergillus
5	F (70)	M (63)	HCV	Chol-chol	ABL	Drainage	6 d	-	-	Deceased (1 m): BC-infection
6	M (70)	M (64)	Alcohol + HCC	Chol-chol	ABS	CT scan	1 m	-	Roux-en-Y HJ	Alive (119 m)
7	M (73)	M (67)	HCV	Chol-chol	ABS	US, MRIC	1 m	4	Roux-en-Y HJ	Alive (86 m)
8	M (75)	M (59)	HCV + HCC	Chol-chol	ABS	US, MRIC	12 m	4	-	Alive (65 m)
9	F (73)	F (37)	Policystic disease	Chol-chol-T tube	ABL	Drainage	8 d	-	Primary suture	Alive (55 m)
10	F (79)	M (69)	Cryptogenic	Chol-chol	ABS	US, MRIC	32 m	-	Roux-en-Y HJ	Alive (46 m)
11	F (73)	M (57)	HCV + HCC	Chol-chol	ABL	Drainage	10 d	-	-	Alive (44 m)
12	M (79)	M (63)	HCV + HCC	Chol-chol	ABL	Drainage, CT scan	6 d	-	Primary suture	Alive (21 m)
13	M (75)	M (55)	HCV + HCC	Chol-chol	ABS	MRIC	13 m	-	Roux-en-Y HJ	Alive (19 m)
Donors ≥ 80 yr (8/75, 10.7%)										
14	M (84)	M (52)	Alcohol	Chol-chol	ABS	CT scan	11 m	-	Roux-en-Y HJ	Alive (249 m)
15	M (85)	M (71)	Alcohol + HCC	Chol-chol	ABS	CT scan	13 m	-	-	Alive (126 m)
16	M (89)	M (58)	Autoimmune	Chol-chol	NABS	MRIC	21 m	-	-	Alive (52 m)
17	M (80)	M (54)	Alcohol	Chol-chol	ABS	MRIC	5 m	2	Roux-en-Y HJ	Alive (48 m)
18	F (81)	F (54)	NASH	Chol-chol	ABS	MRIC	38 m	6	-	Alive (45 m)
19	F (83)	M (61)	Alcohol + HCC	Chol-chol	ABS	MRIC	16 m	2	Roux-en-Y HJ	Alive (39 m)
20	F (85)	M (59)	NASH	Chol-chol	ABS	CT scan, MRIC	3 m	3	Roux-en-Y HJ	Alive (39 m)
21	M (84)	M (67)	SBC	Roux-en-Y HJ	ABL	Drainage, CT scan	8 d	-	Several procedures	Deceased (2 M): BC-infection

ABL: Anastomotic biliary leakage; ABS: Anastomotic biliary stricture; BC: Biliary complication; Chol-chol: Choledocho-choledochostomy; CT: Computed tomography; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; MRIC: Magnetic resonance imaging cholangiography; NABS: Non-anastomotic biliary stricture; NASH: Nonalcoholic steatohepatitis; LT: Liver transplantation.

HCV cirrhosis, the patient and graft survival did not differ between the recipients of octogenarian and septuagenarian donors[29]. Currently, the scenario has dramatically changed, and well-selected liver grafts without an age limit can be used, without the fear of HCV recurrence on treating the patients with DAA[30]. The liver is the most permissive organ, in relation to the donor age because of its regenerative property[31]. However, older livers are more susceptible to

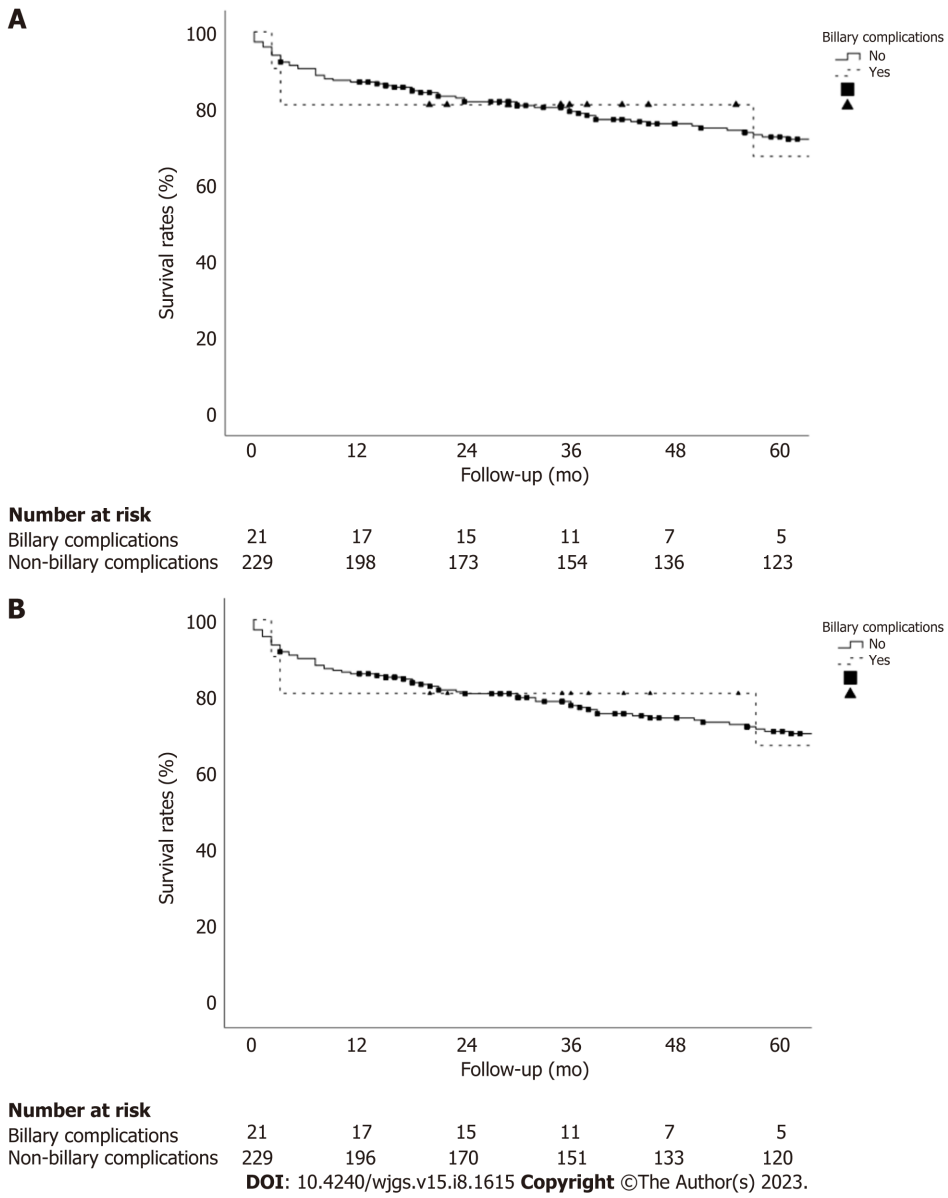

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Figure 2 Comparison of patient and graft survival between the recipients of donors older than 70 years who developed biliary complications *vs* those without biliary complications. A: The 1-, 3-, and 5-year patient survival rates in the biliary complications (BC) group are 81.0%, 81.0%, and 67.5%, respectively, *vs* 86.9%, 80.2%, and 72.5%, respectively, in the without BC (non-BC) group (P = 0.954); B: The 1-, 3-, and 5-year graft survival rates in the BC group are 81.0%, 81.0%, and 67.5%, respectively, *vs* 86.0%, 78.8%, and 71.1% in the non-BC group (P = 0.909).

prolonged cold ischemia times[32]. Biological and chronological aging of the old liver donors is not always the same because the general status and physiologic reserve vary markedly by lifestyle factors[33] and comorbidities. To obtain good results using older livers, the donors and recipients should be selected carefully to avoid theiruse in sick patients [29].

Most BC are diagnosed within 1-year post-LT, and the overall incidence among the recipients of livers from DBD younger than 80 years reportedly ranges between 12%-44%[8,11,21,23,34-36]. In contrast, the overall incidence of BC using livers older than 80 years ranges between 6.7%-23.9%[6,13-15,29,37-39]. One of these series using only octogenarian livers reported on an overall incidence of 23.9%, corresponding17% of these patients to type NABS[38]. In other study, the same authors found the donor age ≥ 80 years as a risk factor for the development of NABS when performing a single aortic *vs* dual perfusion (aortic and portal) during donor procurement[39]. Three other studies compared post-LT BC for liver grafts younger and older than 70 years, and the incidence ranged between 9%-19% and 12%-15.1% in recipients of septuagenarian and octogenarian livers, respectively, without significant differences between thegroups[8,40,41]. In other comparative study, the incidence of NABS was 13% for liver grafts ≥ 65 years *vs* 19% for grafts < 65 years[35].

The overall rate of BC among our recipients of donors ≥ 70 years was 8.4%, without significant differences between the two groups (7.4% in recipients of septuagenarian donors *vs* 10.7% in recipients of donors ≥ 80 years; P = 0.398). We divided the patients into two groups according to the era of LT (beforeor after December 2004) to investigate an eventual influence of the period of LT over the incidence of BC. The age of the donor was higher in the second era, nevertheless the difference was statistically insignificant. Of note, overall rate of BC (8.4%) in our study was lower than overall rate of 12.1% previously reported in a systematic review analysis of five series of LT using livers older than 70 years[24].

Researchers have described several donor risk factors for BC, such as the use of older liver grafts, donors with extended criteria, DCD livers, macro-steatosis > 25%, atherosclerosis, the use of high viscosity preservation solution, CIT > 10 h, severe hypotension of the donor or recipient, ABO incompatibility, smallbile ducts, bile duct ischemia, anastomotic technique failure, HAT, prior bile leak, autoimmune hepatitis, primary sclerosing cholangitis, or acute or chronic rejection[17,20,22,23,38,42-45]. The policy at our department on the use of donors ≥ 70 years was framed to prevent the aforementioned risk factors for BC, by performing a mandatory liver biopsy in all cases to discard livers with relevant histological alterations[29]. The use of hepatic artery pressure perfusion with low viscosity histidine-tryptophan-ketoglutarate preservation solution to improve peribiliary vascularization has been associated with lower rates of ischemic cholangiopathy[20]. This practice has been routinely performed in 207 of our LT, using Celsior solution as an alternative low viscosity solution. The use of older donors with a CIT longer than 13 h increases the risk of NABS[20], and it reduces the graft survival[5]. In our study, the median values of CIT were under 13 h in both groups and differences were not statistically significant (442 min in BC *vs* 429 min in non-BC; $P = 0.783$).

A careful preservation of arterial vascularization of donor and recipient bile ducts is an important measure to avoid BC [44]. Small bile duct diameter constitutes a risk factor for ABS[23]. A sonographic study revealed that the upper normal limit size of the bile duct in the elderly population should be set at 8.5 mm[46]. In a LT series using liver grafts of a mean age of 55 years, the common bile duct diameter ranged between 6.8 mm and 7.1 mm[47]. The use of old liver grafts could facilitate the performance of the biliary anastomosis because of aging-associated progressive duct dilation.

The technique of biliary reconstruction using a T- tube has demonstrated a higher risk of BC, which has been attributed to a higher ABL rate[23,48]. In the same way, in our series the rate of BC was significantly higher among few patients who underwent choledocho-choledochostomy with a T-tube (two cases of ABS and one of ABL).

Patients with BC were diagnosed based on the clinical features and ultrasound/doppler and were confirmed by CT scan and PTC in the first era, and more recently by MRIC. Patients with ABL were diagnosed during the first 10 d post-LT, with an evolution to spontaneous closure in three patients and the remaining four requiring reoperation. In contrast, 13 patients with ABS were diagnosed at a mean time of 12.2 mo post-LT (range: 1-38). While nine patients underwent an interventional therapy by PTC balloon dilation (1-6 times), eight underwent RYHJ. Alternatively, other authors prefer to use endoscopic retrograde cholangiopancreatography for ABS dilation[49]. Only three (14.3%) of our patients died because of BC (two recipients of septuagenarian livers and one recipient of an octogenarian liver).

We observed no significant differences in the patient and graft survival between the groups. In contrast, other authors have reported on the association between BC and significantly lower patient and graft survival[21,23,49]. Another series demonstrated an association between significantly lower patient and graft survival and more frequent incidence of NABS in recipients of octogenarian livers[38]. A different series using liver grafts younger and older than 75 years showed similar patient and graft survival between the groups, but a higher BC rate between the older group (29.6% *vs* 13%)[11].

The most frequent causes of mortality in octogenarian liver recipients are cardiovascular disease, HCV or HCC recurrence, infection, and the development of de novo tumors[6,12,15,37], similar to our findings, and NABS[38]. As previously reported[30], the multivariate analysis identified female donors as a protective factor of BC owing to better pre-transplant liver function. However, donor cardiac arrest was a risk factor, as demonstrated in recipients of DCD livers suffering cardiac arrest[42,50].

This study had several limitations. We collected data retrospectively for a long duration and, subjected them to some biases typical for such studies.

CONCLUSION

In conclusion, the incidence of BC in our series was lower than others previously reported, and most cases could be managed by multidisciplinary approaches (percutaneous dilation or Roux-en-Y hepaticojejunostomy), which kept patient and graft survival unchanged. None of the patients with BC required re-transplantation. Female donor sex was a protective factor for BC, while donor cardiac arrest was a risk factor. The careful management of older liver grafts and meticulous anastomotic techniques can be associated with a low incidence of BC, confirming that livers older than 70 years are fine to use in LT.

ARTICLE HIGHLIGHTS

Research background

The shortage of liver grafts and subsequent waitlist mortality led us to expand the donor pool using liver grafts from older donors.

Research motivation

There are no studies analyzing the incidence and outcomes of biliary complications (BC) in patients older and younger than 70 years.

Research objectives

The aim of this study was to determine the incidence, outcomes, and risk factors for BC in liver transplantation (LT) using liver grafts from donors aged > 70 years.

Research methods
A retrospective case-control study was performed comparing patients who developed biliary complications with patients who did not after liver transplantation with donors ≥ 70 years.

Research results
Twenty-one patients (8.4%) developed biliary complications (13 anastomotic strictures, 7 biliary leakages, and 1 non-anastomotic biliary stricture). There were no significant differences in the patient and graft survival between the groups. Only three deaths were related to biliary complications. Female donors were protective factors for biliary complications and donor cardiac arrest was a risk factor.

Research conclusions
The incidence of biliary complications was relatively low on using liver grafts > 70 years.

Research perspectives
Prospective studies are necessary to confirm these results. It would be interesting to analyze the diameter of the bile duct and technical aspects when we perform the anastomosis.

FOOTNOTES

Author contributions: Jimenez-Romero C and Caso-Maestro O designed the research and wrote the paper; Jimenez-Romero C, Justo-Alonso I, san Román R and Caso-Maestro O analyzed data; Justo-Alonso I, del Pozo-Elso P, Marcacuzco-Quinto A, Manrique-Municio A, Calvo-Pulido J and García-Sesma A collected data; Martín-Arriscado-Arroba C peformed the statistical analysis.

Institutional review board statement: The study was reviewed and approved by the `12 de Octubre´ University Hospital Institution Review Board.

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

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Data sharing statement: Technical appendix, statistical code, and dataset is available from the corresponding author if required.

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Country/Territory of origin: Spain

ORCID number: Carlos Jimenez-Romero 0000-0002-1965-0666; Iago Justo-Alonso 0000-0002-0553-5835; Pilar del Pozo-Elso 0000-0003-1793-1226; Alberto Marcacuzco-Quinto 0000-0001-6266-8792; Cristina Martín-Arriscado-Arroba 0000-0002-2147-2811; Alejandro Manrique-Municio 0000-0003-4758-9927; Jorge Calvo-Pulido 0000-0003-3144-4555; Alvaro García-Sesma 0000-0002-4377-7501; Ricardo San Román 0000-0001-8516-1978; Oscar Caso-Maestro 0000-0002-8953-269X.

Corresponding Author's Membership in Professional Societies: Asociacion Española de Cirujanos; Sociedad Española de Trasplante; Sociedad Española de Trasplante Hepático; and The Transplantation Society.

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ORIGINAL ARTICLE

Case Control Study

Goldilocks principle of minimally invasive surgery for gastric subepithelial tumors

Wei-Jung Chang, Lien-Cheng Tsao, Hsu-Heng Yen, Chia-Wei Yang, Hung-Chi Chang, Chew-Teng Kor, Szu-Chia Wu, Kuo-Hua Lin

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Wei-Jung Chang, Lien-Cheng Tsao, Hung-Chi Chang, Kuo-Hua Lin, Department of General Surgery, Changhua Christian Hospital, Changhua 50006, Taiwan

Hsu-Heng Yen, Chia-Wei Yang, Department of Gastroenterology, Changhua Christian Hospital, Changhua 50006, Taiwan

Hsu-Heng Yen, General Education Center, Chienkuo Technology University, Changhua 50006, Taiwan

Hsu-Heng Yen, School of Medicine, Chung Shan Medical University, Taichung 40201, Taiwan

Chew-Teng Kor, Big Data Center, Changhua Christian Hospital, Changhua 50006, Taiwan

Chew-Teng Kor, Graduate Institute of Statistics and Information Science, National Changhua University of Education, Changhua 50007, Taiwan

Szu-Chia Wu, Transplant Medicine & Surgery Research Center, Changhua Christian Hospital, Changhua 50006, Taiwan

Corresponding author: Kuo-Hua Lin, MD, Surgeon, Department of General Surgery, Changhua Christian Hospital, No. 135 Nanxiao Street, Changhua 50006, City, Changhua County, Taiwan. khlin120380@gmail.com

Abstract

BACKGROUND

Minimally invasive surgery had been tailored to individual cases of gastric subepithelial tumors (SETs) after comparing the clinical outcomes of endoscopic resection (ER), laparoscopic resection (LR), and hybrid methods.

AIM

To study the use of Goldilocks principle to determine the best form of minimally invasive surgery for gastric SETs.

METHODS

In this retrospective study, 194 patients of gastric SETs with high probability of surgical intervention were included. All patients underwent tumor resection in the operating theater between January 2013 and December 2021. The patients were divided into two groups, ER or LR, according to the tumor characteristics

and the initial intent of intervention. Few patients in the ER group required further backup laparoscopic surgery after an incomplete ER. The patients who had converted open surgery were excluded. A logistic regression model was used to assess the associations between patient characteristics and the likelihood of a treatment strategy. The area under the curve was used to assess the discriminative ability of tumor size and Youden's index to determine the optimal cut-off tumor size.

RESULTS

One-hundred ninety-four patients (100 in the ER group and 94 in the LR group) underwent tumor resection in the operating theater. In the ER group, 27 patients required backup laparoscopic surgery after an incomplete ER. The patients in the ER group had small tumor sizes and shorter procedure durations while the patients in the LR group had large tumor sizes, exophytic growth, malignancy, and tumors that were more often located in the middle or lower third of the stomach. Both groups had similar durations of hospital stays and a similar rate of major postoperative complications. The patients in the ER group who underwent backup surgery required longer procedures (56.4 min) and prolonged stays (2 d) compared to the patients in the LR group without the increased rate of major postoperative complications. The optimal cut-off point for the tumor size for laparoscopic surgery was 2.15 cm.

CONCLUSION

Multidisciplinary teamwork leads to the adoption of different strategies to yield efficient clinical outcomes according to the tumor characteristics.

Key Words: Gastric subepithelial tumors; Endoscopic resection; Laparoscopic resection; Tumor size

Core Tip: Multidisciplinary teamwork leads to the adoption of different strategies for resection of gastric subepithelial tumors: Endoscopic resection (ER) was indicated for a smaller tumor and intraluminal growth, whereas laparoscopic resection was indicated for a larger tumor (optimal cut-off point: 2.15 cm), tumors located in the middle or lower third of the stomach, exophytic growth, and more aggressive malignancy behavior. Backup surgery is preserved for incomplete ER to effectively reduce associated morbidities.

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INTRODUCTION

Gastric subepithelial tumors (SETs) include a broad spectrum of benign and malignant lesions, of which gastrointestinal stromal tumors (GISTs) are the most common. Current guidelines recommend the complete resection of gastric SETs if the size is > 2 cm, malignant features are present, or the patient is symptomatic and would prefer surgical management[1-5]. As small GISTs pose a risk for malignancy, endoscopic resection (ER) could be a good alternative method for obtaining a histological diagnosis and therapeutic resection compared with periodic surveillance[6]. With recent advancements in endoscopic and laparoscopic management, different approaches to minimally invasive surgery have been adopted and tailored to individual cases.

Among the minimally invasive approaches, laparoscopic surgery has proven to be feasible with faster recovery, shorter hospital stays, and equivalent oncological safety compared to open surgery. Initially, open surgery was considered the main treatment for extensive tumors, and laparoscopic surgery was reserved for small tumors (< 5 cm). However, with advanced laparoscopic techniques, tumor size is no longer a restricting factor; even large tumors can be successfully removed *via* laparoscopic surgery[7-9]. For certain tumors in unfavorable locations[10], Hiki *et al*[11] introduced laparoscopic and endoscopic cooperative surgery (LECS), with the combined advantages of endoscopy and laparoscopy[12], which helps to achieve precise localization, minimal resection, and functional preservation. Endoscopic submucosal dissection (ESD) techniques have advanced in the resection of tumors located deeper than the submucosal layer[13]. The ER of small gastric SETs (< 5 cm) involves a shorter surgery and less intraoperative blood loss in selected cases of intraluminal tumors[14,15]. By considering complications, such as perforation or bleeding, we modified the LECS procedure as a backup laparoscopic surgery to provide timely management, which required more operative time but reduced postoperative morbidity[16].

Although different minimally invasive approaches can be applied to gastric SETs, the effectiveness and safety of ER, laparoscopic resection (LR), or hybrid methods have not been well established. Thus, in this study, we aimed to use the Goldilocks principle to determine the best type of treatment for gastric SETs by comparing the clinical outcomes of ER,

LR, and our hybrid method, as this information can be crucial in improving options for minimally invasive surgery considering the risks and potential benefits in this setting.

MATERIALS AND METHODS

Patients and study design

We conducted a retrospective study of patients with gastric SETs who underwent ER or LR at the operating theater in our institution between January 2013 and December 2021. Medical records were retrospectively reviewed to define the patient/tumor characteristics and operative outcomes. Based on pathologic diagnosis, the tumor was further divided into two groups: benign disease and malignant or malignant potential disease. All patients underwent endoscopic ultrasonography (EUS) or abdominal computed tomography (CT) to evaluate the tumor size, invasion depth, and characteristics before resection.

Ethical permission

The study was approved by the Institutional Review Board of Changhua Christian Hospital (approval No. 220117) and registered at ClinicalTrials.gov (NCT05452265). This work has been reported in line with the "Strengthening the Reporting of Observational studies in Epidemiology (STROBE)" criteria[17]. All relevant data are included in the paper and its Supporting Information files.

Patient management strategy

Complete resection of gastric SETs is recommended if the tumor size is > 2 cm, malignant features are present, or if the patient is symptomatic, declined periodical surveillance, and preferred to undergo diagnostic and therapeutic resection. Patients with gastric SETs in the superficial layer underwent ER in the endoscopic room and those with a high probability of surgical intervention were evaluated both by endoscopists and general surgeons preoperatively[16,18]. ER with backup surgery was indicated for patients with endoscopic intent, and a small tumor size tolerated the endoscopic retrieval. On the other hand, LR was indicated for patients with surgical intent and those with the following conditions, which were not suitable for ER: (1) Large tumor size with difficult endoscopic retrieval; (2) Symptoms of gastrointestinal tract bleeding with difficulty in endoscopic visualization; (3) Suspicion of tumor rupture that required intra-abdominal exploration; and (4) Histologic diagnosis of GIST with initial treatment of target therapy. Open surgery was performed in patients who were not amenable to laparoscopy due to pulmonary compliance and cardiovascular disease, had large tumors that eventually needed a large incision wound for specimen extraction, and had tumors with suspected multivisceral involvement.

Inclusion and exclusion criteria

In total, we included 194 patients who underwent tumor resection under general anesthesia at the operating theater, with 100 and 94 patients in the ER and LR groups, respectively. We excluded three patients in the ER group due to anatomic changes in the stomach following previous surgery and four patients in the LR group due to converted open surgery. Among the four patients who underwent converted open surgery, one had splenic metastasis with difficult dissection plain intraoperatively (tumor size 12.5 cm, posterior aspect of the upper third stomach), two had difficulty in tumor localization of the upper third stomach with one receiving preoperative endoscopic tattoo (size 4 cm, posterior side and size 1 cm, lesser curvature side with tattooing), and one was concerned with post-gastrectomy stenosis with further gastro-gastrostomy (size 7 cm, posterior aspect of the lower third stomach).

ER only, ER with backup surgery, and LR were performed according to the protocols in our previous studies[16,18]. In the ER group, most patients (92, 92%) underwent endoscopic submucosal dissection (ESD) and endoscopic mucosal resection if necessary for an R0 attempt, except for eight cases of submucosal tunneling ER (STER). Some cases with iatrogenic perforation could be successfully repaired by endoscope (Video 1). In the LR group, most patients (92, 97.9%) underwent wedge gastrectomy, except for two cases who underwent distal gastrectomy with Roux-en-Y reconstruction (2, 2.1%), given the risk for postoperative stenosis. In addition, 12 patients (12.8%) underwent intraoperative endoscope-assisted LR to localize the tumor more precisely.

Statistical analysis

Categorical and continuous variables are expressed as number (proportion) and median and interquartile range (IQR), respectively. Chi-squared test was used to compare categorical variables, and Kruskal-Wallis *H* test was used to compare continuous variables. A logistic regression model was used to assess the association between patient characteristics and likelihood of a treatment strategy. Odds ratios were calculated using a crude multivariate analysis and a 1:1 propensity-matched dataset. Forest plots provide a data visualization method to present multivariate adjustment factors for the likelihood of undergoing treatment. Linear regression models were used to assess the impact of the three treatment strategies on clinical outcomes (procedure time, length of hospital stay, and Clavien grade ≥ III complications). Furthermore, we used the area under the curve (AUC) to assess the discriminative ability of tumor size and Youden's index to determine the optimal cut-off tumor size. Kaplan–Meier curves and log-rank tests were used to compare the disease-free survival rates and overall survival between the ER and LR groups during long-term surveillance. Statistical analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, United States), and a visualization plot was constructed using the R software (version 4.1.0; Comprehensive R Archive Network: http://cran.r-project.org). All two-

sided *P* values less than 0.05 were considered statistically significant.

RESULTS

A total of 194 patients were included: 100 in the ER group and 94 in the LR group. In the ER group, 73 patients underwent ER only, and 27 underwent further backup laparoscopic surgery due to uncontrolled bleeding or incidental perforation. There were no significant differences in sex, the layer of tumor origin, length of hospitalization, or major postoperative complications between the ER and LR groups (Table 1). In the ER group, patients who were slightly younger (56 *vs* 62 years) had a significantly higher percentage of small tumor sizes of ≤ 2 cm (72% *vs* 16%) and shorter procedure times (75 *vs* 130 min). In the LR group, significant differences were observed in the percentage of tumors > 3 cm in size (84% *vs* 28%), tumors in the middle third of the stomach (14.9% *vs* 6%), exophytic tumor growth (56.4% *vs* 11%), and pathology of malignancy or malignant potential (85.1% *vs* 45%). Multivariable analysis results showed that patients tended to undergo laparoscopic surgery rather than ER when the following factors were present: tumor size of > 2 cm (3-5 cm adjusted odds ratio (aOR) 6.643, > 5 cm aOR 30.158), tumor in the middle or lower third of the stomach (aOR 2.625), exophytic growth (aOR 6.0782), or pathology of malignancy (aOR 3.552). However, it is possible that these factors resulted from preoperative selection bias (Figure 1A).

A total of 27 patients who underwent backup surgery after incomplete ER were compared with those in the LR group (Table 2). No significant differences were observed in age, sex, tumor location, the layer of tumor origin, exophytic tumor growth, or major postoperative complications; however, a higher percentage of tumors of size > 2 cm (84% *vs* 40.7%), pathology of malignancy or malignant potential (85.1% *vs* 59.3%), prolonged procedure duration (130 *vs* 185 min), and a shorter length of hospital stay (6 *vs* 7 d) were observed in the LR group. Multivariable analysis showed that patients tended to undergo laparoscopic surgery rather than an initial ER attempt if the tumor size was > 2 cm (aOR 5.81), if the tumor was in the middle or lower third of the stomach (aOR 5.22), and if there was pathology of malignancy (aOR 4.37); these results were statistically significantly different (Figure 1B).

To compare the operative outcomes between ER with backup surgery and LR, the predictor of a prolonged procedure was tumor location in the middle or lower third of the stomach, and the predictor of a prolonged stay was advanced age. However, these factors were not significant after propensity-score matching. More importantly, patients who underwent ER with backup surgery had longer procedures (56.4 min) and prolonged hospital stays (2 d) on average (Table 3). Furthermore, the optimal cut-off point for the tumor size for laparoscopic surgery was 2.15 cm, with an AUC of 0.841, sensitivity of 84%, and specificity of 74% (Figure 2).

Among patients with major complications (Clavien grade ≥ III), there were five patients (5.3%) in the ER group (three graded IIIa and two graded IIIb), none after backup surgery, and three patients (3.2%) in the LR group (two graded IIIa and one graded IVa). In the ER group, three patients were graded IIIa, two patients had gastric ulcer bleeding and received endoscopic hemostasis, and one patient had massive pneumoperitoneum without peritonitis and received sonography-guided air tapping. Two patients with grade-IIIb perforation had delayed perforation and underwent laparoscopic surgery[15]. In the LR group, two patients with grade IIIa had delayed gastric emptying after laparoscopic wedge gastrectomy and received endoscopic duodenal tube insertion for enteral feeding on postoperative days (POD) 18 and 19, respectively. One patient with grade IVa developed pneumonia with acute respiratory failure on POD 3 and received intensive critical care thereafter. All patients recovered from the complications and were discharged.

The pathology of the gastric SETs is shown in Table 4. Before laparoscopic surgery, the rate of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) was 17% (16/94), and the diagnostic accuracy was 10.6% (10/94), with one complication and one perforation. Nine patients had cytopathological diagnoses of GIST, and two patients received neoadjuvant target therapy with imatinib at a dose of 400 mg/day for one year preoperatively. Overall, the percentage of malignant pathology (85.1% *vs* 45%, $P < 0.001$), particularly the composition of GIST with intermediate and high risk (39.7% vs. 11.6%), and the recurrence rate (6.4% *vs* 0, $P = 0.012$) were significantly higher in the LR group, except for disease-related mortality (Table 4). In the ER group, the majority of the patients diagnosed with GIST were categorized into the very low-risk group (60.5%), followed by the low-risk (27.9%), and the intermediate-risk (11.6%) groups, according to the NIH classification[18]. They underwent long-term surveillance for a mean duration of 27.5 mo, and no recurrence was detected. One patient, diagnosed with neuroendocrine tumor grade 1, received further gastrectomy and adjuvant chemotherapy without recurrence during a 64-month follow-up period. In the LR group, 78 patients were diagnosed with GISTs, with five cases of complicated bleeding and two ruptures, and were categorized into the very low-risk (11, 14.1%), low-risk (36, 46.2%), intermediate-risk (20, 25.6%), and high-risk (11, 14.1%) groups. A total of 12 patients (15.4%) received post-operative adjuvant imatinib therapy. They had long-term surveillance for a mean duration of 37.3 mo; four cases were reported to have recurrences (two local recurrences, one liver metastasis, and one mesenteric metastasis) with a mean disease-free survival of 12.3 mo. Four patients who were still alive during follow-up received target therapy, and one patient with mesenteric metastasis underwent further surgery for tissue proof and occult obstruction. One patient diagnosed with lipoleiomyosarcoma had liver metastasis, with a disease-free survival time of 23.5 mo. The liver metastasis progressed, and the patient died of inferior vena cava syndrome, with an overall survival of 47 mo. Another patient with a neuroendocrine tumor also had liver metastasis, with a disease-free survival time of 66.5 mo. She received octreotide treatment but died due to multiple distant metastases, with an overall survival of 80 mo. The remaining five patients died from other disorders, with an overall mortality rate of 7.4% and a disease-related mortality rate of 2.1%. Overall, although the disease-free survival and survival rates were slightly decreased in the LR group during long-term surveillance, the difference was not significant (log-rank $P = 0.600$, 0.200) (Figure 3).

Table 1 Characteristics of patients undergoing endoscopic submucosal dissection and laparoscopic surgery

	ESD with/without backup surgery (*n* = 100)	Laparoscopic surgery (*n* = 94)	OR (95%CI)	*P* value
Age, yr, median (range)	56 (49-62)	62 (52-70)	1.04 (1.02-1.07)	0.001[a]
Male gender, *n* (%)	46 (46)	47 (50)	1.17 (0.67-2.06)	0.577
Tumor size, *n* (%)				
≤ 2 cm	72 (72)	15 (16)	1	
3-5 cm	26 (26)	54 (57.4)	9.97 (4.82-20.62)	< 0.001[a]
> 5 cm	2 (2)	25 (26.6)	60 (12.81-281)	< 0.001[a]
Tumor location, *n* (%)				
Upper	81 (81)	61 (64.9)	1	
Middle	6 (6)	14 (14.9)	3.1 (1.13-8.53)	0.029[a]
Low	13 (13)	19 (20.2)	1.94 (0.89-4.23)	0.096
Layer of tumor origin, *n* (%)				
Submucosa	6 (6)	3 (3.2)	1	
Muscularis propria	94 (94)	91 (96.8)	1.94 (0.47-7.97)	0.36
Exophytic growth, *n* (%)	11 (11)	53 (56.4)	10.46 (4.95-22.08)	< 0.001[a]
Pathology, *n* (%)				
Benign	55 (55)	14 (14.9)	1	
Malignant or malignant potential	45 (45)	80 (85.1)	6.98 (3.5-13.94)	< 0.001[a]
Procedure time, min, median (IQR)	75 (40-138)	130 (100-169)	-	< 0.001[a]
Length of stay, d, median (IQR)	5 (4-7)	6 (4-6)	-	0.923
Clavien ≥ III complication, *n* (%)	5 (5)	3 (3.2)	-	0.527

[a]*P* < 0.05.

ESD: Endoscopic submucosal dissection; OR: Odds ratio; CI: Confidence interval; IQR: Interquartile range.

DISCUSSION

For gastric SETs, complete tumor removal with a free margin, minimal resection of the normal stomach, and avoiding pseudocapsule rupture are the goals of the present treatment. With recent advances in endoscopic techniques, ER has become an alternative option because the endoscopic approach maintains the integrity and anatomical function of the stomach without damaging the abdominal wall. More studies have compared clinical outcomes between ER and LR for gastric SETs of size ≤ 5 cm, and ER has the advantages of lower invasiveness, a shorter procedure duration[14,15,19-23], faster recovery[20,21,23,24], and a shorter hospital stay[20,21,24,25] in selected cases with smaller tumor sizes[14,15,19,20,24,25] and intraluminal growth[14,15,20]. However, ER-related complications are still a greater concern for prolonged hospital stays than those for LR[22]. From our experience, we also found that ER had the advantage of a shorter procedure duration than LR, while similar outcomes for hospital stays and major postoperative complications were observed. Where backup surgery was required to address incomplete ER, which could effectively reduce post-ER morbidity[16], prolonged procedures and hospital stays were observed compared with LR. Thus, ER is considered an effective and less invasive approach in selected cases if the tumor can be successfully resected.

Although ER tends to be used to manage smaller tumors, debates regarding the usual size for minimally invasive surgery for gastric SETs continue. For ER, a systematic review has recorded the average diameter of gastric GISTs, which ranges from 1.1 to 3.8 cm[14]. Recently, the European Society of Gastrointestinal Endoscopy (ESGE) guidelines have suggested that ER for gastric GISTs of size < 3.5 cm with intraluminal growth is an alternative to laparoscopic surgery[6]. With advances in endoscopic techniques for the closure of large gastric wall defects, a Chinese study found that it is feasible to treat giant gastric SETs of size ≥ 6 cm by ER with favorable long-term outcomes, although the minimum diameter of the tumor was associated with *en bloc* resection[26]. In our early period of ER, there were two cases of tumors > 5 cm in size, and we found it difficult to perform endoscopic retrieval of the entire tumor. Although piecemeal ER was feasible for complete resection, we tended to use *en bloc* resection for smaller tumors, with a rate of 90.4% based on our data.

On the other hand, laparoscopic surgery was initially suggested for tumors < 5 cm in size with a risk for tumor rupture and concern for oncological safety[27]. However, with the development of techniques and energy devices, laparoscopic surgery is no longer limited by the tumor size. Laparoscopic surgery provides a clear and broad field of vision that

Table 2 Characteristics of endoscopic submucosal dissection with backup surgery and laparoscopic surgery

	ESD with backup surgery (*n* = 27)	Laparoscopic surgery (*n* = 94)	OR (95%CI)	*P* value
Age, yr, median (range)	56 (50-64)	62 (52-70)	1.03 (1.00-1.06)	0.053
Male gender, *n* (%)	9 (33.3)	47 (50)	2.00 (0.82-4.90)	0.13
Tumor size, *n* (%)				
≤ 2 cm	16 (59.3)	15 (16)	1	
3-5 cm	11 (40.7)	54 (57.4)	7.66 (2.98-19.72)	< 0.001[a]
> 5 cm	0 (0)	25 (26.6)		
Tumor location, *n* (%)				
Upper	23 (85.2)	61 (64.9)	1	
Middle	1 (3.7)	14 (14.9)	3.11 (0.99-9.76)	0.052
Low	3 (11.1)	19 (3.2)		
Layer of tumor origin, *n* (%)				
Submucosa	0 (0)	3 (3.2)	-	1
Muscularis propria	27 (100)	91 (96.8)	-	
Exophytic growth, *n* (%)	10 (37)	53 (56.4)	2.20 (0.91-5.3)	0.08
Pathology, *n* (%)				
Benign	11 (40.7)	14 (14.9)	1	
Malignant or malignant potential	16 (59.3)	80 (85.1)	3.93 (1.51-10.21)	0.005[a]
Procedure time, min, median (IQR)	185 (150-245)	130 (100-169)	-	< 0.001[a]
Length of stay, d, median (IQR)	7 (7-8)	6 (4-6)	-	< 0.001[a]
Clavien ≥ III complication, *n* (%)	0 (0)	3 (3.2)	-	0.347

[a]*P* < 0.05.

ESD: Endoscopic submucosal dissection; OR: Odds ratio; CI: Confidence interval; IQR: Interquartile range.

facilitates more sophisticated dissection and timely treatment of intraoperative bleeding, thereby realizing equivalent oncological safety and even better 5-year disease-free survival for large tumors (> 5 cm) compared to open surgery[7-9]. In our study, 26.6% of the tumors in the LR group were large tumors, and we also used this for two cases with preoperative target therapy for one year. We continued adjuvant therapy with imatinib at a dose of 400 mg/d postoperatively, and the patients were still disease-free at 25 and 39.5 mo during follow-up. Nevertheless, laparoscopy was limited by its decreased tactile feedback and difficulty in tumor localization; therefore, endoscopic assistance is suggested for small tumors (≤ 1.8 cm) and intraluminal growth types[28]. In our study, intraoperative endoscopy was required to precisely localize the tumors in 12 patients (12.8%) in the LR group. Overall, from our practical experience, we found that the optimal cut-off point for the tumor size for laparoscopic surgery is 2.15 cm.

In our study, patients with tumors in the middle or lower third of the stomach tended to undergo laparoscopic surgery rather than ER or backup surgery, which might have resulted from the initial selection bias of endoscopists and surgeons considering the tumor size. However, the location in the upper third of the stomach has been reported as a risk factor for perforation due to the relatively thin gastric wall and difficultly in endoscopic angulation[18,29]. With the technical expertise of experienced endoscopists, gastric SETs in the upper third of the stomach could be successfully removed with ER. In addition, we considered that ER for gastric SETs in the anterior wall of the stomach body had a high probability of surgical intervention because intragastric gas leakage into the peritoneal cavity without a soft tissue boundary made endoscopic repair more difficult, owing to a poor visual field and a gradually distended abdominal wall[16]. A Japanese study reported that surgeons found it difficult to endoscopically repair large defects on the anterior gastric wall and resorted to laparoscopic surgery[15]. These reasons may explain why tumors in the middle or lower third of the stomach tend to be treated *via* laparoscopic surgery.

Tumors with exophytic growth have a high risk for perforation[16], and their size may be larger than those without exophytic growth. In the present study, exophytic growth was significantly different between the ER and LR groups; however, no significant difference was observed between the backup surgery and LR groups. Patients with exophytic tumor growth eventually underwent laparoscopic surgery because of the high risk for incidental perforation after ER and easy localization during laparoscopic exploration. Based on the above findings, we assumed that exophytic tumor growth was undoubtedly indicative of LR.

Table 3 Factors affecting procedure time and length of stay in endoscopic submucosal dissection with backup surgery and laparoscopic surgery

Factors	Without matched data			Propensity score matching		
	Adjusted mean difference	SE	*P* value	Adjusted mean difference	SE	*P* value
Procedure time						
Surgery type						
ESD with backup surgery	Reference			Reference		
Laparoscopic surgery	-63.42	14.70	< 0.001[a]	-56.40	18.60	0.005[a]
Age	-0.43	0.42	0.304	-	-	-
Tumor size 2	22.04	13.35	0.101	-	-	-
Tumor location: middle or low	33.58	12.54	0.008[a]	-	-	-
Exophytic growth	-4.54	10.98	0.680	-	-	-
Pathology with malignancy	-13.81	15.59	0.378	-	-	-
Length of stay						
Surgery type						
ESD with backup surgery						
Laparoscopic surgery	-1.215	1.089	0.267	-2.00	0.516	0.001[a]
Age	0.081	0.031[a]	0.009[a]	-	-	-
Tumor size 2	-0.348	0.988	0.726	-	-	-
Tumor location: middle or low	0.457	0.928	0.624	-	-	-
Exophytic growth	-0.218	0.813	0.789	-	-	-
Pathology with malignancy	-0.268	1.154	0.817	-	-	-

[a]$P < 0.05$.
ESD: Endoscopic submucosal dissection.

Table 4 Malignant pathology and clinical outcomes after endoscopic submucosal dissection and laparoscopic surgery

	ESD with/without backup surgery (*n* = 100)	Laparoscopic surgery (*n* = 94)	*P* value
Malignant pathology in the group, *n* (%)	45 (45)	80 (85.1)	< 0.001[a]
Malignant pathology			
GIST, *n* (%)	43 (43)	78 (83.1)	< 0.001[a]
High risk	0 (0)	11 (14.1)	0.001[a]
Intermediate risk	5 (11.6)	20 (25.6)	0.002[a]
Low risk	12 (27.9)	36 (46.2)	< 0.001[a]
Very low risk	26 (60.5)	11 (14.1)	0.019[a]
Neuroendocrine tumor, *n* (%)	1 (1)	1 (1)	1.000
Lipoleiomyosarcoma, *n* (%)	0	1 (1)	0.485
Recurrence, *n* (%)	0	6 (6.4)	0.012[a]
Disease related mortality, *n* (%)	0	2 (2.1)	0.233

[a]$P < 0.05$.
ESD: Endoscopic submucosal dissection; GIST: Gastrointestinal stromal tumors.

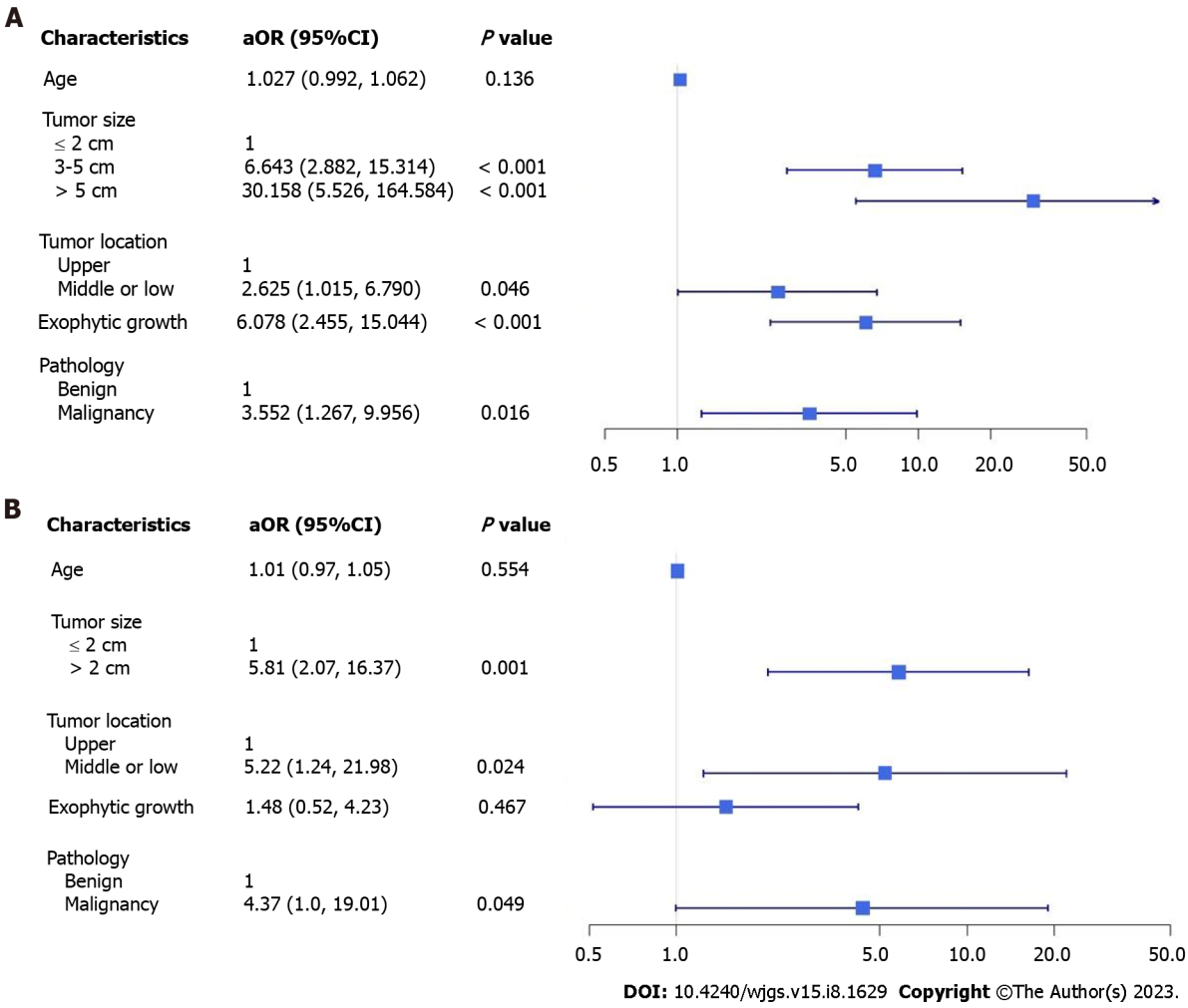

Figure 1 Multivariate adjustment factor for the likelihood of patients undergoing laparoscopic surgery compared to endoscopic submucosal dissection patients and endoscopic submucosal dissection with backup surgery. A: Endoscopic submucosal dissection patients; B: Endoscopic submucosal dissection with backup surgery. aOR: adjusted odds ratio; CI: Confidence interval.

Furthermore, patients with malignant tumors or malignant potential tended to undergo LR (85.1% *vs* 45%; OR, 6.98; $P < 0.001$). For malignant pathology, oncological safety is still a concern for ER because the complete resection rate has been found to be lower in ER than that in surgery[23,25]. Nevertheless, ER for small tumor sizes has still achieved R0 resection rates of up to 97%, according to a systematic review and meta-analysis[14,30,31], and no significant differences in long-term oncological outcomes for GISTs have been observed between ER and LR [23]. For gastric GISTs, tumor size is a key factor for recurrence risk rather than resection status, if no macroscopic residual tumor exists[24,29,32] and should be cautiously considered for different strategies of minimally invasive surgery. A previous study suggested that gastric GISTs that were completely resected endoscopically carry a lower stratified risk for aggressive clinical outcomes[24,32,33], and we found similar results in our study. In the ER group, the majority (60.5%) of the GISTs had a very low risk due to their small sizes and lack of disease recurrence during follow-up. In the LR group, 39.7% of the GISTs were categorized as intermediate- or high-risk. Overall, a higher recurrence rate (6.4%) and disease-related mortality rate (2.1%) were observed in the LR group; however, no significant difference was observed during long-term surveillance. Although all the patients underwent complete resection, the *en bloc* resection rate after ER was only 90.4%, which is not of high concern for LR. For tumors with suspected aggressive behavior of malignant pathology preoperatively, we preferred laparoscopic surgery to achieve similar oncological outcomes.

This study has some limitations. First, it was conducted at a single center with a relatively small sample size. Second, selection bias existed between the ER and LR groups because endoscopists and surgeons evaluated the patients preoperatively to make collaborative decisions regarding minimally invasive surgical methods. A few patients with gastric SETs in the superficial submucosal layer who underwent ER in the endoscopic room were not included in this database. Third, although GISTs are the most common type of malignant pathology, we focused on gastric SETs and other malignant pathologies. Thus, we focused on perioperative clinical outcomes after ER and LR, whereas the long-term outcomes of malignant pathologies require further analysis. Fourth, different ER and LR methods were chosen by endoscopists and surgeons according to tumor characteristics and location. However, we were unable to perform a detailed comparison of the different methods because of the small sample size.

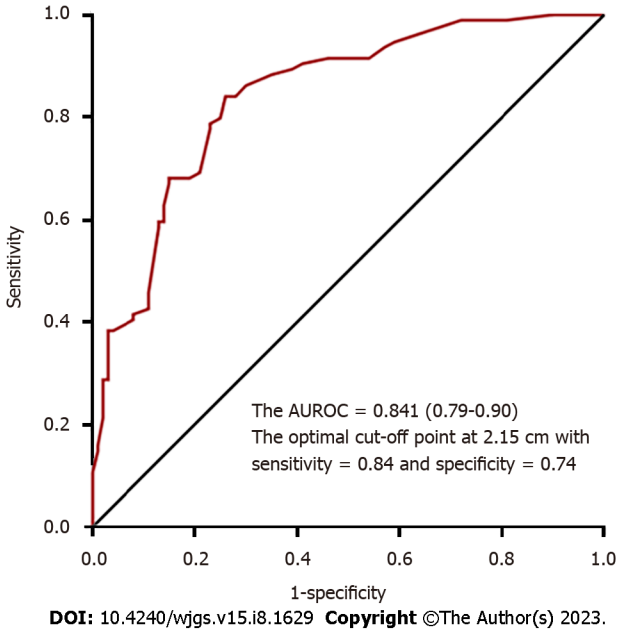

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Figure 2 Optimal cut-off point for tumor size for laparoscopic surgery. AUROC: Area under the receiver operating characteristic curve.

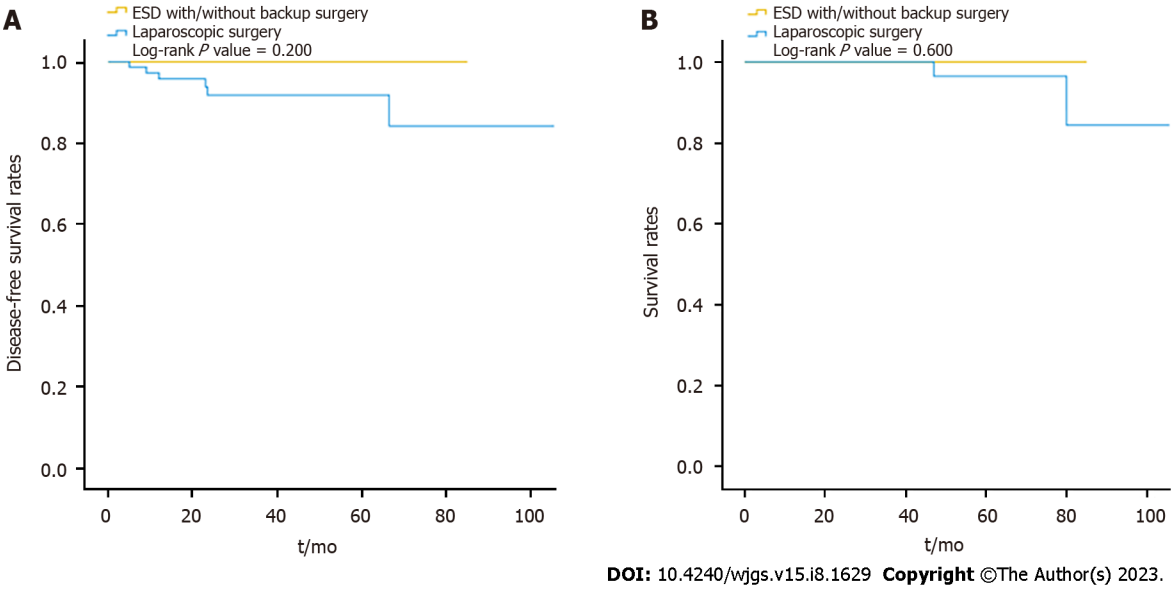

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Figure 3 Comparison of disease-free survival rates and survival rates between the endoscopic and laparoscopic resection groups during long-term surveillance. A: Disease-free survival rates; B: Survival rates. ESD: Endoscopic submucosal dissection.

CONCLUSION

There are different approaches to minimally invasive surgery for gastric SETs with the objective of achieving better perioperative clinical outcomes. ER was indicated for smaller tumor sizes and intraluminal growth, whereas LR was indicated for larger tumor sizes, with an optimal tumor size cut-off point of 2.15 cm, tumors located in the middle or lower third of the stomach, exophytic tumor growth, and more aggressive malignant behavior. Multidisciplinary teamwork is an effective strategy for selecting suitable treatments, leading to better clinical outcomes.

ARTICLE HIGHLIGHTS

Research background

With recent advancements in endoscopic and laparoscopic management of gastric subepithelial tumors (SETs), different

approaches to minimally invasive surgery have been adopted to improve the clinical outcomes.

Research motivation

To treat gastric SETs, the effectiveness and safety of endoscopic resection (ER), laparoscopic resection (LR), or our hybrid method were compared in terms of procedure duration, duration of hospital stay, and major complications.

Research objectives

This retrospective study compared the differences between ER and LR, and between ER with backup surgery and LR, in terms of demographic data, tumor characteristics, and perioperative outcomes. Thus, Goldilocks principle was used to determine the best type of minimally invasive surgery for gastric SETs.

Research methods

This retrospective review of records was performed on all patients of gastric SETs with high probability of surgical intervention undergoing tumor resection in the operating theater between January 2013 and December 2021. All patients were divided into two groups, either group of ER or group of LR.

Research results

Totally, 194 patients were divided into the ER group (n = 100) and LR group (n = 94). In the ER group, 27 patients required backup laparoscopic surgery after an incomplete ER. The patients in the ER group had small tumor sizes and shorter procedure durations while the patient in the LR group had large tumor sizes, exophytic growth, malignancy, and tumors that were more often located in the middle or lower third of the stomach. Both groups had similar durations of hospital stays and a similar rate of major postoperative complications. For the patients in the ER group who underwent backup surgery required longer procedures (56.4 min) and prolonged stays (2 d) compared to the patients in the LR group without the increased rate of major postoperative complications. The optimal cut-off point for the tumor size for laparoscopic surgery was 2.15 cm.

Research conclusions

ER was indicated for a smaller tumor and intraluminal growth, whereas LR was indicated for a larger tumor (optimal cut-off point: 2.15 cm), tumors located in the middle or lower third of the stomach, exophytic growth, and more aggressive malignancy behavior. Backup surgery is preserved for incomplete ER to effectively reduce associated morbidities.

Research perspectives

Multidisciplinary teamwork adopts different strategies to yield the efficient clinical outcome according to the tumor characteristics.

FOOTNOTES

Author contributions: Yen HH, Chang HC, and Lin KH designed research; Tsao LC, Yen HH, Yang CW, Chang HC, and Lin KH performed research; Tsao LC, Yen HH, and Kor CT contributed new reagents/analytic tools; Kor CT and Wu SC analyzed the data; Chang WJ and Lin KH wrote the paper.

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ORCID number: Wei-Jung Chang 0000-0002-0647-2864; Lien-Cheng Tsao 0000-0002-2153-4517; Hung-Chi Chang 0000-0002-0038-3895; Chew-Teng Kor 0000-0002-5665-9635; Szu-Chia Wu 0000-0003-3815-2176; Kuo-Hua Lin 0000-0003-3360-9747.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Prognosis after splenectomy plus pericardial devascularization *vs* transjugular intrahepatic portosystemic shunt for esophagogastric variceal bleeding

Wei-Li Qi, Jun Wen, Tian-Fu Wen, Wei Peng, Xiao-Yun Zhang, Jun-Yi Shen, Xiao Li, Chuan Li

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Wei-Li Qi, Jun Wen, Tian-Fu Wen, Wei Peng, Xiao-Yun Zhang, Jun-Yi Shen, Chuan Li, Department of Liver Surgery, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Jun Wen, Section for HepatoPancreatoBiliary Surgery, Department of General Surgery, The Third People's Hospital of Chengdu, Affiliated Hospital of Southwest Jiaotong University & The Second Affiliated Hospital of Chengdu, Chongqing Medical University, Chengdu 610041, Sichuan Province, China

Xiao Li, Department of Interventional Therapy, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Xiao Li, Department of Interventional Therapy, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100000, China

Corresponding author: Chuan Li, MD, PhD, Associate Professor, Department of Liver Surgery, West China Hospital, Sichuan University, No. 37 Guoxue Lane, Chengdu 610041, Sichuan Province, China. lichuan@scu.edu.cn

Abstract

BACKGROUND

Portal hypertension combined with esophagogastric variceal bleeding (EGVB) is a serious complication in patients with hepatitis B virus (HBV)-related cirrhosis in China. Splenectomy plus pericardial devascularization (SPD) and transjugular intrahepatic portosystemic shunt (TIPS) are effective treatments for EGVB. However, a comparison of the effectiveness and safety of those methods is lacking.

AIM

To compare the prognosis after SPD *vs* TIPS for acute EGVB after failure of endoscopic therapy or secondary prophylaxis of variceal rebleeding (VRB) in patients with HBV-related cirrhosis combined with portal hypertension.

METHODS

This retrospective cohort study included 318 patients with HBV-related cirrhosis

and EGVB who underwent SPD or TIPS at West China Hospital of Sichuan University during 2009-2013. Propensity score-matched analysis (PSM), the Kaplan-Meier method, and multivariate Cox regression analysis were used to compare overall survival, VRB rate, liver function abnormality rate, and hepatocellular carcinoma (HCC) incidence between the two patient groups.

RESULTS

The median age was 45.0 years (n = 318; 226 (71.1%) males). During a median follow-up duration of 43.0 mo, 18 (11.1%) and 33 (21.2%) patients died in the SPD and TIPS groups, respectively. After PSM, SPD was significantly associated with better overall survival (OS) (P = 0.01), lower rates of abnormal liver function (P < 0.001), and a lower incidence of HCC (P = 0.02) than TIPS. The VRB rate did not differ significantly between the two groups (P = 0.09).

CONCLUSION

Compared with TIPS, SPD is associated with higher postoperative OS rates, lower rates of abnormal liver function and HCC, and better quality of survival as acute EGVB treatment after failed endoscopic therapy or as secondary prophylaxis of VRB in patients with HBV-related cirrhosis combined with portal hypertension. There is no significant between-group difference in VRB rates.

Key Words: Portal hypertension; Liver cirrhosis; Esophagogastric variceal bleeding; Splenectomy; Pericardial devascularization; Transjugular intrahepatic portosystemic shunt

Core Tip: The choice between splenectomy plus pericardial devascularization (SPD) and transjugular intrahepatic portosystemic shunt (TIPS) in the treatment of esophagogastric variceal bleeding (EGVB) in cirrhosis with portal hypertension is controversial, and few studies have compared the advantages and disadvantages of the two treatments. We compared the efficacy of the two treatments for acute EGVB that failed endoscopic treatment or secondary prevention of variceal rebleeding (VRB). We found no difference in the VRB rate between the two treatments, but the SPD group had a higher overall survival rate and a lower incidence of abnormal liver function and hepatocellular carcinoma than the TIPS group.

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INTRODUCTION

Chronic hepatitis B virus (HBV) infection is an important cause of liver cirrhosis in China. Patients with cirrhosis that progresses to the portal hypertension stage will face a series of complications, including esophagogastric variceal bleeding (EGVB), ascites, splenomegaly, hypersplenism, primary bacterial peritonitis, hepatic encephalopathy, and hepatorenal syndrome[1]. EGVB is one of the most serious emergency complications of cirrhosis. The mortality rate for the first bleeding is as high as approximately 20%[2,3]. Moreover, the rate of variceal rebleeding (VRB) within two years is nearly 60%, and the mortality rate is 30%[4].

The management strategy for EGVB is oriented toward prevention of the first EGVB (primary prophylaxis), control of acute EGVB, and prevention of VRB (secondary prophylaxis). Endoscopic treatment, including endoscopic variceal ligation and endoscopic injection sclerotherapy, and nonselective beta-blockers are the mainstay of primary and secondary prophylaxis for EGVB[5]. Similarly, endoscopic therapy is also recommended by the major clinical practice guidelines as a first-line treatment option for patients with acute EGVB[6-8]. In China, transjugular intrahepatic portosystemic shunt (TIPS) and splenectomy plus pericardial devascularization (SPD) are recommended as salvage therapies for patients with acute EGVB who failed endoscopic treatment or as secondary prevention of EGVB[9]. TIPS results in rapid control of acute EGVB and a significant reduction in VRB rates. Especially for patients at high risk of EGVB, early TIPS has been shown to significantly reduce VRB rates and improve prognosis in these patients[10,11]. SPD not only has a high hemostasis rate and low VRB rate, but can also improve liver function and has a relatively low incidence of hepatic encephalopathy[12,13]. However, the effectiveness and safety of SPD *vs* TIPS in the management of acute EGVB and as secondary prophylaxis for VRB are unknown.

The purpose of this study was to compare the prognosis after SPD *vs* TIPS for acute EGVB after failure of endoscopic therapy or secondary prophylaxis of VRB in patients with HBV-related cirrhosis combined with portal hypertension. We

compared the differences in VRB, abnormal liver function, and incidence of hepatocellular carcinoma (HCC) between patients treated with SPD and TIPS.

MATERIALS AND METHODS

Study population

This was a retrospective cohort study. We retrospectively collected clinical data from 823 consecutive patients with portal hypertension combined with EGVB who received SPD or TIPS as a treatment for bleeding uncontrolled by endoscopic therapy or as secondary prophylaxis for VRB at West China Hospital of Sichuan University from January 1, 2009 to December 31, 2013. According to the inclusion and exclusion criteria, 318 patients were finally included in the analysis. Patients were divided into either an SPD group (n = 162) or a TIPS group (n = 156) based on treatment modality (Figure 1). All participants were diagnosed with portal hypertension with esophagogastric varices by endoscopy.

The inclusion criteria included the following: (1) Age 18-70 years; (2) clinical diagnosis of HBV-related cirrhosis combined with EGVB; (3) presence of acute EGVB uncontrolled by endoscopic therapy or VRB after secondary prophylaxis; (4) treatment with SPD or TIPS; (5) good liver function (Child-Pugh class A or B); and (6) good other organ function. The exclusion criteria included the following: (1) Cirrhosis due to other etiologies, such as alcoholic cirrhosis, schistosomal cirrhosis, and primary biliary cirrhosis; (2) gastrointestinal bleeding due to other causes, such as peptic ulcer bleeding; (3) coexistence of serious infectious or hematological diseases; (4) coexistence of serious organ impairment, such as cardiopulmonary and renal diseases, thus indicating patients who cannot tolerate surgery; (5) coexistence of malignancy; (6) poor liver function (Child-Pugh class C); (7) no history of EGVB; (8) coexistence of portal vein thrombosis or portal vein cavernous lesions; and (9) history of previous relevant surgical procedures, such as liver transplantation or TIPS.

Baseline patient data were obtained from electronic medical records and included demographic data, degree of esophagogastric varices, length of bleeding history, liver function tests, renal function tests, blood cell counts, coagulation tests, Child-Pugh classification, HBV markers, and HBV-DNA levels.

The study complied with the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University (No. 2023-354). The ethics committee waived the requirement for informed consent due to the retrospective nature of this research.

Surgical procedures

All procedures were performed by specialists with more than 10 years of experience. The SPD procedure was performed routinely by splenectomy, complete dissection of at least 6 cm of the lower esophagus and all vessels of the upper plasma layer of the stomach, and preservation of the gastric coronary vein and the main trunk of the paraesophageal vein. The surgeon performed the procedure with a common monopolar electric knife, ultrasonic knife, or Ligasure, depending on his personal preference. The splenic hilum was closed with suture ligation, hemo-lock or titanium clips, or off-segment closure with a vascular closure device, depending on the situation. According to the American Association for the Study of Liver Diseases guidelines[14], the TIPS procedure was performed by ultrasound-guided puncture of the right internal jugular vein, insertion of a catheter into a branch of the hepatic vein and venography, and placement of a stent from the hepatic vein through the portal vein to create an artificial shunt. The application of polytetrafluoroethylene (PTFE)-covered stents (Viatorr stents) has greatly reduced the rate of stenosis and occlusion of the shunt and the incidence of hepatic encephalopathy[15,16]. The Director of the Interventional Center supervised and controlled the quality of the TIPS procedure.

Outcomes and follow-up evaluation

The primary outcome measure in this study was overall survival (OS), and secondary outcomes were VRB, abnormal liver function, and the occurrence of HCC. All included patients were followed up to the last follow-up date (December 31, 2016) or until they died. The OS, rate of VRB, rate of abnormal liver function, and rate of HCC were calculated for all patients. Abnormal liver function was defined as total bilirubin (TB) > 28.2 μmol/L, albumin (ALB) < 35 g/L, or alanine aminotransferase or aspartate aminotransferase more than twice the reference value for a duration of more than 3 mo.

All patients were followed at months 1, 3, 6, and 12 after surgery and every 6 mo thereafter. The follow-up protocol included physical examination, multiphase enhanced computed tomography (CT), blood cell and differential counts, liver function tests, alpha-fetoprotein (AFP) levels, HBV markers, and HBV-DNA levels. During the follow-up period, patients presenting with VRB underwent endoscopy.

Statistical analysis

Continuous variables were tested by the t test, categorical variables by the chi-square test or Fisher's exact probability method, and ordered categorical variables by the rank sum test. Survival analysis was performed using the Kaplan-Meier method with the occurrence of death, VRB, abnormal liver function, and HCC as endpoint events. The log-rank test was used to compare the differences between the two groups for each outcome event. Univariate and multivariate COX regression analyses were used to identify risk factors associated with outcome indicators. Univariate Cox regression analysis was used to assess the significance of the variables to investigate the risk factors associated with outcome indicators. All variables with significant associations with death (P < 0.1) were further included in the multivariate COX regression analysis. Nearest neighbor 1:1 propensity score matching (PSM) with a caliper size of 0.02 was used to reduce

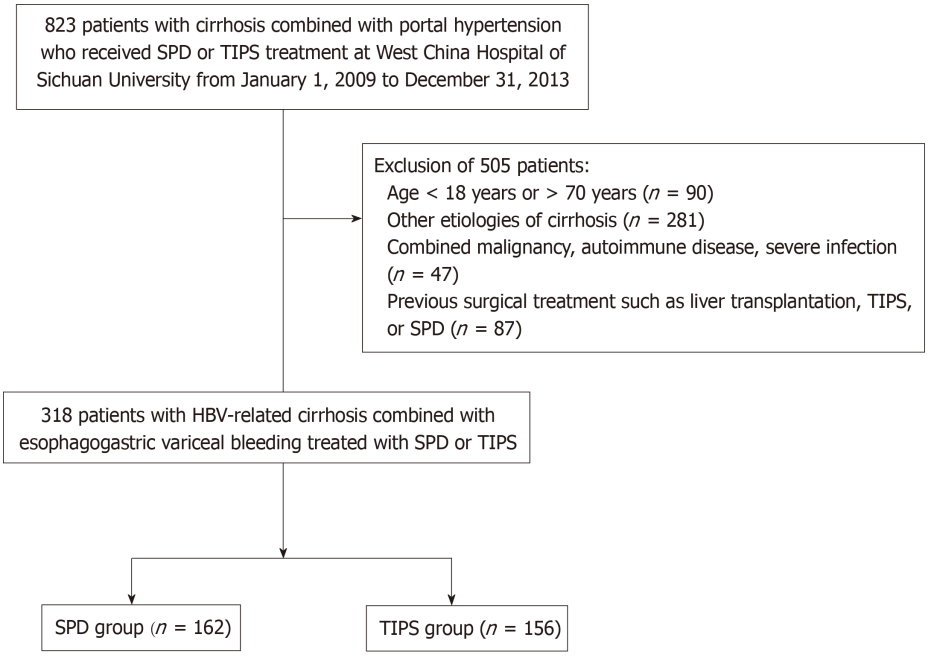

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Figure 1 Flowchart of the process for patient selection. SPD: Splenectomy plus pericardial devascularization; TIPS: Transjugular intrahepatic portosystemic shunt; HBV: Hepatitis B virus.

the effect of selection bias and potential confounding between the SPD group and the TIPS group.

R, version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria), was used to conduct all statistical analyses. The threshold for statistical significance was set at 0.05 for all two-sided statistical tests.

RESULTS

Patient characteristics

Baseline data for all patients are shown in Table 1. The median age was 45.0 years, and 226 (71.1%) of patients were male. The median follow-up duration of this study was 43 mo. There were statistically significant differences in the variables of age ($P < 0.001$), ALB ($P < 0.001$), hemoglobin (HGB) ($P < 0.001$), red blood cells ($P < 0.001$), and international normalized ratio ($P = 0.02$) between the two groups of patients.

To minimize the effect of potential confounders, we generated 90 pairs of patients by PSM. After PSM, there were no significant differences in baseline characteristics between the two groups of patients.

Overall patient survival

During the study period, 18 (11.1%) patients died in the SPD group, and 33 (21.2%) patients died in the TIPS group. Patient survival rates at 1, 3, and 5 years were 98.1%, 90.5%, and 86.5% in the SPD group and 94.8%, 81.0%, and 74.7% in the TIPS group, respectively. The mean survival time was 84.7 mo for patients in the SPD group and 73.6 mo in the TIPS group. In comparison to the TIPS group, the OS was significantly longer in the SPD group ($P = 0.004$; Figure 2A). After PSM, the SPD group still showed significantly better OS than the TIPS group ($P = 0.01$; Figure 2B).

Multivariate Cox regression analysis of 318 patients showed that the SPD group had a significantly lower risk of death than the TIPS group [hazard ratio (HR), 0.47; 95% confidence interval (CI): 0.25-0.90; $P = 0.02$; Table 2], which was independent of other predictors. Other significant factors associated with death were age (HR, 1.03; 95%CI: 1.01-1.06; $P = 0.02$), albumin/globulin ratio (A/G; HR, 0.11; 95%CI: 0.03-0.48; $P = 0.003$), and prothrombin time (PT; HR, 1.09; 95%CI: 1.02-1.16; $P = 0.01$; Table 2).

Cumulative incidence of variceal rebleeding, abnormal liver function, and hepatocellular carcinoma

For the duration of the study, VRB occurred in 40 (24.7%) patients in the SPD group and 59 (37.8%) patients in the TIPS group. The 1-, 3-, and 5-year cumulative VRB rates were 8.6%, 19.1%, and 24.1% in the SPD group and 20.5%, 34.6%, and 37.8% in the TIPS group, respectively ($P = 0.001$, Table 3). After PSM, the 1-, 3-, and 5-year cumulative VRB rates were 7.8%, 15.6%, and 23.3% in the SPD group and 11.1%, 27.8%, and 31.1% in the TIPS group, respectively ($P = 0.09$, Table 3). Multivariate COX regression analysis of 318 patients showed that the independent influential factors associated with VRB were treatment strategy (SPD *vs* TIPS; HR, 0.58; 95%CI: 0.37-0.89; $P = 0.01$), gamma-glutamyl transpeptidase (GGT; HR, 1.005; 95%CI: 1.001-1.008; $P = 0.01$), and HGB (HR, 0.99; 95%CI: 0.98-1.00; $P = 0.01$; Table 4).

Table 1 Baseline features of the study population

Characteristic	Before PSM			After PSM		
	SPD group	TIPS group	*P* value	SPD group	TIPS group	*P* value
Age, yr	44.14 ± 10.64	49.57 ± 11.24	< 0.001	46.41 ± 10.81	47.16 ± 10.95	0.65
Male, *n* (%)	121 (74.7)	105 (67.3)	0.15	64 (71.1)	60 (66.7)	0.520
Bleeding history, mo	12.70 ± 24.19	12.83 ± 21.95	0.961	13.64 ± 26.76	13.6 ± 22.62	0.99
Spleen length, cm	20.121 ± 4.49	19.27 ± 4.05	0.08	19.86 ± 4.47	18.85 ± 3.57	0.10
Spleen thickness, cm	6.47 ± 1.43	6.20 ± 1.42	0.09	6.31 ± 1.29	6.05 ± 1.07	0.14
TB, μmol/L	22.81 ± 9.93	22.18 ± 10.22	0.58	23.68 ± 10.60	21.99 ± 9.65	0.26
ALT, IU/L	34.561 ± 27.68	32.08 ± 35.49	0.49	29.81 ± 19.33	29.34 ± 15.25	0.86
AST, IU/L	40.651 ± 29.05	41.218 ± 35.80	0.88	36.37 ± 22.78	37.32 ± 18.09	0.76
ALB, g/L	37.71 ± 5.28	33.13 ± 6.19	< 0.001	36.35 ± 4.58	35.46 ± 5.15	0.22
A/G	1.311 ± 0.29	1.52 ± 3.40	0.45	1.31 ± 0.27	1.28 ± 0.29	0.58
ALP, IU/L	87.10 ± 39.98	85.08 ± 52.93	0.70	86.42 ± 37.50	86.93 ± 57.34	0.94
GGT, IU/L	50.13 ± 59.94	49.26 ± 61.59	0.90	53.35 ± 71.03	49.14 ± 63.91	0.68
BUN, mmol/L	6.038 ± 7.87	5.89 ± 2.76	0.82	6.48 ± 10.44	5.56 ± 2.00	0.42
CREA, μmol/L	72.92 ± 17.01	73.02 ± 18.40	0.96	73.20 ± 18.54	69.36 ± 14.59	0.13
HGB, g/L	99.74 ± 27.85	84.38 ± 23.18	< 0.001	94.42 ± 30.02	91.07 ± 23.76	0.41
RBC, × 10^{12}/L	3.71 ± 0.82	3.06 ± 0.79	< 0.001	3.46 ± 0.81	3.39 ± 0.79	0.54
PLT, × 10^{9}/L	51.85 ± 43.11	55.13 ± 37.11	0.47	50.76 ± 45.62	52.86 ± 24.49	0.70
WBC, × 10^{9}/L	3.68 ± 3.85	3.59 ± 3.93	0.83	3.10 ± 2.56	3.38 ± 2.26	0.43
PT, s	14.67 ± 3.79	14.76 ± 2.08	0.79	14.38 ± 1.95	14.21 ± 1.75	0.54
INR	1.27 ± 0.17	1.32 ± 0.19	0.02	1.28 ± 0.17	1.27 ± 0.15	0.46
HBV-DNA Positive	80 (49.4)	81 (51.9)	0.65	47 (52.2)	48 (53.3)	0.88
Child-Pugh classification, *n* (%)			0.17			1.00
A	89 (54.9)	75 (48.1)		49 (54.4)	49 (54.4)	
B	73 (45.1)	81 (51.9)		41 (45.6)	41 (45.6)	
Severe EGV, *n* (%)	131 (80.9)	124 (79.5)	0.78	73 (81.1)	74 (82.2)	1.00

SPD: Splenectomy plus pericardial devascularization; TIPS: Transjugular intrahepatic portosystemic shunt; TB: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALB: Albumin; A/G: Albumin/globulin; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transpeptidase; HGB: Hemoglobin; RBC: Red blood cell count; WBC: White blood cell count; PLT: Platelets; PT: Prothrombin time; INR: International normalized ratio; HBV: Hepatitis B virus; EGV: Esophagogastric varices; PSM: Propensity score-matched analysis.

A total of 40 (24.7%) patients in the surgical group and 92 (60.9%) patients in the TIPS group experienced persistent abnormal liver function. The rates of abnormal liver function at 1, 3, and 5 years were 13.6%, 19.8%, and 22.8% in the SPD group and 48.7%, 57.7%, and 60.3% in the TIPS group, respectively (P < 0.001; Table 3). After PSM, the rates of abnormal liver function at 1, 3, and 5 years were 13.3%, 18.9%, and 20.0% in the SPD group and 46.7%, 53.3%, and 56.7% in the TIPS group, respectively (P < 0.001, Table 3). Multivariate COX regression analysis of 318 patients showed that the independent influential factors associated with abnormal liver function were treatment strategy (SPD *vs* TIPS; HR, 0.26; 95%CI: 0.17-0.39; P<0.001), TB (HR, 1.03; 95%CI: 1.02-1.05; P < 0.001), alkaline phosphatase (ALP) (HR, 1.004; 95%CI: 1.000-1.007; P = 0.03) and PT (HR, 1.06; 95%CI: 1.00-1.13; P = 0.045; Table 4).

There were 11 (6.8%) patients in the SPD group and 18 (11.5%) patients in the TISP group who developed HCC. The proportions of progression to HCC at 1, 3, and 5 years were 2.5%, 3.7%, and 4.9% in the SPD group and 3.8%, 9.0%, and 11.5% in the TIPS group, respectively (P = 0.03, Table 3). Following adjustment by PSM, the proportions of progression to HCC at 1, 3, and 5 years were 2.2%, 2.2%, and 2.2% in the SPD group and 4.4%, 10.0%, and 12.2% in the TIPS group, respectively (P = 0.02, Table 3). In a multifactorial COX regression analysis of 318 patients, the independent influential factors associated with HCC were treatment strategy (SPD *vs* TIPS; HR, 0.43; 95%CI: 0.20-0.93; P = 0.03), TB (HR, 1.03; 95%CI: 1.00-1.07; P = 0.045), and ALP (HR, 1.006; 95%CI: 1.000-1.012; P = 0.043; Table 4).

Table 2 Univariate and multivariate Cox regression analyses of factors associated with death

Variable	Univariable analysis		Multivariable analysis	
	HR (95%CI)	*P* value[1]	HR (95%CI)	*P* value
Treatment strategy (SPD *vs* TIPS)	0.43 (0.24-0.78)	0.005	0.47 (0.25-0.90)	0.02
Age, per 1-year increase	1.04 (1.02-1.07)	0.001	1.03 (1.01-1.06)	0.02
TB, per 1 μmol/L increase	1.03 (1.01-1.06)	0.01		
ALB, per 1 g/L increase	0.94 (0.91-0.98)	0.004		
A/G, per 1 increase	0.06 (0.02-0.18)	< 0.001	0.11 (0.03-0.48)	0.003
ALP, per 1 IU/L increase	1.01 (1.00-1.01)	< 0.001		
GGT, per 1 IU/L increase	1.003 (1.00-1.01)	0.03		
PT, per 1 s increase	1.07 (1.02-1.12)	0.004	1.09 (1.02-1.16)	0.01
INR, per 1 increase	6.38 (1.68-24.24)	0.006		
HBV-DNA (Positive *vs* negative)	1.78 (1.00-3.15)	0.05		
Child-Pugh classification (B *vs* A)	1.83 (1.07-3.15)	0.03		

[1]Variables that were found significant at $P < 0.1$ in the univariable analyses were entered into the multivariable analyses. SPD: Splenectomy plus pericardial devascularization; TIPS: Transjugular intrahepatic portosystemic shunt; TB: Total bilirubin; ALB: Albumin; A/G: Albumin/globulin; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transpeptidase; PT: Prothrombin time; INR: International normalized ratio; HBV: Hepatitis B virus.

Table 3 Proportions of 1-, 3-, and 5-year cumulative variceal rebleeding, abnormal liver function, and hepatocellular carcinoma in the two groups before and after propensity score matching, %

Outcome/Time	Before PSM			After PSM		
	SPD group	TIPS group	*P* value[1]	SPD group	TIPS group	*P* value[1]
Variceal rebleeding						
1-yr	8.60	20.50	0.001	7.80	11.10	0.09
3-yr	19.10	34.60		15.65	27.80	
5-yr	24.10	37.80		23.30	31.10	
Abnormal liver function						
1-yr	13.60	48.70	< 0.001	13.30	46.70	< 0.001
3-yr	19.80	57.70		18.90	53.30	
5-yr	22.80	60.30		20.00	56.70	
Hepatocellular carcinoma						
1-yr	2.50	3.80	0.03	2.20	4.40	0.02
3-yr	3.70	9.00		2.20	10.00	
5-yr	4.90	11.50		2.20	12.20	

[1]Log-rank test was used to compare the differences between the two groups for each outcome event. SPD: Splenectomy plus pericardial devascularization; TIPS: Transjugular intrahepatic portosystemic shunt; PSM: Propensity score-matched analysis.

Comparison of postoperative hospital days and number of reoperations and adverse events between the two groups

The mean postoperative hospital stay was 9.5 d in the SPD group, which was significantly longer than the 6.6 d in the TIPS group ($P < 0.001$; Table 5). In the SPD group, 162 patients had a total of five reoperations, and in the TIPS group, 156 patients had a total of 92 reoperations. The reoperation rate of patients in the SPD group was significantly lower than that in the TIPS group ($P < 0.001$; Table 5). In the SPD group, one patient died during hospitalization due to abdominal hemorrhage, and in the TIPS group, one patient died during hospitalization due to liver failure. Each group one patient who died during hospitalization, with no significant difference ($P = 0.98$, Table 5). The 90-d mortality was one patient in the SPD group and four patients in the TIPS group, with no statistically significant difference ($P = 0.21$; Table 5). Hepatic encephalopathy occurred in one patient in the SPD group and 25 patients in the TIPS group, which was significantly

Table 4 Multivariate Cox regression analysis of factors associated with variceal rebleeding, abnormal liver function, and hepatocellular carcinoma

Outcome/Variable	HR (95%CI)	*P* value
Variceal rebleeding		
Treatment strategy (SPD *vs* TIPS)	0.58 (0.37-0.89)	0.01
GGT, per 1 IU/L increase	1.005 (1.001-1.008)	0.01
HGB, per 1 g/L increase	0.99 (0.98-1.00)	0.01
Abnormal liver function		
Treatment Strategy (SPD *vs* TIPS)	0.26 (0.17-0.39)	< 0.001
TB, per 1 μmol/L increase	1.03 (1.02-1.05)	< 0.001
ALP, per 1 IU/L increase	1.004 (1.000-1.007)	0.03
PT, per 1 s increase	1.06 (1.00-1.13)	0.045
Hepatocellular carcinoma		
Treatment Strategy (SPD *vs* TIPS)	0.43 (0.20-0.93)	0.03
TB, per 1 μmol/L increase	1.03 (1.00-1.07)	0.045
ALP, per 1 IU/L increase	1.006 (1.000-1.012)	0.043

SPD: Splenectomy plus pericardial devascularization; TIPS: Transjugular intrahepatic portosystemic shunt; TB: Total bilirubin; ALB: albumin; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transpeptidase; PT: Prothrombin time; HGB: Hemoglobin.

