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REVIEW

Drain fluid biomarkers for prediction and diagnosis of clinically relevant postoperative pancreatic fistula: A narrative review

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Abstract

Clinically relevant postoperative pancreatic fistula (CR-POPF) has continued to compromise patient recovery post-pancreatectomy despite decades of research seeking to improve risk prediction and diagnosis. The current diagnostic criteria for CR-POPF requires elevated drain fluid amylase to present alongside POPF-related complications including infection, haemorrhage and organ failure. These worrying sequelae necessitate earlier and easily obtainable biomarkers capable of reflecting evolving CR-POPF. Drain fluid has recently emerged as a promising source of biomarkers as it is derived from the pancreas and hence, capable of reflecting its postoperative condition. The present review aims to summarise the current knowledge of CR-POPF drain fluid biomarkers and identify gaps in the field to invigorate future research in this critical area of clinical need. These findings may provide robust diagnostic alternatives for CR-POPF and hence, to clarify their clinical utility require further reports detailing their diagnostic and/or predictive accuracy.

Key Words: Biomarkers; Clinically relevant postoperative pancreatic fistula; Diagnosis; Drain fluid; Prediction

Core Tip: This review demonstrates the potential for drain fluid biomarkers to overcome the limitations of the current diagnostic definition of clinically relevant postoperative pancreatic fistula. Numerous future directions for drain fluid research have been identified, where ideally, new biomarkers would report the accuracy of surgery-specific, risk-stratified cut-offs to clarify their clinical utility. Hence, decisions regarding drain removal and further monitoring can accordingly be made to either expediate or make recovery safer respectively. These improvements will invariably bolster pancreatic ductal adenocarcinoma survival outcomes by tapering the high morbidity of pancreatectomies and ensuring better quality of life for patients.

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INTRODUCTION

Pancreatic cancer represents a grave diagnosis in which incidence closely parallels mortality[1]. Manifesting as adenocarcinomas, neuroendocrine tumors, acinar carcinomas, colloid carcinomas, pancreatoblastomas and solid-pseudopapillary neoplasms, pancreatic cancer is predicted to be the second most diagnosed cancer by 2030[2]. Both the challenges of early diagnosis and treatment contribute to its dismal prognosis, whereby its failure to manifest symptoms early and resistance to conventional treatments leaves surgery as the only curative option[3,4]. The greatest contributor to the burden of pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC) which occurs in 90% of cases and has the highest fatality rate of all solid tumors[3,5]. The majority of PDACs develop in the head of the pancreas (60%-70%) and require pancreaticoduodenectomy. The remainder arise in the body and tail (15% of cases each) which require a distal pancreatectomy to excise the tumor[6] (Figure 1). As only 20%-25% of PDAC patients are diagnosed with resectable disease, maximising their surgical outcomes is of utmost importance, particularly as 5-year survival can improve from < 7% without surgery[3] to 39% after surgery[7]. Necessarily, this involves minimising surgical complications, not only to improve recovery, but to avoid increasing the challenges of cancer which already include compromised nutrition, immunity, metabolism as well as mental and financial wellbeing[8-10]. Clinically relevant postoperative pancreatic fistula (CR-POPF) has persisted as the leading cause of postoperative morbidity and mortality despite decades of improving pancreatectomy techniques and perioperative care[11-15]. Affecting up to 50% of cases[16], CR-POPF has been shown to increase readmission rates, length of stay, health-related costs and particularly relevant for pancreatic cancer patients, potentiate recurrence and delay the delivery of adjuvant therapy, both of which can compromise the curative intent of surgery[17-22].

CR-POPF definition

POPF was initially stratified into grades A-C[23], with grade A since being reclassified by the International Study Group on Pancreatic Surgery (ISGPS) as a biochemical leak in favour of recognising the clinically relevant grades B and C[24]. CR-POPF is diagnosed once drain amylase on postoperative day (POD) three exceeds three times the upper limit of normal for serum amylase and the patient develops a clinically relevant change in their condition, necessitating intervention (Figure 2). Grade B fistulae are characterised by prolonged drainage exceeding three weeks, pharmaceutical interventions, additional imaging and infections. Grade C sequelae are more severe, potentiating sepsis, organ failure and in up to 35% of cases, death[25]. This definition does not require imaging to confirm a diagnosis of CR-POPF, particularly as intra-abdominal fluid collections may be transiently increased after surgery. Imaging, however, may be necessary for planning interventions in confirmed cases[26]. Recently, non-contrast-enhanced computed tomography paired with machine learning has been shown capable of evaluating pancreatic texture to predict CR-POPF, doing so with a sensitivity of 0.96 and specificity of 0.98[27]. Similarly, transabdominal pancreatic ultrasound elastography has been associated with CR-POPF, occurring more in patients with softer parenchyma (P = 0.002)[28].

Pathophysiology of CR-POPF: Pancreatic fistulae often occur in pancreata with preserved exocrine function in which pancreatic enzymes are released and activated, damaging tissues, and potentiating systemic complications. Such glands are characterised by soft texture and at least normal acinar cell density at the surgical margin, both of which have been associated with CR-POPF after pancreatoduodenectomy and distal pancreatectomy[29-33]. In advanced PDAC, obstructive pancreatitis may develop[34], contributing to a firm parenchyma. Recently, neoadjuvant therapy has been explored as a

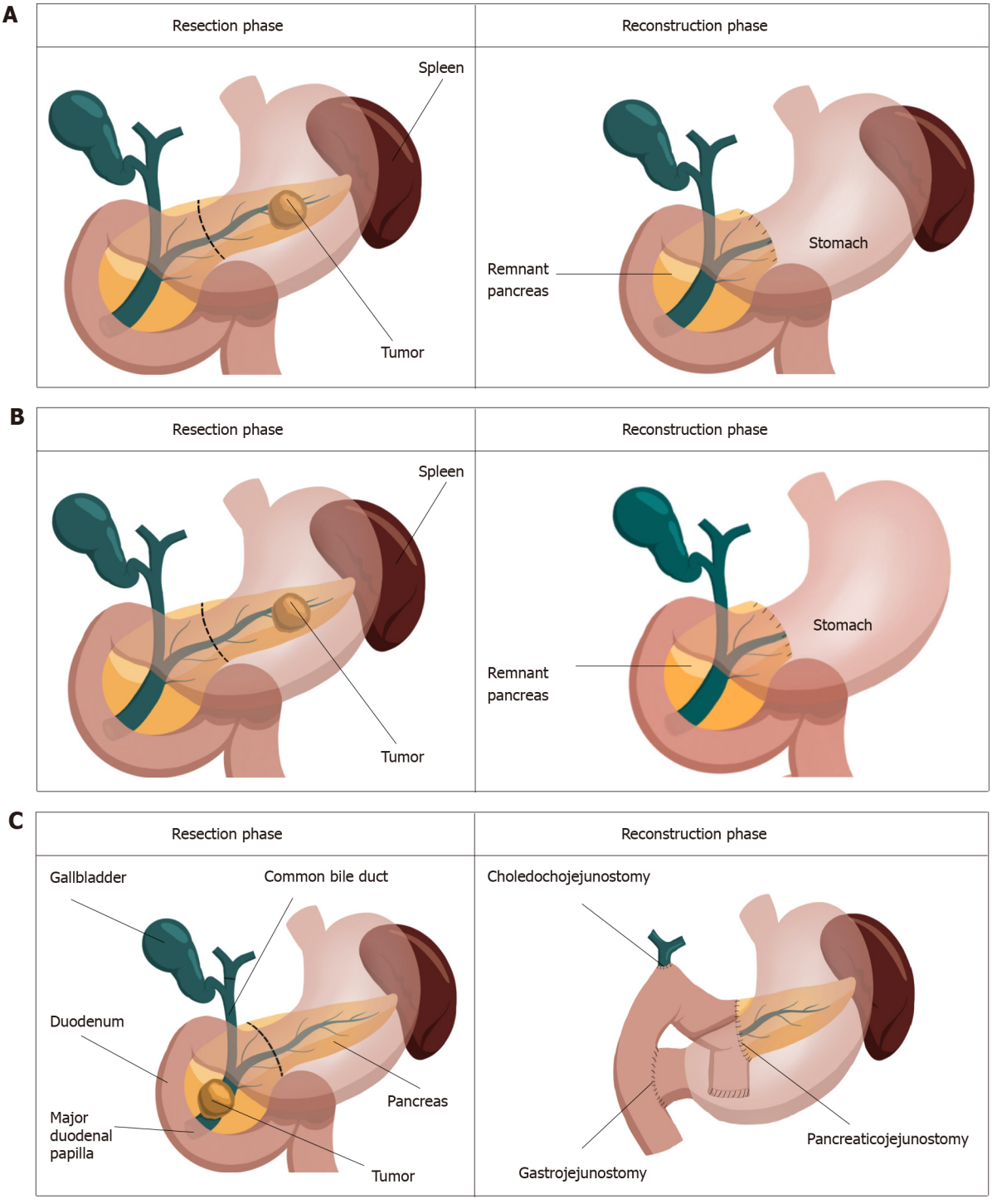

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Figure 1 Resection and reconstruction phases of different pancreatic surgeries. A: Resection and reconstruction phases of distal pancreatectomy, the spleen is preserved; B: Resection and reconstruction phases of distal pancreatectomy with splenectomy; C: Resection and reconstruction phases of pancreatoduodenectomy.

potential protector against CR-POPF[35], being shown to favour a more fibrotic and acinar-deplete parenchyma[36]. However, pancreatic texture has been shown to not predict CR-POPF after distal pancreatectomy[37], emphasising the clinical importance of the distinct risk profiles for both resection types.

CR-POPF can develop following the reconstruction phase of surgery (Figure 1). In pancreatoduodenectomy, fistula is often attributed to failure of the pancreatoenteric anastomosis whereby pancreatic fluid destined for the duodenum leaks into the abdomen[38]. Leakage can also occur from the gland itself, in what is referred to as a parenchymal leak[39]. In distal pancreatectomy, increased pressure in the pancreatic duct due to obstruction at the sphincter of Oddi has been thought to result in pancreatic

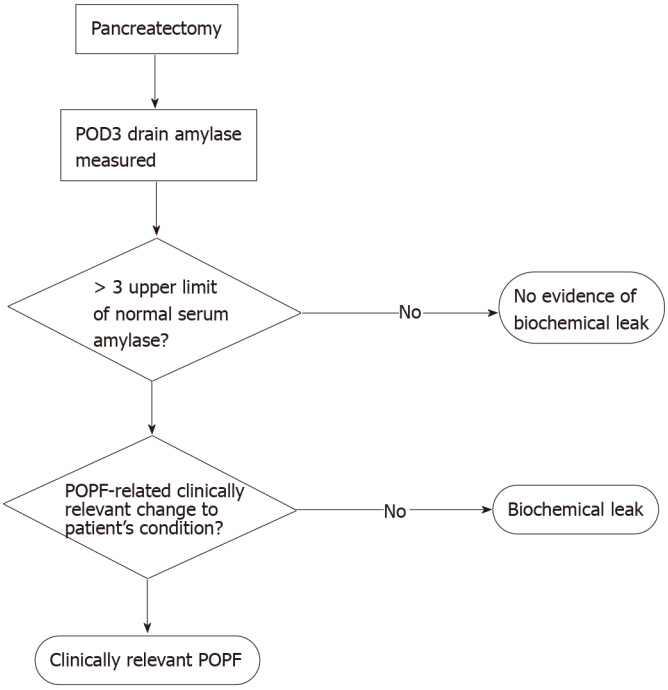

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Figure 2 Current standard pathway for the diagnosis of clinically relevant postoperative pancreatic fistula. POD: Postoperative day; POPF: Postoperative pancreatic fistula.

juice leakage[40,41]. As distal resections do not cause downstream obstruction of the pancreatic duct, they are not predisposed to leakage in the same way as pancreases after pancreatoduodenectomy. Splenic preservation has been seen effective in preventing CR-POPF, owing this to the avoidance of pancreatic ischemia secondary to splenic vessel ligation[42,43]. Indeed, the higher morbidity inherent to multi-visceral resection is avoided in spleen-preserving distal pancreatectomy. Moreover, the former facilitates shorter operative times, which may be advantageous given that operations exceeding 480 min were at greater risk of developing pancreatic fistula (P = 0.02)[44]. This finding however did not persist in pancreatoduodenectomy patients[31,45]. Whilst the location of the tumour matters in determining the surgical approach, the size of the tumour has not been shown to influence the development of CR-POPF in pancreatoduodenectomy patients[46] but has so in distal pancreatectomy patients undergoing staple closure (P = 0.009, univariate analysis)[47].

Drain biomarkers for CR-POPF: Predictive biomarkers have commonly been investigated in both drain fluid and blood. The operative placement of drains and close relationship of drain fluid to the pancreas highlights its potential as a convenient biofluid capable of reflecting CR-POPF risk. Hence, the present review synthesises all drain fluid biomarkers identified for the prediction and diagnosis of CR-POPF.

Drain amylase

Drain amylase has been extensively explored given its evaluation being embedded in the current diagnostic pathway (Figure 2). Where diagnostic cut-offs have been defined for drain amylase, many measures of accuracy beyond sensitivity and specificity have been reported[48-57] (Table 1). While postoperative evaluation of drain amylase are common, earlier assessments may represent a simple way to improve the utility of drain amylase observations. Particularly, intraoperative measures provide an immediate assessment of pancreatic exocrine function and hence, its propensity to secrete erosive enzymes and predispose the pancreas to leak and subsequent CR-POPF. Indeed, Nahm *et al*[32] reported a significant association between intraoperative amylase concentration and CR-POPF with an area under the receiver operating characteristic curve (AUC) of 0.76 (P = 0.004) in their cohort of 61 pancreatectomy patients. The accuracy of intraoperative amylase has also been evaluated in surgery-exclusive cohorts with de Reuver *et al*[58] reporting an AUC of 0.83 in their cohort of 62 pancreatoduodenectomy patients. Wang *et al*[59] investigated this time point in 40 distal pancreatectomy patients, obtaining a sensitivity and specificity of 0.846 and 0.889 respectively for a cut-off of > 3089 U/L. These studies indicate that the enzymatic leak which can catalyse the development of a CR-POPF begins at the time of surgery, presenting an opportunity to expediate the diagnostic pathway which currently begins on POD3.

To better facilitate earlier diagnosis of CR-POPF, the sensitivity and specificity of POD1 drain amylase has been widely reported with cut-offs ranging from 282 U/L - 5000U/L[34,49,60-79]. Beyond

Table 1 Drain amylase accuracy evaluated beyond sensitivity and specificity

Ref.	Cut-off (U/L)	Predictive Performance	Evaluated (POD)	Patients *n*	Surgery	CR-POPF (%)	Study design	Publication
Giovinazzo *et al* [48], 2018	350	AUC = 0.92	1	568	PD	NS	R	Abstract
Partelli *et al*[49], 2017	500	AUC = 0.881, OR = 21.72	1	463	PD	13.82	R	Abstract
Kerem *et al*[50], 2018	1363	AUC = 0.91	1	135	PD	13.33	R	Abstract
Kawai *et al*[51], 2009	5000	*P* = 0.1002 (univariate)	1	244	PD	28	R	Full paper
Teixeira *et al*[52], 2018	< 270 271-5000 > 5000	Higher median values statistically predicted CR-POPF	1	102	PD	25.5	P	Full paper
Mimura *et al*[53], 2012	2000	AUC = 0.81	1	240	PD	23.4	R	Abstract
Mimura *et al*[53], 2012	100	AUC = 0.86	5	240	PD	23.4	R	Abstract
Kawaida *et al*[54], 2018	860	*P* = 0.002 (univariate)	3	75	DP	9.3	P	Full paper
Recreo Baquedano *et al*[55], 2019	< 400	NPV = 0.968	3	278	PD	14	P	Abstract
Newhook *et al*[56], 2020	49	Sensitivity = 1	1	45	DP	24	P	Full paper
Newhook *et al*[56], 2020	26	Sensitivity = 1	3	45	DP	24	P	Full paper
van Dongen *et al* [57], 2021	100	Sensitivity = 1	2	285	PD	18.24	R	Abstract

POD: Postoperative day; AUC: Area under the receiver operating characteristic curve; OR: Odds ratio; CR-POPF: Clinically relevant postoperative pancreatic fistula; PD: Pancreatoduodenectomy; DP: Distal pancreatectomy; P: Prospective; R: Retrospective; NS: Not stated; NPV: Negative predictive value.

discrete cut-offs, Hiraki *et al*[80] found median drain amylase concentration in a prospective study of 30 pancreatoduodenectomy patients to have a sensitivity and specificity of 0.933 and 0.867 respectively. Moreover, Kühlbrey *et al*[81] found POD1 drain amylase to effectively predict CR-POPF after pancreatectomy returning AUCs of 0.829 ($P < 0.001$) and 0.637 ($P < 0.01$) for pancreatoduodenectomy and distal pancreatectomy respectively. This was corroborated by Wüster *et al*[82] who reported similar AUCs of 0.830 and 0.854 respectively. POD1 drain amylase concentrations have been noted as significantly higher in CR-POPF patients[32,83], correlated with CR-POPF following univariate analysis [84] and identified as an independent risk factor for CR-POPF after pancreatoduodenectomy[49,85-87]. In contrast, in a cohort of 74 pancreatectomy patients, no significant differences in POD1 drain amylase were found in patients who did and did not develop CR-POPF[88]. However, this study may have been underpowered as only nine (12.2%) patients developed CR-POPF.

The accuracy of POD2 drain amylase has been less explored with all reports evaluating pancreatoduodenectomy patients alongside POD1 drain[65,69] or serum amylase[57]. Sensitivity has been reported by two independent studies as 0.88, with the specificity of 0.83 in Ansorge *et al*'s work[69] surpassing Caputo's group's specificity of 0.74 when cut-offs of 314 U/L and 368 U/L were used respectively[65]. Odds ratios of 35 and 29 have further been reported in prospective studies[89,90]. While measuring on POD2 does allow greater time for the biochemical leak to develop thereby enhancing diagnostic accuracy, it does require a change to monitoring protocols which predominantly sample drain fluid on odd PODs (*e.g.*, POD1, POD3 or POD5). Moreover, this relatively unexamined timepoint reflects current preferences to either assess drain amylase early on POD1 or to abide by the recommended testing day of POD3.

The close relationship of POD3 amylase to the ISGPS definition has resulted in few explorations of its true diagnostic performance[24]. Following pancreatoduodenectomy, POD3 drain amylase has been noted to be significantly higher in CR-POPF patients[91]. Diagnostic cut-offs for POD3 drain amylase have ranged between 26 U/L and 1026 U/L for distal pancreatectomy cohorts[54,56,92,93], 93-2820 U/L

for pancreatoduodenectomy cohorts[55,56,83,84,94-99] and 200-3000 U/L in studies analysing the biomarker in pancreatectomy patients[16,56,75,100-103]. When cut-off accuracy was reported, sensitivity ranged from 0.316-1.00 and specificity, from 0.631-0.968[16,55,75,84,92,94-98,101-103], showing drain amylase alone does not completely include or exclude CR-POPF. This reinforces the importance of clinically relevant sequelae developing for accurate diagnosis as stipulated by the consensus definition [24]. POD4 drain amylase was found by Kosaka *et al*[104] to be significantly elevated in CR-POPF patients after pancreatoduodenectomy later defining a cut-off of 646 U/L as having an AUC of 0.87 [105]. After distal pancreatectomy, Suzumura *et al*[106] identified ≥ 1200 U/L as the predictive cut-off and Hiyoshi's group reported a sensitivity and specificity of 0.938 and 0.7 for a cut-off of ≥ 800 U/L [107]. POD5 drain amylase has been significantly correlated with CR-POPF post-pancreatoduodenectomy[108] where after distal pancreatectomy, a cut-off of > 1000 U/L was significantly associated with CR-POPF[109], with the cut-off of > 538 U/L by Coayla *et al*[98] predicting CR-POPF with a sensitivity and specificity of 0.86 and 0.91 respectively.

Median drain amylase levels post-pancreatoduodenectomy have been observed as significantly higher in CR-POPF patients[110] on POD1[52], POD2[57] and POD3[69]. Similarly, Moskovic *et al*[111] found median drain amylase concentration post-pancreatectomy to be significantly elevated on PODs 1-6 in CR-POPF patients. However, this offered no diagnostic advantage and given the wide day range, would prevent diagnosis on a designated day and limit early intervention. Both median and statistically derived cut-offs are limited in their ability to determine specific patient risk as they are summarised from entire patient cohorts which exhibit a spectrum of risk profiles.

Studies stratifying CR-POPF risk using drain amylase have been few and pancreatoduodenectomy exclusive. On POD1, Sutcliffe's group reported drain amylase < 2000 U/L excluded grade C POPF with a negative predictive value (NPV) of 0.99[112], whereas Caputo *et al*[113] found POD1 drain amylase ≥ 807 U/L to significantly predict grade C POPF with a sensitivity and specificity of 0.727 and 0.644 respectively. However, Chiba *et al*[114] did not find drain amylase to be a significant grade C POPF risk factor during the first postoperative week, owing this potentially to the difficulty of ensuring adequate pancreatic juice drainage post-operatively. Drain amylase was similarly examined by Li *et al*[115] to better identify low and high-risk patients. Here, a POD1 cut-off of 921.7 U/L (AUC = 0.85) had a sensitivity and specificity of 0.789 and 0.828 whereas their POD3 cut-off of 4021.5 U/L had overall higher accuracy favouring specificity at 0.954 (sensitivity = 0.778). In low-risk patients undergoing PD, Newhook *et al*[56] reported a POD1 cut-off of 661 U/L and POD3 cut-off of 141 U/L could completely exclude CR-POPF when drain amylase was below these levels (sensitivity = 1). Amongst high-risk PD patients, the POD1 and POD3 cut-offs to exclude CR-POPF were < 136 U/L and < 93 U/L respectively. Whilst these cut-offs ensure no false negative results, they may be rarely encountered and hence, rarely utilised. As such, clinicians may prefer higher cut-offs, compromising on sensitivity, to clarify the danger of higher amylase levels more likely to be encountered in clinical practice. These risk-stratified approaches are a welcome advance on previous reports which have predominantly derived predictive cut-offs from entire patient populations, limiting targeted risk prediction. Similar investigations should be conducted in distal pancreatectomy cohorts to define risk-specific cut-offs in these patients. As such, accounting for the operation, patient risk and corresponding predictive drain amylase levels will help refine CR-POPF diagnosis, ultimately decreasing complication rates.

The majority of drain amylase investigations have reported the biomarker at singular timepoints, with others considering its accuracy across multiple PODs. Tzedakis' group found in their cohort of pancreatectomy patients that drain amylase elevated beyond three times the upper limit of normal on POD1 and POD3 had a sensitivity of 0.974 and NPV of 0.971[101]. Similarly, Linnemann *et al*[116] reported a NPV of 0.95 in pancreatoduodenectomy patients with a peak drain amylase of 1000 U/L on PODs 1-3. These studies evidence a superior ability to exclude CR-POPF which may justify the additional monitoring of drain amylase which differs from the popular, singular day approach. Hence, early, and continued monitoring can strengthen the identification and selection of low-risk patients for accelerated recovery pathways. In pancreatoduodenectomy cohorts, numerous reports have investigated changes in drain amylase across the postoperative period. This measure possesses the potential to reflect existing and imminent CR-POPF risk. Dugalic *et al*[110] reported a moderate decline of < 50% between POD 1 and POD3 to be significantly associated with CR-POPF. Seemingly supporting these findings, Koizumi *et al*[117] found a notable decrease in drain amylase between POD1 and POD5 in patients without CR-POPF. This suggests the relative persistence of elevated drain amylase may be predictive of CR-POPF, a finding which corroborates reports of drain amylase being significantly elevated in CR-POPF patients during this time period[118,119]. However, Furukawa *et al*[120] identified a decline of pancreatic amylase of greater than 80% between POD1 and POD3 to be predictive of CR-POPF after pancreatoduodenectomy. Further into the postoperative period, Kuhara *et al*[121] appear to support this in identifying a decrease in drain POD5 amylase to a third of the POD3 level to be a significant risk factor for CR-POPF. To bolster day-specific tracing of CR-POPF risk, future studies should clarify these discrepancies and quantify the drain amylase changes that would indicate impending CR-POPF. Similar investigations in distal pancreatectomy cohorts are also warranted. Nobuoka *et al*[122] evaluated CR-POPF risk by considering the product of drain amylase and volume. This combined variable was found to be significantly higher in CR-POPF patients on POD1 and POD7. Extending this, Okano *et al*[119] evaluated the product of drain amylase and volume on POD3 and

POD1 in ratio. Here, patients who did not develop CR-POPF had significantly lower values. Together, these indicate that involving drain volume in the assessment of CR-POPF risk may provide opposite findings to when drain amylase is exclusively evaluated, persisting at elevated levels and potentially decreasing, respectively.

Drain lipase

Drain lipase has gained momentum as a potential accompaniment or replacement for drain amylase in diagnosing CR-POPF given its similar ability to capture the exocrine function of the remnant pancreas. Moreover, serum lipase assists in acute pancreatitis diagnosis[123,124], a postoperative complication which itself has been shown to independently predict CR-POPF[125,126]. Lipase drives intraperitoneal lipolysis which can exacerbate systemic inflammation and trigger multi-organ dysfunction specifically as the subsequent high systemic unsaturated fatty acid levels can cause mitochondrial toxicity[127], lipotoxicity[128] and kidney[129,130] or liver damage[131]. Diagnostic cut-offs have ranged from 4.88 U/L to 1000 U/L with the majority exploring both pancreatoduodenectomy and distal pancreatectomy patients[100-102,132]. However, pancreatoduodenectomy[97] and distal pancreatectomy[107] exclusive studies have also been conducted. Amongst these reports, the sensitivity and specificity has ranged from 0.8-0.938 and 0.649-0.95, respectively[97,100-102,107,132]. Suzuki *et al*[133] reported POD1 drain lipase levels to be an independent risk factor for CR-POPF (P = 0.037). Tzedakis *et al*[101] further considered the evolution of drain lipase and its relation to CR-POPF risk with sustained elevation of drain lipase across POD1 and POD3 having a sensitivity of 0.948 which was then confirmed in their validation cohort.

In the way of risk stratification, Frymerman *et al*[134] identified the combination of elevated POD3 and POD5 drain lipase (> 5000 U/L) and soft pancreatic texture to be predictive of grade C fistula. As this combination includes the most widely reported risk factor for CR-POPF, soft parenchyma, the contribution of elevated drain lipase to overall grade C risk remains unclear. Hence, drain lipase-exclusive risk stratification requires further investigation particularly during the early postoperative period as the majority of the aforementioned studies evaluated drain lipase on or after POD3.

Drain culture

The extent and character of drain fluid infection has been explored in surgery-specific and all-inclusive analyses of CR-POPF patients (Table 2). Pancreatoduodenectomy has been more extensively explored, with infection of the ascitic fluid and surgical site potentially explained by preoperative bile duct infection[135,136]. Moreover, the construction of the gastrointestinal anastomosis exposes the pancreas to the densely colonised duodenum and jejunum, causing intra-abdominal translocation of species that is further facilitated by bile and pancreatic outflow[137].

Investigations in pancreatoduodenectomy cohorts: A significantly higher prevalence of CR-POPF in pancreatoduodenectomy patients with positive drain culture has been widely reported[138-144], where internal and preoperative biliary drainage, elevated drain amylase, combined colectomy and a longer duration of surgery have been identified as significant risk factors for contaminated drain fluid[140,145].

Kimura *et al*[146] identified contaminated drain fluid on POD1 and POD3 to be an independent risk factor for CR-POPF which has since been corroborated in the early postoperative period PODs 1-3[139], POD1[147,148] and POD3[142,149]. The accuracy of POD1 drain culture was reported by Hata *et al*[145] as having a sensitivity of 0.45 and specificity of 0.813 resulting in a positive predictive value (PPV) of 0.479, with specificity (0.99) similarly prevailing over sensitivity (0.32) in Morimoto *et al*'s analysis of POD3 drain fluid smear tests which reported a superior PPV of 0.89[142].

The great diversity of microorganisms in post-pancreatoduodenectomy drain fluid is evident in the wide identification of *Enterococcus*[137-139,141,148,150-153], *Enterobacter*[138,141,148,151,152], *Pseudomonas*[151,153,154], *Klebsiella*[137,153], Methicillin-resistant *Staphylococcus aureus*[153], *Candida*[150,151], *Citrobacter* and *Escherichia coli* (*E. coli*)[137,155]. Yang *et al*[139] identified fungi, *Staphylococcus*, *Enterococcus*, *Pseudomonas*, *Acinetobacter*, *Stenotrophomonas*, *E. coli* and *Klebsiella* significantly more often in their CR-POPF patients. *E. coli* has specifically been implicated in bacterobilia whereby its colonisation of the bile stent has been significantly associated with grade C POPF (P = 0.028, odds ratio = 4.07)[156].

During the first postoperative week, Chiba *et al*[114] found gram-positive bacteria to predominate in grade B POPF patients while gram-negative rods were identified an independent predictor for grade C fistula. As McMillan's group isolated gram-negative organisms more commonly than gram positive (78.3% *vs* 68.1% respectively)[157], this could indicate that infections, being more commonly comprised of high-risk bacteria, predispose patients to more severe POPF. Indeed, Yamashita *et al*[154] isolated *Pseudomonas aeruginosa* exclusively in CR-POPF patients and identified the bacteria as the source of proteases which activated trypsin from trypsinogen. Belmouhand's group corroborated this latter finding and further identified drain *Enterobacter cloacae* as a source of trypsin-activating proteases thereby contextualising the role of gram-negative rods in CR-POPF development[150].

Nagakawa *et al*[141] found the bacteria detected on POD1 and POD3 to be similar in CR-POPF patients. This taken with the consistent number of non-intestinal bacterium observed on POD3 and POD7 highlights an opportunity for early risk assessment on POD3 as clinicians could anticipate a CR-

Table 2 Investigations of drain culture across different pancreatic surgery cohorts

Clinical condition	Pancreatoduodenectomy patients	Distal pancreatectomy patients
Present in CR-POPF patients	Fungi, gram-positive bacteria, *Acinetobacter*, *Stenotrophomonas*, *Citrobacter spp*, *Staphylococcus*, *Enterococcus*, *Enterococcus faecalis Candida spp.*, *Klebsiella*, *Klebsiella pneumoniae*, *Pseudomonas*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Enterobacter cloacae*	Fungi, *Staphylococcus*, *Enterococcus*, *Pseudomonas*, *Acinetobacter*, *Stenotrophomonas*, *Escherichia coli and Klebsiella spp*
Predictor of CR-POPF	Polymicrobial infections, *Candida*	
Predictor of grade C	Gram-negative rods, *Candida*	

CR-POPF: Clinically relevant postoperative pancreatic fistula.

POPF diagnosis when diagnostic bacteria are first detected[149]. Hence, the concurrent assessment of drain culture alongside POD3 drain amylase may assist earlier CR-POPF diagnosis, potentially reducing the reliance on complication development as is stipulated by the current consensus definition. Hence, patient safety will be increased as despite developing CR-POPF, patients will not have to endure challenging sequelae prior to diagnosis.

Beyond individual microorganisms, Demir *et al*[158] reported patients presenting with both CR-POPF and positive drain culture had significantly more polymicrobial infections with De Pastena's group noting the number of CR-POPF patients with polymicrobial infections to be significantly higher than those with biochemical leak (P = 0.003)[159]. The prevalence of polymicrobial infections in CR-POPF patients has ranged from 0.478-0.681, however their association with the complication has not been noted[157,159,160]. Belmouhand's group did not find polymicrobial drain fluid infections to be associated with anastomosis leakage[150], neither did Maatman *et al*[161] find this for any postoperative complication.

Rather than investigating polymicrobial infections as a risk factor for CR-POPF, risk stratification would be best assisted by the specific identification of problematic bacteria within polymicrobial drain fluid samples. Hence, an exploration of microorganisms associated with CR-POPF naturally assists in this. Abe *et al*[162] reported *Candida* to be significantly associated with CR-POPF and an independent risk factor for grade C fistulae (P = 0.043) which supported McMillan *et al*'s findings where *Candida* was found in 87.3% of grade C cases for which microbiological data was available[157]. Here, *Enterococcus* and *Staphylococcus* were also detected, conflicting later findings by Belmouhand's group who reported no significant difference in the severity of POPF when drain fluid was similarly contaminated[150]. The commonly identified *Enterococcus* and *Enterobacter* species have been detected on POD1[146] and proposed to originate from bile[140]. Abe *et al*[162] detected *Enterococcus* and *Enterobacter* species in drain fluid with Yamashita *et al*[138] specifically identifying *Enterococcus faecalis* and *Enterobacter cloacae* as precipitating CR-POPF. Interestingly, McMillan *et al*[157] found mortality to be significantly lower in patients with *Enterobacter* positive cultures despite it being widely identified in the drain fluid of CR-POPF patients. The inconclusive relevance of *Enterobacter, Enterococcus* and *Staphylococcus* to CR-POPF risk and concurrent identification of *Candida* in drain fluid confirms the findings of *Candida* as characteristic of polymicrobial infections[150] and more likely to appear in grade C POPF[162].

Investigations in distal pancreatectomy cohorts: Similar to pancreatoduodenectomy studies, distal pancreatectomy patients with positive drain culture have been associated with significantly higher rates of CR-POPF[163,164] with positive drain culture being an independent risk factor for the complication before POD3[165] and on POD4[166]. However, abdominal infection was not found to be a risk factor for CR-POPF by Sato *et al*[167] in their cohort of 49 patients which may have been underpowered. Yang *et al*[165] identified *Staphylococcus*, *Enterococcus*, *Pseudomonas*, *Acinetobacter*, *Stenotrophomonas*, *E. coli* and *Klebsiella spp* significantly more often in their CR-POPF patients. Here, 74.2% of patients contaminated with *Staphylococcus* and 92.9% of patients with *Klebsiella* subsequently developed CR-POPF. Loos *et al*[137] similarly identified *Staphylococcus spp.* and *Enterococcus spp.* most frequently in the drain fluid of CR-POPF patients. Harino *et al*[163] found *Staphylococcus* numbers to increase in patients when drains were removed after POD5, with Yang's group reporting rapid increases in positive drain culture when drains remained between POD3 and POD7 with a prevalence of 21.6% and 73.3% respectively[165]. Hence, earlier drain removal may assist in curbing the growth of bacteria and its subsequent role in CR-POPF development.

Yang *et al*[165] also found fungi to be isolated significantly more often in distal pancreatectomy patients who developed CR-POPF, while Abe *et al*[162] noted the absence of *Candida* which contrasted findings after pancreatoduodenectomy. Hence, the distinct drain culture portfolios following each resection type facilitate the identification of specific high-risk bacteria, the predictive potential of which would be enhanced by identifying the day of earliest detection and strongest association with CR-POPF. Moreover, it should be investigated whether mere presence of certain bacteria is predictive of CR-POPF

Table 3 Recommendations for future research

Drain biomarker	To investigate	To confirm
Amylase	Accuracy of intraoperative predictive cut-offs in pancreatoduodenectomy patients	Diagnostic accuracy of proposed cut-offs
	Accuracy of POD2 cut-offs in distal pancreatectomy patients	The change in postoperative drain amylase required to be predictive of CR-POPF in pancreatoduodenectomy patients
	Accuracy of POD4 cut-offs in surgery specific cohorts	If a persistently high value for drain amylase x drain volume postoperatively is predictive of CR-POPF
	Accuracy of risk-stratified cut-offs in distal pancreatectomy patients	
	The change in postoperative drain amylase required to be predictive of CR-POPF in distal pancreatectomy patients	
	When drain amylase has the highest predictive accuracy	
Lipase	The change in postoperative drain lipase required to be predictive of CR-POPF in surgery specific cohorts and its accuracy	Diagnostic accuracy of proposed cut-offs
	The accuracy of predictive cut-offs before POD3 in surgery specific cohorts	Diagnostic value of drain lipase in multi-factorial predictive models
	Accuracy of risk-stratified cut-offs in surgery specific cohorts	When drain amylase has the highest predictive accuracy
Drain culture	Bacteria within polymicrobial drain fluid samples which predict grade B and C POPF in surgery specific cohorts	Clinical relevance of *Enterobacter, Enterococcus* and *Staphylococcus* to CR-POPF risk in pancreatoduodenectomy patients
	When particular microorganisms are most predictive of CR-POPF	
	The concentrations of high-risk bacteria that accurately predict CR-POPF in surgery specific cohorts	
Other biomolecules	Accuracy of predictive cut-offs for each biomarker in surgery specific cohorts	
	Accuracy of novel enzymes compared to drain amylase and lipase in matched surgical cohorts and PODs	
Fluid appearance	Accuracy on specific days before POD3	

POD: Postoperative day; CR-POPF: Clinically relevant postoperative pancreatic fistula.

or if there is a level at which risk is higher. Here, additional understanding of the time course for bacterial growth would assist close monitoring of colony numbers to facilitate better complication anticipation and prevention.