Table 5 Comparison of postoperative hospital days and number of reoperations and adverse events between the two groups

Variable	SPD group	TIPS group	*P* value
Postoperative hospital stay, days	9.5 ± 3.4	6.6 ± 3.9	< 0.001
Reoperation, times	5	92	< 0.001
In-hospital mortality	1	1	0.98
The 90-d mortality	1	4	0.21
The 30-d readmission	1	22	< 0.001
Occurrence of hepatic encephalopathy	1	25	< 0.001

SPD: Splenectomy plus pericardial devascularization; TIPS: Transjugular intrahepatic portosystemic shunt.

lower in the SPD group than in the TIPS group ($P < 0.001$; Table 5). Within 30 d, one patient was readmitted in the SPD group and 22 patients in the TIPS group, and the 30-d readmission was significantly lower in the SPD group than in the TIPS group ($P < 0.001$; Table 5).

DISCUSSION

Cirrhotic portal hypertension is very common in China due to the high prevalence of HBV infection. SPD and TIPS are commonly used to treat portal hypertension combined with EGVB. This study compared the two treatment modalities in terms of long-term survival, postoperative VRB rate, postoperative liver function status, HCC incidence, quality of life, and safety. It can provide a reference for clinicians in the selection of the protocol for the treatment of EGVB.

In this study, we found that the SPD group had higher long-term survival rate, sustained normal liver function rate, and no-HCC rate than the TIPS group. Moreover, compared to the TIPS group, the SPD group also showed a noninferiority trend before and after PSM in terms of VRB. In addition, the incidence of hepatic encephalopathy, 30-d readmission rate, and reoperation rate were significantly lower in the SPD group than in the TIPS group, and there was no significant difference between the two groups in terms of in-hospital mortality and 90-d mortality. These results suggest that SPD treatment is no less safe and effective than TIPS treatment and that SPD treatment is even better than TIPS treatment in some aspects.

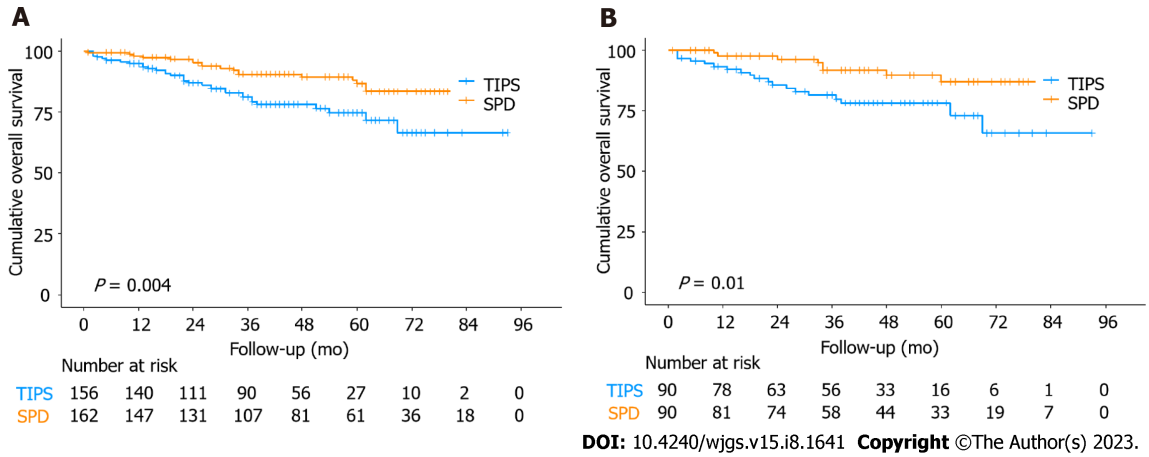

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Figure 2 Overall patient survival. A: Kaplan-Meier analysis of overall survival (OS) in the splenectomy plus pericardial devascularization (SPD) group and transjugular intrahepatic portosystemic shunt (TIPS) group before propensity score-matched analysis (PSM); B: Kaplan-Meier analysis of OS in the SPD group and TIPS group after PSM. SPD: Splenectomy plus pericardial devascularization; TIPS: Transjugular intrahepatic portosystemic shunt.

High portal vein pressure is the direct cause of EGVB; therefore, reducing portal vein pressure plays a critical role in the treatment of EGVB[17,18]. TIPS significantly reduces portal vein resistance by creating a direct shunt between the hepatic and portal veins[19,20]. However, decreased portal perfusion after TIPS can lead to deterioration of liver function [21]. Moreover, shunts can allow portal blood flow to bypass hepatocytes and enter the circulation directly, resulting in the failure to metabolize toxic substances such as ammonia and γ-aminobutyric acid, which can lead to hepatic encephalopathy[22-24]. SPD is also effective in reducing portal vein pressure. Several studies have shown that the loss of splenic vein blood flow after splenectomy subsequently leads to a reduction in portal flow and thus a reduction in portal pressure[25,26]. However, blood flow in the hepatic artery increased after splenectomy and thus facilitated hepatocyte regeneration and improved liver function[25,27].

Whether to perform splenectomy is a controversial aspect of SPD. First, proponents of preserving the spleen argue that splenectomy increases the risk of thrombosis and infection. However, many previous studies have found that TGF-β1 endothelin and platelet-derived growth factors produced by splenic macrophages exacerbate liver fibrosis and inhibit liver regeneration in cirrhotic conditions[28,29]. A recent study by Zhang *et al*[30] showed that CD11b(+)CD43(high)Ly6C-(low) splenic monocytes migrating to the liver and transforming into macrophages can aggravate the liver fibrosis process. This further suggests that splenectomy may slow the process of liver fibrosis and promote liver regeneration. In addition, the traditional view is that splenectomy may impair the immunity of the body and may have a detrimental effect on resistance to tumorigenesis. However, Wang *et al*[31] reported that patients with cirrhosis secondary to hypersplenism and HCC who underwent simultaneous splenectomy and hepatectomy improved their tumor immunity in the long term. McKenna *et al*[32] reported that splenectomy promotes intraocular tumor elimination by affecting tumor-associated cell subsets. Nomura *et al*[33] reported that splenectomy not only improved liver fibrosis but also increased the CD8+ cell percentage and decreased the CD4+/CD8+ ratio, which helped to improve antitumor immunity. Stöth *et al*[34] found that splenectomy reduced the number of tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), and tumor-infiltrating dendritic cells (TIDCs), which in turn affected tumor growth and metastasis. This suggests that splenectomy not only does not decrease the immunity of the body but also may improve the potential antitumor ability. Finally, splenectomy is also effective in improving hypersplenism in patients with cirrhosis. Takahashi *et al*[35] reported that in ten patients with biliary atresia combined with hypersplenism who underwent splenectomy prior to liver transplantation, the patients' hematocrit recovered to normal levels 1 mo after surgery, and the mean Model for End-stage Liver Disease (MELD) score improved significantly.

There are some limitations to this study. First, although we applied PSM to reduce selection bias and potential confounding, unmeasured bias and confounding in this retrospective study might still exist. Second, due to the retrospective nature of this study, hepatic venous pressure gradient testing was not performed in both groups to more accurately assess portal vein pressure between the two groups of patients. Third, this study failed to collect data related to the occurrence of postoperative venous thrombosis in both groups of patients for analysis. Fourth, the medications (including nonselective beta-blockers and antiviral therapy) and endoscopic treatment of patients were not studied in detail in this study.

CONCLUSION

In conclusion, compared with TIPS, SPD is associated with higher postoperative OS rates, lower rates of abnormal liver function and HCC, and better quality of survival as acute EGVB treatment after failed endoscopic therapy or as secondary prophylaxis of VRB in patients with HBV-related cirrhosis combined with portal hypertension. There is no significant difference in the VRB rates between the two groups.

ARTICLE HIGHLIGHTS

Research background

The primary goals of the portal hypertension management program are prevention of first esophagogastric variceal bleeding (EGVB), control of acute EGVB, and prevention of variceal rebleeding (VRB). Splenectomy combined with pericardial devascularization (SPD) and transjugular intrahepatic portosystemic shunt (TIPS) are suggested in China as salvage therapies for patients with acute EGVB who have failed endoscopic treatment or as secondary prophylaxis of VRB. However, it is unclear whether SPD or TIPS is more effective and safe in the treatment of acute EGVB and as secondary prevention of VRB.

Research motivation

Both SPD and TIPS are effective treatments for EGVB, but the effectiveness and safety of both methods are currently controversial.

Research objectives

To compare the prognosis after SPD *vs* TIPS for acute EGVB after failure of endoscopic therapy or secondary prophylaxis of VRB in patients with HBV-related cirrhosis combined with portal hypertension.

Research methods

This was a retrospective study. We used propensity score matching analysis (PSM), Kaplan-Meier method, and multivariate Cox regression analysis to compare the effectiveness and safety of the two treatment modalities for comparative analysis.

Research results

We found that SPD was significantly associated with better overall survival (OS) ($P = 0.01$), lower rates of liver function abnormalities ($P < 0.001$), and a lower incidence of HCC ($P = 0.02$) than TIPS. There was no significant difference in VRB rates between the two groups ($P = 0.09$).

Research conclusions

Compared with TIPS, SPD is associated with higher postoperative OS rates, lower rates of abnormal liver function and HCC, and better quality of survival as acute EGVB treatment after failed endoscopic therapy or as secondary prophylaxis of VRB in patients with HBV-related cirrhosis combined with portal hypertension. There is no significant between-group difference in VRB rates.

Research perspectives

This study may provide a clinical basis for the treatment of patients with portal hypertension combined with EGVB.

FOOTNOTES

Author contributions: Wen TF, Li X, and Li C conceptualized and designed the study, and provided the study materials or patients; Wen TF provided administrative support; Qi WL, Wen J, Li C, Peng W, and Zhang XY collected and assembled the data; Qi WL, Wen J, and Shen JY performed data analysis and interpretation; all authors participated in manuscript writing and approved the final manuscript. Qi WL and Wen J contributed equally to this work.

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Institutional review board statement: The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University (No. 2023-354).

Informed consent statement: The ethics committee approved the waiver of informed consent because the study was retrospective in nature.

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ORCID number: Wei-Li Qi 0000-0001-8899-4836; Jun Wen 0000-0002-5553-8890; Tianfu Wen 0000-0002-8260-7601; Wei Peng 0000-0002-5780-2157; Xiao Li 0000-0001-9420-9558; Chuan Li 0000-0001-5450-6961.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Initial suction drainage decreases severe postoperative complications after pancreatic trauma: A cohort study

Kai-Wei Li, Kai Wang, Yue-Peng Hu, Chao Yang, Yun-Xuan Deng, Xin-Yu Wang, Yu-Xiu Liu, Wei-Qin Li, Wei-Wei Ding

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Kai-Wei Li, The First School of Clinical Medicine, Southern Medical University, Guangzhou 510515, Guangdong Province, China

Kai-Wei Li, Yue-Peng Hu, Wei-Qin Li, Department of Critical Care Medicine, Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing 210002, Jiangsu Province, China

Kai Wang, Chao Yang, Yun-Xuan Deng, Xin-Yu Wang, Wei-Wei Ding, Division of Trauma and Surgical Intensive Care Unit, Research Institute of General Surgery, Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing 210002, Jiangsu Province, China

Yu-Xiu Liu, Division of Data and Statistics, Department of Critical Care Medicine, Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing 210002, Jiangsu Province, China

Corresponding author: Wei-Wei Ding, MD, PhD, Professor, Surgeon, Division of Trauma and Surgical Intensive Care Unit, Research Institute of General Surgery, Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University, No. 305 East Zhongshan Road, Nanjing 210002, Jiangsu Province, China. dingwei_nju@hotmail.com

Abstract

BACKGROUND

Few studies have addressed the question of which drain types are more beneficial for patients with pancreatic trauma (PT).

AIM

To investigate whether sustained low negative pressure irrigation (NPI) suction drainage is superior to closed passive gravity (PG) drainage in PT patients.

METHODS

PT patients who underwent pancreatic surgery were enrolled consecutively at a referral trauma center from January 2009 to October 2021. The primary outcome was defined as the occurrence of severe complications (Clavien-Dindo grade ≥ III_b). Multivariable logistic regression was used to model the primary outcome, and propensity score matching (PSM) was included in the regression-based sensitivity analysis.

RESULTS

In this study, 146 patients underwent initial PG drainage, and 50 underwent initial NPI suction drainage. In the entire cohort, a multivariable logistic regression model showed that the adjusted risk for severe complications was decreased with NPI suction drainage [14/50 (28.0%) *vs* 66/146 (45.2%); odds ratio (OR), 0.437; 95% confidence interval (CI): 0.203-0.940]. After 1:1 PSM, 44 matched pairs were identified. The proportion of each operative procedure performed for pancreatic injury-related and other intra-abdominal organ injury-related cases was comparable in the matched cohort. NPI suction drainage still showed a lower risk for severe complications [11/44 (25.0%) *vs* 21/44 (47.7%); OR, 0.365; 95%CI: 0.148-0.901]. A forest plot revealed that NPI suction drainage was associated with a lower risk of Clavien-Dindo severity in most subgroups.

CONCLUSION

This study, based on one of the largest PT populations in a single high-volume center, revealed that initial NPI suction drainage could be recommended as a safe and effective alternative for managing complex PT patients.

Key Words: Pancreatic trauma; Drainage; Postoperative complications; Clavien-Dindo; Propensity score matching

Core Tip: Few studies have addressed the question of which drain types are more beneficial for patients with pancreatic trauma (PT). A total of 196 PT patients were selected from 2009 to 2021, of whom 146 underwent closed passive gravity (PG) drainage, and 50 underwent low negative pressure irrigation (NPI) suction drainage. In the entire cohort, multivariate analysis showed that the risk for severe complications (Clavien-Dindo grade $\geq$ III_b) was decreased with NPI suction drainage. After 1:1 propensity score matching between the PG and NPI groups, the results were consistent with multivariate analysis.

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INTRODUCTION

Pancreatic trauma (PT) is relatively rare; however, injury to the pancreas can be challenging for even the most experienced trauma surgeon[1-3]. Significant morbidity and mortality are usually related to the cumulative effect of all injured organs[4]. Surgical management is nearly always adopted for PT in the emergency setting of abdominal trauma[5, 6].

Consensus regarding the need for drainage has been formulated in many management strategies for PT[7-9]. The rationale is to evacuate intra-abdominal exudate, pancreatic juice or blood that can accumulate after surgery and serve as an early warning sign of possible pancreatic fistula, anastomotic fistula and associated hemorrhage[8-10]. Moreover, peripancreatic drainage alone is an important therapeutic measure[11,12]. The following two drain types are mainly placed for pancreatic surgery: Closed passive gravity (PG) drainage and sustained low negative pressure irrigation (NPI) suction drainage. PG drainage applies no pressure, evacuating fluid by gravity alone with intra-abdominal pressure[13]. NPI suction drainage actively flushes the abdominal cavity with normal saline under low negative pressure[14,15]. In fact, high-level evidence has not yet been provided to support the choice of drain type for PT[16].

Several issues related to drainage are considered counterproductive, leading to constant evaluation of the roles of these methods[16,17]. First, the drains can serve as portals of entry for bacteria[18]. Second, fistula, hemorrhage, or hollow-organ perforation can be caused by mechanical pressure, suction or erosion around the anastomosis and fragile tissue [19]. It is of paramount importance to understand the extent to which drains influence the development and severity of complications. Therefore, based on one of the largest PT populations in our high-volume center, we performed a retrospective study to investigate whether NPI is superior to PG drainage.

MATERIALS AND METHODS

We performed a retrospective cohort study of consecutive patients who underwent pancreatic surgery at a tertiary trauma referral center between January 2009 and October 2021 in our PT database. The study was approved by the Institutional Review Board (IRB) of Jinling Hospital (Approval No. 2021DZGZR-YBB-009). Informed consent was waived by the IRB because of the retrospective nature of the study. This study was conducted in accordance with the principles of the Declaration of Helsinki. The exclusion criteria were as follows: Early death (< 48 h) after admission; Glasgow Coma Scale score ≤ 8; Abbreviated Injury Scale score = 6 for any area of the body; nonoperative treatment; pregnancy status;

and previous history of malignancy, immune system or hematological diseases.

Operative and drainage management

Pancreatic injuries are classified into 5 grades (I-V) according to the Organ Injury Scale, proposed by the American Association for the Surgery of Trauma in 1990. For low-grade PT (I-II), drainage alone was performed after complete exposure of the pancreas. For high-grade PT (III-V), distal pancreatectomy with or without splenectomy was usually adopted for grade III injury; debridement/resection of the area of injury, closure of the proximal stump and distal Roux-en-Y pancreaticojejunostomy or drainage alone was implemented for grade IV injury; and one-stage damage control drainage and subsequent definitive operative or pancreaticoduodenectomy was utilized for grade V injury.

After distal pancreatectomy, a drain was inserted *via* the left flank and was placed near the pancreatic remnant; the other drain was placed in the left subphrenic area, but only when splenectomy was performed. Similarly, a drain was inserted *via* the left flank and was placed between the pancreaticojejunostomy and pancreatic remnant after middle pancreatectomy. After pancreatoduodenectomy, a drain was inserted *via* the right flank and placed posterior to the biliary anastomosis, extending to the proximal margin of the pancreatic remnant. The other drain was inserted *via* the left flank and was placed posterior to the stomach, extending to the posterior surface of the pancreatic anastomosis in proximity to the contralateral drain. In addition, individualized operative management was performed, and drains were placed as appropriate after careful assessment of the other intra-abdominal organs.

The two drain types adopted are shown in Figure 1. The decision regarding which drain type to place was made on a case-by-case basis and according to the surgeon's preference. Drains were routinely kept in situ for at least postoperative days (POD) 7 to 10. Computed tomography (CT) scans were performed every other week postoperatively. Once pancreatic fistula grade B/C or gastrointestinal fistula was confirmed by fistulography, the duration of drain placement was prolonged. For these patients, PG drainage was replaced by NPI suction drainage through the sinus tract for irrigation to minimize erosion of the surrounding tissue by the digestive juice. A controlled pancreaticocutaneous fistula or enterocutaneous fistula was created by retaining the catheter in situ until the fistula healed spontaneously. When necessary, a CT-guided percutaneous drainage procedure was performed in patients with local pancreatic complications after failed initial drainage and/or new-onset gastrointestinal fistula and localized intra-abdominal abscess requiring source control, and the PG drain was then replaced with NPI suction drainage following the guidewire.

We regularly replaced the catheter to maximize the effect of sustained irrigation drainage and reduce the size of the tube by degrees as appropriate. Two replacement strategies are employed for the management of NPI suction drainage in clinical practice: (1) Planned replacement for prophylactic drainage; and (2) On-demand replacement for therapeutic drainage. If patients do not develop pancreatic fistula grade B/C or gastrointestinal fistula and the volume of drainage fluid is decreasing, prophylactic NPI suction drainage is planned to be replaced every 3 d. For patients with pancreatic fistula grade B/C or gastrointestinal fistula, on-demand replacement is adopted because the role of NPI has been converted to therapeutic drainage. The catheter was retained in situ to create a controlled pancreaticocutaneous fistula or enterocutaneous fistula when there was a large volume of drainage fluid. In addition, the nature of the drainage fluid and the irrigation and drainage fluid in and out volume per unit of time were used to judge whether catheter blockage occurred. If blockage occurred, it was replaced promptly. Moreover, in the presence of a decreasing volumes of drainage fluid and no evidence of intra-abdominal infection, we switched the NPI suction drainage from on demand to planned replacement.

We adhered to the following drain removal policy: Lack of infection-induced systemic inflammatory response syndrome; pancreatic fistula defined by the International Study Group of Pancreatic Fistula was absent or grade A; the evidence provided by CT excluded intra-abdominal abscess or undrained fluid collections; drained fluid was less than 20 mL per day and turned clear; and lack of any gastrointestinal fistula. Additional management methods included the administration of antibiotics, supplemental parenteral or enteral nutrition, reinterventions (reoperation, endoscopic or interventional radiological procedures), and organ function support.

Study variables and outcomes

Data analyzed included demographics, vital signs, injury parameters, operative procedures, types and locations of drains, complications, reinterventions, bacterial culture information about drainage fluid samples, mortality and length of stay (LOS). The primary outcome was the occurrence of severe complications defined as Clavien-Dindo grade III_b-V during hospitalization. Further details on the definitions of outcome variables are provided in Supplementary Table 1.

Statistical analysis

Student's *t* test and Wilcoxon's rank sum test were used to compare normal or nonnormal continuous variables, respectively. The chi-square test and Fisher's exact test were used to compare categorical variables. A multivariate logistic regression model was applied to evaluate the associations between the primary outcome and different drain types. Variables with $P < 0.2$ in the univariate test were included in the multivariate analysis.

To study effect modification by different drainage methods and to adjust for confounding factors, we performed sensitivity analysis based on propensity score matching (PSM). The PG group was matched 1:1 with the NPI group using their propensity scores with the nearest neighbor matching algorithm without replacement (the caliper was set at 0.2). A standardized mean difference (SMD) of less than 10% indicates appropriate balance. A univariable logistic regression model was adopted to estimate the odds ratio (OR) and corresponding 95% confidence interval (CI) for the primary outcome. Prespecified subgroup analyses were performed in the matched cohort to determine whether the effect of drainage varied across stratification factors of covariates. R software, version 4.0.3, was used for statistical analysis.

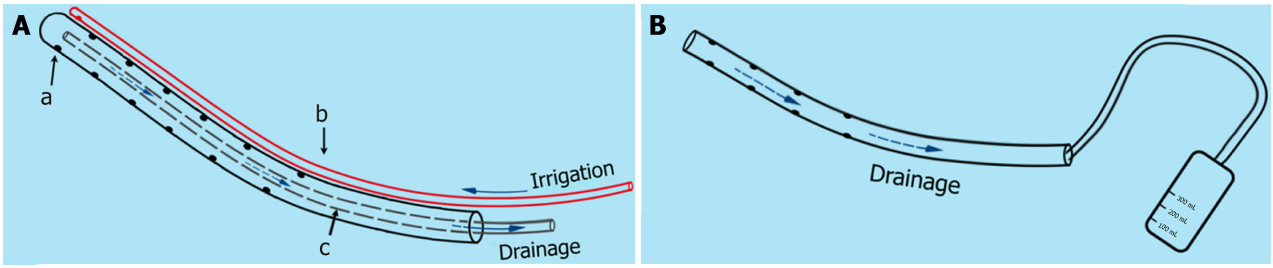

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Figure 1 Sketch map of the negative pressure irrigation suction drainage and passive gravity drainage systems. A: Negative pressure irrigation suction drainage. A cranial margin closed the outer silicone cannula with a diameter between 24 French and 30 French, and multiple side apertures with diameters of 3-5 mm were arranged along the cannula (part a). A 12 French urinary catheter and the cranial margin are connected to part a with silk thread for continuous irrigation with sterile normal saline at a rate of 100 to 125 mL/h after surgery (part b). An inner silicone cannula without side aperture was placed into part a, with approximately half the diameter of part a, for connection to a low negative pressure (-10 kPa to -20 kPa) system[28] (part c); B: Passive gravity (PG) drainage. PG drainage is defined as a latex catheter drain that maintains a pathway for fluid to follow from the surgical site by gravity, connected to a liquid storage bag maintained at atmospheric pressure.

RESULTS

Patient characteristics

Two hundred thirteen PT patients were managed by operative management with drain placement during the study period. Of these patients, 196 met the inclusion criteria: 146 (74.5%) in the PG group *vs* 50 (25.5%) in the NPI group. The screening process is shown in Figure 2. The patients' preoperative demographics, clinical characteristics and injury parameters are summarized in Table 1. In the entire cohort, the NPI group had less duodenum injury and more concomitant vascular injury ($P < 0.05$). Regarding the time from trauma to operation, delayed operative treatment (24 h) occurred more frequently in the NPI group (46.0% *vs* 20.5%, $P = 0.001$).

PSM with a 1:1 ratio resulted in 88 patients (PG 44, NPI 44). Before PSM, 13 of 15 baseline characteristics were unequally distributed between the two groups; following PSM, all of the variables reached an SMD < 0.10 (Supplementary Figure 1), suggesting that the two matched cohorts were well balanced. In the matched cohort, the pancreatic injury grades and the extent of injury to intra-abdominal organs exhibited approximately proportional distributions ($P > 0.05$) (Table 1). Moreover, the proportion of each operative procedure performed for pancreatic injury-related and other intra-abdominal organ injury-related cases was comparable in the matched cohort (Table 2).

Primary outcome

In the entire cohort, the incidence of severe complications in the NPI group was significantly lower than that in the PG group [14/50 (28.0%) *vs* 66/146 (45.2%), $P = 0.033$] (Table 3). In univariate logistic regression analysis, injury severity score, abdominal abbreviated injury scale, isolated pancreatic injury, and different drain types were associated with severe complications ($P < 0.05$) (Supplementary Table 2). Notably, the NPI group was significantly less likely to develop severe complications (OR: 0.471; 95%CI: 0.235-0.947; $P = 0.035$). In multivariate analysis, the adjusted risk for severe complications was decreased in the NPI group (OR: 0.437; 95%CI: 0.203-0.940; $P = 0.034$) (Figure 3). After PSM, the results of the sensitivity analysis were consistent with those of the multivariate analysis (OR: 0.365; 95%CI: 0.148-0.901; $P = 0.029$) (Figure 3).

Secondary outcomes

Among the matched cohort, no significant difference in in-hospital mortality was observed between the two groups. The drainage period in the NPI group was shorter than that in the PG group [median (inter-quartile range), 35.0 (20.0-54.75) *vs* 47.0 (30.0-68.0) d; $P = 0.009$]. The proportion of patients who underwent CT drainage in the NPI group was still significantly lower (15.9% *vs* 34.1%, $P = 0.042$). Moreover, the NPI group was associated with a lower incidence of pancreatic fistula grade B/C, a lower incidence of gastrointestinal fistulas, a lower reoperation rate, and a shorter LOS ($P < 0.05$) (Table 3). The POD 7 infection rate of drainage fluid in the NPI group was significantly lower [11/36 (30.6%) *vs* 27/43 (62.8%), $P = 0.004$] (Supplementary Table 3). With regard to the qualitative microbiological analysis, the incidence of G+ bacterial infection was higher in the NPI group [7/11 (63.6%) *vs* 5/27 (18.5%), $P = 0.017$] (Supplementary Table 4). In this prespecified subgroup analysis, the difference in the rate of the primary outcome between the PG and the NPI group was greater among patients without concomitant vascular injury (Figure 4). We detected no significant interactions of treatment with the other baseline factors $P > 0.10$ for all comparisons.

DISCUSSION

Few comparative studies have focused on the potential differences in the postoperative outcomes related to drain types for PT patients. Most western countries recommend closed suction drainage, but conclusive evidence is lacking[7-9,20]. The Memphis group found that closed suction drainage reduced septic complications, while sump drainage caused

Table 1 Baseline characteristics of patients before and after matching

Characteristics	Before matching			After matching		
	PG (*n* = 146)	NPI (*n* = 50)	*P* value	PG (*n* = 44)	NPI (*n* = 44)	*P* value
Male sex, *n* (%)	137 (93.8)	43 (86.0)	0.148	41 (93.2)	39 (88.6)	0.518
Age, median (IQR)	40 (30.75-48.25)	44.5 (26.25-52.25)	0.058	39 (30.25-47.00)	44.5 (27-51)	0.843
BMI, mean ± SD	23.04 (3.68)	23.46 (3.62)	0.477	23.59 (4.48)	23.36 (3.57)	0.787
Blunt injury, *n* (%)	137 (93.8)	48 (96.0)	0.733	42 (95.5)	42 (95.5)	1.000
ISS, median (IQR)	17 (9-21)	16 (9-20)	0.183	16 (9-20)	16 (9-20)	0.936
Abdominal AIS, median (IQR)	3 (3-4)	3 (3-4)	0.146	3 (3-4)	3 (3-4)	0.985
Pancreatic injury grade, *n* (%)			0.090			0.829
I + II	45 (30.8)	22 (44.0)		19 (43.2)	18 (40.9)	
III + IV + V	101 (69.2)	28 (56.0)		25 (56.8)	26 (59.1)	
Isolated pancreatic injury, *n* (%)			0.489			1.000
No	123 (84.2)	40 (80.0)		35 (79.5)	35 (79.5)	
Yes	23 (15.8)	10 (20.0)		9 (20.5)	9 (20.5)	
Duodenum injury, *n* (%)			0.043			1.000
No	116 (79.5)	46 (92.0)		39 (88.6)	40 (90.9)	
Yes	30 (20.5)	4 (8.0)		5 (11.4)	4 (9.1)	
Vascular injury, *n* (%)			0.032			0.787
No	127 (87.0)	37 (74.0)		35 (79.5)	36 (81.8)	
Yes	19 (13.0)	13 (26.0)		9 (20.5)	8 (18.2)	
Parenchyma organ injury, *n* (%)			0.242			0.831
No	62 (42.5)	26 (52.0)		22 (50.0)	23 (52.3)	
Yes	84 (57.5)	24 (48.0)		22 (50.0)	21 (47.7)	
Hollow organ injury, *n* (%)			0.144			1.000
No	53 (36.3)	24 (48.0)		20 (45.5)	20 (45.5)	
Yes	93 (63.7)	26 (52.0)		24 (54.5)	24 (54.5)	
Shock on admission, *n* (%)			0.597			0.777
No	127 (87.0)	42 (84.0)		36 (81.8)	37 (84.1)	
Yes	19 (13.0)	8 (16.0)		8 (18.2)	7 (15.9)	
Number of abdominal organ injuries, *n* (%)			0.093			0.631
2	49 (33.6)	22 (44.0)		18 (40.9)	20 (45.4)	
≥ 3	74 (50.7)	18 (36.0)		17 (38.6)	15 (34.1)	
Time to operation, *n* (%)			0.001			1.000
< 24 h	116 (79.5)	27 (54.0)		27 (61.4)	27 (61.4)	
≥ 24 h	30 (20.5)	23 (46.0)		17 (38.6)	17 (38.6)	

PG: Passive gravity; NPI: Negative pressure irrigation; IQR: Inter-quartile range; BMI: Body mass index; SD: Standard deviation; ISS: Injury severity score; AIS: Abbreviated injury scale.

retrograde infections *via* catheters[21]. However, it is difficult to derive robust results from this study due to the heterogeneity of study participants, injury parameters, and operative procedures. In this study, we evaluated the severity of complications for different drain types after PT and found that NPI suction drainage is superior to PG drainage.

The reduced Clavien-Dindo severity for NPI suction drainage can be attributed to several factors. First, NPI suction drainage can effectively remove residual infection within intra-abdominal or between intestinal loops through continuous and active irrigation with sterile normal saline, thereby reducing the incidence of abscess, systemic inflammation or

Table 2 Operative procedures between two drain types before and after matching cohorts

Operative procedure	Before matching			After matching		
	PG (*n* = 146)	NPI (*n* = 50)	*P* value	PG (*n* = 44)	NPI (*n* = 44)	*P* value
Pancreas injury-related, *n* (%)						
Peripancreatic drainage alone	61 (41.8)	22 (44.0)	0.784	19 (43.2)	19 (43.2)	1.000
Distal pancreatectomy	37 (25.3)	10 (20.0)	0.445	10 (22.7)	8 (18.2)	0.597
Distal pancreatectomy + splenectomy	22 (15.1)	9 (18.0)	0.624	6 (13.6)	8 (18.2)	0.560
Pancreaticojejunostomy	21 (14.4)	7 (14.0)	0.947	8 (18.2)	7 (15.9)	0.777
Whipple	5 (3.4)	2 (4.0)	0.850	1 (2.3)	2 (4.5)	1.000
Other intra-abdominal organ injury-related, *n* (%)						
Gastric or duodenal	38 (26.0)	6 (12.0)	0.040	5 (11.4)	5 (11.4)	1.000
Jejunal or ileal	25 (17.1)	9 (18.0)	0.888	9 (20.5)	9 (20.5)	1.000
Colorectal	30 (20.5)	11 (22.0)	0.828	10 (22.7)	10 (22.7)	1.000
Parenchymal organ	58 (39.7)	12 (24.0)	0.045	11 (25.0)	10 (22.7)	0.803
Vascular	19 (13.0)	13 (26.0)	0.032	9 (20.5)	8 (18.2)	0.787

PG: Passive gravity; NPI: Negative pressure irrigation.

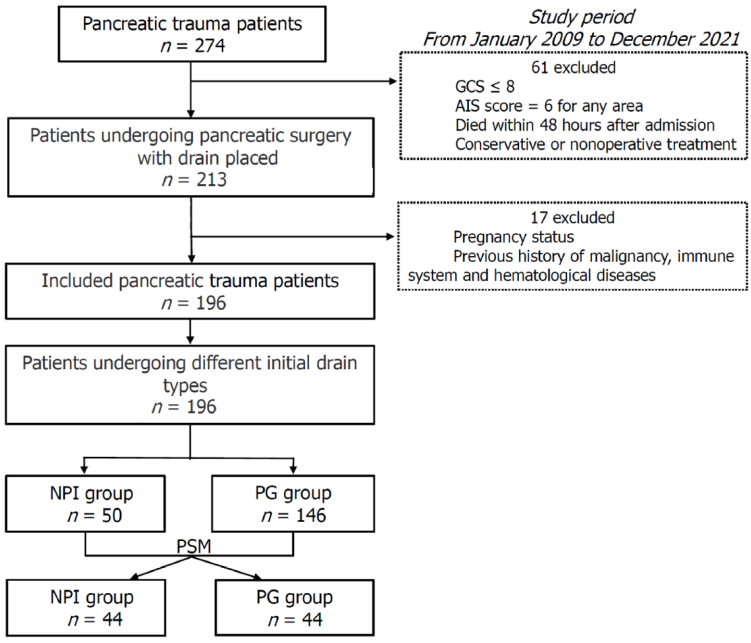

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Figure 2 Flow chart of the patient selection process. GCS: Glasgow coma scale; AIS: Abbreviated injury scale; PG: Passive gravity; NPI: Negative pressure irrigation; PSM: Propensity score matching.

sepsis[22]. Second, NPI suction drainage can rapidly drain collected pancreatic juice by a low negative pressure system to reduce accumulation and diffusion, and it can dilute the accumulated fluid collection by irrigating sterile normal saline to minimize erosion and impairment to other tissues, thus preventing mild pancreatic leakage from developing into a serious pancreatic fistula and avoiding hemorrhage and the formation of gastrointestinal fistulas. Jiang *et al*[15] verified that pancreatic fistula grade C in patients with NPI suction drainage was significantly less common than in patients with passive drainage after pancreaticoduodenectomy. Under dual effects, NPI suction drainage could achieve significant clinical benefits for patients. PG drainage generally relies on the pressure difference and gravity, which might not obtain adequate drainage and predispose patients to catheter blockage. In this study, the incidence of catheter blockage was 9.6% (14/146) in the PG group, whereas it did not occur in the NPI group.

Table 3 Postoperative outcomes of passive gravity *vs* negative pressure irrigation group before and after matching cohorts

Outcomes	Before matching			After matching		
	PG (*n* = 146)	NPI (*n* = 50)	*P* value	PG (*n* = 44)	NPI (*n* = 44)	*P* value
Clavien-Dindo grade ≥ III_b, *n* (%)	66 (45.2)	14 (28.0)	0.033	21 (47.7)	11 (25.0)	0.045
Pancreas-related, *n* (%)	70 (47.9)	15 (30.0)	0.027	23 (52.3)	13 (29.5)	0.050
Pancreatic fistula grade B/C	62 (42.5)	13 (26.0)	0.039	22 (50.0)	11 (25.0)	0.027
Pancreatic pseudocyst	2 (1.4)	2 (4.0)	0.269	0	2 (4.5)	0.494
Peripancreatic abscess	6 (4.1)	0	0.341	1 (2.3)	0	1.000
Organ failure, *n* (%)	37 (25.3)	9 (18.0)	0.290	6 (13.6)	3 (6.8)	0.484
Circulatory failure	23 (15.8)	6 (12.0)	0.519	4 (9.1)	2 (4.5)	0.676
Respiratory failure	20 (13.7)	5 (10.0)	0.499	4 (9.1)	1 (2.3)	0.360
Renal failure	24 (16.4)	7 (14.0)	0.683	5 (11.4)	3 (6.8)	0.713
Gastrointestinal fistulas, *n* (%)	50 (34.2)	10 (20.0)	0.059	17 (38.6)	7 (15.9)	0.030
Hemorrhage grade B/C, *n* (%)	34 (23.3)	7 (14.0)	0.163	12 (27.3)	6 (13.6)	0.080
Intra-abdominal abscess, *n* (%)	20 (13.7)	8 (16.0)	0.688	7 (15.9)	5 (11.4)	0.534
Sepsis, *n* (%)	27 (18.5)	7 (14.0)	0.469	4 (9.1)	3 (6.8)	1.000
In-hospital mortality, *n* (%)	16 (11.0)	3 (6.0)	0.412	3 (6.8)	2 (4.5)	1.000
Reoperation, *n* (%)	55 (38.2)	11 (22.0)	0.037	16 (36.4)	7 (15.9)	0.029
CT-drainage, *n* (%)	47 (32.2)	9 (18.0)	0.038	15 (34.1)	7 (15.9)	0.042
Drainage period, median (IQR)	47.0 (30.0-75.25)	37.0 (20.0-54.25)	0.002	47.0 (30.0-68.0)	35.0 (20.0-54.75)	0.009
LOS, median (IQR)	65.5 (47.75-97.0)	43.5 (30.5-69.25)	0.002	62.5 (43.75-97.0)	44.0 (33.0-69.75)	0.047

Clavien–Dindo complications in this category include those that resulted in surgical, endoscopic, or radiologic intervention (Clavien–Dindo grade III), those without general anesthesia (III_a), those that required general anesthesia (III_b), those that required care in the intensive care unit (Clavien–Dindo grade IV), and those that resulted in death (Clavien–Dindo grade V). PG: Passive gravity; NPI: Negative pressure irrigation; CT: Computed tomography; IQR: Inter-quartile range; LOS: Length of stay.

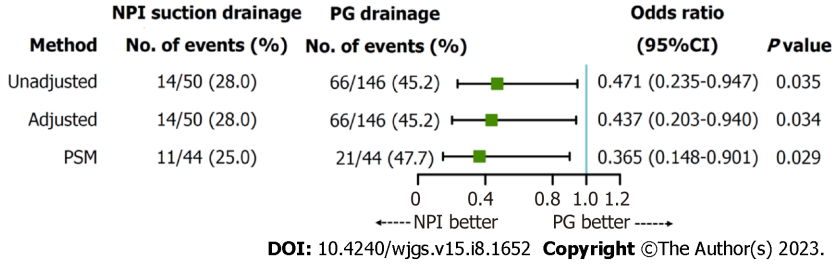

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Figure 3 Events of severe complications for passive gravity *vs* negative pressure irrigation and sensitivity analysis results. Events of severe complications associated with different drain types are measured as those with a Clavien-Dindo grade ≥ III_b. PG: Passive gravity; NPI: Negative pressure irrigation; Unadjusted: Univariate logistic regression model; Adjusted: Multivariate logistic regression model; PSM: Propensity score matching; CI: Confidence interval.

More importantly, postoperative digestive tract fistulas often contribute to various other complications, such as hemorrhage, sepsis, multisystem organ failure, and even death. These complications require reinterventions, such as percutaneous drainage or reoperation[23]. Nevertheless, resection and anastomoses should not be considered suitable procedures due to the edematous and friable nature of and adhesions adjacent to the fistula site. Fistulography is performed to evaluate the possibility of conservative treatment. For patients able to be treated conservatively, we uniformly adopted NPI suction drainage. The outer cannula can prevent both aspiration damage to surrounding tissues and blockage of the inner suction cannula. The patency provided by NPI suction drainage is a fundamental principle in the formation of a stable and controlled pancreaticocutaneous or enterocutaneous fistula, which is beneficial for facilitating the formation of the fistula tract[24].

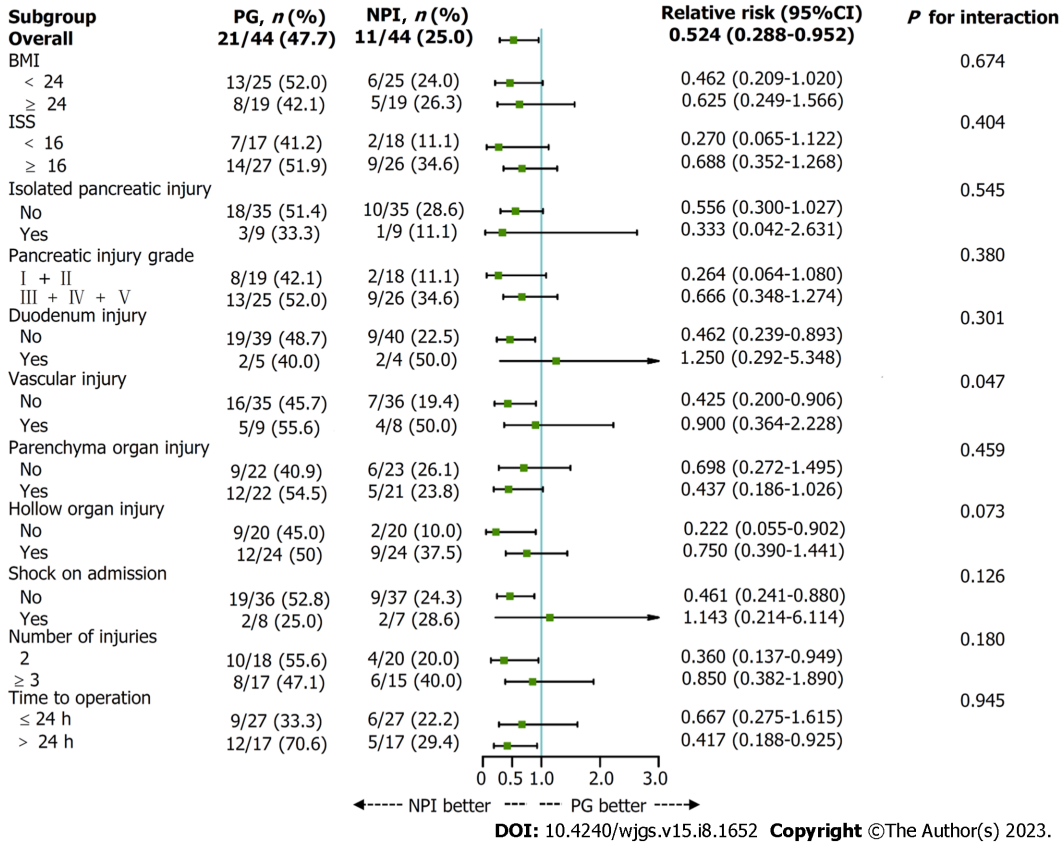

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Figure 4 Relative risk for the primary outcomes in prespecified subgroups. The forest plot presents, for each subgroup, the relative risk of severe complications between different drain types by a square and its 95% confidence interval (CI) by a horizontal line. On the left side of the figure, the subgroup sample size by drain type is presented with the corresponding severe complication rate. The right side of the figure lists the relative risk and its 95%CI; the x-axis of the plot is the risk estimate of severe complications. The last column shows the *P* values for relative risk interactions between subgroups. Subgroup-specific relative risk was derived from modified Poisson regression. PG: Passive gravity; NPI: Negative pressure irrigation; BMI: Body mass index; ISS: Injury severity score; CI: Confidence interval.

In the matched cohort, the incidence of gastrointestinal fistulas and the reoperation rate were higher in the PG group. Sixteen patients required reoperation for one or more intra-abdominal complications: Intra-abdominal hemorrhage grade B/C in 10 patients, small intestinal fistulas in 3, colonic fistulas in 5, pancreatic fistula grade C in 2, and infectious pancreatic necrosis in 2. Correspondingly, 7 patients required reoperation in the NPI group, due to intra-abdominal hemorrhage grade B/C in 1 patient, gastric fistula in 1, colonic fistulas in 3, and pancreatic fistula grade C in 3. For patients who underwent CT-guided percutaneous drainage, the proportion in the NPI group was significantly smaller than that in the PG group. From the above, it can be determined that patients in the NPI group could undergo fewer invasive reinterventions. Our previous study also found that 74 of 88 gastric and small intestinal fistulas (84.1%) and 21 of 72 colonic fistulas (29.2%) caused by acute pancreatitis could be cured by NPI suction drainage[25]. Some studies have shown that negative pressure contributes by causing local tissue and vascular damage in the area near the drain[26]. However, Čečka *et al*[17] found that the rates of pancreatic fistula, hemorrhage and overall morbidity were not different between closed suction and PG drainage after pancreatic resection. According to the results of our study, low negative pressure did not raise the above concerns.

The overall mortality rate was 9.6% (19/196): 18 patients died of sepsis and related multiple organ failure. Similarly, the Western Trauma Association Multicenter Trials Group on Pancreatic Injuries found that the mortality was 9.1% (79/872) in PT patients who underwent surgery[11,12]. In our matched cohort, no significant differences in mortality were observed. These patients might benefit from good control of the infected source, and most digestive tract fistulas usually heal spontaneously over time[27]. In addition, the improvement of care capacity for severe trauma, parenteral and enteral nutritional support, and effective anti-infection treatment also played important roles.

The POD 7 infection rate of drainage fluid in the NPI suction drainage group was significantly lower; however, the incidence of infectious complications (abscess and sepsis) was not significantly different between the two drain types. This finding could be attributed to antibiotic administration and the application of percutaneous drainage. We speculate that the higher incidence of G+ bacterial infection with NPI suction drainage might be related to the open nature of the drain or retrograde migration of bacteria. Although subgroup analyses were prespecified, this study was not adequately powered to assess the benefit of treatment. Patients without concomitant vascular injury appeared to benefit more from NPI suction drainage than those with vascular injury. Nevertheless, with the limitations of a relatively small sample size and retrospective nature, caution should be exercised in the interpretation of these results.

Our study has several limitations. First, as an observational study, the analyses are subject to selection bias, and residual unmeasured confounding might persist despite adjustment for a variety of known patient variables using PSM to approximate randomization. Second, conducting the study at a single high-volume center limits its generalizability. Third, the volume, microbiology, amylase concentrations of drainage fluid, trends over time and drainage catheter removal time were not included in our data; however, they might also reflect the potential differences between the two drain types.

CONCLUSION

In conclusion, we compared the incidence of severe postoperative complications between the PG and NPI groups and found that NPI suction drainage was associated with decreased Clavien-Dindo severity. These findings suggest that initial NPI suction drainage could be recommended as a safe and effective alternative for managing complex PT patients. Further randomized, controlled trials are warranted to validate these results.

ARTICLE HIGHLIGHTS

Research background

Consensus regarding the necessity for drainage has been formulated in the many management strategies for pancreatic trauma (PT).

Research motivation

Few studies have addressed the question of which drain types are more beneficial for PT patients.

Research objectives

To investigate whether sustained low negative pressure irrigation (NPI) suction drainage is superior to closed passive gravity (PG) drainage in PT patients.

Research methods

We performed a retrospective cohort study of consecutive patients who underwent pancreatic surgery at a tertiary trauma referral center between January 2009 and October 2021 in our PT database. The primary outcome was defined as the occurrence of severe complications (Clavien-Dindo grade ≥ III_b). Multivariable logistic regression was used to model the primary outcome, and propensity score matching (PSM) was included in the regression-based sensitivity analysis.

Research results

In this study, 146 patients underwent initial PG drainage, and 50 underwent initial NPI suction drainage. In the entire cohort, a multivariable logistic regression model showed that the adjusted risk for severe complications was decreased with NPI suction drainage [14/50 (28.0%) *vs* 66/146 (45.2%); odds ratio (OR), 0.437; 95% confidence interval (CI): 0.203-0.940]. After 1:1 PSM, 44 matched pairs were identified. The proportion of each operative procedure performed for pancreatic injury-related and other intra-abdominal organ injury-related cases was comparable in the matched cohort. NPI suction drainage still showed a lower risk for severe complications [11/44 (25.0%) *vs* 21/44 (47.7%); OR: 0.365; 95%CI: 0.148-0.901].

Research conclusions

Initial NPI suction drainage could be recommended as a safe and effective alternative for managing complex PT patients.

Research perspectives

Further randomized, controlled trials are warranted to validate these results.

FOOTNOTES

Author contributions: Li KW designed and performed the research and drafted the manuscript; Wang K, Yang C, Deng YX and Wang XY were involved in the literature search and data extraction; Li KW and Hu YP analyzed and interpreted the data; Ding WW, Liu YX and Li WQ supervised and reviewed the report.

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Institutional review board statement: This study protocol was approved by the Institutional Review Board of Jinling Hospital, No. 2021DZGZR-YBB-009.

Informed consent statement: This is a retrospective study, and patients were not required to give informed consent for 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 read and approved the final manuscript and declared no conflicts of interest.

Data sharing statement: The original anonymous dataset is available upon request from the corresponding author at dingwei_nju@hotmail.com.

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Country/Territory of origin: China

ORCID number: Wei-Wei Ding 0000-0002-5026-689X.

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ORIGINAL ARTICLE

Retrospective Study

Radiation therapy prior to a pancreaticoduodenectomy for adenocarcinoma is associated with longer operative times and higher blood loss

Krist Aploks, Minha Kim, Stephanie Stroever, Alexander Ostapenko, Young Bo Sim, Ashwinkumar Sooriyakumar, Arash Rahimi-Ardabily, Ramanathan Seshadri, Xiang Da Dong

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Krist Aploks, Minha Kim, Alexander Ostapenko, Young Bo Sim, Ashwinkumar Sooriyakumar, Arash Rahimi-Ardabily, Department of General Surgery, Danbury Hospital, Danbury, CT 06810, United States

Stephanie Stroever, Department of Research and Innovation, Nuvance Health, Danbury, CT 06810, United States

Ramanathan Seshadri, Xiang Da Dong, Division of Surgical Oncology/Hepato-Pancreato-Biliary Surgery, Danbury Hospital, Danbury, CT 06810, United States

Corresponding author: Xiang Da Dong, FACS, MD, Chief Doctor, Division of Surgical Oncology/Hepato-Pancreato-Biliary Surgery, Danbury Hospital, 95 Locust Avenue, Danbury, CT 06810, United States. eric.dong@nuvancehealth.org

Abstract

BACKGROUND

Pancreatic adenocarcinoma is currently the fourth leading cause of cancer-related deaths in the United States. In patients with "borderline resectable" disease, current National Comprehensive Cancer Center guidelines recommend the use of neoadjuvant chemoradiation prior to a pancreaticoduodenectomy. Although neoadjuvant radiotherapy may improve negative margin resection rate, it is theorized that its administration increases operative times and complexity.

AIM

To investigate the association between neoadjuvant radiotherapy and 30-d morbidity and mortality outcomes among patients receiving a pancreaticoduodenectomy for pancreatic adenocarcinoma.

METHODS

Patients listed in the 2015-2019 National Surgery Quality Improvement Program data set, who received a pancreaticoduodenectomy for pancreatic adenocarcinoma, were divided into two groups based off neoadjuvant radiotherapy status. Multivariable regression was used to determine if there is a significant correlation between neoadjuvant radiotherapy, perioperative blood transfusion status, total operative time, and other perioperative outcomes.

RESULTS
Of the 11458 patients included in the study, 1470 (12.8%) underwent neoadjuvant radiotherapy. Patients who received neoadjuvant radiotherapy were significantly more likely to require a perioperative blood transfusion [adjusted odds ratio (aOR) = 1.58, 95% confidence interval (CI): 1.37-1.82; $P < 0.001$] and have longer surgeries (insulin receptor-related receptor = 1.14, 95%CI: 1.11-1.16; $P < 0.001$), while simultaneously having lower rates of organ space infections (aOR = 0.80, 95%CI: 0.66-0.97; $P = 0.02$) and pancreatic fistula formation (aOR = 0.50, 95%CI: 0.40-0.63; $P < 0.001$) compared to those who underwent surgery alone.

CONCLUSION
Neoadjuvant radiotherapy, while not associated with increased mortality, will impact the complexity of surgical resection in patients with pancreatic adenocarcinoma.

Key Words: Pancreaticoduodenectomy; Pancreatic adenocarcinoma; Neoadjuvant chemoradiation; National Surgery Quality Improvement Program; Whipple procedure; Operative time

Core Tip: In this retrospective study, we used a national database to investigate the impact that neoadjuvant radiotherapy has on intraoperative and 30-d post-operative outcomes among patients undergoing surgical resection for pancreatic adenocarcinoma. We found that neoadjuvant radiotherapy was associated with longer operative times and the more frequent need for perioperative blood transfusions, but not with increased 30-d mortality. Neoadjuvant radiotherapy was also associated with a lower number of organ space infections and post-operative pancreatic fistula formation. Taken together, the results highlight the challenges that surgeons may face when operating in previously irradiated fields.

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INTRODUCTION

Pancreatic adenocarcinoma currently represents the fourth leading cause of cancer-related deaths in the United States. In patients suffering from the disease, an R0 resection is the primary and preferred method of treatment[1,2]. While this is often obtainable in patients with early-stage pancreatic malignancies, roughly 85% of patients present with disease that is not amenable to cure with surgical resection alone[3]. The tumors in many of these patients are considered borderline resectable, defined by National Comprehensive Cancer Network (NCCN) guidelines as contact with 180 degrees or less of the superior mesenteric artery or the celiac artery, contact with the common hepatic artery, and/or contact with the superior mesenteric vein/portal vein resulting in contour irregularity or vein thrombosis[4]. According to the NCCN guidelines, such cancers may benefit from treatment with neoadjuvant therapy in the form of chemoradiation[5].

When compared to adjuvant therapy, neoadjuvant chemoradiation has the theoretical benefit of testing for chemosensitivity, increasing the control of micrometastases and circulating tumor cells, ensuring a higher rate of systemic therapy completion, potentially downstaging a disease to make it amenable to surgical therapy and reducing pancreatic leak rates[6-8]. Multiple studies have demonstrated the morbidity benefits that comes with neoadjuvant treatment of patients with borderline resectable pancreatic adenocarcinoma prior to surgery compared with just surgical treatment alone. Among others, these benefits include a decrease in tumor size at the time of surgery, decreased number of positive lymph nodes, fewer organ space infections, and fewer post-operative pancreatic fistulae[9-12].

Despite the purported benefits, neoadjuvant therapy is still regarded with caution and its use remains low in the United States[13]. It is theorized that neoadjuvant therapy increases the rate of gastrointestinal toxicity and impairs post-operative wound healing, which can result in preoperative decompensation and subsequent post-operative morbidities. Neoadjuvant therapy can also theoretically delay definitive surgical resection, which can lead to the development of metastatic disease in non-responders. Radiotherapy, in particular, has been associated with disruption of the pancreatic tissue planes, which is thought to make eventual surgical resection more difficult[14]. Numerous studies have contradicted these ideas, showing that neoadjuvant therapy results in little to no intra- and post-operative increases in morbidity and mortality[9,10,15]. To date, however, many of these prior studies are plagued by single institution analysis with small sample sizes. These samples are even smaller when looking at the number of participants who received neoadjuvant radiotherapy, as chemotherapy remains the lion's share of neoadjuvant therapy.

The aim of this study was to investigate the effects that neoadjuvant radiation therapy have on both intra-operative and 30-d postoperative morbidities using a nationwide dataset. We specifically hypothesize that among patients

receiving a pancreaticoduodenectomy for pancreatic adenocarcinoma, those that also undergo neoadjuvant radiotherapy are more likely to have longer operative times and a perioperative transfusion compared with those who simply receive surgery alone.

MATERIALS AND METHODS

Study design and participants

We performed a cross sectional study utilizing data from the American College of Surgeons (ACS) National Surgery Quality Improvement Program (NSQIP) database from January 1, 2015 to December 31, 2019. Data from the standard public use file was merged with that from the NSQIP Targeted Pancreatectomy Participant Use Data Files (a separate collection of pancreas-specific variables) using the Case Identification Number (CASEID) variable. Patients older than 18 years old, who had a histological diagnosis of pancreatic adenocarcinoma and underwent a pancreaticoduodenectomy, were included in this study. Patients undergoing resection were identified by one or more of the following additional CPT codes: 48150, 48152, 48153, 48154. This study was exempt from our institutional review board review since the data was de-identified and obtained from a participant use data file.

Variables

From the patients included in the study, two groups were formed based on the independent variable of interest: those that received neoadjuvant radiotherapy prior to a pancreaticoduodenectomy, and those that had progressed directly to surgery. For the purposes of this study, neoadjuvant radiotherapy was defined as those receiving treatments within 90 d of the index operation. The primary outcomes of interest were perioperative blood transfusions (defined by the need for a blood transfusion within 72 h of surgery start time; OTHBLEED variable) and total operative time (defined by operative time in minutes; OPTIME variable). The secondary outcomes of interest were 30-d post-operative morbidities and mortality. Specific variables included rate of the following: wound dehiscence, ventilator dependence, stroke, myocardial infarction (MI), deep venous thrombosis (DVT), pulmonary embolism (PE), pneumonia, urinary tract infection, septic shock, superficial surgical site infection (SSI), organ space SSI, 30-d re-operation, 30-d mortality, 30-d readmission, renal failure, hospital length of stay, duration of pancreatic drain, pancreatic fistula, and delayed gastric emptying. Pancreatic fistulae were defined according to the International Study Group for Pancreatic Fistula grading scheme[16].

Statistical analyses

StataSE was used for the statistical analyses. Descriptive statistics including mean ± standard deviation for normally distributed continuous variables, median/interquartile range for skewed continuous variables, and number/percentage for categorical variables. We assessed bi-variable differences in outcomes between patients with upfront surgery and neoadjuvant radiotherapy with surgery using the χ^2 test, univariable logistic regression, and Fisher's exact test for categorical variables. Two-tailed Student's t-tests were used for continuous variables. Variables that were statistically associated ($\alpha < 0.05$) with both the outcome and the independent variable, as well as those that were predicted theoretical confounders, were included in the multivariate regression analyses. Multivariable negative binomial regression was used for the total operative time variable, and multivariable logistic regression was used for the remaining secondary variables. We used stepwise, backward selection, and tested full/reduced models with the likelihood ratio test to determine the most parsimonious model. For 30-d outcome variables occurring less than 5% of the time, multivariable regression was not performed. For variables missing less than 5% of data, the listwise deletion method was used. Variables missing greater than 5% of data were reported as "unknown" in the tables.

RESULTS

Query of the ACS-NSQIP database identified a total of 11775 patients who underwent surgery for pancreatic adenocarcinoma from 2015 to 2019. Patients who had data missing with regards to neoadjuvant radiation therapy status, and patients in whom SSIs were reported upon admission, were excluded from the analyses. This left a final cohort of 11458 patients. The cohort was then split into two study groups based off neoadjuvant radiotherapy exposure: 1470 patients (12.8%) received neoadjuvant radiation therapy, compared with 9988 (87.2%) patients who proceeded directly to surgery (Figure 1).

Patients undergoing neoadjuvant radiotherapy were more likely to be younger, female, non-Hispanic white, diabetic, and of normal body weight (all $P < 0.04$). Conversely, patients undergoing surgery without radiotherapy were more likely to be Hispanic, overweight/obese, and jaundiced (all $P < 0.002$). They were also more likely to have chronic obstructive pulmonary disease, dyspnea, and hypertension (all $P < 0.05$) (Table 1).

With regard to tumor characteristics and operative approaches, patients receiving neoadjuvant radiotherapy were more likely to have a lower T-stage, lower N-stage, receive an elective surgery, have a higher wound class, and have a smaller pancreatic duct size (all $P < 0.04$). Such patients were also more likely to undergo an open surgical approach that involved resection of an artery or vein (all $P < 0.001$) (Table 2).

Within the first 30 d following surgery, bi-variable statistical analyses revealed that patients receiving surgical treatment only were more likely to experience an MI, PE, pneumonia, organ space infection, delayed gastric emptying, and pancreatic fistula (all $P < 0.035$). Such patients also had a higher 30-d mortality rate, longer hospital stay, a drain that

Table 1 Demographics and preoperative characteristics of patients with adenocarcinoma of the pancreas undergoing a pancreaticoduodenectomy from 2015 to 2019, *n* (%)

Characteristic	Subcategory	Initial surgery	Neoadjuvant radiation	*P* value
		n = 9988	*n* = 1470	
Age in yr	Less than 50	511 (5.1)	89 (6.1)	
	50-59	1638 (16.4)	304 (20.7)	
	60-69	3526 (35.3)	585 (39.8)	< 0.001[a]
	70-79	3287 (32.9)	430 (29.3)	
	80 and above	1026 (10.3)	62 (4.2)	
Male		5340 (53.5)	743 (50.5)	0.036[a]
Race	White	7392 (81.6)	1203 (84.3)	
	Black/African American	748 (8.3)	127 (8.9)	
	Hispanic	462 (5.1)	54 (3.8)	< 0.001[a]
	Asian	427 (4.7)	38 (2.7)	
	Other	33 (0.4)	5 (0.4)	
	Not reported	926	43	
BMI	Normal	3683 (36.9)	618 (42.0)	
	Underweight	244 (2.4)	37 (2.5)	
	Overweight	3591 (36)	505 (34.4)	0.002[a]
	Obese	1614 (16.2)	203 (13.8)	
	Morbidly obese	856 (8.6)	107 (7.3)	
Diabetes		2859 (28.6)	461 (31.4)	0.031[a]
Smoking		1650 (16.5)	238 (16.2)	0.751
COPD		394 (3.9)	42 (2.9)	0.042[a]
Dyspnea		507 (5.1)	57 (3.9)	0.047[a]
HTN		5418 (54.2)	693 (47.1)	< 0.001[a]
Preoperative steroid use		239 (2.4)	42 (2.9)	0.283
Jaundice		5759 (58.0)	431 (29.7)	< 0.001[a]
Biliary stent		6457 (64.7)	979 (66.6)	0.235
Albumin, mean ± SD		3.69 (0.60)	3.85 (0.50)	< 0.001[a]

[a]$P < 0.05$.

BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; HTN: Hypertension; SD: Standard deviation.

remained in place after 30 d, and a longer total operative time (all $P < 0.041$). Patients undergoing neoadjuvant radiation were more likely to receive a DVT and receive a perioperative transfusion (all $P < 0.024$). On multivariate analyses of the 30-d outcomes that occurred at a rate of greater than 5% in both study groups, neoadjuvant radiotherapy was associated with longer total operative times and the need for a perioperative transfusion. Patients undergoing neoadjuvant radiotherapy, however, were statistically less likely to acquire an organ space infection or a pancreatic fistula compared with patients who underwent surgery alone (Tables 3 and 4). While total hospital stay, presence of drain on post-operative day 30, and delayed gastric emptying occurred at significantly lower rates in the neoadjuvant therapy group upon univariate statistical analyses, this difference was not statistically significant on multivariable analyses.

DISCUSSION

In the past, numerous studies have implicated single and multi-agent neoadjuvant chemotherapy with both tumor downstaging and an increased rate of R0 resections[17,18]. In comparison with neoadjuvant chemotherapy, however, evidence demonstrating similar advantages with neoadjuvant radiation therapy have been somewhat sparce. In 2019,

Table 2 Operative characteristics of patients with adenocarcinoma of the pancreas undergoing a pancreaticoduodenectomy from 2015 to 2019, *n* (%)

Characteristic	Subcategory	Initial surgery	Neoadjuvant radiation	*P* value
		n = 9988	*n* = 1470	
Elective surgery		8921 (89.4)	1423 (96.8)	< 0.001[a]
T-stage	T0/T1	2969 (29.7)	867 (59.0)	
	T2	6133 (61.4)	544 (37.0)	< 0.001[a]
	T3/T4	666 (6.7)	32 (2.2)	
	Tis/unknown	128 (1.3)	39 (2.7)	
N-stage	N0	2969 (29.7)	867 (59.0)	
	N1	6133 (61.4)	544 (37.0)	< 0.001[a]
	N2	666 (6.7)	32 (2.18)	
M-stage	M0	7260 (72.7)	1109 (75.4)	
	M1	172 (1.7)	20 (1.4)	0.073
	Unknown	2556 (25.6)	341 (23.2)	
Wound class	Clean	242 (2.4)	33 (2.2)	
	Clean-contaminated	7915 (79.3)	1142 (77.7)	0.034[a]
	Contaminated	1547 (15.5)	233 (15.9)	
	Dirty	284 (2.8)	62 (4.2)	
Pancreatic duct size	< 3 mm	1987 (24.9)	304 (26.3)	
	3-6 mm	4527 (56.8)	685 (59.2)	
	> 6 mm	1461 (18.3)	168 (14.5)	0.007[a]
	Unknown	2013	315	
Resection of artery or vein		2217 (22.4)	554 (37.9)	< 0.001[a]
Surgery approach	Open	9112 (91.2)	1386 (94.4)	< 0.001[a]
	Robotic/laparoscopic	875 (8.8)	83 (5.7)	

[a]$P < 0.05$.

Jiang *et al*[19] used the NCDB database to show an increased R0 resection and overall survival rate among patients who utilized neoadjuvant stereotactic body radiation therapy in addition to neoadjuvant chemotherapy compared to just neoadjuvant chemotherapy alone[19]. A paper by Chung *et al*[20] showed that higher doses of radiation (*i.e.* intensity-modulate radiation therapy) corresponded to increased 1 year survival and progression-free survival with no significant increase in short or long-term side effects[20]. Upon initial analyses of our study data, we found that patients undergoing neoadjuvant radiotherapy prior to surgery had smaller tumors and less positive lymph nodes on pathologic staging compared with those undergoing surgery alone. This suggests that neoadjuvant therapy successfully worked to downstage the tumors prior to surgical re-section. Although this effect could be confounded by the substantial difference in baseline demographic data between the two study groups, these results are nearly identical to those found in similarly designed NSQIP studies comparing neoadjuvant chemoradiation to surgery alone[9].

When examining our two primary outcome variables, we found a statistically significant increase in total operative time and perioperative transfusion requirements among patients receiving neoadjuvant radiation therapy compared to just surgery alone. This is the first time that such associations have been reported using multivariable analyses with patients receiving only neoadjuvant radiotherapy (*vs* neoadjuvant radiotherapy and/or chemotherapy). An analysis of 2005-2010 NSQIP data from Cho *et al*[14] found similar results, but with bi-variable analysis only[14]. Similarly, a study using NSQIP data from 2014 to 2015 showed that the perioperative transfusion requirement rate among patients receiving neoadjuvant therapy (chemotherapy and/or radiotherapy) was significantly higher than the rate in patients who progressed directly to surgery[21]. In 2021, Krell *et al*[22] showed that (with propensity score matching) there were increased total operative times and more frequent perioperative blood transfusions among those receiving neoadjuvant therapy (chemotherapy and/or radiotherapy) prior to surgery compared to those undergoing surgery alone[22].

Previously, it has been suggested that these differences in perioperative blood transfusions and total operative time are secondary to an increase in the number of borderline resectable cancers in the neoadjuvant therapy groups[14]. By definition, these tumors involve major blood vessels and usually require more complex dissections when compared to

Table 3 Thirty-day postoperative complications for patients with adenocarcinoma of the pancreas undergoing a pancreaticoduodenectomy from 2015 to 2019, *n* (%)

Complication	Initial surgery	Neoadjuvant radiation	*P* value
	n = 9988	*n* = 1470	
Wound dehiscence	110 (1.1)	16 (1.1)	0.965
Ventilator dependent > 48 h	223 (2.2)	38 (2.6)	0.398
Stroke	29 (0.3)	3 (0.2)	0.791
Myocardial infarction	124 (1.2)	9 (0.6)	0.035[a]
DVT	269 (2.7)	55 (3.7)	0.024[a]
Pulmonary embolism	108 (1.1)	5 (0.3)	0.004[a]
Pneumonia	305 (3.1)	30 (2.0)	0.031[a]
UTI	247 (2.5)	32 (2.2)	0.491
Septic shock	207 (2.1)	34 (2.3)	0.545

[a]*P* < 0.05.

DVT: Deep venous thrombosis; UTI: Urinary tract infection.

Table 4 Odds ratios for 30-day postoperative complications for patients with adenocarcinoma of the pancreas undergoing a pancreaticoduodenectomy from 2015 to 2019

Complication	Neoadjuvant radiotherapy crude OR (95%CI)	Crude *P* value	Neoadjuvant radiotherapy adjusted OR/IRR (95%CI)	Adjusted *P* value
Total operative time	0.15 (0.13, 0.16)	< 0.001[a]	1.14 (1.11,1.16)[1]	< 0.001[a]
Perioperative transfusion	1.49 (1.32, 1.69)	< 0.001[a]	1.58 (1.37, 1.82)[2]	< 0.001[a]
Superficial SSI	1.13 (0.93, 1.38)	0.217	NP	NP
Organ space SSI	0.76 (0.63, 0.91)	0.004[a]	0.80 (0.66, 0.97)[3]	0.020[a]
30-d reoperation	1.03 (0.80, 1.32)	0.832	NP	NP
30-d mortality rate	0.40 (0.21, 0.75)	0.005[a]	NP	NP
30-d readmission rate	1.14 (0.98, 1.32)	0.090	NP	NP
Renal failure	0.74 (0.37, 1.47)	0.382	NP	NP
Total hospital stay	0.09 (0.06, 0.12)	< 0.001[a]	0.99 (0.96, 1.02)[4]	0.640
Drain in place on POD 30	0.76 (0.61, 0.99)	0.041[a]	0.82 (0.64, 1.06)[5]	0.124
Pancreatic fistula	0.47 (0.38, 0.58)	< 0.001[a]	0.50 (0.40, 0.63)[5]	< 0.001[a]
Delayed gastric emptying	0.81 (0.69, 0.95)	0.010[a]	0.86 (0.72, 1.01)[5]	0.073

[a]*P* < 0.05.

[1]Odds ratio was adjusted for: Albumin, age, sex, race, body mass index (BMI), diabetes, dyspnea, chronic obstructive pulmonary disease (COPD), hypertension, elective surgery, wound class, biliary stent, pancreatic duct size, perioperative transfusion requirement, surgical approach, resection of artery or vein.

[2]Odds ratio was adjusted for: Albumin, age, sex, race, BMI, diabetes, dyspnea, COPD, hypertension, elective surgery, wound class, biliary stent, surgical approach, resection of artery or vein, T-stage, N-stage.

[3]Odds ratio was adjusted for: Age, race, BMI, diabetes, steroids, wound class, American society of anesthesiologists (ASA) class, surgical approach, resection of artery or vein.

[4]Odds ratio was adjusted for: Age, race, BMI, diabetes, steroids, wound class, ASA class, surgical approach, resection of artery or vein, organ space infection, failure to wean off ventilator by post-operative day (POD) 30, drain in place by POD 30, return to the odds ratio within 30 d of index operation, delayed gastric emptying, T-stage, N-stage, M-stage.

[5]Odds ratio was adjusted for: Age, race, BMI, diabetes, steroids, wound class, ASA class, surgical approach, resection of artery or vein.

IRR: Insulin receptor-related receptor; NP: Not performed; OR: Odds ratio; POD: Post-operative day; SSI: Surgical site infection.

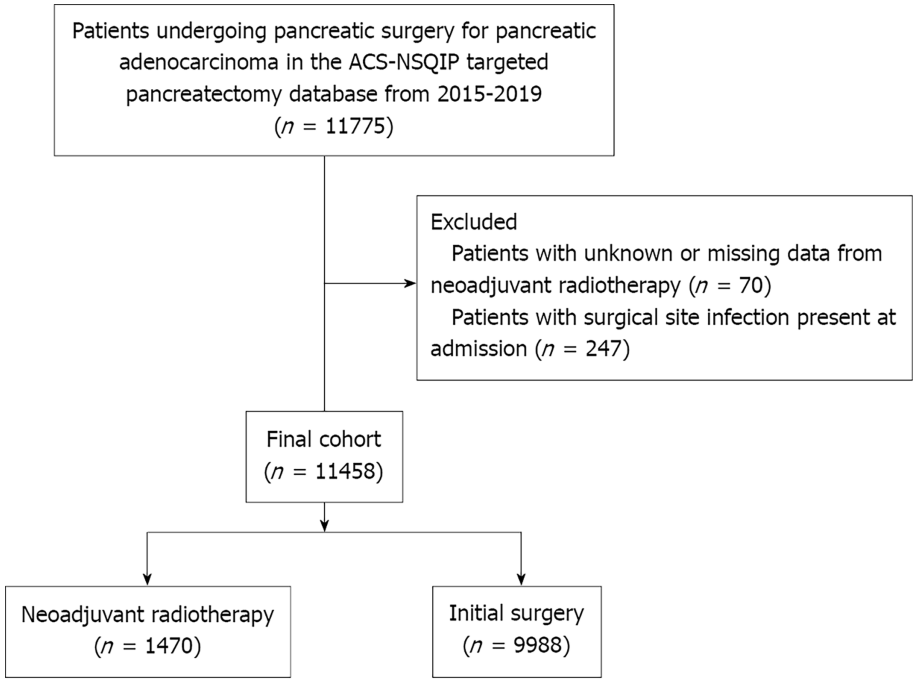

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Figure 1 CONSORT diagram of study cohort. ACS-NSQIP: American College of Surgeons-National Surgery Quality Improvement Program.

lower stage tumors. While the increased number of vascular resections within our neoadjuvant therapy group supports this conclusion, an alternative explanation may be that neoadjuvant radiotherapy itself impacts the complexity of the eventual surgical resection. Histologic evaluation of pancreatic tumors before and after neoadjuvant chemoradiation has shown a significant increase in the ratio of fibrosis to neoplastic cells, indicating a change in the tissue character following neoadjuvant therapy[23]. While such fibrosis has been theorized to be protective against post-operative complications like pancreatic fistulae formation, its distortional effect on classic tissue planes may make the surgery itself more difficult[24]. It is important for the operating surgeon to keep this in mind, as it may impact both the procedure type (*i.e.* open *vs* minimally invasive) and the expected post-operative complications.

Overall, the 30-d post-operative complication and morbidity rates were similar between both study groups. Of the variables that were analyzed using multivariable regression, only organ space infections and pancreatic fistula rates were significantly different between the two study groups. Numerous studies have detailed the decreased rate of both variables in patients receiving neoadjuvant therapy, suggesting that neoadjuvant radiotherapy may have a small positive effect on short term post-operative morbidity[9,10,14,21,25].

Although the data provided in this study lend credence to the safety and efficacy of neoadjuvant radiotherapy, there are some limitations to keep in mind. Data regarding the specific details of neoadjuvant radiotherapy regimen used (duration, intensity, timing, prior to surgery) is not available within the NSQIP database, making it impossible to account for related confounding factors in our data analyses. Additionally, NSQIP only collects data on post-operative outcomes that occur within 30 d of the index operation, making the results of this study difficult to extrapolate over a longer-termed period. Facility and surgeon data are also not reported in NSQIP, which again may represent confounding factors that our analyses did not consider. Finally, it is impossible to determine whether a patient's tumor is resectable or borderline resectable (per NCCN guidelines) based on the information reported in NSQIP. As surgeries may be more difficult in borderline resectable patients, this represents a further confounding factor that could not be completely controlled for.

CONCLUSION

The results of this study contribute to the notion that neoadjuvant radiotherapy is both safe and effective to use prior to a pancreaticoduodenectomy for pancreatic adenocarcinoma. The study does, however, suggest that adverse intraoperative outcomes like total operative time and perioperative transfusion requirements may be increased among patients receiving surgery for cancer resection after neoadjuvant radiotherapy. Surgeons are encouraged to keep in mind the potential positive and negative effects that neoadjuvant radiotherapy has on the complexity of the eventual surgery when it is performed.

ARTICLE HIGHLIGHTS

Research background

Pancreatic adenocarcinoma is currently the fourth leading cause of cancer-related deaths in the United States. In addition to neoadjuvant chemotherapy, neoadjuvant radiotherapy may improve negative margin resection rates. This study seeks to investigate the safety and efficacy of neoadjuvant radiotherapy in patients with pancreatic adenocarcinoma.

Research motivation

By better clarifying the benefits and drawbacks that are associated with neoadjuvant radiotherapy administration in patients with pancreatic adenocarcinoma, practitioners can make informed decisions regarding its use.

Research objectives

The primary objective of the study was to investigate the effect that neoadjuvant radiotherapy has on both intra-operative and 30-d postoperative morbidities in patients with pancreatic adenocarcinoma.

Research methods

Using 2015-2019 data from the National Surgery Quality Improvement Program data set, we divided pancreatic adenocarcinoma patients into two groups based on neoadjuvant radiotherapy status. Then we performed univariable and multivariable analyses to identify differences in baseline characteristics and outcomes between the two groups.

Research results

When compared to patients with pancreatic adenocarcinoma who underwent surgical resection alone, patients who underwent neoadjuvant radiotherapy were more likely to have longer surgeries and higher perioperative blood loss. The neoadjuvant radiotherapy patients were also less likely to have organ space infections and pancreatic fistulae formation.

Research conclusions

Neoadjuvant radiotherapy has significant effects on intraoperative and 30-d postoperative morbidity in patients with pancreatic adenocarcinoma. It may make eventual surgical resection of the cancer more complex.

Research perspectives

Future research should focus on finding new methods that work to minimize the negative side effects associated with neoadjuvant radiotherapy in patients with pancreatic adenocarcinoma.

FOOTNOTES

Author contributions: Aploks K, Kim M, Ostapenko A, Dong XD, and Seshadri R contributed to the conceptualization of the project; Aploks K, Stroever S, Kim M, Ostapenko A, Dong XD, and Seshadri R contributed to the methodology and validation of the data; Stroever S conducted the formal statistical analyses; Aploks K, Kim M, Sim YB, and Sooriyakumar A prepared the original manuscript; Aploks K, Kim M, Ostapenko A, Sim YB, Sooriyakumar A, Rahimi-Ardabily A, Dong XD, and Seshadri R contributed to the final draft revision and editing; Dong XD and Seshadri R supervised the project.

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Country/Territory of origin: United States

ORCID number: Krist Aploks 0000-0003-3775-1775; Xiang Da Dong 0000-0001-9324-1281.

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ORIGINAL ARTICLE

Retrospective Study

Prognostic significance of preoperative lymphocyte to monocyte ratio in patients with signet ring gastric cancer

He-Li Liu, Xiang Feng, Mi-Mi Tang, Hai-Yan Zhou, Huan Peng, Jie Ge, Ting Liu

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He-Li Liu, Xiang Feng, Jie Ge, Department of Gastrointestinal Surgery, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, China

He-Li Liu, The Hunan Provincial Key Laboratory of Precision Diagnosis and Treatment for Gastrointestinal Tumor, The Hunan Provincial Key Laboratory of Precision Diagnosis and Treatment for Gastrointestinal Tumor, Changsha 410008, Hunan Province, China

Mi-Mi Tang, Ting Liu, Institute for Rational and Safe Medication Practices National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, China

Hai-Yan Zhou, Department of Pathology, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, China

Huan Peng, Clinical Nursing Teaching and Research Section, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, China

Corresponding author: Jie Ge, MD, Department of Gastrointestinal Surgery, Xiangya Hospital, Central South University, No. 87 Xiangya Road, Kaifu District, Changsha 410008, Hunan Province, China. gejie@csu.edu.cn

Abstract

BACKGROUND

The ratio of lymphocytes to monocytes (LMR) has been shown to be an effective predictor of gastric cancer prognosis. However, its predictive accuracy for signet ring gastric cancer is currently not well understood.

AIM

To evaluate the prognosis predictive accuracy of preoperative LMR in signet ring gastric cancer.

METHODS

A total of 212 signet ring gastric cancer patients admitted at the Xiangya Hospital of Central South University, Department of Gastrointestinal Surgery, from January 2012 to December 2016 were enrolled in the study. The prognosis predictive accuracy of preoperative LMR was explored based on the area under the receiver operating characteristic. Factors that significantly affect the survival of patients were identified using single factor analysis, and those that were

independently associated with signet ring gastric cancer were identified through multivariate analysis.

RESULTS

The results of the single factor analysis revealed a strong correlation between the survival of signet ring gastric cancer patients and several factors, including tumor invasion (χ^2 = 49.726; P < 0.001), lymph node metastasis (χ^2 = 30.269; P < 0.001), pTNM stage (χ^2 = 49.322; P < 0.001), surgical approach (χ^2 = 8.489; P = 0.004), age (t = -2.213; P < 0.028), carcinoembryonic antigen (CEA) (Z = -3.265; P = 0.001), platelet-to-lymphocyte ratio (Z = -2.196; P = 0.028), LMR (Z = -2.226; P = 0.026), ALB (t = 3.284; P = 0.001), prognostic nutritional index (t = -3.789; P < 0.001) and FIB (Z = -3.065; P = 0.002). Furthermore, the multivariate analysis further demonstrated that age (HR: 0.563, 95%CI: 0.363-0.873), tumor invasion depth (HR: 0.226, 95%CI: 0.098-0.520), pTNM stage (HR: 0.444, 95%CI: 0.255-0.771), preoperative CEA level (HR: 0.597, 95%CI: 0.386-8.790), and preoperative LMR level (HR: 1.776, 95%CI: 1.150-2.741) were independent factors influencing the prognosis of signet ring gastric cancer.

CONCLUSION

In signet ring gastric cancer patients, a low preoperative LMR level predicts poor prognosis. The death risk ratio of the low LMR group compared to the high LMR group is 1.776.

Key Words: Gastric cancer; Signet ring cell carcinoma; Inflammation indexes; Coagulation indexes; Prognosis.

Core Tip: Low preoperative lymphocytes to monocytes levels -predict poor prognosis of patients with signet ring gastric cancer, making it a valuable prognostic factor.

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INTRODUCTION

Signet ring gastric cancer is a type of stomach cancer that is characterized by presence of cells filled with mucus, which push the nucleus to one side of the cell, giving it a ring-like appearance. This type of cancer is highly invasive, progresses rapidly, and has a high degree of malignancy. Although the incidence of gastric cancer has decreased in recent decades, cases of signet-ring cell carcinoma (SRCC) are increasingly being reported. Studies have demonstrated that SRCC accounts for 35 % to 45 % of all cases of gastric adenocarcinoma[1], and its incidence increased by tenfold from 1970 to 2000[2].

Currently, the prognosis of SRCC is not well understood. Given that SRCC is prone to lymph node and peritoneal metastasis, less responsive to chemotherapy, and most patients are diagnosed at an advanced cancer stage, patients with SRCC have a poor prognosis[2].

The occurrence and development of tumors are driven by several factors including inflammatory immune response of the host[3]. Numerous studies have explored the relationship between different inflammatory markers, chemotherapeutic effects, and prognosis in gastric cancer. Among the most easily available inflammatory markers obtained from the whole blood cell count are lymphocyte-to-monocyte ratio (LMR)[4], neutrophil-to-lymphocyte ratio (NLR)[5], platelet-to-lymphocyte ratio (PLR)[6], and systemic immune inflammation (SII)[7]. The prognostic nutritional index (PNI), a simple and easy detection index, has been widely used in clinical practice and shown to be associated with the prognosis of malignant gastric tumors[8,9]. Moreover, the development of tumors is accompanied by changes in the blood coagulation dynamics of the host[10]. Coagulation factor levels, such as platelet count, international standard ratio, fibrin degradation products, fibrinogen, and D-dimer levels, have been associated with tumor stage, metastasis, chemotherapeutic effect, and prognosis of patients with solid tumors[11,12]. Although many scientists have explored the relationship between various indicators and chemotherapy response and prognosis of gastric cancer, few studies have explored the prognostic value of these indicators in SRCC.

Against this background, we explored the relationship between the common inflammatory indicators, nutritional indicators, coagulation indicators and the prognosis of SRCC to identify prognostic predictors of SRCC.