Miscellaneous drain biomarkers

Other biomolecules: Drain lipase activity has been indirectly explored through alternate biomarkers for CR-POPF. Indeed, POD1 drain glycerol (> 800 μmol/L) has been associated with CR-POPF after pancreatoduodenectomy[168]. Similarly, drain free fatty acid has been significantly associated with CR-POPF. In an ensuing rat model, intraperitoneal lipolysis resulted in greater pancreatic juice leakage which risks CR-POPF by eroding the parenchyma and irritating acute pancreatitis[131]. Being products of lipolysis, drain glycerol and free fatty acids could serve as surrogate biomarkers for drain lipase, and hence CR-POPF. To effectively compare the predictive performance of these newer biomarkers however, a better understanding of their accuracy is required. To determine their clinical utility, their accuracy should also be compared against drain amylase and lipase.

Further, trypsin activation peptide (TAP) as a surrogate measure for protease activation has been explored. Xiu *et al*[169] found the TAP to drain amylase ratio in pancreatoduodenectomy patients to be significantly higher in CR-POPF patients, with this predictive measure being significantly higher when compared to distal pancreatectomy and biochemical leak patients. Wüster's group identified TAP and chymotrypsin elevation to be uniquely associated with distal pancreatectomy and pancreatoduodenectomy CR-POPF patients, respectively[82]. Irrespective of resection type, myeloperoxidase and trypsin activity were significantly elevated on PODs 1-2 and PODs 1-7, respectively. However, amongst the CR-POPF patients, elastase was not found to be significantly associated with the complication[82]. Ansorge *et al*[168] identified a significantly higher intraperitoneal lactate to pyruvate ratio in CR-POPF patients which increased significantly between POD1 and POD2 due to increased lactate and decreased pyruvate, thereby implicating metabolic disruption in the pathophysiology of CR-POPF. Hence, these emerging biomarkers may offer new opportunities for bolstering CR-POPF prediction particularly if

combined with established risk factors in future predictive models.

Drain fluid appearance: Observations of "sinister" drain effluent are often relied upon to inform an assessment of CR-POPF risk[76] and were a criteria of the initial consensus definition[23]. Abnormal drain fluid can be brown, green, milky or unusually clear[65]. Non-serous fluid following pancreatoduodenectomy has been independently associated with CR-POPF on POD1, POD3 and POD4[170]. However, Kosaka *et al*[105] did not find drain fluid colour to significantly differ between CR-POPF and non-CR-POPF pancreatoduodenectomy patients on POD4 on multivariate analysis agreeing with Suzumura *et al*'s findings following distal pancreatectomy[106]. Drain turbidity has been significantly correlated with drain fluid amylase on POD5 and beyond[108], suggesting its early observation could anticipate later development of CR-POPF.

CONCLUSION

This review revealed the potential for drain fluid biomarkers to overcome the limitations of the current diagnostic definition which necessitates a reactive management approach[24]. Numerous future directions for drain fluid research include investigating and confirming the accuracy of drain biomarkers in novel and established contexts respectively (Table 3). Through this, reports of biomarkers can specifically detail the accuracy of surgery-specific, risk-stratified cut-offs to clarify their clinical utility. Hence, decisions regarding drain removal and further monitoring can accordingly be made to either expediate or protect patient recovery respectively. Clarifying the clinical utility of drain biomarkers, could also facilitate their inclusion as variables in predictive models alongside blood biomarkers and medical imaging. This would complement recent efforts in which predictive models have sought to improve and expediate diagnosis when compared to the evaluation of individual variables[171-173]. As such, progress can continue to be made towards risk-stratifying patients according to pre- and intra-operative variables.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Performing robot-assisted pylorus and vagus nerve-preserving gastrectomy for early gastric cancer: A case series of initial experience

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Abstract

BACKGROUND

Pylorus and vagus nerve-preserving gastrectomy (PPG) is a function-preserving surgery for early gastric cancer (GC) that has gained considerable interest in the recent years. The operative technique performed using the Da Vinci Xi robot system is considered ideal for open and laparoscopic surgery.

AIM

To introduce Da Vinci Xi robot-assisted PPG (RAPPG)-based operative procedure and technical points as well as report the initial experience based on the clinical pathology data of eight cases of early GC.

METHODS

Da Vinci Xi robot-assisted pylorus and vagus nerve-preserving gastrectomy (RAPPG) was performed for 11 consecutive patients with middle GC from December 2020 to July 2021. Outcome measures were postoperative morbidity, operative time, blood loss, number of lymph nodes harvested, postoperative hospital stay, time to first flatus, time to diet, and resection margins.

RESULTS

Eight of the 11 patients who were pathologically diagnosed with early GC were enrolled in a retrospective study to assess the feasibility and safety of RAPPG. The mean operative time, mean blood loss, mean number of lymph nodes harvested, length of preserved pylorus canal, distal margin, and proximal margin were 330.63 ± 47.24 min, 57.50 ± 37.70 mL, 18.63 ± 10.57, 3.63 ± 0.88 cm, 3.50 ± 1.31 cm, and 3.63 ± 1.19 cm, respectively. None of the cases required conversion to laparotomy. Postoperative complications occurred in two (25.0%) patients. Post-operative complications were hyperamylasemia and gastric stasis in one case and

incision infection in the other. Time to first flatus was 3.75 ± 2.49 d after the operation, and postoperative hospital stay was 10.13 ± 4.55 d.

CONCLUSION

The core technique in the Da Vinci Xi RAPPG is lymph node dissection and the anatomic method of the nerve. Robotic surgical procedures are feasible and safe. With the progress of surgical technology, optimization of medical insurance structure, and emergence of evidence-based medicine, automated surgery systems will have a broad application in clinical treatment.

Key Words: Da Vinci robotic surgery system; Gastric carcinoma; Vagus nerve; Pylorus; Gastrectomy

Core Tip: The robotic surgery system is widely used in the surgical field. Pylorus and vagus nerve-preserving gastrectomy is a function-preserving surgery for early gastric cancer (GC). We introduced an robot-assisted pylorus and vagus nerve-preserving gastrectomy-based operative procedure and technical points as well as report the initial experience. We analyzed the the mean operative time, mean blood loss, mean number of lymph nodes harvested, length of preserved pylorus canal, distal margin, proximal margin, and postoperative complications of 8 patients with early GC. None of the cases required conversion to laparotomy. The main postoperative complications were hyperamylasemia and gastric stasis. These study results are preliminary, and on establishing a standard surgical treatment, large-sample, multicenter, and prospective clinical trial should be conducted.

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INTRODUCTION

Gastric cancer (GC) is the most frequent neoplastic diagnosis and the second most common cause of cancer-related deaths worldwide[1]. The incidence of early GC is increasing annually. Function-preserving surgery for GC has been gaining attention in recent years[2]. Pylorus and vagus nerve-preserving gastrectomy (PPG) as a function-preserving surgical treatment has gained gradual acceptance and promotion. Clinical studies have shown that PPG is a safer option with a better oncological prognosis than distal gastrectomy for managing early GC[3,4].

Moreover, PPG can reduce the incidence of cholelithiasis, diarrhea, and dumping syndrome. It is conducive to the recovery of nutritional indicators and body weight, reducing insulin secretion disorders[5]. Although laparoscopic techniques are improving, the "chopstick" effect caused by the parallel arrangement of the instruments in the umbilicus is considered an obstacle in delicate operations. The tremor filter, scale motions, three-dimensional imaging, and dexterous arm of the Da Vinci robot have advantages in localizing the anatomy of the nerves, vessels, and lymph nodes for clearly demarcated dissections. A meta-analysis evaluated the advantages of robotic gastrectomy (RG) *vs* laparoscopic gastrectomy (LG) for GC. The results showed that the operative time of RG was significantly shorter and the cost was relatively higher, but RG had advantages in increasing the number of retrieved lymph nodes and controlling intraoperative blood loss. Although there was no significant difference in overall complications, complications with Clavien–Dindo classification greater than grade 3 in RG were significantly lower than those in LG. Distal and proximal resection margin distance, conversion rate to open surgery, mortality rate, and recurrence rate were not significantly different between them[6]. Han *et al*[7] from South Korea first compared perioperative efficacy and oncologic safety between robot-assisted and laparoscopy-assisted pylorus-preserving gastrectomy in the treatment of middle-third early GC. The operative time of the robot-assisted pylorus-preserving gastrectomy was longer, but there was no significant difference in complications and the number of examined lymph nodes[7].

Experience showed that reasonable surgical process, close cooperation of the surgical team, rational use of energy equipment, and avoidance of surgical risks are key factors to ensure surgical quality. The purpose of this study was to introduce an robot-assisted pylorus and vagus nerve-preserving gastrectomy (RAPPG)-based operative procedure and technical points as well as report the initial experience based on the clinical pathology data of eight cases.

MATERIALS AND METHODS

After introducing the Da Vinci Xi robot system, RAPPG was performed for 11 consecutive patients with middle GC from December 2020 to July 2021. All patients were diagnosed with GC with gastroscopy and histological examination before surgery. Gastroscopy and upper gastrointestinal radiography were performed to locate the lesion. Complemented with computed tomography (CT) examination, nine patients with early middle GC with preoperative stage cT1N0 were treated with PPG according to the Japanese GC Treatment Guidelines 2018 (5th edition). One patient was preoperatively diagnosed with cT2N0 without enlarged lymph nodes in the superior pyloric region on CT. PPG was correspondingly performed upon indication due to the clinical assessment of tumor enlargement. Another patient was preoperatively diagnosed with cT4aN2M0. This patient's case was complicated with chronic obstructive pulmonary disease, and the patient had dyspnea after activity; ASA grade was 3. PPG was performed by a multi-disciplinary team as an extended indication. All patients' treatment protocols were formulated by preoperative discussion without ethical committee involvement. Before surgery, the procedure details were explained to all patients, and appropriate informed consent was obtained.

The inclusion criteria were as follows: (1) ECOG score ≤ 2 points; (2) Histologically confirmed adenocarcinoma (papillary adenocarcinoma, tubular adenocarcinoma, mucinous adenocarcinoma, signet ring cell carcinoma, poorly differentiated adenocarcinoma) with gastroscopic pathological biopsy before operation; (3) No group 1 and 5 lymph node metastasis on abdominal CT; (4) A distance of ≥4 cm from the distal end of the tumor to the pylorus on gastroscopy, abdominal CT, and upper gastrointestinal angiography; (5) Clinical stage of cT1a-1bN0M0 on transabdominal-enhanced CT (AJCC 8th Edition); and (6) Confirmation that the depth of tumor infiltration was limited to the mucosa or submucosa on postoperative pathology.

Operative technique

Patient and robot position and port placement: The patient's position, setting of the trocar puncture sheath, position of the assistant, and choice of the surgical approach play a role in surgical difficulty. R-PPG operation position: the patient was placed in the supine position, the head is held high at 15°, feet are maintained low at 15°, and the assistant is on the right side of the patient. The "Smile" layout was used for the punch card setting (Figure 1).

The coaxial axis was set as the line connecting the umbilicus to the splenic hilum. Arm 3 was used as the central operation hole, and the Maryland bipolar coagulation forceps, ultrasonic scalpel, and Hem-O-lock applier were used. Arm 1 could be inserted with proGrasp forceps and fenestrated bipolar coagulation forceps, whereas Arm 4 could only be inserted with proGrasp forceps. Arm 2 could be used as the endoscope hole (8 mm, 30 ° endoscope). The assistant used the right B hole (12 mm) to assist the operator in exposing the operation field using a Hem-O-lock, aspirator, electrocoagulation rod, and cutting closure device.

Exploration: The pneumoperitoneum was established, abdominal pressure was maintained at 12 mmHg, and the liver was suspended. Tumor location was determined and marked preoperatively and confirmed again by gastroscopy during the procedure.

Treatment of the left part of the greater curvature of the stomach

In the middle of the stomach, Arm 4 used proGrasp forceps to lift the vascular arch of the greater curvature of the stomach and pull it to the ventral wall and cephalic side. Arm 1 used proGrasp forceps to expand the gastrocolic ligament from the right side. The assistant pulled the greater omentum to the right and foot sides to expand the gastrocolic ligament in a bullfight towel style. Focus should be on observing the distribution of the transverse colon and omental branch blood vessels. The transverse colon should not be damaged during the operation. Hemostasis of omental branch blood vessels should be reliable, and the operation field should be kept clean. Arm 3 used an ultrasonic scalpel or Maryland bipolar electrocoagulation to open the gastrocolic ligament and enter the omental sac. The gastrocolic ligament was cut at the center of the resultant force and clamped directly to the inferior pole of the spleen. The pancreatic tail was used as a landmark to expose the left gastroepiploic vessels from the ventral and dorsal sides. At the same time, group 4 Lymph nodes were cleared, the medium-large clip was placed in Arm 3, and the left gastric omental vessels were clamped using an applier (Figure 2A) and cut off using an ultrasonic scalpel. The repair of the greater curvature of the stomach and preparation for gastric disconnection and anastomosis were correspondingly facilitated.

Treatment of the lower pylorus region

Arm 4 used proGrasp forceps to pull the omentum of the greater curvature of the gastric antrum to the left and abdominal wall side, and the assistant pulled the liver region of the transverse colon to the middle and foot side. The duodenum and pancreatic head were transferred to the abdomen's central part by traction, and the descending duodenum and pancreatic head were fully exposed. Arm 1 used proGrasp forceps to assist exposure and lifting, whereas Arm 3 used Maryland bipolar electrocoagulation. First, the omentum was opened along with the descending duodenum. The transverse mesocolon was dissected along the front of the pancreatic head to nearly reach the horizontal part of the

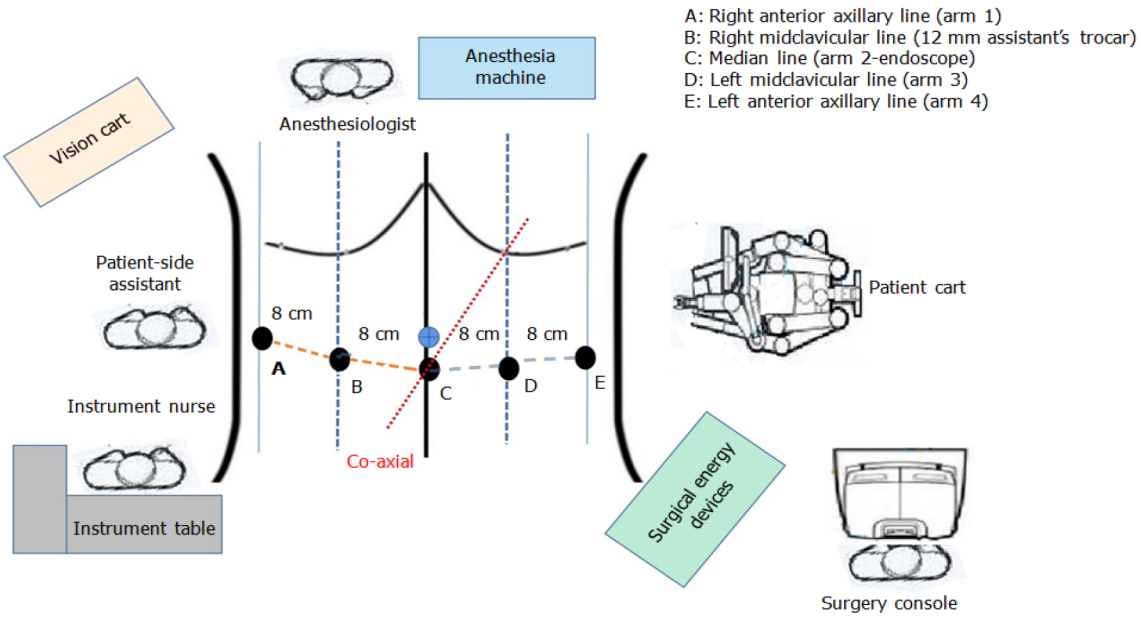

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Figure 1 Smile layout and operation room setting of pylorus and vagus nerve-preserving gastrectomy using the Da Vinci Xi robot system.

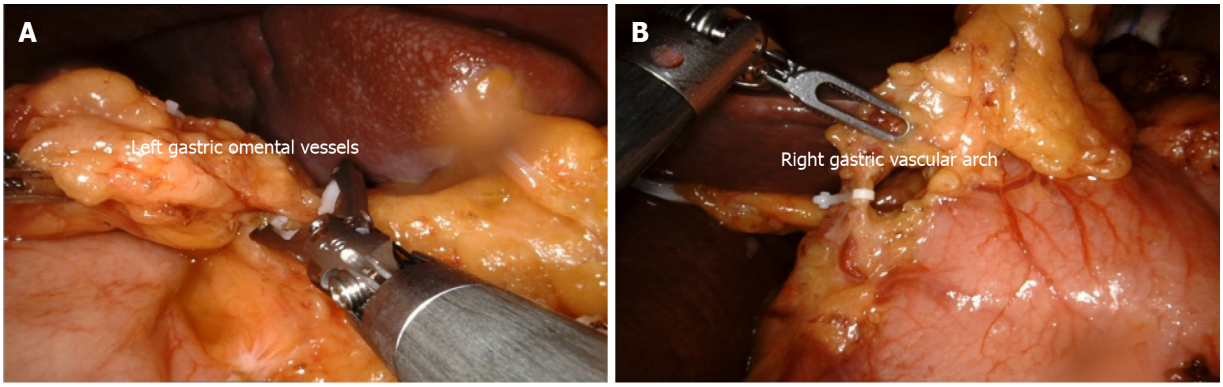

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Figure 2 Hem-O-lock clamping gastric omental vessels. A: Left; B: Right.

descending duodenum. Part of the hepatocolic ligament was opened outside the duodenum to facilitate traction of the colonic liver region and dissociation of the transverse mesocolon. The accessory right colonic vein, superior anterior pancreaticoduodenal vein, and right gastroepiploic vein were exposed on the right side. The operative field was turned to the middle part of the stomach. The gastrocolic ligament incision in the greater curvature of the stomach was dissociated along the transverse colon to the right.

After communicating with the free plane of the descending duodenum, the transverse mesocolon was dissociated from the lower edge of the pancreas to reach the right gastroepiploic vein. The antrum, pylorus, and posterior wall of the duodenum were dissociated to expose the gastroduodenal artery. At this time, the operative field of the area under the pylorus was fully expanded from the right, left, and lower sides. It is safe to dissect the right gastroepiploic vessels and blood vessels under the pylorus and clean the lymph nodes of group 6. First, the lymph nodes in the inferior pylorus region were dissected from the right side along the front of the pancreatic head. The omentum was opened in the avascular area between the inferior pylorus vessel and the first branch of the right gastroepiploic vessel to communicate with the left free plane. The right gastroepiploic vessel branches were cut off one by one along the gastric wall, and the gastric wall of the great curvature of the gastric antrum was exposed by 4–5 cm. The lymph nodes were dissected from the pylorus and duodenum to the bifurcation of the inferior pylorus vessels and right gastroepiploic vessels. Lymph node dissection was performed from the bottom along the root of the right gastroepiploic vein to the top of the bifurcation. Finally, the lymph nodes were dissected from the left side of the pancreas along the blood vessels to reach the bifurcation. The right gastroepiploic vessels were circumscribed 4–5 cm to complete the lymph node dissection in

the lower pylorus region (Figure 3). The inferior pyloric artery and veins were preserved. The right gastroepiploic artery was clamped and severed using a Hem-O-lock near the bifurcation.

Management of the superior pylorus

Arm 4 Lifted the lesser omentum to the oral, left, and abdominal sides, and the assistant pulled the greater curvature of the stomach (the part to be excised) to the left side and under the left side of Arm 3 to fully expose the lesser curvature of the upper pylorus. There was no need to clean group 5 Lymph nodes in the upper pylorus area, and the first to second right gastric vascular branches were preserved. The distance of 4 cm from the lesser curvature to the pylorus was measured as the precut line. Arm 4 Lifted the right gastric artery near the precut line with proGrasp forceps. Arm 3 used an ultrasonic scalpel or Maryland bipolar electrocoagulation. The precut line was close to the gastric wall, and the right gastric vascular arch was circumscribed. Hem-O-lock was used to clamp and disconnect the right gastric vascular arch (Figure 2B). The vascular branches of the gastric wall were cut off one by one along the anterior and posterior wall of the gastric wall to the oral side along the lesser curvature, and the naked gastric wall reached 1 cm distal to the lesion.

Treatment of the superior margin of the pancreas

Arm 4 used proGrasp forceps to lift the descending branch of the left gastric artery and omental adipose tissue together and pull to the abdominal wall, shifting the operation field to the left and right sides to facilitate better exposure. The assistant can carry a piece of gauze to hide the tip of the forceps, press the middle and lower one-third of the pancreatic body, pull the pancreas to the foot side, turn the superior margin of the pancreas outward, and pull the pancreas to the left and right sides with the change in the operative field. Assistant forceps are typically located in the field of operation. Do not use brute force to avoid injury to the pancreas, mesenteric blood vessels, superior mesenteric blood vessels, and intestine. Arm 3 used Maryland bipolar electrocoagulation, which could be operated from a multi-dimensional angle and was convenient for lymph node dissection and nerve exposure at the superior margin of the pancreas. Arm 1 was pulled and exposed with proGrasp forceps.

Left retroperitoneal approach

Arm 4 pulled the stomach to the abdominal wall and right side, while the assistant pulled the pancreas to the foot and right side. The left retroperitoneal approach was performed by double-click electrocoagulation to open the gastropancreatic fold on the upper edge of the pancreas, expose the left edge of the left gastric artery, and continue to expand the gastropancreatic fold up to the main trunk of the left gastric artery to the bifurcation of the descending branch. The left serosa is opened to the posterior wall of the lesser curvature of the stomach and determines the medial edge of the left approach.

The dorsal membrane of the pancreas was opened along the superior margin of the pancreas, and the superficial nerve of the splenic artery was used to clean the lymph nodes of group 11p, which directly contacted the posterior gastric artery. The lower edge of the left approach was determined. An L-shaped section is formed, and along this section, the nerve is dissociated to the direction of the esophageal hiatus to the posterior wall of the lesser curvature of the stomach. The celiac branch of the vagus nerve can be seen behind the left gastric artery (Figure 4A). The nerve is dissociated into the superficial layer without damage.

Right diaphragmatic foot approach

Arm 4 pulled the stomach to the abdominal wall and left side, while the assistant pulled the pancreas to the foot and left side. The right branch of the diaphragmatic foot was exposed and dissociated along with the superficial layer of the nerve bundle on the surface of the common hepatic artery. The portal vein bounded the right side, and the left gastric artery bound the left side. The lymph nodes of groups 8a and 9 were dissected carefully towards the diaphragmatic foot.

The celiac ganglion was not damaged on the left side. The lymphatic vessels in this area were abundant and should be carefully coagulated using the Maryland bipolar coagulation. The serous membrane was opened on the surface of the right branch of the diaphragm crus to reach the cardia from above. From the right surface of the main left gastric artery, the left gastric artery was dissociated to the bifurcation of the cardia branch and descending branch, forming an L-shaped free plane with the right branch of the foot of the diaphragm (Figure 4B). Along this plane, the left gastric artery was pushed along the cardia branch to the lower part of the cardia, and the abdominal branch of the vagus nerve was exposed from the right side.

The transection of the left gastric artery was performed by preserving the abdominal branch of the vagus nerve and the cardia branch of the left gastric artery *via* the esophageal approach.

It is vital to maintain the right surgical field, expose the anterior wall of the lesser curvature of the stomach below the cardia, and determine the cardia branch of the left gastric artery, which should be retained. At the distal end of this branch, the group 1 and 3 Lymph nodes were cleared along the lesser curvature of the gastric wall, and the right branch of the foot of the diaphragm. The distal end of the stomach was dissociated from the lower part of the cardia. The left gastric artery was exposed throughout the entire process, and the esophageal cardia branch went directly to the bifurcation of the

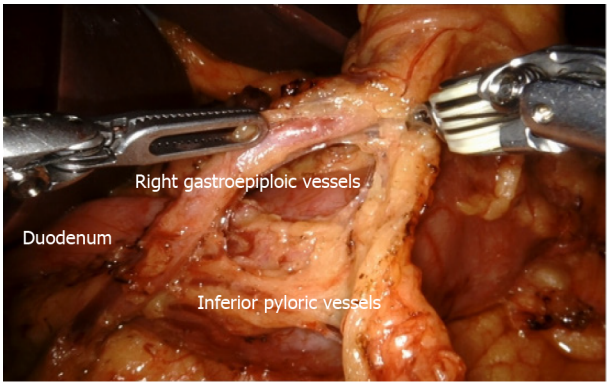

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Figure 3 Lymph node dissection in the inferior pylorus region.

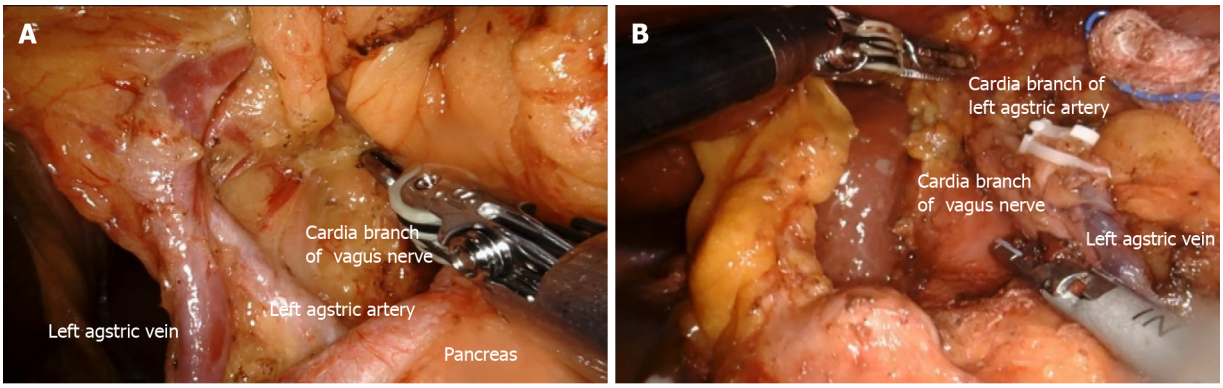

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Figure 4 The celiac branch of the vagus nerve is exposed. A: Through the left approach at the superior margin of the pancreas; B: Through the right approach at the superior margin of the pancreas.

descending branch of the left gastric artery. The left approach can be connected to the descending branch along the bifurcation ring. The descending branch of the left gastric artery can also be seen from the left approach, communicating with the right approach, retaining the abdominal branch of the vagus nerve and the cardia branch of the left gastric artery, and cutting off the left gastric artery (Figure 5).

The gastric wall was repaired, and the stomach was cut 2 cm from the distal and proximal ends of the tumor. The specimens were removed through a small incision in the upper abdomen. Intraoperative pathology confirmed that the cutting edge was negative. Correspondingly, gastrostomy was performed through a small abdominal incision. The length of the pylorus tube was 3–4 cm. No pyloroplasty was performed (Figure 6).

Statistical analysis

Data in the text and tables are presented as mean ± SD. Statistical analysis was performed using the SPSS software ver. 20.0 for Windows.

RESULTS

The clinical data of the 11 patients are shown in Table 1. The postoperative pathological diagnosis results of patients 1, 5, and 8 showed that the depth of tumor infiltration exceeded the submucosa, which represents advanced GC and thus did not meet the inclusion criteria of this study. Therefore, these three patients were excluded. Finally, eight patients remained in this study.

The eight patients had an average BMI of 24.90 ± 2.60 kg/m^2 and successfully underwent RAPPG. Patient characteristics are summarized in Table 2.

There were no laparoscopic conversions or intraoperative complications. The mean intraoperative blood loss was 57.50 ± 37.70 mL, no transfusions were required, and the mean operative time was 330.63 ± 47.24 min (Table 3). Lymph node dissection was D1 + 8a, 9, 11p. Postoperative complications occurred in two patients. The incidence of complications was 25.0%. One patient had gastric stasis and

Table 1 The general clinical data of 11 patients

No.	Sex	Year	Body mass index (kg/m²)	Operative time (min)	Tumor size (cm)	pT	pN	Histology	Number of resected lymph nodes	Number of metastatic lymph nodes
1[1]	M	70	24.20	300	7	3	2	Poorly	29	3
2	M	62	21.70	390	2	1b	0	Well	19	0
3	F	64	20.70	330	3	1a	0	Medium	32	0
4	M	56	27.10	315	3	1a	0	Signet ring cell	8	0
5[1]	M	65	29.50	325	4	4a	3	Poorly	51	13
6	F	72	26.20	410	1.5	1a	0	Well	9	0
7	M	70	26.42	330	2.5	1a	0	Poorly	21	0
8[1]	M	79	28.73	240	3	2	0	Poorly	12	0
9	M	52	28.02	270	3	1a	0	Medium	13	0
10	M	66	23.95	300	2	1a	0	Well	11	0
11	F	66	25.08	300	4	1b	2	Poorly	36	3

[1]Cases do not meet the inclusion criteria, and these case data are excluded from statistics.

Table 2 Patient characteristics

Variables	mean ± SD, *n* = 8
Age (yr)	63.50 ± 6.74 (52.0-72.0)
Sex (male/female)	5/3
Body mass index (kg/m²)	24.90 ± 2.60 (20.70-28.02)
ASA status	
I	7
II	1
Comorbidity	
Chronic obstructive pulmonary dysfunction	0
Diabetes	0
Valvular heart disease	0
Chronic atrial fibrillation	0
Hypertension	1
Occlusive vascular disease	0
History of appendectomy	1

hyperamylasemia postoperatively. The Clavien–Dindo classification of complications was grade 2. The patient had first flatus on day 9, liquid diet on day 11, and semi-liquid diet on day 13 after the operation. On day 1 after the surgery, the blood amylase level increased above 500 U/dL. After the application of somatostatin, the blood amylase level returned to normal. No abdominal infection occurred, and the patient was discharged on day 18 after the operation. The other patient had incision infection about grade 2 of Clavien–Dindo classification.

The pathological data are listed in Table 4. Among the eight patients, one had early GC invading the submucosa; however, three metastatic lymph nodes were found [groups 4d (1/7) and 6 (2/8)]. Pathological diagnosis showed protuberant lesions, invasion of the submucosa, low adhesion carcinoma, and poorly differentiated carcinoma. Immunohistochemistry showed HER-2 (0), Ki67 (+60%), MLH-1 (loss of expression), MSH-2 (expression), MSH-6 (expression), PMS-2 (loss of expression), and EGFR (-). The mean number of resected lymph nodes was 18 in the eight early GC patients.

Table 3 Intraoperative data and early outcome

Variables	mean ± SD, *n* = 8
Operative time (min)	330.63 ± 47.24 (270.0-410.0)
Estimated blood loss (mL)	57.50 ± 37.70 (10.0-100.0)
Postoperative hospital stay (d)	10.13 ± 4.55 (6.0-18.0)
Time to first flatus (d)	3.75 ± 2.49 (2.0-9.0)
Time to diet (d)	
Liquid	5.38 ± 2.56 (3.0-11.0)
Solid	7.63 ± 2.67 (5.0-13.0)
Morbidity	
Stomach stasis	1
Atelectasis	0
Incision infection	1
Anastomotic leakage	0
Hyperamylasemia	1
Valvular heart disease	0
Ascites	0
Trocar bleeding	0
Ileus	0

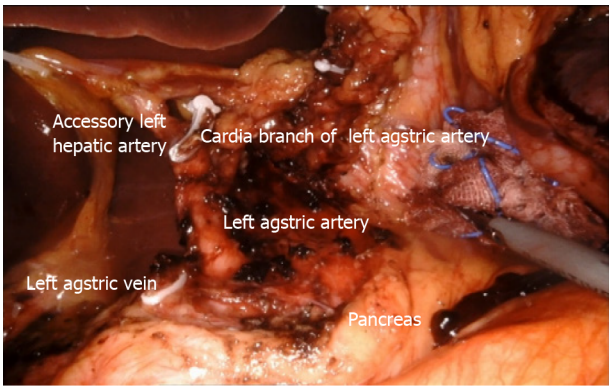

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Figure 5 The left gastric artery is cut off by preserving the celiac branch of the vagus nerve and the cardia branch of the left gastric artery.

DISCUSSION

Current scenario of PPG practice

PPG was first proposed by Maki in the 1960s to treat peptic ulcers. At the beginning of the 1990s, lymph node dissection and the applied PPG technology became popular for early GC treatment in Japan. With the increasing incidence of early GC, this technology is widely used in Asian countries, mainly in China, Japan, and South Korea. The 3rd edition of the Japanese guidelines for the treatment of GC (2010) stipulates the indications for PPG. For early middle GC, the distance from the distal part of the tumor to the pylorus was > 4 cm. Group 5 Lymph nodes above the pylorus were not removed, and the hepatic branches and celiac branches of the vagus nerve were preserved. Clinical studies have found that compared with distal gastrectomy, vagus-preserving gastrectomy can reduce postoperative cholelithiasis, diarrhea, and dumping syndrome and is beneficial for recovering postoperative hemoglobin level[8]. Some scholars worry that PPG surgery without thorough lymph node dissection increases the risk of postoperative recurrence. A Japanese study included 3646 cases of T1 GC in the middle of the stomach. The results showed that the rate of upper pyloric lymph node metastasis was only 0.2%[9].

Table 4 Pathologica features

Variables	mean ± SD, *n* = 8
T	
T1a	6
T1b	2
N	
N0	7
N2	1
Stage (8th AJCC TNM staging system for gastric cancer)	
IA	7
IIA	1
Histology	
Well	3
Medium	2
Poorly	2
Signet ring cell	1
Size of tumor (cm)	2.66 ± 0.82 (1.5-4.0)
Distance between anastomosis and pylorus (cm)	3.63 ± 0.88 (2.5-5.0)
Resection margins (cm)	
Proximal	3.63 ± 1.19 (2.0-5.0)
Distal	3.50 ± 1.31 (2.0-5.0)
Mean resected Lymph nodes	18.63 ± 10.57 (8.0-36.0)
Number of metastatic lymph nodes	0.38 ± 1.06 (0-3)

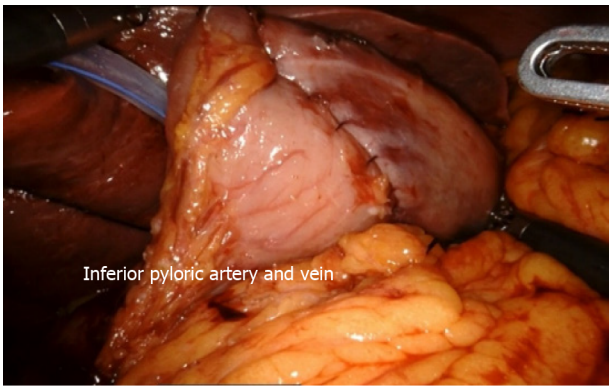

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Figure 6 Four cm length of the pylorus canal was preserved.

Tsujiura *et al*[10] reported 465 cases of laparoscopic pylorus-preserving gastrectomy with a 5-year overall and disease-free survival rate of 98%. The recurrence sites of the two cases were not in the remnant stomach and regional lymph nodes, which proved the non-inferiority of PPG in local recurrence and long-term prognosis. The primary complications of PPG are postoperative gastric stasis, such as delayed duodenal discharge, excessive food residue in the remnant stomach, and postprandial nausea or upper abdominal fullness. In South Korea, Oh *et al*[11] found that the incidence of postoperative gastric stasis was 35% in patients with a pylorus tube length of 1.5 cm and 10% in patients with a length of 3.0 cm. Takahashi *et al*[12] found that 68 (7.6%) of 897 PPG patients with pylorus tube preservation of 3–5 cm had postoperative gastric stasis. Multivariate analysis showed that for patients aged > 61 years, diabetes mellitus and abdominal infection were risk factors. The Korean klass-04 trial is a multicenter, prospective randomized controlled trial (RCT) to explore the safety and feasibility of

laparoscopic PPG and provide evidence-based medicine.

Current status of robotic surgery for GC

The Da Vinci robotic surgery system is widely used in the surgical field because of its advantages of high definition, an enlarged 3D field of vision, good stability, and flexibility. In 2002, Hashizume *et al* [13] reported the first Da Vinci robot-assisted radical gastrectomy. A meta-analysis published in 2019 included 8413 patients with GC from 24 non-randomized studies. A total of 2741 cases were treated with RG, and 5672 cases were treated with LG. The results showed that the operative time in the RG group was longer than that in the LG group, but the number of lymph nodes was higher. Complications such as delayed gastric emptying, intestinal obstruction, abdominal infection, incision infection, anastomotic leakage, and pancreatic complications were not significantly different. There were no significant differences in the 3-year and 5-year overall survival rates[14]. Uyama *et al*[15] reported a multicenter, single-arm, prospective study of robot-assisted distal gastrectomy in 253 patients with stage I/II GC. The results showed that the average operative time of robot-assisted distal gastrectomy was 313 min, and blood loss was 20 mL. No 30 d mortality occurred, the incidence of complications was 2.45%, and incidence of complications was lower than that of laparoscopic distal gastrectomy (6.4%). Wang *et al* [16] compared the incidence of complications between the RG and LG groups.

The results showed that the overall incidence of complications and severe complications in the robotic gastric surgery group was 18.8% and 8.9%, respectively, lower than 24.5% and 17.5% in the laparoscopic group. The robot system is safe and feasible for the surgical treatment of GC. The latest Da Vinci robot system is the Da Vinci Xi. A Korean study compared the short-term effects of the Da Vinci Xi System and the Da Vinci Si System on gastrectomy for GC. Early and advanced GCs were included in this study. Surgical methods included distal gastrectomy, total gastrectomy, and proximal gastrectomy. The results showed no significant difference in operative time, intraoperative blood loss, first postoperative exhaust time, hospital stay, and complications between the two groups[17]. At present, there is no evidence-based medicine such as an RCT comparing robotic GC surgery with laparoscopy and laparotomy. Ojima *et al*[18] carried out an RCT on robot-assisted laparoscopic radical gastrectomy in 2018 and planned to include 240 patients with GC of clinical stages I–III. The primary endpoint was to assess the incidence of postoperative complications of intra-abdominal infection, including pancreatic fistula, intra-abdominal abscess, and anastomotic fistula. Secondary endpoints included the incidence of any complications, surgical outcomes, postoperative course of the disease, and oncological outcomes.

Fundamental techniques of robot-assisted PPG surgery

The fundamental techniques of PPG are (1) Group 6 Lymph node dissection with preservation of the inferior pylorus vessels and (2) Treatment of the upper edge of the pancreas with preservation of the abdominal branch of the vagus nerve. Kiyokawa *et al*[19] proposed that the incidence of gastric stasis after PPG with preservation and disconnection of inferior pyloric vein was 5.4% and 23.4% respectively. Based on the concept of structure-determining function, preserving the blood vessels around the pylorus can maintain the basic shape of the pylorus and has minimal effect on the function of the pylorus after PPG. The inferior pylorus artery and vein were preserved during PPG. The lymph nodes in the inferior pylorus region were dissected and exposed from the upper, lower, right, and left directions and from the ventral and dorsal sides by taking the bifurcation of the right gastroepiploic artery and the inferior pylorus artery as the center. Upper part: duodenal bulb, pylorus, significant curvature of the gastric antrum; lower part: root of the right gastroepiploic vein; right side: medial edge of the descending duodenum; left side: right edge of the first branch of the right gastroepiploic vessel; ventral side: the anterior wall of the stomach; dorsal side: the posterior wall of the stomach. The dissociation order can be as follows: right ventral border, lower dorsal upper left border, right ventral border, and upper-lower dorsal left border.

Moreover, preservation of the esophageal branch of the cardia plays a vital role in maintaining the shape and function of the cardia. The right diaphragmatic foot approach was combined with the left retroperitoneal approach to determine the distribution of the vagus nerve. Lymph node dissection outside the nerve fiber membrane is vital to this technique. In addition, Maryland bipolar electrocoagulation is better than ultrasonic scalpel in treating Arm 3 of the superior margin of the pancreas.

The major limitation of this single center is the retrospective design and small sample size. This study aimed to highlight the surgical process, technical details, technical points, and precautions of RAPPG and retrospectively analyze the short-term prognosis of early GC cases. More cases should be accumulated, long-term follow-up should be conducted, and data should be compared with data for LAPPG to gather more data for RAPPG in the treatment of patients with early GC.

Overall, these study results are preliminary, and on establishing a standard surgical treatment, large-sample, multi-center, and prospective clinical trial should be conducted.

CONCLUSION

Laparoscopic PPG for GC management has advanced, but the chopstick effect of laparoscopic surgery

limits its delicate operation. The robot system functions as a high-degree-of-freedom simulation operation instrument, with a high-definition magnified 3D field of vision and tremor elimination, which significantly improves the safety, flexibility, and stability of a more effective operation platform for PPG operation. However, the application of robot systems remains limited due to its bulky volume and high cost, resulting in decreased operation cost and efficiency. In addition, evidence-based medicine is essential to confirm the safety and feasibility of the Da Vinci surgical system in the treatment of GC. However, with the continuous improvement and upgrading of robot systems, advancement of surgical technology, optimization of medical insurance structure, and accumulation of research samples, the robot system will occupy an important position in the minimally invasive treatment of GC in the future.

ARTICLE HIGHLIGHTS

Research background

Pylorus and vagus nerve-preserving gastrectomy (PPG) as a function-preserving surgical treatment has gained gradual acceptance and promotion. Although laparoscopic techniques are improving, the "chopstick" effect caused by the parallel arrangement of the instruments in the umbilicus is considered an obstacle in delicate operations. The results of study showed that operative time of the robot-assisted pylorus-preserving gastrectomy (RAPPG) was longer, but there was no significant difference in complications and the number of examined lymph nodes compared with laparoscopy-assisted pylorus-preserving gastrectomy (LAPPG).

Research motivation

In order to formulate the reasonable surgical process and technical standards for RAPPG.

Research objectives

To introduce Da Vinci Xi RAPPG-based operative procedure and technical points as well as report theinitial experienc.

Research methods

This retrospective analysis of clinical and pathological data of 8 early middle gastric cancer (GC) cases who have performed RAPPG.The fundamental techniques of RAPPG are (1) The inferior pylorus artery and vein were preserved during operation; and (2) The right diaphragmatic foot approach was combined with the left retroperitoneal approach to determine the distribution of the vagus nerve.

Research results

There were no laparoscopic conversions or intraoperative complications. The mean intraoperative blood loss was 57.50 ± 37.70 mL; the mean operative time was 330.63 ± 47.24 min .The incidence of complications was 25.0%.

Research conclusions

The core technique in the RAPPG is lymph node dissection and the anatomic method of the nerve. Robotic surgical procedures are feasible and safe. Reasonable surgical process, close cooperation of the surgical team, rational use of energy equipment, and avoidance of surgical risks are key factors to ensure surgical quality.

Research perspectives

This study aimed to highlight the surgical process, technical details, technical points, and precautions of RAPPG and retrospectively analyze the short-term prognosis of early GC cases. More cases should be accumulated, long-term follow-up should be conducted, and data should be compared with data for LAPPG to gather more data for RAPPG in the treatment of patients with early GC.

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FOOTNOTES

Author contributions: Zhang C performed the surgery and was responsible for manuscript writing, study design, data collection; Hu X performed the surgery and was responsible for study design; Wei MH and Liu YF performed the surgery; Liang P and Cao L performed the statistical analysis and literature review.

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

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ORIGINAL ARTICLE

Retrospective Study

Long-term efficacy and safety of cap-assisted endoscopic sclerotherapy with long injection needle for internal hemorrhoids

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Abstract

BACKGROUND

Hemorrhoids are a common anal condition and can afflict an individual at any age. Epidemiological survey results in China show that the prevalence of anorectal diseases is as high as 50.1% among which 98.08% of patients have hemorrhoid symptoms.

AIM

To assess long-term efficacy and safety of cap-assisted endoscopic sclerotherapy (CAES) with long injection needle for internal hemorrhoids.

METHODS

This study was retrospective. Data from patients with symptomatic internal hemorrhoids treated with CAES using endoscopic long injection needle from April 2016 to December 2019 were collected. Patients were telephoned and followed at two time points, December 2020 and 2021, to evaluate the improvements in symptoms, complications, recurrence, and satisfaction.

RESULTS

Two hundreds and one patients with internal hemorrhoids underwent CAES with the long needle. The first median follow-up was performed 33 mo post-operatively. Symptoms improved in 87.5% of patients after the first CAES. Efficacy did not decrease with treatment time extension. Fifty-four patients underwent colonoscopy after the first CAES treatment of which 21 underwent CAES again, and 4 underwent hemorrhoidectomy. At the first follow-up, 62.7% of patients had both improved hemorrhoid grades and symptoms, and 27.4% had a significant improvement in both parameters. At the second follow-up, 61.7% of the patients showed satisfactory improvement in their hemorrhoid grade and symptoms when compared with pre-surgery values. 90% of patients reported

CAES was painless, and 85% were satisfied/very satisfied with CAES treatment outcomes.

CONCLUSION

The present study based on the largest sample size reported the long-term follow-up of the treatment for internal hemorrhoid with the CAES using endoscopic long injection needle. Our findings demonstrate that CAES should be a micro-invasive endoscopic technology yields satisfactory long-term efficacy and safety.

Key Words: Hemorrhoids; Cap-assisted endoscopic sclerotherapy; Long injection needle; Efficacy; Prolapse

Core Tip: Cap-assisted endoscopic sclerotherapy (CAES) is a novel procedure to process flexible endoscopic sclerotherapy. Data from patients with symptomatic internal hemorrhoids treated with CAES using endoscopic long injection needle from April 2016 to December 2019 were collected. Patients were telephoned and followed at two time points, December 2020 and 2021, to evaluate the improvements in symptoms, complications, recurrence, and satisfaction. The present study based on the largest sample size reported the long-term follow-up of the treatment for internal hemorrhoid with the CAES using endoscopic long injection needle. Our findings demonstrate that CAES should be a micro-invasive endoscopic technology yields satisfactory long-term efficacy and safety.

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INTRODUCTION

Hemorrhoids are a common anal condition that can afflict an individual at any age. Epidemiological survey results in China show that the prevalence of anorectal diseases is as high as 50.1% among which 98.08% of patients have hemorrhoid symptoms. Epidemiological survey results in the United States show that the prevalence rate of hemorrhoids was higher than 50%, and the risk of hemorrhoids was highest among people aged 45-65 with 44.7% of patients affected by bleeding, pain, prolapse, and other symptoms affecting their life quality[1-3].

Injection sclerotherapy is a safe and simple treatment for internal hemorrhoids. However, traditional hardening agent injection therapy is performed *via* an anoscopy, which may present iatrogenic risks due to incorrect injection location[4,5]. Three milestones in the history of flexible endoscopic sclerotherapy have been reported. Ponsky *et al*[6] in 1991 reported the flexible endoscopic injection of 23.4% saline, with 5-mm retractable needle, and retroflexed position for symptomatic hemorrhoids. Tomiki *et al*[7] in 2014 reported the flexible endoscopic injection of aluminum potassium sulfate and tannic acid, with 5-mm retractable needle, retroflexed and anterograde position, and endoscopic cap. Zhang *et al*[5] in 2015 reported cap-assisted endoscopic sclerotherapy (CAES) using a Lauromacrogol injection with a 10-20 mm retractable needle, normal position, endoscopic cap, and proper air delivery for improving endoscopic exposure.

CAES is a novel procedure to process flexible endoscopic sclerotherapy. The special design of the CAES endoscopic needle (generally using a long needle) helps accurately control the injection angle, direction, and depth under direct vision, and avoids iatrogenic injury caused by ectopic injection[5,8]. Although this technique has become a widely used flexible endoscopy procedure in China with expert recommendations[9], few studies have reported long-term follow-up studies of more than one year. This study retrospectively analyzed the clinical data of patients with internal hemorrhoids treated with long needle CAES from April 2016 to December 2019 in our hospital to explore the long-term clinical efficacy and safety of long needle CAES in the treatment of internal hemorrhoids.

MATERIALS AND METHODS

This study was a single-center study. Patients with symptomatic internal hemorrhoids who received CAES treatment at the First Affiliated Hospital of Guangdong Pharmaceutical University from April

2016 to December 2019 were included in this study and followed by telephone.

Inclusion criteria

No gender or age restrictions were placed on study participants. All patients underwent complete bowel preparation and signed an informed consent for colonoscopy diagnosis and treatment.

Exclusion criteria

Patients with external hemorrhoids, asymptomatic internal hemorrhoids, perianal abscesses, anal stenosis, anal fistulas, malignancies involving the anal canal, pregnancy, coagulation dysfunction, decompensated cirrhosis, cerebrovascular accident, and other diseases, such as dementia, stroke, and mental retardation were excluded. Patients who did not comply with follow-ups were also excluded.

Preparation for CAES

All patients completed the coagulation function examination. To prepare for concurrent endoscopic treatments, such as a bowel polypectomy, aspirin is generally discontinued for 5 d and other antiplatelet drugs for 7 d if possible. All patients signed informed consents for colonoscopy diagnosis and treatment. All patients underwent pre-operative intestinal preparation for CAES to meet the requirements of colonoscopy for diagnosis and treatment. If polyps were found during colonoscopy, treatment of polyps was completed before CAES treatment started. The One physician who was familiar with endoscopic operation and two assistants performed the procedures. All endoscopists had experience in with more than 200 endoscopes.

CAES procedure

A short, straight transparent cap was installed at the front end of the endoscope,and an appropriate amount of gas was injected into the rectum. With the help of the transparent cap, the internal hemorrhoids with a blue-purple surface were visible. Under conditions of full exposure, a long needle, such as an injection needle with a diameter of 22 G and a length of 14 mm, was used (DT-EN-W122-14, Detian, Changzhou, China). Lauromacrogol (10 mL:100 mg, 1%, Tianyu, Xi'an, China) was injected into the base of the hemorrhoids. The injection point was located above the dentate line. According to the location of the left, posterior, right, and anterior anus (LPRA), the inclined plane injection was selected for an endoscopic direction of 6 o'clock, and 1-2 mL Lauromacrogol was injected into each injection site (Figure 1). The clockwise order should be followed when choosing the injection sites. The sclerosing agent is injected into submucosal layer within 5 s. After the injection, the needle was left *in situ*, or the needle sheath was pressed for 10 to 20 s to avoid bleeding at the injection site. Very rapid injections and more than a 2 mL injection in one site are not permitted. After retracting the endoscope, a finger massage around the anal ring was performed to help disperse the drug.

Post-operative treatment

Patients were asked to maintain a horizontal position for at least 2 h after surgery, and routine use of antibiotics and hemostatic drugs was not required after surgery. Laxative agents, such as lactulose, were given after surgery to keep the stool soft and thin. The changes in the condition and vital signs were strictly monitored and handle defecation difficulties, bleeding, infection, ulcers, and other issues were addressed in a timely manner.

Overall evaluation of curative effect

Patients self-reported bleeding and other symptoms were taken as the basis for with three classes of evaluation criteria: (1) Excellent, very satisfied no or mild symptoms; (2) good, significant improvement, occasional symptoms; or (3) poor, no improvement, even worse symptoms.

The symptoms and concomitant symptoms before and after treatment, including anal bleeding, anal pain, anal prolapse, defecation difficulties, anal distension, anal pruritus, anal dampness, and others, were evaluated according to the presence/absence of medical records.

Follow-up treatment attitudes after CAES

Several parameters related to satisfaction with the procedure and outcome were rated: (1) Great satisfaction; (2) satisfaction; (3) general; (4) less satisfaction; and (5) very dissatisfied. Pain level of CAES was rated according to certain levels: (1) No pain; (2) mild and tolerable; and (3) serious and intolerable. Patients' recommendations to undergo the procedure (Would you like to recommend it to other patients?) were based on yes or no answers.

Endoscopic findings

The changes in internal hemorrhoids before, after, and before and during the first CAES and follow-up were compared in patients who returned to the hospital for the second CAES.

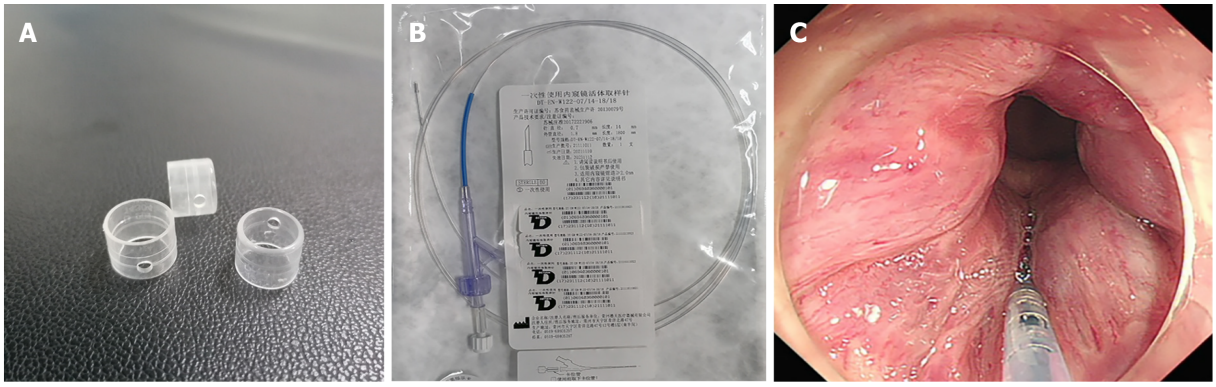

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Figure 1 Long needle and the cap used for the procedure. A: The cap; B: Long needle; C: The injection process.

Statistical analysis

SPSS 25.0 was used for systematic analysis of the data, and a chi-squared test was used to analyze the data differences between the two groups before and after treatment. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 201 patients with internal hemorrhoids who underwent CAES treatment were admitted to our hospital from April 2016 to December 2019. These patients were followed by telephone between December 2020 and December 2021. In December 2020, 201 patients were followed, and none were lost to follow-up. In December 2021, 149 patients were followed up of which 52 were lost to follow-up. The patient did not use Ayurveda, Chinese medicine, or herbal medicines during follow-up. Prior to the first treatment, patients with hemorrhoids based on Goligher classification were divided into four stages: (1) 88 patients with stage I hemorrhoids; (2) 53 patients with stage II hemorrhoids; (3) 50 patients with stage III hemorrhoids; and (4) 10 patients with stage IV hemorrhoids (Table 1).

Treatment outcomes

At the first follow-up, 62.7% (126/201) patients showed satisfactory improvement in hemorrhoid grade and symptoms when compared with pre-operative parameters, and 27.4% (55/201) patients had significant improvement in grade and symptoms of hemorrhoids compared with pre-operative parameters but occasionally had symptoms. Twenty out of 201 (9.9%) patients experienced the same grade and/or no improvement or even worsening of symptoms (Table 2).

Fifty-four patients underwent colonoscopy after CAES treatment (Figure 2), and 21 of those patients underwent CAES treatment again. Four additional patients underwent hemorrhoidectomy. At the second follow-up, 61.7% (92/149) of the patients had satisfactory improvement in hemorrhoid grade and symptoms when compared with the pre-operative level, and 33.6% (50/149) of the patients had significant improvement in hemorrhoid grade and symptoms compared with the pre-operative level but occasionally had symptoms. Seven out of 149 patients (4.7%) showed no improvement or even deterioration (Table 3). In our long-term follow-up, we did not identify patients who developed ulcers after treatment.

In terms of internal hemorrhoid improvements, anal bleeding was taken as an example. At the first follow-up, 31 patients had no bleeding either before or after treatment. Bleeding frequency ranged from occasional occurrence in the first defecation samples to asymptomatic after treatment in 107 patients, and 37 patients had no change. Bleeding frequency varied at each defecation before treatment to asymptomatic after treatment in 11 patients, occasionally in nine patients, and no change in four patients after treatment. Bleeding frequency ranged from pretreatment with or without defecation to occasionally in one patient after treatment to asymptomatic in one patient (Figure 3).

126 patients had no anal prolapse either before or after treatment, 57 patients had significant improvement in symptoms, 14 patients had no changes in symptoms either before or after treatment, and 4 patients reported symptom worsening after treatment. 10 patients had stage 4 internal hemorrhoids, 5 patients showed no improvement in prolapse symptoms, 3 patients with less prolapse than before, and 2 patients without prolapse.

131 patients had no pain either before or after treatment, 49 patients had significant improvement in symptoms after treatment, 20 patients had no change in symptoms after treatment, and 1 patient had aggravation of symptoms after treatment. One hundred and forty patients had no distension either

Table 1 Basic patient information and distribution of internal hemorrhoids

Basic situation	Follow-up of 2020 (*n* = 201)	Follow-up of 2021 (*n* = 149)
Median follow-up	33 (24-45)	45 (34-57)
Age	54.71 ± 13.016	54.77 ± 13.495
Gender, *n* (%)		
Male	116 (57.7)	92 (61.7)
Female	85 (42.3)	57 (38.3)
Hemorrhoids installment, *n* (%)		
Stage I	88 (43.8)	67 (45.0)
Stage II	53 (26.4)	38 (25.5)
Stage III	50 (24.8)	37 (24.8)
Stage IV	10 (5.0)	7 (4.7)

Table 2 Long-term efficacy evaluation after cap-assisted endoscopic sclerotherapy treatment (follow-up in 2020, *n* = 201), *n* (%)

Efficacy	Excellent	Good	Poor	χ^2	*P* value
Stage I	54 (61.4)	26 (29.5)	8 (9.1)		
Stage II	35 (66.1)	13(24.5)	5 (9.4)	8.90	0.177
Stage III	34 (68.0)	13 (26.0)	3 (6.0)		
Stage IV	3 (30.0)	3 (30.0)	4 (40.0)		

Table 3 Long-term efficacy evaluation after cap-assisted endoscopic sclerotherapy treatment (follow-up in 2021, *n* = 149), *n* (%)

Efficacy	Excellent	Good	Poor	χ^2	*P* value
Stage I	46 (68.6)	18 (26.9)	3 (4.5)		
Stage II	22 (57.9)	13(34.2)	3 (7.9)	4.78	0.572
Stage III	20 (54.1)	16 (43.2)	1 (2.7)		
Stage IV	4 (57.1)	3 (42.9)	0 (0)		

before or after treatment, 47 patients' symptoms improved significantly after treatment, 12 patients' symptoms did not change after treatment, and 2 patients reported worsening symptoms after treatment. 59 patients had no pruritus either before or after treatment, 28 patients had significant improvement in symptoms after treatment, 11 patients had no change in symptoms after treatment, and 3 patients had aggravation of post-treatment symptoms. 176 patients had no dampness either before or after treatment, 18 patients had significant improvement in symptoms, 5 patients had no changes in symptoms either before or after treatment, and 2 patients had aggravation of symptoms after treatment.

At the second follow-up, 22 patients had no bleeding before or after treatment, 90 patients had significant improvement in symptoms, 35 patients had no change in symptoms before or after treatment, and 2 patients had aggravation of symptoms (Figure 4). 94 patients had no prolapse before and after treatment, 41 patients had significant improvement in prolapse symptoms, 8 patients had no change in symptoms before or after treatment, and 6 patients had symptom worsening. 92 patients had no pain either before or after treatment, 38 patients had significant improvement in pain symptoms after treatment, 10 patients had no change in symptoms after treatment, and 9 patients had aggravation of symptoms after treatment. 94 patients had no distension either before or after treatment, 37 patients had significant improvement in distension symptoms, 8 patients had no change in symptoms either before or after treatment, and 10 patients had symptom aggravation. No pruritus was found in 110 patients either before or after treatment, 25 patients improved significantly after treatment, 5 patients' pruritis symptoms did not change either before or after treatment, and 9 patients' symptoms worsened after treatment. No dampness in 118 patients either before or after treatment was found, 15 patients improved significantly, 4 patients' dampness symptoms did not change either before or after treatment, and 12 patients' symptoms worsened.

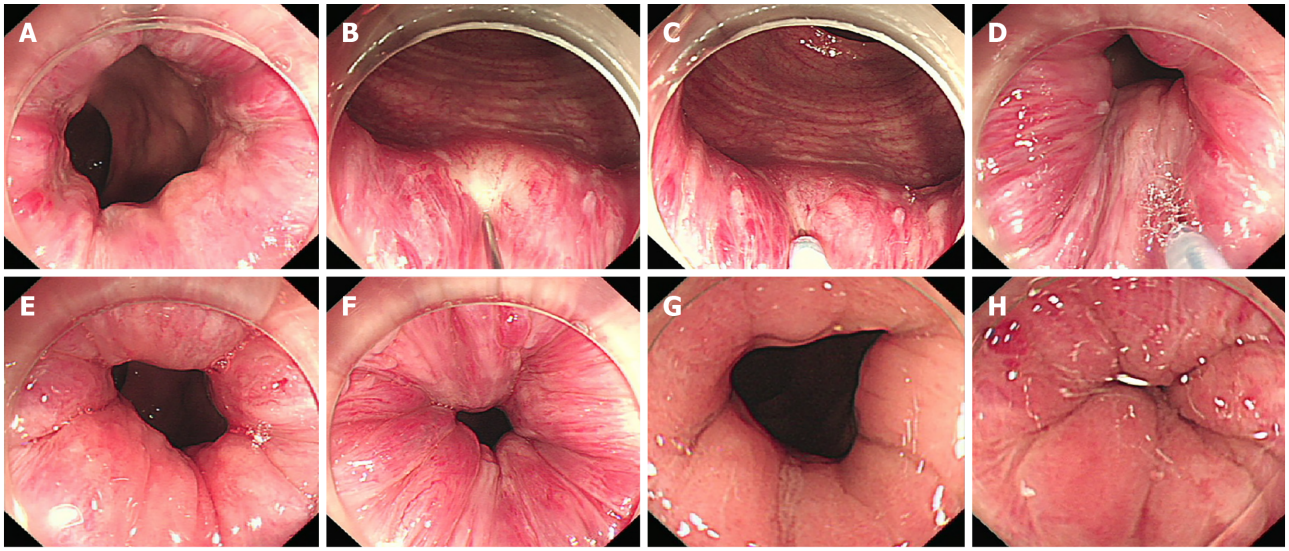

Figure 2 Endoscopic images of the same patient after undergoing one cap-assisted endoscopic sclerotherapy treatment. A: Conditions of internal hemorrhoids and rectal mucosa before surgery; B-D: Intra-operative injection; E and F: Post-operative period; G and H: Re-examination 1 year after treatment (second colonoscopy in 2017).

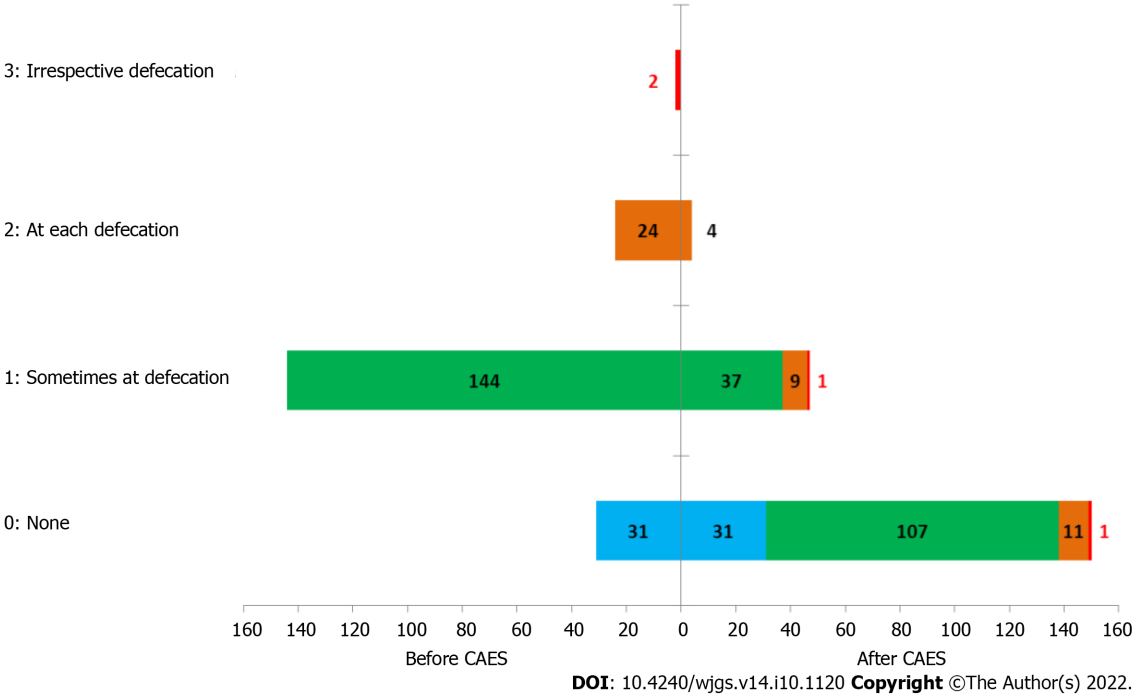

Figure 3 Improvement in anal bleeding after treatment (follow-up in 2020, *n* = 201). CAES: Cap-assisted endoscopic sclerotherapy.

At the second follow-up, 90% of patients reported CAES was painless (Figure 5), and 85% were satisfied/very satisfied with CAES treatment outcomes (Figure 6).

DISCUSSION

As for the pathogenesis of internal hemorrhoids, Thomson[10] proposed the "theory of anal cushion moving down," which has been widely recognized. Internal hemorrhoids are abnormal vascular pads covered by columnar epithelium located in the anal canal above the dentate line. The hemorrhoid pad shrinks during defecation to facilitate stool excretion. During periods of non-defecation, the arterial hemorrhoid pad becomes hyperemic and swollen and then seals the anus[11-13]. The American Society

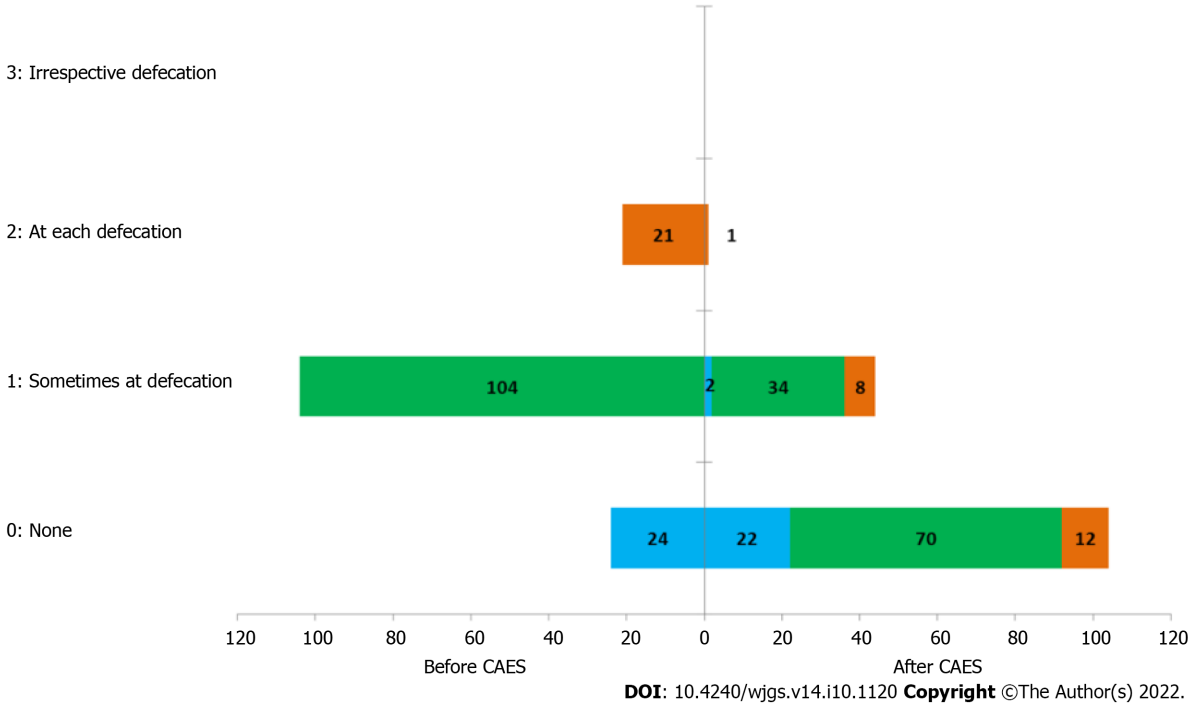

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Figure 4 Improvement in anal bleeding before and after treatment (follow-up in 2021, *n* = 149). CAES: Cap-assisted endoscopic sclerotherapy.

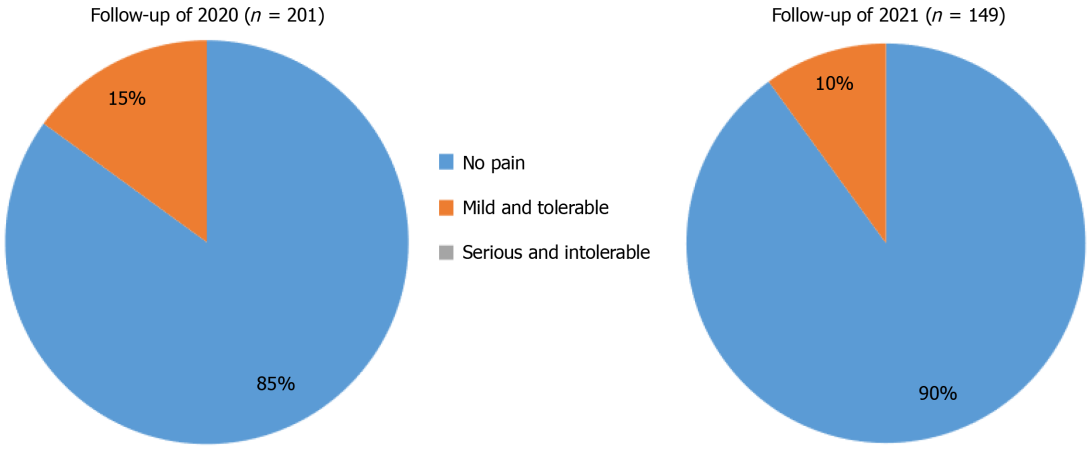

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Figure 5 Patient pain levels during cap-assisted endoscopic sclerotherapy treatment.

of Digestive Endoscopy recommends that endoscopic treatment of hemorrhoids include rubber band ligation (RBL), infrared coagulation, and/or injection sclerotherapy.

Polidocanol is a commonly used injection sclerotherapy that has been widely used for injection sclerotherapy of internal hemorrhoids[14,15]. Polidocanol is injected into the anus mirror or *via* colorectal colonoscopy under direct intravascular injection of pathological changes and causes minimal damage to the mucous membrane tube and anal cushion. However, local intravascular thrombosis resulting from vascular endothelial injury leading to aseptic inflammatory that eventually translates into fiber cords led to occlusion of artery branch blood vessels on rectal hemorrhoids that eventually shrank. In addition, this fibrous action can fix the loose mucous membrane to the anal muscle wall, thereby reducing the symptoms of prolapsed hemorrhoids.