MATERIALS AND METHODS

Patients

The retrospective study included 212 patients with gastric cancer admitted to the Department of Gastroenterology at Xiangya Hospital of Central South University from January 2012 to December 2016. To be included in the study, patients had to meet the following criteria: (1) Postoperative pathology revealed SRCC components greater than 10%; (2) Accepted to undergo radical gastrectomy; and (3) With complete clinical and follow-up data. Moreover, the exclusion criteria are as follows: (1) Preoperative radiotherapy, chemotherapy, targeted therapy, immunotherapy, and other anti-tumor treatments that may affect the patient's blood routine, liver and kidney function, and coagulation routine; (2) Preoperative examination indicated the presence of distant metastases such as liver, lung, and bone metastases; (3) Intraoperative detection of metastasis; (4) Comorbidity hematological diseases and other systemic malignancies; (5) Combined with severe infections, liver disease, kidney disease, and autoimmune diseases; (6) Emergency surgery due to perforation and bleeding of gastric cancer; and (7) Gastric stump cancer. This study was approved by the Ethics Committee of Xiangya Hospital of Central South University.

Measurement of variables

Patient-related results, including demographic data, clinic characteristics, and biochemical test results such as carcinoembryonic antigen (CEA), LMR [= lymphocyte count (× 10^9/L)/monocyte count (× 10^9/L)], NLR [= Neutrophil count (× 10^9/L)/Lymphocyte count (× 10^9/L)], PLR [= platelet count (× 10^9/L)/Lymphocyte coun (× 10^9/L)], SII [= Neutrophil count (× 10^9/L) × Platelet count (× 10^9/L)/Lymphocyte count (× 10^9/L)][13], coagulation index [activated partial thromboplastin time (APTT), fibrinogen degradation product (FDP), fibrinogen (FIB), prothrombin time (PT), thrombin time (TT), and international normalized ratio (INR)] were obtained from the medical database of the hospital. Additionally, albumin (ALB), globulin (GLB), albumin to globulin ratio [AGR = serum albumin (g/L)/serum globulin (g/L)], and prognostic nutritional index [PNI = 5 × Lymphocyte count (× 10^9/L)+serum albumin (g/L)][14] were obtained through peripheral complete blood count and blood biochemistry before the surgery. Cut-off values for each variable were obtained from the receiver operating characteristic (ROC) curves.

Statistical analysis

Statistical analysis was performed using SPSS 25.0 and GraphPad Prism 8.0. The normality of the data was assessed using the Shapiro-Wilk test, and the data which did not fit the normal distribution was represented by M (P25, P75) and analyzed using the Mann-Whitney *U* test. Single factor analysis was performed using the independent-sample *t*-test for normally distributed data, and the counts were presented as percentages (%). The prognostic value of inflammation, blood coagulation and other indicators was evaluated using ROC curves, and the optimal cut-off point of patient survival was determined. The patients were then divided into high and low groups based on the medium levels of the above indicators. Kaplan-Meier survival analysis and the Log-rank tests were used to compare survival rates between the high and low-risk groups. Cox proportional hazards regression analysis was conducted to identify independent predictors of the prognosis of gastric cancer with SRCC by including indicators that significantly affected the survival status. Statistical significance was set at $P < 0.05$.

RESULTS

Baseline data and pathological characteristics

The study included 212 patients with SRCC, of whom 87 patients (41.04 %) died, and 125 patients (58.96 %) survived for the 5-year follow-up period. The mean age of the patients was 51.42 ± 11.27 years, 117 were males (55.19 %), and 95 were females (44.81 %). The tumor location was in the upper, middle and lower third of the stomach in 5 (2.36 %), 58 (27.36 %) and 149 (70.28 %) cases, respectively. Distal gastrectomy was performed in 167 (78.78 %) cases, while total gastrectomy was performed in 45 (21.22 %) cases. The tumor infiltration depth was pT1 or pT2 in 79 cases (37.26 %) and pT3 or pT4 in 133 cases (62.74 %). Lymph node metastasis was found in 118 (55.66 %) cases with pN1, pN2 or pN3, while 94 (44.34 %) cases were classified as N0. The pTNM stage was I or II in 117 cases (55.19 %) and III in 95 (44.81 %) cases (Table 1).

ROC analysis of predictors

Table 2 shows the cut-off value and area under the curve (AUC) for each index, and Figure 1 shows the ROC curves (AUC, 95%CI) of the predictors, including age, CEA, PLR, LMR, ALB, PNI and FIB. Overall, the results indicate good predictive values of CEA (0.632, 0.556-0.708), LMR (0.590, 0.512-0.669), ALB (0.618, 0.540-0.696), PNI (0.644, 0.567-0.721), and FIB (0.624, 0.547-0.701).

Single factor analysis for prognostic factors

Table 3 displays the results of the pathological features and the 5-year survival rate of the patients. The analysis revealed that depth of tumor invasion, lymph node metastasis, pTNM stage and resection range were associated with the survival rate, while gender and tumor location showed no correlation.

As shown in Table 4, firstly, the single factor analysis demonstrated that younger patients had a better survival rate compared with older patients. The survival rate was also significantly better in the lower CEA level group compared with the higher CEA level group. In addition, SRCC patients in the higher PLR value had poorer survival rates than those in

Table 1 Baseline data and pathological features of the study participants

Characteristics	*n* (%)
Gender	
Male	117 (55.19)
Female	95 (44.81)
Tumor site	
Upper third	5 (2.36)
Middle third	58 (27.36)
Lower third	149 (70.28)
pT	
pT1-2	79 (37.26)
pT3-4	133 (62.74)
pN	
pN0	94 (44.34)
pN1-3	118 (55.66)
pTNM stage	
I/II	117 (55.19)
III	95 (44.81)
Resection scope	
Distal stomach	167 (78.78)
Total stomach	45 (21.23)
Survival status	
Survival	125 (58.96)
Dead	87 (41.04)

Table 2 Receiver operating characteristic curve analysis results of predictors

Variables	AUC (95%CI)	*P* value	Cut-off value	Sensitivity	Specificity
Age	0.589 (0.509-0.669)	0.028	55.5	0.494	0.728
PLR	0.589 (0.511-0.666)	0.028	124.63	0.586	0.608
LMR	0.590 (0.512-0.669)	0.025	3.83	0.54	0.632
ALB	0.618 (0.540-0.696)	0.004	38.95	0.414	0.792
PNI	0.644 (0.567-0.721)	< 0.001	49.85	0.632	0.608
FIB	0.624 (0.547-0.701)	0.002	3.115	0.655	0.648
CEA	0.632 (0.556-0.708)	0.001	1.455	0.471	0.744

PLR: Platelet to lymphocyte ratio; LMR: Lymphocyte to monocyte ratio; ALB: Albumin; PNI: Prognostic nutritional index; FIB: Fibrinogen; CEA: Carcinoembryonic antigen; AUC: Area under the curve.

the lower PLR value group, while SRCC patients in the higher LMR value group had a better survival rate than those in the lower LMR value group. Finally, the survival rate of patients with lower FIB was significantly better in those with higher FIB, whereas patients with lower ALB had a significantly lower survival rate compared with higher ALB group.

Grouping of predictors

The predictors, including age, CEA, ALB, PNI, LMR, PLR, and FIB, were grouped as shown in Table 5.

Table 3 Relationship between baseline data, pathological features and 5-year survival rate

Group	Survival status		5-OS (%)	χ^2	*P* value
	Survival (*n*)	Dead (*n*)			
Gender				1.27	0.26
Male	73	44	62.39		
Female	52	43	54.74		
Tumor site				3.556	0.169
Upper third	1	4	20		
Middle third	33	25	56.9		
Lower third	91	58	61.07		
pT				49.726	< 0.001
pT1-2	71	8	89.87		
pT3-4	54	79	40.6		
pN				30.269	< 0.001
pN0	75	19	79.79		
pN1-3	50	68	42.37		
pTNM stage				49.322	< 0.001
I/II	94	23	80.34		
III	31	64	32.63		
Resection scope				8.489	0.004
Distal stomach	107	60	64.07		
Total stomach	18	27	40		

OS: Overall survival.

Kaplan-Meier survival analysis

The Kaplan-Meier survival curves are shown in Figure 2. The Log-rank test indicated no significant difference in survival rate between the low PLR group and the high PLR group ($P = 0.147$). In contrast, significant differences were observed in survival rate between different resection groups ($P < 0.001$), depth of invasion ($P < 0.001$), lymph node metastasis ($P < 0.001$), pTNM stage ($P < 0.001$), age ($P = 0.004$), LMR ($P = 0.003$), ALB ($P = 0.008$), PNI ($P = 0.002$) and FIB ($P = 0.001$).

Multivariate and multiple-factor analysis

To explore the independent factors affecting the prognosis of SRCC, indicators that demonstrated statistical differences by the Log-rank test were included in a Cox proportional hazards regression model for multivariate analysis. The results (HR, 95%CI) are presented in Figure 3. The independent factors for SRCC prognosis were age (0.563, 0.363-0.873, $P = 0.010$), depth of tumor invasion (0.226, 0.098-0.520), pTNM stage (0.444, 0.255-0.771), preoperative CEA level (0.597, 0.386-8.790), and preoperative LMR level (1.776, 1.150-2.741). Advanced age, high CEA level before surgery, low LMR level before surgery, deep tumor invasion, and late pTNM stage were all indicative of a relatively poor prognosis. Specifically, the risk of death in low LMR group before surgery was 1.776 times higher than that of the high LMR group.

DISCUSSION

Currently, surgery is the mainstay treatment for gastric cancer patients, especially those with SRCC. However, despite radical resection or adjuvant chemotherapy, the prognosis of SRCC patients, particularly those in advanced stages, is not optimistic. Therefore, it is crucial to elucidate the mechanism of tumor progression and identify independent prognostic factors to evaluate the overall condition of tumor patients and optimize diagnosis and treatment.

The correlation between inflammation and tumors was first proposed by Rudolf Virchow[14]. Research has shown that inflammation participates in tumor development[15,16]. Furthermore, inflammation can influence the prognosis of tumors by altering immune response[17,18].

Lymphocytes and monocytes play a crucial role in anti-tumor immune response[19]. The relationship between LMR and the prognosis of malignant tumors has been widely reported[20-22]. However, few studies have investigated the

Table 4 Relationship between indicators and survival status

Variables	Survival	Dead	*t*/*Z* value	*P* value
Age	50 ± 10.82	53 ± 11.65	-2.213	0.028
CEA	0.90 (0.58, 1.48)	1.21 (0.75, 2.35)	-3.265	0.001
NLR	1.82 (1.30, 2.43)	2.05 (1.45, 2.71)	-1.668	0.095
PLR	118.33 (99.41, 150.18)	130.59 (108.10, 162.00)	-2.196	0.028
LMR	4.20 (3.40, 5.67)	3.80 (2.80, 5.00)	-2.226	0.026
SII	392.36 (275.38, 565.21)	448.00 (311.67, 600.71)	-1.391	0.164
PT	12.40 (11.96, 12.90)	12.30 (12.00, 12.70)	-1.114	0.265
INR	0.97 (0.93, 1.02)	0.95 (0.93, 0.99)	-1.728	0.084
APTT	32.71 ± 4.16	31.90 ± 3.98	1.425	0.156
TT	17.55 ± 1.73	17.66 ± 1.85	-0.424	0.672
FIB	2.93 (2.56, 3.42)	3.29 (2.81, 3.80)	-3.065	0.002
ALB (g/L)	41.79 ± 3.83	40.09 ± 4.72	2.854	0.005
GLB (g/L)	26.00 (23.80, 29.40)	25.20 (22.80, 28.50)	-1.356	0.175
AGR	1.58 (1.41, 1.80)	1.56 (1.40, 1.75)	-0.716	0.474
PNI	51.11 ± 4.95	48.21 ± 6.15	3.789	< 0.001

CEA: Carcinoembryonic antigen; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; LMR: Lymphocyte to monocyte ratio; SII: Systemic immune inflammation index; PT: Prothrombin time; INR: International normalized ratio; APTT: Activated partial thromboplastin time; TT: Thrombin time; FIB: Fibrinogen; ALB: Albumin; GLB: Globulin; AGR: Albumin to globulin ratio; PNI: Prognostic nutritional index.

Table 5 Grouping of predictors

		Survival (*n*)	Dead (*n*)	5-OS (%)	Total
Age	< 56	91	44	67.41	135
	≥ 56	34	43	44.16	77
CEA (ng/mL)	< 1.455	93	46	66.91	139
	≥ 1.455	32	41	43.84	73
PLR	< 124.63	76	36	67.86	112
	≥ 124.63	49	51	49	100
LMR	< 3.83	81	30	72.97	111
	≥ 3.83	44	57	43.56	101
ALB (g/L)	< 38.95	26	36	41.94	62
	≥ 38.95	99	51	66	150
PNI	< 49.85	49	55	47.12	104
	≥ 49.85	76	32	70.37	108
FIB (g/L)	< 3.115	46	47	49.46	93
	≥ 3.115	79	40	66.39	119

OS: Overall survival; CEA: Carcinoembryonic antigen; PLR: Platelet to lymphocyte ratio; LMR: Lymphocyte to monocyte ratio; ALB: Albumin; PNI: Prognostic nutritional index; FIB: Fibrinogen.

relationship between inflammatory markers and SRCC. Chengcheng Tong *et al*[23], reported that derived monocyte-to-lymphocyte ratio (dMLR) could independently predict lymph node metastasis of SRCC. Zhu *et al*[9] reported the relationship between SII and the prognosis of SRCC, but the relationship between LMR and SRCC has not been investigated.

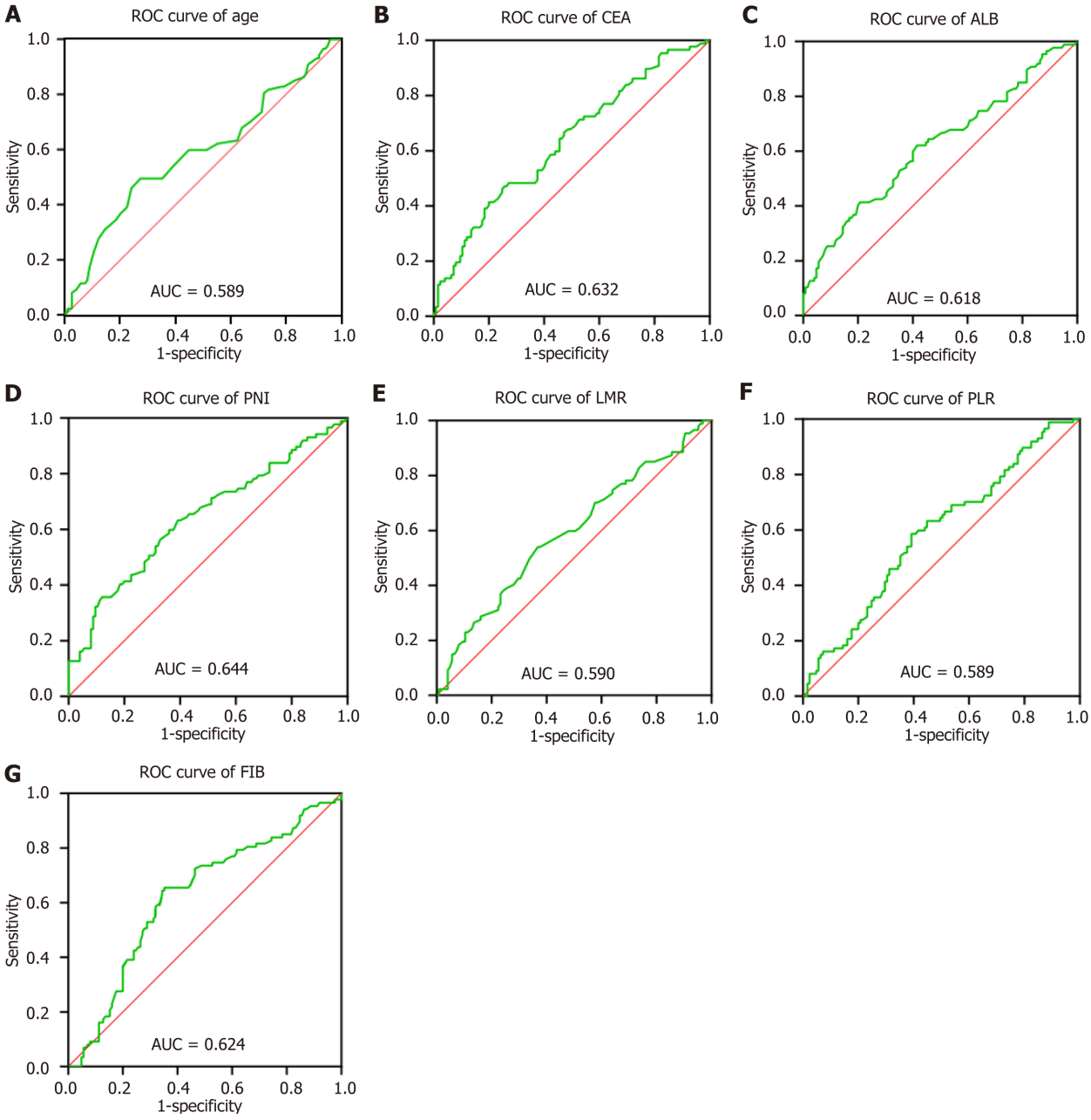

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Figure 1 Receiver operating characteristic curves of all predictors. A: Age; B: Carcinoembryonic antigen; C: Albumin; D: Prognostic nutritional index; E: Lymphocyte to monocyte ratio; F: Platelet to lymphocyte ratio; G: Fibrinogen.

Numerous studies have shown that high levels of peripheral blood lymphocyte count and TILs are associated with a good prognosis in gastric cancer[24-26]. Li *et al*[27] reported that patients with smaller tumors (< 5 cm) had higher counts of peripheral blood CD4 + T cells (P = 0.003) and CD8 + T cells (P = 0.002). In addition, patients with well-differentiated gastric cancer showed higher counts of CD4 + T cells (P = 0.029).

NK cells, which possess potent anti-tumor, anti-viral and antibacterial activity, are crucial in activating and regulating adaptive immune responses. In human peripheral blood, NK cells account for approximately 3%-5% of lymphocytes[28, 29]. The anti-tumor activity of NK cells is mainly determined by a group of inhibitory and activating receptors[30]. Patients with gastric cancer exhibit lower expression of activating receptors such as NKG2D, NKp30, and NKp46, but higher PD-1 expression. Moreover, NK cells of patients with gastric cancer secrete lower cytokines (IFN-γ, IL-2, TNF-α, IL-12) and impaired ability to release perforin and granzyme. Meanwhile, gastric cancer cells express little MICA/B, ULBP, and B7H6, to evade NK cell-mediated innate immunity. Gastric cancer cells can also produce cytokines such as IL-10, TGF-β, and PGE2, which recruit MDSC and Treg cells to suppress NK cell function[31]. The proportion of apoptotic NK cells in patients with gastric cancer is elevated when receiving gastrectomy[32]. Collectively, these lines of evidence show that the number and function of NK cells decrease sharply with the progression of gastric cancer[31].

Monocytes, particularly those that differentiate into tumor-associated macrophages (TAMs), contribute to the development of gastric cancer[33]. M1 TAMs have anti-tumor effects, while M2 TAMs promote tumor growth[34]. Under

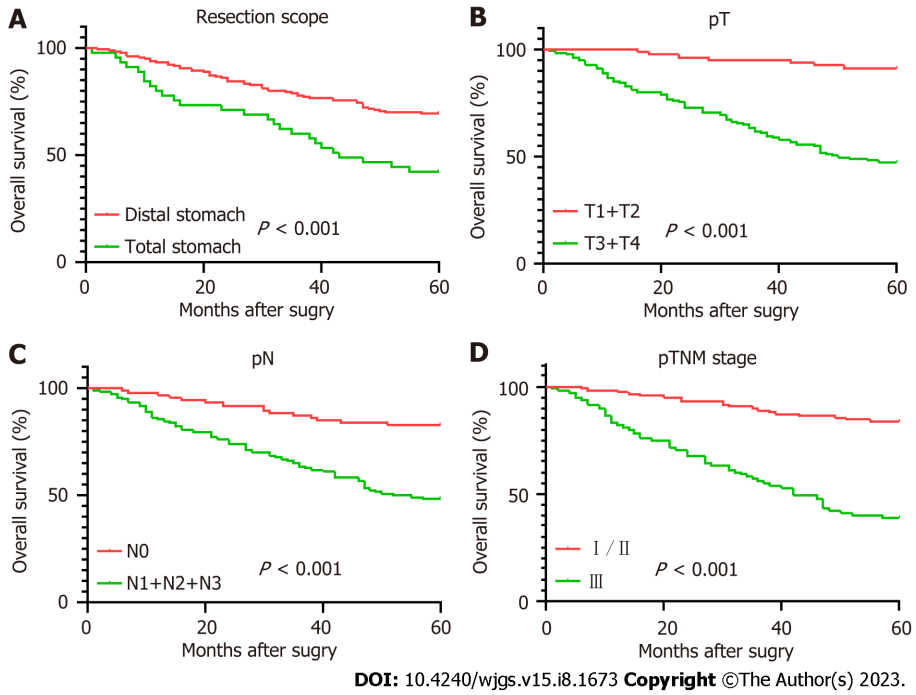

Figure 2 The survival curves of all predictors. A: Resection scope; B: Infiltration depth; C: Lymph node metastasis; D: pTNM staging;

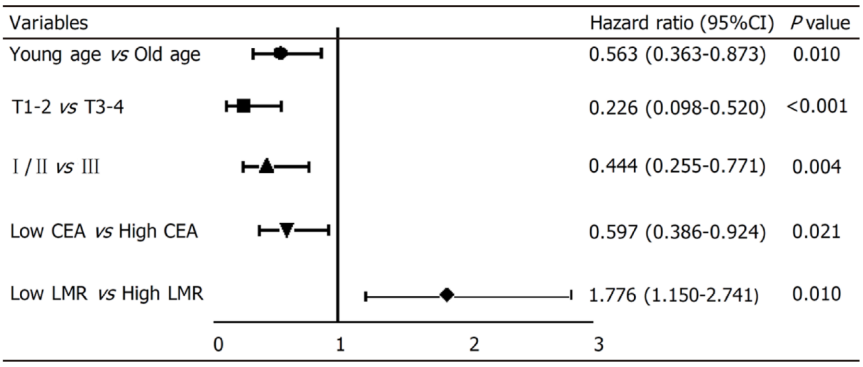

Figure 3 Survival of patients with different characteristics in Cox regression model. CEA: Carcinoembryonic antigen; LMR: Lymphocytes to monocytes.

the influence of cytokines and extracellular matrix secreted by tumour cells and lymphocytes, M1 TAMs can convert into M2 TAMs. In gastric cancer, M2 TAMs are highly expressed in SRCC, mucinous adenocarcinoma and diffuse gastric cancer[35].

Our study found that the 5-year survival rate of patients with low LMR before surgery was significantly lower than that with high LMR. In summary LMR affects the prognosis of SRCC due to reduction of lymphocytes during inflammatory response and increase of tumor-associated macrophages produced by circulating monocytes. However, this study has some limitations. First, this was a retrospective single-center study and no external validation was performed. In addition, studies have suggested that gastric cancer with different SRCC ratios may have varying biological characteristics, although we demonstrated a relationship between LMR and the prognosis of SRCC. Therefore, it is imperative to explore further the predictive value of various indicators in gastric cancer with different SRCC ratios.

CONCLUSION

In summary, this study shows that a low preoperative LMR level indicates a poor prognosis of signet ring gastric cancer. Particularly, compared with the high LMR group, the risk of mortality in the low LMR group is 1.776.

ARTICLE HIGHLIGHTS

Research background

The incidence of signet ring gastric carcinoma has increased among the past decades. Several inflammation indexes, including ratio of lymphocytes to monocytes (LMR), have been shown to be effective predictors of gastric cancer prognosis.

Research motivation

The predictive accuracy of ratio of LMR for signet ring gastric cancer is unclear now.

Research objectives

To assess the prognosis predictive accuracy of preoperative LMR for signet ring gastric cancer.

Research methods

Our research center conducted a retrospective analysis of clinical data from patients diagnosed with signet ring gastric carcinoma over the past 5 years, identifying factors that significantly affect patients' survival by using single factor analysis, and deciding independent prognostic factors related to signet ring cell gastric cancer by using multivariate analysis.

Research results

The results of the single factor analysis indicated a strong correlation between the survival of signet ring gastric cancer patients and several factors, including tumour invasion, lymph node metastasis, pTNM stage, surgical approach, age, carcinoembryonic antigen (CEA), platelet-to-lymphocyte ratio (PLR), LMR, ALB, PNI and FIB. Furthermore, the multivariate analysis revealed that age, tumor invasion depth, pTNM stage, preoperative CEA level, and preoperative LMR level were independent factors related to the prognosis of signet ring gastric cancer.

Research conclusions

In signet ring gastric cancer patients, a low preoperative LMR level is indicative of a poor prognosis. The death risk ratio of the low LMR group compared to the high LMR group is 1.776.

Research perspectives

The study subjects were followed up for 5 years and divided into survival group and death group. Clinical data, pathological data, and prognosis of the two groups of patients were observed.

FOOTNOTES

Author contributions: Liu HL, Feng X contributed equally to this work; Liu HL, Feng X and Ge J designed research; Tang MM, Zhou HY and Feng X collected and analyzed clinical data; Liu T, Peng H wrote the paper.

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ORCID number: He-Li Liu 0000-0002-3443-6174; Xiang Feng 0000-0003-1490-6789; Mi-Mi Tang 0000-0002-1517-6637; Hai-Yan Zhou 0000-0002-2860-1858; Huan Peng 0000-0002-3073-5708; Jie Ge 0000-0002-4186-4740.

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ORIGINAL ARTICLE

Retrospective Study

Clinical efficacy of total laparoscopic splenectomy for portal hypertension and its influence on hepatic hemodynamics and liver function

Rui-Zhao Qi, Zhi-Wei Li, Zheng-Yao Chang, Wei-Hua Chang, Wen-Lei Zhao, Chuan Pang, Ying Zhang, Xing-Long Hu, Feng Liang

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Rui-Zhao Qi, Zheng-Yao Chang, Wei-Hua Chang, Wen-Lei Zhao, Chuan Pang, Ying Zhang, Xing-Long Hu, Feng Liang, Department of General Surgery, 5th Medical Center, Chinese PLA General Hospital, Beijing 100039, China

Zhi-Wei Li, Department of Hepatobiliary, The 3rd People's Hospital of Shenzhen, Shenzhen 518112, Guangdong Province, China

Corresponding author: Feng Liang, PhD, Doctor, Department of General Surgery, 5th Medical Center, Chinese PLA General Hospital, No. 8 Dongdajie, Fengtai District, Beijing 100039, China. lfpeakcool@126.com

Abstract

BACKGROUND

The liver hemodynamic changes caused by portal hypertension (PH) are closely related to various complications such as gastroesophageal varices and portosystemic shunts, which may lead to adverse clinical outcomes in these patients, so it is of great clinical significance to find treatment strategies with favorable clinical efficacy and low risk of complications.

AIM

To study the clinical efficacy of total laparoscopic splenectomy (TLS) for PH and its influence on hepatic hemodynamics and liver function.

METHODS

Among the 199 PH patients selected from October 2016 to October 2020, 100 patients [observation group (OG)] were treated with TLS, while the remaining 99 [reference group (RG)] were treated with open splenectomy (OS). We observed and compared the clinical efficacy, operation indexes [operative time (OT) and intraoperative bleeding volume], safety (intraperitoneal hemorrhage, ascitic fluid infection, eating disorders, liver insufficiency, and perioperative death), hepatic hemodynamics (diameter, velocity, and flow volume of the portal vein system), and liver function [serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), and serum total bilirubin (TBil)] of the two groups.

RESULTS

The OT was significantly longer and intraoperative bleeding volume was significantly lesser in the OG than in the RG. Additionally, the overall response rate, postoperative complications rate, and liver function indexes (ALT, AST, and TBil) did not differ significantly between the OG and RG. The hepatic hemodynamics statistics showed that the pre- and postoperative blood vessel diameters in the two cohorts did not differ statistically. Although the postoperative blood velocity and flow volume reduced significantly when compared with the preoperative values, there were no significant inter-group differences.

CONCLUSION

TLS contributes to comparable clinical efficacy, safety, hepatic hemodynamics, and liver function as those of OS in treating PH, with a longer OT but lesser intraoperative blood loss.

Key Words: Total laparoscopic splenectomy; Open splenectomy; Portal hypertension; Clinical efficacy; Hepatic hemodynamics and liver function

Core Tip: Portal hypertension (PH) can bring adverse effects to patients such as hepatic hemodynamic changes and decreased liver function. We propose and demonstrate that total laparoscopic splenectomy, although comparable to open splenectomy in clinical efficacy, safety, and effects on hepatic hemodynamics and liver function in patients with PH, has the advantage of less intraoperative blood loss.

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INTRODUCTION

Portal hypertension (PH) and cirrhosis are considered the endpoints of chronic liver injury[1]. Knowledge regarding the pathophysiology of PH has increased enormously over the past decade[2]. Currently, it is believed that increased visceral and peripheral vasodilators increase portal pressure, leading to changes in hepatic hemodynamics[3]. Furthermore, the negative effects of PH on the portal blood entering the liver will impair the patient's liver functional reserve, leading to the deterioration of liver function[4]. Additionally, the hepatic hemodynamic changes caused by PH are closely related to several complications, such as gastroesophageal varices and portosystemic shunt, which can affect the clinical outcome in these patients[5]. Therefore, this study aimed to find a treatment strategy with better clinical efficacy and low risk of complications, which is important for optimizing the clinical treatment and improving the prognosis of patients with PH.

Open splenectomy (OS) is the traditional treatment choice for patients with PH. Despite its advantages of a wide field of view and simple technique, it has the disadvantages of a relatively large amount of blood loss, severe trauma, and slow recovery[6]. With the gradual development of medical technology, total laparoscopic splenectomy (TLS), a minimally invasive surgery, is gradually being accepted by patients. The gastric fundus and deep abdominal cavity of the patients can be observed through an endoscope during TLS, with a small incision and a relatively low risk of complications[7,8]. Thus, TLS is a feasible option for PH patients with conditions such as benign splenic lesions and hematological diseases but not for those with deformed or huge spleen, high pressure of portal blood vessels, and peri-splenic adhesion[9]. Recently, due to the continuous maturation and optimization of clinical practice, TLS combined with porta-azygos devascularization has gradually demonstrated its superiority. For instance, Luo *et al*[10] demonstrated that this method has superior surgical effects and similar long-term effects when compared with those of OS in patients with cirrhotic PH.

This study compares the clinical efficacy of TLS + devascularization and traditional OS + devascularization in patients with PH as well as the influences on the hepatic hemodynamics and liver function to provide a new reference and treatment choice for the management of PH patients.

MATERIALS AND METHODS

General information

This study selected 199 PH patients admitted to the Chinese PLA General Hospital between October 2016 and October 2020. Among them, 100 patients were assigned to the observation group (OG) and 99 to the reference group (RG) to undergo TLS and OS, respectively. The OG comprised 54 males and 46 females, with a mean age of 49.53 ± 9.14 years. Based on the Child-Pugh scores for liver function assessment, 72 and 28 cases in the OG were classified as Class A and

Class B, respectively. The RG comprised 57 males and 42 females, with a mean age of 49.23 ± 9.84 years; 70 and 29 cases were classified as Child-Pugh Class A and Class B, respectively. The inter-group comparison of the baseline data revealed no obvious differences between them ($P > 0.05$). Details of the baseline data can be found in Table 1.

Criteria for patient enrollment

The inclusion criteria of this study were PH diagnosis according to the diagnostic criteria, surgical indications for splenectomy, preoperative liver function classification of Child-Pugh Class A or B, presence of splenomegaly and hypersplenism, availability of complete clinical data, and willingness to cooperate with the research requirements.

On the other hand, the exclusion criteria were as follows: Severe systemic organ function damage contraindicated for surgery; severe hepatatrophy, hepatic encephalopathy, jaundice, refractory ascites, and other liver conditions; malignancies such as carcinoma of the liver, stomach, and/or pancreas; and history of other abdominal operations.

Treatment methods

For performing TLS in the OG, the patient was placed in the supine position with the legs spread, and the head and the left side of the body raised by 15°. The surgeon stood on the right side of the patient, the assistant stood on the opposite side, and the laparoscope assistant stood between the legs of the patient. Conventional four-hole laparoscopy was performed. The upper or lower edge of the umbilicus was selected as the first endoscopic hole, where a 10-12 mm trocar was placed. The second hole was located under the xiphoid process or the costal margin of the midline of the right clavicle, and a 5-mm trocar was placed. The right side of the patient's umbilicus was selected as the third hole, and a 12-mm trocar was placed. The fourth hole (assistant operation hole) was located under the left costal margin, and a 5-mm trocar was placed. An ultrasonic scalpel was used to isolate the stomach omentum layer-by-layer against the gastric wall up to the upper splenic pole and gastric vasa brevia. The upper splenic pole was severed if it was easily separated. The splenic artery could be separated and ligated if the pulse was obvious at the superior border of the pancreas, but a forcible separation was not necessary if it was inconvenient to be exposed. The splenocolic ligament and posterior peritoneal connective tissue attached to the spleen at the lower pole were dissociated, and the splenic pedicle tissue was thinned as far as possible. Endo-GIA, a 3.5-mm thick and 6-cm long endoscopic linear stapler, was used to sever the splenic pedicle. After splenectomy, dissection of the varicose vessels around the cardia-esophagus area was performed, and the esophageal branches of the coronary vessels and gastric branches were clamped or separated. After devascularization, the spleen was put into the retrieval bag, crushed, and removed piece by piece through the abdominal wall using the 12-mm trocar. After examination of the wound and achieving proper hemostasis, a drainage tube was placed in the splenic fossa to lead out from the abdominal wall, and the trocar incision was closed.

Patients in the RG underwent OS. An oblique incision under the costal margin was made in the abdomen, the artery was ligated if necessary, and the splenic pedicle vessels were cut off to complete the splenectomy. This was followed by azygo-portal disconnection. After observation and confirmation of no active bleeding, the abdomen was closed, and the operation was completed.

Detection indicators

Clinical efficacy: The clinical efficacy was classified as follows: Marked response: Markedly improved liver function and significantly relieved clinical symptoms; Response: Improved liver function and relieved clinical symptoms; Non-response: Barely improved or even deteriorated liver function with no improvement in the clinical symptoms; The overall response rate (ORR) was the percentage of the sum of marked response and response patients from the total number of cases.

Surgical indicators: We mainly observed and recorded the operative time (OT) and intraoperative bleeding volume of the two groups.

Safety: The incidence rates of postoperative abdominal hemorrhage, ascitic fluid infection, eating disorders, liver dysfunction, and perioperative death were observed and recorded.

Hepatic hemodynamics: Color Doppler ultrasound was used to measure the diameter, velocity, and flow volume of the portal vein system in the two groups before and 2 wk after the operation.

Liver function: Fasting venous blood (4 mL) was collected from each patient of both groups before and 2 wk after the operation. The serum was collected after centrifugation to quantify the alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBil) using an automatic biochemical analyzer.

Statistical analyses

The data in this study were processed using SPSS, version 24.0 (SPSS Inc., Chicago, IL, United States). Perioperative indicators, liver function indicators, portal system hemodynamics, and other measurement data are expressed as means ± SD; the inter-group comparison was conducted using an independent sample *t*-test. Count data, such as curative effects and postoperative complications, are expressed as numbers (percentages); these data were analyzed using a chi-square test. *P* values < 0.05 were considered statistically significant.

Table 1 Baseline data, *n* (%)

Categories	Observation group (*n* = 100)	Reference group (*n* = 99)	χ^2	*P* value
Sex			0.258	0.612
Male	54 (54.00)	57 (57.58)		
Female	46 (46.00)	42 (42.42)		
Age	49.53 ± 9.14	49.23 ± 9.84	0.223	0.824
Child-Pugh score			0.041	0.840
Class A	72 (72.00)	70 (70.71)		
Class B	28 (28.00)	29 (29.29)		
Place of residence			1.644	0.200
Rural	26 (26.00)	34 (34.34)		
Urban	74 (74.00)	65 (65.66)		
Educational level			1.537	0.215
Senior high school or above	45 (45.00)	36 (36.36)		
Below high school	55 (55.00)	63 (63.64)		

RESULTS

Baseline data

The RG and OG were similar with respect to the sex, age, Child-Pugh score, place of residence, and educational level of the participants ($P > 0.05$; Table 1).

Clinical efficacy of TLS for PH

Based on the statistical analysis of the number of marked response, response, and non-response cases in the two groups, the ORR of the RG and OG was 85.86% and 90.00%, respectively, with no statistically significant difference between them ($P > 0.05$; Table 2).

Surgical indexes of TLS for PH

We statistically analyzed the OT and intraoperative bleeding volumes of the two groups. The mean OT and intraoperative bleeding volume were 3.6 ± 2.1 h and 251.9 ± 31.6 mL in the OG and 3.1 ± 2.1 h and 353.3 ± 34.7 mL in the RG, respectively. Longer OT and lesser intraoperative bleeding volume were observed in the OG than in the RG, with a statistically significant difference ($P < 0.05$; Figure 1).

Safety of TLS for PH

The number of cases of intraperitoneal hemorrhage, ascitic fluid infection, eating disorders, liver insufficiency, and perioperative death in the two groups was recorded. The main complications in the OG were ascitic fluid infection (3.00%), followed by intraperitoneal hemorrhage (2.00%), eating disorders (1.00%), and liver insufficiency (1.00%). The major complications in the RG were ascitic fluid infection (4.04%), followed by intraperitoneal hemorrhage (3.03%), eating disorders (2.02%), liver insufficiency (1.01%), and perioperative death (1.01%). The incidence of postoperative complications did not differ significantly between the OG and RG (11.11% *vs* 7.00%, $P > 0.05$; Table 3).

Influence of TLS on the hepatic hemodynamics of patients with PH

The hemodynamic indexes of the portal vein system, such as blood vessel diameter, blood flow velocity and blood flow volume [blood flow volume = 60 × portal vein velocity × π × (1/2 portal vein diameter)^2], were recorded for both the groups.

In the OG, the average blood vessel diameters, blood flow velocities, and blood flow volumes before and after surgery were 12.4 ± 3.2 mm and 11.2 ± 3.0 mm, 11.6 ± 2.5 cm/s and 10.2 ± 2.2 cm/s, and 915.8 ± 519.1 mL/min and 648.5 ± 370.5 mL/min, respectively.

In the RG, the average blood vessel diameters, blood flow velocities, and blood flow volumes before and after surgery were 12.2 ± 2.9 mm and 11.4 ± 3.2 mm, 11.2 ± 2.1 cm/s and 10.3 ± 2.4 cm/s, and 848.3 ± 454.7 mL/min and 685.4 ± 408.3 mL/min, respectively.

There were no significant inter-group or intra-group differences in the blood vessel diameters before and after surgery ($P > 0.05$). The postoperative blood flow velocities and volumes in both groups decreased significantly when compared with the preoperative values ($P < 0.05$), but without a significant difference between the groups ($P > 0.05$; Figure 2).

Table 2 Clinical efficacy of total laparoscopic splenectomy for portal hypertension, *n* (%)

Categories	Observation group (*n* = 100)	Reference group (*n* = 99)	χ^2	*P* value
Marked response	39 (39.00)	35 (35.35)	-	-
Response	51 (51.00)	50 (50.50)	-	-
Non-response	10 (10.00)	14 (14.14)	-	-
Overall response rate	90 (90.00)	85 (85.86)	0.805	0.370

Table 3 Safety of total laparoscopic splenectomy for portal hypertension, *n* (%)

Categories	Observation group (*n* = 100)	Reference group (*n* = 99)	χ^2	*P* value
Intraperitoneal hemorrhage	2 (2.00)	3 (3.03)	-	-
Ascitic fluid infection	3 (3.00)	4 (4.04)	-	-
Eating disorders	1 (1.00)	2 (2.02)	-	-
Hepatic insufficiency	1 (1.00)	1 (1.01)	-	-
Perioperative death	0 (0.00)	1 (1.01)	-	-
Total incidence	7 (7.00)	11 (11.11)	1.022	0.312

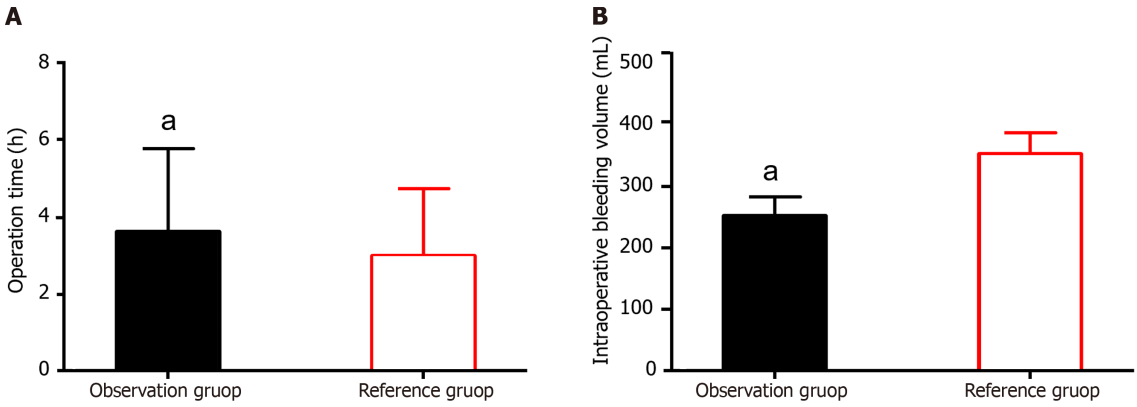

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Figure 1 Surgical indicators of total laparoscopic splenectomy for portal hypertension. A: Operation time of reference and observation groups; B: Intraoperative bleeding volume in reference and observation groups. [a]*P* < 0.05 *vs* reference group.

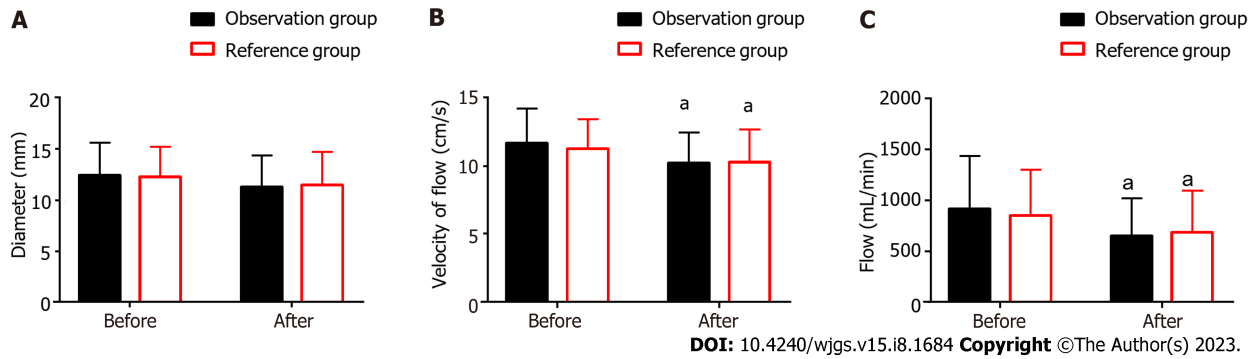

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Figure 2 Influence of total laparoscopic splenectomy on hepatic hemodynamics in patients with portal hypertension. A: Blood flow diameter of reference and observation groups; B: The blood velocity of reference and observation groups; C: The blood flow (volume) of reference and observation groups. [a]*P* < 0.05 *vs* before surgery.

Influence of TLS on the liver function of patients with PH

The liver function indexes, such as ALT, AST, and TBil, were recorded (Figure 3). In the OG, the pre- and postoperative ALT levels were 36.0 ± 22.5 U/L and 40.8 ± 22.5 U/L, respectively; AST levels were 38.3 ± 20.2 U/L and 39.6 ± 20.2 U/L, respectively; and TBil levels were 26.6 ± 20.0 U/L and 28.9 ± 18.9 U/L, respectively.

In the RG, the pre- and postoperative ALT levels were 38.7 ± 25.4 U/L and 39.1 ± 25.1 U/L, respectively; AST levels were 39.3 ± 23.9 U/L and 40.0 ± 23.1 U/L, respectively; and TBil levels were 25.7 ± 19.4 U/L and 27.5 ± 16.7 U/L, respectively.

The data revealed no evident inter-group or intra-group differences before and after surgery in the ALT, AST, and TBil levels ($P > 0.05$).

DISCUSSION

The most common clinical manifestations of PH are hypersplenism and gastric varices, and it accounts for 24%-80% of the cases. The mortality rate is up to 40% within 1 year after the clinical manifestations worsen[11,12]. Therefore, the debate regarding the best treatment for PH has been ongoing worldwide but remains controversial[13]. It has been suggested previously that conventional treatment and surgery for PH cannot prevent emergencies or pain and that long-acting medications offer the opportunity to improve the patient's quality of life[14]. However, some evidence suggests that this treatment may compromise hemodynamic stability[15]. Therefore, in many cases, surgery remains the mainstream treatment for PH, and splenectomy + devascularization has become one of the most effective treatments for gastroesophageal varices in patients with PH after years of development[16]. PH patients have also benefited from the advances in laparoscopic technology, which allow surgery to be performed in a less invasive manner[17]. However, based on the relevant literature, information on hepatic hemodynamics and liver function after TLS + devascularization is lacking. Therefore, we conducted a retrospective study to contribute to the existing knowledge on the clinical treatment of PH.

In our study, the ORR of the treatment did not differ significantly between the OG and RG (90.00% *vs* 85.86%). This indicates that TLS + devascularization had a comparable therapeutic effect as that of OS, which corroborated the research results of Lin *et al*[18] on the laparoscopic application in PH patients. The approach sequence, layout of the trocar, and prediction of surgical risks pre- and postoperatively are important factors affecting the surgical indexes. According to the statistical analysis of the operation indexes, the OT was significantly prolonged in the OG, and despite the significantly lesser intraoperative bleeding volume, the risk of conversion to laparotomy due to bleeding remains. Another study reported that the laparoscopic group presented significantly less blood loss and a short postoperative hospital stay[19]. Moreover, TLS + devascularization is a minimally invasive procedure, which ensures the therapeutic effect while speeding up the postoperative recovery of the patients. In terms of safety, we compared the incidence of intraperitoneal hemorrhage, ascitic fluid infection, eating disorders, liver insufficiency, and perioperative death between the two groups. The results showed no statistical difference in the total complication rate between the RG and OG (11.11% *vs* 7.00%), suggesting that the application of TLS + devascularization does not increase the probability of perioperative complications in PH patients. Chen *et al*'s comparative study on laparoscopic splenectomy plus selective pericardial devascularization (LSSD) and OS showed that laparoscopic splenectomy combined with selective pericardial revascularization could significantly reduce the probability of complications in patients[20]. This has some implications for our study and the reduction of postoperative complications in PH patients. We assessed three hepatic hemodynamic indexes of the patients. Previous studies have shown that abnormally increased blood vessel diameter, velocity, and flow volume of the portal venous system not only increases the risk of PH progression but also causes portal vein thrombosis, which is associated with an increased risk of adverse events such as abdominal distension, hyperthermia, and gastrointestinal bleeding[21,22]. The results showed that the postoperative blood vessel diameters of the two groups did not change significantly from the preoperative values; however, the postoperative blood flow volumes and velocities of both cohorts decreased significantly. This suggests that TLS + devascularization could significantly reduce the portal blood flow; however, whether minimally invasive or not, both procedures have similar effects on the hemodynamics and can relieve gastric varices. Deibert *et al*[23] suggested that if the positive effect on hepatic hemodynamics can be maintained long-term and in a stable manner, it could prevent patients from having further variceal bleeding, which plays an important role in the long-term survival of patients with PH. However, this study did not assess the long-term hepatic hemodynamics of the patients, which should be explored further in future research. Finally, we tested the liver function indexes of patients. The ALT, AST, and TBil are indicators of pathological changes in liver function. Abnormal elevations in these three markers are related to liver function damage. With effective intervention, the abnormal increase in these three indexes can be effectively reduced to achieve torsion and improvement of the liver tissue lesions[24]. The postoperative ALT, AST, and TBil values in the OG did not differ statistically from the preoperative values. Similarly, no significant differences were observed between the OG and RG after surgery, indicating that TLS + devascularization had a limited effect on liver function recovery in PH patients when compared with OS. Thus, based on our research, we highly recommend performing TLS + devascularization in the following patient populations: (1) Patients with a poor clinical response after treatment with drugs and endoscopy, with poorly controlled clinical symptoms such as variceal bleeding, or at a high risk of variceal bleeding; (2) Patients with obvious abdominal distension that is indicative of compression of splenomegaly on the abdominal organs, with significantly reduced quality of life; and (3) Patients with severe hypersplenism that affects other treatment indications

Nevertheless, the decision on surgical interventions should be made considering both the specific medical conditions and the patient's needs.

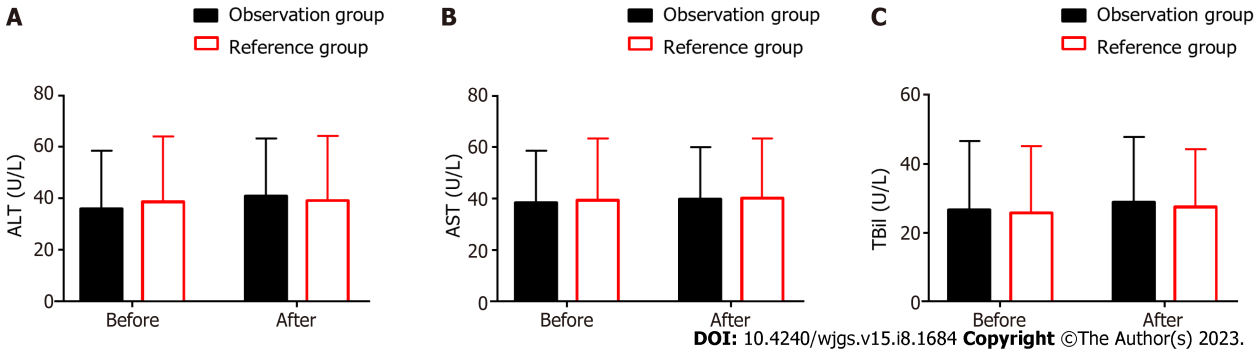

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Figure 3 Influence of total laparoscopic splenectomy on liver function in patients with portal hypertension. A: Alanine aminotransferase in observation and reference groups; B: Aspartate aminotransferase in observation and reference groups; C: Total bilirubin in observation and reference groups. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBil: Total bilirubin.

CONCLUSION

This study confirms that TLS + devascularization in PH patients has the same clinical effect as that of OS, despite having longer OT and lesser intraoperative bleeding volume. In the future, the development of surgical methods should be the goal to further enrich and promote the treatment of PH. Meanwhile, the long-term examinations of liver function and hepatic hemodynamics of postoperative patients in future studies are warranted to understand the long-term effects of these two surgical modalities on them.

ARTICLE HIGHLIGHTS

Research background

In addition to the resulting adverse effects on portal blood entering the liver that lead to decreased liver function in patients, portal hypertension (PH) can also induce liver hemodynamic changes that are closely related to many complications, warranting more clinical attention to this disease.

Research motivation

To help people gain a better understanding of the clinical effect of total laparoscopic splenectomy (TLS) in the treatment of PH.

Research objectives

The clinical effect of TLS on PH and its effect on liver hemodynamics and liver function are analyzed through case discussion and literature review.

Research methods

The clinical efficacy, surgical indexes, safety, liver hemodynamics, and liver function were compared between the observation group (n = 100) receiving TLS and the reference group (n = 99) receiving open splenectomy.

Research results

Although the operation time was significantly longer compared with the reference group, the overall response rate was significantly higher and the intraoperative blood loss and incidence of postoperative complications were significantly lower in the observation group. The detection of liver hemodynamics and liver function revealed significantly lower liver hemodynamics (blood vessel diameter, blood flow velocity and blood flow volume) and liver function indexes in the observation group *vs* the reference group 2 wk after surgery.

Research conclusions

For the treatment of PH, TLS is significantly better than open splenectomy in clinical efficacy, reducing the risk of postoperative complications in patients and improving their liver hemodynamics and liver function.

Research perspectives

In addition to clinical efficacy, we believe that future research and exploration of PH could also focus on the influence on liver hemodynamics and liver function, so as to further screen and optimize the clinical treatment of PH and improve patient outcomes.

FOOTNOTES

Author contributions: Qi RZ and Li ZW contributed equally to this work and are co-first authors; Qi RZ and Li ZW contributed to the research design and thesis writing; Chang ZY, Liang F and Chang WH collected and analyzed the data; Qi RZ, Li ZW, Zhao WL and Pang YZ contributed to the data collection; Liang F overall supervise the study; all authors contributed to the article and approved the submitted version.

Institutional review board statement: The study was reviewed and approved by the Chinese PLA General Hospital Institutional Review Board (Approval No. 2010068D).

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: There is no conflict of interest.

Data sharing statement: No additional data are available.

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ORCID number: Rui-Zhao Qi 0000-0002-9169-9958; Zhi-Wei Li 0009-0009-2986-7138; Zheng-Yao Chang 0000-0003-2836-7862; Feng Liang 0009-0002-5879-7801.

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ORIGINAL ARTICLE

Retrospective Study

Accurate resection of hilar cholangiocarcinoma using eOrganmap 3D reconstruction and full quantization technique

Da-Peng Cui, Shuang Fan, Ying-Xue Guo, Qian-Wei Zhao, Yue-Xin Qiao, Jian-Dong Fei

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Da-Peng Cui, Shuang Fan, Ying-Xue Guo, Qian-Wei Zhao, Yue-Xin Qiao, Jian-Dong Fei, Department of Hepatobiliary Surgery, The First Affiliated Hospital of Hebei North University, Zhangjiakou 075000, Hebei Province, China

Corresponding author: Jian-Dong Fei, MM, Chief Physician, Department of Hepatobiliary Surgery, The First Affiliated Hospital of Hebei North University, No. 12 Changqing Road, Qiaoxi District, Zhangjiakou 075000, Hebei Province, China. feijiandong52@163.com

Abstract

BACKGROUND

For treatment of hilar cholangiocarcinoma (HCCA), the rate of radical resection is low and prognosis is poor, and preoperative evaluation is not sufficiently accurate. 3D visualization has the advantage of giving a stereoscopic view, which makes accurate resection of HCCA possible.

AIM

To establish precise resection of HCCA based on eOrganmap 3D reconstruction and full quantification technology.

METHODS

We retrospectively analyzed the clinical data of 73 patients who underwent HCCA surgery. All patients were assigned to two groups. The traditional group received traditional 2D imaging planning before surgery (n = 35). The eOrganmap group underwent 3D reconstruction and full quantitative technical planning before surgery (n = 38). The preoperative evaluation, anatomical classification of hilar hepatic vessels, indicators associated with surgery, postoperative complications, liver function, and stress response indexes were compared between the groups.

RESULTS

Compared with the traditional group, the amount of intraoperative blood loss in the eOrganmap group was lower, the operating time and postoperative intestinal ventilation time were shorter, and R0 resection rate and lymph node dissection number were higher (P < 0.05). The total complication rate in the eOrganmap group was 21.05% compared with 25.71% in the traditional group (P > 0.05). The levels of total bilirubin, Albumin (ALB) , aspartate transaminase, and alanine transaminase in the eOrganmap group were significantly different from those in the traditional group (intergroup effect: F = 450.400, 79.120, 95.730, and 13.240,

respectively; all $P < 0.001$). Total bilirubin, aspartate transaminase, and alanine transaminase in both groups showed a decreasing trend with time (time effect: $F = 30.270$, 17.340, and 13.380, respectively; all $P < 0.001$). There was an interaction between patient group and time (interaction effect: $F = 3.072$, 2.965, and 2.703, respectively; $P = 0.0282$, 0.032, and 0.046, respectively); ALB levels in both groups tended to increase with time (time effect: $F = 22.490$, $P < 0.001$), and there was an interaction effect between groups and time (interaction effect: $F = 4.607$, $P = 0.004$). In the eOrganmap group, there was a high correlation between the actual volume of intraoperative liver specimen resection and the volume of preoperative virtual liver resection ($t = 0.916$, $P < 0.001$).

CONCLUSION

The establishment of accurate laparoscopic resection of hilar cholangiocarcinoma based on preoperative eOrganmap 3D reconstruction and full quantization technology can make laparoscopic resection of hilar cholangiocarcinoma more accurate and safe.

Key Words: eOrganmap; 3D reconstruction; Full quantification technology; Laparoscopic surgery; Hilar cholangiocarcinoma; Precise resection

Core Tip: The surgical resection rate of hilar cholangiocarcinoma (HCCA) is low, and the overall prognosis is poor. We analyzed 73 patients who underwent HCCA surgery using traditional 2D imaging planning or eOrganmap 3D reconstruction and full quantitative technical planning before surgery. By comparing the preoperative evaluation, anatomical classification of hilar hepatic vessels, indicators associated with surgery, postoperative complications, liver function, and stress response indexes of the two groups of patients, we resolved the problem of poor treatment.

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INTRODUCTION

Hilar cholangiocarcinoma (HCCA) is a mucosal carcinoma of the common hepatic duct, the left and right hepatic ducts, or the confluence of the left and right hepatic ducts[1]. Although the global incidence of this disease is low, between 1 and 2 per 100000, it shows a significant increasing trend[2]. Radical surgery has made long-term survival and even cure possible for HCCA[3]. However, a variety of factors such as complex anatomical structures and high probability of variation of hilar bile ducts and blood vessels, invasion of tumor adjacent blood vessels, combined with obstructive jaundice, and impaired liver function limit the scope of resection and may lead to low resection rate and poor overall prognosis[4]. At present, there are modified liver dissection, associating liver partition and portal vein ligation for staged hepatectomy, and selective portal vein embolization, but a unified surgical selection strategy has not been formed. From the perspective of surgical anatomy, it is important to study the structure of hilum hepatis and find a reasonable surgical plan for treatment of HCCA. Accurate preoperative evaluation is an important basis for improving the surgical resection rate of HCCA and reducing the risk of surgical mortality[5]. At present, preoperative evaluation of HCCA mainly relies on traditional computed tomography (CT) and magnetic resonance imaging (MRI). Surgeons need to construct 3D models from 2D images in their minds according to clinical experience and anatomical knowledge, which is subjective and will affect the formulation of surgical plans. At the same time, this imaging evaluation method lacks an overall and 3D sense; therefore, it can lead to differences in image interpretation among surgeons[6]. In recent years, 3D visualization has been gradually applied in clinical practice with the advantages of stereoscopic and intuitive vision, and has shown high clinical value and application in preliminary studies on preoperative evaluation of HCCA[7]. However, its reliability still needs the support of more clinical data. In this study, we retrospectively analyzed the clinical data of 73 patients undergoing HCCA surgery in The First Affiliated Hospital of Hebei North University, to explore the application of laparoscopic precise resection of HCCA based on preoperative eOrganmap 3D reconstruction and full quantification.

MATERIALS AND METHODS

General data

We retrospectively analyzed clinical data of 73 patients undergoing HCCA surgery in The First Affiliated Hospital of Hebei North University from February 2019 to January 2022. All patients were assigned to two groups. The traditional group received 2D imaging planning before surgery ($n = 35$). The EOrganmap group underwent 3D reconstruction and

full quantitative technical planning before surgery (n = 38). This study was approved by the Medical Ethics Committee of The First Affiliated Hospital of Hebei North University.

The inclusion criteria were as follows: (1) HCCA was diagnosed by preoperative imaging such as CT and MRI, and was diagnosed by postoperative pathology[8]; (2) clear indications for surgery, generally in good condition, with no major heart and lung diseases, and could tolerate anesthesia and surgery after adequate preoperative evaluation; (3) no history of major abdominal trauma or surgery; (4) preoperative liver function assessment was Child–Pugh grade A or B; and (5) pathological data were complete and the treatment compliance was good. The exclusion criteria were: (1) Imaging data showed that the patient had disease other than HCCA; (2) abnormal liver development; (3) extensive tumor metastasis or invasion of important blood vessels; (4) liver function was not significantly improved after the treatment of protecting liver and alleviating jaundice; (5) body mass index > 32 kg/m^2; (6) switch to laparotomy; and (7) perioperative death or loss of follow-up. The clinicopathological characteristics of the two groups were similar (Table 1). The study protocol is shown in Figure 1.

Surgical methods

The eOrganmap group established preoperative eOrganmap 3D reconstruction and full quantification technology. In order to ensure the accuracy of the 3D reconstruction image, the procedure was carried out by experienced radiologists. The 320-slice spiral CT was used for scanning, the current and voltage were set to 110 mAs and 120kV, respectively, and the layer thickness was 5 mm. We input the original image data into the eOrganmap 3D reconstruction system. The system automatically sketched the contour of each layer of liver parenchyma according to its anatomical position and density, and it could be modified. 3D reconstruction of the tumor, blood vessels, bile ducts, and liver was conducted by a radiologist and a surgeon. Multislice spiral CT and 3D reconstruction image analysis were performed by a radiologist and a surgeon. The analysis included the tumor location and size, whether it invaded the bile duct at grade II or higher, whether it involved peripheral blood vessels, and whether it had lymph node or distant metastasis. The results were compared with the actual intraoperative situation and postoperative pathological results.

Surgical plan planning: Complete the surgical plan design on the computer. The surgical plan should meet the multi-dimensional R0 margin; the residual liver volume should be at least 30% greater than the standard. Ensure that the pre-reserved liver's blood flow and bile drainage are unobstructed. According to the preoperative evaluation, the surgical plan was formulated, and the patients were treated with hemihepatic resection, expanded hemicombined caudate lobectomy, extrahepatic bile duct resection, endoskeletonization of the hepatoduodenal ligament, and bile duct and jejunum Roux-en-Y anastomosis. A five-hole small incision was made to perform laparoscopic surgery, and abdominal exploration was performed for abdominal and distant lymph node metastasis. The hepatoduodenal ligament was dissected by skeletonization, and the liver on the side to be resected was fully dissociated. The pre-resection area was separated along the hepatic ischemia line and the whole specimen was resected after an appropriate blood flow blocking method was selected. Rapid cryoscopy was performed to determine whether the upper and lower resection margins reached the R0 resection level. After the trans-sectional bile duct was reconstructed, biliary anastomosis was performed with Roux-en-Y. All patients were followed up for 10 mo after surgery.

Observational indexes

For preoperative evaluation, HCCA tumor progression[9] was evaluated in two aspects: Longitudinal progression (tumor invasion along the bile duct) and vertical progression (tumor invasion through the bile duct into the adjacent portal vein and hepatic artery in the vertical direction). Bismuth–Corlette classification was used for longitudinal progression. For patients in the eOrganmap group, only the tumor and biliary system were displayed after removing other tissues in the 3D model. Longitudinal invasion information was obtained by rotating the field of vision, and the tumor and portal vein or hepatic artery were separately displayed in the 3D model to observe the relationship between the tumor and vasculature from multiple angles. For patients in the traditional group, surgeons judged the degree of longitudinal progression from the CT images, such as middle bile duct stenosis and intraluminal space occupation. The Baek classification[10] was used as the standard to evaluate the degree of hepatic artery and portal vein invasion. Grade 0 tumor invasion indicated no vascular invasion; Grade I indicated that the blood vessels were stained or moved (the tumor was adjacent to the blood vessels); Grade II indicated that the tumor had fused to the blood vessel and completely enclosed it [11]. The Couniaud method was used for bile duct anatomical classification[12], the Cheng method for portal vein classification[13], and the Michels method for hepatic artery variation classification[14].

Indicators associated with surgery: Surgical margin pathology, number of lymph nodes dissected, operating time, amount of intraoperative blood loss, postoperative intestinal ventilation time, and postoperative hospital stay. Postoperative complications included bile leakage, abdominal fluid accumulation, lung infection, postoperative liver insufficiency, and stress ulcers. Evaluation of postoperative bile leakage was based on the diagnostic criteria of the International Liver Surgery Research Group[15]. Total bilirubin (TBIL) level in the abdominal drainage tube was three times higher than in the serum on postoperative day 3. Liver function was detected preoperatively (T1), and on postoperative day 1 (T2), postoperative day 3 (T3), and postoperative day 7 (T4), and the indexes included TBIL, alanine transaminase (ALT), aspartate aminotransferase (AST), and albumin (ALB).

Stress response indexes were: Interleukin (IL)-6, cortisol (Cor), and norepinephrine (NE). For detection, 5 mL venous blood was collected, centrifuged for 10 min at 3000 rpm (Heidelge Medical Equipment, Building 3, 229 Amber Road, Shanghai International Medical Park, Pudong New Area, Shanghai), and the serum was separated and stored at -20°C for testing. ELISA was used to detect the above indicators.

For patients in the eOrganmap group, the software module was used to automatically calculate the volume of each segment of the liver, and the volume of the excised liver was measured by the drainage method after surgery, and the volume of the virtual excised liver measured by 3D reconstruction before surgery was compared with the actual volume

Table 1 Clinicopathological characteristics

Group	Sex (male/female)	Age (yr, mean ± SD)	Child–Pugh grade A/ B	Preoperative biliary drainage (yes/no)	Bismuth classification			
					II	IIIa	IIIb	IV
Traditional group (n = 35)	15/20	58.55 ± 5.13	29/6	27/8	3	14	12	6
eOrganmap group (n = 38)	14/24	57.86 ± 5.67	34/4	30/8	1	16	13	8
χ^2/t	0.275	0.544	0.675	0.035	1.338			
P value	0.600	0.588	0.411	0.852	0.720			

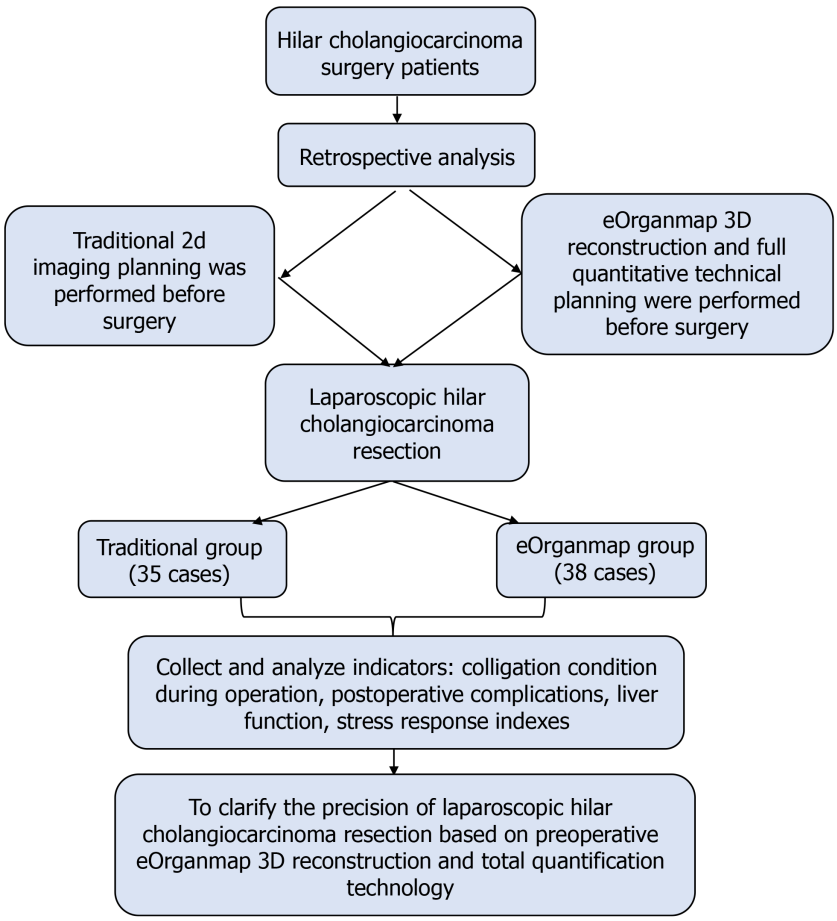

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Figure 1 Study protocol.

of the excised liver specimen during surgery. For the drainage method[16], the excised liver and tumor specimens were wrapped in cling film and placed in a container filled with water. The overflow water was collected and the volume was measured in a measuring cup, which corresponded to the specimen volume.

Statistical analysis

SPSS 22.0 was used for statistical analysis. The measurement data in line with normal distribution were expressed as mean ± SD. The t test was used for comparison of measurement data in the two groups, and repeated-measurement analysis of variance was used for comparison of data at different time points between groups. Numerical data were represented by n (%) and χ^2 test. The χ^2 value was corrected when theoretical frequency was ≥ 1 and < 5, and calculated by exact probability method when theoretical frequency < 1. Pearson correlation test was used for correlation analysis. P < 0.05 was considered statistically significant.

RESULTS

Preoperative evaluation

The accuracy of longitudinal progression was 89.47% (34/38) in the eOrganmap group compared with 82.86% (29/35) in the conventional group (χ^2 = 0.231, P = 0.631). The accuracy of vertical progression in the eOrganmap group was compared with that in the traditional group: Portal vein invasion: 94.74% (36/38) *vs* 91.43% (32/35) (χ^2 = 0.009, P = 0.924); hepatic artery invasion: 89.47% (34/38) *vs* 85.71% (30/35) (χ^2 = 0.017, P = 0.895).

Anatomical classification of hepatic portal

In the eOrganmap group, seven cases of hepatic artery anatomical variation, three of portal vein variation, and four of bile duct anatomical variation were found preoperatively. All the results of preoperative evaluation were identical with the results of intraoperative exploration, and the classification accuracy was 100%. In the traditional group, four cases of hepatic artery anatomical variation, two of portal vein variation, and three of bile duct anatomical variation were found preoperatively. The typing accuracy was 64.29% in three cases of hepatic artery variation, one of portal vein variation and one of bile duct variation. Comparison of typing accuracy between the eOrganmap and traditional groups was χ^2 = 8.027 and P = 0.005.

Indicators associated with surgery

Compared with the traditional group, the amount of intraoperative blood loss in the eOrganmap group was lower, the operating time and postoperative intestinal ventilation time were shorter, and R0 resection rate and lymph node dissection number were higher (P < 0.05) (Table 2).

Postoperative complications

The total complication rate in the eOrganmap group was 21.05%, compared with 25.71% in the traditional group (P > 0.05) (Table 3). All patients with postoperative complications were cured after conservative treatment.

Liver function

The levels of TBIL, ALB, AST, and ALT in the eOrganmap group were significantly different from those in the traditional group (intergroup effect: F = 450.40, 79.120, 95.730, and 13.240, respectively; all P < 0.001). TBIL, AST, and ALT in both groups showed a decreasing trend with time (time effect: F = 30.270, 17.340, and 13.380, respectively; all P < 0.001), and there was an interaction effect between grouping and time (F = 3.072, 2.965, and 2.703, respectively; P = 0.0282, 0.032, and 0.046, respectively); ALB levels in both groups tended to increase with time (time effect: F = 22.490, P < 0.001), and there was an interaction effect between groups and time (interaction effect: F = 4.607, P = 0.004) (Table 4 and Table 5).

Stress response indexes

The levels of IL-6, Cor and NE in the eOrganmap group and traditional group were compared before and after surgery (P > 0.05) (Table 6 and Figure 2).

Liver volume

In the eOrganmap group, the preoperative virtual resection volume was 523.45 ± 112.03 mL, and the actual intraoperative resection volume was 558.43 ± 125.41 mL. There was a high correlation between the actual intraoperative resection volume and the preoperative virtual resection volume (t = 0.916, P < 0.001).

DISCUSSION

The prevalence of HCCA is increasing annually, and surgical resection is the main treatment. Accurate preoperative evaluation of HCCA and optimal surgical planning are important for good prognosis. In recent years, digital medical technology and the concept of 3D visualization precision diagnosis and treatment have been widely promoted and practiced. The 3D visualization and 3D printed models are more intuitive and accurate than traditional 2D CT and MRI images, making it possible to achieve accurate diagnosis, preoperative evaluation, and accurate surgery.

In this study, laparoscopic precise resection of HCCA was established based on preoperative eOrganmap 3D reconstruction and full quantification technology, which achieved good results. In the evaluation of degree of tumor invasion, we found that there was no difference in the accuracy of preoperative evaluation results and postoperative actual results between the two groups. Bismuth–Corlette classification is the most commonly used clinical classification method, which divides HCCA into types I–IV according to the extent of bile duct invasion by tumor. At present, the formulation of HCCA surgical plan is mainly based on this classification. However, there is no unified standard for surgical procedures established according to this classification method, and Bismuth–Corlette classification does not take into account tumor invasion of the portal vein and hepatic artery, which also affects the choice of surgical procedure. The eOrganmap 3D reconstruction and full quantification can make up for the deficiency of traditional preoperative evaluation methods.

Our results showed that the classification accuracy of patients based on preoperative eOrganmap 3D reconstruction and full quantification technology was significantly increased. The images based on eOrganmap 3D reconstruction and full quantification technology clearly showed the anatomical variation of the hilar liver. As a 3D visualization technology,

Table 2 Colligation condition during operation

Group	Traditional group (*n* = 35)	eOrganmap group (*n* = 38)	t/χ^2	*P* value
Surgical procedure, *n* (%)			1.276	0.865
Left/right half liver + caudate lobectomy	23 (65.71)	27 (71.05)		
Extended hemihepatectomy + caudate lobectomy	6 (17.14)	7 (18.42)		
Liver trilobites + caudate lobectomy	2 (5.71)	2 (5.26)		
Mesohepatectomy + caudate lobectomy	1 (2.86)	1 (2.63)		
Other	3 (8.57)	1 (2.63)		
Amount of intraoperative blood loss (mean ± SD, mL)	772.52 ± 112.13	553.62 ± 98.56	8.875	< 0.001
Operating time (mean ± SD, min)	645.29 ± 121.14	523.19 ± 103.15	4.648	< 0.001
Surgical margin pathology, *n* (%)			4.425	0.035
R0	29 (82.86)	37 (97.37)		
R1	6 (17.14)	1 (2.63)		
No. of lymph nodes dissected (mean ± SD)	9.12 ± 2.34	10.75 ± 2.58	2.819	0.006
Postoperative intestinal ventilation time (mean ± SD, d)	3.15 ± 1.02	2.65 ± 0.71	2.447	0.017
Postoperative hospital stay (mean ± SD, d)	22.64 ± 5.26	21.15 ± 4.87	1.257	0.213

Table 3 Postoperative complications, *n* (%)

Complication	Traditional group (*n* = 35)	eOrganmap group (*n* = 38)	χ^2/Z	*P* value
Bile leakage	2 (5.71)	2 (5.26)	2.149	0.708
Abdominal fluid accumulation	3 (8.57)	3 (7.89)		
Lung infection	3 (8.57)	2 (5.26)		
Postoperative liver insufficiency	1 (2.86)	0 (0.00)		
Stress ulcers	0 (0.00)	1 (2.63)		
Total complication rate	9 (25.71)	8 (21.05)	0.222	0.638

Table 4 Total bilirubin and albumin levels (mean SD)

Time	TBIL (μmol/L)				ALB (g/L)			
	Traditional group (*n* = 35)	eOrganmap group (*n* = 38)	*t*	*P* value	Traditional group (*n* = 35)	eOrganmap group (*n* = 38)	*t*	*P* value
T1	211.26 ± 15.31	209.58 ± 16.75	0.446	0.657	27.69 ± 4.13	23.16 ± 3.83	4.863	< 0.001
T2	165.28 ± 14.37	151.22 ± 12.58	4.456	< 0.001	29.39 ± 4.02	27.24 ± 4.12	2.253	0.027
T3	148.56 ± 17.28	140.37 ± 15.47	2.137	0.036	32.25 ± 3.23	30.22 ± 3.54	2.552	0.013
T4	128.62 ± 14.39	113.28 ± 15.27	4.408	< 0.001	34.66 ± 3.15	34.85 ± 4.41	0.210	0.834

TBIL: Total bilirubin; ALB: Albumin.

eOrganmap 3D reconstruction and full quantification technology uses high-quality 2D-enhanced CT images or MR images to carry out 3D reconstruction, so as to display the lesions' location, size, scope, and their anatomical relationship with the hepatic artery and portal vein in a 3D, comprehensive, and multiangular manner. According to this information, the tumor can be judged whether it has vascular invasion[17]. At the same time, it can evaluate the anatomical variation and spatial conformation of the hepatic artery, portal vein and bile duct, accurately measure the volume of each hepatic segment, and calculate the residual liver volume[18]. Accurate assessment of variation of the hepatic artery, portal vein and hepatic vein is important to surgical planning and avoidance of accidental injury during surgery[19]. In terms of vascular reconstruction, as long as CT image layer is thin enough, 3D software can automatically generate a vascular boundary without manual drawing, which reduces the secondary error caused by manual drawing. The 3D vascular

Table 5 Aspartate transaminase and alanine transaminase levels (mean SD)

Time	AST (U/L)				ALT (U/L)			
	Traditional group (*n* = 35)	eOrganmap group (*n* = 38)	*t*	*P* value	Traditional group (*n* = 35)	eOrganmap group (*n* = 38)	*t*	*P* value
T1	112.17 ± 28.42	108.62 ± 30.23	0.516	0.608	122.15 ± 32.48	123.49 ± 31.58	0.179	0.859
T2	81.82 ± 10.67	75.38 ± 15.43	2.057	0.043	112.41 ± 24.15	101.21 ± 23.24	2.019	0.047
T3	75.25 ± 10.58	70.26 ± 6.38	2.462	0.016	108.36 ± 25.58	95.26 ± 26.31	2.154	0.035
T4	74.85 ± 9.20	56.12 ± 8.39	9.098	< 0.001	107.25 ± 28.56	82.28 ± 30.25	3.619	< 0.001

AST: Aspartate transaminase; ALT: Alanine transaminase.

Table 6 Stress response indicators (mean SD)

Indicators	Traditional group (*n* = 35)	eOrganmap group (*n* = 38)	χ^2/Z	*P* value
IL-6 (pg/mL)				
Pre-operation	50.89 ± 4.42	51.02 ± 4.16	0.130	0.897
Post-operation	61.66 ± 5.48	62.07 ± 5.14	1.243	0.742
Cor (ng/mL)				
Pre-operation	62.35 ± 5.16	61.75 ± 5.58	0.476	0.636
Post-operation	72.22 ± 4.48	71.74 ± 5.03	0.429	0.669
NE (ng/L)				
Pre-operation	161.53 ± 10.38	160.85 ± 9.47	0.293	0.771
Post-operation	177.25 ± 10.12	176.95 ± 9.13	0.133	0.894

Cor: Cortisol; IL-6: Interleukin-6; NE: Norepinephrine.

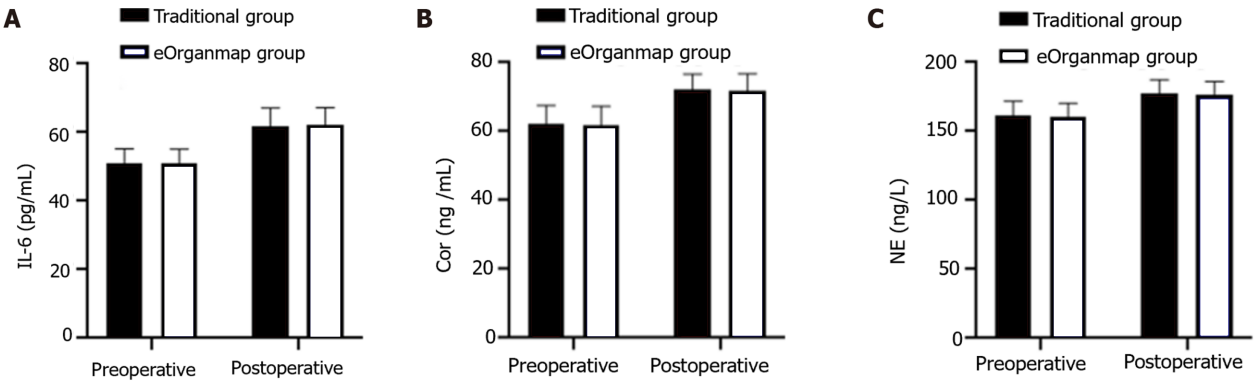

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Figure 2 Interleukin-6, cortisol and norepinephrine levels. There were 35 cases in the traditional group and 38 in the eOrganmap group. A: Interleukin-6 Levels; B: Cortisol levels; C: Norepinephrine levels. Notes: IL-6: Interleukin-6; Cor: Cortisol; NE: Norepinephrine.

images can intuitively discover the variation in blood vessels and the relationship between tumors and blood vessels, which could improve the accuracy of resectable evaluation[20]. eOrganmap 3D reconstruction and full quantification technology is a new development of CT reconstruction. This technique can register and fuse images of different scanning periods, displaying liver, hepatic artery, portal vein, hepatic vein, and bile duct singly or in combination in the same 3D model, which can be observed by several physicians simultaneously[21,22]. Through the adjustment of transparency, the internal structure can be displayed, so that the spatial deformation of the important tubular structure in the liver can be observed, and an individualized surgical plan formulated. Couinaud's anatomical segmentation can be carried out to achieve virtual surgery. Surgical information can be quantified through the built-in measurement tools of the software. The eOrganmap 3D reconstruction and full quantification technology has transformed the previous qualitative evaluation

into quantitative evaluation, so as to accurately carry out individualized preoperative evaluation and surgical planning, which is consistent with the development of precision surgery.

Preoperative reasonable planning of surgery, prior understanding of the anatomical variation of the perihilar bile duct and blood vessels, and possible intraoperative conditions could reduce the possibility of accidental intraoperative injury of the bile duct and blood vessels, thus avoiding the blindness of intraoperative exploration, and improving the safety of surgery and reducing liver dysfunction[23]. eOrganmap 3D reconstruction and full quantification technology can accurately measure liver volume, which prevents postoperative liver failure and ensures the safety of HCCA surgery. The results of this study showed that laparoscopic HCCA resection based on preoperative eOrganmap 3D reconstruction and full quantification technology reduced intraoperative blood loss, shortened operating time, and promoted postoperative intestinal ventilation, without increasing the incidence of complications and alleviating liver function damage. The results of this study also showed that the R0 resection rate and lymph node dissection number in the eOrganmap group were higher, indicating that 3D reconstruction and full quantification had some advantages in surgical margin treatment and lymph node dissection. Surgical margin and lymph node metastasis are both important factors affecting the prognosis of patients with hilar tumor[24]. Improving R0 resection rate and lymph node dissection are important measures to improve therapeutic efficacy and prognosis. Therefore, we hypothesized that laparoscopic HCCA resection based on preoperative eOrganmap 3D reconstruction and full quantification would promote efficacy and improve prognosis. There was a high correlation between the actual volume of intraoperative liver resection and the volume of preoperative virtual liver resection in the eOrganmap group. Accurate calculation of residual liver volume was important to ensure the safety of hepatectomy. Conventional CT or MRI integral measurement method was difficult to complete the measurement of segmental liver volume; however, preoperative eOrganmap 3D reconstruction and full quantification technology could accurately measure the volume of each segment of liver through a portal vein drainage algorithm, and it was consistent with the actual postoperative situation. In conclusion, accurate measurement of liver volume provides a reliable guarantee for the realization of accurate liver resection.