A longer injection needle has advantages as the sclerosing agent injected with short injection needle cannot form hardening pile in the base of hemorrhoids, and the shallow injection depth of the sclerosing agent can easily cause ulcer formation. With the help of a transparent cap, Zhang *et al*[5] used a long needle for submucosal injection and achieved satisfactory efficacy. In 2021, Zhang *et al*[9] on behalf of the CAES-LPRA Study Group released the expert recommendation concerning flexible endoscopic positioning methods. Briefly, endoscopic residual effusion or injected water is the sign for determining the left anus under the left lateral decubitus position. Along the clockwise direction, LPRA are

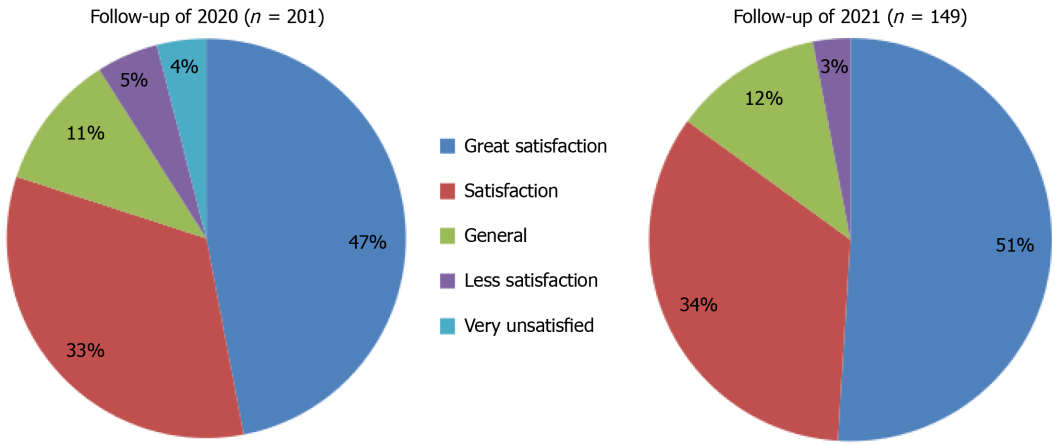

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Figure 6 Patient satisfaction with cap-assisted endoscopic sclerotherapy treatment.

recommended to replace the typical lithotomy position for the precise direction description on the anal lesions and for endoscopic therapy.

The LPRA anal positioning method helps the endoscopist distinguish between injected and un-injected sites and avoids the use of tracers[9]. Our group routinely uses long needles for multi-point injection therapy according to the LPRA anal positioning method. This study evaluated the long-term efficacy and safety of long needle CAES for symptomatic internal hemorrhoids. In Zhang's *et al* report[5,8,9,16,17], the follow-up for CAES treatment did not exceed one year. In our study, the time for following CAES treatment was up to 5 years. This study presents the largest sample size reported so far in the treatment of internal hemorrhoids with CAES long needles. In this study, patients treated with CAES were divided into three effect grades: (1) Excellent (no or mild symptoms); (2) good (obviously improved but occasionally symptomatic); and (3) invalid (no improvement, even worse symptoms). In the 2020 follow-up results, 90.1% of patients with internal hemorrhoids, including 94% of patients with stage III internal hemorrhoids, achieved good or excellent results. At the 2021 follow-up, 95.3% of patients with internal hemorrhoids, including 97.3% of patients with stage III internal hemorrhoids achieved good or excellent outcomes. Zhang *et al*'s study found that CAES was effective for stages I and II and a portion of stage III internal hemorrhoids[5]. However, our study found that symptoms improved significantly before and after CAES treatment, and no difference in the long-term efficacy of the treatment in stages I-III was found (Tables 2 and 3). No statistically significant difference in internal hemorrhoid staging between the four groups in 2020 was found. In 2021, no statistically significant differences in the efficacy of CAES in the treatment of stages I-IV internal hemorrhoids were found, that is, it is not considered that CAES produces different long-term efficacies for different stages of internal hemorrhoids. According to the improvement in symptoms and overall evaluation of follow-up, it was found that as the follow-up years increased, no statistically significant difference between the two groups of patients followed up in 2020 and 2021 was noted, indicating that the curative effect of patients treated with CAES did not decline with the extension of treatment years, and the long-term curative effect was stable.

The limitation of this study is the lack of dose difference analysis although the same hardener was used for all patients. Although the operators in the center are experienced, individual technical differences were not considered in this study. Although CAES is a locally minimally invasive treatment, human conditions (such as constipation and advanced age) were not included in the analysis. Since the LPRA method for the location description of anal lesions was published in 2021[9], this study did not analyze the relationship between disease efficacy, safety, and disease site.

In general, post-operative bleeding is the most common complication of hemorrhoids, but in this study, no complications, such as anal bleeding, anal fistula, and anal stenosis occurred after CAES was performed with a long needle. When compared with RBL and hemorrhoidectomy, long-needle CAES appears to be less likely to cause pain. During the follow-up in 2020, 85% of patients believed that long-needle CAES was painless after treatment, and 80% of patients were satisfied or very satisfied with CAES treatment. During the follow-up in 2021, 90% of patients reported that CAES treatment with long needle was painless, and 85% of patients were satisfied or very satisfied with CAES treatment. Patients reported that the pain level during CAES treatment did not increase with the increase in treatment years. This study further confirms that CAES is a simple and effective treatment for internal hemorrhoids that requires no anesthesia and is less painful. Ninety-three percent of patients were willing to recommend CAES treatment to other patients.

CONCLUSION

The present study based on the largest sample size reported the long-term follow-up of the treatment for internal hemorrhoid with the CAES using endoscopic long injection needle. Our findings demonstrate that CAES should be a micro-invasive endoscopic technology yields satisfactory long-term efficacy and safety.

ARTICLE HIGHLIGHTS

Research background

Hemorrhoids are a common anal condition and can afflict an individual at any age. Cap-assisted endoscopic sclerotherapy (CAES) is a novel procedure to process flexible endoscopic sclerotherapy.

Research motivation

There are few previous studies discussing CAES in the treatment of internal hemorrhoids with large sample size and long-term follow-up, so this study can make up for the shortcomings of previous theories.

Research objectives

Long-term efficacy and safety of CAES with long injection needle for internal hemorrhoids were assessed.

Research methods

This retrospective analysis of data from patients with symptomatic internal hemorrhoids treated with CAES using endoscopic long injection needle from April 2016 to December 2019 were collected. Patients were telephoned and followed at two time points, December 2020 and 2021, to evaluate the improvements in symptoms, complications, recurrence, and satisfaction.

Research results

Two hundred and one patients with internal hemorrhoids underwent CAES with the long needle, At the first follow-up, 62.7% of patients had both improved hemorrhoid grades and symptoms, and 27.4% had a significant improvement in both parameters. At the second follow-up, 61.7% of the patients showed satisfactory improvement in their hemorrhoid grade and symptoms when compared with pre-surgery values. 90% of patients reported CAES was painless, and 85% were satisfied/very satisfied with CAES treatment outcomes.

Research conclusions

The present study based on the largest sample size reported the long-term follow-up of the treatment for internal hemorrhoid with the CAES using endoscopic long injection needle. Our findings demonstrate that CAES should be a micro-invasive endoscopic technology yields satisfactory long-term efficacy and safety.

Research perspectives

The improvement of symptoms, complications, recurrence and satisfaction of patients with symptomatic hemorrhoids were cure by CAES.

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FOOTNOTES

Author contributions: He XX, Yuan Y and Xie YT designed the concept of the study; Zhou HM, Wu LH and Liu T collected and analyzed the data; Xie YT and Yuan Y wrote the draft manuscript; all authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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ORIGINAL ARTICLE

Retrospective Study

Reconstructing the portal vein through a posterior pancreatic tunnel: New choice for portal vein thrombosis during liver transplantation

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Abstract

BACKGROUND

Thrombectomy and anatomical anastomosis (TAA) has long been considered the optimal approach to portal vein thrombosis (PVT) in liver transplantation (LT). However, TAA and the current approach for non-physiological portal reconstructions are associated with a higher rate of complications and mortality in some cases.

AIM

To describe a new choice for reconstructing the portal vein through a posterior pancreatic tunnel (RPVPPT) to address cases of unresectable PVT.

METHODS

Between August 2019 and August 2021, 245 adult LTs were performed. Forty-five (18.4%) patients were confirmed to have PVT before surgery, among which seven underwent PV reconstruction *via* the RPVPPT approach. We retrospectively analyzed the surgical procedure and postoperative complications of these seven recipients that underwent PV reconstruction due to PVT.

RESULTS

During the procedure, PVT was found in all the seven cases with significant adhesion to the vascular wall and could not be dissected. The portal vein proximal to the superior mesenteric vein was damaged in one case when attempting thrombolectomy, resulting in massive bleeding. LT was successfully performed in

all patients with a mean duration of 585 min (range 491-756 min) and mean intraoperative blood loss of 800 mL (range 500-3000 mL). Postoperative complications consisted of chylous leakage (n = 3), insufficient portal venous flow to the graft (n = 1), intra-abdominal hemorrhage (n = 1), pulmonary infection (n = 1), and perioperative death (n = 1). The remaining six patients survived at 12-17 mo follow-up.

CONCLUSION

The RPVPPT technique might be a safe and effective surgical procedure during LT for complex PVT. However, follow-up studies with large samples are still warranted due to the relatively small number of cases.

Key Words: Liver transplantation; Portal vein thrombosis; Portal vein reconstruction; Retropancreatic tunnel; Computer tomography angiography; Three-dimensional visualization

Core Tip: In the study, we presented a new choice for reconstructing the portal vein through a posterior pancreatic tunnel (RPVPPT) to address the issue of unresectable portal vein thrombosis in adult liver transplantation (LT). Clinical data of seven recipients who had portal vein thrombosis (PVT) and underwent RPVPPT were analyzed. PVT was found in all the seven cases with significant adhesion to the vascular wall and could not be dissected. LT was successfully performed in all patients without serious complications. Six patients survived at 12-17 mo follow-up. The RPVPPT technique may be a safe and effective surgical procedure in LT for complex PVT.

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INTRODUCTION

Liver transplantation (LT) remains the mainstay treatment for end-stage liver disease. However, the incidence of portal vein thrombosis (PVT) in patients on the waiting list for transplantation has been reported to range from 5% to 26%. Due to the complexity of treatment techniques, PVT has long been regarded as a contraindication of LT until the 1980s[1-3]. However, the past decade has witnessed unprecedented progress achieved in surgical techniques, leading to the advent of many surgical approaches for recipients with PVT, including physiological portal reconstruction (such as thrombectomy, interposition venous grafts, and mesoportal jump grafts) and non-physiological portal reconstruction (such as cavoportal hemitransposition, renoportal anastomosis, and arterialization of PV flow)[4,5]. Importantly, physiological reconstruction can restore the anatomical structure of the portal venous system and ensure adequate blood flow to the graft. In contrast, non-physiological reconstruction exhibits limited ability to resolve portal hypertension due to the inability to drain visceral blood into the liver, resulting in a higher incidence of postoperative complications and mortality than physiological reconstruction[6-10]. Most recipients with PVT can undergo thrombectomy and anatomical anastomosis (TAA), yielding satisfactory results. However, in clinical practice, some patients with PVT present with organized thrombi adhering to vascular walls that cannot be completely removed intraoperatively, compromising blood flow to the graft. Non-physiological reconstruction methods are indicated in such cases, including portal-renal vein anastomosis and bypass, portal vena cava semi-transposition, and portal vein arterialization. An increasing body of evidence suggests that this approach is ineffective and might lead to an insufficient blood supply to the portal vein or postoperative hepatic encephalopathy[10-12].

Kasahara *et al*[13] reported a "pullout technique" for portal vein reconstruction in ten pediatric cases of LT. The portal vein was first pulled out from the back of the pancreas and resected. Then the portal vein reconstruction was completed by bridging the back of the pancreas with allograft or autologous blood vessels. However, this technique has not been widely used, and no relevant reports of its application during adult LT have been documented. Therefore, based on the "pullout technique", our center explored the technique of reconstructing the portal vein through a posterior pancreatic tunnel (RPVPPT) in adult LT recipients where PVT could not be resolved.

MATERIALS AND METHODS

General clinical data

A retrospective analysis was performed on 245 cases of LT at Shenzhen Third People's Hospital from August 2019 to August 2021. PVT was documented in 45 cases, of which 7 underwent RPVPPT for PVT and portal vein reconstruction (6 males, 1 female; age 48-65 years, mean 54 years). All patients in this study underwent LT with the approval of the Ethics Committee of Shenzhen Third People's Hospital, and livers were donated after the death of healthy citizens.

Preoperative assessment method

Before surgery, each patient underwent Doppler ultrasound and abdominal computed tomography angiography (CTA) to determine the incidence of complications such as PVT. Three-dimensional (3D) visualization models were reconstructed according to the DICOM format data of CTA, as previously described in the literature[14], and surgery was simulated on the model.

Main surgical methods of RPVPPT technique

Dissection of the hepatic hilum: First, the varicose veins of the hepatic hilum were separated and ligated successively, the common hepatic artery and the proper hepatic artery were dissected, and the left hepatic artery and the right hepatic artery were separated. The main portal vein was dissected from the caudal to the cephalad direction along the trunk to the left and right branches of the portal vein. Finally, the bile duct was isolated and severed near the hilum.

Establishment of the retropancreatic tunnel: First, the main portal vein was dissected from the cephalad to the caudal direction, and the left gastric vein (coronary vein) and the portal vein branch vessels were ligated successively. When the upper edge of the pancreas was reached, dissection started from the lower edge of the pancreas. The superior mesenteric vein (SMV) and splenic vein (SpV) were first separated and lifted with vascular slings. Then, dissection continued from the back of the pancreas to the cephalic side along the main portal vein to establish a retropancreatic tunnel. Subsequently, the pancreas was lifted with a vascular sling or a fine urinary catheter. Finally, the portal vein and its tributary branches behind the pancreas were completely severed and "naked".

Resection of the main portal vein of the recipient: The severed main portal vein was pulled out from the retropancreatic tunnel to the lower edge of the pancreas. The main portal vein containing the thrombus was removed after interrupting blood flow in the SMV and SpV. If the left gastric vein drained into the SpV or the superior mesenteric-portal vein (SMPV) confluence, it was ligated and severed first to avoid insufficient portal venous flow to the graft due to blood shunting.

Portal vein reconstruction: After the donor-recipient inferior vena cava anastomosis was completed, the donor's portal vein was pulled to the lower edge of the pancreas through the retropancreatic tunnel, and the portal vein reconstruction was conducted at the SMPV confluence (Figure 1).

Main evaluation indicators

The clinical data of each LT recipient with PVT were collected, including the medical history and laboratory, imaging, and 3D reconstruction results. The surgical methods and operation-related indicators were analyzed, including the operation time, bleeding volume, amount of blood transfusion, and surgical complications.

RESULTS

General clinical data

Patients with PVT included in the present study were cases with a preoperative diagnosis of decompensated hepatitis B virus (HBV)-related cirrhosis (n = 3) and hepatocellular carcinoma with decompensated HBV-related cirrhosis (n = 4). Five cases had a history of gastrointestinal bleeding before the operation. All patients underwent preoperative 3D reconstructions to visually assess blood vessels and simulate surgery, and LT was successfully conducted. The mean operation time was 585 min (range 491-756 min), and the mean intraoperative blood loss was 800 mL (range 500-3000 mL). More details are provided in Table 1.

Changes in the structure of the portal vein system

Anatomical structure of the PVT: One patient presented with complete portal vein occlusion with thrombosis proximal to the SMPV confluence, four cases with portal vein stenosis greater than 70% and thrombosis extending to the SMPV confluence, and two cases with portal vein stenosis greater than 70% and thrombosis extending to the proximal segment of the SMV. All seven patients with PVT presented with organized thrombi that could be completely removed intraoperatively during surgery. Moreover,

Table 1 Basic demographics and clinical data of cases with portal vein thrombosis (*n* = 7)

	Gender	Age	Diagnosis	Operation time (s)	Anhepatic stage (s)	Intraoperative blood loss (mL)	Transfusion of red blood cell suspension (U)	Cold ischemia time (s)	Outcome
Case 1	Male	65	HBV-related decompensated liver cirrhosis, HCC	648	34	1300	10	510	Survival
Case 2	Male	48	HBV-related decompensated liver cirrhosis	756	31	1000	6	480	Survival
Case 3	Male	38	HBV-related decompensated liver cirrhosis	564	35	800	0	390	Death
Case 4	Female	64	HBV-related decompensated liver cirrhosis, HCC	585	25	600	0	360	Survival
Case 5	Male	57	HBV-related decompensated liver cirrhosis, HCC	583	47	600	0	360	Survival
Case 6	Male	54	HBV-related decompensated liver cirrhosis	491	30	500	0	360	Survival
Case 7	Male	51	HBV-related decompensated liver cirrhosis, HCC	625	34	3000	20	360	Survival

HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma.

the proximal portal vein was damaged near the SMPV confluence in one case when attempting thrombolectomy, resulting in massive bleeding.

Anatomical structure of varicose vessels: The left gastric vein drained into the main portal vein (*n* = 3), SpV (*n* = 3), and SMPV confluence (*n* = 1), and the maximum diameter of the left gastric vein was greater than 1 cm in four cases. All cases presented with esophageal and gastric fundal varices and splenorenal shunt; the maximum diameter of the splenorenal shunt was 24 mm, and an umbilical vein opening was found in two cases. More details are provided in Table 2.

Surgical results and complications

Portal vein reconstruction and LT were successfully conducted in all cases, with patent and sufficient portal vein flow documented by intraoperative color Doppler ultrasonography. Six patients recovered smoothly after the surgery, and one patient died. The liver and coagulation function indicators are shown in Tables 3 and 4. Postoperative complications consisted of chylous leakage (*n* = 3), insufficient portal venous flow to the graft (*n* = 1), intra-abdominal hemorrhage (*n* = 1), pulmonary infection (*n* = 1), and perioperative death (*n* = 1).

Management of postoperative complications included conservative medical treatment for chylous leaks and antibiotics for pulmonary infection. In cases of insufficient portal venous flow, embolization of splenorenal shunt vessels under digital subtraction angiography (DSA) was used to improve portal venous blood flow (Figure 2). An exploratory laparotomy was performed on a patient with post-operative intra-abdominal bleeding (postoperative day 7) that was attributed to multiple blood vessels at the lower margin of the pancreas. Liver ischemia and hypoxia occurred due to hemorrhagic shock after surgery. The patient died 15 d after LT due to liver failure. At 12-17 mo follow-up, six of the seven cases in this study survived.

DISCUSSION

Management of PVT

PVT refers to thrombosis occurring in the main portal vein and its associated venous system (SMV, inferior mesenteric vein, and SpV). It is one of the most common complications of end-stage liver disease, with an incidence of about 5%-26%[1,15,16]. In the present study, the incidence of PVT was 18.4% (45/245). PVT has long been considered a contraindication for LT due to limited surgical techniques and poor understanding of PVT[17]. With significant inroads achieved in recent years,

Table 2 Vascular anatomical changes in the portal vein system of cases with portal vein thrombosis (*n* = 7)

Case	Left gastric vein (coronary vein)				Esophagogastric fundus vein		Superior mesenteric vein		Splenic vein		Shunt situation		
	Drain into the main portal vein	Drain into the confluence of SMV and SpV	Drain into SpV	Maximum diameter of the blood vessel (mm)	Degree of varicose veins	History of upper gastrointestinal bleeding	With or without thrombus	Maximum diameter (mm)	With or without thrombus	Maximum diameter (mm)	With or without splenorenal shunt	Maximum diameter of the shunt (mm)	With or without umbilical vein opening
1	Yes			30	Severe	Yes	No	18.8	No	21.3	Yes	21	No
2			Yes	10.4	Severe	Yes	Yes	17	No	14.2	Yes	24	Yes
3			Yes	24.2	Severe	Yes	No	15.4	No	12.4	Yes	15.7	No
4			Yes	13.8	Severe	Yes	Yes	10.8	No	10.5	Yes	17.3	No
5	Yes			5.9	Severe	No	No	16.4	No	12.5	Yes	11.2	Yes
6	Yes			6.9	Mild	No	No	11	No	18.4	Yes	15.6	No
7		Yes		8.2	Severe	Yes	No	13.1	No	17.1	Yes	7.6	No

Maximum vessel diameter is measured based on contrast-enhanced computed tomography. SMV: Superior mesenteric vein; SpV: Splenic vein.

various innovative surgical approaches are now available.

Hibi *et al*[10] performed LT in 174 cases of PVT, among which 83 (47.7%) and 91 (52.3%) presented with complete and partial PVT, respectively. In terms of portal vein reconstruction, 149 cases underwent physiological reconstruction [thrombolectomy (n = 123), interposition vein grafts (n = 16), and mesoportal jump grafts (n = 10)]. There were 25 cases of non-physiological reconstruction [cavoportal hemitranspositions (n = 18), renoportal anastomoses (n = 6), and arterialization (n = 1)]. The study found that the non-physiological group suffered a significantly increased incidence of rethrombosis of the portomesenteric veins and gastrointestinal bleeding, with a dismal 10-year overall survival rate of 42% (*vs* no PVT, 61%; P = 0.002 and *vs* PVT: Physiological group, 55%; P = 0.043). Rodríguez-Castro *et al*[12] reported that of 25753 liver transplants, 2004 were performed in patients with PVT (7.78%), and complete thrombosis was observed in nearly 50%. TAA was performed in 75% of patients; other techniques included venous graft interposition and portocaval hemitransposition. It was found that PVT significantly increased post-LT mortality at 30 d (10.5%) and 1 year (18.8%) when compared to patients without PVT (7.7% and 15.4%, respectively). Moreover, rethrombosis occurred in up to 13% of patients with complete PVT, whereby no preventive strategies were used, leading to increased morbidity and mortality. In the present study, there was no recurrence of PVT, but one patient had portal venous insufficiency after LT. Accordingly, the optimal approach for portal vein reconstruction is the restoration of the physiological anatomy of the portal vein system while ensuring adequate portal venous flow[10,18].

Table 3 Laboratory examination indicators on postoperative day 7

	ALB (g/L)	TB (μmol/L)	DB (μmol/L)	ALT (U/L)	AST (U/L)	GGT (U/L)	PT (s)	INR
Case 1	32	98	52	111	43	78	20.4	1.72
Case 2	31.4	11.2	4.9	49	24	85	16.6	1.36
Case 3	38.1	27.8	18.3	204	63	236	18.9	1.61
Case 4	35.1	35.1	22.8	224	175	741	16.4	1.30
Case 5	35.3	39.5	23.1	169	41	89	15.9	1.25
Case 6	50	26.8	14.7	329	62	355	14.8	1.19
Case 7	35	20.1	13.5	48	20	328	15.4	1.21

ALB: Albumin; TB: Total bilirubin; DB: Direct bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; PT: Prothrombin time; INR: International normalized ratio.

Table 4 Laboratory examination indicators on postoperative day 14

	ALB (g/L)	TB (μmol/L)	DB (μmol/L)	ALT (U/L)	AST (U/L)	GGT (U/L)	PT (s)	INR
Case 1	33	66	37	58	21	128	17.6	1.42
Case 2	38.3	12.1	5.2	35	15	75	14	1.09
Case 3	42.1	567	226	246	115	232	52.2	6.0
Case 4	34.3	80	54	135	87	677	15.1	1.18
Case 5	39.1	24.2	13.2	27	21	39	14	1.20
Case 6	39.8	13.8	11.2	57	53	140	13.6	1.12
Case 7	34.5	13.8	8.6	37	15	238	14.7	1.14

ALB: Albumin; TB: Total bilirubin; DB: Direct bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; PT: Prothrombin time; INR: International normalized ratio.

At present, no consensus has been reached on the optimal reconstruction approach for different types of PVT during LT. Some scholars have formulated surgical methods according to Yerdel classification criteria[19-21]. However, in some cases, this classification criteria cannot be used to guide clinical practice since the Yerdel standard is based on the extent that the thrombus occupies the portal vein lumen and does not take into account adhesion to the blood vessel wall.

Application and precautions of RPVPPT

The RPVPPT technique adopted by our team was mainly applied in patients with PVT contraindicated for routine thrombolectomy during the LT surgery. This approach restores the physiological anatomy of the portal vein system while ensuring adequate portal vein blood flow, which is hypothetically ideal for PVT patients. At 12-17 mo follow-up, six of the seven patients survived, preliminarily validating the feasibility and safety of RPVPPT.

However, severe portal hypertension in this patient population accounts for an increase in varicose vessels around the portal vein, or even cavernous transformation of the portal vein, leading to an increased risk of bleeding during the procedure[22,23]. In addition, the RPVPPT technique requires the establishment of a retropancreatic tunnel behind the pancreas in these patients, increasing surgical risks. Accordingly, this surgical approach requires highly skilled surgeons and a transplant team. During the operation, it is recommended to dissect the hepatic hilum along the portal vein to the upper margin of the pancreas and then successively ligate each branch of the portal vein at the lower margin of the pancreas. When separating the lower edge of the pancreas, the SMV and SpV branches should be dissected first, and vascular slings should be placed to lift them for prompt hemostasis during the establishment of the retropancreatic tunnel or the separation of the surrounding tissues of the portal vein. After a successful retropancreatic tunnel is established, lifting the pancreas with a vascular sling or urinary tube is recommended to facilitate portal vein reconstruction (Figure 1).

Intraoperative traction of the pancreas should be as gentle as possible to avoid pancreatic damage and pancreatitis. Based on our experience, we recommend successfully ligating the branches of the blood vessels that merge into the portal vein behind the pancreas. Given that the blood vessels in this

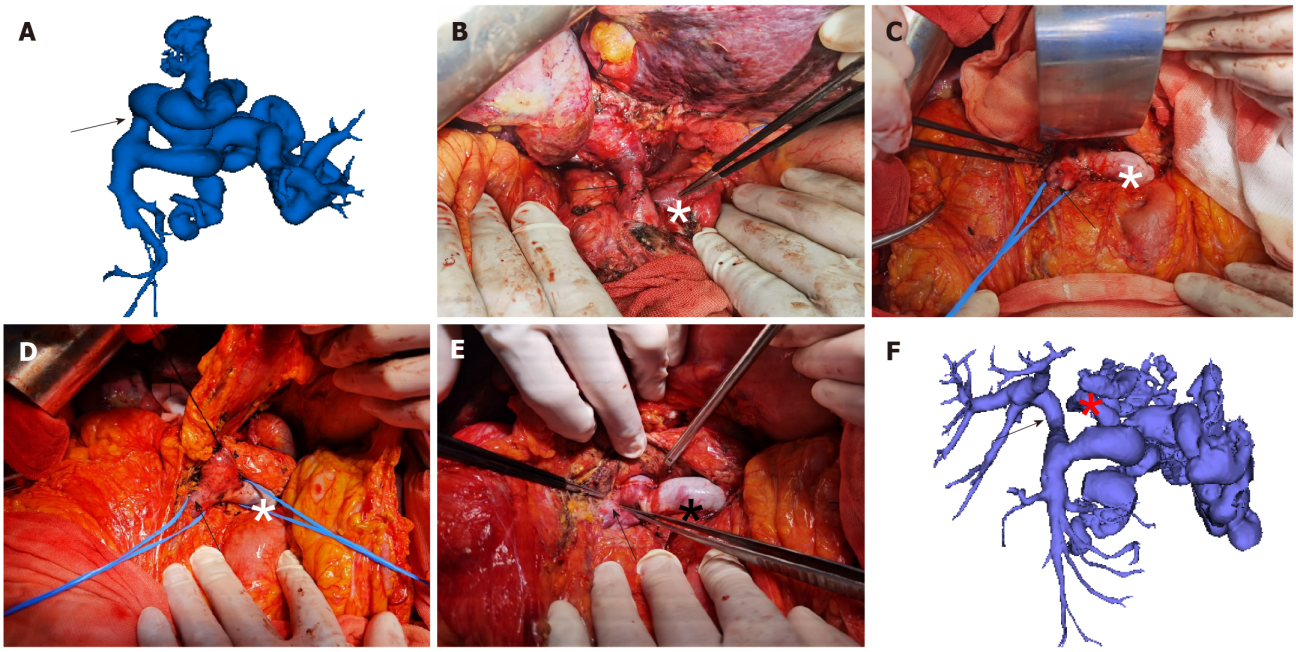

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Figure 1 Main steps of reconstructing the portal vein through the posterior pancreatic tunnel technique during portal vein reconstruction in liver transplantation recipients with complex portal vein thrombosis. A: Three-dimensional (3D) visualization model of the portal vein system constructed before surgery showed that the main portal vein was occluded, and the left gastric veins (coronary veins) were visible (arrow); B: After the varicose vessels were severed, the main portal vein (arrow) was exposed, the portal vein was dissected from the cephalic side to the upper edge of the pancreas, and the coronary varicose was ligated (*); C: Dissection started from the lower edge of the pancreas. The superior mesenteric vein (SMV) (arrow) and splenic vein (SpV) (*) were dissected successively, and the rear of the pancreas was separated towards the cephalic side along the main portal vein to establish a retropancreatic tunnel; D: The main portal vein was pulled out from the retropancreatic tunnel, and the main portal vein, SMV (arrow), and SpV (*) presented a triangular structure; E: Blood flow in the SMV and SpV was blocked. After the portal vein containing the thrombus was resected, the portal vein of the donor was pulled to the lower edge of the pancreas through the retropancreatic tunnel, and portal vein reconstruction was completed at the confluence of the SMV (arrow) and SpV (*); F: 3D visualization model of the portal vein system after surgery showed that the main portal vein was unobstructed (arrow), and the original coronary vein was severed (*).

region are very thin, hemostasis can be challenging once bleeding occurs. In this regard, given the narrow surgical view, it can be challenging to perform suture hemostasis, and the effect of electrocoagulation is often not satisfactory. In such circumstances, we can only resort to compression hemostasis. In addition, due to the brittleness of pancreatic tissue in patients with portal hypertension and the increase of surface varicose vessels, the risk of hemorrhagic shock is relatively high. Therefore, it is advisable to dissect the lower edge of the pancreas during surgery to prevent postoperative abdominal bleeding. In our study, one patient developed intra-abdominal hemorrhage on postoperative day 7. Exploratory laparotomy revealed that the source of the hemorrhage was at the lower edge of the pancreas, with multiple hemorrhagic foci observed. This finding could be attributed to postoperative pancreatitis since the amylase level in drain fluid from the lower edge of the pancreas was 700 U/L. It is highly likely that the extravasation of pancreatic fluid corroded the blood vessel, thus leading to rupture and bleeding. The patient died of liver failure due to hemorrhagic shock resulting in liver ischemia and hypoxia. Based on our experience, we recommend that the drainage tube should be indwelled at the lower margin of the pancreas and properly fixed. Importantly, the drain fluid amylase level should be assessed regularly after surgery.

During the establishment of the retropancreatic tunnel, the varicose vessels around the portal vein were ligated to create the posterior pancreatic tunnel and reduce the blood shunt of the portal vein system to avoid insufficient portal venous flow to the graft after surgery. However, it is often difficult to ligate splenorenal shunt vascular branches intraoperatively due to their deep location. In some cases, postoperative intervention may be required to manage shunt vessels. In this study, one patient developed insufficient portal venous flow to the graft after surgery, mainly due to significant splenic-renal shunting. DSA showed that most splenic venous flow drained into the inferior vena cava through the shunt rather than the portal vein. After shunt embolization, an immediate improvement in portal vein blood supply was observed.

CONCLUSION

With the increased number of LT cases, PVT has become a major conundrum that may be solved by

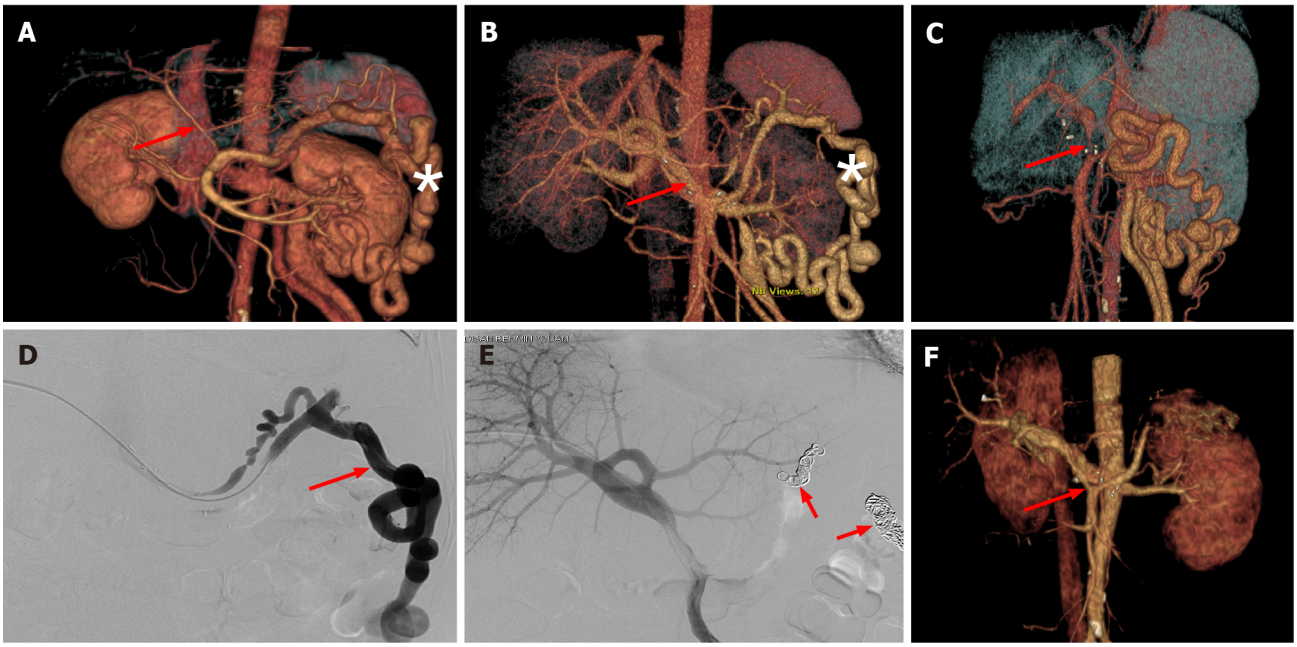

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Figure 2 Embolization of large splenorenal shunt under digital subtraction angiography alleviates portal vein insufficiency after liver transplantation. A: Preoperative three-dimensional (3D) visualization model showed a slender portal vein (arrow) and obvious splenorenal shunt varices (*); B: Postoperative 3D visualization model on day 3 showed a normal portal vein shape and unobstructed blood flow (arrow), and splenorenal shunt varicosity was reduced (*); C: Postoperative 3D visualization model (at 3 wk) showed portal vein stenosis in the initial segment (arrow), and color Doppler ultrasound examination indicated insufficient portal venous blood supply; D: Percutaneous and transhepatic splenic venography showed that most splenic venous flow drained into the inferior vena cava through the splenorenal shunt, but did not drain into the portal vein (arrow); E: After embolization of the splenorenal shunt (arrow), angiography showed that blood flow was mainly present into the portal vein; F: 3D visualization model 1 wk after the vascular intervention showed unobstructed portal vein flow (arrow), and the splenorenal shunt was no longer visible.

portal vein reconstruction. The key point of this technique is to ensure sufficient portal venous blood flow and restore the physiological anatomy of the portal vein system as much as possible. The RPVPPT approach adopted in this study meets the above requirements, and our preliminary assessment yielded good results. We substantiated that the RPVPPT technique is a safe and effective surgical procedure in LT for complex PVT. However, follow-up studies with large samples are warranted due to the relatively small number of cases.

ARTICLE HIGHLIGHTS

Research background

Portal vein thrombosis (PVT) poses a great challenge in liver transplantation (LT). It has been established that thrombectomy and anatomical anastomosis (TAA) can restore the physiological anatomy of the portal vein by complete thrombus excision and has been considered the optimal solution to this problem; however, in some cases, PVT cannot be treated by TAA.