This study was the first to systematically carry out a new liver segmentation method based on three-dimensional reconstruction visualization and comprehensive quantification technology and the establishment of new indicators for liver reserve function evaluation and used a variety of mathematical models to analyze its feasibility and accuracy, providing a potential evaluation method for preoperative planning and postoperative risk prediction of hilar cholangiocarcinoma. On this basis, laparoscopic precise resection of HCCA was convenient for the application and promotion of this technology. However, this study also had some shortcomings. This study was retrospective and lacked prospective randomized controlled trials, so the reliability of the results could not be guaranteed. In addition, the number of cases included in this study was small, and the results may be biased, which needs to be confirmed by studies with a larger sample size.

CONCLUSION

Laparoscopic precise resection of HCCA based on preoperative eOrganmap 3D reconstruction and full quantification technology made preoperative assessment, hilar vasculature anatomical classification, and resected liver volume assessment more accurate. It improved the rate of R0 resection and the number of lymph nodes dissected. It also had a low impact on liver function and stress response. Therefore, the method is safe and worthy of wider application.

ARTICLE HIGHLIGHTS

Research background

The incidence of hilar cholangiocarcinoma (HCCA) has shown a significant upward trend, and radical surgery is an effective treatment. However, the complexity of the anatomical structure of the hilar bile duct and blood vessels, the invasion of the adjacent blood vessels of the tumor, jaundice, and the scope of hepatectomy have resulted in a low resection rate for HCCA and poor prognosis.

Research motivation

The preoperative evaluation of HCCA mainly relies on traditional computed tomography and magnetic resonance imaging. Surgeons need to construct 2D images into 3D models in their minds based on clinical experience and anatomical knowledge. Such a method is subjective and will affect the formulation of surgical plans.

Research objectives

This study aimed to establish a laparoscopic precise resection of HCCA based on preoperative eOrganmap 3D reconstruction and full quantification technology, to provide a new method for precise treatment of HCCA.

Research methods

We retrospectively analyzed the clinical data of 73 patients with HCCA who underwent surgery. Patients were divided into the traditional group (2D imaging planning before surgery) and eOrganmap group (3D reconstruction and full quantification technology planning before surgery). To compare the relevant indicators of the two groups of patients and

to further explore the difference between eOrganmap 3D reconstruction and full quantification technology and traditional 2D image planning treatment.

Research results

eOrganmap 3D reconstruction and full quantification technology planning have obvious advantages in classification accuracy, blood loss, operating time, postoperative intestinal ventilation time, R0 resection rate, number of lymph nodes dissected, total complication rate, and liver function. In the eOrganmap group, there was a high correlation between the volume of the actual resected liver specimen and the volume of the virtual resected liver specimen before the operation.

Research conclusions

Establishing laparoscopic precise resection of hilar cholangiocarcinoma based on preoperative eOrganmap 3D reconstruction and full quantification technology can make laparoscopic HCCA resection more accurate and safe.

Research perspectives

The results of this study were verified by a retrospective study with a large sample size, which enhanced the reliability of the results and contributed to the clinical promotion of eOrganmap 3D reconstruction and full quantification technology.

FOOTNOTES

Author contributions: Cui DP conceived this study, collected clinical data, interpreted the results, wrote, and revised the manuscript; Fan S, Guo YX participated in collecting data and data statistics; Zhao QW, Qiao YX, Fei JD participated in the study design and revised the manuscript; and All authors read and approved the final manuscript.

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

Informed consent statement: All patients have signed the previous consent form before the surgery. According to institutional policy, this retrospective study does not require informed consent.

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

Data sharing statement: The data set used for this study can be obtained from the corresponding author.

Country/Territory of origin: China

ORCID number: Da-Peng Cui 0009-0001-7942-8207; Shuang Fan 0000-0001-7483-4081; Ying-Xue Guo 0009-0007-4953-2752; Qian-Wei Zhao 0009-0008-7707-6392; Yue-Xin Qiao 0009-0003-3225-382X; Jian-Dong Fei 0009-0008-4024-4831.

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ORIGINAL ARTICLE

Retrospective Study

Regional differences in islet amyloid deposition in the residual pancreas with new-onset diabetes secondary to pancreatic ductal adenocarcinoma

Rui Wang, Ya Liu, Yan Liang, Li Zhou, Mao-Jia Chen, Xu-Bao Liu, Chun-Lu Tan, Yong-Hua Chen

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Rui Wang, Xu-Bao Liu, Chun-Lu Tan, Yong-Hua Chen, Division of Pancreatic Surgery, Department of General Surgery, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Ya Liu, Department of General Surgery, Chengdu Second People's Hospital, Chengdu 610041, Sichuan Province, China

Yan Liang, Li Zhou, Core Facilities, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Mao-Jia Chen, Animal Experimental Center, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Corresponding author: Yong-Hua Chen, MD, PhD, Associate Professor, Division of Pancreatic Surgery, Department of General Surgery, West China Hospital, Sichuan University, No. 37 Guoxue Alley, Wuhou District, Chengdu 610041, Sichuan Province, China.
chenyonghua2007@163.com

Abstract

BACKGROUND

Islet amyloid deposition and reduced β-cell mass are pathological hallmarks in type 2 diabetes mellitus subjects. To date, the pathological features of the islets in diabetes secondary to pancreatic ductal adenocarcinoma (PDAC) have not been specifically addressed.

AIM

To provide further insight into the relationship between islet amyloid deposition of the residual pancreas in PDAC patients and to explore whether regional differences (proximal *vs* distal residual pancreas) are associated with islet amyloid deposition.

METHODS

We retrospectively collected clinical information and pancreatic tissue removed from tumors of 45 PDAC patients, including 14 patients with normal glucose tolerance (NGT), 16 patients with prediabetes and 15 new-onset diabetes (NOD) patients diagnosed before surgery by an oral glucose tolerance test at West China

Hospital from July 2017 to June 2020. Pancreatic volume was calculated by multiplying the estimated area of pancreatic tissue on each image slice by the interval between slices based on abdominal computer tomography scans. Several sections of paraffin-embedded pancreas specimens from both the proximal and/or distal regions remote from the tumor were stained as follows: (1) Hematoxylin and eosin for general histological appearance; (2) hematoxylin and insulin for the determination of fractional β-cell area (immunohistochemistry); and (3) quadruple insulin, glucagon, thioflavin T and DAPI staining for the determination of β-cell area, α-cell area and amyloid deposits.

RESULTS

Screening for pancreatic histologic features revealed that duct obstruction with islet amyloid deposition, fibrosis and marked acinar atrophy were robust in the distal pancreatic regions but much less robust in the proximal regions, especially in the prediabetes and NOD groups. Consistent with this finding, the remnant pancreatic volume was markedly decreased in the NOD group by nearly one-half compared with that in the NGT group (37.35 ± 12.16 cm^3 *vs* 69.79 ± 18.17 cm^3, $P < 0.001$). As expected, islets that stained positive for amyloid (islet amyloid density) were found in the majority of PDAC cases. The proportion of amyloid/islet area (severity of amyloid deposition) was significantly higher in both prediabetes and NOD patients than in NGT patients ($P = 0.002$; $P < 0.0001$, respectively). We further examined the regional differences in islet amyloid deposits. Islet amyloid deposit density was robustly increased by approximately 8-fold in the distal regions compared with that in the proximal regions in the prediabetes and NOD groups (3.98% ± 3.39% *vs* 0.50% ± 0.72%, $P = 0.01$; 12.03% *vs* 1.51%, $P = 0.001$, respectively).

CONCLUSION

In conclusion, these findings suggest that robust alterations of the distal pancreas due to tumors can disturb islet function and structure with islet amyloid formation, which may be associated with the pathogenesis of NOD secondary to PDAC.

Key Words: Pancreatic ductal adenocarcinoma; Diabetes; Amyloid deposits; Islet amyloid polypeptide; Residual pancreas

Core Tip: This retrospective study investigated the relationship between islet amyloid deposition of the residual pancreas in 45 pancreatic ductal adenocarcinoma (PDAC) patients with different glycemic status and to explore whether regional differences (proximal vs. distal residual pancreas) are associated with islet amyloid deposition. Our findings suggest that robust alterations of the distal pancreas due to tumors can disturb islet function and structure with islet amyloid formation, which may be associated with the pathogenesis of new-onset diabetes secondary to PDAC.

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INTRODUCTION

Type 3c (pancreatogenic) diabetes mellitus (T3cDM) occurs due to inherited or acquired pancreatic disease or resection[1] and accounts for 5%-10% of patients with diabetes in Western countries[2]. Although it is similar to the more prevalent type 1 diabetes mellitus and type 2 diabetes mellitus (T2DM), T3cDM has a unique pattern of metabolic and hormonal characteristics and a high incidence of pancreatic tumors in the majority of patients[3]. Moreover, longstanding T2DM has been recognized as a modest risk factor for pancreatic ductal adenocarcinoma (PDAC)[4]. In turn, there is increasing evidence that PDAC is a markedly diabetogenic state and can cause new-onset diabetes (NOD)[3,5].

The formation of islet amyloid occurs by aggregation of islet amyloid polypeptide (IAPP, or amylin), which is normally cosecreted with insulin by β cells and has a regulatory effect on metabolism[6,7]. Islet amyloid deposition and reduced β-cell mass are pathological hallmarks in T2DM subjects[8,9]. Although islet amyloid deposits occur in the majority of patients with diabetes, they have also been reported in a small proportion of subjects who are apparently nondiabetic, especially in elderly individuals[10]. A recent study reported that islet amyloid deposits are not restricted to patients with T2DM alone but also occur at similar abundancies in patients with diabetes due to exocrine pancreatic disorders[11]. In addition, in patients with diabetes secondary to PDAC, insulin secretion is often diminished despite the presence of insulin resistance[12]. Thus, the etiologies and pathophysiological hallmarks of T2DM and diabetes secondary to PDAC appear to be largely different from each other.

To date, the pathological features of the islets in diabetes secondary to PDAC have not been specifically addressed. In the present study, we sought to provide further insight into the relationship between islet amyloid deposition in the residual pancreas in PDAC patients and hyperglycemia and to explore, for the first time, whether regional differences (proximal vs. distal residual pancreas) are associated with islet amyloid deposition and/or reduced β-cell area.

MATERIALS AND METHODS

Subjects

In the present study, we retrospectively collected pancreatic tissue from 45 PDAC patients, including 14 patients with normal glucose tolerance (NGT), 16 patients with prediabetes and 15 NOD patients diagnosed before surgery by oral glucose tolerance test (OGTT)[13] at West China Hospital from July 2017 to June 2020. Subjects were excluded if the patients' history indicated a diagnosis of DM before the diagnosis of PDAC. A 2 h OGTT was performed on the day before the operation. After an overnight fast of at least 8 h, a 75-g OGTT was performed in all subjects at 8:00 AM. Blood samples were drawn at baseline and 120 min as collection information of fasting plasma glucose (FPG) and 2 h plasma glucose. Diabetes and prediabetes were diagnosed and classified based on glucose tolerance according to World Health Organization (WHO) recommendations[13]. Accordingly, individuals were classified as normoglycemia (FPG < 6.1 mmol/L and 2 h plasma glucose < 7.8 mmol/L), prediabetes (FPG = 6.1-6.9 mmol/L and/or 2 h plasma glucose = 7.8-11 mmol/L) or diabetes (FPG ≥ 7.0 mmol/L and/or 2 h plasma glucose ≥ 11.1 mmol/L). The study was approved by the Biomedical Research Ethics Committee of West China Hospital, Sichuan University (2014No.37). Informed consent was acquired from all individual participants and/or guardians included in the study.

Determination of remnant pancreatic volume

To determine the remnant pancreatic volume of the PDAC patients, abdominal computed tomography scans were analyzed as described in our previous study. Using all slices involving pancreatic tissue, the pancreatic tissue contours were annotated by freehand to generate the area of the pancreas for each slice. In the next step, the estimated area of pancreatic tissue on each image slice was multiplied by the interval between slices to derive the volume of the entire pancreas.

Tissue preparation and histological assessments

Specimens were routinely sampled from both the head and distal regions adjacent to the tumor site and fixed in 10% buffered formalin. Only tumor-distant tissue (at least 0.5 cm distant from the tumor margin) was analyzed. Several consecutive 4 mm thick sections of paraffin-embedded pancreas specimens from both the proximal and/or distal regions remote from the tumor were stained as follows[11,14]: (1) Hematoxylin and eosin for general histological appearance; (2) hematoxylin and insulin for the determination of fractional β-cell area (immunohistochemistry); and (3) quadruple insulin, glucagon, thioflavin T and DAPI staining for the determination of β-cell area, α-cell area and amyloid deposits (Thioflavin T#T1892-25G and DAPI#28718-90-3, Sigma; insulin#EM80714 and glucagon#ET1702-20; Huabio). Together with conventional microscopic observations, morphometric analysis of the islet and islet endocrine cells was conducted on immunostained sections.

Image acquisition and analysis

Quadruple-stained tissue slices were scanned with a laser-scanning confocal microscope, and images were acquired with NIS-Elements Viewer software (Nikon, Japan). The extent of islet amyloid deposits was expressed as the average percentage of amyloid-positive area relative to total islet area[11]. As in previous studies in the field of β-cell research[11,15], one tissue section was examined per patient. Quadruple-stained tissue slices were imaged at 200-fold magnification, and 20 islets larger than four cells were studied in detail from each individual. The ratio of α- to β-cell area (α/β) was digitally measured using NIS-Elements Viewer software (Nikon, Japan) as previously reported[16]. Our primary outcome was a comparison of the islet amyloid deposition of the proximal and distal regions of the residual pancreas in patients with NOD secondary to PDAC.

Statistical analysis

All the data were analyzed by SPSS version 26.0 (IBM, New York, NY, United States). Data are presented as frequencies for categorical variables and mean ± SD for continuous variables. Differences between groups were analyzed using the Wilcoxon signed-rank test or independent samples *t* test for continuous data and Pearson's chi-square test for categorical data. A two-sided *P* value less than 0.05 indicated a statistically significant difference.

RESULTS

Clinical data

As shown in Table 1, the major clinical profiles were comparable among the three groups. The average body mass index (BMI) and age were comparable among all groups. No statistically significant differences were detected in the plasma lipid, serum creatinine and CA19-9 concentrations among all groups. The surgical method and the TNM stage were

Table 1 Clinical summary and islet amyloid deposits of investigated subjects

Parameter	Normal glucose tolerance (*n* = 14)	Prediabetes (*n* = 16)	Diabetes (*n* = 15)
Sex (female/male)	7/7	4/12	8/7
Age, yr	59.86 ± 12.01	61.36 ± 10.56	63.13 ± 11.34
Body-mass-index, kg/m^2	22.23 ± 2.44	21.76 ± 2.55	22.43 ± 3.44
Fasting glucose, mmol/L	5.02 ± 0.39	5.48 ± 0.83	7.57 ± 1.93[e]
2 h glucose (OGTT), mmol/L	6.41 ± 0.81	9.12 ± 1.16[c]	15.84 ± 4.08[f]
HbA1c, %	5.33 ± 0.73	5.88 ± 0.59	7.42 ± 1.66[e]
CA19-9	247.53 ± 338.37	412.15 ± 391.46	492.39 ± 441.24
Serum creatinine	62.21 ± 11.17	67.75 ± 15.16	64.80 ± 19.59
Triglycerides	1.23 ± 0.56	1.22 ± 0.45	1.97 ± 1.68
Cholesterol	4.67 ± 2.51	4.29 ± 1.19	4.34 ± 1.30
High density lipoprotein	1.21 ± 0.50	1.21 ± 0.35	0.93 ± 0.56
Low-density lipoprotein	2.26 ± 0.52	2.56 ± 0.98	2.08 ± 0.83
Operation			
Pancreaticoduodenectomy	10	8	9
Distal pancreas resection	3	8	6
Total pancreatectomy	1	0	0
TNM stage			
IA and IB	5	8	6
IIA	2	1	2
IIB	7	4	5
III	0	3	2
Gross tumor volume (cm^3)	15.59 ± 12.54	12.35 ± 11.07	13.75 ± 10.15
Remnant pancreatic volume (cm^3)	69.79 ± 18.17	51.99 ± 15.63[b]	37.35 ± 12.16[d]
Islet amyloid density, %	0.27 ± 0.40	3.63 ± 3.17[b]	10.45 ± 6.78[f]
Head regions[1]	0.006 ± 0.013	0.50 ± 0.72	1.51 ± 2.51
Distal regions[1]	0.37 ± 0.43[g]	3.98 ± 3.39[h]	12.03 ± 7.29[i]

[1]10 cases per group.
$P \leq 0.05$ *vs* normal glucose tolerance subjects.
[b]$P \leq 0.01$.
[c]$P \leq 0.001$.
[d]$P \leq 0.05$ *vs* prediabetes subjects.
[e]$P \leq 0.01$.
[f]$P \leq 0.001$.
[g]$P \leq 0.05$ *vs* head regions.
[h]$P \leq 0.01$.
[i]$P \leq 0.001$.
OGTT: Oral glucose tolerance test; HbA1c: Hemoglobin A1c; CA19-9: Carbohydrate antigen 19-9; TNM: Tumor-node-metastasis.

comparable among the three groups.

Pathological features and remnant pancreatic volume

Screening for pancreatic histologic features revealed that duct obstruction with islet amyloid deposition, fibrosis and marked acinar atrophy were robust in the distal pancreatic regions but much less robust in the proximal regions, especially in the prediabetes and NOD groups (Figures 1 and 2). Consistent with this finding, the remnant pancreatic volume was markedly decreased in the NOD group by nearly one-half compared with that in the NGT group (37.35 ± 12.16 cm^3 *vs* 69.79 ± 18.17 cm^3, $P < 0.001$). The remnant pancreatic volume was decreased in the prediabetic group, and the average was smaller than that in the NGT group (51.99 ± 15.63 cm^3 *vs* 69.79 ± 18.17 cm^3, $P = 0.003$).

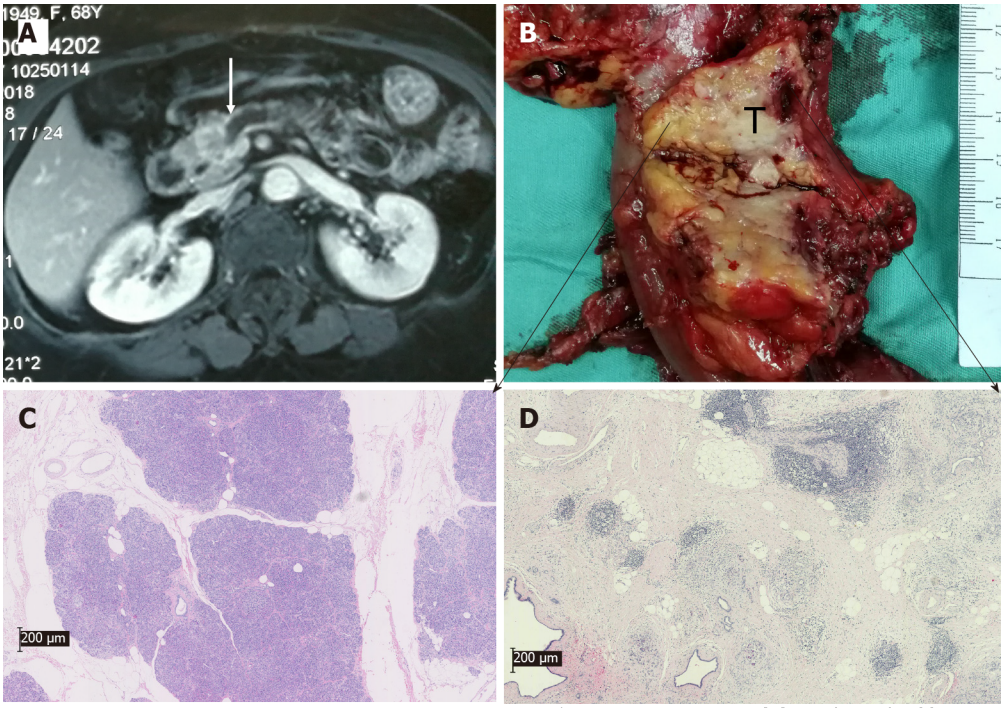

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Figure 1 Preoperative magnetic resonance imaging image and histopathologic image of the surgical resection of pancreatic specimens of pancreatic ductal adenocarcinoma patients with new-onset diabetes. A and B: Magnetic resonance imaging images (A) and images of surgical specimens (B) from pancreatic ductal adenocarcinoma patients showed pancreatic head tumor invading the main pancreatic duct, leading to dilation of the pancreatic duct and atrophy of the body and tail of the pancreas; C and D: Representative images of hematoxylin and eosin staining from the proximal (C) or distal (D) pancreas.

Islet amyloid deposits in the remnant pancreas

None of the specimens that were stained positive for amyloid were related to malignant tumors of the pancreas. As expected, islets that stained positive for amyloid (islet amyloid density) were found in the majority of prediabetes and NOD cases but not in NGT cases (93.75% and 93.33% *vs* 50%). The proportion of amyloid/islet area (severity of amyloid deposition) was significantly higher in both prediabetes and NOD patients than in NGT patients ($P = 0.002$; $P < 0.0001$, respectively). The proportion of the islet occupied by amyloid was 3.63 ± 3.17% in pre-DM and 10.45 ± 6.78% in DM ($P = 0.006$). One case (6.25%) in NOD and one case (6.67%) in pre-DM were completely free from amyloid. Among 14 cases of NGT, seven (50%) showed minimal amyloid deposition, and the other 7 cases were completely free from amyloid.

Regional differences in islet amyloid deposits

We further examined the regional differences in islet amyloid deposits (10 cases per group). The comparison of islet amyloid density in the head and distal regions is shown in Table 1. Interestingly, islet amyloid deposit density was robustly increased approximately 8-fold in the distal regions compared with the proximal regions in the prediabetes and NOD groups. In the NOD cases, the mean islet amyloid density was 12.03% in the distal regions *vs* 1.51% in the proximal regions ($P = 0.001$). Furthermore, a similar increase in islet amyloid density was observed in patients with prediabetes between the proximal and distal regions (0.50 ± 0.72% and 3.98 ± 3.39%, respectively, $P = 0.01$). In the NGT cases, there was a proportionate increase in islet amyloid density in the distal regions compared to the proximal regions (0.006 ± 0.013% and 0.37 ± 0.43%, respectively, $P = 0.026$).

DISCUSSION

In the present study, to the best of our knowledge, we characterized for the first time the regional heterogeneity of islet amyloid deposition in the remnant pancreas of patients with NOD secondary to PDAC. We also revealed the differences between the distal and proximal pancreas in NOD patients, which was characterized by ductal lesions and pancreas atrophy accompanied by islet amyloid deposition. In the NOD groups, the islet amyloid deposit density in the distal regions was approximately 8-fold higher than that in the proximal regions. Consistent with this finding, the remnant pancreatic volume was markedly decreased in the NOD group by nearly one-half compared with that in the normoglycemia groups.

The pathophysiology of diabetes is generally divided into insulin resistance and pancreatic islet dysfunction. In particular, the loss of endocrine cells due to islet amyloid deposits is an important pathological change in T2DM patients [17,18]. Intraislet capillary density was linearly correlated with the severity of islet amyloid deposits, which might be both a cause and a consequence of islet amyloid and T2DM[19]. In addition, pathological changes in the islets may be different

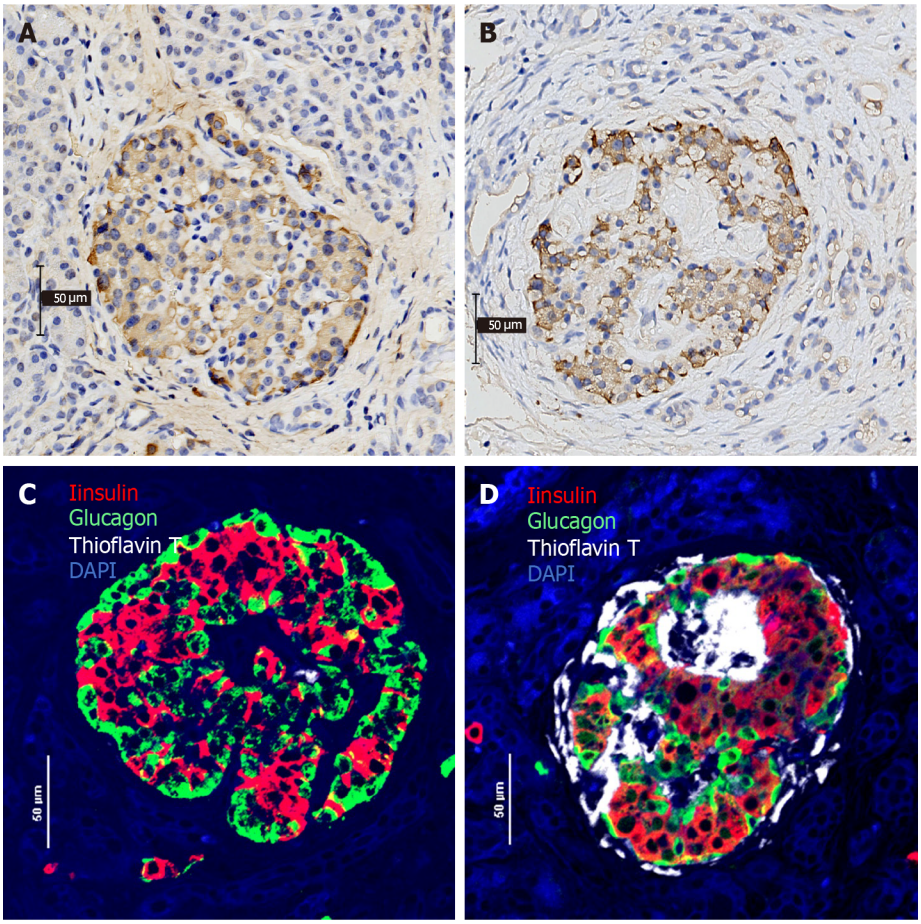

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Figure 2 Islet immunohistochemical and immunofluorescent analysis of the proximal/distal pancreas of pancreatic ductal adenocarcinoma patients with new-onset diabetes. A and B: Representative images of immunohistochemical staining for insulin from the proximal (A) or distal (B) pancreas; C and D: Representative quadruple insulin (red), glucagon (green), thioflavin T (white) and DAPI (blue) staining from the proximal (C) or distal (D) pancreas for the determination of β-cell area, α-cell area and amyloid deposits.

in each individual with T2DM and reflect each pathophysiology[8]. Amyloid aggregation and deposition have an influence on diabetic pathology and may be drivers of the pathogenesis of diabetes[20,21]. Islet amyloid was more common with severe β-cell loss and high BMI and associated with macrophage infiltration in Japanese patients with T2DM[15]. Interestingly, detection of circulating cell-free DNA, including IAPP, by sera is valuable in identifying type 2 diabetes and healthy individuals[22]. In addition, endoplasmic reticulum stress is a mechanism of IAPP-induced β-cell apoptosis that is characteristic of β-cells in humans with type 2 diabetes[23].

One of the main pathologic features of PDAC is the obstruction of the pancreatic ducts due to tumors with distal exocrine atrophy, inflammation and fibrosis. In turn, autodestruction and inflammation of exocrine acinar tissue may cause islet destruction and amyloid deposition and likely combine to suppress the ability of β-cells to exhibit normal insulin secretory dynamics in NOD, resulting in the onset of diabetes. Rivera *et al*[24] indicated that autophagy/Lysosomal degradation can defend β cells against proteotoxicity induced by oligomerization-prone human IAPP. In fact, NOD caused by PDAC is associated with proinflammatory alterations, insulin resistance, and perturbations in β-cell functions that lead to loss of glucose homeostasis[25]. Recent research has suggested that transdifferentiation and dedifferentiation are involved in the decrease in β-cell volume in patients with PDAC and that β-cell volume might change dynamically depending on the glucose metabolic state[12]. Our finding is consistent with prior research on the occurrence of amyloid deposits in both diabetes secondary to pancreatic disorders and T2DM[11]. Therefore, islet amyloid deposition may be associated with the pathogenesis of NOD secondary to PDAC.

In the human pancreas, islet cellular composition and structure are similar throughout the pancreas, and there is no difference in insulin secretion stimulated by glucose in islets isolated from different regions[26]. In diabetic cats, there was no difference in the amount of amyloid between the left limb middle segment and right limb of the pancreas[27]. However, Wang *et al*[26] revealed distinct characteristics of the human pancreas in that there was preferential loss of large islets in the head region in patients with T2DM. In the present study, the abundance of amyloid deposits in the distal pancreas, not the proximal pancreas, of PDAC patients was a novel finding, and we noted various disruptions in distal pancreas morphology, with pancreatic atrophy and massive fibrosis accompanied by amyloid deposition. Consistent with this finding, the remnant pancreatic volume was markedly decreased in the NOD group by nearly one-half compared with that in the normoglycemia groups. In one study, patients with Type 1 Diabetes had a 26% reduction in pancreatic volume within a few months after diagnosis, suggesting that pancreatic atrophy occurs before the onset of clinical disease

[28]. Together, pancreatic atrophy may be a risk factor for the development of NOD secondary to PDAC in patients.

Some limitations of the present study should be acknowledged. Most importantly, the clinical correlations cannot establish a causal relationship between amyloid deposition and NOD caused by PDAC. Furthermore, the number of pancreatic tissue specimens included in this study was relatively limited. Third, to minimize the confounding effects of concomitant T2DM, patients diagnosed before PDAC were not included in the present study.

CONCLUSION

These findings suggest that robust alterations in the distal pancreas due to tumors can disturb islet function and structure with islet amyloid formation, which may be associated with the pathogenesis of NOD secondary to PDAC.

ARTICLE HIGHLIGHTS

Research background

Islet amyloid deposition and reduced β-cell mass are pathological hallmarks in type 2 diabetes mellitus subjects.

Research motivation

To date, the pathological features of the islets in diabetes secondary to pancreatic ductal adenocarcinoma (PDAC) have not been specifically addressed.

Research objectives

This study aimed to provide further insight into the relationship between islet amyloid deposition of the residual pancreas in PDAC patients and to explore whether regional differences (proximal *vs* distal residual pancreas) are associated with islet amyloid deposition.

Research methods

This retrospectively collected pancreatic tissue removed from tumors from 45 PDAC patients, including 14 patients with normal glucose tolerance (NGT), 16 patients with prediabetes and 15 new-onset diabetes (NOD) patients. Pancreatic volume was calculated by multiplying the estimated area of pancreatic tissue on each image slice by the interval between slices based on abdominal computer tomography scans. Several sections of paraffin-embedded pancreas specimens from both the proximal and/or distal regions remote from the tumor were stained and analyzed.

Research results

Screening for pancreatic histologic features revealed that duct obstruction with islet amyloid deposition, fibrosis and marked acinar atrophy were robust in the distal pancreatic regions but much less robust in the proximal regions, especially in the prediabetes and NOD groups. Consistent with this finding, the remnant pancreatic volume was markedly decreased in the NOD group by nearly one-half compared with that in the NGT group (37.35 ± 12.16 cm^3 *vs* 69.79 ± 18.17 cm^3, $P < 0.001$). As expected, islets that stained positive for amyloid (islet amyloid density) were found in the majority of PDAC cases. The proportion of amyloid/islet area (severity of amyloid deposition) was significantly higher in both prediabetes and NOD patients than in NGT patients ($P = 0.002$; $P < 0.0001$, respectively). We further examined the regional differences in islet amyloid deposits. Islet amyloid deposit density was robustly increased by approximately 8-fold in the distal regions compared with that in the proximal regions in the prediabetes and NOD groups (3.98 ± 3.39% *vs* 0.50 ± 0.72%, $P = 0.01$; 12.03% *vs* 1.51%, $P = 0.001$, respectively).

Research conclusions

In conclusion, these findings suggest that robust alterations of the distal pancreas due to tumors can disturb islet function and structure with islet amyloid formation.

Research perspectives

Future studies to evaluate the role of islet amyloid deposition in the pathogenesis of NOD secondary to PDAC may be justified.

FOOTNOTES

Author contributions: Chen YH and Tan CL contributed equally to this work; Chen YH, Tan CL and Liu XB conceived and designed the research; Wang R, Liu Y, Liang Y, Zhou L and Chen MJ collected the data and conducted the research; Wang R, Liu Y, Liang Y, Zhou L and Chen MJ analysed and interpreted the data; Wang R and Liu Y wrote the initial paper; Chen YH and Tan CL revised the paper; all authors contributed to the article and approved the submitted version.

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Country/Territory of origin: China

ORCID number: Rui Wang 0000-0003-0829-152X; Chun-Lu Tan 0000-0002-7315-1964; Yong-Hua Chen 0000-0001-8485-0755.

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ORIGINAL ARTICLE

Retrospective Study

Risk factors and their interactive effects on severe acute pancreatitis complicated with acute gastrointestinal injury

Jian-Hui Chen, Mei-Fen Zhang, Wen-Chao Du, Yan-An Zhang

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Jian-Hui Chen, Mei-Fen Zhang, Wen-Chao Du, Yan-An Zhang, Emergency Department, Longyan First Affiliated Hospital of Fujian Medical University, Longyan 364000, Fujian Province, China

Corresponding author: Yan-An Zhang, MBBS, Professor, Emergency Department, Longyan First Affiliated Hospital of Fujian Medical University, No. 105 Jiuyibei Road, Xinluo District, Longyan 364000, Fujian Province, China. zhangyanan6870@163.com

Abstract

BACKGROUND

There are many risk factors for severe acute pancreatitis (SAP) complicated with acute gastrointestinal injury (AGI), but few reports on the interaction between these risk factors.

AIM

To analyze the risk factors for SAP complicated with AGI and their interactive effects.

METHODS

We selected 168 SAP patients admitted to our hospital between December 2019 and June 2022. They were divided into AGI group and non-AGI group according to whether AGI was present. Demographic data and laboratory test data were compared between the two groups. The risk factors for SAP with concomitant AGI were analyzed using multifactorial logistic regression, and an analysis of the interaction of the risk factors was performed.

RESULTS

The percentage of patients with multiple organ dysfunction syndrome, acute physiological and chronic health scoring system II (APACHE II) score, white blood cell count and creatinine (CRE) level was higher in the AGI group than in the non-AGI group. There was a statistically significant difference between the two groups ($P < 0.05$). Logistic regression analysis indicated that an APACHE II score > 15 and CRE > 100 μmol/L were risk factors for SAP complicating AGI. The interaction index of APACHE II score and CRE level was 3.123.

CONCLUSION

An APACHE II score > 15 and CRE level > 100 μmol/L are independent risk factors for SAP complicated with AGI, and there is a positive interaction between

them.

Key Words: Severe acute pancreatitis; Acute gastrointestinal injury; Risk factors; Interactions; Acute physiological and chronic health scoring system II; Creatinine

Core Tip: Acute gastrointestinal injury (AGI) is a common complication of severe acute pancreatitis (SAP). Patients with AGI are prone to gastrointestinal dysfunction and mucosal injury, aggravating the degree of pancreatic inflammation, causing multiple organ dysfunction and endangering patients' lives. In this study, 168 patients with SAP were divided into the AGI group and non-AGI group. The risk factors of SAP complicated with AGI were analyzed, and the interaction of these risk factors was analyzed. The study findings have guiding value for controlling the development of AGI and improving the prognosis of SAP.

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INTRODUCTION

Severe acute pancreatitis (SAP) refers to a disease in which pancreatic enzymes are activated due to a variety of reasons, resulting in a local inflammatory response. This disease is a common critical condition of the digestive system[1,2]. Statistically, the death rate due to SAP is up to 10%-30%[3], and has been on the rise in recent years, which seriously endangers the life and health of patients. Acute gastrointestinal injury (AGI) is a common complication of SAP. AGI patients have gastrointestinal dysfunction and mucosal injury, which can cause gastrointestinal motility slowing, intestinal obstruction, intestinal flora shift, impaired immune function, ulcer, gastrointestinal bleeding, *etc*., which aggravates the degree of pancreatitis, causes multiple organ dysfunction, and endangers the life of patients[4]. AGI is an important prognostic factor for SAP patients. Relevant studies have found that when AGI occurs in SAP patients, the mortality and incidence of complications are significantly increased[5]. However, there are numerous risk factors for AGI[6,7]. Therefore, examining the risk factors for AGI is of great significance for controlling the development of AGI, improving the prognosis of SAP, and taking effective intervention measures to improve the treatment of patients. However, most studies have investigated the risk factors for AGI, while reports on the interaction between risk factors are few. Therefore, the present study aimed to analyze the risk factors for AGI and determine their interactive effects on SAP to provide a rationale for clinical treatment.

MATERIALS AND METHODS

General information

A retrospective analysis of 168 patients with SAP treated in our hospital, and enrolled between December 2019 and June 2022 was conducted. Inclusion criteria were as follows: (1) According to the "Guidelines for the diagnosis and treatment of acute pancreatitis in China (2021)"[8], all patients were diagnosed by abdominal color Doppler ultrasound, CT or MRI; and (2) The age of patients ranged from 18 to 65 years. Exclusion criteria were: (1) Patients with gastrointestinal bleeding and complete intestinal obstruction; (2) Severe heart, kidney or other important organ dysfunction; and (3) Long-term use of corticosteroids or immunosuppressants. According to the AGI diagnostic criteria "European Society for the Critical Care Medicine (2012) Consensus on Acute Gastrointestinal Injury"[9], patients were divided into the AGI group (n = 64) and non-AGI group (n = 104).

Clinical data collection

Clinical data were collected from the patients. These data included gender, age, comorbidities (hypertension, diabetes, coronary heart disease), smoking history, acute physiological and chronic health scoring system II (APACHE II) score, and multiple organ dysfunction syndrome (MODS). Admission laboratory indicators included white blood cell (WBC) count in peripheral blood, hemoglobin, total bilirubin, creatinine (CRE), and serum amylase.

Statistical analysis

The SPSS 23.0 software was applied for analysis and processing. Quantitative data that conformed to a normal distribution are shown as mean ± SD, and t-tests were used for comparisons between the groups. Count data are expressed as n (%), and the χ^2 test was used for comparisons between the groups. Logistic regression was applied to analyze the

associated risk factors. The interaction of two factors was investigated using regression models. The attributable proportion of interaction (API), relative excess risk of interaction (RERI) and the synergy index (S) were calculated. $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of clinical and laboratory data between the two groups

Univariate analysis showed that the percentage of patients with MODS, APACHE II score and CRE level were higher in the AGI group than in the non-AGI group, with a significant difference between the two groups ($P < 0.05$), as shown in Table 1.

Logistic multi-factor analysis of SAP and concurrent AGI

Variables that were statistically significant in univariate analysis were included as independent variables, and the influencing factor variable assignment is shown in Table 2. The results of the multifactorial regression analysis indicated that an APACHE II score > 15 and CRE > 100 μmol/L were risk factors for complications of AGI in patients with SAP ($P < 0.05$), as shown in Table 3.

Interaction analysis of risk factors for AGI

The RERI of the interaction between the increase in APACHE II score and the increase in CRE level was 220.059, the API was 0.678%, and the S was 3.123. This indicated that there was a positive interaction between the two factors, as shown in Table 4.

Receiver operating characteristic curve analysis on the predictive value of APACHE II and creatinine

Receiver operating characteristic (ROC) curve analysis showed that the predictive value of joint detection of APACHE II and CRE was better than that of single detection ($P < 0.001$). The ROC curves of the three were significantly different ($P < 0.05$) (Figure 1).

DISCUSSION

SAP is a special type of acute pancreatitis, which is caused by biliary tract disease, overeating, and heavy drinking, which leads to the activation of pancreatic enzymes and an acute chemical inflammatory reaction of pancreatic tissue[10]. In the early stage of SAP, a large number of inflammatory mediators, cytokines and bacterial toxins are produced, which lead to hemodynamic abnormalities and damage to organs such as heart, liver, kidney and the gastrointestinal tract, and in severe cases, organ failure[11]. AGI is one of the most common complications in SAP patients. As the gastrointestinal tract is the reservoir for systemic flora, it has functions such as regulating immune and inflammatory functions. When AGI occurs, it causes intestinal flora shift, gastrointestinal ulcer, gastrointestinal nutrition disorders, *etc*., which aggravate the inflammatory response, induce multiple organ failure in patients, prolong the length of hospital stay, and increase patient mortality[12]. Wang *et al*[13] found that AGI was an independent risk factor for SAP. Therefore, active treatment of AGI to promote the recovery of gastrointestinal function is the key to alleviating SAP, reducing mortality, and improving prognosis.

The results of this study indicated that patients with SAP complicated by AGI had a significantly higher MODS ratio, leukocyte level, CRE level, and APACHE II score compared to the non-AGI group, with significant differences. Logistic regression analysis indicated that APACHE II scores > 15 and increased CRE levels were the main risk factors for complications of AGI in SAP. Targeted measures should be taken against the above factors to strengthen prevention. The gastrointestinal tract plays an important role in the human body. Various injuries, surgeries, severe infections, massive bleeding and so on can promote the release of inflammatory factors. These inflammatory factors can activate the signal transduction of nuclear factors in gastrointestinal mucosal epithelium, causing microcirculation disorders in the gastrointestinal tract resulting in impaired gastrointestinal function[14]. The findings in the present study indicate that AGI patients have higher levels of WBCs than non-AGI patients. It is suggested that the increase in these indices may be the risk factors of SAP complicated by AGI. CRE is a product of human muscle metabolism, and increased CRE will have a considerable impact on the body. When the CRE level increases, this indicates that the body's metabolism is abnormal, and a large amount of toxins and waste are accumulated, which results in disordered human functions and leads to various metabolic imbalances[15]. In addition, increased CRE level will accumulate in the heart, respiratory system, gastrointestinal system, *etc*., and will indirectly reflect glomerular and gastrointestinal system dysfunction, which will lead to gastrointestinal injury and systemic injury[16]. Jin *et al*[17] found that elevated serum CRE level was a risk factor for gastrointestinal failure, and the results of this study were consistent with these findings.

The APACHE II scoring system consists of a total score of three components: Acute physiology, age, and chronic health status. It is widely applied in the assessment of critically ill patients, and is also a commonly used scoring system to judge the severity of acute pancreatitis[18,19]. An APACHE II score > 15 indicates a poor prognosis, and patients with higher scores have severe disease[20]. Greenberg *et al*[21] showed that the higher the APACHE II score within 72 h of admission in SAP patients, the higher the death rate. The findings of the present research indicated that patients in the AGI group had higher APACHE II scores than those in the non-AGI group. It is suggested that SAP patients with AGI are more

Table 1 Comparison of clinical and laboratory data between the two groups, *n* (%)

Influencing factors	AGI group (*n* = 64)	Non-AGI group (*n* = 104)	χ^2/t	*P* value
Gender			0.464	0.496
Male	31 (48.44)	56 (53.85)		
Female	33 (51.56)	48 (4 6.15)		
Age (mean ± SD, yr)	50.16 ± 7.56	49.42 ± 8.12	0.583	0.560
Hypertension			0.168	0.682
Yes	31 (48.44)	47 (45.19)		
No	33 (51.56)	57 (54.81)		
Diabetes			0.101	0.751
Yes	33 (51.56)	51 (49.04)		
No	31 (48.44)	53 (50.96)		
Coronary heart disease			0.008	0.927
Yes	34 (53.13)	56 (53.85)		
No	30 (46.87)	48 (46.15)		
Smoking			0.059	0.809
Yes	32 (50.00)	54 (51.92)		
No	32 (50.00)	50 (48.08)		
MODS			21.263	< 0.001
Yes	43 (67.19)	32 (30.77)		
No	21 (32.81)	72 (69.23)		
APACHE II score (mean ± SD)	17.45 ± 4.74	10.79 ± 3.95	-9.836	< 0.001
Leukocytes (mean ± SD, × 10^9/L)	15.12 ± 3.03	13.87 ± 2.27	-2.834	0.006
Hemoglobin (mean ± SD, g/L)	140.87 ± 14.93	144.50 ± 15.87	1.470	0.143
Creatinine (mean ± SD, μmol/L)	115.15 ± 12.18	93.07 ± 10.22	-12.116	< 0.001
Amylase (mean ± SD, U/L)	761.43 ± 73.90	751.20 ± 70.95	-0.894	0.373
Total bilirubin (mean ± SD, μmol/L)	22.09 ± 3.68	21.78 ± 3.61	-0.529	0.597

AGI: Acute gastrointestinal injury; MODS: Multiple organ dysfunction syndrome; APACHE II: Acute physiological and chronic health scoring system II.

Table 2 Factor assignment for logistic regression analysis

Influencing factors	Assignment of factors
Presence or absence of AGI	0 = Non-AGI group, 1 = AGI group
MODS	0 = no, 1 = yes
APACHE II	≤ 15 points = 0, > 15 points = 1
Creatinine	≤ 100 μmol/L = 0, > 100 μmol/L = 1
Leukocytes	Original value input

AGI: Acute gastrointestinal injury; MODS: Multiple organ dysfunction syndrome; APACHE II: Acute physiological and chronic health scoring system II.

critically ill and have a higher risk of death. The complexity of gastrointestinal function also lies in its internal dynamic changes. Disorder and translocation of intestinal flora is another potential mechanism for the occurrence of AGI. Intestinal flora activate the immune response through the lymphatic system, leading to the occurrence and even deterioration of MODS[22]. This research found a higher percentage of patients with AGI than with non-AGI, which was similar to the findings of Laterre *et al*[23]. It is suggested that MODS is closely related to SAP complicated by AGI.

Table 3 Logistic regression analysis of severe acute pancreatitis patients with acute gastrointestinal injury

Influencing factors	B value	SE value	Wald value	*P* value	OR (95%CI)
APACHE II	1.716	0.613	7.820	0.005	5.560 (1.671-18.502)
MODS	-0.398	0.598	0.442	0.506	0.672 (0.208-2.169)
Leukocytes	0.196	0.101	3.769	0.052	1.216 (0.998-1.482)
Creatinine	3.380	0.553	37.366	< 0.001	29.365 (9.936-86.788)

MODS: Multiple organ dysfunction syndrome; APACHE II: Acute physiological and chronic health scoring system II.

Table 4 Interaction of creatinine and acute physiological and chronic health scoring system II score on acute gastrointestinal injury in severe acute pancreatitis patients

APACHE II	Creatinine	AGI group	Non-AGI group	OR	95%CI	RERI	API	S
		1	79	1.00		220.059	0.678	3.123
+		5	4	98.75	9.228-1056.778			
	+	21	12	138.25	16.998-1124.444			
+	+	37	9	0.024	0.002-0.314			

AGI: Acute gastrointestinal injury; APACHE II: Acute physiological and chronic health scoring system II; API: Attributable proportion of interaction; RERI: Relative excess risk of interaction.

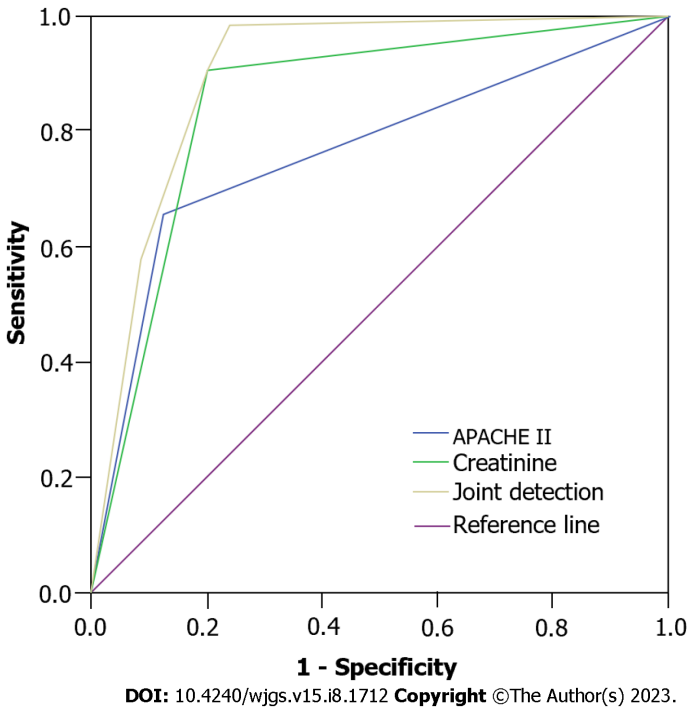

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Figure 1 Receiver operating characteristic curve analysis of acute physiological and chronic health scoring system II, creatinine and joint detection. APACHE II: Acute physiological and chronic health scoring system II.

From the interaction study of risk factors, it was found that there was a statistically positive interaction between the APACHE II score and CRE level in SAP patients with AGI. The RERI of the interaction effect between high APACHE II score and elevated CRE level was 220.059, indicating that the risk of AGI increased by 220.059 times. The API was 0.678% and S was 3.123, indicating that 0.678% of AGI in these patients was caused by the coexistence of increased APACHE II score and increased CRE level, and the coexistence of both was 3.123 times that of AGI induced by the existence of either factor alone. Therefore, APACHE II score > 15 and CRE level > 100 μmol/L can lead to AGI in SAP patients. The changes in gastrointestinal function should be closely monitored, and timely and effective treatment should be provided to control

the development of the patient's disease, reduce the body's inflammatory response, and avoid the involvement of other organs.

The present research was conducted to investigate the risk factors of SAP complicated by AGI and analyze the interaction between these risk factors. In this way, measures to prevent the incidence of AGI were implemented to improve the prognostic outcome of patients with SAP. However, the sample size in this study was limited, and the results may be biased to some extent. It is necessary to expand the sample and conduct a multicenter study to further confirm the risk factors of AGI in SAP patients.

CONCLUSION

An APACHE II score > 15 and CRE level > 100 μmol/L are both independent risk factors for SAP complicated with AGI, and there is a positive interaction between them. Therefore, in SAP patients with AGI, attention should be paid to managing the risk factors of AGI in SAP patients, and timely and effective interventions should be carried out to reduce the incidence of AGI and to improve the prognosis of SAP patients.

ARTICLE HIGHLIGHTS

Research background

Acute gastrointestinal injury (AGI) patients are prone to gastrointestinal dysfunction and mucosal injury, aggravating the degree of pancreatic inflammation and causing multiple organ dysfunction.

Research motivation

Examining the risk factors of AGI is of great significance for controlling the development of AGI and improving the prognosis of severe acute pancreatitis (SAP).

Research objectives

The purpose of this study was to analyze the risk factors of SAP complicated by AGI and their interaction.

Research methods

This study retrospectively analyzed SAP patients admitted to our hospital and divided them into the AGI group and non-AGI group to analyze the risk factors of SAP complicated with AGI and their interaction.

Research results

An acute physiological and chronic health scoring system II score > 15 and creatinine level > 100 μmol/L were independent risk factors for SAP complicated with AGI, and there was a positive interaction between them.

Research conclusions

When risk factors of SAP complicated with AGI are found, timely effective measures should be taken to improve the prognosis of SAP patients.

Research perspectives

In SAP patients with AGI, attention should be paid to managing the risk factors of AGI in SAP patients, and timely and effective interventions should be carried out to reduce the incidence of AGI and to improve the prognosis of SAP patients.

FOOTNOTES

Author contributions: Chen JH designed and performed the research and wrote the paper; Zhang YA designed the research and supervised the report; Zhang MF designed the research and contributed to the analysis; Du WC supervised the report.

Institutional review board statement: This study was approved by the Medical Ethics Committee of Longyan First Affiliated Hospital of Fujian Medical University (Approved No. LYREC2023-k016-01).

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ORCID number: Jian-Hui Chen 0009-0002-3734-7676; Mei-Fen Zhang 0009-0001-4005-7453; Wen-Chao Du 0009-0006-0826-8409; Yan-An Zhang 0009-0003-2341-6789.

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ORIGINAL ARTICLE

Retrospective Study

Effects of ultrasound monitoring of gastric residual volume on feeding complications, caloric intake and prognosis of patients with severe mechanical ventilation

Xiao-Yan Xu, Hui-Ping Xue, Ming-Jun Yuan, You-Rong Jin, Chun-Xia Huang

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Xiao-Yan Xu, Department of Emergency Medicine, The Affiliated Hospital of Nantong University, Nantong 226001, Jiangsu Province, China

Hui-Ping Xue, Ming-Jun Yuan, You-Rong Jin, Emergency Medical Intensive Care Unit, Nantong University Affiliated Hospital, Nantong 226001, Jiangsu Province, China

Chun-Xia Huang, Department of Emergency Outpatient, Nantong University Affiliated Hospital, Nantong 226001, Jiangsu Province, China

Corresponding author: Chun-Xia Huang, RN, Associate Chief Nurse, Department of Emergency Outpatient, Nantong University Affiliated Hospital, No. 20 Xisi Road, Chongchuan District, Nantong 226001, Jiangsu Province, China. 1289811956@qq.com

Abstract

BACKGROUND

Monitoring of gastric residual is an important approach for assessing gastric emptying in patients with mechanical ventilation. By monitoring gastric contents, the enteral nutrition scheme can be adjusted in time to ensure feeding safety.

AIM

To investigate the effects of ultrasound monitoring on the incidence of feeding complications, daily caloric intake and prognosis of patients with severe mechanical ventilation. To analyze the clinical significance of ultrasound monitoring of gastric residual volume (GRV) up to 250 mL to provide a theoretical basis for clinical practice.

METHODS

Patients admitted to the department of emergency medicine of the Affiliated Hospital of Nantong University from January 2018 to June 2022 who received invasive mechanical ventilation and continuous enteral nutrition support within 24-48 h after admission were enrolled in this study. Medical records for patients within 7 d of hospitalization were retrospectively analyzed to compare the incidence of feeding complications, daily caloric intake and clinical prognosis between patients with gastric residual ≥ 250 mL and < 250 mL, as monitored by ultrasound on the third day.

RESULTS

A total of 513 patients were enrolled in this study. Incidences of abdominal distension, diarrhea, and vomiting in the < 250 mL and ≥ 250 mL groups were: 18.4% *vs* 21.0%, 23.9% *vs* 32.3% and 4.0% *vs* 6.5%, respectively; mortality rates were 20.8% *vs* 22.65%; mechanical ventilation durations were 18.30 d *vs* 17.56 d while lengths of stay in the intensive care units (ICU) were 19.87 d *vs* 19.19 ± 5.19 d. Differences in the above factors between groups were not significant. Gastric residual ≥ 250 mL was not an independent risk factor for death and prolonged ICU stay. However, target feeding time of patients in the ≥ 250 mL group was longer than that of patients in the ≥ 250 mL group, and caloric intake (22.0, 23.6, 24.8, 25.3 kcal/kg/d) for patients in the ≥ 250 mL group from the 4th day to the 7th day of hospitalization was lower than that of patients in the ≥ 250 mL group (23.2, 24.8, 25.7, 25.8 kcal/kg/d). On the 4th day (Z = 4.324, P = 0.013), on the 5th day (Z = 3.376, P = 0.033), while on the 6th day (Z = 3.098, P = 0.04), the differences were statistically significant.

CONCLUSION

The use of ultrasound to monitor GRV and undertaking clinical interventions when the monitoring value is ≥ 250 mL has no significant effects on incidences of feeding complications and clinical prognostic outcomes, however, it significantly prolongs the time to reach target feeding, reduces the daily intake of calories during ICU hospitalization, and increases the risk of insufficient nutrition of patients. The accuracy and necessity of monitoring gastric remnants and monitoring frequencies should be investigated further.

Key Words: Gastric residual monitoring; Mechanical ventilation; Vomit; Caloric intake; Prognosis

Core Tip: Gastric residue is only one of the indicators of feeding intolerance and cannot predict whether a patient will experience feeding intolerance. It is not recommended for evaluating the patient's feeding tolerance or prognosis solely based on gastric residue.

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INTRODUCTION

Patients with invasive mechanical ventilation in intensive care units (ICU) are in a high catabolic state and are prone to malnutrition, resulting in intestinal ischemia and reperfusion injury and affecting intestinal immune functions[1]. As one of the important therapeutic nutritional support interventions for severe patients, enteral nutrition can maintain the normal physiological functions of the gastrointestinal tract, prevent intestinal villus atrophy, and guarantee intestinal barrier functions[2]. The nutrition guidelines recommend that if there is no contraindication, enteral nutrition support can be started at 24-48 h after ICU admission[3]. To reduce the mortality rates, infection incidences, as well as hospitalization time and improve the prognostic outcomes of patients, early implementation of enteral nutrition should conform to the physiological needs of the gastrointestinal tract of patients[4]. However, for ICU patients, their gastrointestinal functions are impaired, and there are feeding intolerance (FI) risks during enteral nutrition implementation. There is no unified standard definition for FI. Currently, the definitions proposed by the European Society of Intensive Care Medicine in 2012 [5] are widely used, including gastrointestinal adverse reactions, low rate of energy requirements and termination of enteral nutrition. Incidence of FI during early enteral nutrition have been reported to be between 30.5%-67.5%. Therefore, timely and accurate evaluation of gastrointestinal functions is particularly important. Monitoring of gastric residual is an important approach for evaluating gastric emptying of patients with mechanical ventilation. By monitoring gastric contents, the enteral nutrition scheme can be adjusted in time to ensure feeding safety[6,7]. Various methods for monitoring gastric residual volume (GRV) in clinics have been proposed. The most traditional and common method is aspiration, which involves using a syringe to extract gastric contents through the gastric tube. Even though this method is simple to operate, its measurement results are affected by many factors, such as position of the tip of the gastric tube and suction force degree. The extracted gastric contents are exposed to the air and are easily contaminated[8]. Moreover, when the gastric contents are discarded, it is easy to lose the nutrient solution and the digestive fluid in the stomach, and when target feeding amount cannot be attained, it increases the malnutrition risk in patients. Gastric ultrasound can provide information about the nature and volume of gastric contents at the bedside[9]. The accuracy and repeatability of gastric ultrasound has been reported in previous studies. Although it cannot fully assess the gastric functions and state (such as pH value), it can provide important and useful information, such as volume and nature of gastric contents

(transparent liquid, solid or not)[9-11]. The accuracy of ultrasonic monitoring of GRV is also high, and there is no need to withdraw gastric contents, which reduces body fluid exposure risks[12]. However, the correlation between gastric residual and poor prognostic outcomes, such as aspiration, ventilator-related pneumonia and FI has not been fully elucidated[13-15]. The guidelines[16] issued by the critical illness Association and the American Association for parenteral and enteral nutrition in 2016 do not recommend monitoring of gastric residual amounts in clinical routine or assessing the feeding tolerance of patients by only relying on gastric residual amounts. However, a previous survey[6,17-19] revealed that 97.1% of nurses judge whether patients have FI by monitoring gastric residual amounts because the monitoring method is simple and convenient.

The aim of this study was to investigate the effects of ultrasound monitoring on incidence of feeding complications, daily caloric intake and clinical prognosis of patients with severe mechanical ventilation. Moreover, we analyzed its clinical significance to provide a theoretical basis for guiding clinical practice.

MATERIALS AND METHODS

Study participants

Patients admitted to the department of emergency medicine of the Affiliated Hospital of Nantong University from January 2018 to June 2022, and who received invasive mechanical ventilation and continuous enteral nutrition support within 24-48 h after admission were enrolled in this study. Medical records of the patients within 7 d of hospitalization were retrospectively analyzed to compare incidences of feeding complications, daily caloric intake and clinical prognosis between patients with gastric residual ≥ 250 mL and those with < 250 mL, as monitored by ultrasound on the third day of admission.

Patient data were retrospectively collected from the electronic medical records system of the intensive care units. Screening of study participants and data collation were performed as shown in Figure 1.

The inclusion criteria were: (1) No previous gastrointestinal dysfunction and enteral nutrition for 3 d; (2) Aged ≥ 18 years; and (3) Patients or family members who agreed to sign the informed consent form.

The exclusion criteria were: (1) Presence of aspiration pneumonia, diarrhea or diabetes before admission to intensive care units; (2) Shock, gastrointestinal bleeding, gastrointestinal surgery, severe intestinal obstruction, severe abdominal distension and diarrhea; (3) Abdominal space syndrome; (4) Enteral nutrition treatment *via* jejunum feeding or gastroenterostomy; and (5) Patients with incomplete case data records.

General observation index

The general data and clinical characteristics of study participants, including age, sex, body mass index (BMI), acute physiology and chronic health evaluation II (APACHE II), sequential organ failure assessment (SOFA), and disease diagnosis among others were collected.

Feeding complications

Vomiting: Stomach contents flow out of the mouth and nose through the esophagus. Diarrhea: The number of daily defecations is more than 3 times, feces are thin, the water content is high, and the daily defecation volume is more than 200 g. Abdominal distension: Discomfort caused by abdominal swelling or fullness.

Prognostic indicators

Data on time of mechanical ventilation, daily caloric intake from day 3 to day 7 after hospitalization in the ICU, the time to reach the feeding target, ICU hospitalization days and mortality were collected. The time to reach the feeding target: the number of days to reach 25 kcal/kg/D in gastrointestinal nutrition.

Daily caloric intake: Obtained by multiplying the volume of nutrient solution (mL) taken by the patient every day by the energy density of the nutrient solution (kcal/mL) divided by body weight.

Ultrasonic monitoring of gastric remnants

The monitoring frequency of gastric remnants was once every 4 h. Briefly, patients were placed in supine positions (the head of the bed was raised by 30°-45°), the portable color ultrasound diagnostic instrument was selected, the probe frequency was set at 2-5 mhz, and the single section of the antrum selected, that is, the ultrasound probe was placed under the xiphoid process of the patient and perpendicular to the abdomen angle. The antrum, the superior mesenteric artery, the left lobe of the liver and the abdominal aorta were examined to locate the position of the antrum, and ultrasound used to determine the size of the antrum. The area of the antrum was calculated by measuring the transverse and anterior posterior diameters of the antrum, after which the gastric residual was obtained by comparing the area of the antrum with age. When residual amount of the stomach exceeded 250 mL, enteral nutrition was stopped and further monitoring performed after 2-4 h. If < 250 mL, enteral nutrition was continued. If the gastric residual was still high, the jejunal nutrition tube or drug treatment was reserved according to patient's conditions, and if necessary, it was changed to parenteral nutrition support. Since some patients were hospitalized for 24-48 h, continuous enteral nutrition was not given until the condition was relatively stable. The GRV of patients was collected on the third day of ICU hospitalization, and the patients were assigned into ≥ 250 mL and < 250 mL groups.

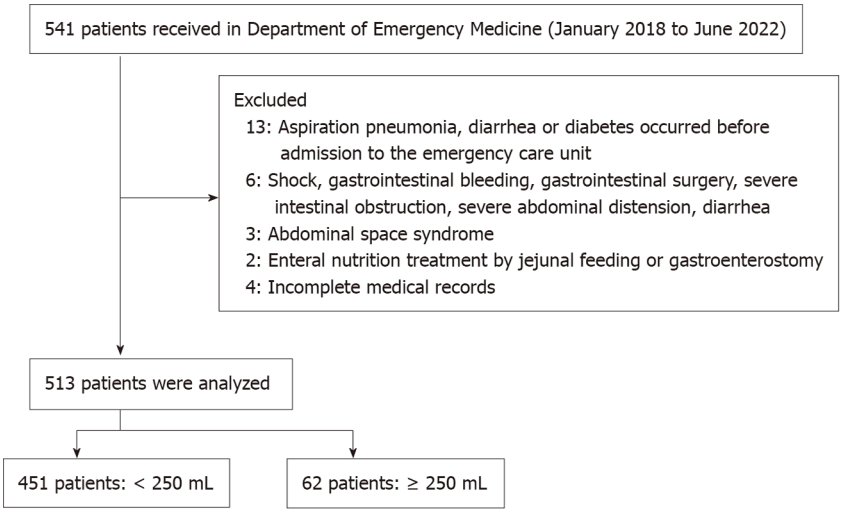

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Figure 1 Study flowchart.

Statistical analysis

The results for each scale were input into the computer for score conversion. The SPSS 24.0 software (IBM Corp., Armonk, NY, United States) was used for statistical analyses. Measurement data are expressed as means ± SD, while the counting data are expressed as frequencies and percentages. *t*-tests, analysis of variance, and chi square tests were used for inter-group statistical analyses. Logistic regression models were established for multivariate analyses. Bilateral $P < 0.05$ was set as the threshold for statistical significance.

RESULTS

Baseline data

A total of 513 patients (451 in the < 250 mL group and 62 in the ≥ 250 mL group) were enrolled in this study. There were 267 (59.2%) males in the 250 mL group, with age (53.04 ± 3.9 years), BMI (20.39 ± 2.5), APACHE II scores (6.39 ± 2.44), and SOFA (3.51 ± 0.53). There were 33 (53.2%) males in the ≥ 250 mL group, with age (53.92 ± 4.29 years), BMI (20.87 ± 2.49), APACHE II scores (16.71 ± 2.41), and SOFA (3.47 ± 0.5). Differences in general data between the groups were insignificant (Table 1).

Comparisons of medication and complications between the groups

Results showed that 29.9% and 25.1% of patients in the < 250 mL group used sedatives or sedatives, compared to 48.4% and 38.7% in the ≥ 250 mL group ($P < 0.05$). The probabilities of abdominal distension, diarrhea and vomiting in the < 250 mL group were 18.4%, 23.9% and 4.0%, compared with 21.0%, 32.3% and 6.5% in the ≥ 250 mL group ($P > 0.05$; Table 2).

Comparisons of prognostic outcomes between groups

The time to reach the feeding target was significantly shorter for the ≥ 250 mL group, compared to that of the < 250 mL group ($P < 0.05$). Differences in mechanical ventilation time, ICU hospitalization days and mortality rates between the two groups were not significant ($P > 0.05$). Caloric intake (22.0, 23.6, 24.8, 25.3 kcal/kg/d) for patients in the < 250 mL group was lower compared with that of patients in the < 250 mL group (23.2, 24.8, 25.7, 25.8 kcal/kg/d). Caloric intakes on the 4th day ($Z = 4.324$, $P = 0.013$), 5th day ($Z = 3.376$, $P = 0.033$) and 6th day ($Z = 3.098$, $P = 0.04$) were significant (Figure 2 and Table 3).

Effects of each variable on prognosis

When residual gastric volume > 250 mL, sedative drugs, analgesics, vomiting, and time to reach the feeding target were taken as independent variables and respectively introduced into the logistic regression model for analysis, it was found that the time to reach the target feeding was an independent risk factor influencing the prognosis and extension of ICU stay. However, GRV > 250 mL had no significant effects on patient death and ICU stay outcomes (Tables 4 and 5).

DISCUSSION

The 2016 guidelines of the American Society of critical care medicine and the society of enteral and parenteral nutrition recommend monitoring of tolerance of enteral tube feeding (ETF) for critically ill patients in combination with

Table 1 Baseline characteristics of participants: Comparisons of the 2 groups, *n* (%)

Item	< 250 mL (*n* = 451)	≥ 250 mL (*n* = 62)	t/χ^2	*P* value
Gender			0.802[2]	0.371
Female	184 (40.8)	29 (46.8)		
Male	267 (59.2)	33 (53.2)		
Age (yr)	53.04 ± 3.9	53.92 ± 4.29	1.652[1]	0.099
BMI	20.39 ± 2.5	20.87 ± 2.49	1.420[1]	0.156
APACHE II	16.39 ± 2.44	16.71 ± 2.41	0.982[1]	0.327
SOFA	3.51 ± 0.53	3.47 ± 0.5	0.587[1]	0.557
Acute cerebrovascular accident	133 (29.5)	23 (37.1)	1.490[2]	0.222
Acute pneumonia	84 (18.6)	9 (14.5)	0.620[2]	0.431
Acute heart failure	122 (27.1)	14 (22.6)	0.559[2]	0.455
Craniocerebral injury	112 (24.8)	16 (25.8)	0.028[2]	0.868
Other	20 (4.4)	3 (4.8)	0.021[2]	0.885
Hypertension	271 (60.1)	45 (72.6)	3.596[1]	0.058
Diabetes	106 (23.5)	12 (19.4)	0.530[2]	0.467
Coronary heart disease	161 (35.7)	23 (37.1)	0.046[2]	0.830

[1]Independent samples *t* test.
[2]Chi-square test.
BMI: Body mass index; APACHE II: Acute physiology and chronic health evaluation II; SOFA: Sequential organ failure assessment.

Table 2 Comparisons of medication and complications between the groups, *n* (%)

Item	< 250 mL (*n* = 451)	≥ 250 mL (*n* = 62)	χ^2	*P* value
Sedative drug use rate	135 (29.9)	30 (48.4)	8.507	0.004
Analgesic drug use rate	113 (25.1)	24 (38.7)	5.192	0.023
Abdominal distention	83 (18.4)	13 (21.0)	0.236	0.627
Diarrhea	108 (23.9)	20 (32.3)	2.011	1.156
Vomit	18 (4.0)	4 (6.5)	2.382	0.336

Table 3 Comparisons of prognostic outcomes between the groups, *n* (%)

Item	< 250 mL (*n* = 451)	≥ 250 mL (*n* = 62)	χ^2	*P* value
Mechanical ventilation time, d	18.30 ± 4.56	17.56 ± 5.04	1.174[1]	0.241
Days to reach feeding target, d	5.01 ± 0.32	6.02 ± 0.95	16.779[1]	0.000
ICU hospitalization days, d	19.87 ± 4.64	19.19 ± 5.19	1.059[1]	0.290
Mortality	94 (20.8)	14 (22.6)	0.099[2]	0.753

[1]Independent samples *t* test.
[2]Chi-square test.

radiological images, physical examination, flatulence and defecation[20]. The ETF intolerance is mainly manifested by nasal feeding tube withdrawal, abnormal imaging, vomiting, abdominal distension or diarrhea, which can occur in up to one third of hospitalized patients. The TF intolerance is associated with poor prognostic outcomes[21]. The 2021 international guidelines for management of sepsis and gastric shock recommend that GRV should be routinely measured for patients with FI or high risk of aspiration[22]. Currently, the definition of GRV has not been standardized. A meta-analysis[23] involving 72 articles showed that the definition of FI includes one or all of the three aspects: large gastric

Table 4 Logistic regression analysis of risk factors for death

Related factor	β	SE	χ^2	*P* value	OR	95%CI
≥ 250 mL	0.031	0.338	0.008	0.928	1.031	0.532-2.000
Sedatives	0.082	0.678	0.015	0.903	0.921	0.244-3.481
Analgesics	0.229	0.231	0.984	0.321	0.795	0.505-1.251
Time to reach feeding target	1.186	0.311	5.659	0.039	1.205	0.655-2.217
Constant	-1.240	1.042	1.417	0.234	0.289	

Table 5 Linear regression analysis of risk factors for length of stay in the intensive care unit

Related factor	β	SE	*t*	*P* value
≥ 250 mL	-0.634	0.659	-0.963	0.336
Sedatives	-0.307	1.340	-0.229	0.819
Analgesics	0.324	0.452	0.717	0.474
Time to reach feeding target	-1.393	0.613	-3.641	0.034
Constant	20.608	1.268	16.252	0.000

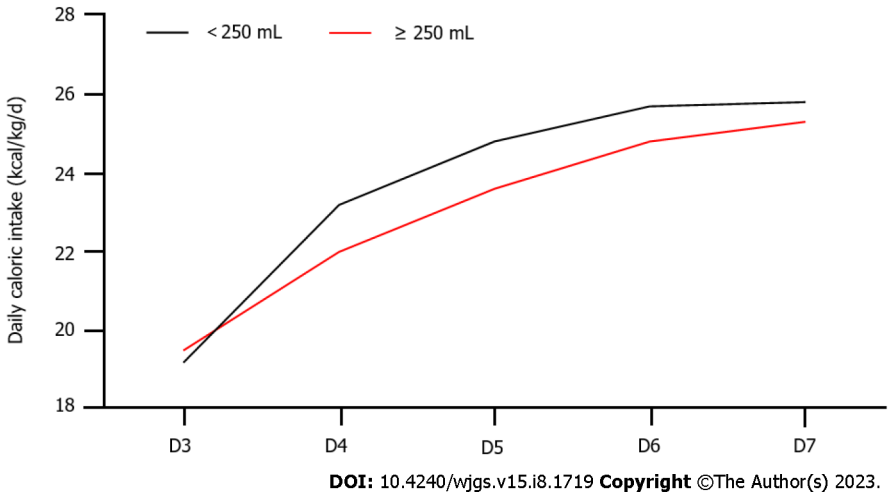

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Figure 2 Daily caloric intake for the two groups.

residues (average 250 mL), gastrointestinal symptoms, and insufficient intake of calories. A previous study[24] revealed that the degree of influence of FI on poor prognostic outcomes is associated with definition of FI, and that the definition of high GRV (more than 500 mL for 24 h) and gastrointestinal symptoms is strongly correlated with 90-day mortality. The 2017 European Society of critical care clinical practice guidelines recommend delayed gastrointestinal nutrition for critically ill patients with GRV > 500 mL/6 h[25]. In 2021, expert consensus recommendation in China reported that residual gastric residue ≥ 250 mL suggest FI, and intervention treatments should be started as soon as possible [26]. This is why 250 mL was selected as the grouping standard in this study. Studies[23,27-30] have confirmed that FI increases mortality outcomes and prolongs the ICU hospitalization as well as mechanical ventilation times. Currently, there is no unified definition standard for FI. Abdominal distension, diarrhea and vomiting are regarded as the signs of FI and increased aspiration risk. In this study, it was found that when gastric residues of patients > 250 mL, clinical interventions did not significantly increase the incidences of abdominal distension, diarrhea and vomiting. Regarding the relationship between gastric residual allowance and enteral nutrition complications, studies[13-15] have confirmed that occurrences of vomiting, diarrhea, aspiration, pneumonia and other complications in ICU patients are not directly related to setting of critical values of gastric residual allowance, and that increasing the critical value of gastric residual allowance has no significant impact on enteral nutrition complications. In 2016, the Association for critical illness and the American Association for parenteral and enteral nutrition proposed the nutrition treatment guidelines[16]: They recommend monitoring gastric residual allowance in an irregular manner in clinical practice. For ICU patients, when the gastric residual allowance is less than 500 mL and if the patient has no abdominal symptoms such as vomiting and diarrhea, enteral nutrition should not be stopped. Therefore, we do not recommend clinical interventions to prevent vomiting

when the patient's gastric residue exceeds 250 mL, unless the patient has abdominal symptoms or the gastric residue exceeds 500 mL. We found that > 250 mL gastric remnants for ICU patients had no significant effects on mortality outcomes and ICU hospitalization time. Therefore, we postulate that gastric residue is only one of the signs of FI, and it cannot predict whether the patient has FI, thus, it will not have a significant impact on prognostic outcomes. Assessment of feeding tolerance or estimating its impact on prognostic outcomes should not be based on gastric residues only.

We also found that food intake for ICU patients with gastric residual > 250 mL from the 4th to the 7th day was lower than that of patients with gastric residual < 250 mL, and that differences between the groups from the 4th to the 6th day were significant. This may have been because enteral nutrition was stopped for 2-4 h when the GRV exceeded 250 mL. The higher the number of times the patient suspends enteral nutrition, the less calories he consumes on that day. If the GRV cannot accurately reflect the gastrointestinal movement, it causes unnecessary interruption of nutrition supply and increases the mortality as well as complication rates for patients, which is attributed to insufficient energy supply. When monitoring the gastric residual amount, interruption or cessation of enteral nutrition due to high gastric residual amounts leads to insufficient feeding of the patient, which affects the patient's caloric intake, and ultimately increases the mortality outcomes[31,32]. The monitoring frequency of GRV also has an impact on daily caloric intake for patients. A multicenter study involving a large sample size by Reignier *et al*[33] reported that the proportion of patients who did not routinely monitor GRV and reached the target feeding volume was significantly higher than that of the routine monitoring group. It was 1.77 times that of the routine monitoring group. Wiese *et al*[15] found that 84.5% of patients who did not routinely monitor gastric residual amounts had their actual enteral nutrition feeding amounts reaching more than 90% of the target feeding amount within 24 h, and that 83.3% of patients had their actual enteral nutrition feeding amount being more than 90% of the target feeding amount during ICU hospitalization, which were significantly higher than those in the routine monitoring group (46.4% in 24 h and 61.9% in ICU hospitalization).

CONCLUSION

Ultrasound monitoring of gastric residual and clinical interventions when the monitoring value exceeds 250 mL have no significant impacts on complication rates and clinical prognosis of ICU patients, but significantly reduces the intake of calories during ICU hospitalization, prolongs the time to reach the feeding target, increases the risk of insufficient nutrition of patients, and affects the prognostic outcomes of patients. When the gastric residual exceeds 250 mL, clinical interventions that increase the nutritional intake are not recommended. This study has some limitations. As a retrospective single center study, there may be some information bias, therefore, our findings should be further confirmed by prospective and large sample studies.

ARTICLE HIGHLIGHTS

Research background

Gastric residual monitoring is considered an important way to evaluate gastric emptying in mechanically ventilated patients, but its correlation with adverse outcomes such as aspiration, ventilator-associated pneumonia, and feeding intolerance is controversial.

Research motivation

To analyze the impact of intervention with ultrasound monitoring of gastric residual volume (GRV) reaching 250mL on the incidence of feeding complications, daily calorie intake, and clinical prognosis in patients with severe mechanical ventilation.

Research objectives

To provide theoretical basis for clinical practice.

Research methods

Retrospective analysis method.

Research results

The use of ultrasound to monitor gastric residue and clinical intervention at monitoring value ≥ 250ml did not significantly affect the incidence of feeding complications and clinical prognosis of patients.

Research conclusions

This study suggests that ultrasound monitoring of gastric residue and clinical intervention when the monitoring value exceeds 250 mL have no significant impact on the incidence of complications and clinical prognosis of intensive care unit (ICU) patients. However, it significantly reduces the calorie intake of patients during ICU hospitalization, prolongs the time to reach feeding goals, increases the risk of insufficient nutrition, and affects patient prognosis.

Research perspectives

It is not recommended to judge the patient's feeding tolerance or estimate the impact on the patient's prognosis solely based on GRV in clinical practice.

FOOTNOTES

Author contributions: Xu XY designed research; Xue HP performed research; Yuan MJ contributed new reagents or analytic tools; Jin YR analyzed data; Huang CX and Xu XY wrote the paper.

Institutional review board statement: The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Affiliated Hospital of Nantong University (Approval No. 2022015).

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study.

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ORCID number: Xiao-Yan Xu 0009-0009-1930-4219; Hui-Ping Xue 0000-0001-9215-5728; Chun-Xia Huang 0009-0006-6692-1939.

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ORIGINAL ARTICLE

Retrospective Study

Enhanced recovery nursing and mental health education on postoperative recovery and mental health of laparoscopic liver resection

Dong-Xia Li, Wei Ye, Yi-Lu Yang, Lei Zhang, Xiang-Jun Qian, Ping-Hua Jiang

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Dong-Xia Li, Lei Zhang, Xiang-Jun Qian, Ping-Hua Jiang, Department of Pancreatic Hepatobiliary Surgery, Department of General Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou 510655, Guangdong Province, China

Dong-Xia Li, Wei Ye, Yi-Lu Yang, Lei Zhang, Xiang-Jun Qian, Ping-Hua Jiang, Biomedical Innovation Center, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou 510655, Guangdong Province, China

Wei Ye, Yi-Lu Yang, Department of Orthopedics, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou 510655, Guangdong Province, China

Corresponding author: Ping-Hua Jiang, BSc, Nurse, Department of Pancreatic Hepatobiliary Surgery, Department of General Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, No. 26 Erheng Road, Yuancun, Tianhe District, Guangzhou 510655, Guangdong Province, China. jiangph3@mail.sysu.edu.cn

Abstract

BACKGROUND

Patients undergoing laparoscopic resection of liver metastases of colorectal cancer are prone to negative emotions and decrease of digestive function. Early nursing and psychological intervention are necessary.

AIM

To observe the effect of enhanced recovery nursing combined with mental health education on postoperative recovery and mental health of patients undergoing laparoscopic resection of liver metastases of colorectal cancer.

METHODS

One hundred and twenty patients who underwent laparoscopic resection of liver metastases of colorectal cancer at our hospital between March 2021 and March 2023, were selected as participants. The patients admitted from March 1, 2021 to February 28, 2022 were set as the control group, and they were given routine nursing combined with mental health education intervention. While the patients admitted from March 1, 2022 to March 31, 2023 were set as the observation group, they were given accelerated rehabilitation surgical nursing combined with mental health education intervention. The differences in postoperative recovery-related

indices, complications and pain degrees, and mental health-related scores were compared between groups. The T lymphocyte subset levels of the two groups were also compared.

RESULTS

The postoperative exhaust, defecation, eating and drainage time of the observation group were shorter than those of the control group. The pain scores of the observation group were lower than those of the control group at 6, 12, 24, 48, and 72 h after surgery. The cumulative complication rate of the observation group was lower than that of the control group ($P < 0.05$). The CD4+/CD8+ in the observation group was higher than that in the control group 3 d after surgery ($P < 0.05$). After intervention, the self-rating depression scale, self-rating anxiety scale, avoidance dimension, and yielding dimension in Medical coping style (MCMQ) scores of the two groups were lower than those prior to intervention, and the scores in the observation group were lower than those in the control group ($P < 0.05$). The face dimension score in the MCMQ score was higher than that before intervention, and that of the observation group was higher than that of the control group ($P < 0.05$). After intervention, the total scores of the life function index scale (FLIC) and psychological well-being scores of cancer patients in the two groups, and the physical and social well-being scores in the observation group, were higher than those before intervention. The nursing satisfaction of the observation group was higher than that of the control group ($P < 0.05$). The physical, psychological, and social well-being, and the total FLIC scores of the observation group were higher than those in the control group after surgery ($P < 0.05$).

CONCLUSION

Enhanced recovery nursing combined with mental health education can promote the recovery of gastrointestinal function, improve the mental health and quality of life of patients after laparoscopic resection of colorectal cancer liver metastases, and reduce the incidence of complications.

Key Words: Accelerated surgical rehabilitation; Mental health education; Laparoscopy; Liver metastasis of colorectal cancer; Gastrointestinal function; Mental health

Core Tip: This study analyzed the effect of accelerated rehabilitation surgical nursing combined with mental health education on postoperative recovery and mental health of patients undergoing laparoscopic resection of colorectal cancer liver metastases. Enhanced recovery after surgical nursing combined with mental health education can promote the recovery of gastrointestinal function, improve the mental health and quality of life of patients after laparoscopic resection of colorectal cancer liver metastases, and reduce the incidence of complications.

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INTRODUCTION

Colorectal cancer is a common gastrointestinal malignant tumor, and the morbidity and mortality of this disease are high. However, the early symptoms are not obvious. When patients gradually develop obvious symptoms such as hematochezia and diarrhea, they are usually in the advanced stage. With the continuous proliferation and differentiation of tumor cells, most patients will have tumor cell metastasis[1]. The liver is the most common organ of distant metastasis in colorectal cancer. Approximately 53% of colon cancer patients will have liver metastasis[2]. Laparoscopic tumor resection is a common surgical treatment method for liver metastasis of colorectal cancer in clinical practice, which reduces the tumor burden of patients by removing liver metastases and has the advantages of a small wound, less bleeding, and quick recovery[3]. However, surgical treatment cannot completely control the disease. Patients will also need to accept chemotherapy and other rehabilitation maintenance, and there is still a risk of postoperative recurrence. Therefore, patients will have negative emotions such as fear and anxiety. The surgical method is in the abdomen of the patient, so it will affect the digestive function after surgery. And therefore, early nursing and psychological intervention are necessary[4,5]. Accelerated rehabilitation surgical nursing is a new nursing concept and rehabilitation model. Based on medical evidence, perioperative intervention is performed to reduce the physiological and psychological traumatic stress of patients and achieve rapid rehabilitation[6,7]. This study analyzed the effect of accelerated rehabilitation surgical nursing combined with mental health education on postoperative recovery and mental health of patients undergoing laparoscopic resection of colorectal cancer liver metastases.

MATERIALS AND METHODS

Data and methods

General information: From March 2021 to March 2023, 120 patients who underwent laparoscopic resection of liver metastases from colorectal cancer in our hospital were selected as subjects. Among them, patients admitted from March 1, 2021 to February 28, 2022 were set as the control group, and routine nursing combined with mental health education intervention was given. The group consisted of 30 men and 27 women, aged 31–78 years, with an average age of (62.25 ± 9.74) years. In addition, patients admitted from March 1, 2022 to March 31, 2023 were set as the observation group and given accelerated rehabilitation surgical nursing combined with mental health education intervention. This group included 35 men and 28 women, aged 28–80 years, with an average age of (63.26 ± 10.14) years. The general data of the two groups were similar ($P > 0.05$). See Table 1.

Inclusion and exclusion criteria: Inclusion criteria: (1) Colorectal cancer in line with the 'colorectal cancer diagnosis and treatment norms'[8] standards and underwent radical surgery; postoperative pathology confirmed; (2) Age 18 ≤ 80 years; (3) Abdominal computed tomography or magnetic resonance imaging confirmed liver metastasis, in line with surgical indications; and (4) Complete clinical data.

Exclusion criteria[9]: (1) Laparotomy or conversion to laparotomy; (2) Palliative excision; (3) With colorectal obstruction or perforation; (4) Combination with other serious diseases; and (5) Have comprehension or hearing impairment.

Methods

Mental health education intervention methods: The patients were administered psychological evaluation and intervention according to their existing situation. The goals were to perform mental health education for patients, to encourage patients to express their negative emotions, to take corresponding measures to alleviate them, and to monitor patients' psychological status and emotions in real time.

Routine nursing intervention methods: The patients were given routine preoperative education, routine postoperative treatment according to the doctor's advice, and recommendations of postoperative precautions.

Accelerated rehabilitation surgical nursing methods: (1) Health education and psychological counseling: The nurses were trained on the specific properties of the disease, surgery, and mental health; the patients were then introduced to the disease characteristics and surgical methods in a specific manner, using video, brochures or slides to reduce fear of the disease and surgery. The nurses guided patients in discussions surrounding psychological challenges, encouraged them to vent negative emotions, listened patiently and gave guidance, and established patient confidence in overcoming the disease; (2) Analgesia: Teaching patients to correctly express pain signals to help medical staff to quickly and accurately judge pain symptoms, and inform patients of the rationality of postoperative pain and the importance of reflecting the condition. Nurses guided patients in the use of a self-controlled intravenous analgesia pump, and if necessary, administered oral antipyretic analgesics to enhance the analgesic effect; (3) Diet: After surgery, patients were still not allowed water but if thirsty could dampen their lips with a wet cotton swab. After 6 h, moderate water consumption was allowed, and after 12 h rice soup could be consumed. On the second postoperative day, a number of small semi-liquid meals could be eaten throughout the day. After 3 d of the liquid diet, the principle of consuming numerous small meals throughout the day was continued, while gradually increasing the amount of food, until the patient could return to their normal diet. Patients were advised to eat easily digestible, protein-rich foods that were rich in cellulose, and to avoid spicy foods; (4) Rehabilitation exercise: Nurses informed patients of the necessity of postoperative rehabilitation exercise and strived for the active cooperation of patients and their families. In the early postoperative stage, a semi-reclining position could be assumed, and the patient could be turned onto their back or front every hour. From the third day after surgery, the patients were guided in performing bed exercises such as hip lifting and kicking, which continued daily until they were allowed to get out of bed; and (5) Acupoint massage: Hegu, Zusanli, Weizhong, and other acupoints were massaged to relieve pain, and abdominal massage was performed to promote gastrointestinal motility.

Observation indicators and detection methods

The differences in postoperative recovery-related indices, complications and pain degrees, and mental health-related scores were compared between groups. The T lymphocyte subset levels of the two groups were examined.

Detection method: Fasting fresh blood samples were collected from patients in the morning, using an automatic blood biochemical detector, at a speed of 5500 r/min, centrifugal radius of 10 cm, for a centrifugal processing time of 20 min, allowing separation of serum into the detector, and detection of T lymphocyte subsets.

Degrees of pain: The visual analogue scale score was used to evaluate pain at different time points after surgery[10]. Pain was scored out of 10, where 0 was no discomfort, and 10 was the most severe pain; the score was positively correlated with the degree of pain.

Mental health: The self-rating depression scale (SDS)[11] and self-rating anxiety scale (SAS)[12] that were used to evaluate the mental health of patients included 20 items, and the critical values were 53 and 50 respectively; the higher the score, the worse the mental health of patients.

Medical coping style (MCMQ) score[13]: A total of 20 items, covering the face (8 items), avoidance (7 items), and yield (5 items). For each of these three aspects, a single item was given a score of 1–4 points; the higher the score, the greater the patient was adopting the coping style.

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

General information	Control group (*n* = 57)	Observation group (*n* = 63)	χ^2/t	*P* value
Gender			0.063	0.802
Male	41 (71.93)	44 (69.84)		
Female	16 (28.07)	19 (30.16)		
Age [(mean ± SD), age]	57.79 ± 9.28	56.70 ± 11.27	0.57	0.57
BMI [(mean ± SD), kg/m^2]	23.43 ± 3.73	23.17 ± 3.06	0.433	0.666
Type of disease			0.02	0.887
Rectal cancer	21 (36.84)	24 (38.10)		
Colon cancer	36 (63.16)	39 (61.90)		
Maximum diameter of metastatic lesion [(mean ± SD), cm]	3.46 ± 0.94	3.39 ± 0.98	0.398	0.691
Number of liver metastatic lesions				
1	20 (35.09)	23 (36.51)	0.036	0.982
2	19 (33.33)	21 (33.33)		
≥ 3	18 (31.58)	19 (30.16)		
Surgical program [*n* (%)]			0.3	0.956
Partial hepatectomy	21 (36.84)	24 (38.10)		
Segmentectomy	16 (28.07)	15 (23.81)		
Lobectomy	14 (24.56)	17 (26.98)		
Other	6 (10.53)	7 (11.11)		

BMI: Body mass index.

Cancer patients living function index scale (FLIC) score[14]: This consisted of a total of 22 items covering physical condition, psychological state, cancer-related difficulties, social well-being, and nausea. For each of these 5 aspects, a single item was given a score of 1–7 points; the higher the score, the better the quality of life.

Nursing satisfaction: The self-made satisfaction score table of the department was used to evaluate the 0-10 points with the patient when the treatment was completed, 0-4 points were dissatisfied, 5-8 points were satisfied, and 9-10 points were very satisfied.

Statistical processing

SPSS 26.0 software was used to process the data. FLIC score, MCMQ score, and other measurement data that conformed to normal or approximate distribution were described by (`c ± s), and a t-test was used for comparison. Countable data such as those for the surgical plan and number of liver metastases were described by the number of patients (%), and a χ^2 test was used for comparison.

RESULTS

Comparison of postoperative recovery between two groups

The postoperative exhaust, drainage, defecation and eating time in the observation group were shorter than those in the control group ($P < 0.05$). See Table 2.

Comparison of T lymphocyte subsets between two groups

T lymphocyte subsets were similar between the two groups ($P > 0.05$). At 3 d after operation, CD4+ in the two groups and CD3+ and CD4+/CD8+ in the control group were lower than before, while CD8+ in the control group was higher than before, and CD3+, CD8+ and CD4+/CD8+ in the observation group were similar with those before operation ($P > 0.05$). CD4+/CD8+ in the observation group was higher than that in the control group at 3 d after operation, and CD3+, CD4+ and CD8+ were compared with the control group ($P > 0.05$). See Table 3.

Comparison of pain degree between two groups

The pain scores of the observation group were lower than those of the control group at 6 h, 12 h, 24 h, 48 h and 72 h after operation ($P < 0.05$). See Figure 1.

Table 2 Comparison of postoperative recovery between two groups (mean ± SD)

Group	*n*	Exhaust time (hour)	Defecation time (hour)	Eating time (day)	Drainage time (day)	Postoperative hospital stay (day)
Control group	57	42.56 ± 10.23	66.36 ± 15.23	1.96 ± 0.27	8.25 ± 1.63	14.12 ± 3.13
Observation group	63	31.54 ± 8.67	49.93 ± 9.77	1.48 ± 0.32	6.58 ± 1.44	12.03 ± 2.87
t		6.384	7.1	8.831	5.959	3.816
P value		0	0	0	0	0

Table 3 Comparison of T lymphocyte subsets between the two groups (mean ± SD)

Group	*n*	CD3+ (μL)		CD4+ (μL)		CD8+ (μL)		CD4+/CD8+	
		Preoperative	3 d after operation	Preoperative	3 d after operation	Preoperative	3 d after operation	Preoperative	3 d after operation
Control group	57	1214.36 ± 256.36	1108.33 ± 241.25[a]	859.63 ± 210.36	778.52 ± 189.69[a]	658.52 ± 187.25	736.33 ± 214.05[a]	1.36 ± 0.25	1.07 ± 0.36[a]
Observation group	63	1197.68 ± 267.33	1163.69 ± 287.11	867.44 ± 225.59	842.52 ± 200.13[a]	647.96 ± 193.24	665.36 ± 204.78	1.34 ± 0.28	1.28 ± 0.34[a]
t		0.348	1.137	0.196	1.793	0.303	1.856	0.411	3.286
P value		0.728	0.258	0.845	0.076	0.762	0.066	0.682	0.001

[a]*P* < 0.05, compared with preoperative.

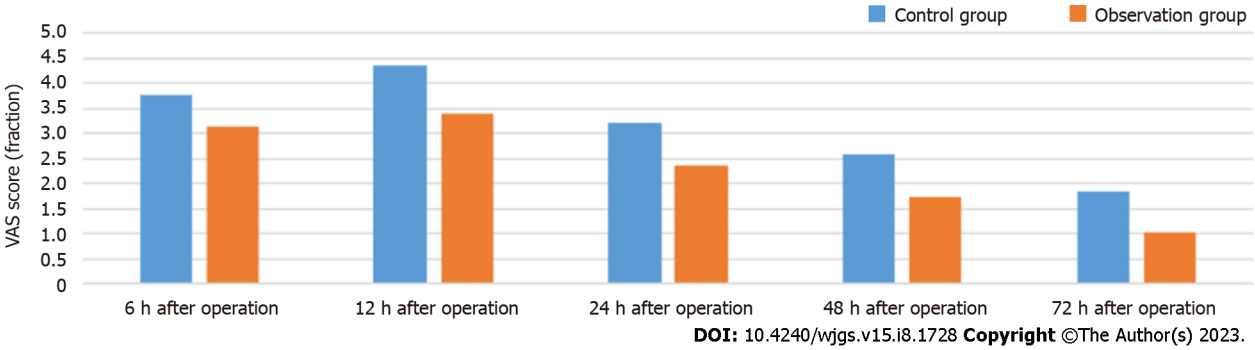

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Figure 1 Comparison of pain degree between two groups. VAS: Visual analogue scale.

Comparison of mental health related scores between two groups

The mental health related scores of the two groups were similar before intervention ($P > 0.05$). After intervention, the SAS and SDS scores of the two groups were lower than those before intervention, and the observation group was lower ($P < 0.05$). See Figures 2 and 3.

Comparison of MCMQ scores between two groups

MCMQ scores of the two groups were similar before intervention ($P > 0.05$). After intervention, the face scores of the two groups were higher than those before intervention, and the observation group was higher ($P < 0.05$). The avoidance and yield scores of the two groups were lower than those before intervention, and the observation group was lower ($P < 0.05$). See Table 4.

Comparison of FLIC scores between two groups

The FLIC scores of the two groups were similar before intervention ($P > 0.05$). After intervention, the total scores of FLIC and good psychology in the two groups and the scores of good body and good society in the observation group were higher than those before intervention. The scores of good body, difficulty due to cancer, good society and nausea in the control group were compared with those before intervention ($P > 0.05$). The scores of good body, good psychology, good society and the total score of FLIC in the observation group were higher ($P < 0.05$). See Table 5.

Table 4 Comparison of medical coping style scores between two groups [(mean ± SD), fraction]

Group	*n*	Face		Avoid		Yield	
		Before intervention	After intervention	Before intervention	After intervention	Before intervention	After intervention
Control group	57	18.36 ± 3.23	21.04 ± 3.34[a]	20.36 ± 3.15	16.89 ± 2.44[a]	14.96 ± 2.77	11.25 ± 1.93[a]
Observation group	63	17.78 ± 3.26	24.15 ± 2.06[a]	21.05 ± 3.34	14.12 ± 2.05[a]	15.12 ± 2.16	10.01 ± 1.27[a]
t		0.978	6.202	1.161	6.754	0.355	4.195
P value		0.33	0	0.248	0	0.724	0

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

Table 5 Comparison of the life function index scale scores between two groups [(mean ± SD), fraction]

Group	*n*	Good body		Psychologically sound		Difficulty due to cancer	
		Before intervention	After intervention	Before intervention	After intervention	Before intervention	After intervention
Control group	57	40.58 ± 3.96	41.35 ± 4.23	24.02 ± 3.36	25.26 ± 3.07[a]	12.23 ± 2.09	12.75 ± 2.26
Observation group	63	41.07 ± 3.75	46.96 ± 3.87[a]	23.87 ± 3.41	26.89 ± 3.31[a]	12.14 ± 2.28	12.83 ± 2.07
t		0.696	7.587	0.242	2.788	0.225	0.202
P value		0.488	0	0.809	0.006	0.823	0.84
Group	***n***	**Good society**		**Nausea**		**Total score of FLIC**	
		Before intervention	**After intervention**	**Before intervention**	**After intervention**	**Before intervention**	**After intervention**
Control group	57	10.26 ± 1.38	10.87 ± 1.47	3.05 ± 1.14	3.11 ± 1.05	81.89 ± 4.56	93.34 ± 5.16[a]
Observation group	63	10.19 ± 1.44	12.68 ± 1.51[a]	2.97 ± 1.21	3.23 ± 1.11	80.74 ± 4.61	102.96 ± 6.44[a]
t		0.271	6.64	0.372	0.607	1.372	8.869
P value		0.787	0	0.711	0.545	0.173	0

[a]*P* < 0.05, compared with before intervention.
FLIC: The life function index scale.

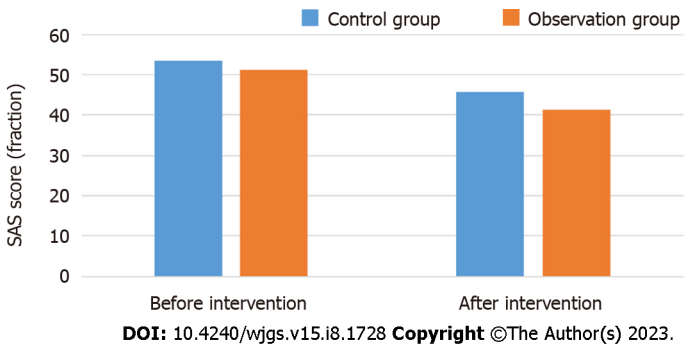

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Figure 2 Comparison of self-rating anxiety scale scores between two groups. SAS: Self-rating anxiety scale.

Comparison of complications between two groups

The cumulative complication rate of the observation group was 3.17% (2/63), which was lower than 14.04% (8/57) of the control group ($P < 0.05$). See Table 6.

The nursing satisfaction of the observation group was 93.65%, which was higher than that of the control group (80.70%) ($P < 0.05$). See Table 7.

Table 6 Comparison of complications between the two groups, *n* (%)

Group	*n*	Incision infection	Pleural effusion	Intestinal obstruction	Celiac hemorrhage	Cumulative
Control group	57	3 (5.26)	3 (5.26)	1 (1.75)	1 (1.75)	8 (14.04)
Observation group	63	1 (1.59)	1 (1.59)	0 (0.00)	0 (0.00)	2 (3.17)
χ^2						4.621
P value						0.032

Table 7 Comparison of nursing satisfaction between the two groups, *n* (%)

Group	*n*	discontent	satisfied	Very satisfied	Satisfaction rate
Control group	57	11 (19.30)	23 (40.36)	23 (40.36)	46 (80.70)
Observation group	63	4 (6.35)	29 (46.03)	30 (47.62)	59 (93.65)
χ^2					6.666
P value					0.01

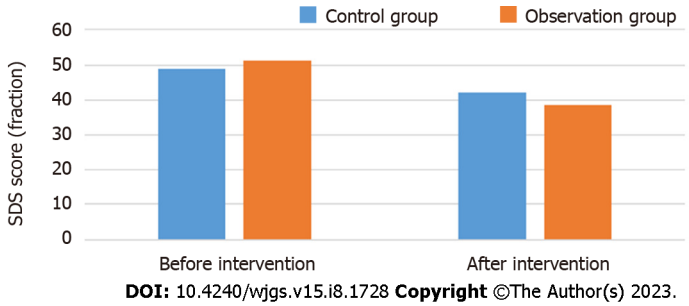

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Figure 3 Comparison of self-rating depression scale scores between two groups. SDS: Self-rating depression scale.

DISCUSSION

Surgical resection is the best treatment for long-term survival of patients with colorectal cancer and liver metastasis. Simultaneously, one-stage resection of primary and metastatic lesions has become widely accepted[15]. The minimally invasive, safe, and effective characteristics of laparoscopic surgery give it unique advantages in simultaneous resection of colorectal liver metastases[16]. The implementation of targeted nursing and psychological intervention during the perioperative period can further promote the postoperative recovery of patients and help to achieve better therapeutic effects [17]. Accelerated rehabilitation surgical nursing is an innovative treatment revolution, and it is mainly patient centered. Through the cooperation of surgery, anesthesia, nursing, nutrition, and other disciplines, it achieves win-win results for doctors and patients' families[18].

In this study, the postoperative recovery-related indicators of the two groups were compared. The results showed that the postoperative exhaust, defecation, eating, drainage, and hospitalization time of the observation group were shorter than those of the control group, indicating that accelerated rehabilitation surgical nursing combined with mental health education can accelerate the recovery of gastrointestinal function. The reason is that accelerated rehabilitation surgical nursing provides targeted nursing for patients on postoperative diet. According to the recovery guidelines for postoperative gastrointestinal function, a phased diet plan is formulated to avoid spicy and other stimulating foods and reduce the hyperstimulation of gastrointestinal function. At the same time, the patient's abdomen is massaged to promote gastrointestinal peristalsis and accelerate the recovery of postoperative gastrointestinal function[19-21].

In this study, the degrees of pain experienced by the two groups were compared. The pain score of the observation group was lower than that of the control group at 6, 12, 24, 48, and 72 h after surgery, indicating that education can reduce the degree of postoperative pain in patients. The reason is that education promotes the understanding of the importance of surgery and postoperative precautions. The diversification of education methods can enable patients to understand the operation process and treatment principle in different aspects; this may reduce patients' fear of postoperative pain and improve compliance[22]. Simultaneously, accelerated rehabilitation surgical nursing, combined with the use of a self-controlled intravenous analgesia pump, and non-steroidal anti-inflammatory drugs for analgesia treatment, can reduce incision pain[23]. Massage of the Hegu, Zusanli, Weizhong, and other acupoints also helps to reduce the degree of pain and reduce the pain score[24].

This study compared the mental health-related scores of the two groups. The SAS and SDS scores of the two groups were lower than those before the intervention, and the postoperative observation group score was lower than that of the control group. The MCMQ scores of the two groups were compared. The scores of the two groups were higher than those before the intervention, and the observation group score was higher than that of the control group after surgery. The avoidance and yield scores of the two groups were lower than those before the intervention, and the observation group scores were lower than those of the control group after surgery. These results show that accelerated rehabilitation surgical nursing combined with mental health education can more effectively alleviate patients' negative emotions such as anxiety and depression, improve patients' psychological state, and help patients actively face the disease. This is because mental health education through the psychological assessment of patients and use of the full range of psychological interventions, prompting patients to vent their negative emotions, help patients to resolve bad mood and establish a good mentality[25]. Accelerated rehabilitation surgical nursing reduces patients' fear of disease and surgery, by improving the professional and psychological nursing level of staff, allowing the timely psychological counseling of patients, and conveying knowledge of the disease to patients in an accessible manner, so as to better improve their psychological state [26,27].

After the intervention, the physical, psychological, social well-being, and FLIC in the observation group were higher than those in the control group, and the incidence of complications was lower. The nursing satisfaction of the observation group was better than that of the control group, indicating that accelerated rehabilitation surgical nursing combined with mental health education can help reduce complications and improve the quality of life of patients and nursing satisfaction. As mentioned above, accelerated rehabilitation surgical nursing can promote the recovery of gastrointestinal function and improve the psychological state of patients. Concurrently, through postoperative rehabilitation training, accelerated rehabilitation surgical nursing guides patients to promote physical recovery. The hip lifting and kicking exercises are used to exercise the patients' lower limbs, thereby promoting their functional recovery, and reducing complications such as intestinal obstruction and incision infection, improving patient activities of daily life and quality of life[28-30]. The prevention of various complications can improve the postoperative comfort of patients, and pay more attention to psychological nursing in the nursing process, timely help patients solve difficulties, and establish a good doctor-patient relationship.

The patients included in this study were from the same center, and the number of patients was also limited. The results of this study need to be confirmed by large cohort study in the future.

CONCLUSION

In summary, enhanced recovery after surgical nursing combined with mental health education can promote the recovery of gastrointestinal function, improve patients' mental health and quality of life, and reduce the incidence of complications after laparoscopic resection of liver metastases from colorectal cancer.

ARTICLE HIGHLIGHTS

Research background

Laparoscopic tumor resection is a common surgical treatment method for liver metastasis of colorectal cancer in clinical practice. However, surgical treatment cannot completely control the disease, and patients will also need to accept chemotherapy and other rehabilitation maintenance, and there is still a risk of postoperative recurrence.

Research motivation

These patients will have negative emotions such as fear and anxiety. The surgical method is in the abdomen of the patient, so it will affect the digestive function after surgery. Therefore, early nursing and psychological intervention are necessary.

Research objectives

To analyze the effect of accelerated rehabilitation surgical nursing combined with mental health education on postoperative recovery and mental health of patients undergoing laparoscopic resection of colorectal cancer liver metastases.

Research methods

One hundred and twenty patients who underwent laparoscopic resection of liver metastases of colorectal cancer were selected and divided into two groups. The control group was given routine nursing combined with mental health education intervention, while the observation group was given accelerated rehabilitation surgical nursing combined with mental health education intervention. The differences in postoperative recovery-related indices, complications and pain degrees, and mental health-related scores were compared between groups. The T lymphocyte subset levels of the two groups were also compared.

Research results

The results in the observation group were better in postoperative recovery-related indices, complications, pain degrees, and mental health-related scores than those in the control group. The nursing satisfaction of the observation group was higher than that of the control group. The physical, psychological, and social well-being, and the total FLIC scores of the observation group were higher than those in the control group after surgery.

Research conclusions

Enhanced recovery nursing combined with mental health education can promote the recovery of gastrointestinal function, improve the mental health and quality of life of patients after laparoscopic resection of colorectal cancer liver metastases, and reduce the incidence of complications.

Research perspectives

The results of this study will be confirmed in large cohort studies performed in multiple centers.

FOOTNOTES

Author contributions: Li DX and Ye W contributed equally to this work; Li DX, Ye W, and Jiang PH designed the research study; Li DX, Yang YL, Zhang L and Qian XJ performed the research; Li DX, Jiang PH and Yang YL analyzed the data and wrote the manuscript; All authors have read and approved the final manuscript.

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Country/Territory of origin: China

ORCID number: Dong-Xia Li 0009-0004-4799-8805; Xiang-Jun Qian 0000-0001-6485-0731; Ping-Hua Jiang 0009-0001-2336-163X.

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ORIGINAL ARTICLE

Retrospective Study

Changing trends in gastric and colorectal cancer among surgical patients over 85 years old: A multicenter retrospective study, 2001–2021

Ke Chen, Ming Li, Ran Xu, Ping-Ping Zheng, Meng-Ding Chen, Liang Zhu, Wen-Bin Wang, Zheng-Guang Wang

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Ke Chen, Department of Vascular Surgery, Drum Tower Hospital Affiliated to Medical School of Nanjing University, Nanjing 210000, Jiangsu Province, China

Ming Li, College of Pharmacy of Anhui Medical University, Hefei 230001, Anhui Province, China

Ran Xu, Department of General Surgery, First Affiliated Hospital of Wannan Medical College, Wuhu 241000, Anhui Province, China

Ping-Ping Zheng, Department of General Practice, First Affiliated Hospital of Bengbu Medical College, Bengbu 233000, Anhui Province, China

Meng-Ding Chen, Zheng-Guang Wang, Department of General Surgery, First Affiliated Hospital of Anhui Medical University, Hefei 231000, Anhui Province, China

Liang Zhu, Department of General Surgery, First Affiliated Hospital of University of Science and Technology of China, Hefei 230001, Anhui Province, China

Wen-Bin Wang, Department of General Surgery, Second Affiliated Hospital of Anhui Medical University, Hefei 231000, Anhui Province, China

Corresponding author: Zheng-Guang Wang, MD, PhD, Chief Doctor, Professor, Research Scientist, Department of General Surgery, First Affiliated Hospital of Anhui Medical University, No. 218 Jixi Road, Hefei 230001, Anhui Province, China.
wangzhengguang@ahmu.edu.cn

Abstract

BACKGROUND

Whether patients over 85 years old with gastrointestinal cancer should undergo surgery remains controversial. We aimed to describe the changing trends of characteristics to provide more information to decision makers, and strive to find appropriate surgical plan.

AIM

To describe the changing trends of characteristics to provide more information to

decision makers, and strive to find appropriate surgical plan.

METHODS

A total of 218 gastric cancer (GC) patients and 563 colorectal cancer (CRC) patients who underwent surgery between 2001 and 2021 were enrolled in this retrospective analysis. Changes in clinicopathological features, surgical treatments, and survival status were analyzed longitudinally at 5-year intervals.

RESULTS

Only 14 GC patients underwent laparoscopic surgery where 219 CRC patients had this procedure. Cardia and esophagogastric junction cancer increased in GC patients, and the proportion of sigmoid colon cancer decreased in CRC patients. Pulmonary infection gradually became the most common postoperative complication, its incidence in period 4 reached 48.79%. However, the incidence of anastomotic leakage decreased from 26.79% to 9.38% ($P < 0.01$). Additionally, 30-d mortality significantly decreased from 32.14% to 9.01%. Increases were observed in 5-year overall survival (OS) in GC patients from period 1 to period 4 (18.18% *vs* 33.32%, respectively) and CRC patients (0 *vs* 36.32%, respectively). Disease-free survival (DFS) also increased in GC and CRC patients (7.14% *vs* 27.74% and 0 to 36.03%, respectively). The average survival time of GC patients following radial lymphadenectomy was higher than in patients that underwent limited lymphadenectomy (26 *vs* 22 mo, respectively), the same was seen in CRC patients (44 *vs* 33 mo, respectively). This advantage was particularly evident in patients with TNM I, but not in patients with TNM II/III period cancer.

CONCLUSION

The safety as well as effectiveness of surgery in ultra-elderly patients is increasing. Radical lymphadenectomy has advantages in patients with TNM I gastrointestinal cancer, but not TNM II/III.

Key Words: Gastric cancer; Colorectal cancer; Retrospective analysis

Core Tip: The safety as well as effectiveness of surgery in ultra-elderly patients is increasing. Radical lymphadenectomy has advantages in patients with TNM I gastrointestinal cancer, but not TNM II/III.

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INTRODUCTION

Gastric cancer (GC) and colorectal cancer (CRC) are common digestive system cancers worldwide. The latest world cancer data report showed that in 2021[1], there were 1089103 new cases of GC and an expected 768793 deaths worldwide, making it the fifth highest in incidence rate. In addition, there were 1880725 new cases of CRC worldwide, and this cancer is expected to cause more than 1.3 million deaths, ranking second after lung cancer.

At present, the incidence and mortality of gastrointestinal cancer remain high. With the development of increased living standards, improved screening techniques and medical advances, all-cause mortality has declined. Consequently, most countries are facing an aging society. From 2000 to 2020, the number of people over 85 in China increased to more than 14 million, with a corresponding increase from 0.31% to 1.64%[2]. In America, the number of adults aged 85 years and older is expected to nearly triple from 6.4 million in 2016 to 19.0 million by 2060[3]. Factors that may slow or even reverse progress include high blood pressure, rising rates of diabetes, and a widening gap between the rich and poor. However, relatively little is known about the burden of gastrointestinal cancer in this special age group and most guidance related to the management of gastrointestinal cancer is based on trials undertaken in the fit, younger patient. Historically the elderly have been underrepresented in clinical trials, which frequently have a restricted inclusion to an upper age limit of 75. For this reason, knowledge about appropriate treatment methods and the complex healthcare needs of elderly cancer patients is limited.

In Japan, the life expectancy of men and women aged 85 is 8.4 and 6.2 years, respectively[4]. Therefore, the probability of diagnosis of gastrointestinal cancer in patients aged 85 and above will only increase. Due to the increase in life expectancy and progress in medical technology, patients may be more willing to undergo radical surgery. However, elderly patients inevitably experience a decline in major organ function, and postoperative complications are higher than in younger patients. These factors may lead to a significant increase in mortality. Besides, a significant number of elderly patients live in rural China, where they receive only basic medical security and the poor referral system limits access to

high quality medical care. Diagnosis and treatment of gastrointestinal cancer in older individuals are often complicated by factors such as comorbidities and cognitive impairment. Many studies have investigated the outcomes of GC and CRC surgery in different age groups[3,5-9]. However, there is very little information on the oldest old.

David *et al*[10] studied patients over 85 years old who underwent CRC resection in a single center from 2010 to 2018. The treatment effects of 48 patients over 85 years old and 136 patients between 75 and 84 years old were compared. The results revealed no significant difference in short-term effects such as severity of complications, anesthesia score, or 30-d mortality between the two groups. However, the author did not follow up on long-term survival. A study from Japan included 134 GC patients over 85 years old seen in nine centers between 2000 and 2014 and found that surgical treatment was necessary and effective in patients with stage II[11].

In this report, we present surgical information and trends from a multicenter population aged 85 years and older diagnosed with GC and CRC in China. We also discuss some of the unique challenges affecting these patients and attempt to summarize the existing evidence on how to best optimize the treatment of patients with gastrointestinal cancer in the oldest old.

MATERIALS AND METHODS

Patients and follow up

In the high incidence area of gastrointestinal cancer in China, the first affiliated hospital of Anhui Medical University, the first affiliated hospital of the University of Science and Technology of China, the first affiliated hospital of Bengbu Medical College and the first affiliated hospital of Wannan Medical College have completed more than 80000 surgeries for GC and CRC over the past 21 years. This included 781 patients over 85 years old and among these, 218 patients had GC and 563 patients had CRC.

The clinicopathological data of these patients, including age, sex, length of stay, surgical time, 30-d mortality rate after surgery, TNM period, surgical mode, pathological differentiation, tumor size, tumor location, and survival status were collected. Inclusion criteria included: pathological results clearly diagnosed GC or CRC, all patients underwent radical resection from 2001 to 2021, and all cases had complete surgical information, postoperative pathology, and follow-up data. Patients were excluded if they underwent endoscopic resection of the malignant lesion without surgical intervention, patients whose preoperative examination indicated possible distant metastasis or serious organ dysfunction, or any other special circumstances that made them not suitable for surgery.

In this study, survival time ranged from the day of surgery to the day of death (if the specific day of death was unknown, survival time was recorded as the last follow-up day). Follow-up methods included telephone follow-up and outpatient follow-up. The first follow-up was in February 2022, the second follow-up was conducted by telephone in August 2022, and the last follow-up was in January 2023.

Surgical therapy

The standard operability of each case was determined according to the Japanese guidelines for the treatment of stomach [12-14] and colorectal cancer[15-18]. Based on the clinical period and location of the cancer, each institution selects the appropriate surgical procedure and determines the scope of resection, including possible lymph node resection. Radical lymphadenectomy is applicable to cT1N0 patients who have undergone D1 or more extensive lymphadenectomy, as well as cN+ or cT2-4 patients who have undergone D2 Lymphadenectomy.

According to the Japanese Classification of Gastric Cancer, 3rd edition[19], the state of the residual tumor after surgery is also described as the R state. R0 represents no residual tumor, R1 represents a microscopic residual tumor (with a positive resection margin), and R2 represents a macroscopic residual tumor visible to the naked eye. In this study, R2 patients included patients with bypass or non-resection surgery.

Short- and long-term postoperative outcomes

Short-term outcomes included complications, operative time, blood transfusion, 30-d mortality and length of hospital stay. Postoperative complications were defined as those that arose up to 30 d postoperatively. Operative mortality was defined as death from any reason occurring less than 30 d after surgery (in or out of the hospital) and more than 30 d after surgery during the same hospitalization.

Long-term outcomes included 5-year survival [overall survival (OS) and disease-free survival (DFS)], tumor recurrence or distant metastasis, metastasis site (if distant), and postoperative chemotherapy or other treatment.

Statistical analyses

Unadjusted analysis was performed for each independent variable. Continuous variables are shown as means plus standard deviation and were compared by One Way Analysis of Variance. A P value < 0.05 was used to define statistical significance, and all analyses were performed using SPSS 19.0.

RESULTS

Anatomical distribution

Between 2000 and 2021, more than 80000 cases of gastrointestinal cancer were captured in the database of our four high-volume centers in China. This included 786 patients over 85 years old. Among these, 218 patients had GC, five patients had small intestinal cancer, and 563 patients had CRC. Five years was considered a "period," and this study covered a total of four periods (2001-2021). There were 64 people in the first period (18 GC, 46 CRC, 2001-2005), 107 people in the period phase (23 GC, 84 CRC, 2006-2010), 176 people in the third period (40 GC, 136 CRC, 2011–2015), and 434 people in the fourth period (137 GC, 297 CRC, 2016-2021).

Of the hospitals, the first affiliated hospital of Anhui Medical University had the highest number of patients (38.35%), where the first affiliated Hospital of Wannan Medical College had the lowest number (19.41%, Figure 1). Among all patients, the percentage of adenocarcinoma cases was 93.12% (203/218). This included four patients with squamous cell carcinoma and 11 patients with adenosquamous carcinoma). Tumor location data is shown in Table 1.

The location of the tumor has also been changing in these two decades, but this result is not sustainable. In the field of GC, the tumor at the antrum is still ahead of other parts at present, accounting for nearly 50% in period 4, while the proportion of cancer at the cardia or gastroesophageal junction reached the highest level in 2011-2015, nearly 40%, but shrunk to around 25% in 2016-2021. However, this is still significantly higher than the first stage, with a statistically significant difference (Figure 2A). In the field of CRC, rectal cancer has always accounted for a high proportion, while the proportion of sigmoid colon cancer has decreased significantly, with a statistically significant difference, especially in the third stage. The change trend of upper or lower rectal cancer is relatively close (Figure 2C).

Percent change of GC and CRC subgroups based on TNM stage

Of the 218 super-aged patients with GC who received surgical treatment, a total of 18 patients were included in the study in period 1, 23 patients were included in period 2, and 40 and 137 patients were enrolled in period 3 and period 4, respectively. According to the postoperative pathological results, each patient was accurately phased using the TNM staging system. The percentage of TNM I stage tumors decreased from 72.23% in period 1 to 13.14% in period 4, where the percentage of TNM III tumors increased from 16.67% to 47.75% ($P < 0.001$, Figure 2B). In CRC patients, 44.74% of cases had TNM I stage tumors in period 1 and this decreased to 14.98% in period 4. Overall, the number of TNM II tumors increased by more than half in two decades. However, the number of TNM III remained almost unchanged (Figure 2D).

Changes in clinicopathological characteristics of GC and CRC in patients over 85 years old

Among the 218 patients with GC who underwent surgery, the ratio of men to women was 4.32:1. This was much higher than GC patients in other age groups (2.6:1, data not shown). In the CRC group, the ratio of men to women was 3.61:1, which was higher than CRC patients in other age groups (2.49:1, data not shown). The average age of all GC cases increased from period 1 (87.12 ± 1.98 years) to period 5 (88.81 ± 2.34 years), however, the change was not statistically different. A similar trend was seen in patients with CRC. In GC patients, the largest tumor size decreased from period 1 (4.45 ± 3.09 cm) to period 4 (3.63 ± 2.74 cm). The percentage of highly differentiated tumors decreased from 45.7% in period 1 to 9.08% in period 5. However, the percentage of poorly differentiated tumors increased from 24.31% to 69.24% ($P < 0.001$). The percentage of pT1 tumors gradually decreased over time from 72.22% in period 1 to 13.14% in period 5 ($P < 0.001$, Table 2).

In CRC patients, the largest tumor size decreased from period 1 (5.41 ± 3.07 cm) to period 4 (5.02 ± 2.76 cm). The percentage of highly differentiated tumors decreased from 35.7% in period 1 to 19.8% in period 5, where the percentage of poorly differentiated tumors increased from 34.35% to 65.22% ($P < 0.001$). The percentage of pT1 tumors gradually decreased over time from 55.32% in phase 1 to 10.81% in phase 5 ($P < 0.001$). Additionally, 65.14% of GC patients (142/218) and 78.68% of CRC patients underwent radical lymphadenectomy.

Changes in surgical treatment

Another noteworthy change was the use of laparoscopic surgery. In the first and second periods, there was no record of laparoscopic surgery use in GC or CRC patients. However, this increased rapidly starting in period 3, especially in patients with CRC.

Of the 218 patients with GC, 204 underwent open surgery and 14 underwent laparoscopic surgery. The first case of GC laparoscopic surgery in a patient over 85 years old occurred in 2016. Roux-en-Y reconstruction gradually became the dominant mode, compared to period 1, the incidence of period 4 increased to 71.2% ($P < 0.001$), and the average number of harvested lymph nodes in period 4 increased significantly ($P < 0.001$). The rate of combined organ resection remained low across the four periods. The most common organ resection was the spleen. There were few records of patients entering the intensive care unit (ICU) after surgery in the first and second periods. However, the proportion of GC patients entering ICU after surgery in the fourth period was close to 90%.

Of the 563 CRC patients, 344 underwent open surgery and 219 underwent laparoscopic surgery. The first case of laparoscopic CRC surgery in a patient over 85 years old occurred in 2009. In the fourth period, the percentage of CRC patients undergoing laparoscopic surgery reached 49.97%, and the average number of harvested lymph nodes in the fourth period increased significantly to 17.11 ($P < 0.001$). The rate of combined organ resection in the fifth period increased from 12.8% to 16.4% ($P < 0.001$), and the percentage of patients admitted to the ICU after surgery was 61.00% in period 4.

Table 1 Anatomical distribution of gastric cancer and colorectal cancer between 2001 and 2021, *n* (%)

Tumor location		Period 1 (*n* = 18)	Period 2 (*n* = 23)	Period 3 (*n* = 40)	Period 4 (*n* = 137)
GC	The cardia or gastroesophageal, junction (*n* = 58)	3 (16.67%)	5 (21.74)	16 (40.00)	34 (24.82)
	Stomach body (*n* = 50)	5 (27.78)	10 (43.48)	7 (17.50)	28 (20.44)
	Gastric antrum (*n* = 91)	10 (55.55)	7 (30.43)	8 (20.00)	66 (48.18)
	Whole stomach (*n* = 19)	0	1 (4.35)	9 (22.50)	9 (6.56)
Tumor location		**Period 1 (*n* = 38)**	**Period 2 (*n* = 64)**	**Period 3 (*n* = 154)**	**Period 4 (*n* = 307)**
CRC	Ileocecal region (*n* = 28)	2 (5.25)	2 (3.13)	3 (1.95)	21 (6.84)
	Ascending colon or the hepatic, curvature of the colon (*n* = 28)	0	3 (4.69)	7 (4.55)	18 (5.86)
	Transverse colon (*n* = 28)	1 (2.63)	6 (9.37)	10 (6.49)	11 (3.58)
	Splenic or descending colon (*n* = 19)	1 (2.63)	4 (6.25)	3 (1.95)	11 (3.58)
	Sigmoid colon (*n* = 149)	17 (44.75)	23 (35.94)	30 (19.48)	79 (25.74)
	Uppermost segmzent of the rectum (*n* = 181)	10 (26.32)	16 (25.00)	60 (38.96)	95 (30.94)
	Lower segment of the rectum (*n* = 130)	7 (18.42)	10 (15.62)	41 (26.62)	72 (23.46)

GC: Gastric cancer; CRC: Colorectal cancer.

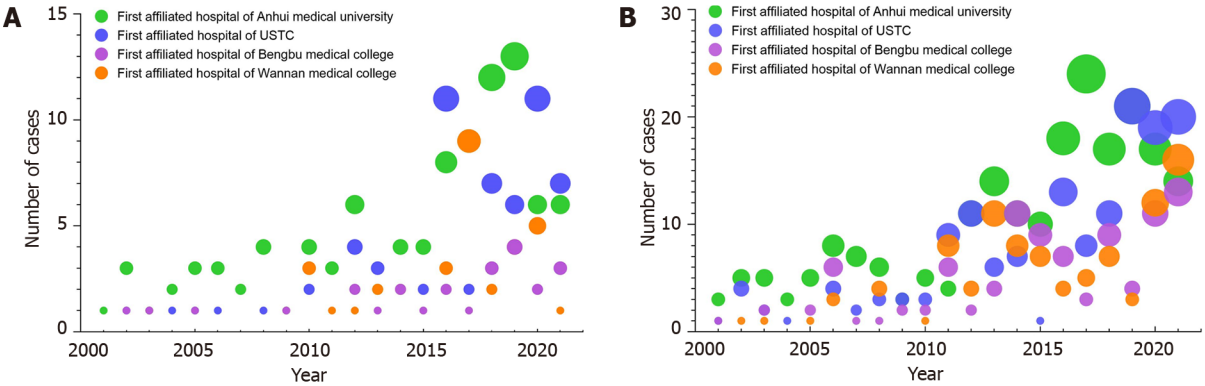

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Figure 1 The numbers of radical surgery for the oldest old patients with gastric cancer and colorectal cancer in four top hospitals in China. A: The numbers of radical surgery for the oldest old patients with gastric cancer from 2001 to 2021; B: The numbers of radical surgery for the oldest old patients with colorectal cancer from 2001 to 2021.

Changes in postoperative complications

A changing trend was also observed in postoperative complications over the past 21 years. The overall complication rate was at a relatively high level (100% in the first period) but it dropped to 84.01% in the fourth period. The main causes of death included multiple organ failure, severe infection, hemorrhage, and possible thrombosis, which are all significantly related to organ dysfunction in elderly patients. However, progress in medical technology and the optimization of advanced life support have significantly reduced perioperative mortality, as evidenced by a decrease from 32.14% in period 1 to 9.01% in period 4. Pulmonary infection gradually became the largest source of postoperative complications, rising from 16.07% in period 1 to 48.79% in period 4. We believe that the number in period 1 may be underestimated, although the observed change may be consistent with the actual trend. Further, anastomotic leakage is another common and serious complication whose incidence decreased significantly from 26.79% in period 1 to 9.38% in period 4. This change may be related to the use of staplers and progress in nutritional support (Table 3).

Changes in OS and DFS

Trends in OS and DFS of patients over 85 years old was examined across the 12-264 mo of follow-up. DFS data from some patients could not be included due to the long follow-up time or uncertain causes of death, so these patients were deleted when drawing the DFS curve. In this study, the longest survival time after surgery for GC was 152 mo (TNM I, died in 2015), and the longest survival time after surgery for CRC was 121 mo (TNM I, died in 2017). The prognosis of patients with TNM I is significantly better than that of other periods. This has been confirmed many times in patients from the general age group, but is also true in the ultra-elderly group. The 5-year OS (18.18% in period 1 *vs* 33.32% in period 4) and

Table 2 Patients' characteristics and perisurgical outcomes

	GC (*n* = 218)	CRC (*n* = 563)
Age (yr)	85-95	85-96
Sex (male/female)	177/41	441/122
hospital stay	19.45 ± 7.22	15.61 ± 6.07
(Post-operation, d)		
Comorbidity		
Hypertension	194	510
Respiratory disease	17	50
Diabetes mellitus	29	61
ASA stage		
I	11	25
II	144	416
III	55	103
Missed	8	19
Procedure		
Open	204	304
Laparoscopy	14	219
Lymphadenectomy		
Limited	76	120
Radical	142	443
Resection		
R0	197	471
R1	21	92
Number of resected LN	12.78 ± 5.33	11.44 ± 6.17
Operative time (mins)	155.04 ± 69.52	129.90 ± 47.76
Blood transfusion	148	157
Tumor size (cm)	3.24 ± 2.03	4.37 ± 2.10
Differentiation		
High	29	48
Middle	68	118
Low	121	397
TNM stage		
I	65	73
II	68	384
III	85	106

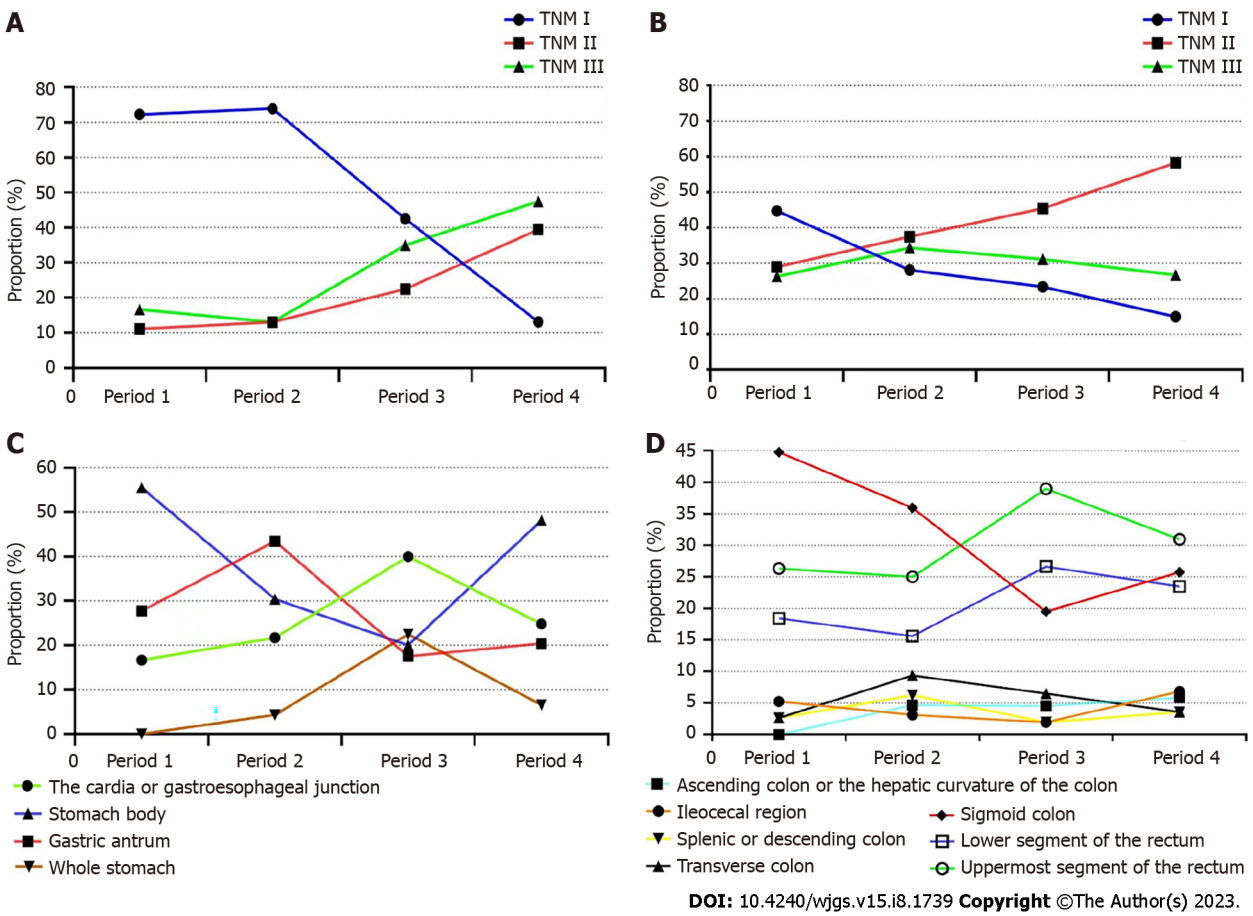
GC: Gastric cancer; CRC: Colorectal cancer; ASA: American Society of Anesthesiologists:

DFS (7.14% *vs* 27.74%, respectively) in patients with GC increased (Figure 3), this was also noted in CRC (5-year OS: 0%-36.32% and 5-year DFS: 0%-36.03%). Compared to patients that underwent limited lymphadenectomy, the average survival time of patients who underwent radical lymphadenectomy for GC (22 *vs* 26 months for limited and radical treatments, respectively) and CRC (33 *vs* 44 mo, respectively) was higher (Figure 4). This advantage was particularly evident in patients with TNM I, but not in patients with TNM II/III.

Table 3 Changes in postoperative complications, *n* (%)

	Period 1 (*n* = 56)	Period 2 (*n* = 87)	Period 3 (*n* = 194)	Period 4 (*n* = 444)	*P* value[1]
Postoperative complications	56 (100)	80 (91.95)	182 (93.81)	373 (84.01)	< 0.01
Pulmonary complications	9 (16.07)	28 (35.00)	73 (40.12)	182 (48.79)	
Pleural effusion	9 (16.07)	8 (10.00)	25 (13.74)	39 (10.46)	
Intra-abdominal infection	6 (10.71)	6 (7.50)	17 (9.34)	30 (8.04)	
Intra-abdominal hemorrhage	6 (10.71)	4 (5.00)	11 (6.04)	21 (5.64)	
Leakage	15 (26.79)	16 (20.00)	28 (15.38)	35 (9.38)	
Wound infection	8 (14.30)	9 (11.25)	13 (7.14)	33 (8.845)	
Others[2]	3 (5.35)	9 (11.25)	15 (8.24)	33 (8.845)	
Operative mortality[3]	18 (32.14)	17 (19.54)	29 (14.95)	40 (9.01)	< 0.01

[1]Comparisons were performed with χ^2 test for categorical variables.
[2]Others include chest hemorrhage, pancreatitis, cardiocerebral events, venous thrombosis and someone who has multiple complications at the same time.
[3]Operative mortality was any death, regardless of cause, occurring less than 30 days after surgery in or out of the hospital and more than 30 days, during the same hospitalization, after the operation.



DOI: 10.4240/wjgs.v15.i8.1739

Figure 2 From 2001 to 2021, the change of the proportion of lesion sites and TNM stage of postoperative pathology in all patients aged 85 and over. A: The change of lesion sites in patients with gastric cancer; B: The change of lesion sites in patients with colorectal cancer; C: The change of TNM stage in patients with gastric cancer; D: The change of TNM stage in patients with colorectal cancer.

DISCUSSION

Significant changes in the epidemiological characteristics and treatment of GC and CRC in elderly patients in the past two

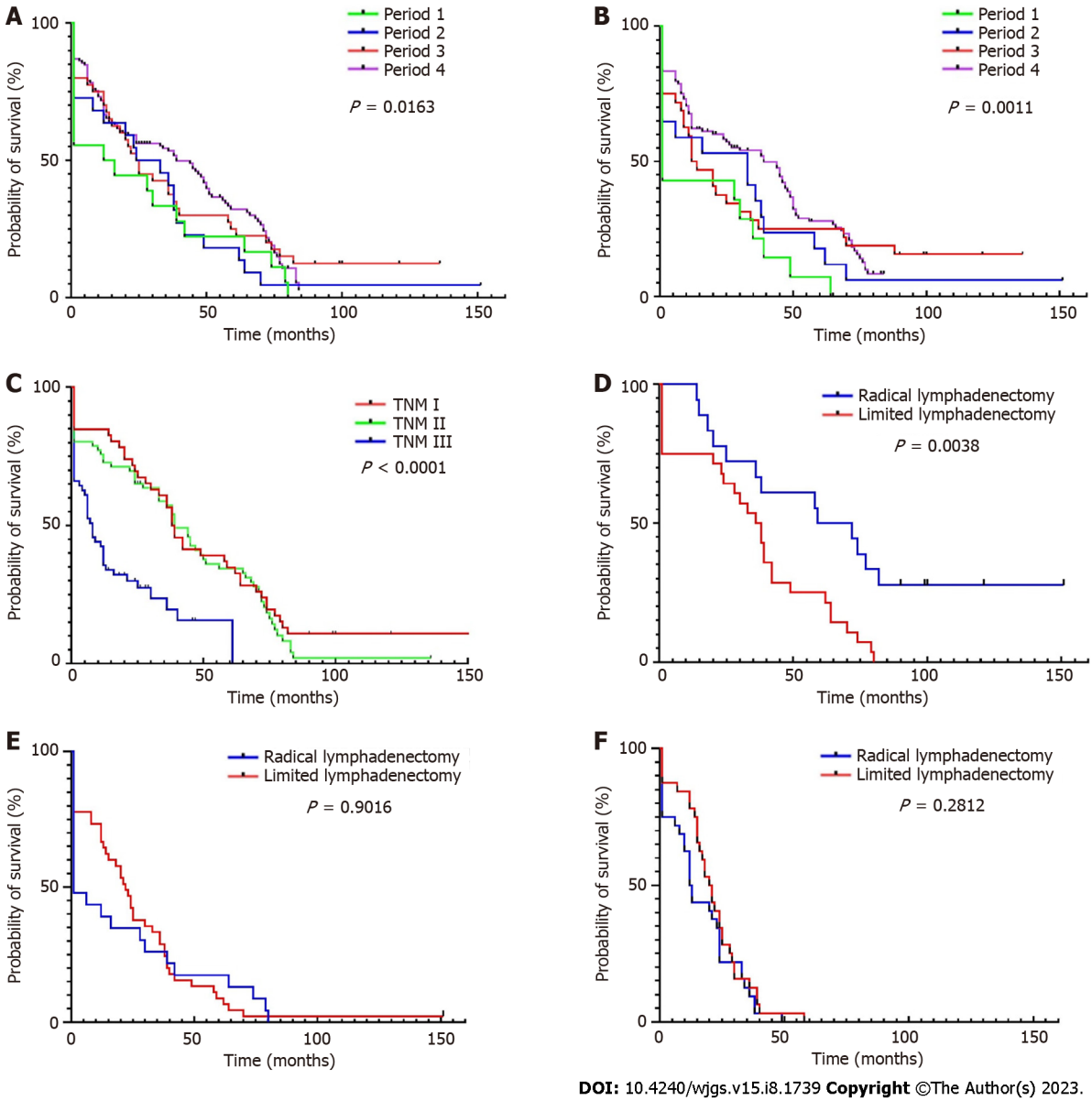


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Figure 3 Survival of gastric cancer patients. A and B: The overall survival and disease-free survival in different periods; C: The overall survival of patients with different TNM stage; D-F: The differences in survival of patients at different TNM stages (I-III) undergoing radical and limited lymphadenectomy.

decades have been noted[20,21]. However, the incidence of gastrointestinal cancer in the elderly over 85 years old is rarely reported, especially in China. In this retrospective study, data from four top hospitals over the past 20 years were collected. Among more than 80000 patients who underwent gastrointestinal surgery, the clinicopathological data of 781 patients over 85 years old were finally selected for analysis. The goal was to describe the changing trends of various influencing factors.

GC accounted for 34.1% of all gastrointestinal cancers in this multicenter study. The prevalence of GC is higher in China than in western countries. However, due to the relatively high trauma and risk of surgery, the number of ultra-elderly patients receiving radical surgery for GC in the first two periods was very low. Starting from the third period, these numbers increased rapidly. A study included 2914 oldest old patients from 2006 to 2015 demonstrated that the oldest old patients with period I-III GC could benefit from elective surgery[22], this is consistent with our results. Surgical trauma and time were significantly less in laparoscopic surgery than in traditional open surgery. Therefore, patients in good physical condition and health choose surgery to prolong their lives for as long as possible. It is worth noting that starting in the third period, the application rate of laparoscopic surgery in CRC patients began increasing. This is because laparoscopic technologies, including surgical robot technology, have been increasingly applied in China, and surgeons are becoming more familiar with laparoscopic surgery. Additionally, patients are embracing the advantages of laparoscopy such as the dramatic reduction in surgical incisions and in some cases, incision-free surgery (*via* the natural duct). The fine and individual control of the procedure and more accurate control of negative incisional margins are also advantages, but these are at the expense of longer surgical time and a high CO_2 abdominal environment. However, most patients do benefit from this procedure.

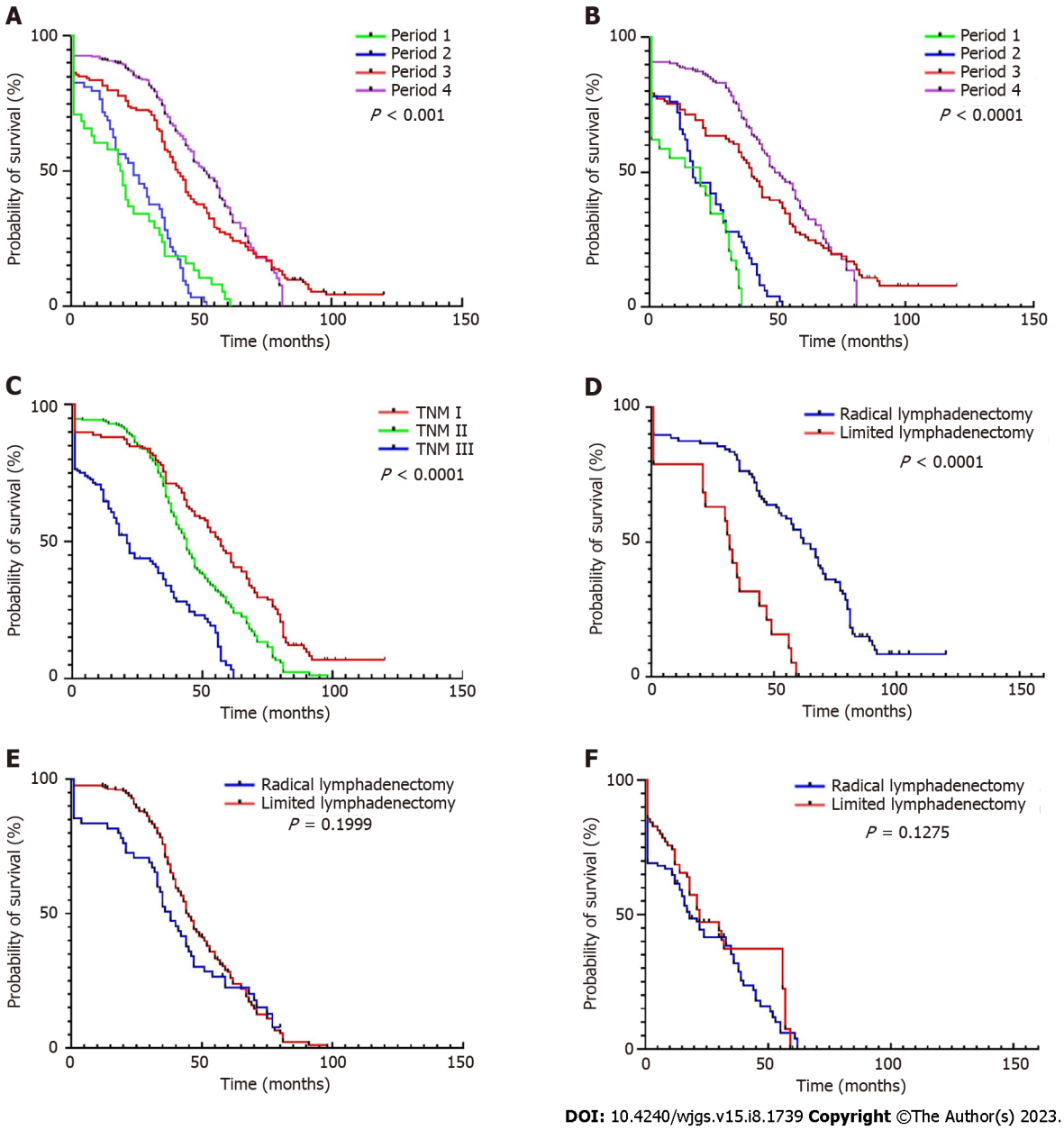

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Figure 4 Survival of colorectal cancer patients. A and B: The overall survival and disease-free survival in different periods; C: The overall survival of patients with different TNM stage; D-F: The differences in survival of patients at different TNM stages (I-III) undergoing radical and limited lymphadenectomy.

Correspondingly, the proportion of people receiving laparoscopic radical gastrectomy in the elderly population remains low, which may be due to its complex anatomical position, the fact that laparoscopic radical gastrectomy may require a longer learning curve, and the need for long-term tacit cooperation of assistants. Even in the fourth period of the most rapid development of laparoscopy, only seven patients over the age of 85 had received laparoscopic radical gastrectomy for GC in this study. In addition to the above common factors, this may also be because manual surgery minimizes the surgical time, resulting in a shorter recovery time. As can be seen from the surgical time, the duration of laparoscopic radical gastrectomy in the seven cases was significantly higher than that of conventional open surgery, although no cases were transferred to open surgery. There was no statistical difference between laparoscopic and open surgical time for CRC, which may be because the advantages of laparoscopic surgery in lower rectal cancer or complex CRC surgery compensate for the long duration of traditional laparoscopic surgery. We should also note that the number of intraoperative or postoperative blood transfusions decreased significantly over the 20-year period, particularly in CRC (51.04% in period 1 to 30.17% in period 4 ($P < 0.01$). In addition, the number of surgical transfusions for GC also decreased significantly; the percentage of intraoperative or postoperative transfusions for GC was 100% in period 1 and 67.79% in period 4 ($P < 0.01$). These results indicate that a more complete system has been established in the past 20 years in terms of gastrointestinal tumor anatomy, surgical approach, and lymph node dissection scope, leading to a shorter net surgical time and better control of bleeding.

It is important to note that in this multicenter series, the proportion of TNM period I gastrointestinal tumors in surgical procedures decreased, despite an increase in the overall number of procedures. It is particularly noteworthy that this

change was particularly obvious in period 4. The significant advantages of digestive endoscopy in addressing early gastrointestinal tumors in elderly patients is evident from this study. We collected the relevant endoscopic-submucosal-dissection (ESD)/endoscopic mucosal resection (EMR).

ESD/EMR information of ultra-elderly patients from the First Affiliated Hospital of Anhui Medical University and Anhui Provincial Hospital (not shown in the results). The earliest clinical cases were from 2015. The patients who underwent radical surgery for period I gastrointestinal cancer in these two hospitals during the same time-period were collected. When no metastatic lymph nodes were indicated by postoperative pathology, there was no statistically significant difference in 3-year survival between patients who underwent ESD/EMR surgery and those who underwent radical surgery, and the cost of surgery was halved.

We also noted changes in focal sites over the two decades. The incidence of cardia cancer is increasing in developed countries. Before 2010, the main site of GC in China was the antrum. However, after 2015, the main site became the junction of the stomach and esophagus. This may be due to progress in digestive endoscopy technologies, which has increased the identification of lesions at the base of the cardia stomach, consistent with the changing epidemiologic characteristics of GC. The incidence of non-cardia GC has been steadily declining over the past half century. This is associated with the eradication of *Helicobacter pylori* and improved food preservation technologies. Further, the incidence of colon cancer is also gradually increasing. Prior to 2010, rectal cancer accounted for more than 70% of all CRC cases. However, during 2015-2020, this trend fundamentally changed, and colon cancer now accounts for 50% of CRC. This is consistent with the epidemiological characteristics of colon cancer in Chinese society, and may be due to changes in lifestyle and diet.

Surgical resection plus D2 Lymphadenectomy is becoming the standard treatment for gastrointestinal cancers. With these changes, the number of lymph nodes harvested during surgery increased from 6.1 in period 1 to 19.2 in period 4. The dissection and examination of lymph nodes have become increasingly standardized over the last two decades. Improvement in surgical skills involves the accumulation of experience by the surgeon, the use of monopolar electrocautery and an ultrasonic scalpel during the procedure, and the adoption of standardized lymph node dissection techniques[23-25].

A limitation of this study is that it was restricted to surgical cases; patients with non-resective surgery (bypass or biopsy only) were excluded. This may have led to selection bias. Ultra-aged patients who ultimately decided to undergo surgery are generally considered to be in good health and able to complete their activities of daily life, which does not reflect the actual situation of all ultra-elderly patients. Another shortcoming is that the 5-year survival period of all patients could not be included, which may have impacted the overall survival status.

CONCLUSION

The safety as well as effectiveness of surgery in ultra-elderly patients is increasing. Radical lymphadenectomy has advantages in patients with TNM I gastrointestinal cancer, but not TNM II/III.

ARTICLE HIGHLIGHTS

Research background

An increasing number of patients over 85 years old are receiving surgical treatment for gastric cancer (GC) and colorectal cancer (CRC). The number of surgical patients in 2016-2021 was nearly eight times that of patients in 2001-2005 in China. TNM stage and the number of tumor prone sites changed significantly, and the incidence of perioperative complications significantly decreased. Perioperative mortality in the last period was 71.97% lower than it was in the first period. Laparoscopic technology is increasingly used in elderly patients with CRC, but its uptake in the field of GC is slow. In patients with TNM I stage, radical rather than limited lymphadenectomy should be prioritized.

Research motivation

Whether patients over 85 years old with gastrointestinal cancer should undergo surgery remains controversial.

Research objectives

describe the changing trends of characteristics to provide more information to decision makers, and strive to find appropriate surgical plan.

Research methods

Retrospective analysis.

Research results

Only 14 GC patients underwent laparoscopic surgery where 219 CRC patients had this procedure. Cardia and esophagogastric junction cancer increased in GC patients, and the proportion of sigmoid colon cancer decreased in CRC patients. Pulmonary infection gradually became the most common postoperative complication, its incidence in period 4 reached 48.79%. However, the incidence of anastomotic leakage decreased from 26.79% to 9.38% ($P < 0.01$). Additionally, 30-d

mortality significantly decreased from 32.14% to 9.01%. Increases were observed in 5-year OS in GC patients from period 1 to period 4 (18.18% *vs* 33.32%, respectively) and CRC patients (0 *vs* 36.32%, respectively). DFS also increased in GC and CRC patients (7.14% *vs* 27.74% and 0 to 36.03%, respectively). The average survival time of GC patients following radial lymphadenectomy was higher than in patients that underwent limited lymphadenectomy (26 *vs* 22 mo, respectively), the same was seen in CRC patients (44 *vs* 33 mo, respectively). This advantage was particularly evident in patients with TNM I, but not in patients with TNM II/III period cancer.

Research conclusions

The safety as well as effectiveness of surgery in ultra-elderly patients is increasing. Radical lymphadenectomy has advantages in patients with TNM I gastrointestinal cancer, but not TNM II/III.

Research perspectives

Gastric cancer, colorectal cancer.

FOOTNOTES

Author contributions: Chen K and Ming Li and Ran Xu contributed equally to this work; Chen K, Li M, Xu R, Zheng PP, Chen MD and Zhu L collected data; Chen K, Li M and Xu R wrote the manuscript; Zheng PP, Chen MD and Zhu L analyzed the data; Wang WB and Wang ZG designed ideas.

Institutional review board statement: The study was reviewed and approved by the Clinical Medical Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University (PJ2023-07-56).

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Country/Territory of origin: China

ORCID number: Ke Chen 0000-0001-9354-5197; Ping-Ping Zheng 0000-0001-8995-2195; Zheng-Guang Wang 0000-0001-9354-4443.

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ORIGINAL ARTICLE

Observational Study

Knowledge, attitude, and practice of monitoring early gastric cancer after endoscopic submucosal dissection

Xiao-Yun Yang, Cong Wang, Yi-Ping Hong, Ting-Ting Zhu, Lu-Jia Qian, Yi-Bing Hu, Li-Hong Teng, Jin Ding

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Xiao-Yun Yang, Cong Wang, Yi-Ping Hong, Ting-Ting Zhu, Yi-Bing Hu, Li-Hong Teng, Jin Ding, Department of Gastroenterology and Hepatology, The Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua 321000, Zhejiang Province, China

Lu-Jia Qian, Department of Pathology, The Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua 321000, Zhejiang Province, China

Corresponding author: Jin Ding, MD, Associate Professor, Chief Physician, Department of Gastroenterology and Hepatology, The Affiliated Jinhua Hospital, Zhejiang University School of Medicine, No. 365 Renmin East Road, Jinhua 321000, Zhejiang Province, China. jhdingjin@zju.edu.cn

Abstract

BACKGROUND

Early gastric cancer (EGC) is typically treated with endoscopic submucosal dissection (ESD). However, recurrence may occur after ESD, requiring surveillance.

AIM

To examine the knowledge, attitude, and practice (KAP) of EGC survivors following ESD regarding gastric cancer recurrence.

METHODS

This cross-sectional study was conducted between June 1, 2022 and October 1, 2022 in Zhejiang, China. A total of 400 EGC survivors who underwent ESD at the Affiliated Jinhua Hospital, Zhejiang University School of Medicine participated in this study. A self-administered questionnaire was developed to assess KAP monitoring gastric cancer after ESD.

RESULTS

The average scores for KAP were 3.34, 23.76, and 5.75 out of 5, 30, and 11, respectively. Pearson correlation analysis revealed positive and significant correlations between knowledge and attitude, knowledge and practice, and attitude and practice (r = 0.405, 0.511, and 0.458, respectively; all $P < 0.001$). Multivariate logistic regression analysis showed that knowledge, attitude, 13-24 mo since the last ESD (*vs* ≤ 12 mo since the last ESD), and ≥ 25 mo since the last ESD (*vs* ≤ 12 mo since the last ESD) were independent predictors of proactive practice (odds ratio = 1.916, 1.253, 3.296, and 5.768, respectively, all $P < 0.0001$).

CONCLUSION
EGC survivors showed inadequate knowledge, positive attitude, and poor practices in monitoring recurrences after ESD. Adequate knowledge, positive attitude, and a longer time since the last ESD were associated with practice.

Key Words: Attitudes; Endoscopic submucosal dissection; Gastric cancer; Knowledge; Practice; Recurrence

Core Tip: This is the first study to examine the knowledge, attitude, and practice regarding monitoring of gastric cancer recurrence after endoscopic submucosal dissection (ESD). Participants' average knowledge, attitude, and practice scores indicated inadequate knowledge, good attitude, and poor practice. Significant and positive correlations were found between knowledge and attitude, knowledge and practice, and attitude and practice. Sufficient knowledge, a positive attitude, and at least 12 mo since the last ESD were independent predictors for correct practice. The lack of knowledge and insufficient practice in monitoring cancer recurrence may explain the 89.2% of pathologically confirmed early tumors after ESD.

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INTRODUCTION

Gastric cancer is the fifth most common cancer and the third leading cause of cancer deaths globally[1]. In China, gastric cancer is the third leading cause of cancer-related deaths, with more than 500000 new cases expected in 2022[2]. Early gastric cancer (EGC) refers to cancers located in the mucosa or submucosa of the stomach regardless of local lymph node metastasis, with a better prognosis than advanced gastric cancer[3].

Endoscopic submucosal dissection (ESD) is considered the first-line treatment for EGC regardless of its size or ulceration[4]. When compared to gastrectomy, ESD provides faster recovery, lower costs, and superior quality of life for patients with EGC. However, non-curative resection can occur after ESD and is strongly associated with the incidence of local recurrence resulting from incomplete resection, undifferentiated histology, a tumor-positive resection margin, lymphovascular invasion, or a depth of invasion greater than one-third of the submucosa[5]. In the 5 years following ESD, there is a cumulative incidence of 11.9% of local recurrences[6]. EGC survivors following ESD have a higher recurrence rate compared with those following gastrectomy[7]. A clinical application of the expanded criteria for ESD further increases the local recurrence rate of EGC[8,9]. Since early detection of recurrence improves survival for patients with gastric cancer[10,11], monitoring the recurrence of gastric cancer after ESD is essential in patients as part of a surveillance strategy. However, little is known if patients understand the importance and how to monitor the recurrence of gastric cancer after ESD.

This is the first study to assess knowledge, attitude, and practice (KAP) regarding monitoring the recurrence of gastric cancer among EGC survivors after ESD in Zhejiang, China. We evaluated the KAP related to gastric cancer recurrence, reexamination, and follow-up. Furthermore, we examined sociodemographic factors associated with the practice of monitoring gastric cancer recurrence. The results may help medical practitioners improve the KAP of patients with EGC after ESD and facilitate early detection of gastric cancer recurrence.

MATERIALS AND METHODS

Study design and subjects

This cross-sectional study survey was conducted at the Affiliated Jinhua Hospital, Zhejiang University School of Medicine between June 1, 2022 and October 1, 2022. The design phase started in June, focusing on feasibility and ethical considerations. Participants were recruited in July. Data collection and questionnaire surveys began in August. We conducted individual follow-ups and communicated with patients *via* phone calls. A total of 400 EGC survivors following ESD were recruited by phone. This study was approved by the Ethics Committee of Jinhua Hospital [Approval No. (2022) Lunshendi (211)]. All participants provided informed consent. The inclusion criteria were as follows: (1) Patients underwent ESD for EGC at Jinhua Hospital; (2) Pathology after ESD revealed high-grade intraepithelial neoplasia, intramucosal carcinoma, or submucosal invasion < 500 μm; and (3) Participants were willing to take part in this study. The exclusion criteria were as follows: (1) Patients were unable to complete the questionnaire survey due to their inability to write or psychological diseases; and (2) Patients who underwent further gastric surgery.

Questionnaire

The questionnaire was self-designed based on previous studies[12,13] and contained 40 questions in four categories in Chinese, including personal information (18 questions), knowledge (5 questions), attitude (6 questions), and practice (11 questions). The knowledge category scored 0-5 points, with 1 point awarded for each correct answer and 0 points for each wrong or unclear answer. The attitude category scored 6-30 points, with 5 points for a positive attitude and 1 point for a negative attitude. The practice category scores ranged from 0-11. Answers of "yes" were given 1 point, whereas answers of "no" were given 0 points. Cronbach's α of the questionnaire was 0.841. Patients were recruited by telephone calls from the hospital. Patients who agreed to participate in this study were surveyed when they came to the hospital for follow-up. After the questionnaire survey was completed, investigators assessed the completeness, internal continuity, and rationality of the questionnaire. In cases where the questionnaire was incomplete, we contacted the patient by phone and, if necessary, assisted their family in answering it. Twenty-five patients did not come for follow-up. A cut-off point of at least 70% was used to categorize good knowledge, positive attitude, and good practice[14].

Sample size

Due to the lack of relevant literature, the sample size was calculated based on an anticipated proportion of 50% of ECG survivors engaging in monitoring EGC, with a 95% confidence level and a 5% margin of error[15,16]. As a result, we determined that a sample size of 384 was required.

Statistical analysis

Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. If conforming to the normal distribution, they were expressed as mean ± SD and compared between two groups using the Student's *t*-test. If not conforming to the normal distribution, they were expressed as medians (ranges) and compared between two groups using the Mann-Whitney *U*-test. As for continuous variables among three or more groups, they were compared using the analysis of variance (a normal distribution with equal variance) or the Kruskal-Wallis test (skew distribution or unequal variance). Correlations were tested using Spearman's test. Categorical variables were expressed as *n* (%). The influencing factors of proactive practice (categorized according to at least 70%) were explored using multivariate logistic regression. Variables with $P < 0.05$ were included in the multivariate logistic regression analysis. Two-sided P values < 0.05 were considered statistically significant. The data were analyzed using SPSS 26.0 (IBM Corp., Armonk, NY, United States).

RESULTS

The KAP scores were 3.34 ± 1.42 (66.8%), 23.76 ± 2.81 (79.2%), and 5.75 ± 2.35 (52.3%), respectively (Table 1). Knowledge scores were significantly higher for participants from urban areas, with higher education levels, with professional or technical occupations, with higher family incomes, with a longer time since the last ESD, and without smoking or alcohol use history (all $P < 0.05$). The participants with a longer time since the last ESD and without alcohol drinking had significantly more positive attitudes regarding monitoring gastric cancer after ESD (both $P < 0.01$). Compared to their counterparts, patients with medical insurance, with a longer time since their last ESD, and who did not smoke or drink alcohol were more likely to practice well in monitoring cancer recurrence after ESD (all $P < 0.05$). The distribution of knowledge scores showed that over 80.0% of patients were aware that follow-up, reexamination, and cessation of smoking and drinking alcohol following ESD are necessary, while less than 20.0% knew that gastric cancer will relapse after ESD (Figure 1). In the attitude assessment, 66.3% of participants believed that reexamination after ESD is not necessary, and none wanted to undergo regular follow-ups after ESD (Table 2). According to the practice assessment (Table 3), over 80.0% of patients followed a low-salt diet, stopped drinking alcohol, and took dietary supplements or Traditional Chinese Medicine after ESD. A surprising 96.5% of patients gained or lost more than 5 kg after ESD, with only 18.0% of them exercising regularly.

Table 4 shows significant positive correlations between knowledge-attitude, knowledge-practice, and attitude-practice, with correlation coefficients of 0.405, 0.511, and 0.458, respectively (all $P < 0.0001$). The multivariate analysis further revealed that knowledge scores [odds ratio (OR) = 1.916; 95% confidence interval (CI): 1.424-2.578; $P < 0.001$], attitude scores (OR = 1.253; 95%CI: 1.124-1.396; $P < 0.001$), and the duration since the last ESD of 13-24 mo (*vs* ≤ 12 mo since the last ESD; OR = 3.296; 95%CI: 1.761-6.172; $P < 0.001$) and ≥ 25 mo (*vs* ≤ 12 mo since the last ESD; OR = 5.768; 95%CI: 2.963-11.226; $P < 0.001$) were independent predictors of proactive practice (Table 5).

DISCUSSION

This is the first study to examine KAP regarding monitoring of gastric cancer recurrence after ESD. In terms of monitoring gastric cancer recurrences after ESD, participants' average KAP scores indicated inadequate knowledge, good attitude, and poor practice. Significant and positive correlations were found between knowledge and attitude, knowledge and practice, and attitude and practice. Sufficient knowledge, a positive attitude, and at least 12 mo since the last ESD were independent predictors for correct practice. The lack of knowledge and insufficient practice in monitoring cancer recurrence may explain 89.2% (43/400) of pathologically confirmed early tumors after ESD.

In our study, KAP scores were significantly higher among patients with a longer time since ESD, indicating that these patients have more time to gain knowledge and improve their attitude and practice related to monitoring cancer

Table 1 Participant' demographics and knowledge, attitude, and practice scores regarding gastric cancer recurrence after endoscopic submucosal dissection

Characteristic	Number of participants	Knowledge score		Attitude score		Practice score	
		mean ± SD	*P*	mean ± SD	*P*	mean ± SD	*P*
Total	400	3.34 ± 1.42		23.76 ± 2.81		5.75 ± 2.35	
Sex			0.266		0.517		0.537
Male	192	3.26 ± 1.46		23.86 ± 3.04		5.83 ± 2.46	
Female	208	3.42 ± 1.38		23.68 ± 2.58		5.68 ± 2.25	
Age in yr			0.063		0.930		0.689
≤ 40	35	3.57 ± 1.12		23.83 ± 2.47		5.31 ± 1.94	
41-50	56	3.57 ± 1.28		23.88 ± 2.34		5.73 ± 2.39	
51-60	117	3.49 ± 1.36		23.62 ± 2.72		5.75 ± 2.45	
> 60	192	3.15 ± 1.52		23.81 ± 3.05		5.84 ± 2.35	
Residency			0.001		0.425		0.510
Rural areas	333	3.25 ± 1.46		23.71 ± 2.88		5.72 ± 2.34	
Urban areas	67	3.79 ± 1.10		24.01 ± 2.40		5.93 ± 2.40	
Education			0.001		0.418		0.737
Junior middle school or lower	297	3.20 ± 1.48		23.66 ± 2.90		5.72 ± 2.33	
Senior middle school/technical secondary school	55	3.71 ± 1.13		24.04 ± 2.50		5.69 ± 2.27	
Junior college/college or higher	48	3.81 ± 1.10		24.13 ± 2.59		6.00 ± 2.59	
Occupation			0.000		0.512		0.407
General staff or relevant personnel	77	3.70 ± 1.15		23.95 ± 2.45		5.92 ± 2.45	
Professional and technical staff	10	4.50 ± 0.53		24.60 ± 2.95		6.80 ± 2.97	
Others	313	3.22 ± 1.47		23.69 ± 2.89		5.68 ± 2.30	
Medical insurance			0.125		0.128		0.013
Yes	384	3.32 ± 1.43		23.72 ± 2.69		5.69 ± 2.35	
No	16	3.88 ± 1.03		24.81 ± 5.01		7.19 ± 2.07	
Family income in Yuan			0.002		0.116		0.977
< 2000	51	2.92 ± 1.59		23.12 ± 2.30		5.69 ± 2.08	
2000-5000	247	3.29 ± 1.47		23.89 ± 2.91		5.77 ± 2.37	
> 5000	102	3.69 ± 1.09		23.79 ± 2.79		5.75 ± 2.45	
The time since last ESD in mo			0.001		0.000		0.000
≤ 12	193	3.10 ± 1.41		23.17 ± 2.86		4.92 ± 1.92	
13-24	121	3.40 ± 1.44		24.24 ± 2.72		6.13 ± 2.53	
≥ 25	86	3.80 ± 1.28		24.44 ± 2.56		7.09 ± 2.24	
Family history			0.215		0.479		0.639
Yes	19	3.74 ± 1.05		24.21 ± 2.72		6.00 ± 1.97	
No	381	3.32 ± 1.43		23.74 ± 2.82		5.74 ± 2.37	
Infection with *Helicobacter pylori* in the past or present			0.984		0.295		0.886
Yes	59	3.34 ± 1.17		24.12 ± 2.34		5.71 ± 2.11	
No/unclear	341	3.34 ± 1.46		23.70 ± 2.89		5.76 ± 2.39	
Smoking history			0.000		0.181		0.053

Yes	53	2.53 ± 1.67		23.28 ± 2.57		5.17 ± 2.35	
No	347	3.47 ± 1.34		23.84 ± 2.84		5.84 ± 2.34	
Drinking alcohol			0.000		0.001		0.000
Yes	70	2.57 ± 1.53		22.71 ± 3.04		4.71 ± 2.16	
No	330	3.51 ± 1.34		23.99 ± 2.71		5.97 ± 2.33	
Pathological confirmation of early tumors after ESD			0.033		0.611		0.031
Yes	357	3.39 ± 1.40		23.79 ± 2.82		5.84 ± 2.33	
No/not detected	43	2.91 ± 1.49		23.56 ± 2.80		5.02 ± 2.41	

ESD: Endoscopic submucosal dissection; SD: Standard deviation.