Research motivation

We describe our experience of reconstructing the portal vein through a posterior pancreatic tunnel (RPVPPT) to address the issue of unresectable PVT, which may achieve a similar effect to TAA and provide a new approach to solve this intricate clinical problem.

Research objectives

We sought to describe a new strategy of RPVPPT to address cases of unresectable PVT.

Research methods

A retrospective analysis was performed on 245 adult patients that underwent LT from August 2019 to August 2021. Forty-five (18.4%) patients presented with PVT before surgery, among which seven underwent portal vein reconstruction using RPVPPT. Preoperative clinical data, operation-related indicators, and postoperative complications were statistically analyzed.

Research results

During the operation, PVT was found in all seven cases with significant adhesion to the vascular wall and could not be dissected. LT was successfully performed in all patients without serious postoperative complications. At 12-17 mo follow-up, there were six patients who survived.

Research conclusions

The RPVPPT technique can restore the physiological anatomy of the portal vein system through a retropancreatic tunnel, which might be a safe and effective surgical procedure in LT for complex PVT.

Research perspectives

Due to the relatively small number of cases in the study, follow-up studies with large samples are still required.

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FOOTNOTES

Author contributions: Zhao D and Huang YM were involved in the conception and design of this study; Zhao D provided administrative support in this study; Tang JX, Zhang KJ, Fang TS, and Zeng XC contributed to the provision of study materials or patients; Liang ZM, Yan X, Jin X, and Xie LJ were involved in the collection and assembly of data; Zhang Y and Huang YM analysed and interpreted the data; and all authors approved this manuscript to publish.

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Informed consent statement: All cases involved in this study proved written informed consent.

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

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ORIGINAL ARTICLE

Retrospective Study

Topological approach of liver segmentation based on 3D visualization technology in surgical planning for split liver transplantation

Dong Zhao, Kang-Jun Zhang, Tai-Shi Fang, Xu Yan, Xin Jin, Zi-Ming Liang, Jian-Xin Tang, Lin-Jie Xie

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Abstract

BACKGROUND

Split liver transplantation (SLT) is a complex procedure. The left-lateral and right tri-segment splits are the most common surgical approaches and are based on the Couinaud liver segmentation theory. Notably, the liver surface following right tri-segment splits may exhibit different degrees of ischemic changes related to the destruction of the local portal vein blood flow topology. There is currently no consensus on preoperative evaluation and predictive strategy for hepatic segmental necrosis after SLT.

AIM

To investigate the application of the topological approach in liver segmentation based on 3D visualization technology in the surgical planning of SLT.

METHODS

Clinical data of 10 recipients and 5 donors who underwent SLT at Shenzhen Third People's Hospital from January 2020 to January 2021 were retrospectively analyzed. Before surgery, all the donors were subjected to 3D modeling and evaluation. Based on the 3D-reconstructed models, the liver splitting procedure was simulated using the liver segmentation system described by Couinaud and a blood flow topology liver segmentation (BFTLS) method. In addition, the volume of the liver was also quantified. Statistical indexes mainly included the hepatic vasculature and expected volume of split grafts evaluated by 3D models, the

actual liver volume, and the ischemia state of the hepatic segments during the actual surgery.

RESULTS

Among the 5 cases of split liver surgery, the liver was split into a left-lateral segment and right tri-segment in 4 cases, while 1 case was split using the left and right half liver splitting. All operations were successfully implemented according to the preoperative plan. According to Couinaud liver segmentation system and BFTLS methods, the volume of the left lateral segment was 359.00 ± 101.57 mL and 367.75 ± 99.73 mL, respectively, while that measured during the actual surgery was 397.50 ± 37.97 mL. The volume of segment IV (the portion of ischemic liver lobes) allocated to the right tri-segment was 136.31 ± 86.10 mL, as determined using the topological approach to liver segmentation. However, during the actual surgical intervention, ischemia of the right tri-segment section was observed in 4 cases, including 1 case of necrosis and bile leakage, with an ischemic liver volume of 238.7 mL.

CONCLUSION

3D visualization technology can guide the preoperative planning of SLT and improve accuracy during the intervention. The simulated operation based on 3D visualization of blood flow topology may be useful to predict the degree of ischemia in the liver segment and provide a reference for determining whether the ischemic liver tissue should be removed during the surgery.

Key Words: Three-dimensional visualization; Couinaud liver segmentation; Blood flow topology liver segmentation; Split liver transplantation; Surgical planning

Core Tip: This is the first study to explore the application of the topological approach of liver segmentation based on 3D visualization technology in surgical planning of split liver transplantation. Clinical data of 10 recipients and 5 donors were analyzed. Couinaud liver segmentation and blood flow topology liver segmentation (BFTLS) methods were used to simulate operation, respectively. The volume of segment IV (the portion of ischemic liver lobes) allocated to the right tri-segment was 136.31 ± 86.10 mL as determined using BFTLS. Results showed that the approach of BFTLS may be useful to predict the range of ischemia in the liver section.

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INTRODUCTION

The Couinaud liver segmentation is based on the distribution of the Glisson system in the liver and the division of the hepatic vein system. Three hepatic veins are used as vertical planes to form the main longitudinal fissure, and the liver is divided into different liver segments by the left and right branches of the portal vein. This segmentation method provides an anatomical basis for the clinical imaging diagnosis of liver diseases and has been widely used in clinical practice[1-3]. However, only 30%-50% of the segmented results are consistent with the actual anatomy of the liver as the segmented results are derived from the cast liver specimen *ex vivo*, and the variation in hepatic blood vessels is not taken into account[4,5]. The blood flow topology segmentation method is based on the blood flow topology of the hepatic portal vein[6,7]. Therefore, this method can truly reflect the anatomical structure of the liver and is the theoretical basis of anatomical hepatectomy *via* indocyanine green fluorescence imaging[8-10].

Split liver transplantation (SLT) is complex, and the commonly used surgical technique is the left-lateral segment and right tri-segment splits, which are implemented based on the theory of Couinaud liver segmentation. Previous studies uncovered that the right tri-segment liver surface might show different degrees of ischemic changes related to the destruction of the local portal vein blood flow topology following the intervention[11-13].

However, opinions diverge on the management of ischemia found on the surface tissues of the liver segment following SLT, as well as liver tissue necrosis, infection, and bile leakage[11,14]. Some experts postulate that the direct resection of segment IV of the ischemic liver tissue is necessary, while others

believe no treatment is needed. This difference in opinion is due to a lack of preoperative evaluation and predictive strategy for hepatic segmental necrosis after SLT and a dearth of relevant publications worldwide. Therefore, this study aimed to investigate the application value of 3D visualization technology in the surgical planning of SLTs.

MATERIALS AND METHODS

General clinical data

A retrospective analysis was performed on 10 patients who underwent SLT in the Third People's Hospital of Shenzhen from January 2020 to January 2021 and the corresponding data of 5 donors. All cases in this study were performed after the approval of the Hospital Ethics Committee. The livers were donated after the death of the donors.

Pre-operation evaluation

For each organ donor, preoperative blood routine, liver function, kidney function, coagulation function, tumor markers, and infection-related tests, as well as abdominal Doppler ultrasound and liver computed tomography (CT) angiography examination, were performed. A preoperative 3D visualization model of the liver was constructed for each case. The model was acquired by importing high-quality THIN-layer enhanced CT DICOM data into the medical 3D reconstruction software: (1) For organ reconstruction: The region-growing method was used to perform a 3D reconstruction of the liver, tumor, pancreas and spleen; and (2) For vascular reconstruction: The segmentation based on threshold method was used to perform a 3D reconstruction of the portal vein, hepatic artery and hepatic vein[15]. The model was utilized to evaluate the vascular pattern and hepatectomy simulation.

Simulated surgery

(1) The SLT procedure was simulated on a 3D visualization model and included a segment of the hepatic artery, portal vein, and hepatic vein and the disconnection of the liver parenchyma; and (2) The SLT procedure was simulated according to the Couinaud liver segmentation and blood flow topology liver segmentation (BFTLS) methods. The volume of the two liver segments and the ischemic volume were also quantified (Figure 1).

Actual operation

The combination of *in-situ* and *ex vivo* splitting was used for liver splitting. The surgical methods included left-lateral and right tri-segment splits, and left and right hepatic splits. During the operation, Doppler ultrasound was employed to identify and mark the shape of the middle hepatic vein, and a cavitron ultrasonic surgical aspirator and an ultrasonic knife were used to separate the liver parenchyma.

Main statistical indicators

The classification of hepatic vasculatures was based on 3D visualization technology, the hepatic and ischemic volume was estimated using simulated surgery, and hepatic ischemia was measured during the actual surgery.

RESULTS

Preoperative hepatic vascular evaluation and simulated surgical results. The preoperative 3D visualization model revealed that all the donor hepatic portal veins were Cheng *et al*'s type I[16], the hepatic arteries were Michels[17] type I, the middle hepatic vein and left hepatic vein shared trunk in 5 cases, and a single hepatic vein of segment IV directly flowed into the inferior vena cava in 1 case. Among the 5 simulated operations, 4 cases were split into left-lateral segment and right tri-segment; 1 case was split into left and right half liver, and the middle hepatic vein was split by median segmentation.

The results revealed that the resection plane simulated by the Couinaud liver segmentation method or BFTLS method was inconsistent, the former was flat, while the latter was irregularly shaped. 4 cases were simulated using left-lateral and right tri-segment splits. As measured by the above two liver segmentation methods, the volumes of the left-lateral segments were 359.00 ± 101.57 mL and 367.75 ± 99.73 mL, respectively. According to the BFTLS method, the volume of segment IV (*i.e.*, the ischemic part of the liver) cleaving to the right tri-segment was 136.31 ± 86.10 mL. 1 case of left and right liver splitting was simulated, and median segmentation of the middle hepatic vein was performed after strictly evaluating two adult recipients with low body weight. The operation was simulated according to the above two segmentation methods. 99.95 mL of tissues in segment IV was assigned to the left half of the liver according to Couinaud classification; if splitting was carried out according to this method, 99.95 mL of liver tissues might experience postoperative ischemia or even necrosis.

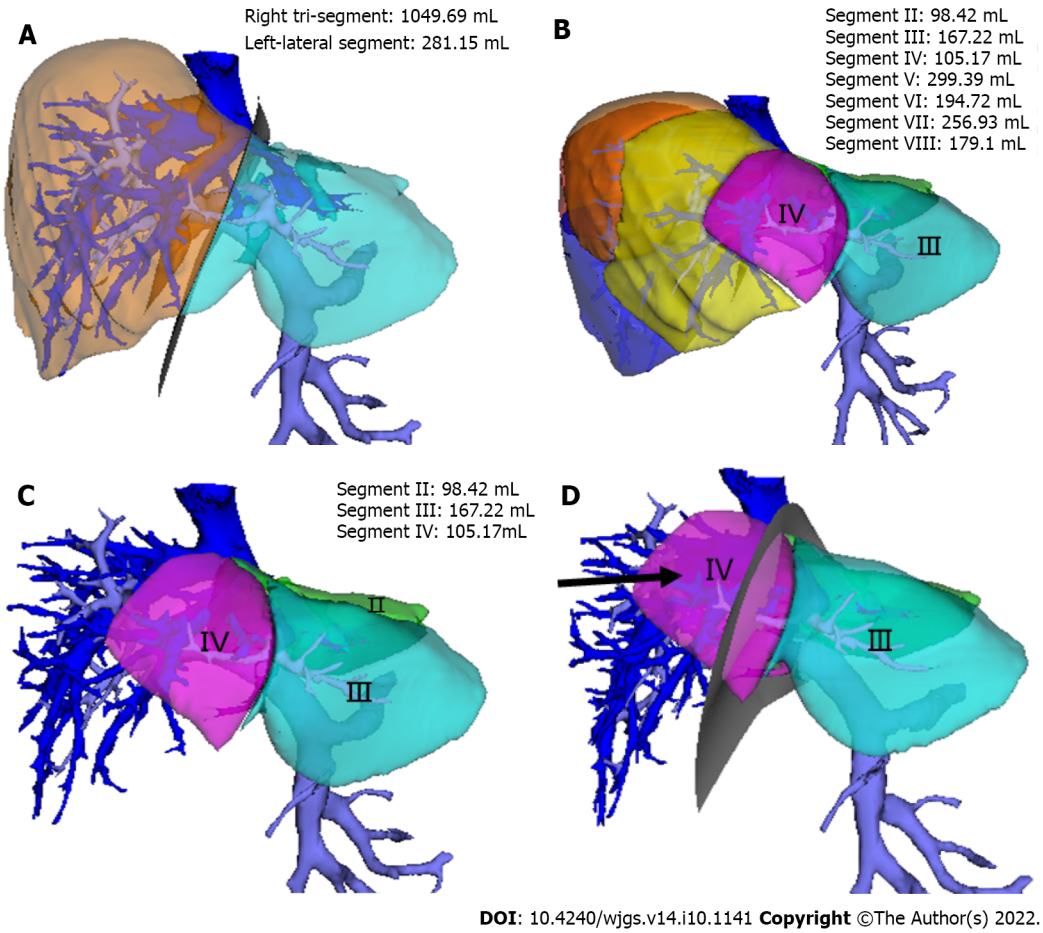

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Figure 1 The range of hepatic ischemia was calculated by simulating the left-lateral segment and right tri-segment splitting. A: The simulated operation based on Couinaud liver segmentation; B: The liver segments constructed *via* the topological structural relationship of portal vein blood flow; C: The calculated liver volume of the II/III/IV segments based on the blood flow topology liver segmentation method; D: The volume of ischemic range in the hepatic segment of the right tri-segment after split liver transplantation (black arrow).

Actual surgical results

In practice, *in-situ* and *ex vivo* splits were performed successfully according to the preoperative plan. According to the Couinaud liver segmentation method, left-lateral and right tri-segment splitting was performed in 4 cases. The left branch of the portal vein, the main trunk of the left hepatic artery, and the left branch of the hepatic vein were distributed to the left-lateral segment. The hepatic artery and portal vein branches entering segment IV of the liver were severed. The actual volume of the left-lateral segment was 397.50 ± 37.97 mL. The liver sections of the 4 cases exhibited ischemic changes after the operation (Figure 2). 1 case experienced necrosis of the liver section and bile leakage and underwent reoperation to remove the necrotic tissues. The volume of the ischemic liver calculated before the operation was 238.7 mL.

In the other case, the operation was performed by left and right half liver splitting based on the portal vein BFTLS method. The middle hepatic vein was segmented in the middle, and the donor's external iliac vein was used to reconstruct the middle hepatic vein of the left and right halves of the liver. No apparent changes in hepatic sectional ischemia were detected post-surgery (Figure 3).

Post-transplant outcomes

The operation was successfully completed in all 10 patients corresponding to the split livers, and postoperative biliary leakage occurred in 1 case without small-for-size syndrome. During the perioperative period, 1 patient who underwent a right tri-segment split suffered from a sudden intracerebral hemorrhage on the 7th postoperative day and died on the 18th postoperative day.

DISCUSSION

Couinaud liver segmentation is an artificial segmentation method based on anatomical markers of the liver. Moreover, its segmentation plane limits the drainage area of the hepatic vein and does not

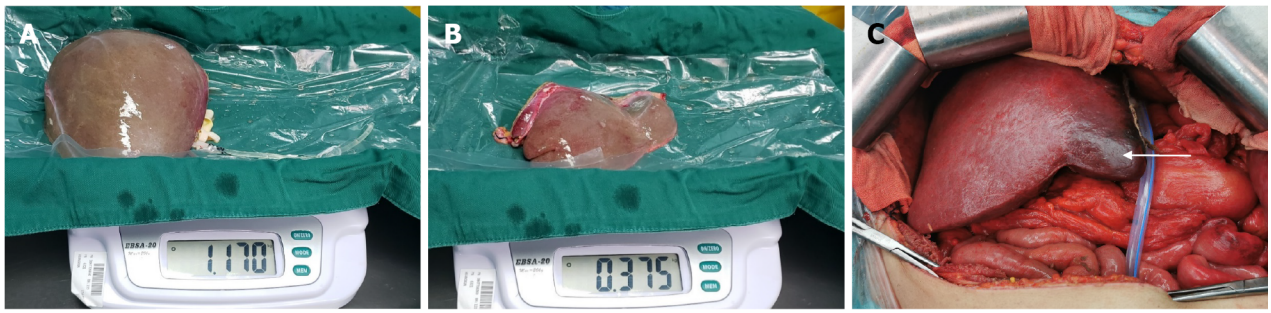

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Figure 2 Based on the Couinaud liver segmentation method, left-lateral segment and right tri-segment splits were performed. During the operation, obvious ischemic changes in the cross-section of the right tri-segment were observed. A: The right tri-segment graft; B: The left-lateral segment graft; C: Cleaved right tri-segment with distinct ischemia in the hepatic segment after hepatic reflow (white arrow).

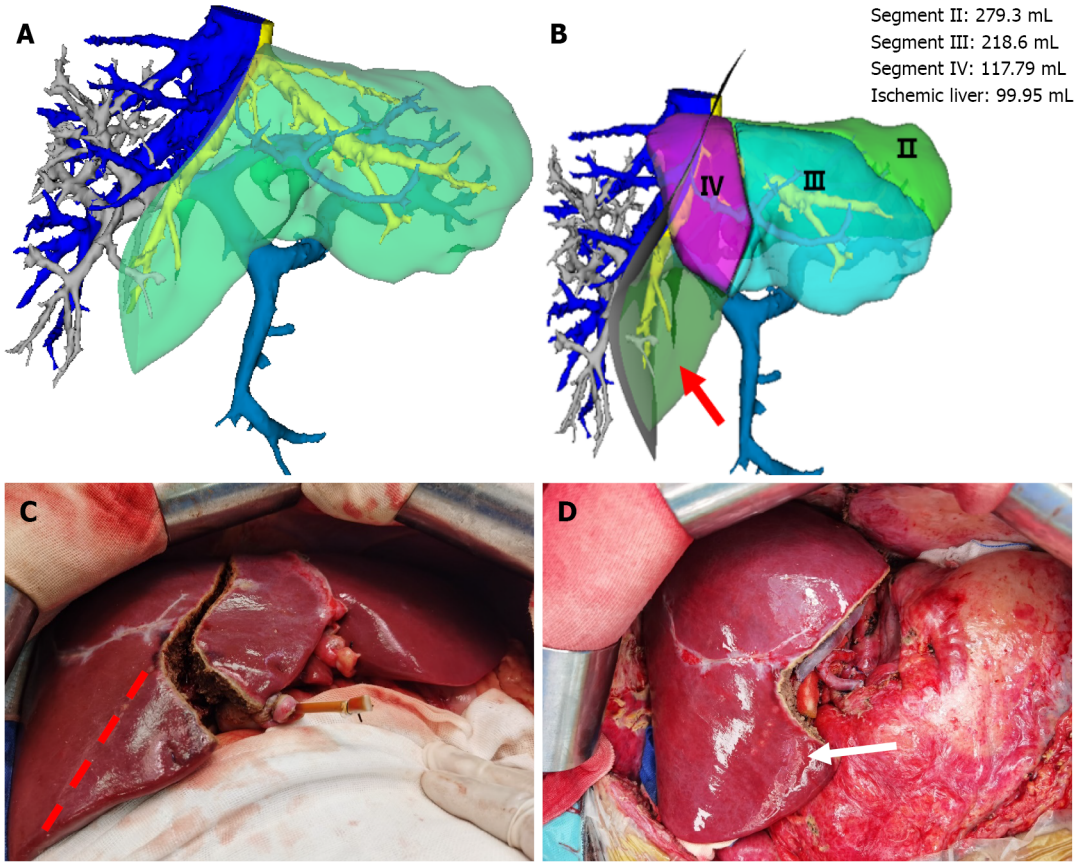

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Figure 3 Left and right half-split liver transplantation was performed according to the portal vein blood flow topology liver segmentation method. There was no ischemic change in the liver segment after reflow. A: Left and right half liver splitting were simulated based on the Couinaud liver segmentation method, while the middle hepatic vein was split in the middle; B: The simulation of left and right half liver splitting based on the portal vein blood flow topology liver segmentation method. It can be seen that a portion of segment V liver tissues (99.95 mL) is partitioned into the left liver (arrow); C: Surgery based on the portal vein blood flow topology liver segmentation method was implemented for left and right half liver splitting instead of the Couinaud liver segmentation method (red dotted line); D: No ischemic changes in the hepatic segment after reflow (white arrow).

consider the topology of portal vein branches in the liver[6,7,18]. For instance, when a vascular variation occurs in the liver, multiple portal or hepatic vein branches may co-exist within the same Couinaud liver segment. However, the BFTLS approach used herein was based on the topological structural relationship of the hepatic portal vein, which can truly display anatomical structural relationships in the liver[6,7]. Indeed, this concept is also widely used in clinical practice[19-21].

The initial aim of SLT is to save two lives with a single liver. However, inappropriate preoperative evaluation of the liver donor or splitting method may bring a well-functional liver into 2 marginal donors, which may delay the recovery of graft function and even lead to graft failure or recipient death

[22,23]. Therefore, compared with other hepatobiliary surgeries, adequate preoperative evaluation of SLT is monumental. At the time of preoperative donor evaluation, enhanced CT of the liver must be performed, with initial vascular and biliary evaluation followed by re-evaluation based on the 3D visual model. If the donor has significant portal vein variation, SLT is not recommended to ensure the safety of both recipients. Herein, only donors with good liver function and no significant anatomical variation were included in the SLT cohort. All the patients undergoing SLT in our center underwent an initial simulation using the 3D visualization model, and the portal vein, hepatic vein, and hepatic artery were segmented accordingly. Furthermore, the liver volume was also calculated so that a detailed preoperative plan could be drawn up.

In this study, all patients underwent simulated surgeries using the Couinaud liver segmentation method and BFTLS method, and the measured volumes of the left-lateral segment were 359.00 ± 101.57 mL and 367.75 ± 99.73 mL, respectively. Moreover, according to the above two methods, the volume of the segment IV (the portion of the ischemic liver lobe) allocated to the right tri-segment was 136.31 ± 86.10 mL, obtained by adding the volume of segments II/III/IV minus the volume of the left-lateral segment. Based on these data, we can obtain a detailed evaluation of the surgery, predict the degree of ischemic tissue changes and necrosis in the liver segments, as well as assess the need to remove ischemic segments during liver transplantation.

Hepatic segmental ischemic necrosis is extremely common following SLT, mainly because the branches of the portal vein[13] and hepatic artery[14,24,25] entering this part of the liver are not connected, and the corresponding hepatic vein[26-28] may also be cut off in some cases. Therefore, this part of the liver may undergo pathological changes such as hepatocyte ischemia, necrosis, fibrosis, and atrophy, and in some cases, tissue necrosis and bile leakage. Indeed, one of the 5 cases in this study suffered from ischemic tissue necrosis and bile leakage on the surface of the right tri-segment. The necrotic tissue was eventually resected by reoperation in that particular case, with a preoperative ischemic liver volume of 238.7 mL. The ischemic areas of the right tri-segment in the other 3 cases, calculated preoperatively, were 76.9 mL, 54.4 mL, and 175.3 mL, respectively. Therefore, we postulate that if the scope of hepatic segmental ischemia can be accurately determined before the operation, hepatic segmental tissue necrosis can be predicted in advance, avoiding reoperation and alleviating the pain and economic burden of patients.

CONCLUSION

In conclusion, in the case of the left-lateral segment and right tri-segment splits, preoperative evaluation based on three-dimensional visualization technology could calculate the ischemic range of the right tri-segment. Judging by the results, the operator could predict the postoperative ischemic range and make clinical judgments accordingly. For instance, when the branches of the hepatic artery and portal vein of segment IV supplying the right tri-segment are disconnected, and the calculated ischemic range is large, the operator can directly remove this section during the operation to avoid further damage to the body due to tissue necrosis, infection or bile leakage. Nevertheless, due to the small number of cases, it was not possible to determine a specific cut-off value to predict the likelihood of postoperative hepatic ischemic necrosis. Therefore, it is imperative to include a large number of cases for future clinical or multi-center research.

ARTICLE HIGHLIGHTS

Research background

Split liver transplantation (SLT) is complex, and the commonly used surgical technique is the left-lateral segment and right tri-segment splits, which is implemented based on Couinaud liver segmentation. The right tri-segment liver surface may have different degrees of ischemic changes after SLT, which was related to the destruction of the local portal vein blood flow topology.

Research motivation

To our best knowledge, opinions diverge on the management of ischemia in surface tissues of the liver segment following SLT and there was no a consensus of pre-operative evaluation and predictive strategy for hepatic segmental necrosis after SLT worldwide.

Research objectives

Herein, we sought to investigate the application of the topological approach of liver segmentation based on 3D visualization technology in the surgical planning of SLT.

Research methods

A retrospective analysis was performed on 10 recipients and 5 donors who underwent SLT from January 2020 to January 2021. All the donor livers were subjected to 3D modeling and evaluation before surgery, based on which the liver splitting procedure was simulated by the Couinaud liver segmentation and blood flow topology liver segmentation (BFTLS) methods respectively, and the volume of the liver was calculated. Clinical data were analyzed, including the hepatic vasculature and expected volume of split grafts evaluated by 3D models, the actual liver volume, and the ischemia state of hepatic section in actual surgery.

Research results

The donor liver was split into a left-lateral segment and right tri-segment in 4 cases, while 1 case was split by left and right half liver splitting. According to Couinaud liver segmentation and BFTLS methods, the volume of the left lateral segment was 359.00 ± 101.57 mL and 367.75 ± 99.73 mL, respectively. The volume of segment IV (the portion of ischemic liver lobes) allocated to the right tri-segment was 136.31 ± 86.10 mL as determined using the topological approach to liver segmentation. Yet, during the actual operations, ischemia of the right tri-segment section was observed in 4 cases, including 1 case of necrosis of the surfaces cut and bile leakage.

Research conclusions

The application of the topological approach of liver segmentation based on 3D visualization technology may be useful to predict the range of ischemia in the liver section and provide a basis for determining whether the ischemic liver tissue should be removed during the surgery.

Research perspectives

However, the follow-up studies with large samples are still warranted due to the relatively small number of cases.

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FOOTNOTES

Author contributions: Zhao D conceived and designed, and made contributions to administrative support; Zhang KJ, Fang TS and Tang JX made contributions to providing research materials or patients; Liang ZM, Yan X, Jin X and Xie LJ collected and compiled data; Zhao D, Zhang KJ and Fang TS conducted data analysis and interpretation; All authors wrote the manuscript and contributed to the final approval of manuscript.

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ORIGINAL ARTICLE

Observational Study

Can DKI-MRI predict recurrence and invasion of peritumoral zone of hepatocellular carcinoma after transcatheter arterial chemoembolization?

Xin Cao, Hao Shi, Wei-Qiang Dou, Xin-Yao Zhao, Ying-Xin Zheng, Ya-Ping Ge, Hai-Chao Cheng, Dao-Ying Geng, Jun-Ying Wang

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is a major cause of cancer-related mortality worldwide. Transcatheter arterial chemoembolization (TACE) has been performed as a palliative treatment for patients with HCC. However, HCC is easy to recur after TACE. Magnetic resonance imaging (MRI) has clinical potential in evaluating the TACE treatment effect for patients with liver cancer. However, traditional MRI has some limitations.

AIM

To explore the clinical potential of diffusion kurtosis imaging (DKI) in predicting recurrence and cellular invasion of the peritumoral liver zone of HCC after TACE.

METHODS
Seventy-six patients with 82 HCC nodules were recruited in this study and underwent DKI after TACE. According to pathological examinations or the overall modified response evaluation criteria in solid tumors (mRECIST) criterion, 48 and 34 nodules were divided into true progression and pseudo-progression groups, respectively. The TACE-treated area, peritumoral liver zone, and far-tumoral zone were evaluated on DKI-derived metric maps. Non-parametric *U* test and receiver operating characteristic curve (ROC) analysis were used to evaluate the prediction performance of each DKI metric between the two groups. The independent *t*-test was used to compare each DKI metric between the peritumoral and far-tumoral zones of the true progression group.

RESULTS
DKI metrics, including mean diffusivity (MD), axial diffusivity (DA), radial diffusivity (DR), axial kurtosis (KA), and anisotropy fraction of kurtosis (Fak), showed statistically different values between the true progression and pseudo-progression groups ($P < 0.05$). Among these, MD, DA, and DR values were higher in pseudo-progression lesions than in true progression lesions, whereas KA and FAk values were higher in true progression lesions than in pseudo-progression lesions. Moreover, for the true progression group, the peritumoral zone showed significantly different DA, DR, KA, and FAk values from the far-tumoral zone. Furthermore, MD values of the liver parenchyma (peritumoral and far-tumoral zones) were significantly lower in the true progression group than in the pseudo-progression group ($P < 0.05$).

CONCLUSION
DKI has been demonstrated with robust performance in predicting the therapeutic response of HCC to TACE. Moreover, DKI might reveal cellular invasion of the peritumoral zone by molecular diffusion-restricted change.

Key Words: Diffusion kurtosis imaging; Hepatocellular carcinoma; Transcatheter arterial chemoembolization; Recurrence

Core Tip: This study demonstrated feasible performance and advantages of diffusion kurtosis imaging metrics (*i.e.*, mean diffusivity, axial diffusivity, radial diffusivity, axial kurtosis, and anisotropy fraction of kurtosis) in evaluating liver cancer and tumoral cell invasion of peritumoral zone between hepatocellular carcinoma progressive group and pseudo-progressive group after transcatheter arterial chemoembolization treatment.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a major cause of cancer-related mortality worldwide[1]. Unfortunately, most patients with HCC are diagnosed at the advanced stage and thus lose the opportunity for surgical resection. Transcatheter arterial chemoembolization (TACE), which blocks local blood supply of cancerous lesions to induce ischemia and necrosis with a mixture of chemotherapeutic agents[2], has been performed as a palliative treatment for patients with advanced stage HCC. With TACE, the survival rate and prognosis of patients with HCC could be significantly improved[3]. However, due to hypervascular feature and possibly established new collateral circulation[4], HCC is prone to being recurrent after TACE treatment. Thus, an accurate evaluation method is essential to help guide subsequent therapeutic planning for patients with HCC after TACE in clinical practice. In addition, after TACE, there may be microscopic changes prior to morphological changes in the peritumoral liver parenchyma zone of the true progression. While, no related studies have been conducted regarding this.

Magnetic resonance imaging (MRI) has clinical potential in evaluating the effect of TACE in patients with liver cancer[5]. However, anatomical MRI has some limitations. These include the following: (1) MRI signals are easily affected by various time points and different treatment methods; (2) para-

magnetic substances, such as hemorrhage, granulation tissue, protein components, and steatosis, present high signal on T1-weighted imaging (T1WI) and may interfere with the enhancement of recurring lesions; and (3) disordered collateral circulation in TACE area can lead to false-negative diagnosis in arterial enhancement measurement.

Diffusion MRI, as a promising method of measuring the diffusion behavior of water molecules, sensitively reflects the physiological and morphological changes of tissues[6]. Diffusion-weighted imaging (DWI) has been relatively stable to different treatment methods[7] and has shown higher diagnostic performance in liver cancer after TACE than contrast-enhanced MRI[8]. However, the DWI metric apparent diffusion coefficient, derived in mono-exponential model, tends to be affected by various factors, such as macromolecule concentration, viscosity, and capillary perfusion[9]. In contrast, diffusion kurtosis imaging (DKI), a relatively novel diffusion imaging technique describing the deviations of water molecules diffusing away from Gaussian distribution, enables the precise depiction of microstructural environment[10]. With the DKI-derived parameter mean kurtosis (MK), HCC lesions can be well distinguished between the true progression and pseudo-progression groups[11]. Moreover, together with another DKI metric, mean diffusivity (MD), MK can assess the therapeutic response to TACE in HCC[12]. Although the effectiveness of both MK and MD has been validated, the remaining DKI parameters including fractional anisotropy of kurtosis (FAk), axial and radial kurtosis (KA and KR), and axial and radial diffusivity (DA and DR) have not yet been investigated for their clinical potential on HCC diagnosis after TACE. In addition, whether there are microscopic or molecular level changes in the liver parenchyma around the surviving lesion needs to be investigated.

Therefore, this study aimed to systematically explore the clinical feasibility of all DKI-derived metrics in predicting recurrence and cellular invasion of the peritumoral liver zone of HCC after TACE.

MATERIALS AND METHODS

Subjects

The local institutional review board approved this study, and each subject provided written informed consent. From January to May 2019, 76 patients (46 males *vs* 30 females; mean age, 55 years ± 12 years) with 82 HCC nodules were recruited in this study after receiving TACE treatment (1.4 mo ± 0.8 mo). Based on the pathological examination or the overall modified response evaluation criteria in solid tumors (mRECIST) criteria, 48 relapse/residual lesions and 34 stable and inactive lesions were divided into true progression and pseudo-progression groups, respective. The true progression was pathologically manifested as viable tumor cells in the foci, including primary liver cancer among the incisions, necrotic material, and granulomatous inflammation. The pseudo-progression was manifested as absence of the cancer cell infiltration in the operation area, only liver cirrhosis nodules, and some fibrous necrosis components (Figure 1).

According to the mRECIST criteria proposed by the American Association for the Study of Liver Diseases and European Association for the Study of the Liver and combined clinical indications, we considered the following lesions as true progression lesions[13]: (1) Progressive disease: Target lesion diameter increased by at least 20% on enhanced imaging compared with previous examination; (2) stable disease: Target lesion did not change; (3) partial response: The sum of initial lesion diameters in all target areas was reduced by at least 30%; (4) digital subtraction angiography (DSA): Lipiodol angiography found tumor staining in the focus area; and (5) alpha-fetoprotein (AFP) was significantly increased. However, if lesions met the following criteria, they were classified into the pseudo-progression group: (1) After TACE, DSA revealed that the focus was stable (no clear tumor blood vessels, tumor staining, clear arterial-venous/portal fistula, or vein-portal fistula); (2) after follow-up for a period of time (7.8 mo ± 0.5 mo), previous foci showed no signs of recurrence (all target lesions disappeared during the arterial enhancement phase of imaging); and (3) AFP was normal.

Imaging acquisition

All MRI studies were performed using a 3T MRI scanner (Discovery MR750, GE, United States), with eight-channel abdomen coils employed. A respiratory-gated spin-echo echo-planar imaging DKI sequence was performed in the axial plane. The corresponding applied scan parameters were as follows: Repetition time (TR), 3333 ms; echo time (TE), 69.4 ms; slice thickness, 6 mm; slice spacing, 2.0 mm; field of view, 360 mm × 288 mm; and matrix size, 128 × 128. In addition, five *b* values (400, 800, 1200, 1600, and 2000 s/mm^2) and 15 directions at each *b* value were used. The total scan time was 10 min. Conventional MRI was also performed, with the following parameters: T1WI: TR 3.7 ms, TE 1.1 ms, and slice thickness 6 mm; T2WI: TR 2319.5 ms, TE 68.0 ms, and slice thickness 6.0 mm; FS-T2WI: TR 9000.0 ms, TE 81.0 ms, and slice thickness 6.0 mm; and DWI sequence: TR 5000 ms and TE 50.8 ms. Dynamic-enhanced MRI with gadopentetate dimeglumine, captured the arterial (20 s), venous (60 s), delayed (2 min) and hepatobiliary (45-120 min) phases. Gadolinium-diethylenetriamine penta-acetic acid of 15-20 mL was injected intravenously through the back of the hand at a rate of 2 mL/s.

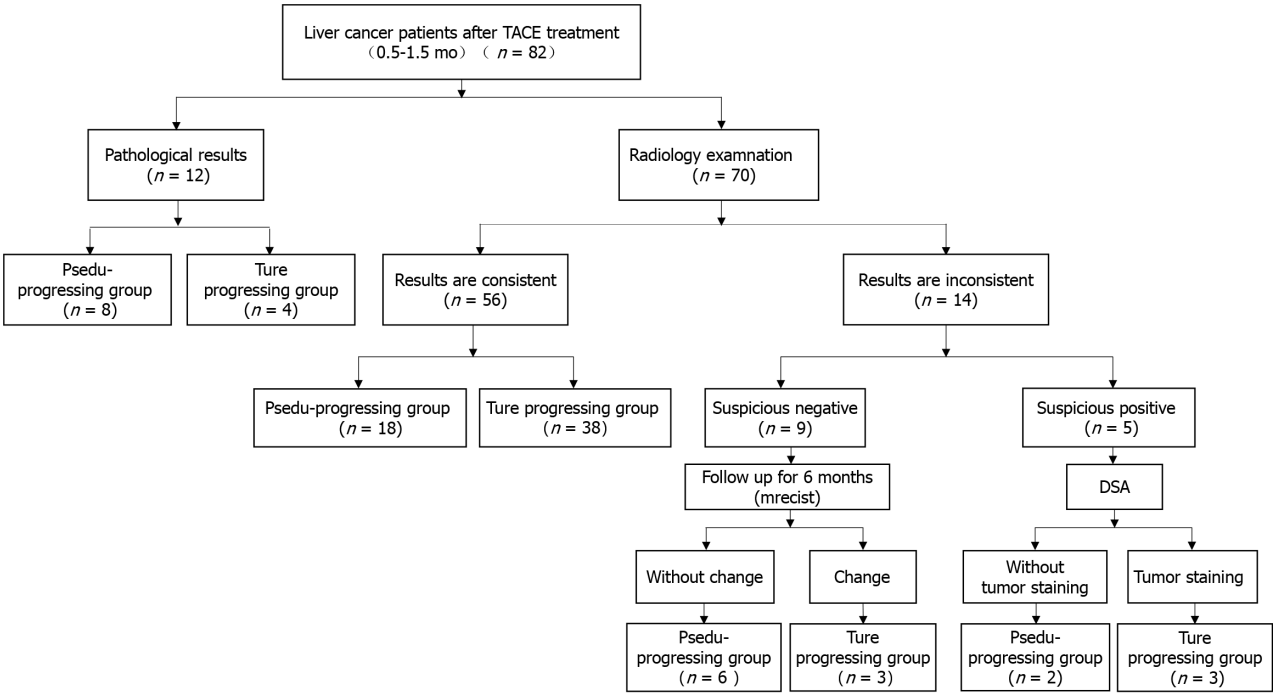

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Figure 1 Flowchart of patient enrollment. *n*: Number of cases; TACE: Transcatheter arterial chemoembolization; mRECIST: Modified response evaluation criteria in solid tumors; DSA: Digital subtraction angiography.

DSA was performed under guidance on a Toshiba rotary DSA (GEIGS530, United States) machine. All patients were approached *via* the femoral artery and routinely underwent skin preparation, disinfection, draping, and local anesthesia in the groin area. After the artery was successfully inserted, the guide wire and catheter sheath were sequentially inserted. The Cook 5-F RH tube was introduced to select the abdominal trunk or common hepatic angiography to observe the tumor staining.

Data analysis

Two professional radiologists (Hansen and HC), with 30 and 10 years of experience in MRI assessment, respectively, independently recorded the imaging and clinical data of the true progression and pseudo-progression groups (Table 1). All acquired DKI images were examined on the workstation using vendor-supplied postprocessing software (GE AW4.6 advantage, United States). The corresponding mappings of DKI-derived parameters (*i.e.*, MD, DA, DR, MK, KA, KR, and FAk) were obtained. The two radiologists independently selected the regions of interest (ROIs) for TACE-treated area, peritumoral area (distance < 2 cm to the tumor), and long-distance area (distance > 5 cm) on anatomical DKI image at b = 0 s/mm^2 and then copied them on each of the DKI-derived parametric maps (Figure 2). Each expert selected two different ROIs and calculated the average value. All chosen ROIs of a circular or oval form were selected carefully to avoid necrotic area. Considering the inter-subject variation, all obtained values were standardized based on the following formulas: $Std_{pseudoprogression}$ = ROI (pseudo-progression lesion)/ROI (normal parenchyma) and $Std_{progression}$ = ROI (progression lesion)/ROI (normal parenchyma).

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences version 22.0 statistical software. Intra-class correlation coefficient (ICC) analysis was performed to evaluate the inter-agreement of DKI parameter assessment by the two professional experts. The non-parametric U test and receiver operating characteristic (ROC) curve analysis were used to evaluate the differences and prediction performance of the DKI-derived parameters. The independent sample t-test was used to compare all DKI metrics in the peritumoral zone (distance < 2 cm) and the far-tumoral zone (distance > 5 cm) of the true progression group. $P < 0.05$ was considered statistically significant.

Table 1 Summary of clinical data of patients in true and pseudo-progressing groups

Characteristic	All cases (*n* = 82)	True group (*n* = 48)	Pseudo-group (*n* = 34)	*P* value
Age range (yr)	55 ± 12	50 ± 16	53 ± 14	0.745
Male/female (*n*)	46/30	26/18	20/12	0.402
AFP (ng/mL) (+/-)	49/33	47/1	2/32	0.001
	Tumor-related characteristics			
Tumor size (cm)	4.0 ± 1.8	4.2 ± 1.6	2.7 ± 1.3	0.142
Enhancement (+/-)	50/32	46/2	4/30	0.006
DSA (+/-)	42/27	42/2	0/25	< 0.010
Resection (+/-)	10	9	1	-
TACE times (single/repeated)	26/56	4/44	22/12	< 0.011
Follow-up for > 6 mo (+/-)	39/33	39/0	0/33	< 0.001

AFP: Alpha-fetoprotein; DSA: Digital subtraction angiography; TACE: Transcatheter arterial chemoembolization.

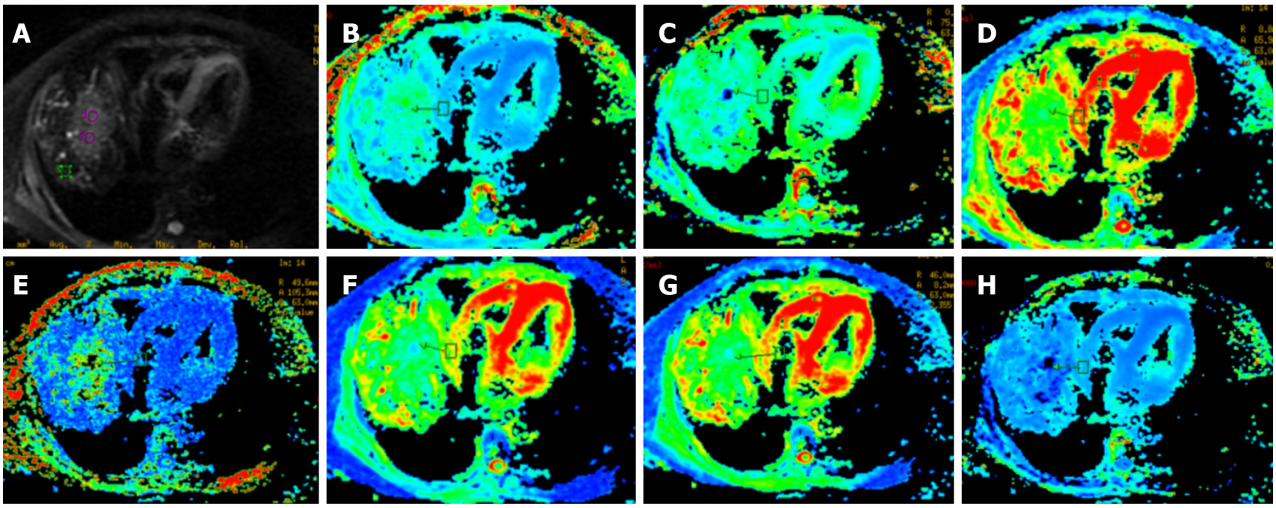

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Figure 2 Representative maps of transcatheter arterial chemoembolization-treated and recurrent hepatocellular carcinoma foci. The patient was a 46-year-old man with transcatheter arterial chemoembolization-treated and recurrent hepatocellular carcinoma foci. A: Diffusion map with b = 0 s/mm^2; B: Maps of mean kurtosis (MK); C: Maps of mean diffusivity (MD); D: Maps of radial kurtosis (KR); E: Maps of axial kurtosis (KA); F: Maps of axial diffusivity (DA); G: Maps of radial diffusivity (DR); H: Maps of anisotropy coefficient of kurtosis (FAk). In the first map (A), the region of interest (ROI) (1) corresponds to the arrow pointing to a new lesion. The peritumoral zone (distance < 2 cm) refers to ROI (2) (red circle), and far-tumoral zone (diameter > 5 cm) refers to ROI (3) (green square).

RESULTS

Clinical data analysis

Clinical data, including age, gender, and tumor-related characteristics, of patients in the true progression and pseudo-progression groups are summarized in Table 1. There were significantly more patients in the true progression group than in the pseudo-progression group. Moreover, the true progression group had higher serum AFP level (> 200 ng/mL) (P < 0.05) than the pseudo-progression group. In addition, significantly greater proportions of patients in the progression group showed typical enhancement (95.8%) and more or less tumor staining in lipiodol angiography (95.5%). In contrast, tumor size and age range were similar between the two groups (P > 0.05). Among the 48 nodules in the progression group, 44 received repeated TACE, and the mean number of TACE sessions per nodule was 1-3. Four nodules underwent only a single course of TACE.

Inter-observer agreement analysis

As shown in Table 2, ICC analysis was utilised by two radiologists to assess the inter-agreement of each DKI parameter measurement on the TACE-treated region, peritumoral zone, and far-tumoral zone,

Table 2 Evaluation of inter-observer agreement using intra-class correlation coefficient analysis

	MK	MD	KA	KR	DA	DR	FAk
ROI (T)	0.86	0.85	0.80	0.83	0.76	0.78	0.62
ROI (N)	0.79	0.74	0.71	0.76	0.72	0.75	0.54
ROI (F)	0.70	0.73	0.69	0.68	0.64	0.70	0.50

FAk: Anisotropy coefficient of kurtosis; ROC: Receiver operating characteristic curve; MD: Mean diffusivity; MK: Mean kurtosis; KA: Axial kurtosis; KR: Radial kurtosis; DA: Axial diffusivity; DR: Radial diffusivity.

Table 3 Diffusion kurtosis imaging derived metrics in true and pseudo-progressing lesions

	MK	MD	KR	KA	DR	DA	FAk
N	0.60 ± 0.15	1.90 ± 0.65	0.55 ± 0.16	0.60 ± 0.13	1.88 ± 0.55	2.20 ± 0.63	0.10 ± 0.09
Y	0.71 ± 0.24	1.60 ± 0.45	0.65 ± 0.29	0.70 ± 0.15	1.4 ± 0.38	2.10 ± 0.60	0.32 ± 0.22
Std-N	0.68 ± 0.27	1.89 ± 0.58	0.70 ± 0.31	0.61 ± 0.16	2.01 ± 0.54	1.60 ± 0.42	0.54 ± 0.32
Std-Y	0.81 ± 0.23	0.91 ± 0.18	0.75 ± 0.24	1.03 ± 0.20	0.88 ± 0.22	0.92 ± 0.22	1.07 ± 0.78
P value	0.270	0.009	0.679	0.000	0.003	0.000	0.000

N = pseudo-progressing group; Y = true progressing group. FAk: Anisotropy coefficient of kurtosis; MD: Mean diffusivity; MK: Mean kurtosis; KA: Axial kurtosis; KR: Radial kurtosis; DA: Axial diffusivity; DR: Radial diffusivity.

separately. General excellent inter-agreement was confirmed by high ICC values. Among these, optimal measurement consistency was obtained in TACE-treated area for DKI-derived parameter values showing the best consistency, whereas the worst measurement consistency was found in the far-tumoral zone.

Diffusion kurtosis imaging-derived parameter analysis

Compared to pseudo-progression inactive lesions, true progression recurrence lesions were associated with lower values of MD, DA, and DR (1.60 ± 0.45 × 10^{-3} mm/s *vs* 1.90 ± 0.65 × 10^{-3} mm/s, 2.10 ± 0.60 × 10^{-3} mm/s *vs* 2.29 ± 0.63 × 10^{-3} mm/s, and 1.40 ± 0.38 × 10^{-3} mm/s *vs* 1.88 ± 0.55 × 10^{-3} mm/s, respectively; Table 3). However, higher KA and FA values were found in the foci area of true progression lesions than of pseudo-progression lesions (0.70 ± 0.15 *vs* 0.60 ± 0.13 and 0.32 ± 0.22 *vs* 0.10 ± 0.09, respectively; Table 3). Moreover, ROC curve analysis was performed to compared the DKI-derived metrics in predicting recurrence performance (Figure 3). High AUC values were obtained for the parameters MD (0.80), FAk (0.78), KA (0.82), DA (0.82), and DR (0.80), whereas low ICC values were found in MK (0.6) and KR (0.54).

For the true progression group, DA and DR values were lower in the peritumoral zone (distance < 2 cm) than in the far-tumoral zone (distance > 5 cm) (2.11 ± 0.52 × 10^{-3} mm/s *vs* 2.44 ± 0.59 × 10^{-3} mm/s and 1.382 ± 0.440 × 10^{-3} mm/s *vs* 1.647 ± 0.470 × 10^{-3} mm/s, respectively; Figure 4), whereas FAk and KA values showed opposite trends (0.309 ± 0.110 *vs* 0.228 ± 0.060 and 0.809 ± 0.340 *vs* 0.783 ± 0.120, respectively; Figure 3).

In addition, the MD values of the liver parenchyma (peritumoral and far-tumoral zones) were significantly lower in the true progression group than in the pseudo-progression group (0.866 ± 0.330 × 10^{-3} mm/s *vs* 1.677 ± 0.630 × 10^{-3} mm/s and 0.843 ± 0.170 × 10^{-3} mm/s *vs* 1.569 ± 0.410 × 10^{-3} mm/s, respectively; Figure 4D).

DISCUSSION

In this study, we explored the prediction performance of DKI for recurrence and cellular invasion of the peritumoral liver zone of HCC after TACE and further investigated the characteristics of the DKI-derived metrics between the true progression and pseudo-progression groups. Considering the high data consistency between the two experts, we found that most DKI metrics, including MD, DA, DR, KA, and FAk, showed statistically different values between the true progression and pseudo-progression groups ($P < 0.05$). Moreover, for the true progression group, except the metrics MK and KR, all other parameters of the peritumoral liver zone (distance < 2 cm) were significantly different from those of the far-tumoral liver parenchyma (distance > 5 cm). Therefore, we concluded that DKI with derived

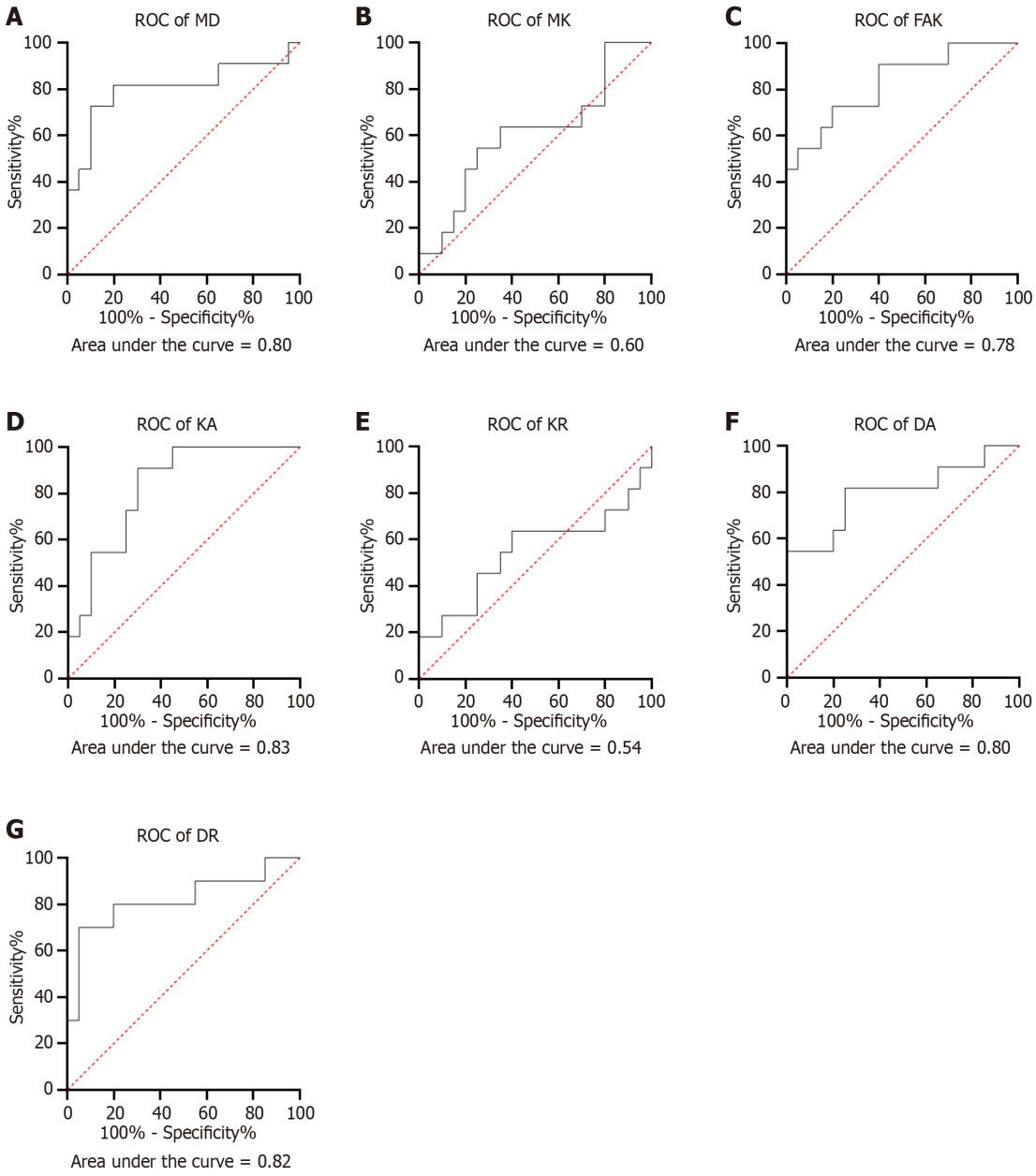

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Figure 3 Receiver operating characteristic curves of diffusion kurtosis imaging metric in predicting recurrence. AUC value greater than 0.7 indicates a higher diagnostic value. A: Mean diffusivity; B: Mean kurtosis; C: Anisotropy coefficient of kurtosis; D: Axial kurtosis; E: Radial kurtosis; F: Axial diffusivity; G: Radial diffusivity. FAk: Anisotropy coefficient of kurtosis; ROC: Receiver operating characteristic curve; MD: Mean diffusivity; MK: Mean kurtosis; KA: Axial kurtosis; KR: Radial kurtosis; DA: Axial diffusivity; DR: Radial diffusivity.

functional metrics showed advantages in assessing the therapeutic response of HCC to TACE and also provided robust performance in evaluating peritumoral zone invasion.

Except for FAk, especially in ROI (F) (far-tumoral zone, distance > 5 cm), all other DKI metrics showed excellent consistency measured by two professional experts. FAk has been shown to have a significant benefit in the central nervous system, where the nerve fibre structure exhibits full fractional anisotropy[14]. Nevertheless, the fibre structure in the liver lacks a defined fractional anisotropy, making it difficult to identify the specificity of FAk. Furthermore, Nasu *et al*[15] established the idea of "pseudo-fractional anisotropy artefact of the liver", which asserts that manual selection of ROI (F) is inherently subjective and can be influenced by heartbeat and breathing artifact. This artefact might be another explanation for low consistency of FAk.

Important findings in this study were that DKI parameters, including MD, DA, DR, KA, and FAk, showed statistical differences between the true progression and pseudo-progression groups ($P < 0.05$). MD, DA, and DR values of pseudo-progression lesions were higher than those of true progression lesions, whereas KA and FAk values were higher in true progression lesions than in pseudo-progression lesions. Yuan *et al*[11] showed significant potential of DKI in assessing the therapeutic response of HCC

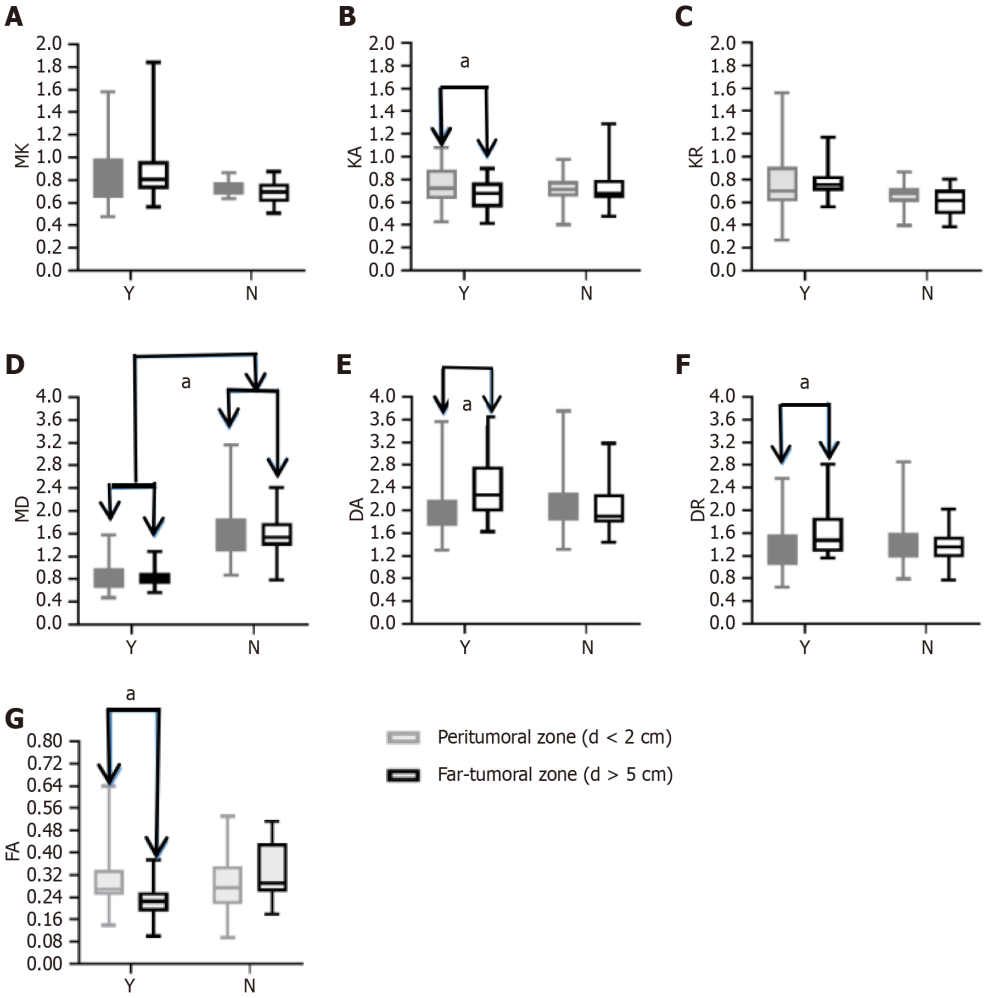

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Figure 4 Box plots showing diffusion kurtosis imaging derived metrics of peritumoral zones between true and pseudo-progressing groups. A: Mean kurtosis (MK); B: Axial kurtosis (KA); C: Radial kurtosis (KR); D: Mean diffusivity (MD); E: Axial diffusivity (DA); F: Radial diffusivity (DR); G: Anisotropy coefficient of kurtosis (FAk). $^{a}P < 0.05$; the unit of MD, DA, and DR is 10^{-3} mm^2/s. N = pseudo-progressing group; Y = true progressing group. FAk: Anisotropy coefficient of kurtosis; MD: Mean diffusivity; MK: Mean kurtosis; KA: Axial kurtosis; KR: Radial kurtosis; DA: Axial diffusivity; DR: Radial diffusivity.

to TACE. Thus, they believed that MK is an effective biomarker in the assessment of HCC progression after TACE. This conclusion, however, is not fully consistent with our results. Compared with the pseudo-progression group with inactive foci after TACE, the normalized MK value of the true progression group with residual/recurrent foci was not higher. Since MK can reflect the complexity and density of tissues[16], high cell density usually shows high MK value. We hypothesized that after TACE, foci cells are swelling and experience degeneration or necrosis, while leads to a decreased cell density. Moreover, some low-activity tumor cells have been severely damaged in structure, but still retain the ability to metastasize and recur. This type of condition cannot be effectively screened out based on the characteristics of tissue density, leading to the absence of statistical difference of the MK value between the true progression and pseudo-progression groups. It is worth mentioning that KA in this study revealed certain sensitivity in assessing tumor recurrence. Follow-up studies should be further conducted to explore the underlying mechanism.

Additionally, the clinical potential of DKI in determining the invasion of peritumoral zone of the residual foci for the true progression group was assessed. We discovered that diffusion metrics (DA and DR) differed considerably between the far-tumoral zone (distance > 5 cm) and the peritumoral zone (distance < 2 cm). The peritumoral zone (distance < 2 cm) had lower DA and DR values than the far-tumoral zone (distance > 5 cm), indicating that microenvironmental alterations may occur in the peritumoral zone, which is close to residual/recurrent foci and may be sensitive in representing cancer cell infiltration. However, only KA revealed a larger value in the peritumoral zone than the far-tumoral zone among the three kurtosis coefficients (MK, KR, and KA).

Despite the fact that a variety of DKI implementations have investigated the correlations of MK and MD with fibrosis or liver function[17-20], no similar DKI findings have been published in these studies. Yoshimaru *et al*[17] investigated the relationship between MK and Child-Pugh score in 79 patients with varying degrees of hepatic decompensation and found a minor correlation. In comparison, Goshima *et al*

[18] investigated the relationship between MK and Child-Pugh score but found no association. There was also disagreement about whether MK or MD had a superior diagnostic effectiveness for liver fibrosis. In another study, Hu *et al*[19] concluded that MD correlated strongly with the degrees of liver fibrosis, and the parameter MK may provide complementary information. In contrast, Li *et al*[20] claimed that MK could best predict the liver fibrosis stage. In this study, we did not analyze the relationship between DKI parameters and liver fibrosis or function. However, the MD value of the liver parenchyma (peritumoral and far-tumoral zones) was lower in the true progression group than in the pseudo-progression group. Moreover, the MK value did not show any difference between the two groups. The results obtained in this study were more inclined to the view that MD has a higher sensitivity to detect the degree of fibrosis. We thus hypothesized that poor liver function and high grade of liver fibrosis may lead to poor prognosis and high recurrence rate.

There are some limitations in the present study. First, manual selection of active ROIs is inevitably subjective. According to the results of dynamic enhancement and DSA imaging, independent measurement by two experienced radiologists can minimize measurement errors. Second, DKI with 5 *b* values and 15 directions per *b* value currently takes a long time of 10 min for imaging. Third, each patient showed different fibrosis state and liver function. To minimize this effect, we selected the liver parenchyma far away from the focus area for standardization. Fourth, there was a lack of pathological examination of tumor changes before and after TACE treatment. Further studies with more pathologically confirmed cases are required to be conducted. Fifth, it was difficult to obtain the histological results for each lesion after TACE. Therefore, no pathological support could determine whether the surrounding liver parenchyma was invaded. Relevant pathological study is requested to further explore the relationship among DKI parameters, liver fibrosis, and peripheral infiltration.

CONCLUSION

In conclusion, DKI metrics (MD, DA, DR, KA, and FAk) have been demonstrated with robust performance in predicting the therapeutic response of HCC to TACE and evaluating cellular invasion of the peritumoral zone.

ARTICLE HIGHLIGHTS

Research background

Transcatheter arterial chemoembolization (TACE) has been used to treat patients with hepatocellular carcinoma (HCC) as a palliative therapy. Nevertheless, HCC is prone to recur after TACE. Traditional anatomical MRI has certain limitations in assessing recurrence. Diffusion kurtosis imaging (DKI) provides a detailed depiction of the microstructural environment. Whether DKI-derived metrics can provide clinical feasibility in predicting HCC recurrence and cellular invasion of the peritumoral liver zone after TACE remains to be a concern.

Research motivation

To investigate the clinical use of DKI in predicting recurrence and cellular invasion of HCC in the peritumoral liver zone after TACE.

Research objectives

In this study, 76 patients with 82 hepatic cancer nodules were enrolled and underwent DKI after TACE. Forty-eight and 34 nodules were divided into two groups: True progression and pseudo-progression, respectively.

Research methods

DKI-derived metric maps were used to assess the TACE-treated area, peritumoral liver zone, and far-tumoral zone. To compare the prediction performance of each DKI metric between the true progression and pseudo-progression groups, the non-parametric *U* test and receiver operating characteristic curve (ROC) analysis were performed. The independent *t*-test was utilized to compare each DKI metric between the peritumoral and far-tumoral zones in the true progression group.

Research results

DKI metrics, including mean diffusivity (MD), axial diffusivity (DA), radial diffusivity (DR), axial kurtosis (KA), and anisotropy fraction of kurtosis (Fak), exhibited significantly different values between the true progression and pseudo-progression groups, respectively ($P < 0.05$). Furthermore, the peritumoral zone had substantially different DA, DR, KA, and FAk values than the far-tumoral zone in the true progression group. Additionally, MD values of the liver parenchyma (peritumoral and far-

tumoral zones) were substantially lower in the true progression group compared to the pseudo-progression group ($P < 0.05$).

Research conclusions

DKI has been shown to predict the therapeutic response of HCC to TACE with high accuracy. Furthermore, DKI may indicate cellular invasion of the peritumoral zone by molecular diffusion-restricted change.

Research perspectives

This study systematically investigated the clinical feasibility of all DKI-derived metrics in predicting recurrence and cellular invasion of the peritumoral liver zone of HCC after TACE, providing an accurate evaluation method to help guide subsequent therapeutic planning in clinical practice for patients with HCC after TACE.

FOOTNOTES

Author contributions: Cao X and Wang JY designed and performed the research, and wrote the paper; Shi H designed the research and supervised the report; Zheng YX, Ge YP, and Cheng HC contributed to the analysis; Dou WQ, Zhao XY, and Geng DY provided clinical advice.

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Data sharing statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to protecting patient privacy.

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CASE REPORT

Cecocutaneous fistula diagnosed by computed tomography fistulography: A case report

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Abstract

BACKGROUND

Enterocutaneous fistula (ECF) is an abnormal communication between the skin and the gastrointestinal tract and is associated with considerable morbidity and mortality. To diagnose ECF, X-ray fistulography and abdominal computed tomography (CT) with intravenous or oral contrast are generally used. If the anatomic details obtained from CT are insufficient, CT fistulography may help diagnose and determine the extent of the abnormal channel. However, CT fistulography is seldom performed in patients with insufficient evidence of a fistula.

CASE SUMMARY

A 35-year-old man with a prior appendectomy presented with purulence over the abdominal wall without gastrointestinal tract symptoms or a visible opening on the abdominal surface. His history and physical examination were negative for nausea, diarrhea, muscle guarding, and bloating. Local abdominal tenderness and redness over a purulent area were noted, which led to the initial diagnosis of cellulitis. He was admitted to our hospital with a diagnosis of cellulitis. We performed a minimal incision on the carbuncle to collect the pus. The bacterial culture of the exudate resulted positive for *Enterococcus* sp. ECF was thus suspected, and we arranged a CT scan for further investigation. CT images before

intravenous contrast administration showed that the colon was in close contact with the abdominal wall. Therefore, we conducted CT fistulography by injecting contrast dye into the carbuncle during the CT scan. The images showed an accumulation of the contrast agent within the subcutaneous tissues, suggesting the formation of an abscess. The contrast dye tracked down through the muscles and peritoneum into the colon, delineating a channel connecting the subcutaneous abscess with the colon. This evidence confirmed cecocutaneous fistula and avoided misdiagnosing ECF without gastrointestinal tract symptoms as cellulitis. The patient underwent laparoscopic right hemicolectomy with re-anastomosis of the ileum and transverse colon.

CONCLUSION
CT fistulography can rule out ECF in cases presenting as cellulitis if examinations are suggestive.

Key Words: Cecocutaneous fistula; Enterocutaneous fistula; Computed tomography fistulography; Laparoscopy; Hemicolectomy; Case report

Core Tip: Computed tomography (CT) fistulography is seldom performed on patients with insufficient evidence of fistula; however, it provides more accurate anatomical details than X-ray fistulography and abdominal CT. A 35-year-old man with swelling and purulence over the abdominal wall was admitted to our hospital under the diagnosis of cellulitis. Serial examinations suggested a possible enterocutaneous fistula (ECF); thus, we performed CT fistulography. Images showed the subcutaneous contrast agent tracked down through the muscle and peritoneum into the cecum, confirming a cecocutaneous fistula. CT fistulography may rule out ECF in patients presenting with cellulitis if examinations are suggestive.

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INTRODUCTION

Enterocutaneous fistula (ECF) is an abnormal channel connecting the skin and the gastrointestinal tract. It occurs most often after abdominal surgery (75%-85%), and only 15%-25% of cases occur spontaneously[1,2]. X-ray fistulography with oral contrast and abdominal computed tomography (CT) with intravenous or oral contrast are generally used to diagnose ECF. If radiographic findings from X-ray fistulography and CT scan are insufficient, CT fistulography is a good alternative[3,4]. However, CT fistulography is seldom used without strong evidence of ECF.

Herein, we present the case of a 35-year-old man admitted to the hospital with presumed abdominal wall cellulitis. However, a series of events provided evidence supporting the diagnosis of ECF. Therefore, we elected to conduct CT fistulography, which provides more accurate anatomical details compared to a simple CT scan.

CASE PRESENTATION

Chief complaints

Abdominal wall swelling and pain for a week.

History of present illness

A 35-year-old man presented to the outpatient department with painful swelling and mass formation over the right lower quadrant abdominal wall for one week. No fever or gastrointestinal symptoms were reported. Oral intake and defecation were normal. The patient was hospitalized with a suspected diagnosis of cellulitis.

History of past illness

The patient was diagnosed with acute appendicitis and underwent an appendectomy 15 years ago in 2006. No history of underlying abdominal malignancy, inflammatory bowel disease, abdominal trauma,

or other gastrointestinal diseases was reported.

Personal and family history

There was no family history of abdominal neoplasms, inflammatory bowel disease, or ECF. The patient exhibited normal social functioning and self-care.

Physical examination

The vital signs, including body temperature, were within the normal ranges. Abdominal palpation revealed a mass over the right lower abdominal wall without visible opening and suspected abscess formation. Local abdominal tenderness and redness over purulence were noted. No nausea, diarrhea, muscle guarding, or bloating was observed, which led to the initial diagnosis of cellulitis.

Laboratory examinations

In outpatient department, we performed a minimal incision of the lesion to collect discharge for bacterial culture and blood analysis was also performed. Lab reports revealed a white blood cell count of 20.17 × 10^3/μL, 79.9% neutrophils and 12.4% lymphocytes, and a serum C-reactive protein concentration of 19.60 mg/dL. The bacterial culture of the lesion pus revealed the presence of *Enterococcus* sp. Based on these results, ECF was suspected.

Imaging examinations

We performed a colonoscopy and observed inflammation in the ileocecal valve region (Figure 1). CT of the abdomen in the axial view suggested that the colon was in close contact with the abdominal wall (Figure 2A), highly suggestive of ECF. We conducted CT fistulography by injecting contrast dye into the carbuncle for a more detailed radiographic view and a definitive diagnosis. Images after contrast administration showed the presence of contrast dye in both the abdominal wall and the colon (Figure 2B). Coronal images showed contrast dye retention in the subcutaneous area (Figure 2C) with penetration through the abdominal wall (Figure 2D) into the colon (Figure 2E).