Table 2 Questions and answers of attitude assessments, *n* (%)

Questions	Strongly agree	Agree	Fair	Disagree	Strongly disagree
1. I am afraid of gastric cancer	0	0	28 (7.0)	219 (54.8)	153 (38.3)
2. I am satisfied with the endoscopic submucosal dissection	0	0	27 (6.8)	213 (53.3)	160 (40.0)
3. Despite receiving endoscopic submucosal dissection, I am still terrified of gastric cancer	0	0	27 (6.8)	220 (55.0)	153 (38.3)
4. I am terrified of gastric cancer recurrence	0	0	27 (6.8)	217 (54.3)	156 (39.0)
5. I do not believe reexamination is necessary after endoscopic submucosal dissection	19 (4.8)	265 (66.3)	69 (17.3)	47 (11.8)	0
6. I am willing to undergo regular reexaminations and follow-ups according to the doctor's advice	0	0	98 (24.5)	185 (46.3)	117 (29.3)

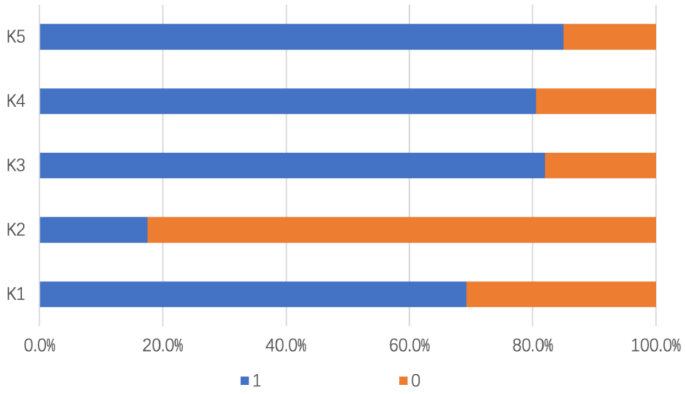

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Figure 1 Distribution of knowledge scores. K: Knowledge; K1: The gold standard for monitoring gastric cancer is gastroscopy; K2: Gastric cancer will not relapse after endoscopic submucosal dissection; K3: Follow up is still necessary after an operation; K4: It is not necessary to quit smoking or drink alcohol after surgery; K5: There is no need for reexamination after surgery. "1" indicates correct, while a "0" indicates wrong or unclear.

recurrences. Cancer survivors with higher education and higher income were more likely to have the screening for second cancer or cancer recurrence[13]. In our study, in addition to the duration since the last ESD, residency, education, occupation, family income, and history of smoking or alcohol use were significantly associated with knowledge about monitoring cancer recurrences. Over 80% of the participants agreed that reexamination, follow-up, and quitting smoking and alcohol drinking are necessary after ESD. Surprisingly, less than 20% of participants correctly answered the question regarding the possibility of gastric cancer recurrence after ESD. Insufficient knowledge about cancer relapse may delay early detection of cancer recurrence, even if awareness may induce psychological stress that contributes to cancer incidence and progression[17]. Therefore, increasing awareness of cancer recurrence among EGC survivors is vital.

For patients with EGC after curative ESD, annual or biannual surveillance esophagogastroduodenoscopy and abdominal computed tomography are recommended for at least 5 years[18]. In spite of the fact that the majority of the

Table 3 Questions and answers of practice assessments, *n* (%)

Questions	No	Yes
1. Do you have regular follow-up appointments in the Gastroenterology Outpatient Department after surgery?	161 (40.3)	239 (59.8)
2. Do you follow a low-salt diet after surgery?	66 (16.5)	334 (83.5)
3. Did you stop drinking alcohol after surgery?	63 (15.8)	337 (84.3)
4. Did you have *Helicobacter pylori* reexamination after surgery, such as a C-urea breath test?	309 (77.3)	91 (22.8)
5. Do you undergo regular gastroscopy reexaminations after surgery (3 mo, 6 mo, 9 mo, and 12 mo after surgery, then one gastroscopy every year afterward)?	234 (58.5)	166 (41.5)
6. Do you undergo yearly reexaminations by abdominal and chest CT scans after surgery?	286 (71.5)	114 (28.5)
7. Do you undergo yearly reexaminations of blood tumor biomarkers after surgery?	275 (68.8)	125 (31.3)
8. Do you regularly exercise after surgery?	328 (82.0)	72 (18.0)
9. Did you have significant body weight changes after surgery (more than 5 kilograms increased or decreased)?	14 (3.5)	386 (96.5)
10. Has your sleep status improved since the surgery?	296 (74.0)	104 (26.0)
11. Do you use dietary supplements or Traditional Chinese Medicine after surgery?	67 (16.8)	333 (83.3)

CT: Computed tomography.

Table 4 Pearson correlation analysis between knowledge, attitude, and practice of monitoring gastric cancer after endoscopic submucosal dissection

	Knowledge	Attitude	Practice
Knowledge	1.000	-	-
Attitude	0.405 ($P < 0.001$)	1.000	-
Practice	0.511 ($P < 0.001$)	0.458 ($P < 0.001$)	1

participants were within 2 years of their last ESD, only 28.5% had yearly reexaminations by abdominal and chest computed tomography scans. It was interesting to note that over 80% of patients were aware of follow-up, reexamination, and cessation of smoking and drinking alcohol following an ESD. This paradox indicates that monitoring EGC recurrences after ESD requires putting knowledge into practice.

Despite the overall unsatisfactory practice score, we noticed some highlights. After ESD, 83.5% of the participants followed a low-salt diet, and 84.3% of the participants quit smoking and drinking alcohol. These actions may reduce the risk of recurrence of gastric cancer since high salt intake, heavy smoking, and combined smoking and alcohol exposure are associated with an increased risk of gastric cancer[19,20].

We noticed that higher knowledge and attitude scores were generally accompanied by increased practice scores. Pearson correlation analysis showed that knowledge-attitude, knowledge-practice, and attitude-practice were positively correlated, consistent with similar studies[21,22]. Moreover, multivariate linear regression analysis revealed that knowledge, attitude, and duration since the last ESD were independent predictors of practice. Therefore, providing patients with more time and improving their knowledge is a potentially effective way to promote practice in monitoring gastric cancer recurrence after ESD.

The discrepancy between a positive attitude, inadequate knowledge, and poor practice can be attributed to several factors. First, there may be a lack of awareness and education about the specific details and importance of post-ESD care. While participants may have positive attitudes based on a general understanding that monitoring is necessary, they lack in-depth knowledge about the specific actions required for effective monitoring and preventing cancer recurrence. Second, misconceptions or misunderstandings about post-ESD care may contribute to the disparity. Participants may hold positive attitudes but have incorrect beliefs or assumptions about the necessity of certain practices or the risks involved. Third, limited access to educational materials, healthcare professionals, and facilities providing post-ESD care, especially among participants from rural areas or lower socioeconomic backgrounds, can contribute to inadequate

Table 5 Influencing factors of proactive practice

Factors	Univariate logistic regression		Multivariate logistic regression	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Knowledge score	2.528 (1.893-3.375)	< 0.001	1.916 (1.424-2.578)	< 0.001
Attitude score	1.395 (1.260-1.545)	< 0.001	1.253 (1.124-1.396)	< 0.001
Sex				
M	Reference	-		
F	0.943 (0.606-1.466)	0.794		
Age in yr				
≤ 40	Reference	-		
41-50	2.289 (0.807-6.495)	0.119		
51-60	1.820 (0.691-4.793)	0.226		
> 60	1.795 (0.705-4.752)	0.220		
Registered residence				
Rural area	Reference	-		
Urban area	1.085 (0.605-1.946)	0.784		
Educational level				
Junior middle school or lower	Reference	-		
Senior middle school/technical secondary school	0.840 (0.428-1.645)	0.611		
Junior college/college or higher	1.233 (0.636-2.390)	0.535		
Occupation				
General staff or relevant personnel	Reference	-		
Professional and technical staff	1.472 (0.380-5.701)	0.576		
Others	0.758 (0.440-1.308)	0.320		
Medical insurance				
Yes	Reference	-		
No	1.659 (0.588-4.680)	0.339		
Family income in Yuan				
< 2000	Reference	-		
2000-5000	1.066 (0.535-2.125)	0.856		
> 5000	1.161 (0.542-2.490)	0.701		
The time since last ESD in mo				
≤ 12	Reference	-	Reference	-
13-24	3.788 (2.130-6.736)	< 0.001	3.296(1.761-6.172)	< 0.001
≥ 25	7.743 (4.220-14.208)	< 0.001	5.768(2.963-11.226)	< 0.001
Family history				
Yes	Reference	-		
No	1.370 (0.365-2.952)	0.945		
Infection with *Helicobacter pylori* in the past or present				
Yes	0.652 (0.331-1.282)	0.215		
No/unclear	Reference	-		
Smoking history				
Yes	Reference	-		

No	1.952 (0.918-4.148)	0.082		
Alcohol drinking				
Yes	Reference	-	Reference	-
No	2.534 (1.246-5.154)	0.010	1.160 (0.500-2.691)	0.729
Pathological confirmation of early tumors after ESD				
Yes	Reference	-		
No/not detected	0.493 (0.212-1.144)	0.099		

CI: Confidence interval; ESD: Endoscopic submucosal dissection; F: Female; M: Male; OR: Odds ratio.

knowledge and poor practice. Furthermore, ineffective communication and a lack of clear instructions from healthcare providers can hinder the translation of positive attitudes into practical actions. Addressing these factors requires comprehensive efforts to facilitate the translation of positive attitudes into informed knowledge and effective practices.

The KAP concerning the monitoring of gastric cancer recurrence after ESD holds significant clinical implications. Primarily, it identifies patient understanding, attitudes, and behavioral gaps that can be addressed to enhance patient outcomes and decrease recurrence rates. Furthermore, understanding the KAP of patients allows for a more personalized approach to patient education and intervention strategies, helping to bridge the gap between positive attitudes and effective practices, especially in areas like follow-up schedules and lifestyle adjustments. Lastly, studying KAP has essential implications for resource allocation and healthcare policy, as it underlines areas of need such as patient education, access to healthcare services, and efficient communication between healthcare providers and patients.

In this study, data were collected by self-reporting, which might be less reliable than medical records and laboratory measurements due to self-reporting bias. In addition, as this study was conducted in Zhejiang, China, the results do not reflect the KAP of monitoring cancer recurrence globally. To better understand the KAP of monitoring gastric cancer recurrence around the world, more studies in more areas with larger sample sizes are needed.

CONCLUSION

In this study, the KAP of monitoring gastric cancer recurrences after ESD was assessed for the first time in EGC survivors following ESD. Participants showed a positive attitude toward monitoring gastric cancer recurrence after ESD, but more efforts are needed to improve their knowledge and practice.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer is a prevalent and deadly form of cancer worldwide, particularly in China, where it ranks as the third leading cause of cancer-related deaths. Early gastric cancer (EGC) refers to tumors located in the mucosa or submucosa of the stomach, and endoscopic submucosal dissection (ESD) is the recommended treatment. However, non-curative resection can occur, leading to an increased risk of local recurrence. Therefore, monitoring the recurrence of gastric cancer after ESD is crucial for early detection and improved survival.

Research motivation

Although monitoring gastric cancer recurrence is important, little is known about the knowledge, attitude, and practice (KAP) of EGC survivors regarding this issue. Understanding the KAP of patients can help healthcare practitioners develop strategies to improve monitoring practices and promote early detection of recurrence.

Research objectives

To assess the KAP of EGC survivors after ESD regarding monitoring the recurrence of gastric cancer. Specifically, the study aimed to evaluate KAP related to gastric cancer recurrence, reexamination, and follow-up. Additionally, the study aimed to identify sociodemographic factors associated with monitoring practices.

Research methods

This cross-sectional study was conducted at a hospital in Zhejiang, China and involved 400 EGC survivors who underwent ESD. Participants completed a self-designed questionnaire consisting of 40 questions divided into four categories: Personal information and KAP. The questionnaire scores were calculated and analyzed using statistical methods, including *t*-tests, χ^2 tests, and logistic regression analysis.

Research results

The study found that participants had moderate levels of knowledge, positive attitudes, and moderate levels of practice regarding monitoring gastric cancer recurrence. Knowledge scores were higher among participants from urban areas, with higher education levels, professional occupations, higher family incomes, longer time since the last ESD, and without smoking or alcohol use history. Participants with a longer time since their last ESD and without alcohol consumption had more positive attitudes. Factors associated with good monitoring practices included having medical insurance, longer time since the last ESD, and not smoking or drinking alcohol.

Research conclusions

The study highlights the need to improve the knowledge and monitoring practices of EGC survivors after ESD. Educational interventions and targeted strategies should focus on enhancing patient understanding of the importance of monitoring gastric cancer recurrence and promoting regular reexamination and follow-up. Improving knowledge and attitudes can positively influence monitoring practices and contribute to early detection of gastric cancer recurrence.

Research perspectives

Future research should focus on developing effective educational programs and interventions to improve patient knowledge and awareness of gastric cancer recurrence after ESD.

FOOTNOTES

Author contributions: Yang XY carried out the studies, participated in collecting data, and drafted the manuscript; Wang C, Hong YP, and Zhu TT proposed the questionnaire and revised it; Qian LJ was the pathologist who participated in collecting pathological data; Hong YP and Teng LH performed the statistical analysis and participated in its design; Ding J reviewed the literature and contributed to revising the article; and all authors read and approved the final manuscript.

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Country/Territory of origin: China

ORCID number: Xiao-Yun Yang 0000-0002-9164-5573; Cong Wang 0000-0003-1531-3176; Yi-Ping Hong 0000-0003-1043-7145; Ting-Ting Zhu 0000-0002-6068-1501; Lu-Jia Qian 0000-0001-8548-0717; Yi-Bing Hu 0000-0002-9821-6699; Li-Hong Teng 0000-0003-4439-1472; Jin Ding 0000-0003-0748-4362.

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ORIGINAL ARTICLE

Observational Study

Anti-reflux effects of a novel esophagogastric asymmetric anastomosis technique after laparoscopic proximal gastrectomy

Li-Qun Pang, Jie Zhang, Fang Shi, Cong Pang, Cheng-Wan Zhang, Ye-Liu Liu, Yao Zhao, Yan Qian, Xiang-Wei Li, Dan Kong, Shang-Nong Wu, Jing-Fang Zhou, Cong-Xue Xie, Song Chen

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Li-Qun Pang, Jie Zhang, Ye-Liu Liu, Yao Zhao, Yan Qian, Xiang-Wei Li, Cong-Xue Xie, Department of General Surgery, The Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University, Huaian 223300, Jiangsu Province, China

Fang Shi, Jiangsu Key Laboratory of Advanced Manufacturing Technology, Huaiyin Institute of Technology, Huaian 223300, Jiangsu Province, China

Cong Pang, Department of Neurosurgery, The Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University, Huaian 223300, Jiangsu Province, China

Cheng-Wan Zhang, Department of Central Laboratory, The Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University, Huaian 223300, Jiangsu Province, China

Dan Kong, Department of Imaging, The Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University, Huaian 223300, Jiangsu Province, China

Shang-Nong Wu, Jing-Fang Zhou, Department of Gastroenterology, The Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University, Huaian 223300, Jiangsu Province, China

Song Chen, Institute of Medicinal Biotechnology, Jiangsu College of Nursing, Huaian 223300, Jiangsu Province, China

Corresponding author: Li-Qun Pang, MD, PhD, Chief Physician, Surgeon, Surgical Oncologist, Department of General Surgery, The Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University, No. 1 Huanghe West Road, Huaian 223300, Jiangsu Province, China. hayypanglq@njmu.edu.cn

Abstract

BACKGROUND

Reflux esophagitis is a common postoperative complication of proximal gastrectomy. There is an urgent need for a safer method of performing esophageal-gastric anastomosis that reduces the risk of reflux after proximal gastrectomy. We hypothesize that a novel technique termed esophagogastric asymmetric anastomosis (EGAA) can prevent postoperative reflux in a safe and feasible manner.

AIM

To observe a novel method of EGAA to prevent postoperative reflux.

METHODS

Initially, we employed a thermal stress computer to simulate and analyze gastric peristalsis at the site of an esophagogastric asymmetric anastomosis. This was done in order to better understand the anti-reflux function and mechanism. Next, we performed digestive tract reconstruction using the EGAA technique in 13 patients who had undergone laparoscopic proximal gastrectomy. Post-surgery, we monitored the structure and function of the reconstruction through imaging exams and gastroscopy. Finally, the patients were followed up to assess the efficacy of the anti-reflux effects.

RESULTS

Our simulation experiments have demonstrated that the clockwise contraction caused by gastric peristalsis and the expansion of the gastric fundus caused by the increase of intragastric pressure could significantly tighten the anastomotic stoma, providing a means to prevent the reverse flow of gastric fluids. Thirteen patients with esophagogastric junction tumors underwent laparoscopic proximal gastrectomy, with a mean operation time of 304.2 ± 44.3 min. After the operation, the upper gastroenterography in supine/low head positions showed that eight patients exhibited no gastroesophageal reflux, three had mild reflux, and two had obvious reflux. The abdominal computed tomography examination showed a valve-like structure at the anastomosis. During follow-up, gastroscopy revealed a closed valve-like form at the anastomosis site without stenosis or signs of reflux esophagitis in 11 patients. Only two patients showed gastroesophageal reflux symptoms and mild reflux esophagitis and were treated with proton pump inhibitor therapy.

CONCLUSION

EGAA is a feasible and safe surgical method, with an excellent anti-reflux effect after proximal gastrectomy.

Key Words: Esophagogastric junction tumor; Proximal gastrectomy; Digestive tract reconstruction; Esophagogastric asymmetric anastomosis; Reflux esophagitis; Gastroenterography

Core Tip: Reflux esophagitis is a common postoperative complication after proximal gastrectomy that can seriously affect the quality of life of these patients. We studied the novel surgical procedure termed esophagogastric asymmetric anastomosis (EGAA) as a potential solution to this post-surgery complication. Post-operatively, the results of upper gastroenterography showed no signs of gastroesophageal reflux while abdominal computed tomography examination findings showed a valve-like structure at the anastomosis. During follow-up, gastroscopy results revealed a closed valve-like form at the anastomosis site without stenosis or signs of reflux esophagitis. Our data suggest that EGAA is a feasible and safe procedure with excellent anti-reflux outcomes after proximal gastrectomy.

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INTRODUCTION

Gastric cancer is a common malignant tumor of the gastrointestinal tract, with over 1 million new cases and 769000 deaths globally in 2020. It ranks fifth in terms of incidence and fourth in terms of mortality among malignant tumors[1]. Interestingly, the proportion of proximal gastric cancer (including upper gastric cancer and adenocarcinoma of the esophagogastric junction) has been on the rise for the past 40 years[2-5].

For early esophagogastric junction tumors, esophageal-residual gastric anastomosis after proximal gastrectomy is an effective method to reconstruct the digestive tract. Compared to total gastrectomy, this method maintains normal anatomy and functionality of the stomach and duodenum, and improves nutritional status and quality of life of patients post-operatively[6,7].

However, the loss of anti-reflux function due to surgical resection of the cardia, the decline in gastric peristalsis due to vagotomy, and the emptying delay caused by preserved pylorus can lead to several postoperative complications such as intractable reflux esophagitis, anastomotic stomatitis and stenosis, Barrett esophagus, and esophageal cell carcinoma[8-12], impacting quality of life post-surgery.

To address reflux esophagitis, several different gastrointestinal reconstruction modalities have been developed over the years. The primary anti-reflux surgical modalities in current use involve several common strategies[13-16]: (1) Extending the distance to reduce reflux using jejunal inter-positioning or double tract reconstruction; (2) reducing discharge resistance to reduce reflux, such as pyloric molding; and (3) in the esophageal-residual gastric anastomosis, improving anti-reflux function by rebuilding the structure of the gastric base and anastomotic opening using approaches such as the double-flap technique (Kamikawa anastomosis) or removing most of the stomach to reduce gastric acid secretion, *via* gastric tube reconstruction.

However, each of these techniques has its own limitations in terms of insufficient effectiveness of anti-reflux in the supine position, inadequate storage function or delayed emptying of the residual stomach, inadequate flow of food through the duodenum, and complexity of surgical approach[17-20].

Esophagogastrostomy is considered the simplest reconstruction method used after proximal gastrectomy because it requires only one anastomosis, allowing easy postoperative endoscopic surveillance. A survey of 145 Japanese medical institutions showed that esophagogastric anastomosis was chosen for gastrointestinal reconstruction in approximately 50% of medical institutions[21,22]. However, it is not widely accepted because of severe postoperative complications such as reflux esophagitis and anastomotic stricture[11,12].

To improve the procedure of esophagogastric anastomosis to prevent reflux after proximal gastrectomy, we designed and implemented a novel reconstruction technique called esophagogastric asymmetric anastomosis (EGAA) based on years of clinical experience. Additionally, we established the EGAA mode to study the anti-reflux theory mechanism of asymmetric anastomosis aided by computer simulation technology using finite element analysis.

Herein, we present the technical details of EGAA and elaborate on its short-term outcomes after laparoscopic anti-reflux surgery.

MATERIALS AND METHODS

Critical features of the EGAA

There are four critical features of the EGAA method: The asymmetric cut of the lower esophagus, the asymmetry of the esophageal diameter in relation to the incision length in the anterior wall of the residual stomach, asymmetrical torsion of the esophagus with respect to the residual stomach, and asymmetrical suturing of the seromuscular layer of the residual stomach with the esophagus.

First, because of the oblique cut of the lower esophagus, the length of the anterior wall of the esophagus at the anastomotic site is approximately 1.5 cm longer than that of the posterior wall, forming a "door and block" frame with the folded stomach parts to prevent reflux and leakage after anastomosis (Figure 1A and D).

Second, a transverse incision was made in the anterior wall of the stomach about 3.5 cm from the proximal end of the residual stomach. The length of the incision is approximately 3.2-3.5 cm that is greater than the diameter of the esophagus but equal to the length of the distal oblique incision in the flat state of the esophagus (*i.e.*, half of the circumference of the distal oblique incision).

This design facilitates the closure of the lower end of the esophagus and helps to prevent stenosis (Figure 1A). The following formula was applied to improve the grasp of the criteria for the size of the anterior gastric wall incision:

Criterion length of gastric incision size (cm) $\approx \sqrt{(\pi r)^2+g^2}$ (where r is the esophageal radius and g is the gap between the front and rear lengths of the esophageal wall).

Third, the esophagus and the residual stomach are asymmetrical on the sagittal surface after suturing the lower segment of the esophagus, which has undergone a 90-degree anticlockwise torsion, to the anterior incision of the residual stomach in an end-to-side anastomosis (Figure 1B). Both the distal esophagus and anastomotic sites tended to close in a resting state.

Finally, in the posterior wall of the anastomosis, the edge of the gastric stump (about 3.0 cm from the anastomosis) is sutured to the seromuscular layer of the esophagus (0.5-1.0 cm from the anastomosis) to form a flap-like structure by folding the wall of the partial residual stomach in the gastric lumen.

The criteria for this procedure were as follows: Except for the gastric margin of approximately 0.3 cm for the anastomosis, the distance between the gastric stump margin and the suture site of the posterior esophageal wall must be greater than 2.5 cm. The length of the valve-like structure formed by the folded gastric wall must be longer than 1.0 cm to ensure the effectiveness of closure.

In the anterior wall of the anastomosis, the seromuscular layer of the residual stomach and esophagus was sutured, pushing the anterior lip toward the posterior lip of the anastomosis and increasing the tendency for anastomotic closure in synergy with asymmetrical suturing of the posterior wall of the anastomosis (Figure 1C and D).

Computer simulations of EGAA mechanisms using the finite element method

To determine whether the procedure for asymmetric anastomosis of the esophagus and stomach could achieve the expected outcome theoretically, simulations were performed according to the procedure for EGAA (Figure 1D). The contraction movement of the stomach was modeled by applying thermal strain. Rubber materials were used to simulate the elastic behavior of the stomach and esophagus. Additionally, the esophageal and duodenal ends are restricted as displacement boundary conditions, and the pressure inside the stomach was also considered.

Adobe Illustrator was used to draw the curve of the gastric section (Figure 2A). The gastric curve was then transferred into SolidWorks to generate the geometric model, and this was then used to perform the finite element simulation using the ANSYS Workbench.

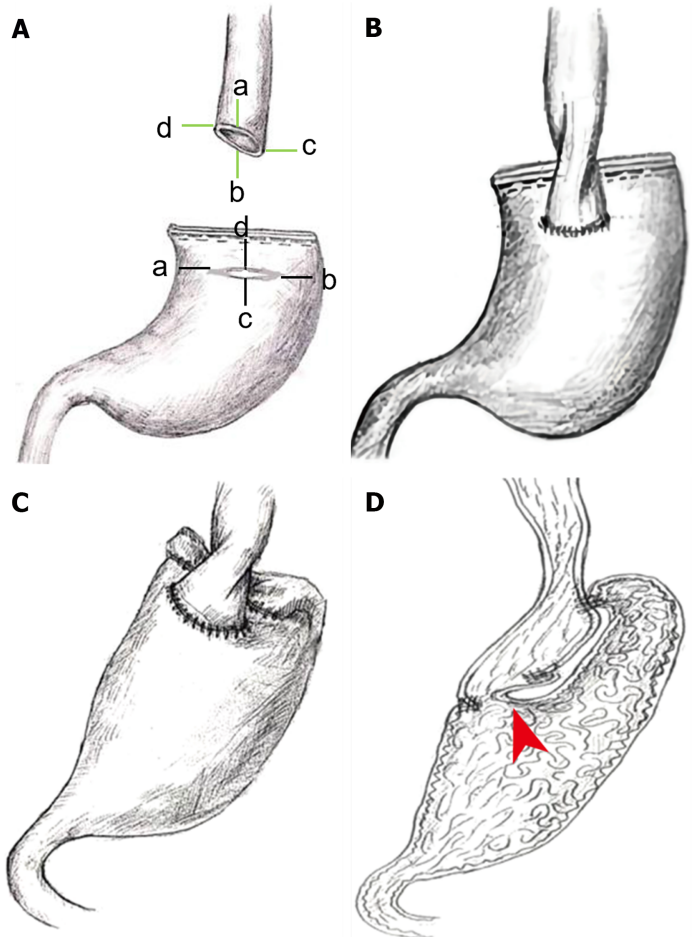

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Figure 1 Critical design features of the esophagogastric asymmetric anastomosis technique. A: (1) The diameter of the esophagus and the incision size of the residual gastric anterior wall are asymmetric; and (2) The length of the two sides of the lower esophagus is asymmetrical; The points a/b/c/d shows the corresponding points of asymmetric anastomosis respectively between esophagus and residual stomach; B: Asymmetry of the longitudinal section (or sagittal surface) of the esophagus and the residual stomach after anastomosis; C: After anastomosis, the seromuscular layer of the residual stomach and esophagus is asymmetrically sutured; D: The sagittal plane of esophagogastric asymmetric anastomosis: Showing the suture point of the asymmetric anastomosis; the red arrow indicates a flap structure formed by the folded gastric wall in the gastric cavity.

Patients

Thirteen patients (9 males and 4 females) were recruited for laparoscopic proximal gastrectomy (LPG) with EGAA at the Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University between September 2021 and March 2023. One patient had a gastric stromal tumor. The other 12 patients had tumors that were histologically confirmed as adenocarcinoma of esophagogastric junction (AEG). The age range was 57–78 years (66.3 ± 7.0), with body mass index (BMI, kg/m^2) ranging from 21.3-32.4 (24.5 ± 3.0).

Preoperative diagnosis and evaluation included endoscopy, upper gastrointestinal series, and computed tomography (CT). Tumor stages were classified according to the International Anti-Cancer Alliance TNM staging system[23], and lymph node stations were numbered according to the definition of the Japanese Gastric Cancer Association[24]. Surgical complications were classified according to the Craven-Tindo classification[25]. Endoscopic evaluation of esophagitis was performed using the Los Angeles classification[26].

Surgical technique

Mobilization and transection of the stomach and lymphadenectomy: Under general anesthesia, patients were placed in the reverse Trendelenburg position with their legs apart. The surgeon and the first assistant were positioned on the right and left sides of the patient, respectively. After pneumoperitoneum was established using an open technique at the umbilicus and maintained at approximately 13-15 mmHg abdominal pressure, an electro-laparoscope was introduced through the 12-mm umbilical trocar before placing the remaining four working trocars (Figure 3A).

Omentectomy was performed along the superior edge of the transverse colon. The right parts of the omentum were dissected from the mesocolon around the transition zone of lymph node (LN) stations 4d–6, and the right gastroepiploic vessels were preserved.

The origin of the left gastroepiploic vessel (LGEV) was divided and ligated using hemo-clips. Dissection of the short gastric vessels (SVG) was continued along the spleen up to the esophagogastric junction before performing lymphaden-

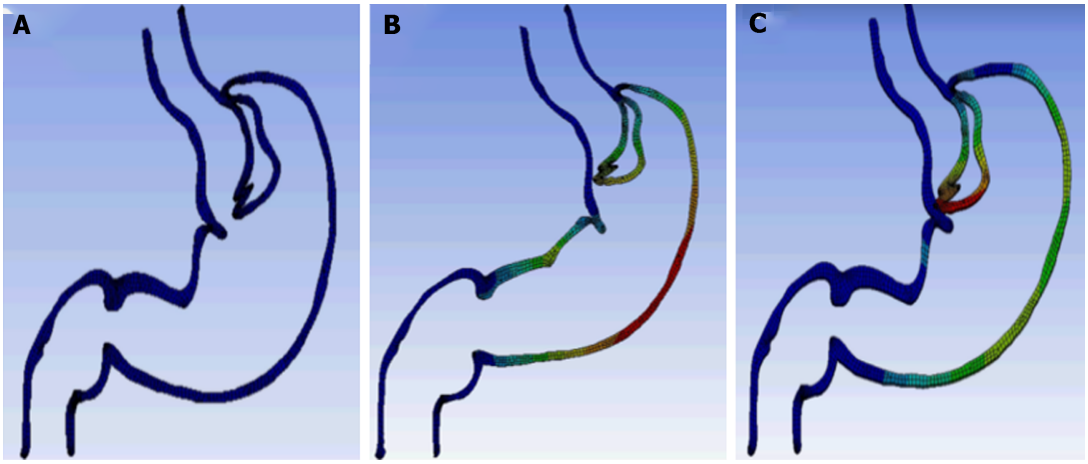

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Figure 2 Computer simulations of esophagogastric asymmetric anastomosis mechanisms using the finite element method. A: Adobe Illustrator was used to draw the curve of the gastric section; B: The valve-like structure of the folded gastric wall and the posterior wall of the lower esophagus move to the upper left side like a lever at the site of anastomotic stoma, causing tightening of the anastomotic stoma; C: Because of the increased pressure in the gastric cavity and the expansion of the gastric fundus, the folded gastric wall and the esophageal wall moved to the left, which effectively tightened the anastomotic stoma.

ectomy, including LNs 4sb and 4sa along the LGEV and SVG. The stomach was then elevated and the peritoneum along the superior edge of the pancreas was mobilized. LNs along the left gastric artery (No. 7), common hepatic artery (No. 8a), celiac artery (No. 9), and proximal splenic artery (No. 11p) were retrieved. The root of the left gastric artery in the coronary vein was clipped and divided. The esophagogastric junction was mobilized. After complete exposure of the abdominal esophagus with the division of the anterior and posterior vagal trunks, LPG was completed by transection of the esophagus 2 cm proximal to the tumor with a 45-mm endoscopic linear stapler. The right pericardial (No. 1), left pericardial (No. 2), lesser curvature (No. 3), and lower thoracic para-esophageal nodes (No. 110) were completely retrieved using this procedure.

Proximal gastrectomy with an assisted abdominal incision: A small incision was made in the upper abdomen, and the stomach was exteriorized and stapled using a 60-mm linear cutting suture about 4 cm from the distal end of the tumor. The proximal margin of the specimen was examined pathologically when necessary. At the anterior wall 3.5 cm from the proximal end of the residual stomach, the transverse incision was marked and cut approximately 3.2-3.5 cm (Figure 3B).

Procedure of laparoscopic-assisted EGAA: The residual stomach was placed back into the abdominal cavity, the incision was temporarily closed, and pneumoperitoneum was re-established. A laparoscopic-assisted EGAA (hand suture) was performed following the critical features outlined previously.

The distal end of the esophagus was incised with an oblique short right and long left margin, with a difference of approximately 1.5 cm between the two sides (Figure 3C).

With a longitudinal anticlockwise torsion of the esophagus at 90°, an end-to-side anastomosis was performed between the cut end of the esophagus and the residual stomach incision.

First, one full-thickness intermittent suture was performed between the right side (point d) of the lower esophagus and the middle point (point d) of the posterior wall in gastric incision. Then, the right point of the gastric wall incision (point a) was sutured to the middle point (point a) of the anterior wall in the lower esophagus, and the left point (point b) of the gastric incision was sutured to the middle point (point b) of the posterior wall in the lower esophagus (Figure 3D). After this three-stitch full-layer suture was used to complete the positioning suture of the posterior wall of the EGAA, the points a/b/d of the esophageal and gastric wall incisions were aligned in the posterior wall of the anastomosis (Figure 1A), and the lower esophageal segment was rotated anticlockwise at 90°. The whole muscle layer was continuously sutured in the posterior and anterior walls of the anastomosis with ETHICON SXMD1B405 (tensile strength size 3-0) (Figure 3E and F), and the anterior wall of the anastomosis was further strengthened by a suture in the seromuscular layer (Figure 3G).

Then, 50 mL saline with 2 mL methylene blue was injected through the gastric tube (dimensioning 35 cm) to confirm that no anastomotic leak occurred.

The cut end of the residual stomach (approximately 3.0 cm from the anastomosis) was sutured with 3-5 stitchs to the posterior wall of the esophagus at a site 0.5-1.0 cm from the anastomosis in the seromuscular layer (Figure 3H). The residual stomach was sutured fixedly to the bilat with 3-5 stitchs eral diaphragmatic feet.

Ethical considerations

This study used clinicopathological, surgical, and follow-up data. All patients were counseled about the operative procedure, including the potential merits and disadvantages of our approach and the uncertainty of clinical outcomes. All patients were in stable condition and written informed consent was obtained from each patient prior to the procedure. All experimental and surgical procedures of the study were approved by the ethics committee of The Affiliated Huaian No. 1

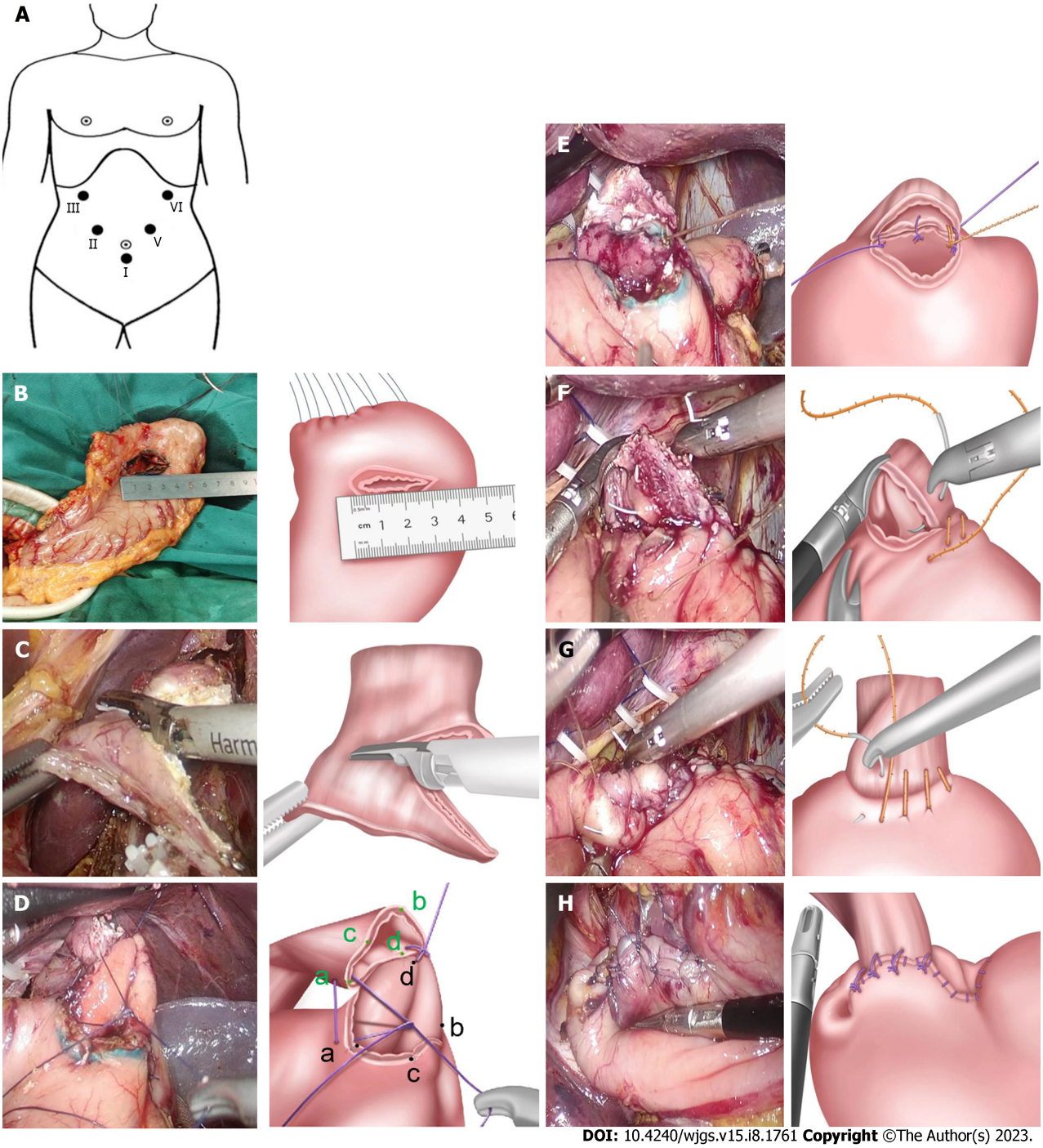

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Figure 3 Surgical Procedure of laparoscopic-assisted esophagogastric asymmetric-anastomosis. A: Reverse Trendlenborg position with both legs separated. Using five-hole method, the points I-V show the location of Trocars and operators respectively; B: The transverse incision of residual stomach wall is about 3.2-3.5 cm away from the proximal end at approximately 3.5 cm; C: The lower end of the esophagus is cut oblique, the length of both sides is asymmetric, the difference is approximately 1.5 cm; D: First, a full-thickness intermittent suture was performed between the right side (point d) of the lower esophagus and the middle point (point d) of the posterior wall in gastric incision. Then, the right point of the gastric wall incision (point a) was sutured to the middle point (point a) of the anterior wall in the lower esophagus, and the left point (point b) of the gastric incision was sutured to the middle point (point b) of the posterior wall in the lower esophagus. After performing a three-needle whole-layer positioning suture of the posterior wall in oesophagogastric anastomosis, oesophageal torsion was completed at a 90° anticlockwise; E: The back wall of the anastomosis was continuously stitched; F: The front wall of the anastomosis was continuously stitched; G: The seromuscular layer of the anterior wall of the anastomosis was further stitched; H: The residual gastric cutting end (approximately 3 cm from the anastomosis) was stitched to the posterior wall of the esophagus, about 0.5-1 cm away from the anastomosis.

People's Hospital of Nanjing Medical University and strictly adhered to the guidelines of the Helsinki Declaration of 1964 and its latest amendments.

RESULTS

Gastric peristalsis was simulated using the thermal-strain method. After decreasing the temperature, the model size was reduced by 30% in a clockwise direction. However, the suture of the incisal gastric margin and the posterior esophageal wall caused the valve-like folded gastric wall and posterior lower esophageal wall to move to the upper left, tightening of the anastomotic stoma (Figure 2B, Video 1).

Gastric fundus dilation simulation

To simulate the dilation of the reconstructed gastric fundus under gastric peristalsis and intragastric pressure, we applied different pressures to the gastric fundus, gastric body and antrum. During gastric peristalsis and contraction, the gas and liquid contents in the gastric cavity were observed to flow to the proximal end, increasing the pressure and expanding the gastric fundus gradually. According to the simulation results, because of the increased pressure in the gastric cavity and the expansion of the gastric fundus, the folded gastric wall and the esophageal wall moved to the left, tightening the anastomotic stoma (Figure 2C).

Following the simulations, EGAA surgeries were performed. All procedures were completed with a mean operation time of 304.2 ± 44.3 min, and the mean blood loss was 88.5 ± 46.3 mL. No intraoperative complications, conversions, or operative mortality was observed in the 13 patients. Two postoperative complications (minor grade II anastomotic leakage, cured conservatively) occurred, and patients recovered (median postoperative hospital stay: 19.2 ± 11.7 d). Patient background and surgical outcome are shown in Table 1.

One week post-surgery, abdominal CT examination (oral CO_2 powder) revealed that 11 patients had valve-like structures, inflatable stomach cavity and closed anastomosis (Figure 4). Upper gastroenterography showed good residual gastric excretion, no anastomotic leakage/stenosis, and no reflux (all patients, upright position). In supine/low head positions, eight patients exhibited no gastroesophageal reflux, three had mild reflux, and two had obvious reflux (Figure 5, Video 2).

Gastroscopy during postoperative follow-up (2 to 19 mo) revealed a closed valve-like structure at the anastomosis site in 11 patients. Additionally, good extensibility and gastric residual discharge were observed, with no signs of stenosis or apparent reflux esophagitis. Only two patients exhibited an uncharacteristic valve-like structure and reflux esophagitis (class LA-B, Los Angeles classification). Inverted gastroscope revealed a reconstructed gastric base (all patients), with 11 patients showing good coverage by the gastric mucosal valve-like structures at site of anastomosis. Follow-up endoscopic findings in representative cases are shown in Figure 6 and Video 3).

In the average 10.2 ± 6.2 mo of questionnaire follow-up, 11 patients recovered well with no symptoms such as stomach distension, heartburn, and dysphagia. Two patients exhibited gastroesophageal reflux (controlled by proton pump inhibitors, gastric dynamic drugs, and functional exercise). No recurrence or fatalities occurred during the median 10.2-month follow-up period (range, 2-19 mo).

By last follow-up, of the 13 EGAA surgery patients, four lost weight (one developed fatty diarrhea post-cholecystectomy 6 month post-surgery). Five patients showed no change in body weight and four showed weight gain. The specific changes in BMI are shown in Table 1.

DISCUSSION

Esophagogastrostomy is considered the simplest and most convenient reconstruction procedure following proximal gastrectomy, as it preserves digestion and absorption. However, it is associated with a high incidence of reflux esophagitis and anastomotic stenosis, which significantly impact the patient's quality of life[21,27].

There are three problems to be addressed for anastomosis stoma of the esophagus and stomach to alleviate postoperative complications such as reflux and anastomosis stenosis[28-30]: (1) Maintaining closed state of anastomosis stoma and reducing gastric fluid reflux in the supine position; (2) maintaining gastric cavity tension to prevent weakness and gastric retention; and (3) prevent anastomosis narrowing.

To overcome these problems, we designed a four-asymmetric suture technique to reconstruct the gastric fundus and form a valve shape by folding part of the residual stomach wall at the posterior lip of the anastomosis in the gastric cavity. To improve study design processes and confirm a specific anti-reflux function, a computer simulation was applied using finite element analysis.

The anti-reflux effect of asymmetric anastomosis was further evaluated by imaging and endoscopy post-operatively. Abdominal CT examination (oral CO_2) showed circular expansion of the residual stomach cavity, and a valve-like tightly closed stoma at the site of anastomosis. The CO_2 did not leak easily, confirming the "one-way valve" function. Upper gastroenterography showed good efficiency of stomach discharge or excretion to the small intestine, no gastric weakness, and no reflux even when most of the patients reached 15° in the supine and head lowered position, indicating an anti-reflux effect of the reconstructed anastomosis. Digestive endoscopy showed that the anastomosis was not narrowed, softened, or extended and had no mucus lake in the gastric cavity. The reconstructed gastric base and valve-like structures were observed *via* an inverted gastroscope and revealed the gastric mucosa wrapped around the mirror body wall.

The results of our computer simulation and theoretical analysis further support the findings of the clinical examination. The computer simulation results demonstrate that during the peristaltic state, the folded stomach wall and the esophageal wall move in a clockwise forward motion, primarily due to the suture fixation of the residue and the rear wall of the esophagus. This movement leads to further tightening of the anastomosis stoma. Additionally, the expansion of the

Table 1 Preoperative data and clinical outcome of the patients

Case	Age	Gender	Preoperative BMI	Operation method	Siewert type	Operation time (min)	Anastomosis time (min)	Blood loss (mL)	Final TNM	Final stage[1]	Discharge (POD)	Operative morbidity	Reflux esophagitis	Postoperative BMI	Symptom of reflux	Postoperative follow-up (mo)
1	68	F	32.4	LPG	II	340	45	200	T2N0M0	IB	12	None	Class LA-B	33.5	+	19
2	57	F	27	LPG	III	360	55	100	T1N0M0	IA	17	None	Class LA-B	23.2	+	18
3	65	M	22.5	LPG	II	315	50	150	T1N0M0	IA	12	None	None	23.7	None	18
4	64	M	22.1	LPG	II	260	40	50	T1N0M0	IA	10	None	None	22.1	None	18
5	67	M	24.6	LPG	II	290	45	50	T1N0M0	IA	11	None	None	24.9	None	12
6	63	M	25.1	LPG	II	270	45	50	T3N1M0	IIB	45	Grade II Anastomotic leakage	None	25.1	None	9
7	77	M	26.1	LPG	II	320	50	100	T3N0M0	IIA	14	None	None	24.4	None	9
8	71	F	21.3	LPG	II	280	45	100	T1N0M0	IA	18	None	None	22.6	None	9
9	66	M	23.5	LPG	I	200	35	100	T1N0M0	IA	15	None	None	23.5	None	7
10	57	F	25.2	LPG	II	350	50	100	T3N0M0	IIA	11	None	None	22.3	None	5
11	57	M	21.5	LPG	II	330	40	50	T2N1M0	IIB	43	Grade II Anastomotic leakage	None	20.3	None	4
12	72	M	24.4	LPG	II	340	45	50	T1N0M0	IA	18	None	None	24.4	None	3
13	78	M	22.9	LPG	II	300	40	50	T1N0M0	IA	24	None	None	22.9	None	2
mean ± SD	66.3 ± 6.993		24.51 ± 2.953			304.2 ± 44.34	45.00 ± 5.401	88.46 ± 46.34			19.23 ± 11.66			24.07 ± 3.121		10.23 ± 6.207

[1]Staging was performed according to the 7th edition of the International Union against Cancer tumor–node–metastasis staging system for gastric cancer.
M: Male; F: Female; LPG: Laparoscopic proximal gastrectomy; TNM: Tumor–node–metastasis; POD: Postoperative day.

gastric cavity through increased peristaltic pressure applies pressure on the lower esophageal tissue, resulting in an enhanced anti-reflux effect.

Based on the above results, we speculate that in the resting state, the anastomotic stoma and lower esophageal end are closed by four synergistic actions: longitudinal torsion of the lower section of the esophagus, asymmetric size of the esophageal diameter and residual gastric wall incision, suture of the seromuscular layer in the anterior wall, and the valve-like structure at the site of the posterior wall of the anastomosis stoma, acting as an anti-reflux function. Meanwhile, the joint effect of the pylorus can maintain a certain pressure in the stomach cavity, promote gastric emptying, and reduce the symptoms of fullness and discomfort caused by stomach retention.

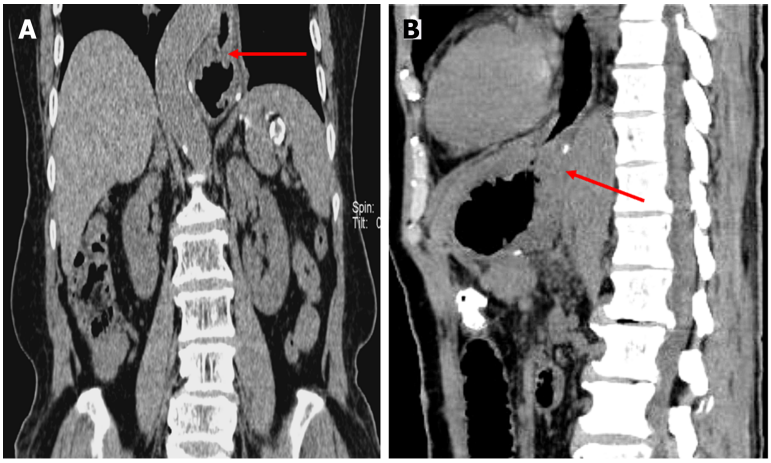

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Figure 4 Abdominal computed tomography (oral CO_2 powder). A: coronal surface: The valve-like structure can be seen at the anastomosis, tightly closed; B: Sagittal plane: The gastric cavity is inflated, seeing the anastomotic valve-like structure with gear sample occlusion and a small amount of gas overflow in the esophagus.

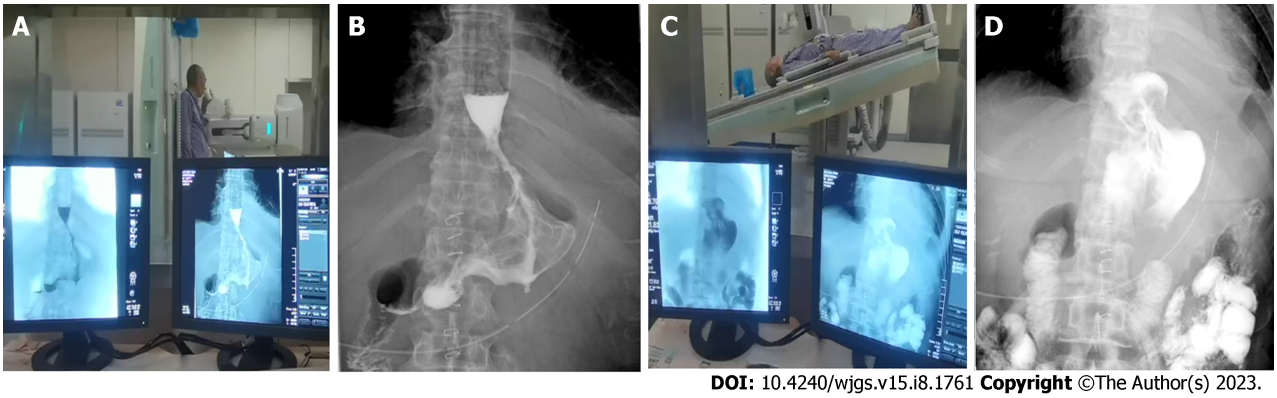

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Figure 5 Upper gastrointestinal tract angiography. A and B: Upright position: Unobstructed anastomosis, such as a normal cardia-like image; C and D: Head low foot high level: See the anastomosis is completely closed, no contrast agent reflux.

Three functional changes may occur in the state of gastric peristalsis: (1) With gastric contraction and an increase in gastric cavity pressure, gastric reflux to the esophagus occurs, pushing the valve-like stoma and further closing the anastomotic site. This valve-like structure functions as a unidirectional valve that is not prone to slip and cause reflux and leakage. However, while eating, the peristaltic pressure of the proximal esophagus and esophageal expansion by food clumps make the valve-like structure move distally but does not affect the passage of food; and (2) With peristalsis carried out from proximal to distal, the relaxation of the reconstructed gastric fundus and the subsequent passive expansion also have a certain anti-reflux effect on the compression of the lower end of the esophagus. According to computer simulation results, when the stomach contracts and shrinks, the valve-like structure moves to the upper left side, tightening the anastomotic stoma.

During follow-up, the majority of patients showed satisfactory recovery outcomes, except for two early EGAA patients who developed complications of reflux esophagitis, characterized by acid reflux and belching. This suggests that the four different asymmetric suture techniques might not have met the design standards due to lack of practical experience in the early stage of attempting the surgery, leading to incomplete closure of the valve-like structure, a half-folded gastric wall, and poor anti-reflux effect. However, with experience and improved surgical techniques, subsequent EGAA procedures were successful in achieving good anti-reflux effects, as observed in 11 patients. Notably, in the last 8 patients, gastroenterography revealed no reflux even in the supine and low head positions.

Finally, despite the advantages of our new approach, we acknowledge the limitations of the present study. As this was a single-center study with a small number of patients, more objective comparisons in multicenter trials are required to validate the procedure. Moreover, as a new technique, this requires a learning curve for surgeons to gain the necessary skills before satisfactory results can be achieved.

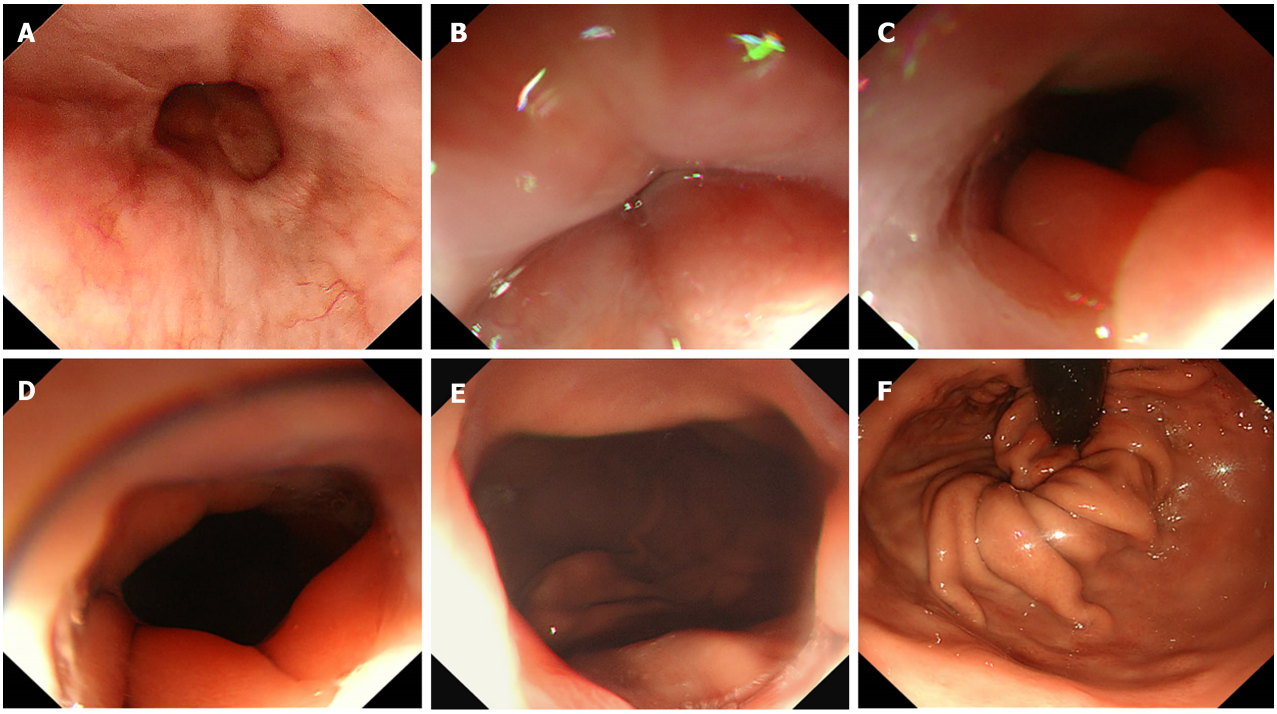

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Figure 6 Gastroscope. A: The esophageal mucosa is smooth, without hyperemia and edema, with a clear capillary network; B: The valve-like structure of the anastomosis is closed in the non-inflated state; C-E: The valve-like structure of the anastomosis opens gradually in the inflated state, with good dilation and extensibility, showing a visible dentate linear-like structure; F: The reconstructed gastric base can be seen under the inverted gastroscope, which was wrapped well by the valve-like structures of the folded gastric wall mucosa at the site of the anastomosis;

CONCLUSIONS

In this clinical study, we designed the valve-like structure and anti-reflux function of the EGAA. The surgical procedures we adopted adhered to basic medical principles as well as being relatively easy to master. The clinical outcomes of 13 patients indicated that this surgical technique is practical, safe, and reliable. However, it is necessary to further investigate its long-term anti-reflux effectiveness with more patients and randomized controlled studies.

ARTICLE HIGHLIGHTS

Research background

The direction of future research will be focused on investigating the long-term effectiveness of anti-reflux measures with larger patient populations and randomized controlled studies.

Research motivation

The implementation of esophagogastric asymmetric anastomosis (EGAA) proved to be a secure and viable procedure, yielding outstanding anti-reflux results following proximal gastrectomy.

Research objectives

The objective of this research was to investigate the effectiveness of the EGAA technique in preventing reflux after proximal gastrectomy that represents a new approach to anti-reflux surgery.

Research methods

First, we utilized a thermal stress computer simulation to replicate gastric peristalsis at the EGAA site. This was conducted to gain a deeper understanding of the mechanism and efficacy of the anti-reflux function. Subsequently, we performed digestive tract reconstruction on 13 patients who had undergone laparoscopic proximal gastrectomy using the EGAA technique. We closely monitored the structural and functional changes of the reconstruction through imaging exams and gastroscopy after the surgery. Lastly, we conducted follow-up assessments on the patients to determine the effectiveness of the anti-reflux effects.

Research results

The research findings suggest that the valve-like reconstructed structure at the site of EGAA was effective in preventing gastroesophageal reflux in patients who underwent the procedure. However, further studies are needed to evaluate the long-term efficacy and safety of this technique.

Research conclusions

The limitations of current anti-reflux surgical techniques have led to the development of novel methods to prevent postoperative reflux. The EGAA technique is designed to address the shortcomings of conventional techniques by utilizing computer simulation technology to study the anti-reflux mechanism of asymmetric anastomosis. Solving these problems and improving the effectiveness of anti-reflux techniques will have significant implications for the future of gastrointestinal reconstruction and postoperative patient outcomes.

Research perspectives

Our study highlights the increasing proportion of proximal gastric cancer over the past few decades that has resulted in reflux esophagitis becoming a common postoperative complication after proximal gastrectomy. There is a need for a safer method of performing esophageal-gastric anastomosis to reduce the risk of reflux and other complications for patients undergoing this surgery. Esophageal-residual gastric anastomosis after proximal gastrectomy is an effective way to reconstruct the digestive tract, but the loss of anti-reflux function can lead to several postoperative complications, affecting the quality of life of the patient. The significance of this study lies in finding ways to reduce these complications and improve the outcomes for patients.

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FOOTNOTES

Author contributions: Pang LQ, Zhang J, Shi F, Pang C and Chen S conceived and designed the study; Pang LQ and Zhang J performed the operation; Zhang CW, Shi F, Pang C, Liu YL, Zhao Y, Qian Y, Li XW, Xie CX, Kong D, Wu SN, Zhou JF and Chen S contributed to the study design, analysis, and interpretation of the data; Pang LQ and Chen S wrote the manuscript; all authors reviewed and approved the manuscript; Pang LQ, Zhang J, Shi F, Pang C and Chen S contributed equally to this work.

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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: The authors have no conflicts of interest to declare.

Data sharing statement: The data that support the findings of this study are available on request from the corresponding author.

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ORCID number: Li-Qun Pang 0000-0003-0624-6362; Shang-Nong Wu 0000-0003-2102-5269; Song Chen 0000-0001-6412-5740.

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ORIGINAL ARTICLE

Observational Study

Prognostic scores in primary biliary cholangitis patients with advanced disease

Juan Feng, Jia-Min Xu, Hai-Yan Fu, Nan Xie, Wei-Min Bao, Ying-Mei Tang

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Juan Feng, Jia-Min Xu, Hai-Yan Fu, Nan Xie, Ying-Mei Tang, Department of Gastroenterology, The Second Affiliated Hospital of Kunming Medical University, Kunming 650101, Yunnan Province, China

Wei-Min Bao, Department of General Surgery, Yunnan Provincial First People's Hospital, Kunming 650032, Yunnan Province, China

Corresponding author: Ying-Mei Tang, PhD, Teacher, Department of Gastroenterology, The Second Affiliated Hospital of Kunming Medical University, No. 374 Dianmian Road, Wuhua District, Kunming 650101, Yunnan Province, China. tangyingmei_med@kmmu.edu.cn

Abstract

BACKGROUND

Due to the chronic progressive disease characteristics of primary biliary cholangitis (PBC), patients with advanced PBC should not be ignored. Most prognostic score studies have focused on early stage PBC.

AIM

To compare the prognostic value of various risk scores in advanced PBC to help PBC patients obtain more monitoring and assessment.

METHODS

This study considered patients diagnosed with PBC during hospitalization between 2015 and 2021. The clinical stage was primarily middle and late, and patients usually took ursodeoxycholic acid (UDCA) after diagnosis. The discriminatory performance of the scores was assessed with concordance statistics at baseline and after 1 year of UDCA treatment. Telephone follow-up was conducted to analyze the course and disease-associated outcomes. The follow-up deadline was December 31, 2021. We compared the risk score indexes between those patients who reached a composite end point of death or liver transplantation (LT) and those who remained alive at the deadline. The combined performance of prognostic scores in estimating the risk of death or LT after 1 year of UDCA treatment was assessed using Cox regression analyses. Predictive accuracy was evaluated by comparing predicted and actual survival through Kaplan-Meier analyses.

RESULTS

We included 397 patients who were first diagnosed with PBC during hospital-

ization and received UDCA treatment; most disease stages were advanced. After an average of 6.4 ± 1.4 years of follow-up, 82 patients had died, and 4 patients had undergone LT. After receiving UDCA treatment for 1 year, the score with the best discrimination performance was the Mayo, with a concordance statistic of 0.740 (95% confidence interval: 0.690-0.791). The albumin-bilirubin, GLOBE, and Mayo scores tended to overestimate transplant-free survival. Comparing 7 years of calibration results showed that the Mayo score was the best model.

CONCLUSION

The Mayo, GLOBE, UK-PBC, and ALBI scores demonstrated comparable discriminating performance for advanced stage PBC. The Mayo score showed optimal discriminatory performance and excellent predictive accuracy.

Key Words: Primary biliary cholangitis; Prognostic value; Liver transplantation; Cholangitis; Mayo score

Core Tip: Primary biliary cholangitis (PBC) is a chronic progressive liver disease that destroys the intrahepatic small bile ducts. PBC in the middle and late stages cannot be ignored. The present study enrolled patients first diagnosed with PBC during hospitalization whose disease stages were primarily in the middle and late stages. We compared the prognostic value of various risk scores in PBC patients with advanced disease stages so that a significant proportion would undergo monitoring, disease evaluation, and timely treatment.

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INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic progressive liver disease that causes the gradual destruction of the intrahepatic small bile ducts[1]. Preclinical PBC may present with specific diagnostic antibodies (anti-mitochondrial antibody, AMA) but remain asymptomatic with normal liver function for over a decade. Approximately 50%-60% are asymptomatic at diagnosis[2]. Ursodeoxycholic acid (UDCA) is the first-line treatment. It increases long-term survival. However, approximately 40% of patients with PBC have incomplete responses, and these patients progress rapidly to the middle and late stages of disease after early diagnosis and treatment[3]. Because of the chronic progressive disease characteristics, PBC patients in the middle and late stages should not be ignored.

Over the past 20 years, several risk-scoring models for PBC have been proposed as tools to estimate the risk of adverse outcomes and to guide management[4]. The most influential scores are GLOBE and UK-PBC, developed for early PBC patients. Recent studies reported that these scores accurately predict outcomes in patients treated with UDCA treatment at various disease stages[5-7]. However, their application to middle and late stage PBC patients remains to be studied. The Mayo score was developed to determine the timing of liver transplantation (LT) in PBC and is now a model for predicting PBC survival[8-10]. The aspartate aminotransferase-to-platelet ratio index (APRI) and fibrosis-4 index (FIB-4) are non-invasive fibrosis scores based on biochemical indicators[11]. All parameters, including aminotransferase, platelets, and age, are associated with PBC outcomes[12,13]. The albumin-bilirubin (ALBI) score was initially developed to assess liver function in hepatocellular carcinoma patients[14]. The total bilirubin (TBil) and albumin in the score are associated with PBC progression, and some studies have used them to predict PBC outcomes[15,16]. There are few studies on the efficacy and differences of the various prognostic scoring systems in PBC patients, especially in patients in advanced stages[17-19].

Some patients with decompensated cirrhosis return to a clinical state consistent with compensated cirrhosis when they undergo appropriate etiological and symptomatic supportive treatment, named the "recompensation phenomenon"[20]. Portal hypertension and systemic inflammation can lead to the progression of decompensated cirrhosis. Recently, studies have been performed on the mechanism and clinical feasibility of reversing decompensation and recompensation in cirrhosis[21-23]. These findings led to updating the stage evaluation concept and an outcomes estimate system for decompensated cirrhosis.

The present study enrolled patients diagnosed with PBC during hospitalization whose disease stages were in the middle and late stages. We compared the effectiveness and differences of various prognostic scoring systems to optimize monitoring, disease evaluation, and timely treatment for advanced stage PBC.

MATERIALS AND METHODS

Population and study design

Patient data were derived from nine hospitals in Yunnan Province, China. Patients whose disease was on the first page of the medical record were diagnosed with PBC (ICD-10 code K74.3) and were treated with UDCA after diagnosis. The diagnostic criteria were as follows: elevated serum alkaline phosphatase; AMA-positive or AMA-negative when there were PBC-specific autoantibodies such as spl00 and gp210; histological evidence suggesting non-suppurative destructive cholangitis; and interlobular bile duct injury. PBC can be diagnosed when two criteria are met, and the diagnostic criteria met the 2018 American Association for the Study of Liver Diseases guidelines[24].

Patients were excluded if they underwent follow-up for less than 6 mo or if the dates of treatment initiation or major clinical events were unknown.

Data collection

Clinical data were obtained from 397 PBC patients diagnosed during hospitalization from May 1, 2015 to December 31, 2021. Clinical data collected from these patients included age, sex, ethnicity, date of PBC diagnosis, past medical and personal histories, clinical manifestations, liver disease complications, liver biopsy results, imaging results, gastroscopy results, and laboratory values (immunological tests, serum biochemistries, complete blood counts, and coagulation times). UDCA (13-15 mg/kg/day) was prescribed after diagnosis, and laboratory results were collected at the 1-year follow-up. Current guidelines and the reports from centers worldwide state that biochemical improvement after 1 year of UDCA treatment accurately predicts long-term outcomes and survival[24-26]; therefore, we collected laboratory results at a 1-year follow-up for prognostic assessment.

All patients were followed up by telephone with a deadline of December 31, 2021. Endpoint events were liver-related death or LT. No endpoint event was non-transplantation survival. Classification of the disease stage was according to the patient's clinical characteristics and examination data. A cirrhosis diagnosis was based on liver imaging examination (B-ultrasound, computed tomography), liver biopsy, or liver transient elastic imaging in the medical records. The diagnosis standard was derived from the 2020 guidelines[27]. We divided the patients into groups without cirrhosis, compensated cirrhosis, and decompensated cirrhosis.

Ethical considerations

This study was performed per the Declaration of Helsinki. The Ethics Committee of the second affiliated hospital of Kunming Medical University approved the study (approval No. YJ-2022-14). Each participating center approved the protocol. We analyzed all data anonymously.

Statistical analyses

The baseline time was the start of UDCA treatment, and the primary endpoint was a composite of death or LT. Patients not meeting this endpoint during follow-up were censored at their final follow-up visit. The formulas of prognostic scores can be found in the Supplementary material. These scores were computed at baseline and after 1 year of UDCA treatment. These risk scores were descriptive statistics to compare patients that did or did not meet the composite endpoint.

Predictive validity was based on model discrimination and calibration. Cox proportional hazard regression analyses were performed to assess the discriminative performance of the risk scoring models at baseline and after UDCA treatment for 1 year. The overall discriminative performance of these models was calculated using the concordance (C)-statistic. Combining these predictive models when assessing the risk of death or LT based on data collected following UDCA treatment for 1 year was further evaluated using Cox regression analyses. C-statistic values were also assessed for various combinations of risk prediction models.

A graphical approach was used to assess model calibration by comparing Kaplan-Meier transplant-free survival estimates produced by these risk prediction models after 1 year of UDCA treatment.

All analyses were performed using R v 4.2.1. To account for missing values, the predictive mean matching of the mice package was applied to interpolate the missing data of laboratory results using multiple interpolation methods. Continuous data were expressed as the median and interquartile range. $P < 0.05$ was the threshold of significance.

RESULTS

Study population characteristics

We enrolled 397 PBC patients initially diagnosed while hospitalized and underwent UDCA treatment. The mean age was 56.84 (standard deviation 11.2) years and included 343 (86.4%) females. The specific staging, clinical, and biochemical characteristics at the beginning of UDCA treatment are displayed in Table 1.

The patients were followed for 6.4 ± 1.4 years, with 3 patients lost to follow-up at the final follow-up. During follow-up, 86 experienced a clinical endpoint: 4 patients underwent LT; and 82 patients died. Liver disease was related to the cause of death in 79/82 (96.3%) patients. The 3-, 5-, and 7-year transplant-free survival rates were 94.0%, 86.9%, and 78.3%, respectively (Figure 1). Advanced stages correlated with lower survival ($P < 0.001$).

At the start of UDCA therapy, 80 (20.2%) patients had no cirrhosis, 43 (10.9%) patients had compensated cirrhosis, and 274 (69.0%) patients had decompensated cirrhosis.

Table 1 Baseline cohort characteristics

Baseline cohort characteristic	Value
Age at diagnosis, yr	56.84 (11.2)
Female, *n* (%)	343 (86.4)
Year of diagnosis, range	2015 to 2021
AMA M2+, *n* (%)	296 (74.6)
AMA M2-, gp210+, *n* (%)	98 (24.7)
AMA M2-, sp100+, *n* (%)	99 (24.9)
Liver biopsy cases, *n* (pathological stage, using the Scheuer classification)	5 (I), 23 (II), 3 (I-II), 5 (II-III), 14 (III), 4 (III-IV), 77 (IV)
PLT as × 10^9/L	88 (142, 207)
PT in s	12.2 (13.3, 14.9)
INR	0.96 (1.06, 1.23)
ALB in g/L	29.9 (35.1, 39.9)
ALT in U/L	27 (52, 98)
AST in U/L	40 (68, 120)
TBil in mol/L	15.8 (24.3, 52.3)
CREA in mmol/L	50 (58, 68)
ALP in IU/L	122 (204, 351)
GGT in IU/L	56 (166, 356)
GLOBE	0.34 (1.56, 2.65)
UK-PBC	0.02 (0.07, 0.26)
APRI	0.69 (1.40, 2.54)
FIB4	2.28 (4.36, 6.93)
ALBI	-2.51 (-2.03, -1.39)
Mayo	1.44 (2.33, 3.52)
Without cirrhosis, baseline time/end of the follow-up, *n* (%)	80 (20.2)/50 (12.6)
Compensated cirrhosis	43 (10.9%)/56 (14.1%)
Decompensated cirrhosis	274 (69.0%)/288 (72.5%)
Death	82
Liver-related death	79
LT	4

The upper limits of normal of each biochemical index in the figure are as follow: platelet (350 × 10^9/L), prothrombin time (15 s), international normalized ratio (1.3), albumin (50g/L), alanine aminotransferase (40 U/L), aspartate transaminase (40 U/L), total bilirubin (20.5 μmol/L), creatinine (97 mmol/L), alkaline phosphatase (125 IU/L), gamma-glutamyl transferase (32 IU/L. ALB: Albumin; ALBI: Albumin-bilirubin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AMA: Anti-mitochondrial antibody; APRI: Aspartate aminotransferase-to-platelet ratio index; AST: Aspartate transaminase; CREA: Creatinine; FIB4: Fibrosis-4 index; GGT: Gamma-glutamyl transferase; GLOBE: The prognostic score using data from the global primary biliary cholangitis group; INR: International normalized ratio; LT: Liver transplantation; PLT: Platelet; PT: Prothrombin time; TBil: Total bilirubin.

Discriminative performance of different prognostic risk scoring models

The overall discriminative performance of the Mayo, APRI, FIB-4, and ALBI models was assessed at baseline based on C-statistic values when used to predict death or LT. GLOBE and UK-PBC scores were based on values measured at baseline and after UDCA treatment for 1 year. The baseline C-statistic values for the Mayo and ALBI scores were 0.702 [95% confidence interval (CI): 0.653-0.751] and 0.705 (95%CI: 0.656-0.755), respectively, while the FIB-4 and APRI scores showed poorer performance (Table 2).

Following UDCA treatment for 1 year, the C-statistic values for Mayo, GLOBE, UK-PBC, and ALBI scores were 0.740 (95%CI: 0.678-0.776), 0.731 (95%CI: 0.681-0.782), 0.727 (95%CI: 0.678-0.776), and 0.725 (95%CI: 0.672-0.778), respectively. In contrast, the FIB-4 score showed poorer discriminatory power, and the APRI scores showed virtually no discriminatory performance (Table 2; Supplementary Figure 1).

Table 2 Discriminative performance of the various risk prediction scores calculated at baseline and after 1 year of ursodeoxycholic acid therapy

C-statistic at various follow-up time points (95%CI)		
Risk prediction model	**Baseline**	**1 yr of UDCA**
GLOBE		0.731 (0.681-0.782)
UK-PBC		0.727 (0.678-0.776)
APRI	0.592 (0.536-0.647)	0.347 (0.296-0.398)
FIB4	0.648 (0.593-0.704)	0.680 (0.628-0.732)
ALBI	0.705 (0.656-0.755)	0.725 (0.672-0.778)
Mayo	0.702 (0.653-0.751)	0.740 (0.690-0.791)

ALBI: Albumin-bilirubin; APRI: Aspartate aminotransferase-to-platelet ratio index; C-statistic: Concordance statistic; CI: Confidence interval; FIB4: Fibrosis-4 index; UDCA: Ursodeoxycholic acid.

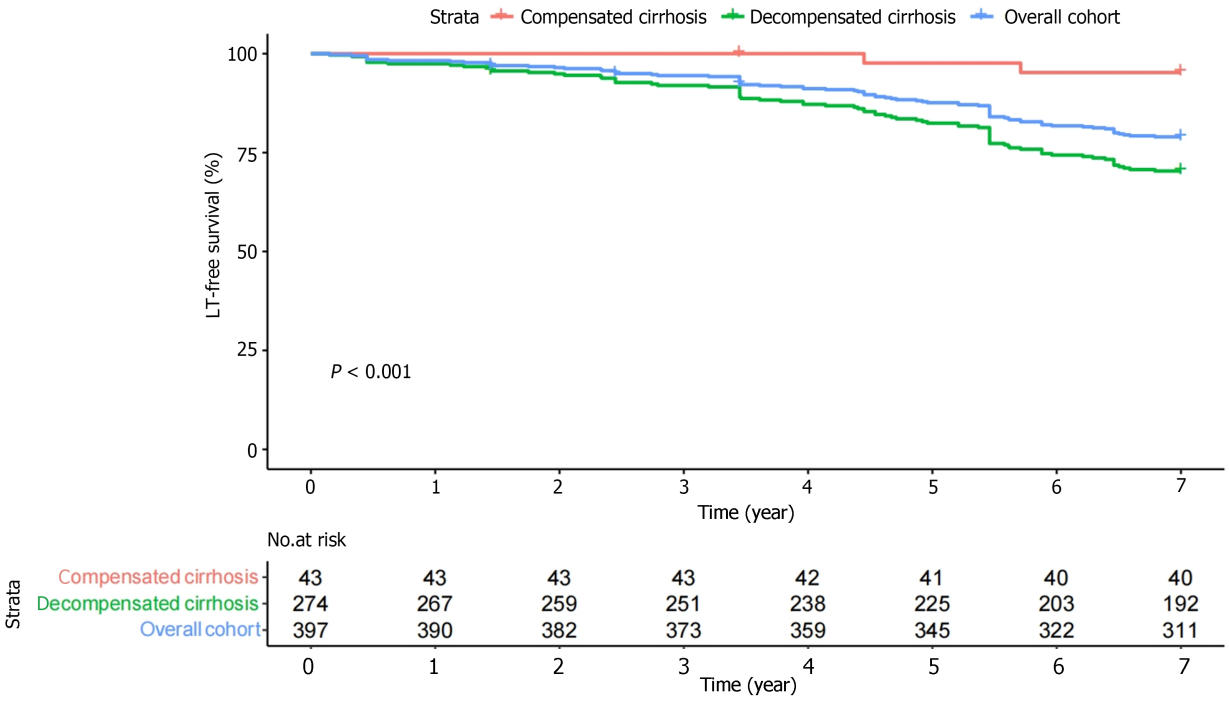

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Figure 1 Kaplan-Meier estimates for the baseline patients survival. The transplant free survival (or death) of primary biliary cholangitis patients with baseline compensated and decompensated cirrhosis. LT: Liver transplantation.

There were no significant differences between the GLOBE, UK-PBC, Mayo, and ALBI scores concerning predictive performance at the start of UDCA treatment or 1 year after (Supplementary Table 1).

Analysis of the combined performance of different risk prediction scores

Cox regression analyses were used to evaluate the availability of combining predictive models when assessing the odds of death or LT based on data collected following UDCA treatment for 1 year. In univariate Cox regression analyses, the UK-PBC, ALBI, GLOBE, and Mayo scores were all significantly associated with death or LT ($P < 0.001$) (Table 3). The hazard ratio of UK-PBC was the largest (hazard ratio: 6.046, 95%CI: 3.479-10.510). In multivariate analysis, only the GLOBE scores remained significantly associated with death or LT (Table 3).

Adding the UK-PBC, APRI, FIB-4, Mayo, and ALBI scores to the GLOBE score did not significantly improve the discriminative performance, with a C-statistic value that remained at 0.73 (Supplementary Table 2). The C-statistics of all scores before adding are displayed in Table 1.

Combining the UK-PBC score with the APRI, FIB-4, and ALBI scores did not cause a significant increase in discrimination performance. The C-statistic remained at 0.72 (Supplementary Table 2); only with the addition of the Mayo score did the C-statistic increase (+0.02).

Table 3 Multivariable analyses of risk prediction scores after 1 year of ursodeoxycholic acid therapy

	Univariate analyses			Multivariable analyses		
Prognostic score	**Hazard ratio**	**95%CI**	***P* value**	**Hazard ratio**	**95%CI**	***P* value**
GLOBE	1.703	1.474-1.967	< 0.001	1.582	1.029-2.433	0.037
UK-PBC	6.046	3.479-10.510	< 0.001	1.012	0.330-3.102	0.983
APRI	0.998	0.971-1.024	0.860	0.918	0.812-1.038	0.171
FIB4	1.005	0.997-1.013	0.242	1.008	0.991-1.024	0.369
ALBI	2.546	1.955-3.316	< 0.001	1.194	0.595-2.40	0.618
Mayo	1.495	1.348-1.676	< 0.001	1.022	0.697-1.497	0.913

ALBI: Albumin-bilirubin; APRI: Aspartate aminotransferase-to-platelet ratio index; CI: Confidence interval; FIB4: Fibrosis-4 index.

The most significant increase in C-statistic values was observed when the Mayo score was combined with the others. The APRI score increased to 0.740 (95%CI: 0.689-0.791), and the FIB-4 score increased to 0.741 (95%CI: 0.69-0.791) (Supplementary Table 2)

Calibration analyses of different predictive risk scores

The ALBI, GLOBE, and Mayo scores with superior discriminatory performance were selected to evaluate the predicted and observed survival (Figure 2). The UK-PBC score was omitted from the analyses because it primarily predicts liver-related death rather than transplant-free survival[28]. The three risk prediction models tended to overestimate transplant-free survival. They showed good calibration for short-term survival; the deviation from observed survival at 1 year to 3 years for ALBI, GLOBE, and Mayo was < 0.2%. After 3 years, the deviation tended to be greater yearly. The most significant deviation was for the GLOBE score (2.0%-4.3%), and the most minor was for the Mayo score (1.0%-2.4%). When these scores were evaluated at yearly intervals for up to 7 years, the deviation of the GLOBE score was the greatest, and the Mayo score was the most minor. By comparison, the Mayo score demonstrated the best calibration.

DISCUSSION

We assessed the PBC-specific scores GLOBE, UK-PBC, and Mayo and compared the ALBI, APRI, and FIB-4 scores. These analyses revealed that the ALBI and Mayo scores showed adequate discriminatory performance and good predictive accuracy at baseline. The Mayo score demonstrated superior discriminatory performance and calibration singly and combined with other risk models, suggesting that this score is the best risk prediction model for predicting liver-related death or LT in PBC patients in the advanced stage. These findings also suggested that the performance of the PBC-specific risk scores was superior to other prognostic scores for advanced PBC.

Models with a C-statistic value greater than 0.7 are considered good prognostic models. The Mayo score was the only model consistently reaching this threshold at baseline and 1 year of UDCA treatment. The C-statistic of the Mayo score was greater after patients received UDCA for 1 year, suggesting an increase in discriminatory performance with prolonged UDCA treatment. The next most effective predictive models were the GLOBE, UK-PBC, and ALBI scores, with no significant differences in predicting liver-related death or LT following UDCA treatment for 1 year.

The Mayo score exhibited consistently better discriminative performance than other scores in this PBC patient cohort. The Mayo score is a traditional risk prediction model developed for PBC patients, primarily developed to evaluate untreated PBC patients. However, this study enrolled patients that had undergone UDCA treatment and were in an advanced stage. The Mayo score has previously been linked to transplant-free survival among patients that underwent UDCA treatment, enabling their stratification into low- and high-risk groups based on the original thresholds[29,30]. However, the reliance of this scoring model on ascites, which can be subjective, may limit its clinical applicability.

In this study, the parameter was derived from the results of imaging examinations during hospitalization, and this examination is a routine item of these hospitalized patients. Therefore, the judgment of the parameter of ascites was relatively objective. In theory, the superior discriminatory performance of the Mayo score may be promoted by ascites and prothrombin time, which are the most relevant parameters in late stage PBC; other parameters are TBil and ALB, which also are indicators of significant changes in patients with more advanced stages. Based on these characteristics, the Mayo score may be more applicable for prognosis assessment in advanced stage PBC patients. Our study verified this point, but the actual evidence remains to be further verified in a large population or more studies.

The discriminatory performance of the GLOBE, UK-PBC, and ALBI scores is secondary to the Mayo score. Both the UK-PBC and GLOBE scores were developed as PBC-specific scoring systems and have previously been applied to evaluate the prognosis of early PBC patients. Our cohort was mainly late stage patients, and the results were inferior to the Mayo score. The ALBI score is calculated using two indicators (TBil, ALB), which are validated biomarkers associated with PBC disease progression[31-33]. APRI and FIB-4 scores had inferior discriminatory performance in this study, while the two were liver fibrosis scores based on biochemical indicators. However, this study's poor performance may be

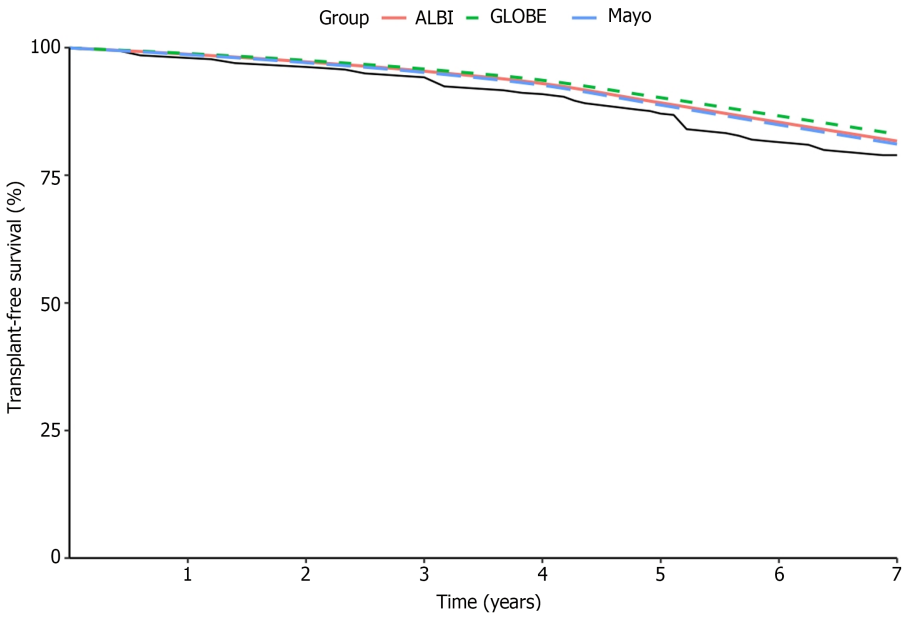

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Figure 2 Calibration analyses of the predictive accuracy of ALBI, GLOBE, and Mayo scores were calculated after ursodeoxycholic acid treatment for 1 year over a 7-year follow-up interval.

because most patients had cirrhosis without significant differences in the progression of liver fibrosis, which is not applicable to predicting advanced PBC patients.