FURTHER DIAGNOSTIC WORK-UP

The laboratory results and the imaging examinations indicated the existence of a cecocutaneous fistula. Therefore, we performed a diagnostic laparoscopy, during which we could observe severe adhesion of the colon to the abdominal wall. This evidence allowed us to formulate the final diagnosis of the cecocutaneous fistula.

TREATMENT

The patient underwent laparoscopic right hemicolectomy, reanastomosis of ileum and transverse colon, and peritoneal repair. During surgery, severe adhesion of the colon to the abdominal wall was noted (Figure 3A). After tissue adhesiolysis (Figure 3B), colon resection, and reanastomosis, a peritoneal defect was reported. We thus performed peritoneal repair with a V-LOC suture line (COVIDIEN™ 1-0 V-LOC, Medtronic, Ireland) to prevent hernia and adhesion (Figure 3C). Upon debridement of the infected abdominal wall, a fascial defect due to the outer opening of the fistula was noted (Figure 4A). Finally, a Penrose drainage tube was placed (Figure 4B). The surgical specimen consisted of the resected colon with attached peritoneum (Figure 4C). The histopathological results suggested a fistula with multifocal chronic inflammation. Microscopically, abscess formation with focal regeneration atypia of the soft tissue were found, with no granulomatous inflammation.

OUTCOME AND FOLLOW-UP

After surgery, we kept administering antibiotics with Ampicillin 1g + Sulbactam 0.5g IV Q6H and used chlorhexidine gluconate 2% solution for daily skin surface disinfection. The wound remained stable without contracting infections. Swelling and redness over the abdominal wall gradually improved. The highest temperature during the hospital stay was 37.3C on the fourth day after the operation. The final data before discharging were a white blood cell count of 11.44 × 103/μL, 68.9% neutrophils and 22.1% lymphocytes, and a serum C-reactive protein concentration of 1.99 mg/dL. The patient was discharged from the hospital one week after surgery. No wound infection or gastrointestinal symptoms were noted during outpatient follow-up 6 mo after surgery. The patient's oral intake recovered due to the short course of treatment and the absence of any further surgical operation. The patient was satisfied with the treatment outcome, and further hospitalization was not required. The treatment timeline from

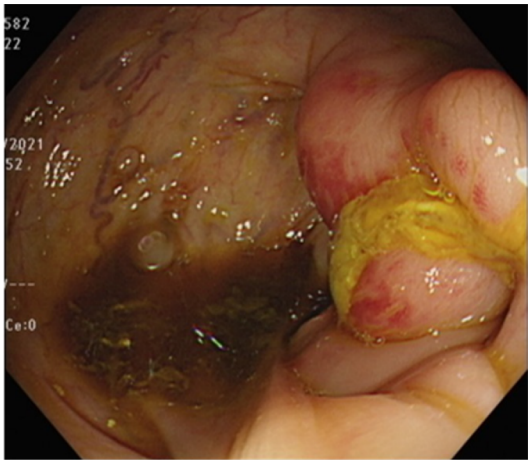

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Figure 1 Colitis in the ileocecal valve region.

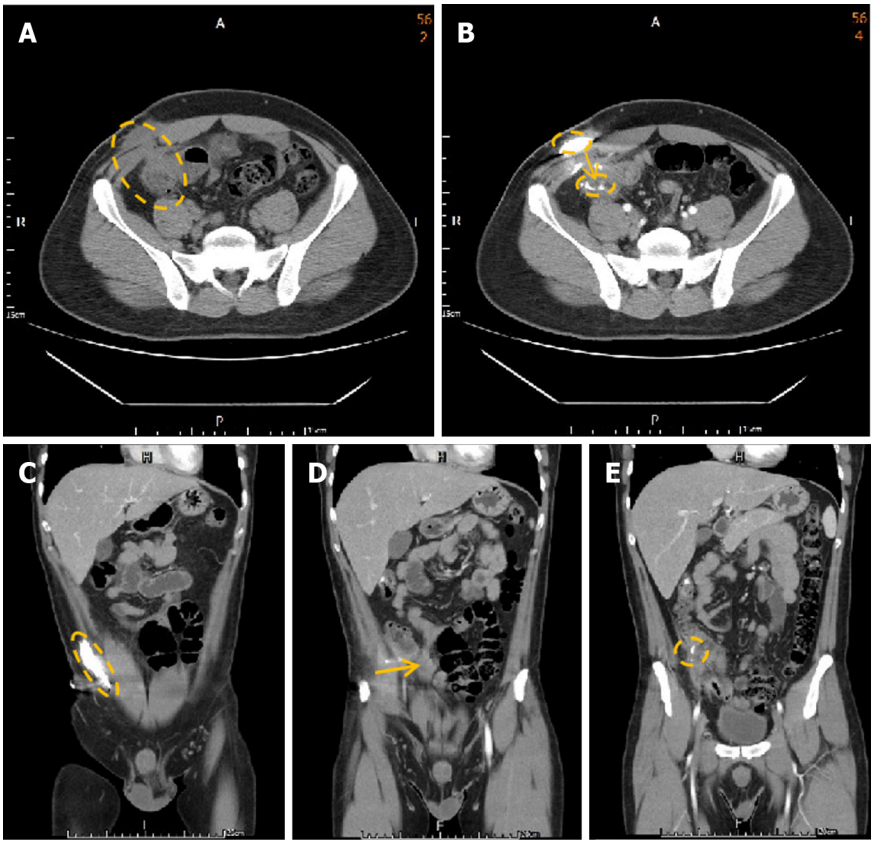

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Figure 2 Abdominal computed tomography with contrast injection from the abdominal opening. A: The axial computed tomography (CT) demonstrates the colon in close contact with the abdominal wall; B: The axial CT with contrast injection into the abdominal carbuncle demonstrates the canal between the abdominal wall and colon; C: Contrast was injected from the carbuncle and accumulated in the subcutaneous area, indicating abscess formation; D: Contrast dye extended through the canal between the abdominal wall and colon; E: Contrast finally arrived at the colon.

admission to discharge is shown in Figure 5.

DISCUSSION

Although cecocutaneous fistulae are rare, they still contribute to considerable morbidity and mortality. Major etiological factors of cecocutaneous fistula include abdominal tuberculosis, neoplasm of the appendix or cecum, leakage from the appendiceal stump, and inflammatory bowel disease[1,5]. In

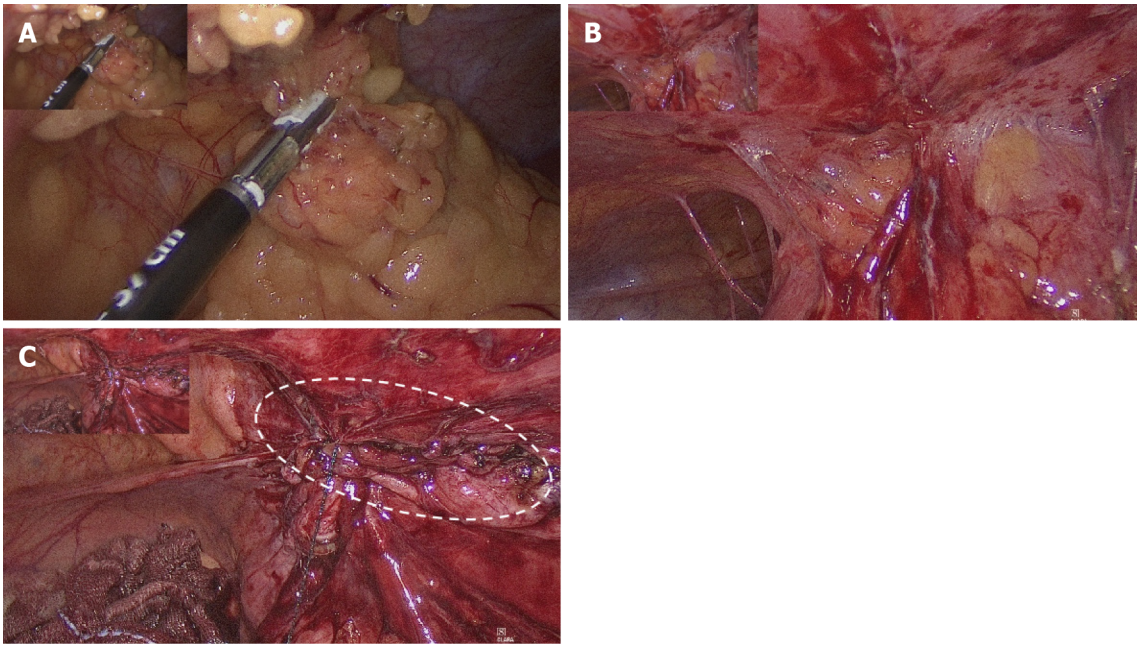

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Figure 3 Intraoperative laparoscopic images. A: Severe adhesion of the colon with the abdominal wall; B: After tissue adhesiolysis, severe peritoneal adhesion was noted; C: After colon resection and re-anastomosis, a peritoneal defect was found; peritoneal repair with V-LOC suture line was thus performed to prevent hernia and adhesion.

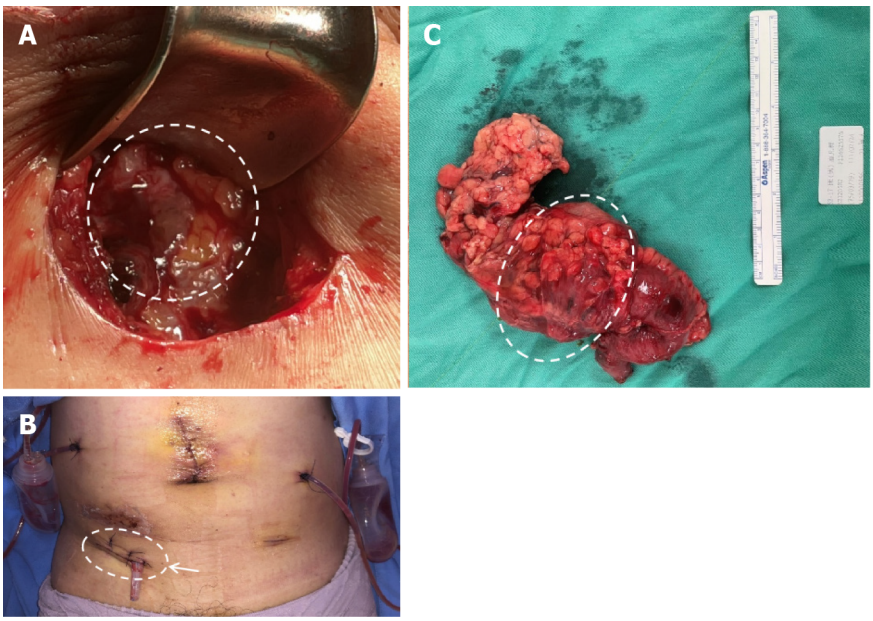

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Figure 4 Postoperative image. A: Fascia defect due to infection caused by the external opening of the fistula into the subcutaneous layer; B: Fascia defect post debridement and closure and Penrose drainage tube placement; C: Specimen including the resected colon with the attached peritoneum.

addition, some cases of cecocutaneous fistula were reported as related to a previous appendectomy[6], while some others were related to an underlying stump appendix[7]. Investigation of the patient's history was negative for abdominal malignancy, inflammatory bowel disease, abdominal trauma, or any other gastrointestinal disease. The histopathological report of the resected colon showed a fistula with multifocal chronic inflammation. Microscopically, it evidenced abscess formation with focal regeneration atypia of the soft tissues, with no granulomatous inflammation. The single abnormal finding in the history was the appendectomy in 2006, which was preliminarily compatible with the result of the diagnostic laparoscopy (cecum attached to the peritoneum). Appendectomy might have been a possible reason for the fistula.

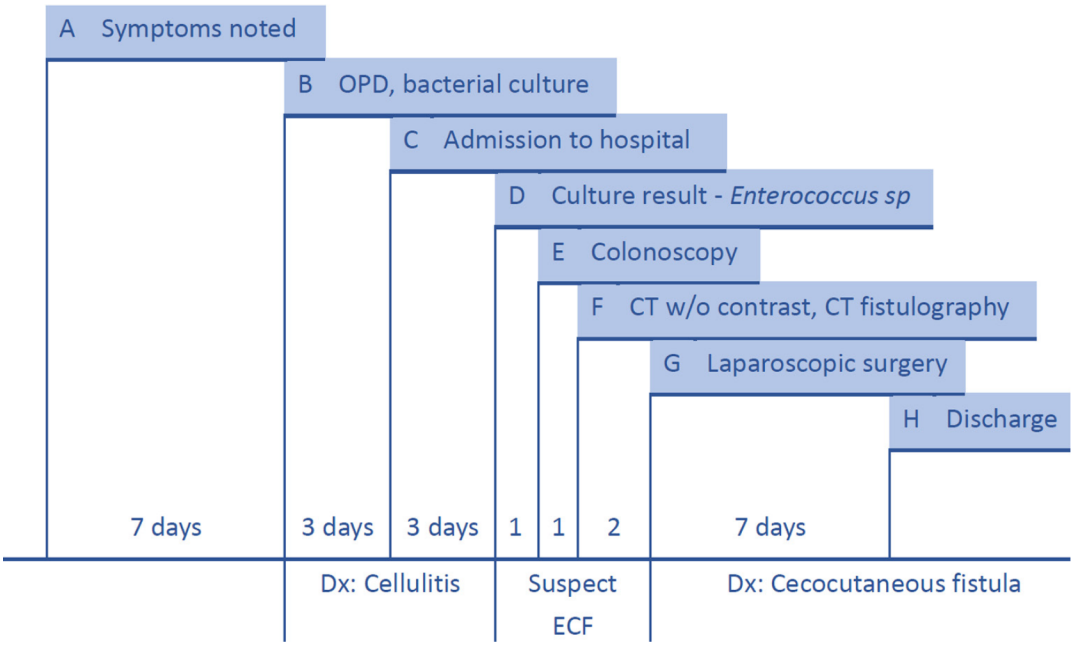

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Figure 5 Timeline. A: Redness and swelling over the right lower quadrant abdominal wall were noted; B: The patient came to the outpatient department for help; discharge from the carbuncle abscess was collected for bacterial culture. Blood analysis was performed; C: The patient was admitted to our hospital under the diagnosis of cellulitis (redness and a mass formation over the abdominal wall without visible opening or intestinal tract symptoms); D: The bacterial culture of the discharge produced Enterococcus sp. Enterocutaneous fistula was suspected; E: We performed a colonoscopy and observed inflammation in the ileocecal valve region; F: Abdominal computed tomography (CT) without contrast suggested that the colon was in close contact with the abdominal wall. We thus performed CT fistulography; G: Diagnostic laparoscopy showed severe adhesion of the colon to the abdominal wall. We conducted laparoscopic right hemicolectomy and reanastomosis; H: The patient was discharged from the hospital one week after surgery.

Different protocols and modalities for the treatment of ECF have been reported in the literature[3,8,9]. Most of them include four phases: Treatment of sepsis, nutrition support, definition of fistula anatomy, and definitive intervention. Surgical intervention is not necessary in all cases; some fistulae close spontaneously. Patients with ECF associated with independent adverse factors conditioning non-spontaneous closure (including sepsis, high output, and multiple fistulae) may need surgical treatment [10]. Besides surgery, there are several other methods for the management of ECF, including negative pressure wound therapy (NPWT), stent placement, fibrin glues, and endoscopic management[5]. Stent placement plays an important role in the drainage of sepsis[11]. Recently, a 3D-printed patient-personalized fistula stent was successfully implanted in patients, reducing the fistula output[12]. NPWT has the advantage of lowering the effluent volume of enteric fistulae, in some cases leading to spontaneous closure; however, it often entails a longer treatment time. Fibrin glues are an option when the fistula has low-to-medium effluent volume, surgery is not possible, the fistula has complex branching, or is only accessible from a small external orifice[13,14]. Endoscopic minimally invasive management is emerging as a choice for gastrointestinal fistulae, and it may be safer and more effective than surgery[15,16]. Surgery is usually time-consuming and requires extensive adhesiolysis[17].

In this case, we suspected adhesions of the colon and peritoneum. The patient opted for a treatment that would ensure low recurrence and a prompt resolution. Considering his young age and his relatively stable condition, we finally opted for surgery rather than endoscopic management or conservative treatment. We performed laparoscopic resection with reanastomosis, which has a lower recurrence rate than oversewing surgery[18].

Despite the wealth of treatments for ECF, diagnosis has always been challenging. The diagnostic process generally includes X-ray fistulography and abdominal CT with intravenous contrast. X-ray fistulography has recently been replaced by abdominal CT, which better reveals the anatomy of the gastrointestinal tract and provides more information about the associated pathology. If anatomical details obtained using X-ray fistulography and CT are insufficient, CT fistulography helps to identify and determine the extent of the abnormal channel[3,4].

In this case, physical examination revealed a mass over the right lower abdominal wall without visible opening and suspected abscess formation. Absence of nausea, diarrhea, abdominal tenderness, muscle guarding, or bloating led to the initial diagnosis of cellulitis. Bacterial culture revealed *Enterococcus* sp., and CT images before administering the contrast agent showed that the colon was in close contact with the abdominal wall. ECF was thus highly suspected. Because CT with intravenous contrast agent may provide insufficient anatomical details concerning fistulae, we conducted CT fistulography by injecting contrast dye into the carbuncle. The resulting images showed definitive evidence of a

cecocutaneous fistula.

Though CT fistulography is an option that provides more detailed anatomical information, it is still seldom utilized in patients with insufficient evidence of fistula[3]. ECF without gastrointestinal symptoms may mimic cellulitis. Once a fistula is suspected according to our diagnostic evaluation (*e.g.*, bacterial culture, X-ray fistulography, CT without contrast), CT fistulography can be used to diagnose or rule out ECF.

A significant problem with CT fistulography is that the contrast agent sometimes cannot be administered through the fistula because of adhesions and continuous purulent discharge; in such cases, magnetic resonance imaging (MRI) may be considered. MRI has superior soft tissue discrimination. Magnetic resonance enterography (which is a variant of MRI, has been used to rule out small bowel pathology and delineate fistula anatomy. Magnetic resonance enterography has also been used to detect colon disease[19], but it was initially used for small bowel investigation. Therefore, its application as diagnostic imaging of the colon still warrants further evidence.

The current challenge is that a simple CT scan may provide insufficient anatomical details of the fistula[3]. Furthermore, most advanced examinations, including CT and MRI, are expensive. Thus, a fistula may get neglected following a plain CT scan, and CT fistulography/MRI may not be arranged. In this case, we suspected ECF due to the positive bacterial culture and performed CT fistulography. However, most physicians may not perform advanced examinations without evidence suggesting fistula. Therefore, several ECF cases may be neglected or misdiagnosed. Despite the availability of various diagnostic methods, the indications for performing further examinations are pivotal in the process and require adequate discussion.

CONCLUSION

ECF without gastrointestinal symptoms or visible openings may be misdiagnosed as cellulitis. X-ray fistulography and abdominal CT sometimes provide insufficient anatomical details, thus leading to misdiagnosis. CT fistulography may rule out ECF in patients presenting with cellulitis if examinations are suggestive.

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FOOTNOTES

Author contributions: Wu TY, Pu TW, Lo KH, Chen CY, Hu JM, and Kang JC designed and performed the research; Wu TY and Pu TW analyzed the data and wrote the manuscript.

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CASE REPORT

Immunoglobulin G4-related disease in the sigmoid colon in patient with severe colonic fibrosis and obstruction: A case report

Wen-Li Zhan, Liang Liu, Wei Jiang, Fang-Xun He, Hai-Tao Qu, Zhi-Xin Cao, Xiang-Shang Xu

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Abstract

BACKGROUND

Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated condition characterized by abundant IgG4 positive plasma cells and fibrosis in the affected tissues. It affects most parts of the body; however, there are not many reports on IgG4-RD involving the colon.

CASE SUMMARY

A 50-year-old man complaining of intermittent fever for more than two years was referred to our hospital. Based on various investigations before surgery, we diagnosed him with chronic perforation of the sigmoid colon caused by inflammatory change or tumor. IgG blood tests before the operation suggested IgG4-RD, and postoperative pathology confirmed this prediction.

CONCLUSION

We present a patient with IgG4-RD with colon involvement, which is an uncommon site. This report will expand the understanding of IgG4-RD in unknown tissues.

Key Words: Immunoglobulin G4-related disease; Chronic colon disease; Plasma cells; Fibrosis; Obstruction; Case report

Core Tip: Immunoglobulin G4-related disease (IgG4-RD) is characterized by abundant IgG4 positive plasma cells and fibrosis in the affected tissues. It can affect most parts of the body, but there were not many reports of IgG4-RD in the intestines. This patient was an IgG4-RD case to be reported in the colon, which was identified by computed tomography, magnetic resonance imaging, pathology and blood tests of IgGs. This case report will help expand the understanding of IgG4-RD in some unknown tissues.

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INTRODUCTION

Immunoglobulin G4-related disease **(**IgG4-RD) is an immune-mediated condition characterized by infiltration of IgG4 positive plasma cells and fibrosis in the affected tissues[1]. It was first identified as a distinct disease in 2003[2]. Due to lack of understanding in the past, this condition was misdiagnosed or could not be diagnosed. In recent years, awareness of the disease has increased over the past 20 years. The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) IgG4-RD criteria were also formed and published[3]. Hence, many patients were diagnosed with IgG4-RD and received personalized treatment. Although it can affect almost any part of the body, it shows a strong preference for some organs (Figure 1), including salivary glands, lacrimal glands and orbitals, pancreas and biliary ducts, lungs, kidneys, aorta and retroperitoneum, meninges, and thyroid gland[4,5]. Typical manifestations of IgG4-RD are enlarged salivary and lacrimal glands, orbital pseudotumor, pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis, tubular interstitial nephritis, and Liddell's thyroiditis[6].

Histopathology is still required to confirm the diagnosis, with the main histological features being IgG4-positive plasma cell infiltration, storiform fibrosis, and obliterative phlebitis[1]. Increased IgG4-positive plasma cells are seen in nearly all affected tissues; however, there is no specific clinical manifestation. Certain diseases such as lymphoma, vasculitis, and inflammatory bowel disease may also exhibit increased IgG4-positive plasma cells without storiform fibrosis and obliterative phlebitis[7,8]. In addition, the latter two features are not evident in the bone marrow and lymph nodes, making these two sites undesirable for histopathological investigations[9]. Additionally, the imaging features of IgG4-RD are as follows: A diffusely enlarged pancreas surrounded by capsule-like edema ("sausage-shaped" pancreas) and the anterolateral aorta wrapped by soft tissue in the case of retroperitoneal fibrosis[10-12]. However, isolated radiological findings are insufficient for diagnosis. ^{18}Fluorodeoxyglucose-positron emission tomography (PET) can scan the entire body for staging and help find the sampling site[13].

IgG4-RD's incidence is still underestimated because the disease is not clinically manifested and rarely leads to immediate organ failure[14]. Many patients are diagnosed accidentally or through histopathology after surgical resection[15]. IgG4-RD is a multi-organ disease that can easily be confused with malignancies, infections, or other conditions. It is also characterized by slow disease progression, but exacerbations to fibrotic disease often lead to irreversible organ dysfunction[8]. Therefore, early recognition and diagnosis are of vital importance.

Intestinal involvement is not common in IgG4-RD, although sporadic reports have been published [16-19]. Therefore, more cases are needed to demonstrate that IgG4-RD can involve the gut. In this article, we will report the data of a patient with IgG4-RD involving the sigmoid colon, hoping to increase the understanding of IgG4-RD disease.

CASE PRESENTATION

Chief complaints

A 50-year-old man presented with intermittent fever for more than two years.

History of present illness

Intermittent fever occurred for more than two years. The body temperature remained at approximately 37.5 °C, and the fever usually occurred in the afternoon for 3–4 d a week. The fever was rarely high and often resolved without any treatment. The patient had been to the department of infectious diseases for treatment; however, no specific infection was found.

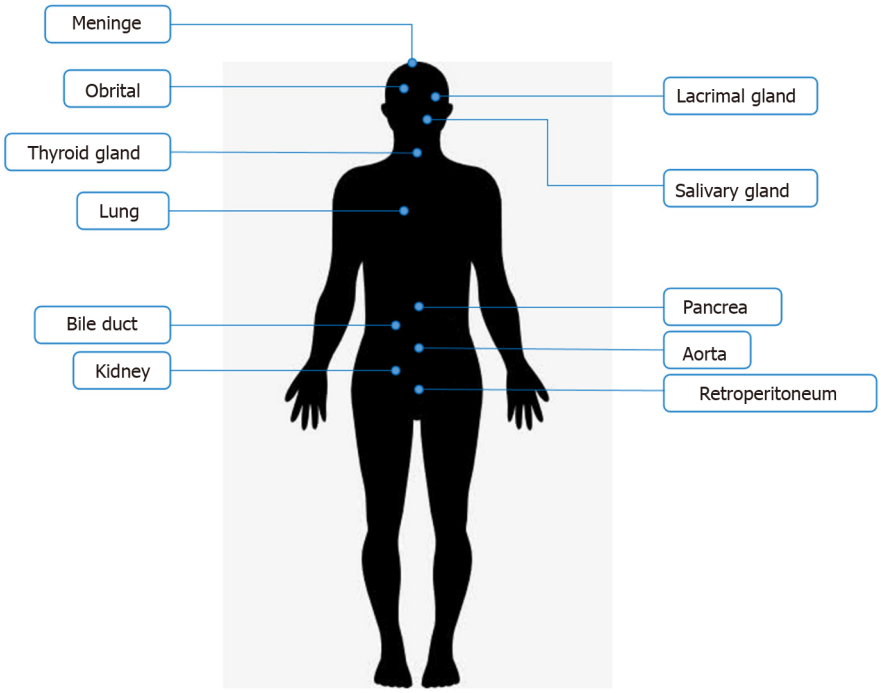

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Figure 1 Commonly affected organs in immunoglobulin G4-related disease. Immunoglobulin G4-related disease often appears in salivary glands, lacrimal glands, pancreas, and biliary tract.

Six months ago, he had frequent and urgent micturition and increased nocturia. He went to the urology department, where prostatic hyperplasia was considered after ultrasound detection, but there was no cystoscopy or biopsy to be done. Then he was treated with tamsulosin hydrochloride and the symptoms, although partially alleviated, did not disappear fully.

Two months ago, he began to experience increased bowel movements and a feeling of incomplete bowel movements, accompanied by a bloated lower abdomen. So he came to the Gastrointestinal Surgery Clinic, and we ordered a colonoscopy and admitted him to the hospital.

History of past illness

Our patient had a 30-year-old history of hepatitis B without blatant virus replication. He also had allergic rhinitis for > 20 years, with the onset usually in August and September every year and relieved by itself after the season. He was allergic to ragweed pollen in 2017 and was cured by mometasone furoate nasal spray combined with cetirizine hydrochloride. He has never developed sinusitis.

Personal and family history

The main drugs used in the patient's medical records were interferon, cetirizine hydrochloride, mometasone furoate, and tamsulosin hydrochloride. He did not have a smoking and alcohol consumption history.

His family had no apparent history of colon tumors and autoimmune disease. Both his father and mother had died of cardiovascular diseases. Additionally, his mother had a history of hepatitis B.

Physical examination

Physical examination showed mild tenderness above the symphysis pubis in the lower abdomen without rebound pain. No other abnormality was seen.

Laboratory examinations

The white blood cells count was normal as the baseline level, and hemoglobin was 92 g/L. The biochemical blood tests were within the normal range, including transaminases, bilirubin, amylase, and lipase. The tumor markers carcinoembryonic assay, cancer antigen 19-9, cancer antigen 72-4, and prostate-specific antigen were normal, while the urine culture and tuberculosis screening tests were negative. Nevertheless, this patient had a positive fecal occult blood test.

Imaging examinations

PET/computed tomography (CT) revealed a thick-walled cystic structure above the bladder, which was approximately 8.1 cm × 7.1 cm in size with increased radioactive uptake, and the maximum standard

uptake value (SUVmax) was 6.0. Thus, a diagnosis of a tumor or chronic infection-related mass was made. PET-CT examination did not find high uptake in the parotid gland, pancreas, biliary tract, and prostate (Figure 2).

An enhancement CT scan of the entire abdomen showed a noticeable expansion of the proximal sigmoid colon with significant intestinal content. The intestinal wall was thickened with contrast enhancement, and the boundary between the sigmoid colon and bladder was not evident in the apparent bladder compression (Figure 3). Hence, the possibility of the colonic diverticulum with infection or tumor was considered. We scanned the pancreas by CT and magnetic resonance imaging (Figure 4) and found an enlarged pancreas similar to the "sausage-shaped" pancreas finding in IgG4-RD.

Endoscopy and biopsy pathology

In the electronic colonoscopy, the lesion was located at the sigmoid colon. It was about 40 cm away from the anus with a blind cavity of 6 cm in diameter. The intestinal cavity is next to the blind hole with a large number of feces. Therefore, the colonoscope could no longer observe upwards (Figure 5).

A tissue biopsy was performed on the thickened and enlarged part of the sigmoid colon. While the intestinal wall of the biopsy was hard, the bleeding was negligible. The biopsy pathology chiefly showed inflammatory necrotic and granulomatous tissue; no defined tumorous cells were seen (Figure 6).

Initial diagnosis

Based on all the preoperational investigations, the initial diagnosis was an inflammatory disease of the sigmoid colon with chronic intestinal perforation, with a localized pelvic abscess formed between the sigmoid colon and bladder. However, the possibility of sigmoid colon tumors could not be ruled out.

Further diagnostic work-up

After the operation, pathological results (Figure 7) showed multiple ulcers distributed in the diseased intestinal wall. The ulcers were surrounded by obliterative phlebitis, widespread inflammatory granulation, and fibrous tissue. Many plasma cells and neutrophils infiltrated the lesion tissues. Furthermore, immunohistochemistry showed high IgG4-positive cells in the diseased tissues ($IgG4^+/IgG^+$ ratio was about 60%, $IgG4^+$/HPF was about 110 cells). Therefore, the pathological diagnosis was IgG4-RD in the sigmoid colon.

Immunology-related blood indices (Tables 1 and 2) showed that the IgG4 level was 1. 830 g/L, which was higher than normal (for IgG4-RD, the cut-off value is > 1. 35 g/L).

FINAL DIAGNOSIS

Combined with pathology results, immunohistochemistry, and blood IgG indices, we diagnosed this patient with IgG4-RD involved sigmoid colon and pancreas.

TREATMENT

After signing the informed consent from the patient, we performed exploratory laparoscopic surgery, and during the surgery, we found that the patient's sigmoid colon was too long, and the proximal sigmoid colon moved down and attached to the left side of the bladder, forming a 6 cm × 6 cm mass. There were no apparent abnormalities in the stomach, small intestine, and the rest of the colon and rectum. We tried to separate the periphery of the mass with a harmonic ultrasonic knife; however, the mass was very hard and closely adherent to the bladder. Therefore, the separation could not be completed under laparoscopy (Figure 8). We then switched to open surgery and used an electric knife to separate the sigmoid colon and mass from the bladder carefully. However, the electrosurgical resection was extremely difficult because the mass's boundary was unclear. Unlike the wall in common chronic abscesses, it was tough and similar to severe fibrotic tissue. After careful separation, we performed sigmoid resection plus descending colorectal anastomosis, and in order to prevent anastomotic leakage, we also performed transverse colostomy. The mass (mainly was the thicken colon wall, about 6 cm × 6 cm) and approximately 20 cm sigmoid colon were removed; however, many feces remained in the proximal colon, which might be caused by stenosis of the intestinal cavity and incomplete obstruction due to the lesion mass compression.

Table 1 Rheumatism immunoassay results

Test items	Results	Reference interval
Antinuclear antibody	Negative	Negative
Anti-nuclear chromatin antibody	1.0	≤ 4.0 negative
Anti-RNP-A antibody	< 0.2	< 1.0 negative
Anti-RNP-68 antibody	< 0.2	< 1.0 negative
Anti-Sm/nRNP antibody	< 0.2	< 1.0 negative
Anti-Sm antibody	< 0.2	< 1.0 negative
Anti-SS-A antibody	< 0.2	< 1.0 negative
Anti-Ro-52 antibody	< 0.2	< 1.0 negative
Anti-SS-B antibody	< 0.2	< 1.0 negative
Anti-Sci-70 antibody	< 0.2	< 1.0 negative
Anti-Jo-1 antibody	< 0.2	< 1.0 negative
Anti-ribosomal p protein antibody	< 0.2	< 1.0 negative
Anti-centromere b protein antibody	< 0.2	< 1.0 negative
Antineutrophil cytoplasmic antibody	Negative	Negative
Anti-protease 3 antibody	< 0.2	< 1.0 negative
Anti-myeloperoxidase antibody	< 0.2	< 1.0 negative
Anti-glomerular basement membrane antibody	< 0.2	< 1.0 negative

Table 2 Immunoglobulin G related indexes detection

Test items	Results	Reference interval
IgG	19.2	7.51-15.6
IgA	3.23	0.82-4.53
IgM	0.64	0.46-3.04
Complement 3	0.89	0.65-1.39
Complement 4	0.24	0.16-0.38
IgG1	10.20	4.05-10.11
IgG2	8.26	1.69-7.86
IgG3	0.368	0.11-0.85
IgG4	1.890	0.03-2.01 for IgG4-RD, cutoff value > 1.35

IgG4-RD: Immunoglobulin G4-related disease.

OUTCOME AND FOLLOW-UP

The patient recovered quickly after the operation and underwent a transverse colostomy three months later. We asked the rheumatology department and immunology doctors to provide a glucocorticoid treatment plan as follow-up treatment. After three months of treatment, the serum IgG4 level decreased to near the normal level. The patient did not have any abdominal discomfort and urination problems and also gained 5 kg in weight relative to before the operation.

DISCUSSION

The 2019 ACR and EULAR classification criteria for IgG4-RD (2019 ACR/EULAR IgG4-RD Criteria) are essential in understanding and treating IgG4-RD[3]. Although they list intestinal involvement as an

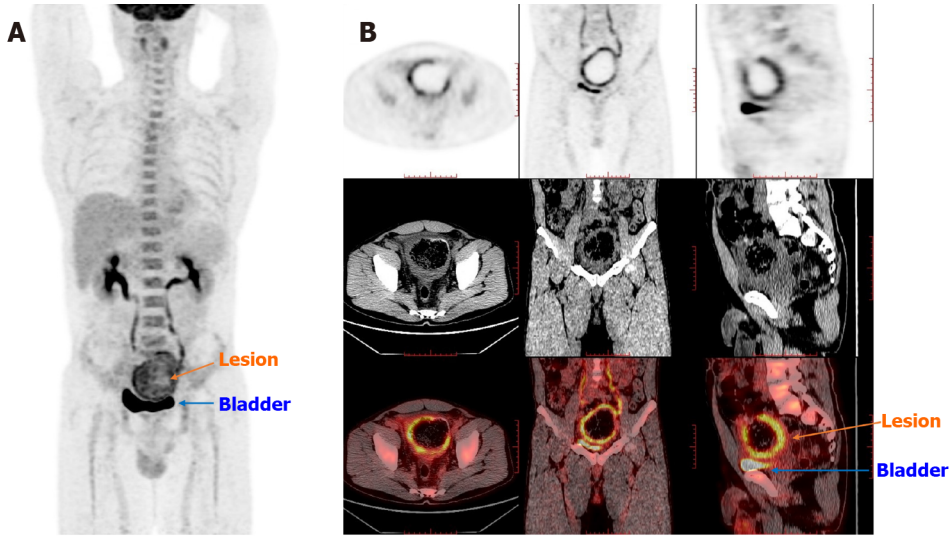

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Figure 2 Positron emission tomography/computed tomography findings. The thick-walled cystic structure above the bladder could be seen, the radioactive uptake was significantly increased, and the maximum standard uptake value reached 6.5. The diagnosis was considered inflammatory or a neoplastic lesion on the sigmoid colon adherent to the bladder. A: Coronal whole-body imaging showing high uptake values at the lesion site; B: Detailed imaging pictures of the lesion, including horizontal, sagittal and coronal.