The different combinations of prognostic models were evaluated for their ability to predict death or LT. The study results showed that GLOBE and UK-PBC were relatively stable, with little change in the C-statistic when other scores were added. Moreover, the univariate and multivariate Cox regression analyses of all predictive models also support this point. The highest C-statistic value increases were observed when the Mayo scores were combined with the other scores. The results demonstrated that the GLOBE and UK-PBC score models have good stability and are applicable for prognosis assessment exclusively. While the APRI and FIB-4 scores were applied to combine with other scores, the best discriminatory performance was combined with the Mayo score.

We chose the ALBI, GLOBE, and Mayo sores for model calibration, which had superior discriminatory performance after UDCA therapy for 1 year, while the UK-PBC model was omitted because it predicts liver-related death and not transplant-free survival[28]. These scores all tended to overestimate the transplant-free survival rate, with better calibration at 1-3 years. The deviation tended to increase yearly after 3 years. In the 1-7-year interval, the deviation of the GLOBE score was the greatest, and the Mayo score was the most minor. In contrast, the best model calibration was the Mayo score. These findings suggested that the Mayo score has the best prediction performance and accuracy for advanced PBC patients.

This study has several limitations. First, we did not have a large study cohort, and the comparison of prognostic scores was calculated at baseline and 1 year later. This limitation indicates the need for verification using large sample sizes and prospective studies. Second, this was a retrospective analysis; some of the included data were missing. We applied predictive mean matching to interpolate the missing values. Third, while the UK-PBC risk score was developed to predict liver-related death and not transplant-free survival (unlike the other score models), the same analyses used the endpoints and indicated similar discriminatory performance. Despite the limitations, the study is significant because of the lack of the comparison of prognostic scores in advanced PBC patients.

CONCLUSION

The Mayo, GLOBE, UK-PBC, and ALBI scores had excellent prediction performance for death and LT. Mayo scores had the best prediction efficacy in discriminating performance and predicting outcomes. The significance of this study was that it enables advanced PBC patients to be monitored and assessed closely in clinical practice to delay PBC progression.

ARTICLE HIGHLIGHTS

Research background

Due to the chronic progressive disease characteristics of primary biliary cholangitis (PBC), patients with advanced PBC should not be ignored. Most prognostic score studies have focused on early stage PBC.

Research motivation
This study was designed to compare the prognostic value of different risk scores in the PBC patients with advanced disease stages.

Research objectives
To determine the best prognostic score to ensure that the clinical majority of PBC patients get more monitoring and assessment.

Research methods
The discriminatory performance of the scores was assessed with concordance statistics at baseline and after 1 year of ursodeoxycholic acid (UDCA) treatment. The combined performance of prognostic scores in estimating the risk of death or liver transplantation after 1 year of UDCA treatment was assessed using Cox regression analyses. Predictive accuracy was evaluated by comparing predicted and actual survival through Kaplan-Meier analyses.

Research results
After receiving UDCA treatment for 1 year, the score with the best discrimination performance was the Mayo score, with a concordance statistic of 0.740 (95% confidence interval: 0.690-0.791). The ALBI, GLOBE, and Mayo scores tended to overestimate transplant-free survival. Comparing 7 years of calibration results showed that the Mayo score was the best model.

Research conclusions
The Mayo, GLOBE, UK-PBC, and ALBI scores demonstrated comparable discriminating performance for advanced stage PBC. The Mayo score showed optimal discriminatory performance and excellent predictive accuracy.

Research perspectives
There is a need for verification of our results with larger sample sizes and prospective studies.

FOOTNOTES

Author contributions: Feng J, Xu JM, Bao WM, and Tang YM designed the research study; Feng J, Xu JM, Fu HY, and Xie N performed the research; All authors contributed to data collection and collation; Feng J and Xu JM analyzed the data and wrote the manuscript; All authors read and approved the final manuscript.

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Institutional review board statement: The Ethics Committee of the second affiliated hospital of Kunming medical university approved the study (Approval No. YJ-2022-14), the protocol was approved by each participating center.

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: The authors declare that they have no competing interests.

Data sharing statement: Not applicable.

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

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ORCID number: Juan Feng 0009-0007-1690-832X; Ying-Mei Tang 0000-0002-0731-4198.

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SYSTEMATIC REVIEWS

Maternal choledochal cysts in pregnancy: A systematic review of case reports and case series

Goran Augustin, Ivan Romic, Iva Miličić, Mislav Mikuš, Mislav Herman

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Goran Augustin, Department of Surgery, School of Medicine, University of Zagreb, Zagreb 10000, Croatia

Goran Augustin, Mislav Herman, School of Medicine University of Zagreb, Zagreb 10000, Croatia

Ivan Romic, Department of Surgery, University Hospital Centre Zagreb, Zagreb 10000, Croatia

Iva Miličić, Mislav Mikuš, Mislav Herman, Department of Obstetrics and Gynecology, University Hospital Centre Zagreb, Zagreb 10000, Croatia

Corresponding author: Goran Augustin, MD, MSc, PhD, Associate Professor, Doctor, Senior Scientist, Surgical Oncologist, Department of Surgery, University Hospital Centre Zagreb, Kišpatićeva 12, Zagreb 10000, Croatia. augustin.goran@gmail.com

Abstract

BACKGROUND

Choledochal cysts (CC) are cystic dilatations of the biliary tract, usually diagnosed during childhood, with an estimated incidence in the general population of 1:100000. Complications related to CC include rupture, biliary obstruction, and cholangitis. Maternal CC in pregnancy are rarely reported, and there are no guidelines on optimal management.

AIM

To systematically review maternal CC diagnosed during pregnancy or postpartum with regard to the clinical presentation of CC, the mode of treatment and delivery, and maternal outcomes.

METHODS

A literature search of cases and case series of maternal CC in pregnancy and postpartum was conducted using MEDLINE/PubMed, Web of Science, Google Scholar, and Embase. There were no restrictions on language or publication year. Databases were lastly accessed on September 1, 2022.

RESULTS

Overall, 71 publications met the inclusion criteria, reporting 97 cases. Eighty-eight cases were diagnosed during pregnancy and nine in the puerperium. The most common symptoms were abdominal pain (81.2%) and jaundice (60.4%). Interventions for CC complications were required in 52.5% of the cases, and 34% of pregnancies were induced. Urgent cesarean section (CS) was done in 24.7%. The

maternal mortality was 7.2%, while fetal mortality was inconsistently reported. Cholangitis, CC > 15 cm, and bilirubin levels > 80 mmol/L were associated with a higher likelihood of urgent CS and surgical intervention for CC. Bilirubin levels positively correlated with CC size. There was no correlation between age and cyst dimension, gestational age at cyst discovery, and CC size.

CONCLUSION

Although rare, maternal CC in pregnancy should be included in the evaluation of jaundice with upper abdominal pain. Symptomatology and clinical course are variable, and treatment may range from an expectative approach to emergent surgical CC treatment and urgent CS. While most cases were managed by conservative measures or drainage procedures, CC > 15 cm and progressive cholangitis carry the risk of CC rupture and septic complications, which may increase the rates of unfavorable maternal and fetal outcomes. Therefore, such cases require specific surgical and obstetric interventions.

Key Words: Choledochal cyst; Pregnancy; Cholangitis; Surgery; Delivery; Cesarean section

Core Tip: Although rare, maternal choledochal cysts (CC) in pregnancy should be included in the evaluation of jaundice with upper abdominal pain. Symptomatology and clinical course are variable, and treatment may range from an expectative approach to emergent surgical treatment of CC and urgent cesarean section. While most cases were managed by conservative measures or drainage procedures, CC > 15 cm and progressive cholangitis carry the risk of CC rupture and septic complications, which may increase the rates of unfavorable maternal and fetal outcomes. Therefore, such cases require specific surgical and obstetric interventions.

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INTRODUCTION

Choledochal cysts (CC) are cystic dilatations of the biliary tract, usually diagnosed during childhood (80%)[1,2]. Todani's classification is based on anatomical characteristics, and it is the most widely used classification method, which divides CC into five types[3]. Type I (cystic dilatation of the common bile duct) is the most common (90%)[4,5]. The incidence significantly varies between the East and the West[1,4]. The estimated incidence in the general population is 1:100000-1:150000 in Western countries, while in the East, it is much higher (up to 1:1000), with a male/female ratio of 1:3-4[1,6]. Although cholecystitis or choledocholithiasis is more commonly associated with upper right abdominal pain or jaundice, CC should be considered in the differential diagnosis because the treatment approach is different. CC may present with a triad of abdominal pain, jaundice, and a palpable right upper quadrant abdominal mass. The presentation of CC depends not only on size but on morphology, the presence of sludge/stones, and the status of the remaining biliary tract. When cholangitis develops, the Charcot triad may be present (jaundice, fever with rigors, and right upper quadrant abdominal pain). CC may result in severe complications such as biliary obstruction, cholangitis, or cyst rupture. Furthermore, CC are considered a premalignant condition, another reason for surgical treatment, even in asymptomatic patients[4,7]. Gomes *et al*[8] made the first report on CC in 1723.

Many theories on the pathogenesis of CC were offered. Some proposed that congenital dysplasia arises from early embryonic development, where dysplasia of the primordial common bile duct (CBD) leads to CBD dilation[9]. Another theory is based on a congenital weakness of the bile duct wall that allows cysts to form[10,11]. Proponents of the CBD obstruction theory believe that CC form due to congenital or acquired obstruction of the ducts[12]. A so-called dual theory states that cyst formation is due to the weakness of the bile duct wall and obstruction of the ducts[13]. However, the most widely accepted theory, the common channel theory, states that the anomalous pancreaticobiliary junction leads to the formation of an abnormally long common channel, which permits reflux of the activated proteolytic pancreatic enzymes, biliary tract wall weakness and, eventually, cystic dilatation[14].

CC treatment in the general population depends on symptomatology and CC features. Most cases require cyst excision, cholecystectomy, and Roux-en-Y hepaticojejunostomy (HJ)[6,14]. Urgent indications are cyst rupture, intraluminal biliary bleeding, or severe cholangitis[12,15]. Todani's classification determines surgical treatment. Types I and IV should be completely excised, in addition to cholecystectomy and bilioenteric continuity formation. Type II is usually treated by diverticulectomy followed by CBD closure at the diverticulum neck. Endoscopic sphincterotomy is usually sufficient for type III cysts[11,12,15]. The treatment of types IV and V is more complex, as both comprise intra- and extrahepatic components, and the intrahepatic component is difficult to treat. When the cyst adheres densely to the portal vein due to an inflammatory reaction, standard full-thickness cyst excision may not be possible. In such cases, the Lilly technique

should be considered, which includes curettage or cauterization of cyst mucosa while the serosa remains attached to the portal vein. This resolves cholestasis, and at the same time, it removes the risk of malignant transformation.

Maternal CC in pregnancy are rarely reported, and no studies suggest a possible facilitating impact of pregnancy on CC development or growth. However, the pregnant uterus possibly causes biliary outflow obstruction promoting cystic dilatation, eventually leading to symptoms in prepregnancy asymptomatic individuals[16]. In addition, physiological changes during pregnancy can mask different clinical scenarios, including CC.

The effects of CC and their complications considering pregnancy outcomes have not been studied. Jaundice in pregnancy has potentially severe maternal and fetal consequences, found with intrahepatic cholestasis of pregnancy (ICP) or hemolysis, elevated liver enzymes, low platelets syndrome. Adverse fetal outcomes include preterm delivery, respiratory distress, or fetal distress. Therefore, CC with cholestasis and jaundice pose a similar risk to the mother and the fetus as ICP or other cholestatic disorders[16-18].

Due to the rarity of CC, reliable data on the risk of fetal loss and optimal CC treatment are lacking, and randomized trials or large prospective series do not exist. Therefore, we aimed to systematically review maternal CC diagnosed during pregnancy and postpartum and to propose optimal treatment strategies.

MATERIALS AND METHODS

Literature search and study selection

A literature search of cases and case series of maternal CC in pregnancy and postpartum was conducted. We searched MEDLINE/PubMed, Web of Science, Google Scholar, and Embase using a combination of MeSH terms: "Maternal", "choledochal cyst", "choledochocele", "pregnancy", "biliary tract disease", "puerperium", and "postpartum." Puerperium was evaluated up to the 6th postpartum week.

The search was limited to human studies published until September 2022, without language or country restrictions. Non-English articles were translated and analyzed with the help of medical scientists proficient in the languages mentioned above. We evaluated articles and references from these articles to identify additional cases. Cases with maternal CC treated and diagnosed before pregnancy were excluded. All potentially relevant articles were reviewed by three investigators (AA, GA, and IR), and all disagreements were settled by discussion.

Data management

Data included demographic data (maternal age, parity, and gestational weeks), clinical presentation (pain, jaundice, palpable mass, and fever), laboratory data (total bilirubin and liver enzymes), radiological examinations [abdominal ultrasound, abdominal magnetic resonance imaging (MRI), cyst dimensions, and cyst type according to Todani's classification], mode of treatment and delivery, maternal and fetal outcomes. The risk of bias or study quality was not assessed, as all articles were case reports or small case series. Bilirubin (μmol/L) was the only laboratory parameter sufficiently reported to be included in the analysis. If mentioned, the highest diameter of the CC and bilirubin value were used in the calculations. Pregnancies were analyzed through gestational months and trimesters; the first trimester counts from week zero to the end of the 13th week, the second from the 14th to the 27th week, and the third from the 28th to term.

Statistical analysis

Results of descriptive analyses are reported as numbers and proportions in percentages. Inferential statistics were executed on the different numbers of patients depending on the availability of analyzed variables. Categorical variables were analyzed using the chi-square test, and results are reported as odds ratios (OR) with 95%CI. A Pearson's correlation analysis was used for an association between continuous parameters (age, cyst size, bilirubin level, and parity). A P value less than 0.05 was considered statistically significant. Statistical analyses were performed *via* the SPSS version 26 (SPSS, Chicago, IL, United States).

RESULTS

Study characteristics

The PRISMA flow diagram (Figure 1) shows a total of 153 screened articles, of which 71 met the inclusion criteria with a total of 97 patients. The earliest report was published in 1932, and the most recent was in 2020. Half of the studies were published in the last 2 decades (Figure 2). Most cases were from Asia (n = 35), followed by Europe (n = 23) and North America (Table 1). There were ten non-English articles: Two in Chinese, two in Japanese, one in Korean, three in German, one in French, and one in Spanish. Complete patient, cyst, and treatment characteristics were described in 55% of cases. All cases reported the mother's age, maternal outcome, and gestational age at delivery (Figure 3). Type of delivery was reported in 91%, and fetal outcome in 21.6% of cases.

Patient characteristics

Patient characteristics are summarized in Table 2. The mean age was 25.3 years (range 15-40 years), and 62/83 (74.6%) patients with reported data were primigravidas. Parity was reported in 83 cases-62 women (74.6) were nulliparous, and seven had more than one previous pregnancy. Among all, eight (8.2%) were diagnosed in the first, 33 (34.8%) in the second, 40 (41.2%) in the third trimester, and nine (9.3%) in the postpartum period. In six (6.1%) cases, CC was known

Table 1 Article/study characteristics of choledochal cysts during pregnancy

Category	*n* (%)
Type of study	
Case reports	56 (78.8)
Two cases	8 (11.2)
Case series (> 2)	7 (9.8)
Country	
United States	21 (29.6)
India	9 (12.7)
Japan	8 (11.3)
United Kingdom	7 (9.9)
China	7 (9.9)
South Korea	3 (4.2)
Mexico	3 (4.2)
Other	13 (18.3)
West *vs* East	38 *vs* 33 (46.5 *vs* 53.5)
Year of publication	
< 1940	2 (2.1)
1940-1960	8 (8.2)
1960-1980	5 (5.2)
1980-2000	20 (20.6)
2000-2020	36 (37.1)
Data completion	
Age	97 (100)
Gestational age	97 (100)
Cyst size	67 (69)
Cyst type	80 (81.4)
Bilirubin levels	70 (72.1)
Maternal outcome	97 (100)
Fetal outcome	21 (21.6)

before conception (Caroli disease).

Symptomatology and diagnostics

The most common symptom was epigastric/right upper quadrant pain in 78 (80%) patients (Table 3). Jaundice was present in 58 (59%) and fever in 30 (30.1%). CC triad was described in 41 (50.5%) and the Charcot triad in 28 (28.8%) patients. Eight patients were asymptomatic, and six of them were diagnosed with Caroli disease before pregnancy. Most CC were diagnosed using ultrasound (n = 58) followed by MRI (n = 18) and CT (n = 2). In two cases, endoscopic retrograde cholangiopancreatography (ERCP) was employed as a diagnostic and therapeutic tool. Data were lacking for the rest of the patients, or the diagnosis was established intraoperatively.

In 28 patients (28.8%), imaging did not show dilation of intrahepatic ducts, while 22 (22.6%) had dilation. One patient had changes consistent with primary sclerosing cholangitis (PSC), while data on bile duct morphology were missing for 47 (48.4%) patients.

Due to missing data, only bilirubin level was included in the analyses. It was reported in 70 (72.1%) cases. The level was 83.2 ± 80.4 mmol/L (range 5-426 mmol/L).

Cyst characteristics

According to Todani's classification, cyst type was mentioned in 79 (81.4%) cases. The type was defined from published radiologic images in an additional five cases. Out of 84 cases, 56 (66.6%) were type I, 15 (17.8%) type IV, and 6 (7.1%) type

Table 2 Patient and choledochal cyst characteristics, *n* (%)

Category	Results	Number of cases with reported variable
Age	25.3 ± 4.03	97
Gestational age at cyst discovery	26.1 ± 8.2	96
Parity	1.37 ± 0.76	83
1	62 (74.6)	
2	13 (15.6)	
> 2	8 (9.6)	
Cyst size (cm)	12.5 ± 6.4	67
0-5	6 (8.9)	
5-10	20 (29.8)	
10-15	19 (28.3)	
15-20	16 (23.8)	
> 20	6 (8.9)	
Bilirubin (mmol/L)	83.2 ± 68.4	71
Cyst type	12.5 ± 6.4	84
I	62 (73.8)	
IV	15 (17.8)	
V	6 (7.1)	
Diagnostic method		93
US	58 (62.3)	
MRI	18 (19.3)	
ERCP	2 (2.1)	
CT	2 (2.1)	
Intraoperatively	13 (13.9)	
Reached gestational age (wk)		97
0-12	2 (2.2)	
12-24	7 (7.2)	
24-36	43 (44.3)	
> 36	45 (46.3)	

US: Ultrasound; MRI: Magnetic resonance imaging; ERCP: Endoscopic retrograde cholangiopancreatography; CT: Computed tomography.

V. In one case, the cyst was described as "transitory type", not included in Todani's classification. It may indicate cyst dilation of the CBD, which resolved after biliary drainage. The cyst size was described in 67 (69%) cases with a mean size of 12.5 cm (range 1.8-40 cm). The cyst was ruptured at presentation in six cases during pregnancy and one case postpartum. Two patients with ruptured CC died, resulting in a mortality rate of ruptured CC in pregnancy of 33%.

Obstetric and surgical management

The treatment approach was divided into four categories (Table 4), according to the management of CC and the management of pregnancy (Figure 4). Among those with radiologic, endoscopic, or surgical interventions, the main indication was cholangitis, followed by cyst rupture and progressive jaundice (Table 5 and Figure 5). The indication for urgent CC surgery was cyst rupture or CC-related bleeding in 11 cases. Outside these indications, the reasons for cesarean section (CS) were severe anemia (2%) and intense abdominal pain (3%). In seven cases, no signs of fetal compromise were present, but CS was performed to prevent potential complications of CC. In 29 (29.9%) patients, the treatment was expectant for both the cyst and pregnancy. These patients were primarily treated with antibiotics, bed rest, and intravenous fluids as a bridge therapy to the anticipated labor. Urgent CS was done in 24 (25%) patients, with indications shown in Table 5. Intervention for both the CC and pregnancy was done in 16 patients, and in four patients, cyst drainage/resection was performed simultaneously with CS.

Table 3 Symptomatology of maternal choledochal cysts

Symptom	*n* (%)
Pain	78 (81.2)
Jaundice	58 (60.4)
Fever	33 (34.3)
Nausea/vomiting	36 (37.5)
Abdominal mass	42 (43.7)
Asymptomatic	8 (8.3)
Charcot triad (fever, jaundice, pain)	28 (29.1)
Triad of choledochal cyst symptoms (abdominal mass, jaundice, pain)	41 (42.7)

Table 4 General management characteristics

Category	Management			
Choledochal cyst	Expectative	Intervention	Expectative	Intervention
Pregnancy	Expectative	Expectative	Intervention	Intervention
Cases, *n* (%)	29 (29.8)	35 (36.0)	17 (17.5)	16 (16.4)

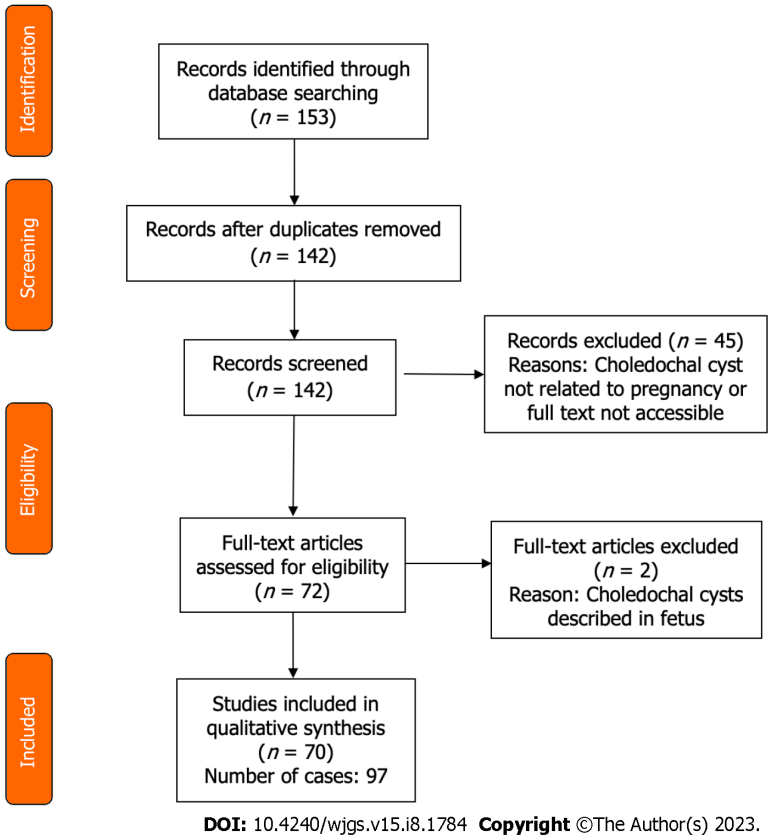

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Figure 1 PRISMA flow diagram.

Maternal and fetal outcomes

The maternal outcome was mentioned in all cases. In 90 (91.7%) patients, recovery after delivery and operation was uneventful, while seven (7.2%) died during or after pregnancy (Table 6).

Three cases of maternal death were published before 1950, and all were diagnosed during surgery for CC rupture/peritonitis. Martínez-Ordaz reported two patients who died postoperatively. The first patient died of postoperative bleeding at 9 wk of gestation following emergent surgery (HJ) for a giant CC (20 cm) with cholangitis. The second patient

Table 5 Indications and types of intervention

Category	*n*	%
CC treatment		
Conservative	46	47.9
Intervention	51	53.1
Surgical resection and reconstruction	22	22.9
Percutaneous drainage	16	16.6
Surgical drainage	7	7.2
Cholecystostomy	3	3.1
ERCP	3	3.1
Pregnancy		
Expectative approach	67	69.7
Vaginal labor	35	36.4
Planned Cesarean section	12	12.5
Spontaneous abortion	2	2
Induced vaginal labor	3	3.1
NR	15	15.6
Intervention	33	34.3
Cesarean section	24	25
Induced vaginal labor	3	3.1
Induced abortion/curettage	2	2
NR	4	4.1
Indications for CC management		
Cholangitis	22	22.9
Jaundice	9	9.3
Rupture	6	5.2
Sepsis	4	4.1
Pylorus obstruction	2	3.1
Bleeding	2	2
NR	9	9.3
Indications for pregnancy management		
CC complications	11	11.4
Fetal compromise	6	6.2
Severe anemia	2	2
Placental abruption	2	2
Preeclampsia	5	5.2
Prevention of potential CC complications	7	7.2

CC: Choledochal cyst; NR: Not reported; ERCP: Endoscopic retrograde cholangiopancreatography.

died after upper digestive tract bleeding and ischaemic perforation in the gastric fundus and hemoperitoneum following elective Roux-en-Y HJ made 4 wk postpartum. The cause of death was not defined. The third patient, in the 7th month of pregnancy, was successfully treated for CC rupture by surgical drainage and ERCP. Still, the patient died of "some unknown cause". Another patient underwent postpartum hepaticoduodenostomy (HD) and died after 1 year from peritonitis of unknown cause (excluded from the mortality because the period is outside of puerperium). The fifth patient, at 20 wk of gestation, with typical CC symptoms and imminent abortion, underwent cyst resection and

Table 6 Maternal and fetal mortality

Outcomes	*n* (%)
Maternal mortality	7 (7.2)/6 (6.1)[1]
Peritonitis, cyst rupture	3
Surgery complications	2
Not specified	2
Fetal mortality	8 (8.2)
Spontaneous abortion	2
Induced abortion	2
Stillborns	2
Newborn deaths	2

[1]The patient who died 1 year postpartum was excluded from the mortality analysis.

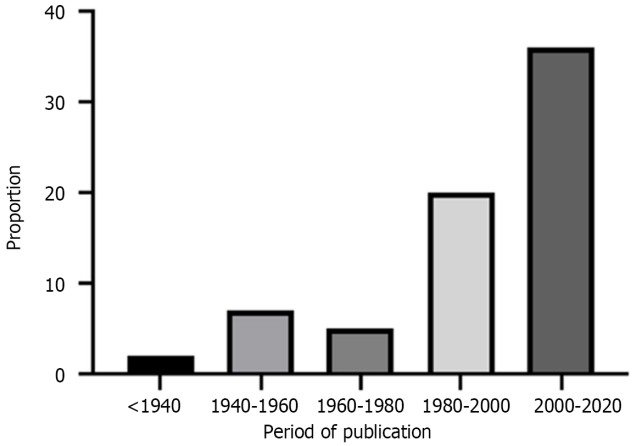

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Figure 2 Diagram showing the period (years) in which studies were published.

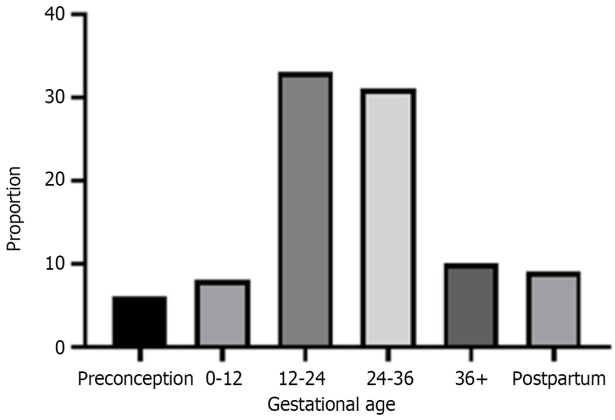

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Figure 3 Diagram showing gestational age (weeks) of choledochal cyst diagnosing.

reconstruction and died from multiorgan failure and cholangitis postoperatively. In 1932, Zinninger reported a patient at 4 mo of gestation with cholangitis and CC diagnosed intraoperatively. The cyst was emptied, the anterior wall of the cyst was excised, and the defect was closed with sutures. The patient died 11 d after the operation from multiorgan failure due to progressive sepsis.

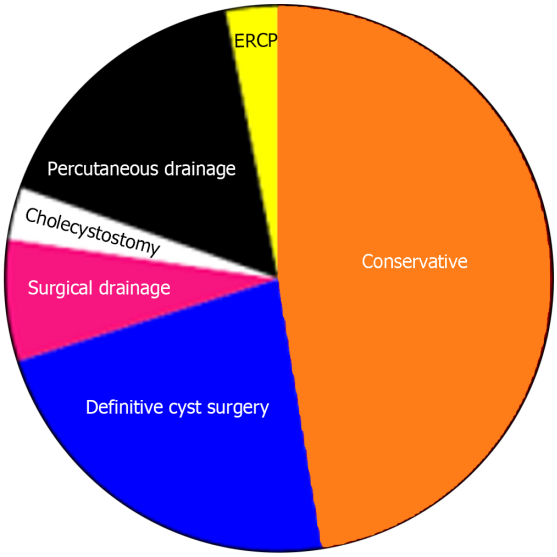

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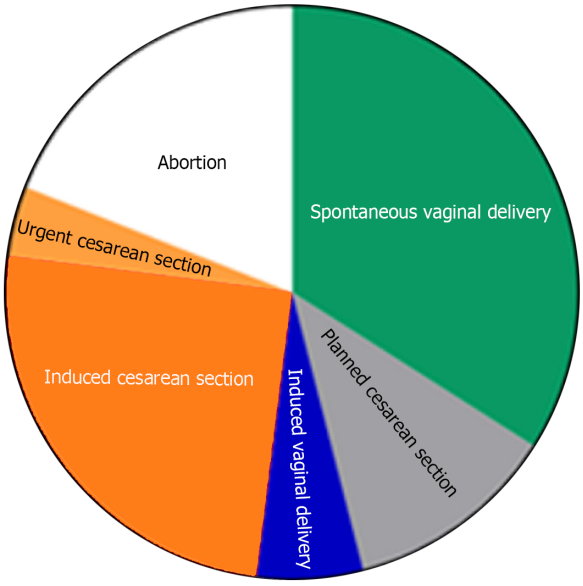
Figure 4 Pie chart illustrating the type and proportion of different management approaches for choledochal cyst. ERCP: Endoscopic retrograde cholangiopancreatography.



DOI: 10.4240/wjgs.v15.i8.1784

Figure 5 Pie chart illustrating the type and proportion of different management approaches for pregnancy.

No complications related to labor were reported in patients who received interventional treatment of CC with the continuation of pregnancy. Regarding the postpartum treatment of patients who did not have definitive CC treatment during pregnancy (n = 76, 78.3%), surgical management was reported in 54 (71.0%), conservative in 8 (10.5%), while in 14 (18.4%) cases, further postpartum treatment was not specified. In surgically treated patients, after delivery, Roux-en-Y HJ was done in most cases (90.7%), followed by cystogastrostomy (5.5%) and cystoduodenostomy (3.7%). The average gestational age of pregnancy termination (induced and spontaneous) was 33.6 wk (range 9-40 wk). Fetal outcomes were reported in 21 (21.6%) cases. However, we presumed that the authors would mention fetal or newborn death, so the above mentioned fetal mortality could be reliable. From described cases, four children died postpartum, and two were stillborn. There were two spontaneous abortions (in the 8th and 20th gestational weeks) and two elective abortions (in the 20th and 14th weeks) due to cholangitis and progressive septic complications.

Correlation analysis

Both cyst dimension and bilirubin level were described in 51 patients with a weakly positive, statistically non-significant linear relationship (r = 0.32, P < 0.001) (Figure 6). We found no relationship between age and cyst dimension (r = 0.06, P = 0.7) for 67 patients with available data. Similarly, no correlation was found between gestational age at cyst discovery and

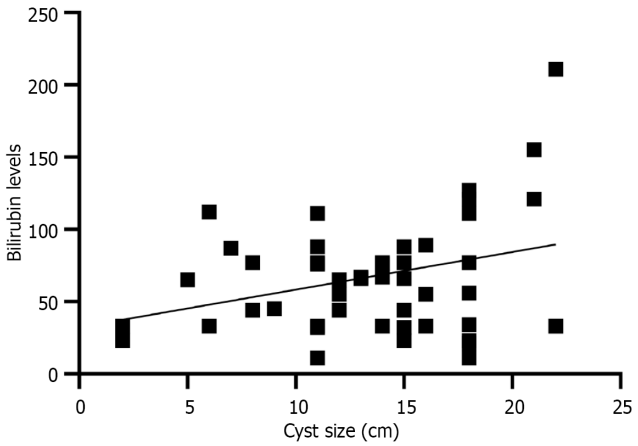


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Figure 6 Correlation analysis between cyst size and bilirubin levels.

cyst size (r = 0.11, P = 0.54).

Univariate analysis of factors related to choice of treatment

Cyst size is not necessarily related to the severity of symptoms, but cysts larger than 15 cm had a significantly higher likelihood of treatment intervention during pregnancy. Similarly, the Charcot triad was associated with a high likelihood of CC intervention (OR = 4.3; P = 0,006), induced labor (OR = 5.4; P = 0.028), and CC triad (OR = 2.88; P = 0.017). Other analyzed factors were not associated with the odds of interventional treatment (Table 7).

DISCUSSION

Incidence

Our study confirms the extreme rarity of maternal CC during pregnancy since less than 100 cases were collected. However, many cases of CC in pregnancy may not have been recognized or were asymptomatic, so the incidence is probably underestimated. Our collection of patients is the largest so far, and this study will contribute to a more precise estimation of the incidence of CC in pregnancy. Articles were systematically screened and reviewed, and in only two cases, we could not extract necessary data since we did not get a response from one author who presented a case in a Slovak journal[19], and we could not adequately translate a case from Alizadeh *et al*[20] due to the Arabic alphabet and language.

Patient and disease characteristics

Similarities and differences between CC in the general and pregnant populations exist. First, the distribution of CC types appears similar. In pregnancy, type I is the most common (73.8%), followed by type IV, comparable to the general population, where type I ranges between 80%-90%. Types II and III have not been reported, while Caroli disease occurred in six cases, corresponding to an incidence of 7.1%, several times higher than that in the general population (1%-2%)[2,3,21]. Four cases of Caroli disease were managed expectantly, and elective CS was performed in two cases, indicating a better prognosis than that in newly diagnosed symptomatic CC type I or IV. However, a better prognosis of Caroli disease in pregnancy may be attributed to a milder clinical course than other CC types.

Second, the CC size differed compared to that in the general population. In our study, more than two-thirds of CC could be classified as giant since the largest diameter was > 10 cm. The mean reported size in the general population is 3-4 cm, rarely exceeding 9 cm[4,11,15]. Hormonal changes and the compressive effect of the gravid uterus on CC with consequent cyst enlargement could be causative. To confirm this, serial sonographic exams and measurements of CC size in pregnant women in future studies are mandatory. Pregnancy may trigger CC symptoms in previously asymptomatic cases due to increasing CC size, which, along with physiological changes during pregnancy, may precipitate symptoms related to CC, such as jaundice, abdominal pain, or abdominal mass. This hypothesis is supported by the fact that almost 91% of CC from our study were discovered in the 2nd or 3rd trimester when the gravid uterus reaches the upper abdomen [9]. There is no data on the incidence of CC triad in the general population for females. However, a typical CC triad in more than 40% of women in our study indicates that the CC triad could be several-fold higher in pregnant women than in the general population (10%-20%)[11,12]. The incidence of CC rupture in our study was 7/97 (7.1 %), which is higher than that in the general population (1%-2%)[10]. Cyst rupture was seen in six cases during pregnancy and one postpartum. Most (5/7) were reported in studies before 1990. Today, the wide availability of ultrasound, more frequent biochemical laboratory testing, and closer monitoring of pregnant women should maximally reduce the rate of severe consequences of CC. No CC rupture was noted during spontaneous or induced vaginal labor. Therefore, it remains debatable if vaginal delivery increases the risk of CC rupture.

Table 7 Factors influencing the likelihood of intervention during pregnancy

Parameter	OR	*P* value	95%CI	*Z* statistic
Presence of the Charcot triad	4.3	0.006	1.57-11.1	3.35
Presence of the CC triad	2.88	0.017	1.20-6.92	2.37
Bilirubin (≥ 80 mmol/L *vs* < 80 mmol/L)	1.37	0.78	1.42-15.20	0.84
CC size (≥ 15 cm *vs* < 15 cm)	4.6	0.011	0.28-3.29	3.72
CC type (I *vs* IV)	0.96	0.97	0.34-1.80	0.15
Parity (nulliparous *vs* multiparous)	0.79	0.57	0.42-2.45	0.55
Gestational age (≥ 6 mo *vs* < 6 mo)	1.01	0.96	0.41-1.66	0.04

OR: Odds ratio; CC: Choledochal cyst.

Nausea and vomiting were reported in 37.5% of cases, comparable to previous studies[6,11,22]. Interpretation of these symptoms is difficult as it is a common consequence of hormonal changes during pregnancy. CC resulting in duodenal or pyloric compression were an indication for surgery in three cases. Abdominal distension or mass may be more prominent than that in nonpregnant patients with CC. However, the women may neglect this symptom as it may be attributed to a normal pregnancy. The pain in the upper abdomen or right subcostal area should result in evaluating potential causes other than physiological pressure from the growing uterus. ICP, acute fatty liver of pregnancy, or other cholestatic disorders may contribute to the complexity of CC diagnosis and treatment (3% of pregnant women are affected by liver disorders during pregnancy[16,23]). Hence, other liver and biliary diseases, especially cholestatic, may lead to earlier or more pronounced jaundice in CC patients or could be the only cause of cholestasis unrelated to an asymptomatic pregnant CC patient.

Treatment

Due to the risk of malignancy, complete excision with biliodigestive reconstruction is the procedure of choice for nonpregnant patients with type I, II, or IV CC. Type III cysts may be managed by ERCP or endoscopic resection[5,24,25]. Our results show that Roux-en-Y HJ was a predominant operation in patients requiring cyst resection and reconstruction (92%). In two cases, HD was reported, and hepaticogastrostomy in one[26-28].

The variety of reported treatment approaches indicates no standardized management for such a clinical condition. Treatment was based on previous knowledge and experience related to CC in nonpregnant adults and general obstetric principles. The application of novel and minimally invasive percutaneous or endoscopic methods depended on the institutional availability of these procedures and the year of publication. Since this is a retrospective analysis, no control groups were available, and reliable comparative analysis of treatment approaches was not possible. However, by analyzing the severity of the clinical presentation, chosen medical approach, and outcomes, we constructed an algorithm that may help to guide clinical decisions (Figure 7).

The treatment in asymptomatic patients or patients with smaller CC without cholangitis or gastric outlet obstruction includes observation until term, with planned postpartum CC management. Almost half cases (47.3%) did not require any intervention for CC. Even when the labor was induced, in most cases, it was indicated more as a precaution than urgent obstetric indication, reported in only 39%. A prerequisite for conservative treatment is the absence of surgical or obstetric urgencies. It includes antibiotic therapy for septic complications, hospitalization, and more frequent follow-ups after discharge to prevent delayed identification of fetal compromise or CC rupture.

The decisive clinical characteristics that guided the treatment approach were the presence of cholangitis, cyst size, and to a lower degree, the presence of CC triad (Table 7). Parity, the mother's age, or jaundice alone did not affect the treatment choice. In cases of symptomatic CC, a conservative approach should be initiated, comprising analgesia, antibiotics, dietary changes, and ursodeoxycholic acid (in Caroli disease). Further steps depend on the course of the disease.

In only 22.9% of cases, open surgery, cyst excision, and reconstruction were done during pregnancy. The majority (81.0%) were operated on in the first trimester (54.5%). Possibly, most authors adopted a more conservative approach, particularly in the 2nd and 3rd trimesters. This is due to: (1) The minimization of the risk of complications from major surgery; and (2) the availability of less invasive methods for preventing CC complications.

In patients who require intervention, the minimally invasive methods have a high success rate. Only 3/22 (13.6%) cases required surgery for CC complications after unsuccessful percutaneous drainage/ERCP. Percutaneous cyst drainage may resolve symptoms, decrease the risk of cholangitis, and allow further intrauterine fetal development until viable gestational age[8,29,30]. On the other side, such procedures may carry a risk of pregnancy complications, although no severe complications of percutaneous drainage were reported in the present study. It remains unclear whether endoscopic or radiologic drainage should be performed for asymptomatic or mildly symptomatic cysts during the 3rd trimester since such procedures may trigger premature labor, while commonly, symptoms resolve on conservative measures.

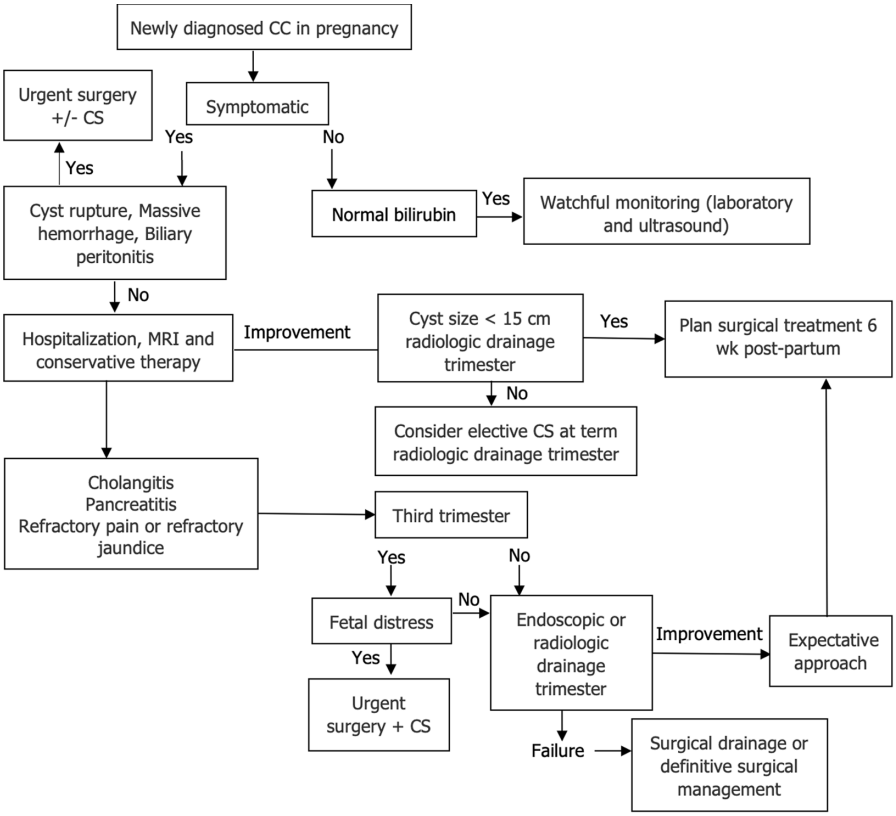

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Figure 7 Proposed treatment algorithm for maternal choledochal cysts in pregnancy. CC: "choledochal cyst", CS: "Cesarean section".

Surgical urgencies (cyst rupture/peritonitis, massive bleeding, or severe cholangitis) mandate immediate "damage control" procedures such as internal/external cyst drainage, T-drainage, or cholecystostomy. Synchronous CS and cyst excision plus HJ were done in only two cases in the earlier study period. Therefore, synchronous surgical and obstetric procedures should be done exceptionally.

In conservatively treated women, the timing of surgery after the delivery was 6-8 wk postpartum in most cases. No cases of CC complications during this "waiting" period were reported, so we consider this to be a sufficient recovery time for the patient without increased CC complications related to delayed management.

The treatment of Caroli disease generally differs from that of other CC types in the general popu-lation, and the same principles can be applied to Caroli disease in pregnancy[31-33]. It includes supportive care with antibiotics for cholangitis and ursodeoxycholic acid for hepatolithiasis[31,34,35]. Surgical resection is considered with monolobar disease, but rarely as an urgent procedure[36]. Ursodeoxycholic acid may improve bile flow and reduce the incidence of biliary stones and cholangitis. It has been used to treat cholangiopathies, including primary biliary cholangitis or PSC. Studies suggest that ursodeoxycholic acid is effective and safe in patients with ICP[37]. However, its benefits in CC types 1-4 should yet be evaluated.

Diagnostics

Before the wide clinical usage of transabdominal ultrasound, CC during pregnancy was diagnosed intraoperatively. Since 1976, radiologic methods have enabled preoperative CC diagnosis. MRI became the common diagnostic method for pregnancy disorders in developed countries after 2000[38,39]. Consequently, cases from the first half of the 20th century were mostly diagnosed intraoperatively or at autopsy. Although emergent MRI is still not widespread, we strongly recommend MRI for newly sonographically detected CCs, as MRI defines the exact size and location of the cyst, stones, concomitant biliary anomalies, and compressive effect on surrounding organs, including the uterus.

Maternal mortality

The maternal mortality from CC was 7.2 %, but the accurate mortality appears lower since, in only four cases, a direct association with CC was confirmed. Publication bias (not reporting unfavorable outcomes) may have affected final mortality rates. In addition, in five/seven fatal cases, important variables (bilirubin levels and cyst size) were not reported. Therefore, inferential analysis related to predictive factors for maternal mortality was not appropriate in this setting, particularly if we consider the study design that covered a long period (1932-2020) which is the main reason for heterogeneous diagnostic and therapeutic approaches. Clearly, in earlier studies, the diagnosis was commonly made intraoperatively. Radiologic, endoscopic, and intensive care procedures improved significantly over time[35,40,41]. Consequently, fetal and maternal mortality rates and complications are incomparable to results from more recent studies. Instead, we presented shortly every single case of maternal mortality in the Results section and used multivariate analysis

of factors that contributed to treatment choice.

Limitations of the study

There are several limitations to the study. The first is missing data. In many cases, laboratory data and fetal outcome information are sparse. Indications for CS were not mentioned in many cases, as well as information on clinical presentation and cyst pathology. However, the most important CC characteristics and maternal outcomes were reported at acceptable rates. The second limitation is the inability to collect all cases due to language or unavailable full text. Third, a more thorough comparative statistical analysis could not be conducted regarding the design of the study, long study period, lack of data, and different treatment standards.

CONCLUSION

CC in pregnancy present a great therapeutic dilemma and an under-represented topic in the literature. Our results might contribute to understanding the behavior of CC in pregnancy. Although maternal death was rare, it can occur and was reported predominantly in studies before 1990. Without cholangitis or urgent surgical CC complications, premature labor and fetal loss are uncommon. Treatment should be tailored to the individual patient and primarily based on gestational age, the risk of septic complications, and CC rupture. Careful monitoring and early recognition of CC complications are crucial for favorable maternal and fetal outcomes. CS is indicated when fetal distress, surgical emergencies, progressive cholangitis, or refractory symptoms related to CC exist. In other cases, conservative or minimally invasive CC treatment and an expectant obstetric approach should be the preferred initial approach.

ARTICLE HIGHLIGHTS

Research background

No systematic data on choledochal cysts (CC) in pregnancy exist.

Research motivation

Due to the rarity, no guidelines exist for the diagnostic workup and treatment and obstetric strategy for CC in pregnancy.

Research objectives

To collect the most published case reports on CC in pregnancy.

Research methods

Descriptive statistics of available patient and disease data.

Research results

Cholangitis, CC > 15 cm, and bilirubin levels > 80 mmol/L were associated with a higher likelihood of urgent cesarean section (CS) and surgical intervention for CC. Bilirubin levels positively correlated with CC size. There was no correlation between age and cyst dimension, gestational age at cyst discovery, and CC size.

Research conclusions

Although rare, maternal CC in pregnancy should be included in the evaluation of jaundice with upper abdominal pain. Symptomatology and clinical course are variable. Treatment may range from an expectative approach to emergent surgical CC treatment and urgent CS. While most cases were managed by conservative measures or drainage procedures, CC > 15 cm and progressive cholangitis carry the risk of CC rupture and septic complications, which may increase the rates of unfavorable maternal and fetal outcomes.

Research perspectives

All cases of CC in pregnancy should be published to understand better the epidemiology, etiology, specific diagnostic imaging methods, and treatment strategy of this extremely rare condition.

FOOTNOTES

Author contributions: Augustin G designed the research and wrote the paper; Romic I and Miličić I performed the research and wrote the paper; Mikuš M and Herman M analyzed the data and performed the literature review.

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ORCID number: Goran Augustin 0000-0002-0202-3324; Ivan Romic 0000-0003-4545-2118; Iva Miličić 0000-0002-6093-0870; Mislav Mikuš 0000-0002-1365-8704; Mislav Herman 0000-0003-3341-7390.

Corresponding Author's Membership in Professional Societies: World Society of Emergency Surgery.

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SYSTEMATIC REVIEWS

Intraoperative pancreas stump perfusion assessment during pancreaticoduodenectomy: A systematic scoping review

Francis P Robertson, Harry V M Spiers, Wei Boon Lim, Benjamin Loveday, Keith Roberts, Sanjay Pandanaboyana

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Peer-review model: Single blind

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Francis P Robertson, Wei Boon Lim, Sanjay Pandanaboyana, Department of HPB and Transplant Surgery, Freeman Hospital, Newcastle Upon Tyne NE7 7DN, United Kingdom

Harry V M Spiers, Department of HPB Surgery, Addenbrookes Hospital, Cambridge CB2 0QQ, United Kingdom

Benjamin Loveday, Department of General Surgery, Royal Melbourne Hospital, Melbourne VIC 3050, Australia

Keith Roberts, Department of HPB Surgery, University Hospitals Birmingham NHS Foundation Trust, Birmingham BG15 2GW, United Kingdom

Corresponding author: Francis P Robertson, BSc, FRCS (Ed), MBChB, PhD, Surgeon, Department of HPB and Transplant Surgery, Freeman Hospital, Freeman Road, Newcastle Upon Tyne NE7 7DN, United Kingdom. francis.robertson.13@ucl.ac.uk

Abstract

BACKGROUND

Post-operative pancreatic fistula (POPF) is the primary cause of morbidity following pancreaticoduodenectomy. Rates of POPF have remained high despite well known risk factors. The theory that hypoperfusion of the pancreatic stump leads to anastomotic failure has recently gained interest.

AIM

To define the published literature with regards to intraoperative pancreas perfusion assessment and its correlation with POPF.

METHODS

A systematic search of available literature was performed in November 2022. Data extracted included study characteristics, method of assessment of pancreas stump perfusion, POPF and other post-pancreatic surgery specific complications.

RESULTS

Five eligible studies comprised two prospective non-randomised studies and three case reports, total 156 patients. Four studies used indocyanine green fluorescence angiography to assess the pancreatic stump, with the remaining study assessing pancreas perfusion by visual inspection of arterial bleeding of the pancreatic stump. There was significant heterogeneity in the definition of POPF.

Studies had a combined POPF rate of 12%; intraoperative perfusion assessment revealed hypoperfusion was present in 39% of patients who developed POPF. The rate of POPF was 11% in patients with no evidence of hypoperfusion and 13% in those with evidence of hypoperfusion, suggesting that not all hypoperfusion gives rise to POPF and further analysis is required to analyse if there is a clinically relevant cut off. Significant variance in practice was seen in the pancreatic stump management once hypoperfusion was identified.

CONCLUSION
The current published evidence around pancreas perfusion during pancreaticoduodenectomy is of poor quality. It does not support a causative link between hypoperfusion and POPF. Further well-designed prospective studies are required to investigate this.

Key Words: Pancreatico-duodenectomy; Post-operative pancreatic fistula; Perfusion; Indocyanine green; Post pancreatectomy pancreatitis

Core Tip: The pathology of post-op pancreatic fistula remains to be elucidated, however, hypoperfusion of the pancreatic remanent is a suggested mechanism leading to post-operative pancreatitis and failure of the pancreatic jejunal anastomosis. Indocyanine green assessment of the pancreatic remanent is a safe way to visualise perfusion of the stump prior to anastomosis. Whether it can predict post-operative pancreatic fistula requires further studies.

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INTRODUCTION

Pancreatic resection is a key component in the treatment pathways of various benign and malignant diseases[1]. The postoperative morbidity after pancreatic resection remains high despite centralisation[2,3] and improved surgical techniques[4]. Post-operative pancreatic fistula (POPF), serves as the key risk factor for other post-operative intra-abdominal complications such as delayed gastric emptying (DGE) and intraabdominal collections[5-7], thereby prolonging hospital stay and increasing over all morbidity[8-11]. Furthermore, POPF is the root cause of mortality after pancreaticoduodenectomy[12,13]. Risk factors for POPF are very well defined[14]. Despite numerous trials aimed at reducing the incidence of POPF, its incidence has remained largely unchanged over decades[15]. This is likely due to poor understanding of the underlying pathophysiology, with failure of current interventions to reduce POPF suggesting something more than a mere loss of mechanical anastomotic integrity. One theory is that hypoperfusion of the pancreatic remnant results in pancreas transection margin ischaemia, necrosis and post pancreatectomy pancreatitis with subsequent failure of healing at the pancreatico-enteric anastomosis and resultant pancreatic leak[16-18]. The neck of the pancreas is a watershed area between coeliac and superior mesenteric arterial systems, hence, hypoperfusion in this area may be associated with poor healing and risk of anastomotic leak[15].

There is some evidence from the literature on intraoperative pancreas perfusion assessment and there is a need to identify and map the current evidence for its use in the context of POPF. This will allow identification of techniques used and provide insight into their effectiveness, paving the way for further prospective and randomised studies. Therefore, this scoping review aims to define the current experience with intraoperative pancreas perfusion assessment and highlight the published literature surrounding pancreas stump hypoperfusion as a potential risk factor for POPF.

MATERIALS AND METHODS

This scoping review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Scoping Reviews extension[19]. The study protocol was prospectively registered with the University of York Centre for Review and Dissemination international prospective register of systematic reviews PROSPERO database (2021: CRD42021296863).

Following pilot testing, a systematic search of Medline and EMBASE databases was conducted on 8th November 2022, with screening performed by two independent investigators (HS and FR). The search strategy was conducted using the following search algorithm: ((pancreatic fistula.ti.ab) OR (exp pancreatic fistula) OR (anastomotic leak.ti.ab) OR (exp anastomotic leak)) AND ((pancreatoduodenectomy.ti.ab) OR (exp pancreatoduodenectomy) OR (pancreaticoduodenectomy.ti.ab) OR (exp pancreatoduodenectomy) OR (Whipple's surgery.ti.ab)) AND ((perfusion.ti.ab) OR (exp perfusion)

OR (blood supply.ti.ab) OR (exp blood supply). All studies including patients undergoing pancreaticoduodenectomy were included. Full search strategy and results are presented in Supplementary Table 1. Titles identified following this literature search were entered into the *Reference Citation Analysis* (*RCA*) (Baishideng Publishing Group) to search for further studies related to these articles.

Inclusion and exclusion criteria

Full text studies reporting patients undergoing intraoperative pancreas perfusion assessment, or correlating hypoperfusion with POPF were included regardless of language. Any type of publication reporting primary data on the topic was included. Review articles and studies not reporting primary data were excluded. After excluding duplicates, two researchers (Robertson FP and Spiers HVM) independently reviewed the titles and abstracts of studies identified by the literature search. Where a study was considered relevant to the research question a full copy of the publication was obtained for further review. The reference lists of included articles were hand-searched for any further relevant studies. Any areas of disagreement between the two primary researchers were resolved through discussion with the senior author (Pandanaboyana S).

Data extraction

Data were retrieved from published studies and extraction was performed by an individual author (Spiers HVM) and independently checked by a second author (Robertson FP), with any disagreement resolved by consensus or where necessary with a senior author (Pandanaboyana S). The post-operative outcomes chosen to explore were the development and grade of POPF as defined by the International Study Group of Pancreatic Surgery (ISGPS)[20], the incidence of post-pancreatectomy haemorrhage, grade of DGE as defined by the ISGPS[21,22] and mortality. Study quality was not formally assessed as this is a scoping review.

RESULTS

Following the initial search (Figure 1), 90 studies were identified of which 74 remained following removal of duplicates. The 74 titles and abstracts were reviewed and 9 studies were selected for full review. Studies were excluded when not relevant, or non-primary literature. Of the 9 studies reviewed in detail, 4 were excluded because of operative procedure performed not being pancreaticoduodenectomy, conference abstract only or pancreas perfusion assessment not performed intraoperatively. Five studies including 156 patients were included in the final review. The median number of patients included in each study was 30 (1-123). Characteristics of the included studies are shown in Table 1.

Patient demographics

Studies were published between 2002 and 2021 and included three case reports of a single patient and two prospective non-randomised cohort studies. One hundred and fifty-six patients underwent pancreaticoduodenectomy, two of which were laparoscopic, the rest open. One hundred and forty patients (90%) underwent resection for malignancy and 16 (10%) underwent resection for chronic pancreatitis. Three studies included only patients undergoing pancreaticoduodenectomy with no vascular resection or resection of other organs[23-25]. One study included a patient undergoing open pancreaticoduodenectomy combined with distal pancreatectomy and splenectomy (middle segment-preserving pancreatectomy)[26]. One study included 10 patients undergoing vascular resection[27], 3 patients undergoing simultaneous vascular and arterial resection and 3 patients undergoing synchronous resection of other organs [partial splenectomy (n = 1), partial nephrectomy (n = 1), minor hepatectomy (n = 2)].

Technical details of pancreas perfusion and assessment

In 4 studies pancreas perfusion was measured by intravenous injection of indocyanine green (ICG) into a peripheral vein allowing intra-operative fluorescence angiography under near infrared light[23,24,26,27] (Table 2). Adequate pancreatic perfusion was classified by Doussot *et al*[27] as homogonous perfusion of the pancreatic stump. Time to achieve this was also measured and divided into 3 groups (< 30 s, 30-60 s and > 60 s). One study assessed pancreas perfusion by visual inspection of arterial bleeding of the pancreatic stump following transection of the pancreatic neck[25]. Perfusion was classified as adequate when brisk arterial pulsatile bleeding was visualised superiorly and inferiorly to the pancreatic duct that required sutures to control the bleeding.

When pancreatic hypoperfusion was identified in the study by Strasberg *et al*[25], the pancreatic margin was cut back further by 1.5-2.0 cm until improved perfusion was visualised. Similarly, when hypoperfusion was identified in the study by Subar *et al*[24], further cut back of the margin was performed. In the study by Doussot *et al*[27], the pancreatic stump was only further cut back in one patient. The results of pancreatic perfusion in the case study by Rho *et al*[23] did not alter the operative strategy. Prophylactic octreotide was administered variably throughout the studies.

Outcomes

Perfusion of the pancreatic stump was assessed successfully in all patients recruited to the studies. Perfusion of the pancreatic stump was assessed by ICG angiography in 33 patients and visual inspection of bleeding from the cut surface in 123 patients. Hypoperfusion of the pancreatic stump was identified in 55 (35%) of patients (Subar *et al*[24] n = 1, Doussot *et al*[27] n = 6, Rho *et al*[23] n = 1, Strasberg *et al*[25] n = 47). Of these patients 49 (89%) underwent further cutback of the pancreatic stump prior to formation of the pancreatico-jejunostomy. Two patients in the study of Strasberg *et al*[25]

Table 1 Study characteristics of included articles

Ref.	Country of origin	Study design	Study population	Disease process
Strasberg *et al*[25], 2002	United States	Prospective cohort	Patients undergoing pancreatoduodenectomy with pancreatojejunostomy at a single institution 1996 to 2000	Malignant (n = 107): Pancreatic cancer (n = 48); ampullary cancer (n = 28); NET (n = 6); villous adenoma (n = 6); MCN (n = 6); bile duct cancer (n = 5); duodenal adenocarcinoma (n = 3); serous cystadenoma (n = 3); IPMN (n = 1); GIST (n = 1). Benign (chronic pancreatitis, n = 16)
Subar *et al* [24], 2015	France	Case report	One patient undergoing laparoscopic pancreatoduodenectomy with pancreatojejunostomy	Malignant (ampullary adenocarcinoma)
Rho *et al* [23], 2019	Korea	Case report	One patient undergoing laparoscopic pancreatoduodenectomy with pancreatojejunostomy	Malignant (distal cholangiocarcinoma)
Doussot *et al*[27], 2021	France	Prospective cohort	Consecutive patients undergoing open pancreatoduodenectomy with pancreatojejunostomy at a single institution from January 2020 to November 2020	Malignant (n = 30, periampullary malignancies)
Iguchi *et al* [26], 2021	Japan	Case report	One patient undergoing open middle segment-preserving pancreatectomy with pancreatojejunostomy	Malignant (pancreatic ductal adenocarcinoma in head of pancreas with IPMN in the tail of pancreas)

NET: Neuro endocrine tumour; MCN: Mucinous cystic neoplasm; IPMN: Intraductal papillary mucinous neoplasm; GIST: Gastrointestinal stromal tumour.

Table 2 Intraoperative perfusion assessment and management of hypoperfusion

Ref.	Measurement of hypoperfusion	Description of technique	Total number of patients	Number with hypoperfusion	Management of hypoperfusion
Strasberg *et al*[25]	Visual assessment by surgeon	Blood supply was considered adequate when pulsatile arterial bleeding was present both superior and inferior to the pancreatic duct on the cut surface of the pancreas. The bleeding was required to be brisk (of a level that required sutures to stop the bleeding). If there was no bleeding, or if the bleeding points were of an oozing type that could be controlled without sutures, the blood supply was considered inadequate	123	47	Further 1.5-2 cm of pancreas transected
Subar *et al* [24]	ICG	Peripheral injection of 2 mL (0.5 mg) of Infracyanine™ (concentration was 0.25 mg/mL). The infrared camera is then focused on the transected margin of the pancreas	1	1	Ischaemic segment resected further
Rho *et al* [23]	ICG	ICG in jVR 25.0 mg (Doingin-dang Pharmaceutical Company, Siheung, Gyeonggi, Republic of Korea) given *via* peripheral IV injection at least three minutes before confirmation of pancreatic perfusion. Waited at least 30 s to determine perfusion with IMAGE1 STM H3-LINK and D-LIGHT P system (KARL STORZ SE & Co.KR, Tuttlingen, Germany)	1	1	Reinforcement using surgical glue (Greenplast QVR 2 mL, GREEN CROSS Corp., Yongin, Gyeonggi, Republic of Korea)
Doussot *et al*[27]	ICG	Pancreas stump was inspected after ICG IV injection (INFRACYANINE 0.1 mg/kg; Serb, Paris, France) using a microscope with near-infrared light source allowing real-time ICG perfusion assessment with near-infrared light images	30	6	One patient had further 3 cm pancreatic stump resection
Iguchi *et al*[26]	ICG	10 mg of ICG was administered IV. The presence of fluorescence in the pancreatic remnant was definitively confirmed with a fluorescence camera	1	0	NA

ICG: Indocyanine green; IV: Intravenous; NA: Not available.

who had their stump cut back were found to still exhibit signs of hypoperfusion within their criteria.

The definition of POPF was heterogeneously defined between the studies. Strasberg *et al*[25], which was published in 2002 prior to the ISGPS publication of the consensus definition of POPF in 2016, defined POPF as drainage of > 50 mL of pancreatic fluid (> 500 IU/L) for 3 consecutive days as long as it included post-operative day 10. There was no subclassification of clinically relevant POPF *vs* biochemical leak in the study by Strasberg *et al*[25]. All other studies defined POPF according to the ISPG classification. DGE was defined in the study by Rho *et al*[23] according to the ISGPS definition.

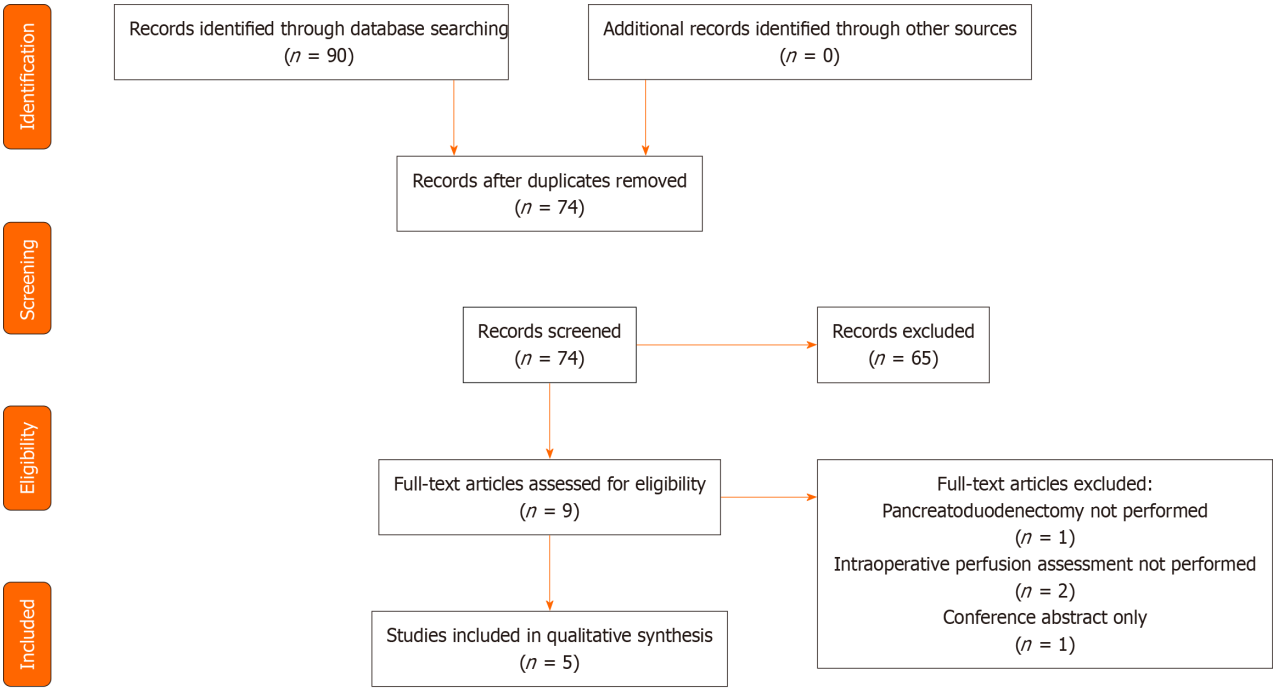

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Figure 1 PRISMA diagram of included studies.

Neither Doussot *et al*[27] nor Strasberg *et al*[25] clarified their definition of DGE. Post-pancreatectomy haemorrhage was measured in the study by Doussot *et al*[27] and was classified according to the ISGPS definition.

POPF

POPF occurred in 18 (12%) of patients (Table 3). No analysis of clinically relevant POPF has been performed as this was not defined in the study by Strasberg *et al*[25] which contributes the majority of patients to the review. In the study by Doussot *et al*[27], 2 of the 3 (67%) clinically relevant POPF occurred in patients with documented hypoperfusion of the pancreatic stump. Rho *et al*[23] identified hypoperfusion in their patient who developed a clinically relevant POPF. In the study by Strasberg *et al*[25], all POPFs were identified in patients with hypoperfusion of the pancreatic stump, however, this should be interpreted with caution as all patients identified as having hypoperfusion underwent further resection of the pancreas prior to anastomosis. In the study by Iguchi *et al*[26], no hypoperfusion of the pancreatic stump was identified however they identified a leak from the distal end of the stump following distal pancreatectomy.

DGE

DGE was seen in 17 (11%) patients (Table 3). The incidence of DGE in patients with and without hypoperfusion of the pancreatic stump was not provided in either of the studies by Doussot *et al*[27] or Strasberg *et al*[25]. The only patient in the case series by Rho *et al*[23] experienced grade B DGE. They were found to have hypoperfusion of the pancreatic stump.

Post pancreatectomy haemorrhage

Post pancreatectomy haemorrhage (PPH) was seen in 2 (1%) patients (Table 3). The incidence of PPH in patients with and without hypoperfusion of the pancreatic stump was not provided.

90-d/inpatient mortality

Post-operative mortality was seen in 1 (0.6%) patient. It was not documented whether they had hypoperfusion of the pancreatic stump.

DISCUSSION

This scoping review mapped studies that assessed hypoperfusion of the pancreatic remnant during pancreaticoduodenectomy and its relationship with POPF. The five primary studies, including two prospective non-randomised studies and three case reports, identified utilisation of intraoperative assessment of perfusion using a range of techniques and variable resultant change in surgical management of the pancreatic remnant after confirmation of hypoperfusion. There was significant heterogeneity in the definition of POPF as the largest study in this series was published prior to the publication of the ISPGS definition. Our findings illustrate the safety and feasibility of intraoperative pancreas perfusion

Table 3 Post-operative outcomes

Ref.	Total number developing POPF	Number hypoperfused developing POPF	Delayed gastric emptying	Post-pancreatectomy haemorrhage	90-d mortality
Strasberg *et al*[25]	4	2 (1.6)	11	0	1
Subar *et al*[24]	0	0 (0)	0	0	NR
Rho *et al*[23]	1	1 grade A	1 grade B	0	NR
Doussot *et al*[27]	12 (9 grade A and 3 grade B)	3 (1 grade A and 2 grade B)	5 (17)	2 (1 grade B and 1 grade C)	0
Iguchi *et al*[26]	1 grade B	1 grade B	0	0	Alive at 2 mo

Post-operative pancreas fistula, delayed gastric emptying and post-pancreatectomy haemorrhage graded according to the International Study Group of Pancreatic Surgery definitions, except Strasberg, which was published prior to these definitions. POPF: Post-operative pancreatic fistula; NR: Not reported.

assessment and highlight its apparent limited usage since the first report twenty years ago. Variation in practice related to some patients having their pancreas remnant trimmed short if deemed to be hypoperfused whilst other patients were not.

The studies identified in this review have a combined POPF rate of 12%. This is lower than the published rate of 20% for clinically relevant POPF in recent randomised controlled trials comparing laparoscopic and open pancreaticoduodenectomies[28]. This is likely related to the Strasberg *et al*[25] study which used a different definition for POPF as it was published pre ISPGS. Intraoperative pancreas perfusion assessment revealed that hypoperfusion was present in 39% of patients who developed POPF. The rate of POPF was 11% in patients with no evidence of hypoperfusion and 13% in those with evidence of hypoperfusion, suggesting that not all hypoperfusion gives rise to POPF and further analysis is required to analyse if there is a clinically relevant cut off. From this review, conclusive incidence of PPH and DGE in patients with hypoperfusion of pancreatic stump is not possible given the limited reporting of these complications. Non-invasive perfusion assessment modalities such as infra-red spectroscopy have been investigated in other surgical specialties and have been shown to accurately identify hypoperfusion, but their role in pancreatic surgery is yet to be investigated[29,30].

The link between hypoperfusion of the pancreatic stump and POPF remains inconclusive. In the large 123 patient study by Strasberg *et al*[25] perfusion was assessed intraoperatively by subjective assessment of bleeding from the pancreatic stump with further resection in those deemed to be hypo-perfused. It demonstrated that 50% of clinically relevant POPFs occurred in patients with hypoperfusion that underwent further resection of the pancreas to well perfused tissue. This suggests that perfusion status of the stump intraoperatively, *i.e.*, local perfusion, may only be one component of the pathophysiology. Hyperlactataemia, a well-recognised hallmark of inadequate tissue perfusion and microcirculatory abnormalities[31], in the early post-operative period has been shown to be predictive of POPF. Hyperlactataemic patients (blood lactate ≥ 2.5 mmol/L) being 4.36 (1.70-11.15; P = 0.002) and 3.58 (1.22-10.48; P = 0.02) times as likely to develop POPF on uni- and multivariate analyses respectively[32].

Whilst several risk factors for POPF have been identified including consistency of the pancreatic parenchyma, size of the pancreatic duct and blood loss and have been combined to create the validated tool to predict POPF - the pancreatic fistula risk score[33], no study included this data and compared between the groups.

Post-operative acute pancreatitis (POAP) of the pancreatic remnant is an emerging entity in pancreas surgery[16], with inadequate tissue perfusion being key to its pathogenesis[34]. POAP exacerbates existing hypoperfusion, which may be why patients with higher vessel density (mm^2) at histology show reduced POPF[35,36]. Intraoperative perfusion assessment may allow surgical optimisation of the pancreatic remnant, reducing the incidence and severity of POAP, in turn reducing POPF. Additionally, overall haemodynamic and perfusion status may contribute to local changes causing hypoperfusion, POAP and subsequent POPF, particularly in patients who are high-risk for POPF. Therefore, intraoperative perfusion assessment, coupled with goal directed therapy may improve pancreas perfusion and improve outcomes.

The use of ICG imaging for perfusion assessment is well established in gastrointestinal surgery, specifically in assessing tissues prior to anastomosis[37], yet it is not widely used in pancreas surgery. Four studies identified in this review demonstrated the feasibility of ICG usage to assess the pancreatic remnant, with an advantage over subjective visual assessment being clear identification and demarcation of hypoperfusion confirmed by a lack of fluorescence over affected areas. Moving forward, it is essential to determine the optimum dosage of ICG, timing of its measurement and distance the camera should be held from the anastomosis at time of imaging, to allow widespread reproducible use of this technique in pancreatic surgery. An objective scoring system would also need to be developed to allow reproducible results.

The findings of this review must be set in the context of its limitations. Firstly, data is only available from a small number of publications and it is plausible that the total number of patients who have had intraoperative perfusion assessment is much higher. Secondly, there is a likely publication bias, with only select centres who have experience with ICG and perfusion assessment publishing their results. Thirdly, there may be confirmation bias in those studies using subjective visualisation methods of perfusion assessment. Finally, current methods to assess perfusion of the stump only allow for assessment of the surface perfusion and not the deep tissues. However as robotic surgery develops further advances may allow for more detailed perfusion assessments using the firefly mode.

CONCLUSION

In conclusion, intraoperative perfusion assessment is technically feasible and appears safe. The quality of the current published literature is poor with the majority of publications included being either case reports or limited case series. The largest study was published prior to the publication of the ISPGS definition of POPF and clinically relevant POPF and their definition of POPF differed from the current accepted definition. There is insufficient evidence currently to evaluate whether poor perfusion of the pancreatic stump during pancreatico-duodenectomy is associated with an increased incidence of POPF. Moving forward further prospective studies are required to confirm the external validity of the studies identified in this review, ideally with creation of objective scoring systems allowing standardisation and improved analysis of data in future. Importantly, identifying the degree of hypoperfusion that is associated with, or predictive of, POPF and how this is best managed is a key priority.

ARTICLE HIGHLIGHTS

Research background

Despite centralization of pancreatic surgery, post-operative pancreatic fistula (POPF) rates remain high. The pathogenesis of the development of POPF remains poorly understood but there is some evidence to support poor perfusion of the pancreatic remanent in the development of this complications.

Research motivation

This research project was designed to identify the current published literature regarding the use of intra-operative perfusion assessment to help guide whether this can be incorporated into clinical use.

Research objectives

The aim of this study was to review the current evidence for assessment of perfusion of the pancreatic remanent prior to anastomosis in patients undergoing pancreatoduodenectomy.

Research methods

The medical literature was searched for studies assessing the perfusion of the pancreatic remanent intra-operatively. Studies were identified and data was extracted by 2 independent authors. A meta-analysis could not be performed and therefore a systematic scoping review was carried out.

Research results

The POPF rate in all studies was 12%. Intraoperative perfusion assessment revealed hypoperfusion was present in 39% of patients who developed POPF. The rate of POPF was 11% in patients with no evidence of hypoperfusion and 13% in those with evidence of hypoperfusion.

Research conclusions

This study has shown that indocyanine green can safely assess pancreatic perfusion intraoperatively. There was insufficient evidence to link poor perfusion of the pancreatic remanent with POPF and further well designed studies are required.

Research perspectives

The results of this study have not changed our clinical practice but ha highlights further areas of clinical research to make pancreatic surgery safer.

FOOTNOTES

Author contributions: Robertson FP, Spiers HVM, and Pandanaboyana S contributed to the manuscript preparation, study concept, and critical review; Loveday B and Roberts K were involved in the study concept and critical review.

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Country/Territory of origin: United Kingdom

ORCID number: Francis P Robertson 0000-0001-5016-5944; Harry V M Spiers 0000-0001-7308-2711; Wei Boon Lim 0000-0002-7125-066X; Keith Roberts 0000-0003-1799-9829; Sanjay Pandanaboyana 0000-0003-3099-2197.

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SYSTEMATIC REVIEWS

Comparison between upfront surgery and neoadjuvant chemotherapy in patients with locally advanced gastric cancer: A systematic review

Stylianos Fiflis, Menelaos Papakonstantinou, Alexandros Giakoustidis, Gregory Christodoulidis, Eleni Louri, Vasileios N Papadopoulos, Dimitrios Giakoustidis

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Stylianos Fiflis, Menelaos Papakonstantinou, Alexandros Giakoustidis, Eleni Louri, Vasileios N Papadopoulos, Dimitrios Giakoustidis, A' Department of Surgery, General Hospital Papageorgiou, Thessaloniki 56429, Greece

Gregory Christodoulidis, Department of General Surgery, University Hospital of Larissa, Larissa 41110, Greece

Corresponding author: Gregory Christodoulidis, PhD, Surgeon, Department of General Surgery, University Hospital of Larissa, Mezourlo, Larissa 41110, Greece. gregsurg@yahoo.gr

Abstract

BACKGROUND

Gastric cancer (GC) is a major health concern worldwide. Surgical resection and chemotherapy is the mainstay treatment for gastric carcinoma, however, the optimal approach remains unclear and should be different in each individual. Chemotherapy can be administered both pre- and postoperatively, but a multidisciplinary approach is preferred when possible. This is particularly relevant for locally advanced GC (LAGC), as neoadjuvant chemotherapy (NAT) could potentially lead to tumor downsizing thus allowing for a complete resection with curative intent. Even though the recent progress has been impressive, European and International guidelines are still controversial, thus attenuating the need for a more standardized approach in the management of locally advanced cancer.

AIM

To investigate the effects of NAT on the overall survival (OS), the disease-free survival (DFS), the morbidity and the mortality of patients with LAGC in comparison to upfront surgery (US).

METHODS

For this systematic review, a literature search was conducted between November and February 2023 in PubMed, Cochrane Library and clinicaltrials.gov for studies including patients with LAGC. Two independent reviewers conducted the research and extracted the data according to predetermined inclusion and exclusion criteria. The Preferred Reporting Items for Systematic Reviews and

Meta-Analyses was used to form the search strategy and the study protocol has been registered in the International Prospective Register of Systematic Reviews.

RESULTS

Eighteen studies with 4839 patients with LAGC in total were included in our systematic review. Patients were separated into two groups; one receiving NAT before the gastrectomy (NAT group) and the other undergoing upfront surgery (US group). The OS ranged from 41.6% to 74.2% in the NAT group and from 30.9% to 74% in the US group. The DFS was also longer in the NAT group and reached up to 80% in certain patients. The complications related to the chemotherapy or the surgery ranged from 6.4% to 38.1% in the NAT group and from 5% to 40.5% in the US group. Even though in most of the studies the morbidity was lower in the NAT group, a general conclusion could not be drawn as it seems to depend on multiple factors. Finally, regarding the mortality, the reported rate was higher and up to 5.3% in the US group.

CONCLUSION

NAT could be beneficial for patients with LAGC as it leads to better OS and DFS than the US approach with the same or even lower complication rates. However, patients with different clinicopathological features respond differently to chemotherapy, therefore currently the treatment plan should be individualized in order to achieve optimal results.

Key Words: Gastric cancer; Locally advanced gastric cancer; Neoadjuvant chemotherapy; Surgery; Survival

Core Tip: Gastric cancer (GC) is a major concern worldwide. According to Globocan there were 1089000 new cases of GC and 768000 GC related deaths worldwide in 2020 with almost twice the prevalence and mortality in males than in females. The highest prevalence is observed in Eastern Asia whereas the lowest in Africa. Gastrectomy is the mainstay approach in patients that can undergo surgery and in recent years with the advances in chemotherapy, neoadjuvant chemotherapy (NAT) has shown potential for better survival chances. That is particularly relevant in patients with locally advanced GC as NAT could potentially lead to tumor downsizing thus allowing for higher complete resection rate. In our review we compare patients receiving NAT and then undergoing D2 gastrectomy to those undergoing upfront surgery.

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INTRODUCTION

According to Globocan there were 1089000 new cases of gastric cancer (GC) and 768000 GC related deaths worldwide in 2020 with almost twice the prevalence and mortality in males than in females. The highest prevalence is observed in Eastern Asia whereas the lowest in Africa and the highest mortality rate in Eastern Asia while the lowest in Northern America, Australia and Europe. GC is subcategorized according to Lauren's classification into intestinal and diffuse subtypes which demonstrate different epidemiology, clinical behavior, chemoresistance, progression and prognosis but there have been no trials or analyses to evaluate whether these two subtypes would potentially benefit more from different treatment modalities[1].

Locally advanced GC (LAGC) is defined as T2 or higher clinical disease, with or without nodal involvement, and surgical resection with an adequate D2-lymphadenectomy is the cornerstone of the medical approach with curative intent alongside with other perioperative treatments such as chemotherapy and radiotherapy[1]. The role of neoadjuvant chemotherapy (NAT) is being rigorously studied as an important treatment regimen that aims to eliminate micrometastasis, downstage tumors and thus prolong OS, DFS and improve recurrence and R0 resection rates. LAGC patients are at high risk of developing distant metastases therefore they should be offered NAT. And patients who undergo surgery without NAT are at high risk of recurrence and should be submitted to adjuvant chemoradiation[2].

Even though NAT is being offered to patients with LAGC in Europe and the United States, the treatment regimens differ between the Western and the Eastern countries. For instance, adjuvant chemoradiotherapy is largely administered in the United States, neoadjuvant followed by adjuvant chemotherapy in the United Kingdom and solely postoperative chemotherapy is administered in Korea and Japan according to INT0116 trial, MAGIC trial, ACT-GC trial and CLASSIC respectively[3-6]. In this systematic review we assess the role of NAT in patients undergoing surgery for LAGC. We aim to investigate the approach that offers the highest overall survival (OS) and disease-free survival (DFS) rates.

MATERIALS AND METHODS

Search strategy

A thorough literature search was performed in PubMed using the terms "gastric cancer", "locally advanced gastric cancer", "adjuvant chemotherapy", "neoadjuvant chemotherapy", "perioperative chemotherapy", "upfront surgery" and "surgical resection" in various combinations. The search yielded 648 results and after excluding duplicates and irrelevant studies by title and abstract, 36 were assessed for full text screening and 18 were finally included in the review. The study selection algorithm is shown in the PRISMA flowchart in Figure 1[7]. Our study protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO, ID CRD42023405111) and the date of the last search was February 18th, 2023.

Data extraction

Two reviewers (Fiflis S and Papakonstantinou M) independently completed the search and extracted the following data into a predetermined datasheet form: Author, year of publication, sample size, population sex and age, follow-up period, TNM stage, esophagogastric junction tumor involvement, length of hospital stay, type of surgery, chemotherapy regimens, OS and DFS rates, mortality and morbidity of the patients, R0 resection rates and tumor recurrence.

Inclusion and exclusion criteria

We included studies in the English language published over the last decade up until February 2023. The inclusion criteria were studies with patients with LAGC who had received no prior treatment and would undergo surgical resection and/or NAT. The outcomes of the studies should include data on the survival of patients after NAT and surgery and compare them to upfront surgery (US). Cohorts of patients with metastases before surgery and studies with less than 10 participants were excluded. Pilot studies, studies investigating predictive factors, case reports and letters to the editor or comments were also excluded (Table 1).

Risk of bias assessment

The risk of bias of each individual cohort study included in our systematic review was assessed with the Cochrane Tool to Assess Risk of Bias in Cohort Studies. This tool consists of the following 8 questions: (1) Was selection of exposed and non-exposed cohorts drawn from the same population? (2) Can we be confident in the assessment of exposure? (3) Can we be confident that the outcome of interest was not present at the start of the study? (4) Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? (5) Can we be confident in the assessment of the presence or absence of prognostic factors? (6) Can we be confident in the assessment of outcome? (7) Was the follow up of cohorts adequate? and (8) Were co-interventions similar between groups? Depending on the answer, which varies from definitely yes to probably yes, probably no or definitely no, each study is classified as low or high risk of bias.

RESULTS

The original search yielded 648 results and after excluding irrelevant and duplicate papers, 18 studies with 4839 patients in total were included in our systematic review[8-25]. The demographics and the clinical characteristics of the patients are shown in Table 2. All patients were treated for LAGC and were separated into two groups; one receiving NAT and then undergoing surgical resection (NAT group) and the other undergoing US (US group). After the initial intervention the patients received either adjuvant chemotherapy or radiotherapy or no adjuvant treatment at all. The outcomes of interest were primarily the OS, the DFS and the morbidity and mortality rate, and secondarily the R0 resection rate. Seven of the studies included were propensity score-matched analyses[10,11,16,21-24]. Only the results of the matched groups were included in our study.

Survival, morbidity and mortality

The OS ranged from 41.6% to 74.2% in the NAT group and from 30.9% to 74% in the US group[14,15,20,21]. The difference was statistically significant in 5 studies[11,21,22,24,17]. Details on the OS and the DFS of each of the included studies can be found in Table 3. In general, the OS was greater in the NAT group in all of the studies except for one, where the OS was 70% in the NAT and 74% in the US group ($P > 0.05$)[14]. Of note, Lin *et al*[17] in their study compared the results between Eastern and Western institutions. The difference in OS of patients with LAGC treated with NAT or US was significantly different in the Eastern cohort (60.1% *vs* 49.3% respectively, $P = 0.02$). In the Western cohort the OS of patients who received NAT was 57.3% and 39.5% for those undergoing US ($P = 0.11$)[17]. The greatest difference in OS was reported in the study of Xu *et al*[24] where after NAT the OS reached 72.29%, while after US it was as low as 36.22% ($P < 0.001$)[24].

The highest DFS was reported in the NAT group of the Kano *et al*[16] cohort and was statistically significantly higher than that of the US group (80% *vs* 58.7%, $P = 0.037$). In all of the studies included, except for one, the DFS was longer after NAT, however the difference was statistically significant in 4 studies[16,24,15,13]. Bracale *et al*[10] reported greater DFS in the US group, but the difference was not significant (75% *vs* 71% after NAT, $P = 0.34$).

The complications related to the chemotherapy or the surgery ranged from 6.4% to 38.1% in the NAT group and from 5% to 40.5% in the US group[10,16,19,22]. The difference in morbidity between the two groups was statistically significant

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Studies published over the last 10 yr	Studies with less than 10 patients
Studies in English language	Pilot studies and case reports
Adult patients	Patients with metastatic disease
Patients with locally advanced gastric cancer	

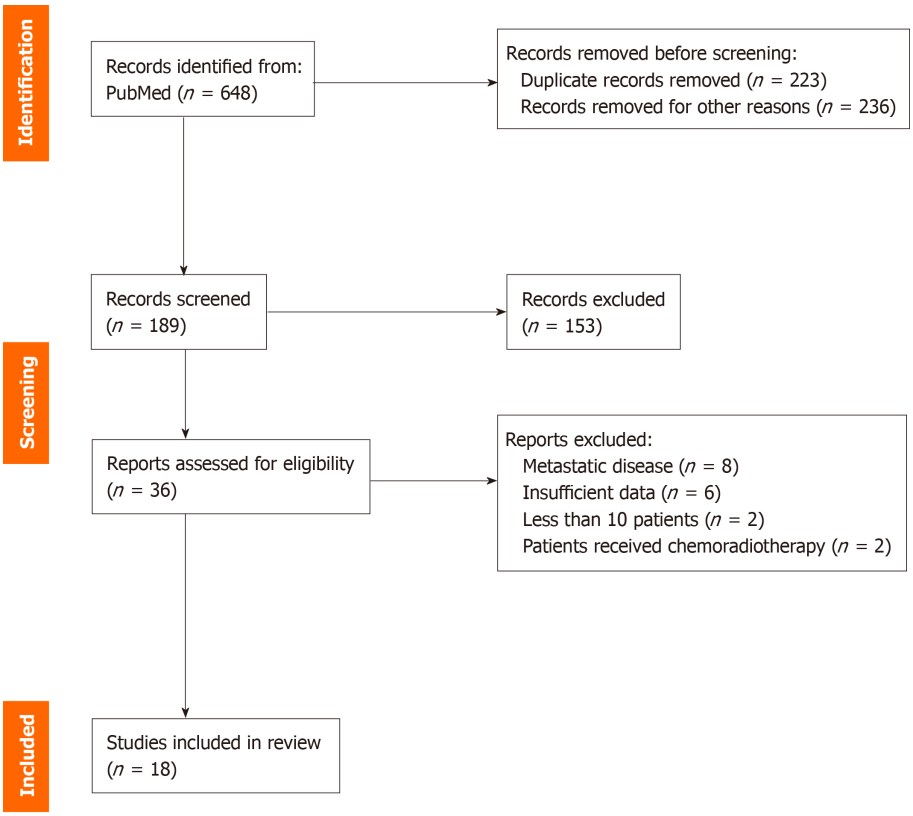

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Figure 1 PRISMA flowchart.

in two studies. In the study of Bracale *et al*[10] the morbidity was 38.1% in the NAT group and 21.6% in the US group (P = 0.019). In the study of Xu *et al*[24] the morbidity after NAT was 6.79%, while after US it was 12.67% (P = 0.037). The morbidity varied among the studies and depended on multiple factors included but not limited to chemotherapy regimen, patient status, surgical team experience, surgical technique and the extend of the disease and as a result a general conclusion could not be drawn. More detailed information is shown in Table 4. Among all the studies, death was more common in the US groups. In 7 studies no deaths occurred in the patients who received NAT, in 3 of which the mortality of the counterpart US group was 2.1%, 2.1% and 3.7% (Table 4)[8-10]. Finally, the highest mortality rate was observed in a US group, however it was not significantly different than that of the NAT group (5.3% *vs* 2.8%, P = 0.142)[20].

R0 resection

Our secondary endpoint was the comparison of the R0 resection rate between patients who received NAT and those who underwent US (Table 5). The R0 resection rates were not statistically significantly different among all the studies except for one. In the study of Wang *et al*[13], 84.6% of the patients underwent a complete tumor resection after NAT, while the corresponding percentage for the US group was significantly lower (56.7%, P = 0.029). In a subgroup analysis where they compared neoadjuvant cheomoradiotherapy with NAT they showed that neoadjuvant cheomoradiotherapy resulted to better R0 resection rate, although not statistically significantly different (96% *vs* 89%, P = 0.06)[22].

Table 2 Patient demographics and clinical characteristics

Ref.	Study population	Sex	Age (yr)	EGJ involvement	Staging
Ahn *et al*[8], 2014	140	101 males, 39 females	NAT, 53.8; US, 58.9	NS	T0, *n* = 2 T1, *n* = 35 T2, *n* = 40 T3, *n* = 31 T4, *n* = 28 Unknown, *n* = 4
Biondi *et al*[9], 2018	417	262 males, 155 females	NAT, 58 ± 10; US, 55 ± 13	*n* = 26	0, *n* = 1 I, *n* = 101 II, *n* = 87 III, *n* = 169 IV, *n* = 59
Bracale *et al*[10], 2021	194	119 males, 75 females	NAT, 69.4; US, 70.5	None	II, *n* = 48 III, *n* = 146
Eom *et al*[11], 2018	129	90 males, 39 females	NAT, 53; US, 57	None	IIIA, *n* = 61 IIIB, *n* = 57 IV, *n* = 11
Feng *et al*[12], 2015	170	134 males, 36 females	60 (21-82)	NS	T1, *n* = 5 T2, *n* = 17 T3, *n* = 29 T4, *n* = 119
Wang *et al*[13], 2021	60	32 males, 28 females	32-70	NS	T3, *n* = 32 T4a, *n* = 28
Xue *et al*[14], 2018	100	76 males, 24 females	69 patients < 65 yr	NS	T2, *n* = 10 T3, *n* = 31 T4a, *n* = 58 T4b, *n* = 1
Kang *et al*[15], 2021	484	384 males, 100 females	58 (20-75)	NS	T2, *n* = 25 T3, *n* = 116 T4a, *n* = 305 T4b, *n* = 38
Kano *et al*[16], 2019	76	61 males, 15 females	NAT, 69.3 ± 7.76; US, 70.4 ± 8.5	None	IIB, *n* = 27 IIIA-C, *n* = 49
Lin *et al*[17], 2022	462	349 males, 113 females	NAT, 58; AT, 61	NS	T0, *n* = 10 T1, *n* = 18 T2, *n* = 65 T3, *n* = 101 T4, *n* = 158
Marino *et al*[18], 2021	177	107 males, 70 females	73.3 ± 10.4	NS	T2, *n* = 4 T3, *n* = 27

					T4, *n* = 16
Molina *et al*[19], 2013	40 (39 surgery)	29 males, 11 females	64.3 (39.1-82.2)	NS	II, *n* = 21 III, *n* = 19
Pardo *et al*[20], 2020	814	513 males, 295 females	351 patients < 70; 399 patients > 70	NS	T1, *n* = 6 T2, *n* = 210 T3, *n* = 375 T4a, *n* = 164 T4b, *n* = 31
Wang *et al*[21], 2019	82	65 males, 17 females	NAT, 23 patients < 60, 18 patients > 60; US, 24 patients < 60, 17 patients > 60	None	II, *n* = 22 III, *n* = 60
Wang *et al*[22], 2021	778	580 males, 198 females	NAT, 56.13; US, 55.94	None	II, *n* = 132 III, *n* = 646
Wu *et al*[23], 2019	172	139 males, 33 females	NAT, 54.83; US, 54.98	NS	II, *n* = 10 III, *n* = 162
Xu *et al*[24], 2021	442	331 males, 114 females	NAT, 63; US, 61	NS	T4, *n* = 442
Zhao *et al*[25], 2017	102	82 males, 20 females	59 (34-77)	NS	IIB, *n* = 23 IIIA, *n* = 39 IIIB/C, *n* = 40

EGJ: Esophagogastric Junction; NAT: Neoadjuvant chemotherapy; US: Upfront surgery; NS: Not stated.

DISCUSSION

In our systematic review we aimed to investigate the effect of NAT in the survival of patients with LAGC in comparison to US. Most of the studies included in our systematic review showed an OS and DFS benefit in patients treated with NAT. In general, NAT does not increase morbidity and mortality after surgery therefore constitutes a safe treatment regimen for patients with LAGC. Whatsmore, Feng *et al*[12], Kang *et al*[15] and Molina *et al*[19] demonstrated that patients treated with NAT accomplished significant tumor downstaging which translates to better surgical outcomes. Kang *et al*[15] also demonstrated that patients with more advanced disease benefited the most from NAT.

However, surgery should not be delayed unnecessarily, as not all patients with LAGC will benefit from perioperative chemotherapy. GC is highly heterogeneous pathologicaly and the response to treatment could vary since different subtypes present with different tumor and clinical characteristics. Zurlo *et al*[1] showed in their retrospective analysis that patients with diffuse type GC had worse OS than those with intestinal type GC when NAT was implemented in their therapeutic approach. Even though histology-driven decisions are appealing, these results need to be confirmed by larger and prospective trials.

There has been a number of trials in Europe such as the MAGIC trial and the FNCLCC/FFCD trial that showed that patients submitted to NAT had longer OS and DFS compared to US patients[4,26]. Moreover, the FNCLCC/FFCD trial showed that the NAT group had higher R0 rates. It is noteworthy that the complication rates remain the same between NAT and US groups which indicates that NAT could be safely administered in clinical practice. NAT followed by surgery and adjuvant chemotherapy is considered the standard of treatment in Europe and the United States.

In the Asian countries the standard of treatment differs from the West. According to the Japanese GC treatment guidelines 2018 (5th edition) NAT should not be offered in LAGC patients. Instead they should undergo US followed by adjuvant chemotherapy[27]. In agreement to these guidelines, the CLASSIC trial with patients from Korea, China and Taiwan demonstrated the necessity of adjuvant chemotherapy due to the significantly higher DFS in adjuvant chemotherapy and surgery group in comparison to surgery only group ($P < 0.0001$)[6]. On the other hand, the RESOLVE trial in China and the PRODIGY in Korea proved that NAT significantly improves DFS and can be safely administered to patients with LAGC.

In the modern era, the research aims at the molecular level and various biomarkers, prognostic factors and immunotherapeutic agents have been introduced in the management and treatment of LAGC. For instance, the MAGIC and the CLASSIC Trials showed that there is no benefit from chemotherapy in patients with GC and microsatellite instability or mismatch repair protein deficiency[4,6]. A study performed in a Western population suggests additional molecular marker testing as patients showed better prognosis when treated with the anti-programmed cell death protein 1 agent, nivolumab[28]. These results are furtherly supported by a phase 3 trial which showed that the addition of nivolumab in the therapeutic regimen of GC patients provided a statistically significant DFS benefit[29]. Lastly, a phase 2 trial, the FIGHT study, demonstrated that Bemarituzumab, an antibody that selectively binds to fibroblast growth factor receptor 2

Table 3 Overall survival and disease-free survival of patients after neoadjuvant chemotherapy and surgery *versus* upfront surgery

Ref.	Overall survival		*P* value	Disease-free survival		*P* value
	NAT	US		NAT	US	
Ahn *et al*[8], 2014	NS	NS		NS	NS	
Biondi *et al*[9], 2018	> 60 mo	45 mo	0.519	NS	NS	
Bracale *et al*[10], 2021	72%	71%	0.41	71%	75%	0.34
Eom *et al*[11], 2018	73.3%	51.1%	0.005	62.8%	49.9%	0.145
Feng *et al*[12], 2015	NS	NS		NS	NS	
Wang *et al*[13], 2021	63.3%	50%	0.215	60%	33.3%	0.019
Xue *et al*[14], 2018	70%	74%	> 0.05	NS	NS	
Kang *et al*[15], 2021	74.2%	73.4%	> 0.05	66.3%	60.2%	0.023
Kano *et al*[16], 2019	NS	NS		80%	58.7%	0.037
Lin *et al*[17], 2022[1]	Eastern: 60.1%. Western: 57.3%	Eastern: 49.3%. Western: 39.5%	Eastern: 0.02. Western: 0.11	NS	NS	
Marino *et al*[18], 2021	50 mo	35 mo	> 0.05	48 mo		> 0.05
Molina *et al*[19], 2013		39.01%			34.05%	
Pardo *et al*[20], 2020	41.6%	38.6%	0.089	NS	NS	
Wang *et al*[21], 2019	58.7%	30.9%	0.008	NS	NS	
Wang *et al*[22], 2021	52 mo	26.4 mo	< 0.001	NS[2]	NS[2]	
Wu *et al*[23], 2019	NS	NS		NS	NS	
Xu *et al*[24], 2021	72.29%	36.22%	< 0.001	58.53%	30.87%	< 0.001
Zhao *et al*[25], 2017	17.9 mo	17.4 mo	> 0.05	16.1 mo	15.8 mo	> 0.05

[1]All patients received neoadjuvant chemotherapy; adjuvant chemotherapy (first column) and non-adjuvant chemotherapy groups (second column) were compared in two independent (an eastern and a western) cohorts.
[2]Not stated for neoadjuvant chemotherapy *vs* upfront surgery. But nCRT (chemoradio-) significantly better than nCT (chemo-) ($P = 0.014$).
NAT: Neoadjuvant chemotherapy; US: Upfront surgery; NS: Not stated.

isoform IIb (FGFR2b) and mediates cytotoxicity, improved the OS, DFS and overall response rate when administered to patients with human epidermal growth factor receptor 2 negative and FGFR2b positive unresectable locally advanced gastric tumor[30].

Limitations

One limitation of our study is that not all of the patients had the same histological type of GC, which as discussed above may affect the efficacy of the chemotherapy regimen. Also, the chemotherapy regimens were not standardized among the studies. Due to that heterogeneity of data a meta-analysis could not be performed. Furthermore, most of the included studies were retrospective cohort studies, a type of study more frequently susceptible to selection or recall bias. Finally, the operations were not performed by the same surgical teams, and even though we included studies from large centers with high volume of patients the surgical technique and experience may vary.

CONCLUSION

NAT followed by surgery is safe for patients with LAGC and offers potentially better OS and DFS compared to US. However, the optimal treatment regimen for patients with LAGC today is still perplexed, as it is not distinct which patients could benefit the most from NAT. Even though D2 gastrectomy remains the gold standard in patients that can be submitted to surgery, more research is needed to clarify which LAGC patients will benefit more from NAT and immune-targeted therapies or other biological agents. Patients should also be stratified into chemosensitive and chemoresistant groups according to the tumor's response to initial treatment for more optimal results. To conclude, since each patient with LAGC presents with different clinicopathological features and responds differently to chemotherapy, the treatment plan should be individualized in order to achieve the optimal results.

Table 4 Morbidity and mortality of patients after neoadjuvant chemotherapy and surgery *versus* upfront surgery

Ref.	Morbidity		*P* value	Mortality		*P* value
	NAT	US		NAT	US	
Ahn *et al*[8], 2014	22.9%	29.3%		0	2.1%	
Biondi *et al*[9], 2018	21.4%	12.9%	0.178	0	3.7%	
Bracale *et al*[10], 2021	38.1%	21.6%	0.019	0	2.1%	
Eom *et al*[11], 2018	14.3%	15.1%	0.999	0	0	
Feng *et al*[12], 2015	18.8%	22.2%	0.704	NS	NS	
Wang *et al*[13], 2021	23.1%	30%	0.56	NS	NS	
Xue *et al*[14], 2018	30%	28%	0.986	2%	2%	
Kang *et al*[15], 2021	8.1%	5.5%	0.175	0.4%		
Kano *et al*[16], 2019	23.1%	40.5%	0.101	NS	NS	
Lin *et al*[17], 2022	NS	NS		NS	NS	
Marino *et al*[18], 2021	Less than US		> 0.05	NS	NS	
Molina *et al*[19], 2013	-	5%		-	2.5%	
Pardo *et al*[20], 2020	11.5%	9.9%	0.268	2.8%	5.3%	0.142
Wang *et al*[21], 2019	9%	17%	0.519	0	0	
Wang *et al*[22], 2021	6.4%	0		0.2%	0	
Wu *et al*[23], 2019	10.5%	15.1%	0.361	0	0	
Xu *et al*[24], 2021	6.79%	12.67%	0.037	*n* = 172 in total		
Zhao *et al*[25], 2017	14%	15.4%	0.844	0	0	

NAT: Neoadjuvant chemotherapy; US: Upfront surgery; NS: Not stated.

Table 5 R0 resection rate of gastric cancer in patients after neoadjuvant chemotherapy and surgery versus upfront surgery

Ref.	R0 resection rate		*P* value
	NAT	US	
Ahn *et al*[8], 2014	92.2%		
Biondi *et al*[9], 2018	82.9%	83.6%	0.449
Bracale *et al*[10], 2021	NS	NS	
Eom *et al*[11], 2018	97.7%	97.7%	
Feng *et al*[12], 2015	95%	94.4%	
Wang *et al*[13], 2021	84.6%	56.7%	0.029
Xue *et al*[14], 2018	100%	96%	
Kang *et al*[15], 2021	NS	NS	
Kano *et al*[16], 2019	100%	100%	
Lin *et al*[17], 2022	90.1%		
Marino *et al*[18], 2021	NS	NS	
Molina *et al*[19], 2013	-	80%	
Pardo *et al*[20], 2020	NS	NS	
Wang *et al*[21], 2019	89.2%	84.6%	> 0.05
Wang *et al*[22], 2021	96%[1]	89%[1]	0.06[1]

Wu *et al*[23], 2019	NS	NS	
Xu *et al*[24], 2021	94.12%	89.14%	0.072
Zhao *et al*[25], 2017	NS	NS	

[1]Neoadjuvant chemoratdiotherapy *versus* neoadjuvant chemotherapy (96% *vs* 89%, $P = 0.06$).
NAT: Neoadjuvant chemotherapy; US: Upfront surgery; NS: Not stated.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer (GC) is a major health concern worldwide. Currently, surgery is the mainstay treatment along with adjuvant or neoadjuvant chemotherapy (NAT) or both. However, in locally advanced GC (LAGC) upfront surgery (US) may not be the optimal approach. NAT may induce tumor downsizing and therefore offer better chances for complete resection of the tumor.

Research motivation

NAT could lead to complete surgical resection of the otherwise unresectable LAGC. Unfortunately, in the current literature, there are conflicting results regarding the role of NAT in the survival of patients with LAGC. We aim to investigate that role and hopefully, future research could focus on optimizing the treatment strategy of LAGC.

Research objectives

In our systematic review we aim to investigate the effects of NAT on the overall survival (OS), the disease-free survival (DFS), the morbidity and the mortality of patients with LAGC in comparison to US. The results of our review may add to the effort of optimizing the treatment strategy for cancer patients regarding longer survival with better quality of life.

Research methods

We conducted a thorough literature search for cohort studies comparing patients with LAGC treated with US to patients treated with NAT followed by surgery. The patients' characteristics were not statistically significantly different before the interventions and only the matched group results were included in our study.

Research results

The OS of patients with LAGC was slightly better in the groups treated with NAT than those undergoing US. Similar results were also found for DFS. Whatsmore mortality rates were higher in the US groups. These results are promising regarding the utilization of NAT in the treatment of LAGC. In the future, research on LAGC should include more patients treated in large centers with similar surgical techniques and focus on investigating the optimal NAT regimens that lead to longer survival with minimal complications.

Research conclusions

NAT may lead to complete surgical resection of LAGC and therefore offers the potential for treatment for patients with otherwise unresectable tumors.

Research perspectives

To clarify which patients will benefit more from which NAT regimen and also investigate the potential role of immune-targeted therapies or other biological agents in treating patients with LAGC.

FOOTNOTES

Author contributions: Fiflis S designed and performed the research and wrote most of the manuscript; Papakonstantinou M performed the research, analyzed the data and wrote part of the results and the discussion; Giakoustidis A resolved conflicts during the article screening, offered guidance and performed manuscript revisions; Christodoulidis G perceived the idea, performed manuscript revisions and assisted as a corresponding author; Louri E wrote part of the discussion and performed manuscript revisions; Papadopoulos VN performed manuscript revisions; Giakoustidis D offered guidance and assisted as a supervising author; and all authors have read and approved the final manuscript.

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Country/Territory of origin: Greece

ORCID number: Stylianos Fiflis 0000-0003-0427-6859; Menelaos Papakonstantinou 0000-0001-5030-7009; Alexandros Giakoustidis 0000-0002-3786-4609; Gregory Christodoulidis 0000-0003-3413-0666; Eleni Louri 0000-0003-4790-419X; Vasileios N Papadopoulos 0000-0002-1009-1685; Dimitrios Giakoustidis 0000-0002-6023-4744.

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CASE REPORT

Long-term survival of patients with hepatocellular carcinoma with hepatic, pulmonary, peritoneal and rare colon metastasis: A case report

Yong-Qiang Gong, Tai-Liang Lu, Chao-Wu Chen

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Yong-Qiang Gong, Tai-Liang Lu, Department of Gastrointestinal Surgery, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha 410005, Hunan Province, China

Chao-Wu Chen, Department of Gastrointestinal Surgery, Hunan Provincial People's Hospital, Changsha 410005, Hunan Province, China

Corresponding author: Chao-Wu Chen, MD, PhD, Doctor, Department of Gastrointestinal Surgery, Hunan Provincial People's Hospital, No. 61 Jiefang West Road, Furong District, Changsha 410005, Hunan Province, China. chenchaowu0@163.com

Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is a highly malignant cancer that often metastasizes and has a poor prognosis. Gastrointestinal tract metastases are rare, and colon metastases are even rarer. The long-term survival of patients with multiple intrahepatic and extrahepatic metastases, especially to the colon, has not been previously reported.

CASE SUMMARY

We present an atypical clinical case of a patient with liver, right lung, peritoneal, and colon metastases diagnosed successively following hepatic resection for primary HCC. Comprehensive treatment, including partial liver, lung and colon resection, palliative management such as systemic chemotherapy, trans-arterial chemoembolization, targeted therapy with sorafenib, and cryotherapy were attempted. Despite his early metastases, the patient remained relatively healthy for 8 years after diagnosis.

CONCLUSION

This case indicates that comprehensive treatment is beneficial for certain patients with metastatic HCC. Clinicians should be alert as to the possibility of rare site metastatic tumors that may be easily misdiagnosed as primary tumors.

Key Words: Hepatocellular carcinoma; Multiple metastasis; Rare colon metastasis; Comprehensive treatments; Long-term survival; Case report

Core Tip: Hepatocellular carcinoma (HCC) is a highly malignant cancer worldwide, which often metastasizes, but unusually to the gastrointestinal tract and particularly rare to the colon. We presented an atypical clinical case of a patient with liver, right lung, peritoneal and colon metastases diagnosed successively following hepatic resection for primary HCC. Despite his early metastases, the patient remained relatively healthy for 8 years. This case indicates that comprehensive treatment is beneficial for certain patients with metastatic HCC. Furthermore, clinicians should be alert as to the possibility of rare site metastatic tumors that may be easily misdiagnosed as primary tumors. We believe this article will be very useful to anyone who is interested in this field.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant cancers, with a high metastatic and invasive potential and a low survival rate[1]. While patients with HCC often present with intrahepatic lung and bone metastasis, digestive tract metastases are rare[2,3]. There are many therapeutic approaches for treating HCC that can be widely classified by their ability to cure or control the tumor. Liver transplant, hepatic resection, and ablative therapies are performed with curative intent, while the majority of locoregional therapies, systemic chemotherapies and sorafenib are considered palliative. Although numerous treatment strategies for metastatic HCC have been evaluated, there has been no significant reduction in HCC mortality. Here we report a case of a long-term survival from primary HCC with early successive liver, lung, peritoneal, and colon metastases following comprehensive treatments.

CASE PRESENTATION

Chief complaints

A 47-year-old male was transferred to our hospital who had received comprehensive treatment for HCC for 4 years and was complaining of hematochezia for 20 d.

History of present illness

The patient was admitted to a local hospital in February 2015 for upper abdominal pain. Computer tomography (CT) revealed several circular low-density shadows with a maximum size of 4.1 cm × 4.5 cm in the right lobe of the liver (Figure 1). Liver cancer with rupture and hemorrhage was suspected, and no evidence of metachronous metastases were observed. A partial right hepatic lobe resection and cholecystectomy was performed on March 5, 2015. The patient also underwent abdominal and pelvic exploration as well as a priming wash. Operative pathology confirmed a moderately differentiated HCC.

The patient was admitted to our hospital for regular follow up 1 mo later. CT showed a small hepatic nodule in his quadrate lobe, suggesting a possible metastasis. He underwent trans-arterial chemoembolization (TACE) for recurrent HCC in the liver on May 13, 2015. The patient recovered well, and no abnormalities were observed at until 1-year follow up in May 2016, when a CT scan found a metastatic tumor in the lower lobe of his right lung and a 2.5 cm × 2.0 cm mass in his peritoneal soft tissue (Figure 2). Based on the Barcelona Clinic Liver Cancer staging system, the patient was started on palliative sorafenib 0.4 g *per os* twice daily on May 17, 2016. The patient's AFP level gradually increased from 2015 to 2017, peaking at 99 ng/ml. The multiple disciplinary team (MDT) suggested the patient undergo surgical resection of his peritoneal and pulmonary metastases. The peritoneal metastases were resected on January 23rd, 2017, and a partial lobectomy was performed on March 27, 2017. A postoperative biopsy confirmed pathologic change within the metastatic deposits (Figure 3). The patient's postoperative AFP decreased to 20-30 ng/mL. His coagulation and liver function remained normal throughout treatment.

Seven months later, in November 2017, a CT scan observed a lesion in the patient's ascending colon and multiple small flaky low-density nodules in his liver. The patient underwent a colonoscopy, and biopsy histology was consistent with metastatic HCC (Figure 4). Immunohistochemical results were Hepatocyte (+), Glypican-3 (+), CD34 (indicating vascularization), CDX2 (-), CK7 (-), and CK20 (-). Magnetic resonance imaging and an abdominal ultrasound suggested recurrent HCC. The patient consequently underwent TACE for multifocal HCC recurrence in his liver. Given concern for the patient's overall condition, a MDT meeting was held and systemic treatment was recommended. The patient was admitted to an anti-programmed death 1 (PD-1) clinical trial in our hospital. The patient received SHR-1210 200mg, i.v. gtt on day 1+ and apatinib mesylate 250 mg, *per os* on days 1-14, a series that was repeated every 2 wk from July 10, 2018

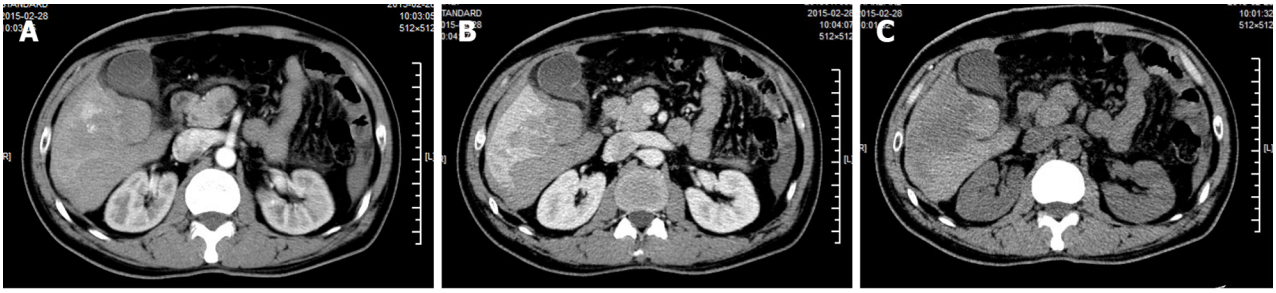

Figure 1 Abdominal computer tomography showing several heterogenous lesions in the right lobe of the liver. A: Arterial phase; B: Venous phase; C: Plain scan.

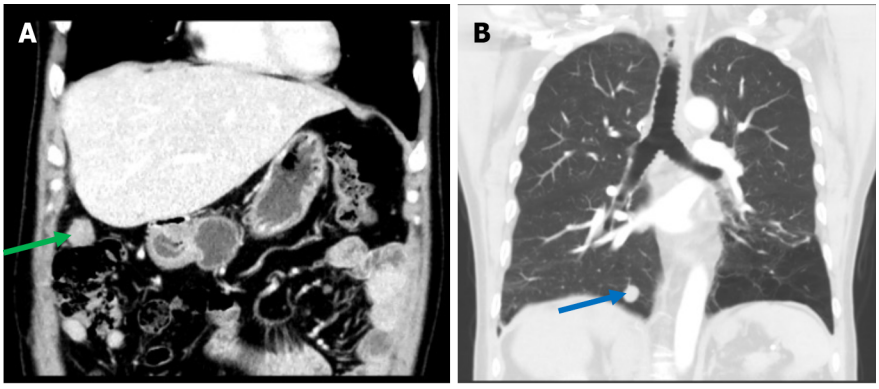

Figure 2 An abdominal computer tomography showed a 2.0 cm × 1.6 cm nodular soft tissue density lesion in the right upper peritoneum (green arrow), and thoracic computer tomography showed a nodular lesion about 1.6 cm in diameter in the basal segment of the right lower lung (blue arrow). A: An abdominal computer tomography; B: Thoracic computer tomography.

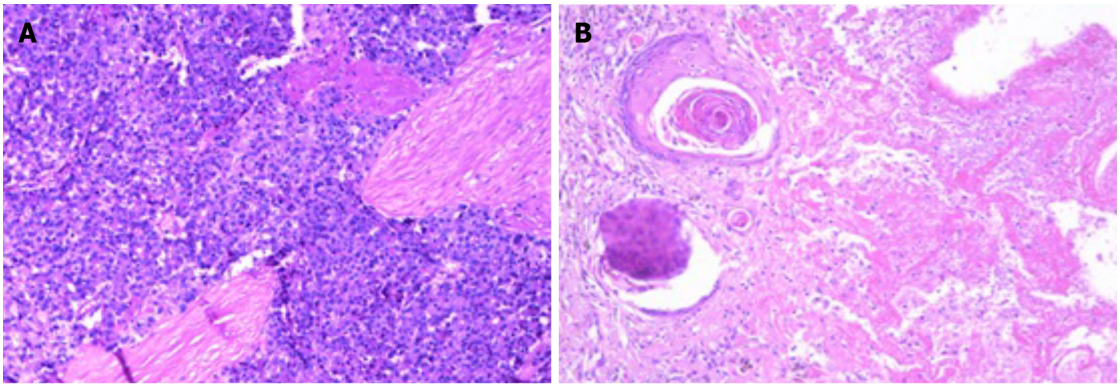

Figure 3 Pathology of the peritoneal mass and pulmonary lesion, which were consistent with metastatic hepatocellular carcinoma. A: Peritoneal mass; B: Pulmonary lesion.

to March 6, 2019. During this period, the patient's AFP levels fluctuated between 25 and 100 ng/mL.

The patient complained of hematochezia for over 20 d. Considering the possibility of colon mass rupture and bleeding, the patient was withdrawn from anti-PD-1 immunotherapy until March 17, 2019.

History of past illness

Hepatitis B diagnosed in 2009.

Personal and family history

The patient denied any special personal or family history.

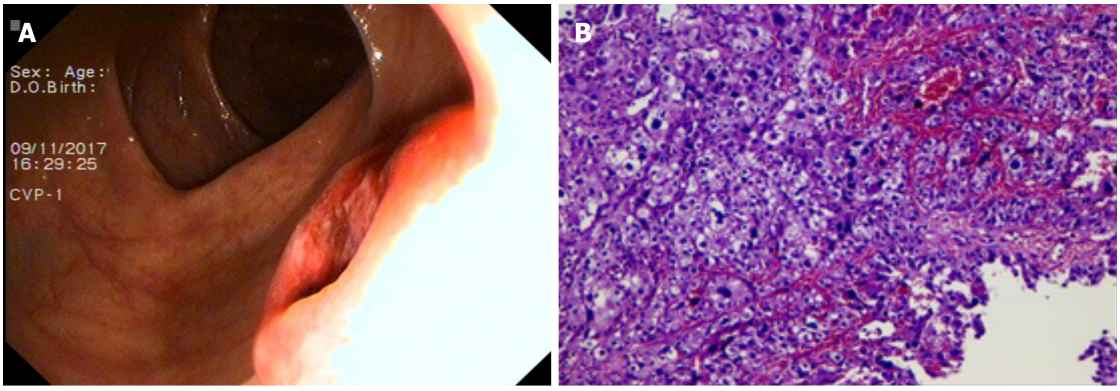

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Figure 4 Colonoscopy found a mass in the ascending colon and the biopsy confirmed metastatic hepatocellular carcinoma in the ascending colon. A: Colonoscopy; B: Biopsy.

Physical examination

A flat and soft abdomen with several visible surgical scars on the epigastrium.

Laboratory examinations

Alpha-fetoprotein (AFP) level was 34 ng/mL (reference range 0-20 ng/mL).

Imaging examinations

A 2015 CT scan revealed multiple circular low-density shadows with a maximum size of 4.1 cm × 4.5 cm in the right lobe of the liver (Figure 1). A May 2016 CT scan showed a metastatic tumor in right lower lobe of lung (Figure 2A) and a 2.5 cm × 2.0 cm mass in the peritoneal soft tissue (Figure 2B). Operative pathology of the peritoneal mass (Figure 3A) and pulmonary lesion (Figure 3B) confirmed pathologic change in the metastatic HCC. In November 2017, a CT scan found a lesion in the ascending colon and multiple small flaky low-density nodules in the liver. A colonoscopy was performed to biopsy the mass in the ascending colon (Figure 4A), which confirmed metastatic HCC in the ascending colon (Figure 4B).

FINAL DIAGNOSIS

HCC with hepatic, pulmonary, peritoneal, and colon metastases.

TREATMENT

The patient was withdrawn from anti-PD-1 immunotherapy on March 17, 2019, because of hematochezia, which was thought to be from a ruptured mass in his colon. A CT scan revealed increased size of the mass in the ascending colon wall. The MDT recommended a colectomy, and a radical resection of the right colon was performed on May 26, 2019, with pathology consistent with metastatic HCC. The patient recovered well postoperatively, and no abnormalities or metastases were observed over the proceeding 4-years of follow-up.

OUTCOME AND FOLLOW-UP

After comprehensive treatment, including partial surgical resection of his liver, lung, and colon, and palliative management such as systemic chemotherapy, TACE, targeted therapy with sorafenib, and cryotherapy, the patient is still alive and relatively healthy 8 years after being diagnosed with HCC.

DISCUSSION

HCC, a major subtype of primary liver cancer, is the third most common cause of cancer-related death worldwide, leading to over 600000 deaths annually[4]. While a significant amount of research has been performed into possible HCC treatments, it still carries an extremely dismal prognosis due to its late diagnosis and its high risk of recurrence and drug resistance. HCC always metastasizes *via* intrahepatic blood vessels, direct infiltration, or the lymphatic system, and thus typically affecting the liver, lung, bone, lymphatics and brain[5]. Metastases to the digestive tract, in particular the colon

are very rare. The patient underwent abdominal and pelvic exploration and irrigation for liver cancer with rupture and hemorrhage. It is worth considering whether the colon metastases occurred *via* normal intestinal metastasis or abdominal implantation. We do not rule out the risk of intraperitoneal implantation, but consider the possibility of metastasis through the normal intestinal pathway to be more likely. First, the patient had successive liver, lung, and peritoneal metastases, with intestinal metastases occurring 2 years later. If the colonic metastases were due to peritoneal implantation, they would have occurred almost simultaneously with the abdominal metastasis. Further, the colonic metastases grew within the intestinal cavity rather than infiltrating it, as shown on imaging and colonoscopy. It is hard to distinguish metastatic carcinoma of the colon from primary colon cancer because the metastases have few specific clinical manifestations. Clinicians should therefore be vigilant to the possibility of rare metastatic tumor sites, such as the colon in the case of our patient, which may avoid misdiagnosis or delayed treatment.

There are many treatments for HCC, which include liver transplantation, surgical resection, locoregional therapy (*e.g.*, TACE), and systemic therapy (*e.g.*, multikinase inhibitor sorafenib). Among the therapies mentioned above, liver transplantation and surgical resection remain the gold standard curative treatments for HCC. Locoregional and systemic therapies are usually considered controlling but not curative, or a means for decreasing tumor size or bridging the patient to surgery. It has been reported that patients treated with TACE have a considerably longer overall survival than the best supportive care in a randomized controlled study[6]. For patients with advanced HCC who are not surgical candidates or who have failed locoregional therapy, the multikinase inhibitor sorafenib may be considered[7]. An expanding body of evidence suggests that cytoreductive surgery can prolong the survival of patients with various metastatic malignancies and improve their quality of life[8,9]. Thus, despite their poor outcomes, the comprehensive treatment of patients with HCC and hepatic or extrahepatic metastases may improve their prognosis[10,11]. The comprehensive use of cytoreductive surgery, regional chemotherapy and other interventions contribute to lowering cancer burden, alleviating the symptoms and improving the quality of life of patients with metastatic HCC. However, patients with advanced HCC require a comprehensive assessment of multiple indicators. A specific preoperative assessment is therefore performed to identify appropriate treatment decisions. The postoperative pathological biopsy of this patient confirmed a moderately differentiated HCC. However, he developed liver, lung, peritoneum, and colon metastases at an early stage, classifying his diagnosis as advanced malignant HCC. According to the National Cancer Institute's SEER database, the average five-year survival rate of HCC patients in the United States is 19.6%, but can be as low as 2.5% for those with advanced metastatic disease. Although this patient had a moderately differentiated HCC, an 8-year effective survival period should still be considered a longer than expected survival.

There are several deficiencies and omissions in this case. The absence of a well-developed PET-CT to most objectively identify the patient's systemic lesions and metastases is a major weakness of this work. Further, it is a great pity that postoperative adjuvant therapy was administered earlier to this patient despite his high risk of recurrence.

CONCLUSION

In conclusion, this case describes a patient with atypical HCC with multiple extrahepatic metastases who survived for 8 years following comprehensive treatment. The primary HCC and metastatic tumors in his liver, lung, peritoneum, and colon were surgically removed. This may indicate that reducing the tumor burden may delay disease progression, thus improving quality of life. This report highlights the role of comprehensive treatment for certain patients with advanced stage HCC. It also supports the early recognition of rare metastatic sites and can provide instruction for the treatment of HCC.

FOOTNOTES

Author contributions: Gong YQ collected the literature and wrote the manuscript. Lu TL supervised the manuscript. Chen CW conceived the idea and drafted the manuscript. All authors have read and approve the final manuscript.

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Country/Territory of origin: China

ORCID number: Yong-Qiang Gong 0000-0002-9215-8790; Tai-Liang Lu 0000-0002-2156-5460; Chao-Wu Chen 0000-0001-5912-9050.

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CASE REPORT

Donor hepatic artery reconstruction based on human embryology: A case report

He-Zhao Zhang, Jun-Hui Lu, Zhi-Yong Shi, Ya-Rong Guo, Wen-Hao Shao, Fan-Xiu Meng, Rui Zhang, An-Hong Zhang, Jun Xu

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He-Zhao Zhang, Jun-Hui Lu, Wen-Hao Shao, Fan-Xiu Meng, Faculty of Graduate Studies, Shanxi Medical University, Taiyuan 030000, Shanxi Province, China

Zhi-Yong Shi, Rui Zhang, An-Hong Zhang, Jun Xu, Department of Hepatopancreatobiliary Surgery, First Hospital of Shanxi Medical University, Taiyuan 030000, Shanxi Province, China

Ya-Rong Guo, Department of Oncology, First Hospital of Shanxi Medical University, Taiyuan 030000, Shanxi Province, China

Corresponding author: Jun Xu, PhD, Chief Physician, Dean, Department of Hepato-pancreatobiliary Surgery, First Hospital of Shanxi Medical University, No. 85 Jiefang South Road, Taiyuan 030000, Shanxi Province, China. junxuty@163.com

Abstract

BACKGROUND

Embryonic hepatic artery anatomy simplifies its identification during liver transplantation. Injuries to the donor hepatic artery can cause complications in this process. The hepatic artery's complex anatomy in adults makes this step challenging; however, during embryonic development, the artery and its branches have a simpler relationship. By restoring the embryonic hepatic artery anatomy, surgeons can reduce the risk of damage and increase the procedure's success rate. This approach can lead to improved patient outcomes and lower complication rates.

CASE SUMMARY

In this study, we report a case of donor liver preparation using a donor hepatic artery preparation based on human embryology. During the preparation of the hepatic artery, we restored the anatomy of the celiac trunk, superior mesenteric artery, and their branches to the state of the embryo at 5 wk. This allowed us to dissect the variant hepatic artery from the superior mesenteric artery and left gastric artery during the operation. After implanting the donor liver into the recipient, we observed normal blood flow in the donor hepatic artery, main hepatic artery, and variant hepatic artery, without any leakage.

CONCLUSION

Donor hepatic artery preparation based on human embryology can help reduce the incidence of donor hepatic artery injuries during liver transplantation.

Key Words: Donor hepatic artery; Abnormality of artery; Liver transplantation; Embryonic development; Anatomical relationship; Case report

Core Tip: The repair of the donor hepatic artery is a very important step in liver transplantation. In the liver with abnormal arterial anatomy, the incidence of hepatic artery injury is very high. We invented a method of donor hepatic artery repair based on human embryology, which is a method of restoring the artery to the embryonic anatomy, greatly reducing the damage probability of the mutated hepatic artery.

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INTRODUCTION

Liver transplantation is the only definitive treatment for end-stage liver disease[1]. However, many patients die while waiting for a liver source, and the shortage of liver sources is the greatest challenge facing liver transplantation[2]. Therefore, it is important to ensure that organ anatomy is not injured during liver transplantation[3].

Liver transplantation consists of several steps, including donor liver acquisition, donor liver preparation, diseased liver resection, and donor liver implantation. The purpose of donor liver preparation is to carefully dissect the blood vessels and biliary tract of the liver, remove excess perihepatic tissue, and reduce postoperative rejection, which is an important factor in determining the success or failure of transplantation.

The common hepatic artery is one of the main arteries that supply the liver, gallbladder, lesser omentum, and gastroduodenum. Its branches and variations are complex[4,5]. Choi *et al*[6] retrospectively studied the hepatic artery imaging data of 5625 patients and found that the overall incidence rate of abnormal hepatic arteries was 27.41%, with the incidence rate of the aberrant right hepatic artery (aRHA) being 15.63%, and the incidence rate of the aberrant left hepatic artery (aLHA) being 16.32%. Additionally, the incidence rate of aRHA combined with aLHA was 4.53%. There are many classification systems for hepatic artery anatomy, among which Michel's classification is the most frequently used[7-12]. Because the branches of the intrahepatic artery are not dissected during donor liver preparation, and angiography is not routinely performed, it is not always possible to determine whether the variant hepatic artery is a substitute or an accessory hepatic artery (accessory replacement). Therefore, once a hepatic artery variation is identified while pruning the hepatic artery, dissection and protection are required. Lack of experience and awareness can easily lead to damage to anatomical variations in the hepatic artery[13].

The incidence of hepatic artery injury has significantly increased during the preparation of donor livers with abnormal hepatic artery anatomy[14]. Accurate identification and correct treatment of the variant hepatic artery during surgery are essential to ensure the integrity of the donor hepatic artery. This is the basis for good postoperative recovery of liver function and reduction of postoperative hepatic artery complications.

Postoperative hepatic artery complications are critical factors that can significantly impact the prognosis of liver transplantation[6-8]. Studies have reported that the incidence of hepatic artery complications ranges from 3% to 9%. Hepatic artery thrombosis (HAT) is the most common and serious vascular complication of liver transplantation, often the leading cause of primary dysfunction and graft loss[11]. Arterial remodeling is necessary when an artery is injured and some studies have suggested that it may increase the risk of HAT. Surgical injury of the donor hepatic artery may increase the incidence of HAT, graft dysfunction, and graft loss, rendering the donor liver unsuitable for transplantation [14].

The commonly used methods of trimming hepatic arteries are as follows: The superior mesenteric artery is dissected within 2-3 cm of the initial part and the right replacement or accessory hepatic artery are searched. Simultaneously, the hepatogastric ligaments are examined for the left replacement or accessory hepatic artery, which originate from the left gastric artery to the liver. Currently, the process of preparing the donor's liver is based on the normal physiological anatomy, which may lead to arterial damage, especially in cases of variant hepatic arteries, where the abnormal shape of the artery and the surgeon's lack of experience can lead to injury. These complications can significantly impact clinical practice, highlighting the need for improved techniques. In this case report, we describe a method of donor hepatic artery preparation based on human embryology, which reduces the risk of arterial damage, especially in variant arteries.

CASE PRESENTATION

Chief complaints

The liver donor was a 43-year-old man who had fallen into a coma from a traumatic accident.

History of present illness

The liver donor was diagnosed with brain stem injury, and the patient was transferred to our hospital six hours after the accident for further treatment.

History of past illness

The liver donor was physically fit.

Personal and family history

His family history was noncontributory.

Physical examination

Liver donors go into coma, their nerve reflexes disappear. No bruising or ecchymosis was observed in the abdomen.

Laboratory examinations

Laboratory examinations including routine blood and blood coagulation, liver function, biochemistry, tumor markers, and infection markers revealed no abnormalities.

Imaging examinations

Head computed tomography scan indicated skull fracture, brain contusion and laceration, intracranial hematoma, brain edema, ventricle compression and displacement, midline structure displacement, abdominal color ultrasound indicated no traumatic injury and benign and malignant diseases in liver.

FINAL DIAGNOSIS

Based on the liver donor's symptoms, examination and imaging findings, the preliminary diagnosis was brain stem injury. And he didn't have any acute or chronic damage to his liver.

TREATMENT

Following organ retrieval, the liver was refrigerated and transported in an organ storage box. The warm ischemia time of the liver was 3 min, the cold ischemia time was 4 h, and the mass of the liver after preparation was 1427 g. Upon arrival in the operating room, the liver was completely immersed in the University of Wisconsin (UW) solution at 0-4℃ for preparation. The superior and inferior hepatic vena cava and biliary tract were then prepared sequentially.

In order to avoid the damage of the potentially mutated hepatic artery, we decided to prepare the donor hepatic artery using a new hepatic artery preparation protocol. In the normal anatomical position, the gastroduodenal artery was identified and dissected until it reached the proper hepatic artery, which was set as the endpoint for the arterial preparation. Next, the liver was rotated counterclockwise by approximately 45° from its normal position, and the superior mesenteric artery was dissected from the severed end. During dissection, it was noted that a variant of the right hepatic artery was present within 5 cm of the root of the superior mesenteric artery, which was then carefully dissociated (Figure 1B). The liver was then rotated clockwise by approximately 90° from the normal anatomical position, beginning at the end of the splenic artery. The splenic artery was dissected and prepared up to its origin at the celiac trunk, followed by the dissection and preparation of the left gastric artery from its distal end. During this dissection, it was noted that a variant of the left hepatic artery was located directly above the left gastric artery and was dissociated carefully (Figure 1C). Finally, the liver was restored to its normal anatomical position, and the proper hepatic artery was dissected and prepared up to its bifurcation into the hepatic artery proper and the gastroduodenal artery. After preparing the portal vein and ligating any possible bleeding sites, excess tissue was removed, and the liver was re-immersed in a 0-4℃ UW solution.

OUTCOME AND FOLLOW-UP

During the liver transplantation procedure, the right accessory hepatic artery originating from the superior mesenteric artery of the donor liver was anastomosed end to end with the gastroduodenal artery of the donor liver, and the left gastric artery was ligation after sending out the left accessory hepatic artery. This treatment ensured the blood supply of the left hepatic artery, right hepatic artery, left accessory hepatic artery, and right accessory hepatic artery simultaneously. Once implanted into the recipient, the blood flow at the proximal end of the anastomosis was opened, and the

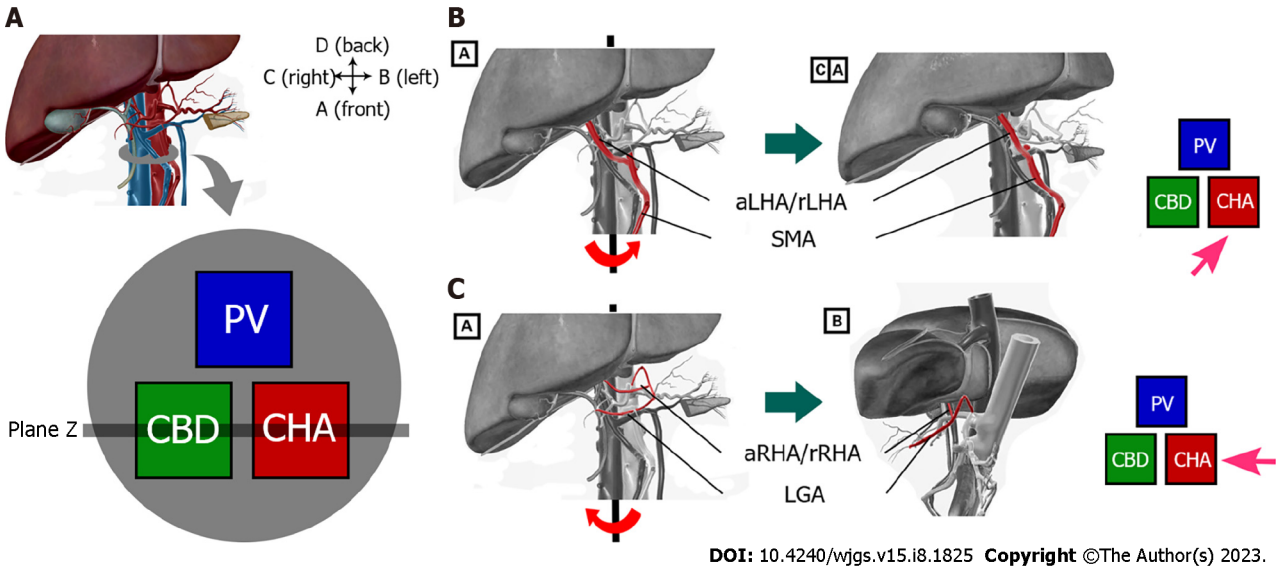

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Figure 1 The operating process of the new surgical protocol. A: Normal hepatic hilar anatomy and cross-sectional diagram. The position relationship between the common bile duct, the portal vein, and the proper hepatic artery is triangular, with the common bile duct located on the right front of the hepatic portal vein and the right side of the proper hepatic artery; B: Dissecting the variant right hepatic artery after rotating the liver counter clockwise; C: Dissecting the variant left hepatic artery after rotating the liver clockwise. aLHA: Accessory left hepatic artery; rLHA: Replaced left hepatic artery; aRHA: Accessory right hepatic artery; rRHA: Replaced right hepatic artery; SMA: Superior mesenteric artery; LGA: Left gastric artery.

anomalous hepatic artery was filled well without any evidence of arterial wall leakage. Intraoperative color Doppler ultrasound confirmed normal blood flow in the intrahepatic arteries, with a flow velocity of 43 cm/s [resistive index (RI):0.42] in the left hepatic artery, and a flow rate of 55 cm/s (RI: 0.54) in the right hepatic artery.

DISCUSSION

The preparation of the donor hepatic artery is a critical step in liver transplantation, and the incidence of hepatic artery injury is significantly higher in livers with abnormal arterial anatomy[6]. The traditional method of donor hepatic artery preparation is based on normal anatomy; however, in cases of variant hepatic artery anatomy, the preparation process can easily damage the surrounding normal tissues, such as arteries, common bile ducts, and portal veins. To address this limitation, we have developed a novel method for donor hepatic artery preparation based on human embryology. This approach involves preparing the artery to restore it to its embryonic anatomy, which significantly reduces the probability of injury to the variant hepatic artery.

During fetal development, paired ventral splanchnic arteries from each dorsal aorta supply the primitive gut and its derivatives. Later in development, these vessels are represented by three arterial trunks: the celiac trunk, superior mesenteric artery, and inferior mesenteric artery, which supply the foregut, midgut, and hindgut, respectively[15]. Approximately 5 wk after conception, the spleen, pancreas, stomach, and liver are situated in the sagittal plane of the embryo, and the arteries are nearly in the same two-dimensional plane, resulting in a relatively simple anatomy. However, in the 6th week after conception, the stomach, pancreas, spleen, and liver all begin to move clockwise to the left, and the blood vessels in the upper abdomen rotate to form a three-dimensional intricate network of blood vessels. The complexity and variation of the upper abdominal vascular system arise from the rotation and fusion of the gastrum during embryonic development.

In normal human anatomy, the hepatic pedicle is a structure within and outside of the first hepatic hilum that runs through the hepatoduodenal ligament. Within the hepatoduodenal ligament, the common bile duct, portal vein, and hepatic artery are positioned in a triangular relationship. The common bile duct was located to the right of the proper hepatic artery and in front of the portal vein (Figure 1A). By adjusting our understanding of the normal anatomy to the embryonic position in the 5th week (before rotation), we can simplify the complex three-dimensional relationship of the vessels into a two-dimensional plane, which greatly simplifies the relationship between the celiac artery and its surrounding tissues, and our understanding of donor hepatic artery preparation. In the anatomical position known as the 'Z plane' (Figure 2), variant hepatic arteries can only exist in this two-dimensional plane. Damage to the variant hepatic artery could be avoided by preparing the artery from top to bottom or from bottom to top in the Z-plane.

CONCLUSION

This case report presents a novel technique based on human embryology for preparing the donor hepatic arteries. This

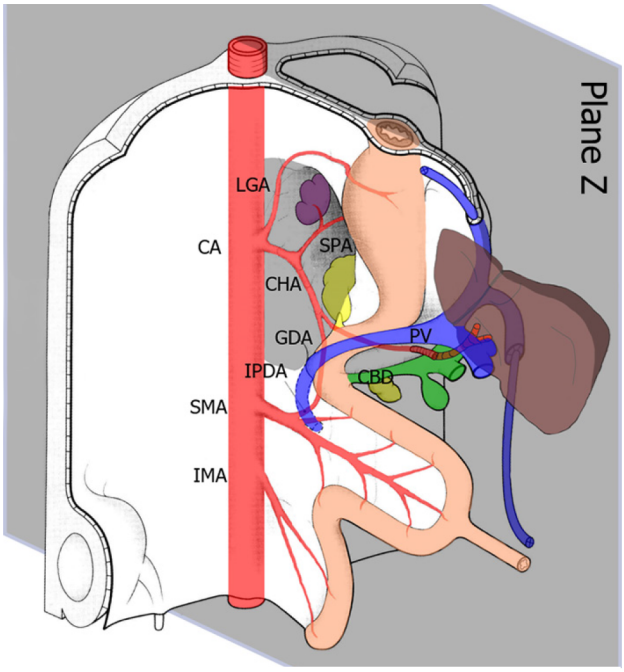

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Figure 2 Relationship between the hepatic artery and liver at 5 wk of embryo development. The grey area represents the position of the 'Z-plane', where the variant hepatic artery exists in a two-dimensional plane. CA: Celiac axis; LGA: Left gastric artery; SPA: Splenic artery; CHA: Common hepatic artery; GDA: Gastroduodenal artery; IPDA: Inferior pancreaticoduodenal artery; PV: Portal vein; CBD: Common bile duct; SMA: Superior mesenteric artery; IMA: Inferior mesenteric artery.

surgical approach has demonstrated efficacy in reducing the risk of intraoperative injury to both the normal and variant arteries.

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FOOTNOTES

Author contributions: All authors contributed to the study conception and design; Xu J conducted a strict review of the article and made a critical review of the content; Zhang HZ and Lu JH were responsible for the design of the subject and the writing of the article; Zhang R, Shi ZY, and Zhang AH were responsible for the implementation of the operation; Guo YR was responsible for the literature retrieval; Meng FX and Shao WH were responsible for the collection and interpretation of data; The first draft of the manuscript was written by Zhang HZ and all authors commented on previous versions of the manuscript; All authors read and approved the final manuscript.

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Country/Territory of origin: China

ORCID number: He-Zhao Zhang 0000-0002-9565-4298; Jun-Hui Lu 0000-0003-2387-5945; Rui Zhang 0000-0002-1078-1467; Jun Xu 0000-0003-3755-9660.

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CASE REPORT

Outpatient hybrid endoscopic submucosal dissection with SOUTEN for early gastric cancer, followed by endoscopic suturing of the mucosal defect: A case report

Renma Ito, Kazuhiro Miwa, Yutaka Matano

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Peer-review model: Single blind

Peer-review report's scientific quality classification

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Renma Ito, Kazuhiro Miwa, Yutaka Matano, Internal Medicine, Komatsu Municipal Hospital, Komatsu 923-0961, Japan

Corresponding author: Renma Ito, MD, Chief Doctor, Internal Medicine, Komatsu Municipal Hospital, 60 Mukaimotoorimachi-ho, Komatsu 923-0961, Japan. remma0504@outlook.jp

Abstract

BACKGROUND

Although endoscopic submucosal dissection (ESD) is becoming more common for early gastric cancer, it requires more advanced techniques and a longer treatment duration than endoscopic mucosal resection. Hybrid ESD using a multifunctional snare (SOUTEN) has been reported to be effective for colorectal lesions, as it can reduce treatment duration. Endoscopic suturing of post-ESD mucosal defects has been reported to reduce the incidence of ESD-related complications.

CASE SUMMARY

This study reports outpatient hybrid ESD for early gastric cancer using SOUTEN, followed by endoscopic suturing of post-ESD mucosal defects in an 86-year-old man. On referral for ESD, a 10-mm flat, depressed lesion was found on the posterior wall of the gastric antrum, the depth of which was expected to be mucosal. Given his history of delirium, we performed outpatient endoscopic treatment. The procedure used was hybrid ESD using SOUTEN to reduce the duration of treatment and endoscopic suturing of post-ESD mucosal ESD defects to reduce complications. The procedure time was 62 min and the lesion was completely resected based on histopathological examination, with no reported postoperative complications.

CONCLUSION

This safe and useful procedure may be especially important for outpatient endoscopic treatment.

Key Words: Outpatient treatment; Hybrid endoscopic submucosal dissection; Multifunctional snare; Early gastric cancer; Endoscopic suturing; Case report

Core Tip: Hybrid endoscopic submucosal dissection (ESD) using a multifunctional snare (SOUTEN) has been reported to be effective in reducing treatment duration, and endoscopic suturing of post-ESD mucosal defects has been reported to reduce complications. Herein, we report an outpatient hybrid ESD for early gastric cancer using SOUTEN, followed by endoscopic suturing of post-ESD mucosal defects in an 86-year-old male. The procedure time was 62 min and the lesion was completely resected based on histopathological examination, with no reported postoperative complications.

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INTRODUCTION

Endoscopic submucosal dissection (ESD) is becoming increasingly common for early gastric cancer[1]. ESD requires more advanced techniques and a longer duration of treatment than endoscopic mucosal resection and is potentially associated with more complications. Hybrid ESD performed with multifunctional snare (SOUTEN, Kaneka Medics, Tokyo, Japan) (Figure 1), has been reported to be clinically effective for endoscopic treatment of colorectal lesions and to reduce the duration of treatment[2-4]. Moreover, endoscopic suturing of post-ESD mucosal defects can reduce complications, such as bleeding and perforation[5-7].

Herein, we report a case of early gastric cancer in which outpatient hybrid ESD with SOUTEN was performed in an elderly man with a history of delirium during hospitalization, after which the mucosal defect was sutured endoscopically to reduce complications.

CASE PRESENTATION

Chief complaints

No complaints.

History of present illness

An 86-year-old male diagnosed with early gastric cancer confirmed by esophagogastroduodenoscopy and biopsy was referred to our hospital for ESD. The medical history included Alzheimer's disease, chronic kidney disease, and dyslipidemia.

History of past illness

The patient's past medical history was non-contributory.

Personal and family history

The patient had no family history of gastric cancer and was neither a smoker nor a drinker.

Physical examination

Physical examination did not reveal abnormalities and the Eastern Cooperative Oncology Group performance status score was 1, which was relatively good.

Laboratory examinations

Laboratory examination results were within the normal range.

Imaging examinations

Esophagogastroduodenoscopy revealed a 10-mm flat, depressed lesion on the posterior wall of the gastric antrum that was identified as a demarcation line and had an irregular microvascular pattern detected by magnifying endoscopy with narrow-band imaging (Figure 2). The lesion had already been diagnosed as gastric cancer on the basis of a biopsy performed in a previous hospital.

FINAL DIAGNOSIS

The lesion was believed to be mucosal; therefore, the diagnosis of early gastric cancer was further confirmed at our hospital, where ESD was deemed necessary.

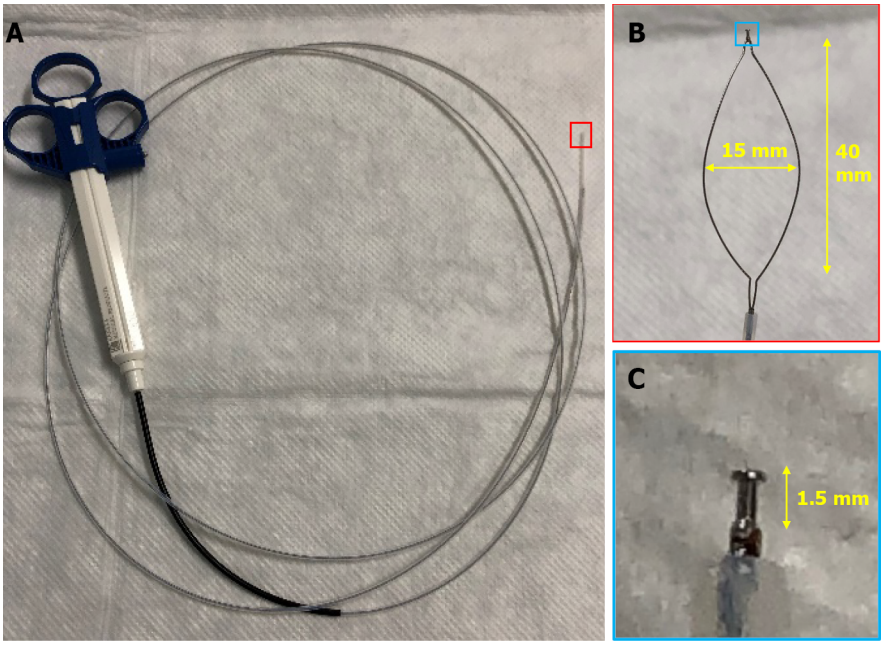

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Figure 1 Details of the SOUTEN device, a multifunctional snare. A: Full view of the SOUTEN device; B: The long diameter of the snare is 40 mm, and the short diameter of the snare is 15 mm; C: A 1.5-mm needle knife with a knob-shaped tip is attached to the top of the snare.

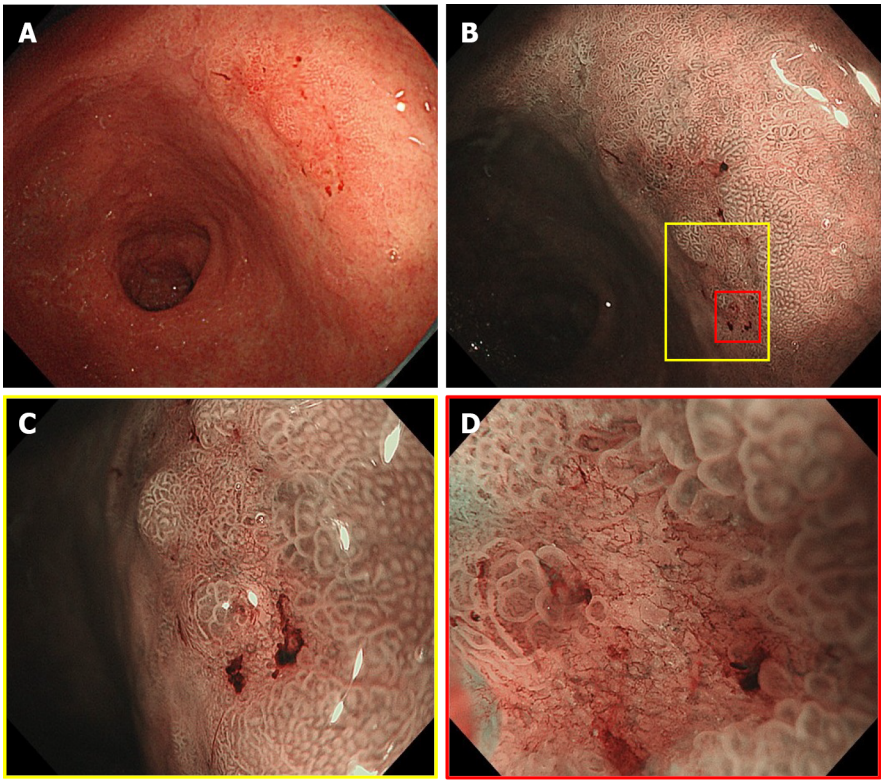

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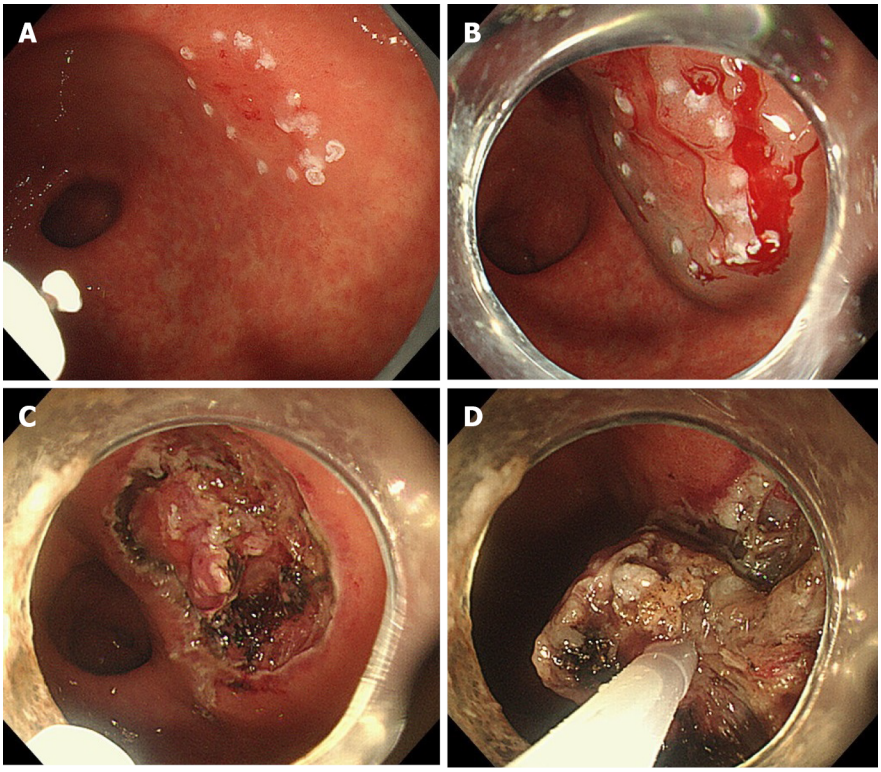
Figure 2 Endoscopic view of the 10-mm flat-depressed lesion on the posterior wall of the gastric antrum. A: Distant view of the lesion under white-light imaging; B: Non-expansion view of the lesion using magnifying endoscopy with narrow-band imaging; C: Weak-expansion view of the lesion using magnifying endoscopy with narrow-band imaging; D: Strong-expansion view of the lesion using magnifying endoscopy with narrow-band imaging.

TREATMENT

The patient was unaware of the early gastric cancer diagnosis due to the symptoms of Alzheimer's disease. The patient's family wanted him to undergo ESD; however, they refused hospitalization due to a history of delirium before admission.



DOI: 10.4240/wjgs.v15.i8.1831

Figure 3 Hybrid endoscopic submucosal dissection process with SOUTEN. A: A knife attached to the top of the snare is used to mark the lesion; B: A mixture of hyaluronic acid and saline is injected into the submucosa around the lesion; C: A knife attached to the top of the snare is used to dissect the submucosal around the lesion; D: Resection of the lesion with the snare.

Therefore, we planned outpatient hybrid ESD with SOUTEN to reduce the duration of treatment, followed by endoscopic suturing of the post-ESD mucosal defect to reduce complications. Informed consent was obtained from all patients and their families. The patient was administered vonoprazan (20 mg/d) for 8 wk from the day of ESD. We performed an outpatient hybrid ESD for early gastric cancer with SOUTEN (Figure 3) and endoscopically sutured the post-ESD mucosal defect using strings and clips (Figure 4). The procedure time was 62 min. We instructed the patient's family that the patient should only drink fluid on the day of outpatient ESD and eat soft food the next day. Regular meal consumption was resumed 1 wk after outpatient ESD.

OUTCOME AND FOLLOW-UP

No complications were observed, including delirium, and follow-up after the procedure was uneventful. Histopathological examination of the resected lesion revealed well-differentiated adenocarcinoma with mucosal depth and no lymphatic or vascular invasion. The margins were negative, indicating complete resection of the lesion. One month after outpatient ESD, esophagogastroduodenoscopy revealed that the ulcer had almost healed and only a part of the ulcer floor was visible (Figure 5).

DISCUSSION

To the best of our knowledge, this is the first report of outpatient hybrid ESD performed for early gastric cancer with SOUTEN and endoscopic suturing of a post-ESD mucosal defect. Treatment was successful and no complications were observed. Hybrid ESD has been reported to achieve a shorter procedure time than ESD with similar *en-bloc* resection rates and adverse events for colorectal lesions[8]. SOUTEN, a device specialized for hybrid ESD, is a multifunctional snare with two features (a high-frequency knife and a snare). Hybrid ESD with SOUTEN is clinically useful for the treatment of colorectal epithelial tumors[2-4]. However, for gastric lesions, it is useful to reduce endoscopic treatment time in basic research, not clinical research[9]. Although we have shown the clinical usefulness of hybrid ESD with SOUTEN for early gastric cancer in this case report, further research is recommended to elucidate its clinical application in gastric lesions.

We believe that hybrid ESD with SOUTEN and endoscopic suturing is advantageous for smaller lesions as in this case, but disadvantageous for large lesions because snaring and suturing large lesions is difficult. Additionally, such treatment might be more difficult for gastric lesions than colorectal lesions because snaring is difficult in some parts such as the

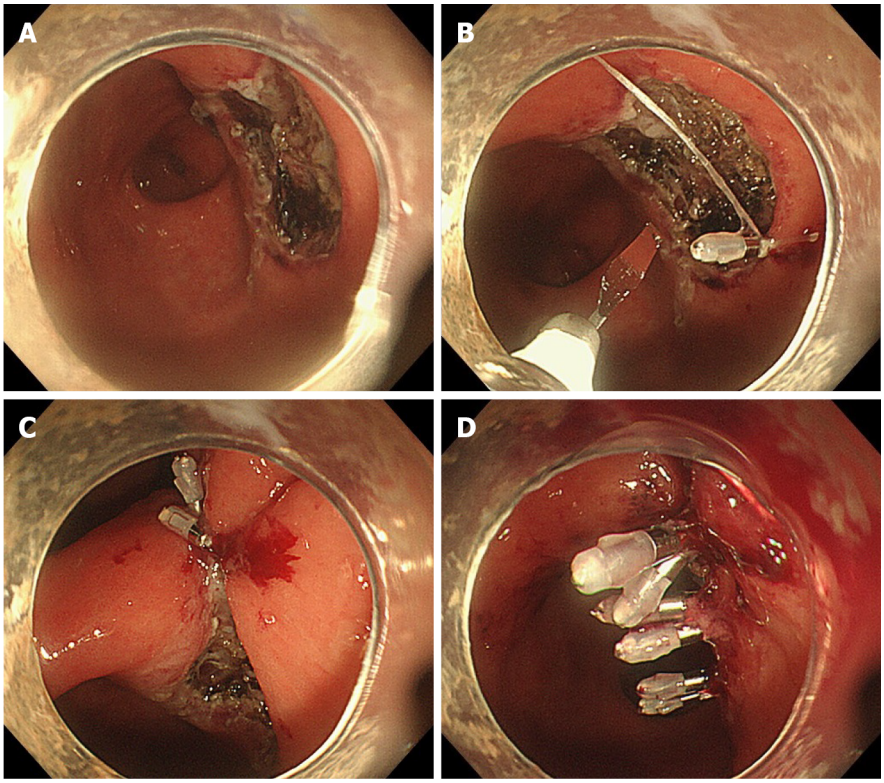


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Figure 4 Endoscopic suturing process for a mucosal defect after endoscopic submucosal dissection. A: Post-endoscopic submucosal dissection mucosal defect in the posterior wall of the gastric antrum; B: A clip with a string attached to the tip is first attached to the anal aspect of the mucosal defect, and an additional clip is attached to the oral aspect of the mucosal defect while sandwiching the string; C: Bring both ends of the mucosa closer by pulling the string out of the mouth; D: Suturing the mucosal defect completely by attaching additional clips to both sides of the mucosal defect and finally burning off the string with the knife of SOUTEN.

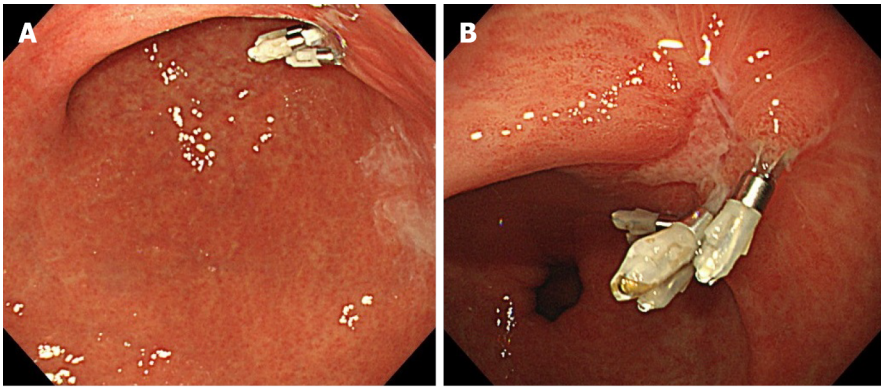

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Figure 5 Endoscopic view of the ulcer one month after endoscopic submucosal dissection. A: Distant view of the ulcer; B: Close-up view of the ulcer.

angle in the stomach.

The post-ESD mucosal defect was sutured endoscopically to reduce post-ESD bleeding[6] and prevent perforation[7]. In a previous report on gastric ESD, perforation occurred in 2.8% of patients and delayed bleeding that required endoscopic hemostasis occurred in 6.2%[10]. Endoscopic suturing of mucosal defects after ESD may prevent these complications. Therefore, it is desirable to endoscopically suture mucosal defects after ESD to reduce the occurrence of complications, particularly when performing outpatient ESD. Although there are some ways to suture mucosal defects using endoscopy, we believe that endoscopic suturing using a clip with a string[11] is simple and useful; therefore, we sutured the mucosal defects using this method.

Although the usefulness and safety of outpatient ESD for gastric lesions has been reported, some complications centered on delayed bleeding occurred in 1.9%-5.7%[12,13]. We believe that minimizing the occurrence of complications during outpatient ESD is important. Therefore, we used vonoprazan, which has been reported to prevent bleeding from

ED-induced gastric ulcers[14]. Endoscopic suturing of the mucosal defect and the use of vonoprazan for ESD-induced gastric ulcers might be important in reducing complications in outpatient ESD.

We performed endoscopic treatment for early gastric cancer in an 86-year-old patient. The treatment of cancer in elderly patients is challenging because it is unclear whether these patients have a positive prognosis. Furthermore, elderly people are prone to developing delirium during hospitalization. Although the patient experienced psychological problems in the present case, his physical condition was relatively good. Outpatient ESD is useful for treating early gastric cancer and preventing delirium in elderly patients. We believe that endoscopic treatment for early gastric cancer in elderly patients with good physical status is beneficial and that outpatient endoscopic treatment is especially useful for elderly patients.

CONCLUSION

Outpatient hybrid ESD for early gastric cancer using SOUTEN followed by endoscopic suturing of post-ESD mucosal defects was safe and useful. This may be particularly important for outpatient endoscopic treatment.

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FOOTNOTES

Author contributions: Ito R, Miwa K, and Matano Y conceived the idea of the treatment in this case; Ito R drafted the original manuscript; all authors reviewed the manuscript draft and revised it critically.

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

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Country/Territory of origin: Japan

ORCID number: Renma Ito 0000-0001-7706-166X; Kazuhiro Miwa 0000-0002-5486-9137; Yutaka Matano 0000-0003-4933-5381.

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LETTER TO THE EDITOR

Is endoscopic mucosal resection-precutting superior to conventional methods for removing sessile colorectal polyps?

Qun-Ying Yang, Qian Zhao, Jian-Wen Hu

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Qun-Ying Yang, Qian Zhao, Jian-Wen Hu, Department of Gastroenterology, Dongyang People's Hospital, Dongyang 322100, Zhejiang Province, China

Corresponding author: Jian-Wen Hu, PhD, Professor, Department of Gastroenterology, Dongyang People's Hospital, No. 60 Wuning West Road, Dongyang 322100, Zhejiang Province, China. cchcsq0529@163.com

Abstract

We reviewed a study that reported a comparative analysis of the effects of endoscopic mucosal resection (EMR) precutting and conventional EMR for removing non-pedunculated, 10-20 mm sized colorectal polyps. We identified some statistical deficiencies in this study. In addition, we believe that the differences between the treatments failed to achieve significance, and therefore, further analysis is required.

Key Words: Comparative analysis; Endoscopic mucosal resection precutting; Endoscopic mucosal resection; Colorectal polyps

Core Tip: This is a comment on an article that reported whether endoscopic mucosal resection (EMR)-precutting (EMR-P) is superior to conventional EMR (CEMR) for removing sessile colorectal polyps. It was a randomised, prospective, multicentre study with high-quality evidence, but we think that some questions remain as to whether EMR-P is superior to CEMR.

Citation: Yang QY, Zhao Q, Hu JW. Is endoscopic mucosal resection-precutting superior to conventional methods for removing sessile colorectal polyps? *World J Gastrointest Surg* 2023; 15(8): 1838-1840

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TO THE EDITOR

The article published by Zhang *et al*[1] caught our attention particularly. In this article, a better method for removing sessile colorectal lesions sized 10-20 mm was investigated. They believed that endoscopic mucosal resection (EMR)-precutting (EMR-P) was a better treatment than the conventional EMR (CEMR). Despite the potential benefits of higher *en bloc* resection and lower recurrence rates, questions remain as to whether EMR-P can be used as an alternative to CEMR for the treatment of medium-sized colorectal polyps.

Commonly, all colorectal polyps are removed, except for rectosigmoid hyperplastic polyps that are ≤ 5 mm in size[2]. The ideal resection is completed or *en bloc* with a negative histologic margin, R0. The most effective way to remove sessile or laterally spreading lesions with a diameter of less than 10 mm is *via* EMR[3]. However, even by expert hands, colorectal polyps larger than 20 mm in size cannot be satisfactorily removed *en bloc* with EMR[4].

EMR with circumferential precutting (EMR-P) is a modification of the conventional EMR technique. To separate the tumor from non-neoplastic tissue, a circumferential mucosal incision is made using a snare tip[1]. Some studies have confirmed that EMR-P is more effective than CEMR in the treatment of large sessile colorectal tumours (> 20 mm in diameter)[5,6]. To date, only two studies have directly compared the efficiency of EMR-P and CEMR in the treatment of polyps sized 10-20 mm[1,7]. However, Yoshida *et al*[6,7] studied the difficult lesions < 20 mm in size, which were defined as lesions in special locations, with flat morphology, poor elevation by injection, and poor access according to the European Society of Gastrointestinal Endoscopy guidelines[8]. Thus, this study showed limited significance in tackling normal, non-pedunculated lesions.

In the study by Zhang *et al*[1], when removing polyps sized 10-20 mm, the EMR-P group showed a higher *en bloc* resection rate compared to the CEMR group in both intention-to-treat and per-protocol analyses. However, these differences were significant in the per-protocol analysis, whereas no significant differences were observed in the intention-to-treat analysis. We believe that certain statistical deficiencies and some questions warrant further attention. First, these two groups were labeled "EMR-P" in the Figure 2 (https://www.wjgnet.com/1007-9327/full/v28/i45/6397.htm). Was this due to a clerical error? Second, the authors mentioned that each group had three patients with pedunculated lesions were not included in the per-protocol analysis. However, one exclusion criterion was the presence of pedunculated lesions, so how were the patients initially included in the intention-to-treat analysis? The per-protocol analysis could have inflated the importance of the differences between the groups, which may not have been clinically meaningful. Therefore, can the results of the intention-to-treat analysis be considered more reliable in this study?

In conclusion, it is difficult to achieve *en bloc* resection by EMR for colorectal tumours which are ≥ 20 mm in size, but EMR is an effective technique for the removal and treatment of sessile polyps sized 10-20 mm. Although in comparison with EMR, PEMR can lead to a high *en bloc* resection rate, these were not significantly different, and therefore, further analysis is required.

FOOTNOTES

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Country/Territory of origin: China

ORCID number: Qun-Ying Yang 0000-0002-4196-440X; Qian Zhao 0000-0001-9173-3821; Jian-Wen Hu 0000-0002-6452-8790.

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