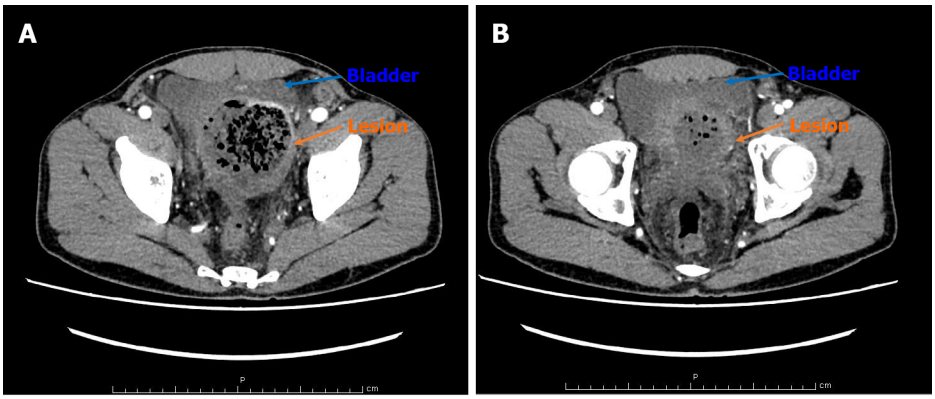

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Figure 3 Contrast-enhanced computed tomography scan of the abdomen findings. A: The proximal sigmoid colon was dilated. The middle colon wall was thickened. It was markedly enhanced in the arterial phase, representing the characteristics of neoplastic lesions or chronic abscesses; B: The sigmoid colon mass compressed the bladder, and the boundary between the bladder and the mass was unclear.

exclusion criterion[3], we reported colonic involvement, which is a unique finding in our patient. Although the patient had a history of allergic rhinitis, the IgG4 level in the blood was increased, exceeding the critical value for IgG4-RD. In the histochemistry detection, we found the plasma cells and IgG4-positive cells infiltration, $IgG4^+/IgG^+$ ratio up to 60%, 110 $IgG4^+$/HPF cells, obliterative phlebitis, and fibrous tissue in the lesion colon. According to the 2019 ACR/EULAR IgG4-RD Criteria[3], if case meets entry criteria and does not meet any exclusion criteria, proceed to step 3 evaluation, this patient could get a score of 42 (Dense lymphocytic infiltrate and storiform fibrosis with or without obliterative phlebitis, +13; Immunostaining, the $IgG4^+$:IgG^+ ratio is 41%–70% and $IgG4^+$ cells/HPF is ≥ 10, +14; Serum IgG4 concentration, > Normal but < 2× upper limit of normal, +4; Diffuse pancreas enlargement and capsule-like rim with decreased enhancement, +11). Therefore, this patient could be diagnosed as IgG4-RD is involved in the colon and pancreas.

When considering IgG4-RD, serum protein electrophoresis and IgG subclass tests should be used as initial investigations because approximately 70% of patients showed elevated serum IgG4 levels[7]. However, since IgG4 levels are not necessary for diagnosing IgG4-RD[8], serological testing, a simple, non-invasive method, can provide essential clues.

Steroids are the first-line treatment for IgG4-RD, and most patients respond well to glucocorticoid therapy[20]. In the 2019 ACR/EULAR IgG4-RD Criteria, failure to respond to glucocorticoids is a vital exclusion criterion for IgG4-RD, which illustrates their significance[3]. However, patients with incomplete remission and recurrence do exist[21]. Additionally, some patients' glucocorticoid-induced

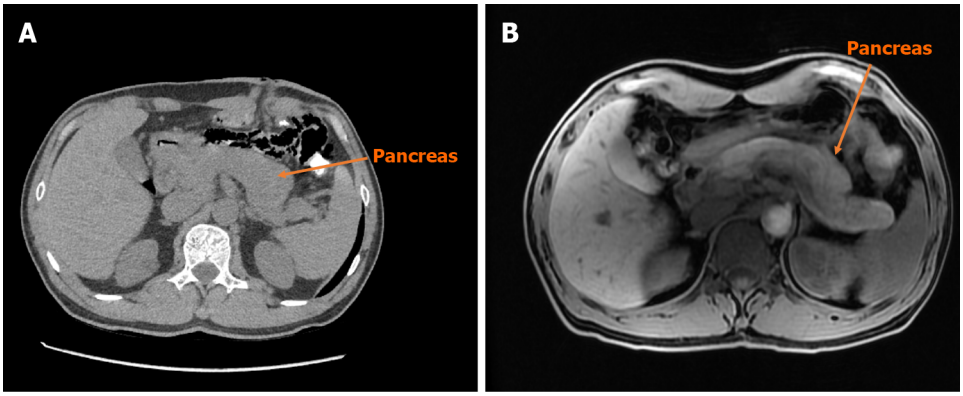

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Figure 4 Computed tomography and magnetic resonance imaging scan of the pancreas. A: The pancreas of the patient is diffusely enlarged, surrounded by capsule-like edema in computed tomography (CT) image; B: Magnetic resonance imaging image of the patient's pancreas is similar to CT.

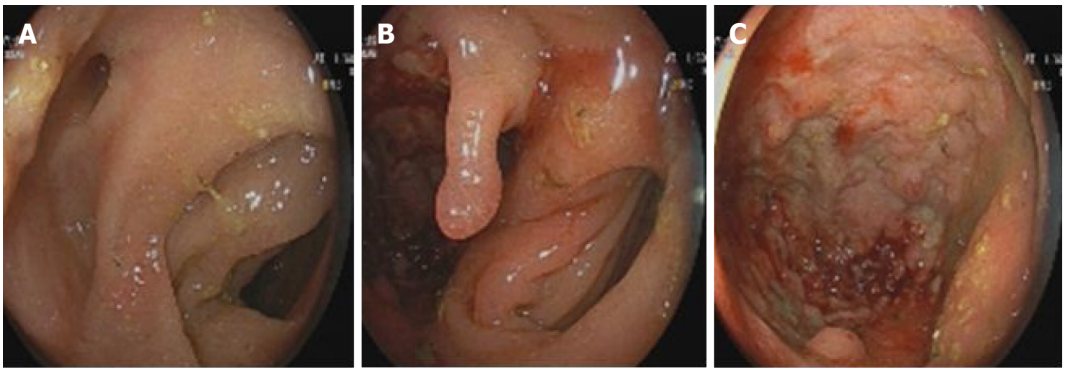

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Figure 5 Findings of the colonoscopy. A and B: From different angles, it could be seen that there were two cavities in the sigmoid colon, one of which was a blind cavity; C: It could be seen that the diseased colon was thickened and rough, and the tissue was so hard to do a biopsy.

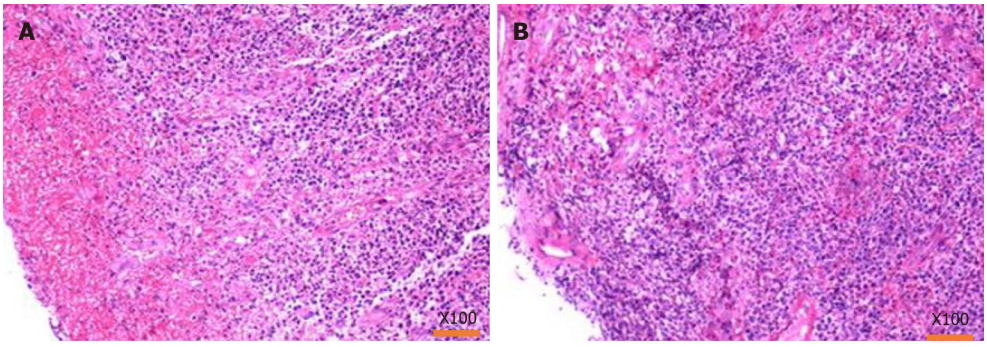

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Figure 6 Pathology of the biopsy by colonoscopy. A: Hematoxylin-eosin staining showed that the tissues were inflammatory hyperplasia changes, and a large number of inflammatory cells were infiltrated; however, there were no tumor cells; B: Results from different sampling sites.

hyperglycemia coupled with secondary pancreatic fibrosis complicates the treatment due to these toxic effects[22].

Significantly, due to hypergammaglobulinemia and plasma cell amplification in IgG4-RD, the clinical efficacy of rituximab (which targets CD20 and depletes B cells) was also remarkable[23]. The use of immunosuppressive drugs such as cyclophosphamide, mycophenolate, leflunomide, and tacrolimus and their combination with glucocorticoids in IgG4-RD remains to be further studied[24-27]. Early identification of IgG4-RD and treatment with glucocorticoids, rituximab, or other immunosuppressive therapies are critical because patients usually respond well to these treatments in the early stages of the disease. Importantly, when chronic pancreatitis and fibrotic disease occur, they are often irreversible [28].

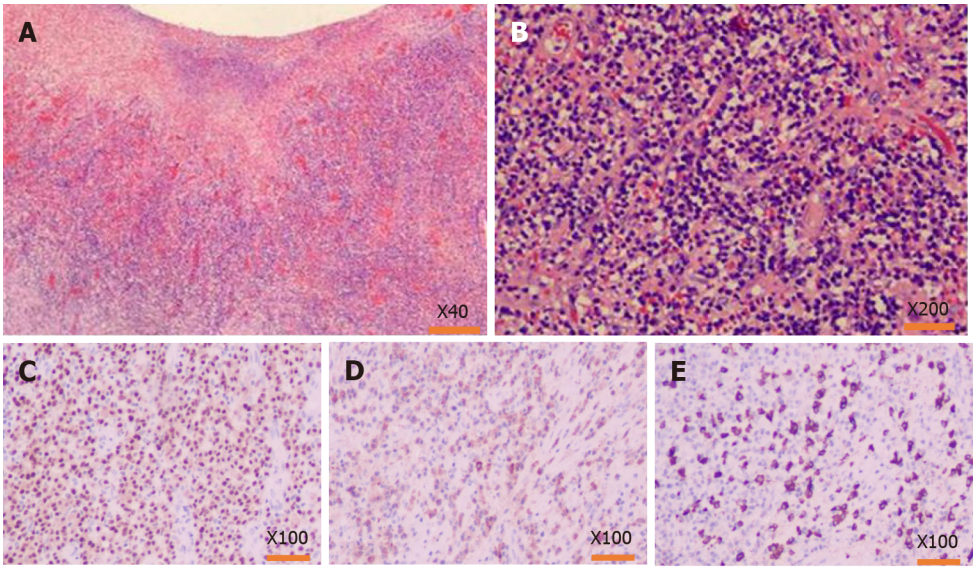

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Figure 7 Pathology findings after the operation. A and B: Hematoxylin-eosin staining of the lesion tissues, inflammatory cell infiltration with plasma cells and neutrophils and increased immunoglobulin G4 (IgG4) positive cells could be seen in the resection colonic mass, accompanied by tissue fibrosis and obliterative phlebitis; C: MMU1 staining showed a high expression state, suggesting a large number of plasma cells infiltration; D: Immunohistochemistry showed a lot of positive IgG staining in the lesion area; E: IgG4 also showed much positive staining in the lesion area, and the number of IgG4-positive cells in the main core area was as high as 110/HPF.

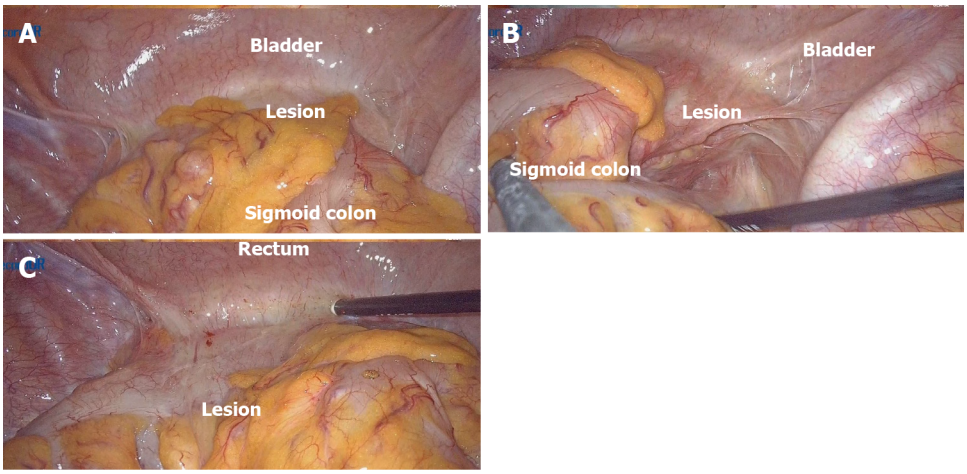

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Figure 8 Operation images from laparoscopy. A: Explore its relationship to surrounding tissue: Dense adhesion of the sigmoid colon to the bladder was observed during the laparoscopic surgery, and it was tough to separate the adhesion; the mass was on the sigmoid colon wall between the bladder and colon; B and C: View the location of the lesion from different angles.

CONCLUSION

In summary, this is a patient with colonic involvement with IgG4-RD. However, recognizing a disease is a gradual process, and the appearance of the disease in rare locations should not be ignored. Since the IgG4 levels in the resected tissue and serological tests were significantly increased, coupled with fibrosis and obliterative phlebitis in the resected colon, the diagnosis of IgG4-RD is reliable. Treatment of IgG4-RD with other immunosuppressive drugs should be further researched. This patient thus provided a rare aspect of IgG4-RD, which may help us further understand this disease.

FOOTNOTES

Author contributions: Zhan WL and Xu XS contributed to conceptualization, data curation, formal analysis, investigation, and methodology; Zhan WL, Liu L, and Jiang W contributed to visualization, roles/writing-original

draft, and writing-review & editing; Cao ZX and Xu XS contributed to conceptualization, project administration, supervision, and writing - review & editing; Qu HT and He FX contributed to investigation; methodology and validation.

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REVIEW

Diagnosis, severity stratification and management of adult acute pancreatitis–current evidence and controversies

Kai Siang Chan, Vishal G Shelat

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Abstract

Acute pancreatitis (AP) is a disease spectrum ranging from mild to severe with an unpredictable natural course. Majority of cases (80%) are mild and self-limiting. However, severe AP (SAP) has a mortality risk of up to 30%. Establishing aetiology and risk stratification are essential pillars of clinical care. Idiopathic AP is a diagnosis of exclusion which should only be used after extended investigations fail to identify a cause. Tenets of management of mild AP include pain control and management of aetiology to prevent recurrence. In SAP, patients should be resuscitated with goal-directed fluid therapy using crystalloids and admitted to critical care unit. Routine prophylactic antibiotics have limited clinical benefit and should not be given in SAP. Patients able to tolerate oral intake should be given early enteral nutrition rather than nil by mouth or parenteral nutrition. If unable to tolerate per-orally, nasogastric feeding may be attempted and routine post-pyloric feeding has limited evidence of clinical benefit. Endoscopic retrograde cholangiopancreatogram should be selectively performed in patients with biliary obstruction or suspicion of acute cholangitis. Delayed step-up strategy including percutaneous retroperitoneal drainage, endoscopic debridement, or minimal-access necrosectomy are sufficient in most SAP patients. Patients should be monitored for diabetes mellitus and pseudocyst.

Key Words: Atlanta classification; Drainage; Infections; Necrosectomy; Pancreatitis; Risk stratification

Core Tip: Acute pancreatitis (AP) is a dynamic and evolving pathology with unpredictable natural course and no specific therapy. Most patients have mild and self-limiting AP where supportive therapy is sufficient. Still, an estimated 20% of patients may have severe AP that consumes healthcare resources and contributes to mortality risk. Risk stratification tools guide clinicians in resource allocation, patient counselling, and clinical audit. A multidisciplinary approach including evidence-based care is integral for good clinical outcomes. With regards to necrotizing pancreatitis, too much, too early and too little, too late should be avoided, and step-up philosophy of intervention should be adopted.

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INTRODUCTION

Acute pancreatitis (AP) is a common cause of acute abdomen, with an incidence of 50-80 *per* 100000 population[1]. The common causes of AP include gallstones (range 40%-70%), alcohol (range 25%-35%), hypertriglyceridemia (range 1%-14%) and post-endoscopic retrograde cholangiopancreatogram (ERCP) (range 3%-5%)[2-5]. Rarer causes include peri-ampullary tumors, autoimmune pancreatitis, hypercalcemia, medications, genetic mutations *e.g.*, *PRSS1* gene, *CFTR* gene, and infections[6-10]. The classical description of the presentation of AP is an acute onset of severe epigastric pain radiating to the back, which worsens when in a supine position. Other accompanying symptoms include nausea, vomiting, fever, or jaundice (for those with concomitant biliary obstruction). Common biochemistry markers used in clinical practice include serum amylase and lipase. Serum amylase and lipase have comparable clinical utility provided the clinician is aware of half-life differences (amylase return to normal limits within 3 to 5 d; lipase return to normal limits within 8 to 14 d)[11,12]. Thus, lipase has higher sensitivity (lipase: 82% to 100%; amylase: 67% to 83%) in patients with delayed presentation *e.g.* more than 24 h of abdominal pain[11]. Diagnosis of AP requires at least two of the three features: (1) Classical history of acute abdominal pain as described above; (2) Serum amylase or lipase at least three times the upper limit of normal; and (3) Characteristic findings of AP on contrast-enhanced computed tomography or magnetic resonance imaging scan[13]. AP is a disease spectrum ranging from mild, moderately severe, to severe AP (SAP) as stratified by the Atlanta classification[13]. While most patients with AP have a mild and self-limiting disease, about 12%-20% have SAP, with high mortality ranging from 15%-30%[13-18]. This editorial will discuss the controversial and emerging themes regarding AP in adults with a critical appraisal of evidence and reference to existing guidelines.

DIAGNOSIS OF AP

While the abovementioned diagnostic criteria are clear, there are inherent limitations[13]. The character of epigastric pain is subject to individual judgment. Serum enzymes also have inherent limitations of half-life (as mentioned above) and clinician must rely on the accuracy of patient recall of onset of abdominal pain, which is prone to error[11,12]. Furthermore, serum enzymes may be falsely elevated in other pathologies like acute cholecystitis, renal impairment, *etc.* Radiological investigations may not be done in a clinically stable patient, rightly so for judicious use of finite resources. Thus, it is possible that some patients may be misdiagnosed as having AP if imaging is not performed. In contrary, early imaging performed for diagnostic purposes will miss necrosis as it typically develops after 3-5 d; and patients may be wrongly stratified as mild AP in absence of evidence of radiological changes. Thus, despite the objective diagnostic criteria, clinical prudence is essential in provision of good quality patient care.

AETIOLOGY OF AP

The next step after making a diagnosis of AP is establishing the aetiology. This is generally a three-step process: (1) History taking for risk factors such as alcohol intake, trauma, medications, recent ERCP procedure, and previous history of gallstone disease[2-5]; (2) Fasting serological tests for calcium and triglycerides[4]; and (3) Radiological imaging *e.g.* abdominal ultrasound scan to look for gallstones[2]. In patients with no obvious aetiology, a clinician must perform extended investigations before resorting to a diagnosis of idiopathic pancreatitis. These extended investigations include a repeat abdominal

ultrasound scan, magnetic resonance cholangiopancreatography (MRCP) scan[2], endoscopic ultrasound (EUS) scan, autoimmune markers like serum immunoglobulin G 4[7], viral markers like coronavirus disease 2019 and genetic tests[10]. The International Association of Pancreatology (IAP)/American Pancreatic Association (APA) guidelines in 2013 suggest that secretin-stimulated MRCP should be performed if EUS is negative for occult microlithiasis, neoplasms and chronic pancreatitis[19] (GRADE 2C evidence). Administration of secretin causes dilatation of pancreatic ducts, allowing better visualization of pancreatic duct disorders[20]. If the above fail to identify a cause, a hereditary cause should be suspected in recurrent, unexplained, early onset AP. Genetic counselling should be considered in these circumstances[19]. A point to note is that genetic counselling is different from genetic testing. Genetic counselling involves risk assessment (*e.g.* detailed past medical history and family history), patient education, psychosocial support and counselling regarding implications and need for genetic testing[21]. In contrary, genetic testing involves assays for gene mutations such as mutations in the *PRSS1* or *CTFR* gene[22]. There are however currently no strict recommendations on the exact indications for genetic counselling and/or testing in AP[19].

In our opinion, a multidisciplinary discussion alongside genetic counselling should definitely be offered when extensive evaluation fails to identify an aetiology for AP. A patient should never be diagnosed with idiopathic pancreatitis without a multidisciplinary team discussion and endorsement. Establishing aetiology is important as this guides management[13]. For example, patients with mild to moderate acute biliary pancreatitis (ABP) will be advised to undergo index admission laparoscopic cholecystectomy to reduce future recurrent biliary events. Also, abstinence from alcohol drinking, omission of the culprit medication, and pharmacological management of hypercalcemia or hypertriglyceridemia can prevent recurrent AP episodes[3,4]. In patients with autoimmune pancreatitis, the immune-mediated pathology affects multiple organs like salivary and lacrimal glands, kidneys, retroperitoneum, lungs, and bile ducts. In addition, autoimmune pancreatitis is implicated in pancreas carcinogenesis[23]. Thus, diagnosis and management of this pathology is unique and requires detailed assessment as well as long-term follow up. Genetic testing however, may be considered only after detailed discussion between clinicians and patients and/or family members due to potential psychosocial impact of results[21].

SEVERITY STRATIFICATION OF AP

Severity stratification is done concurrently with aetiologic determination. There are three broad systems of severity stratification: (1) Two risk categories; (2) Three risk categories; and (3) Four risk categories. The two risk categories include mild *vs* SAP. This is the traditional and time-tested approach that is guided by various scoring systems like the Ranson's score[24], and the Glasgow-Imrie score[25]. Other newer approaches like the Acute Physiology and Chronic Health Evaluation II (APACHE-II) score[26,27], the Bedside Index of Severity in Acute Pancreatitis (BISAP) score[28], computerized tomography scan severity index (CTSI)[29,30], *etc.* continue to provide binomial severity risk stratification. This is important as patients with mild AP have almost no morbidity and mortality. The three-risk category system is proposed by the 2012 revised Atlanta classification system[13]. Here, patients without organ failure or radiological changes are graded as mild, while patients with persistent organ failure (defined as > 48 h) are graded as SAP. The in-between risk category defined as moderately-SAP includes patients having radiological changes or transient organ failure (defined as ≤ 48 h). This system has limitations as some clinically stable patients might not have an imaging performed to assess morphological changes, thus categorized as mild AP. The four-risk category system is widely known as determinant based classification[31]. This system is similar to the Atlanta classification; however, it includes a fourth risk category of "critical AP". This is defined as patients with persistent organ failure and infected (peri)pancreatic necrosis. It is intuitive that these group of patients will be at highest risk of poor clinical outcomes.

Regardless of the type of system used, it is essential to risk stratify to allocate resources, counsel patients and family, and guide clinical care. The presence of many systems itself is a testament that none of them is perfect and their accuracy is not too far apart. The most commonly validated systems include the Ranson's score[24], the Glasgow-Imrie score[25], APACHE-II[26,27,32], BISAP[28], Harmless Acute Pancreatitis Score (HAPS)[33], and Sequential Organ Failure Assessment (SOFA) score[34,35]. We have summarized the abovementioned scoring systems and their respective advantages and disadvantages from the information obtained from recent meta-analyses in Table 1[36-39].

The traditional 11-variable Ranson's score is validated over five decades and has high prognostic accuracy in the prediction of severity and mortality[24,40]. The main criticism of requiring to wait for 48 h for complete scoring is misplaced, as this need for 48 h is indeed the inherent strength[35,40]. The APACHE-II is a 15-variable scoring system which has high accuracy in predicting severity and mortality and may be used at any time point in the disease[36]. However, it is cumbersome for bedside clinical use. Easier to use scoring systems include the BISAP score and the HAPS[28,33]. These are 5-variable and 3-variable scoring systems respectively with external validation. The BISAP score includes altered mental state and requires a chest x-ray to ascertain pleural effusion. Assessment of mental state could be

Table 1 Summary of various scoring systems which has been developed and/or validated for use in acute pancreatitis

Name	Components	Interpretation	Advantages	Disadvantages
Ranson Score	Total of 11 variables to be used	Predicts severity of AP and mortality on admission and 48 h of admission	High prognostic accuracy (AUC 0.81) compared to APACHE II (AUC 0.80), BISAP (AUC 0.79) and CTSI (AUC 0.80) in prediction of AP severity[36]	Low sensitivity (66%) when used before 48 h compared to APACHE II (84%), Glasgow score (78%), HAPS (71%)
	On admission: (1) WBC > 16 × 10^9/L; (2) Age > 55 yr; (3) Glucose > 10 mmol/L (200 mg/dL); (4) AST > 250 IU/L; and (5) LDH > 350 IU/L	Severity of AP: < 3: Unlikely SAP; ≥ 3: Likely SAP	High prognostic accuracy (AUC 0.87) in prediction of mortality, similar to CTSI (AUC 0.87), slightly worse compared to APACHE II (AUC 0.91)[36]	Higher sensitivity than BISAP (54%)[38]
	48-h compared to admission: (1) Hct drop > 10%; (2) BUN increase > 1.79 mmol/L (5 mg/dL); (3) Calcium < 2 mmol/L (8 mg/dL); (4) Arterial P_aO_2 < 60 mmHg; (5) Base deficit > 4 mg/dL; and (6) Fluid needs > 6 L within 48 h	Mortality risk: 0-3: 1%; 3-4: 15%; 5-6: 40%; ≥ 7: Nearly 100%		
The Glasgow-Imrie score	8 variables calculated at 48 h of admission: (1) P_aO_2 < 59.3 mmHg; (2) Age > 55 yr; (3) WBC > 15 × 10^9/L; (4) Calcium < 2 mmol/L (8 mg/dL); (5) BUN > 44.8 mg/dL (serum urea > 16 mmol/L); (6) LDH > 600 IU/L; (7) Albumin < 32 g/L (3.2 g/dL); and (8) Glucose > 10 mmol/L (180 mg/dL)	Predicts risk of SAP	Has decent sensitivity (78%) and specificity (82%) when used even within/before 48 h	Limited prognostic accuracy (< 70%) and positive predictive value (70%)
		Severity of AP: < 3: Unlikely SAP; ≥ 3: Likely SAP	High NPV in prediction for mortality (range 86%-100%)[39]	Unable to provide timely assessment as patients are scored only at 48 h (original design of scoring system)
		Risk of SAP in original study: 0: 7%; 1: 6%; 2: 16%; 3: 20%; 4: 61%; 5: 55%; 6: 100%; 7: 0%; 8: 100%		Low PPV for prediction of mortality (range 18%-66%)[39]
APACHE II	List of 15 variables used[1]: (1) History of severe organ failure/immunocompromised state *e.g.* Heart failure Class IV, cirrhosis, chronic lung disease, dialysis-dependent: (2) Age; (3) Temperature; (4) Mean arterial pressure; (5) Heart rate; (6) Respiratory rate; (7) F_iO_2; (8) Glasgow coma scale; (9) pH; (10) Sodium; (11) Potassium; (12) Creatinine; (13) Acute renal failure; (14) Hct; and (15) WBC count	Original use: Predicts mortality in ICU; Validated studies: Predicts severity and risk of mortality in AP	Can be used at any timepoint during the course of disease	Cumbersome to use in view of long list of variables required
		Interpretation[2][32]: (1) < 8: Low risk of SAP, low risk of mortality; and (2) ≥ 8: High risk of SAP, high risk of mortality	Has decent sensitivity (71%) and specificity (80%) for predicting SAP, and has high sensitivity (92%) with slightly lower specificity (79%) in predicting mortality[36]	Low specificity compared to Ranson score at 48 h (62% *vs* 93%) at 48 h of admission[38]
CTSI	Consists of 2 components	Predicts severity of AP (Sum of Balthazar score and extent of pancreatic necrosis): 0-3: Mild AP; 4-6: Moderate AP; 7-10: SAP	Acceptable sensitivity (81%) and specificity (82%) in prediction of SAP[36]	While able to predict SAP, score did not correlate with subsequent development of organ failure and extra-pancreatic complications
	Balthazar score (grading of pancreatitis): A (0): Normal pancreas; B (1): Enlargement of pancreas; C (2): Inflammatory changes in pancreas and peripancreatic fat; D (3): Ill-defined single peripancreatic fluid collection; and E (4): ≥ 2 poorly defined peripancreatic fluid collection			Patients with > 30% necrosis have similar morbidity and mortality (additional scoring for > 50% is not useful)[29]
	Extent of pancreatic necrosis: None: 0; ≤ 30%: 2; > 30%-50%: 4; > 50%: 6			Requires the use of CT, and ideal time for imaging is ≥ 72 h from onset of symptoms
Modified CTSI (MCTSI)	Consists of 3 components:	Predicts severity of AP: 0-2: Mild AP; 4-6: Moderate AP; 8-10: SAP	Easier to calculate compared to CTSI	CT assessment of severity may not correlate with incidence of organ failure and risk of infection[30]

	Pancreatic inflammation: 0: Normal pancreas; 2: Intrinsic pancreatic abnormalities with/without inflammatory changes in peripancreatic fat; 4: Pancreatic/peripancreatic fluid collection/peripancreatic fat necrosis Pancreatic necrosis: 0: None; 2: ≤ 30%; 4: > 30% Extra-pancreatic complications: 2: ≥ 1 of pleural effusion, ascites, vascular complications, parenchymal complications and/or gastrointestinal involvement		Higher interobserver reliability compared to CTSI Comparable to CTSI in prognostic accuracy for severity of AP; MCTSI (AUC 0.83, sensitivity 88%, specificity 80%); CTSI (AUC 0.80, sensitivity 81%, specificity 82%)[30]	Requires the use of CT, and ideal time for imaging is ≥ 72 h from onset of symptoms
BISAP	List of 5 variables used: (1) BUN > 25 mg/dL; (2) Impaired mental status; (3) SIRS; (4) Age > 60 yr; and (5) Pleural effusion	Predicts mortality in AP. Mortality risk in original study (within 24 h in patients without evidence of organ failure)[28]: 0: 0.1%; 1: 0.4%; 2: 1.6%; 3: 3.6%; 4: 7.4%; 5: 9.5% Varying cut-offs proposed for mortality[37]: ≥ 2: AUC 0.82, sensitivity 81%, specificity 70%; ≥ 3: AUC 0.87, sensitivity 56%, specificity 91% Varying cut-offs proposed for SAP risk: ≥ 2: AUC 0.88, sensitivity 63%, specificity 82%; ≥ 3: AUC 0.87, sensitivity 51%, specificity 91%	Easy to use scoring system which can be used within 24 h of admission	Potential underscoring of patients if done within 24 h as pleural effusion may be a late development Low sensitivity in prediction of SAP Inferior to Ranson score in prediction of mortality[37]
HAPS	List of 3 variables: (1) Absence of rebound tenderness/guarding; (2) Normal Hct (males: ≤ 43.0%, females ≤ 39.6%); and (3) Normal creatinine ≤ 176.8 μmol/L (2 mg/dL)	Predicts risk of mild AP Interpretation: 0: Predicts no pancreatic necrosis, need for dialysis, mechanical ventilation, or fatal outcome (PPV 98%, NPV 18%, specificity 97%, sensitivity 28%) [33]; ≥ 1: Unable to exclude risk of above	Easy and quick to use scoring system to predict risk of mild AP to determine disposition	May miss out cases which appear to be mild AP but progress to moderately severe or severe if patients present early Unable to predict risk of SAP
SOFA	List of 5 variables used[1], within 24 h of admission (graded 0-4 for each variable): (1) Glasgow coma scale; (2) Mean arterial pressure, or need for vasoactive agents; (3) P_aO_2/F_iO_2; (4) Platelet count; and (5) Total bilirubin	Original use: Predicts mortality in ICU Validated studies[35,42]: Predicts risk of SAP, ICU admission and mortality in AP Cut-off score of ≥ 7 to predict SAP, ICU admission and mortality: (1) SAP: AUC 0.966, PPV: 84.6%, NPV: 89.1%, sensitivity: 13.6%, specificity: 99.7%; (2) ICU admission: AUC 0.943, PPV: 61.5%, NPV: 98.1%, sensitivity 40.0%, specificity: 99.2%; and (3) Mortality: AUC: 0.968, PPV: 46.2%, NPV: 99.1%, sensitivity: 50.0%, specificity: 98.9%	Relatively easy to use scoring system compared to APACHE II, Ranson score and Glasgow-Imrie score High NPV which can screen out mild disease or need for ICU admission at onset within 24 h of admission	Underperforms compared to Ranson score (NPV for SAP: 98.0%, NPV for ICU admission: 100%, NPV for mortality: 100%) and Glasgow-Imrie score (NPV for SAP: 95.4%, NPV for ICU admission: 99.3%, NPV for mortality: 99.5%) when scored at 48 h[35]

[1]The APACHE II score and SOFA score are detailed scoring systems which take into account patients' acute and chronic disease, signs, and laboratory values. Each variable consist of multiple components for which a score will be allocated for different range of values. The exact breakdown and scoring of each variable will not be included in this table due to its complexity.

[2]The original Atlanta classification in 1992 defined severe acute pancreatitis as APACHE II ≥ 8.

AP: Acute pancreatitis; APACHE: Acute Physiology and Chronic Health Evaluation; AST: Aspartate transaminase; AUC: Area under curve; BISAP: Bedside Index of Severity in Acute Pancreatitis; BUN: Blood urea nitrogen; CTSI:

Computed tomography severity index; F_iO_2: Fraction of inspired oxygen; HAPS: Harmless Acute Pancreatitis Score; Hct: Hematocrit; ICU: Intensive care unit; LDH: Lactate dehydrogenase; MCTSI: Modified computed tomography severity index; NPV: Negative predictive value; P_aO2: Partial pressure of oxygen; PPV: Positive predictive value; SAP: Severe acute pancreatitis; SIRS: Systemic inflammatory response syndrome; SOFA: Sequential Organ Failure Assessment; U/L: Units *per* litre; WBC: White blood cell.

subjective and pleural effusion may not manifest in the early phase of AP. Similarly, serological markers (hematocrit and creatinine) used in the HAPS may be misleading during the early phase of AP. Serum creatinine may take 24 to 36 h to rise after acute kidney injury[41]. This may mis-stratify patients as mild AP which can progress to moderately-severe or SAP. This phenomenon is opposite to Ranson's score which is shown to over-stratify patients as high risk. In our opinion, it is safer to risk stratify patients as having high risk and then use clinical judgment for resource allocation than to stratify patient wrongly as having low risk. With the revised Atlanta classification, organ failure-based scoring systems are increasingly used. The SOFA score is a 5-variable scoring system used to predict severity and mortality in AP[42]. This can be completed within 24 h and has high accuracy (Table 1)[35].

Age and obesity

Age is a common variable used in traditional as well as modern systems. Elderly patients have reduced physiological reserves, more co-morbidities and are at increased risk of severity and mortality[43]. However, there is a different extent of impact of age across various scoring systems. Li *et al*[44] analyzed Ranson's score, APACHE-II and BISAP scores in elderly patients[44]. They compared the traditional cut-off with an additional point added for elderly patients: ≥ 4 compared to ≥ 3 for Ranson's score, ≥ 9 for compared to ≥ 8 for APACHE-II score and ≥ 3 compared to ≥ 2 for BISAP score. Ranson's score and APACHE-II score were accurate for the prediction of SAP and mortality in younger patients, while BISAP score was accurate in both elderly and young patients. However, recent propensity-score matched studies have shown that outcomes in elderly patients are comparable to younger patients in biliary sepsis[45]; more evidence is necessary, especially to identify the risk into tertiles or quartiles, if not the cut-off value. Nevertheless, AP is a sterile process to begin with. Majority of mortality risk is in the late phase of illness on a background of sepsis-related complications. Thus, it is possible that the impact of age is a surrogate of underlying co-morbidities. In our opinion, patient co-morbidities as assessed by objective scoring systems like Charlson's co-morbidity index may be more accurately associated with risk stratification than age alone. Furthermore, there is emerging data to suggest that obesity and increased body mass index are predictors of severity and mortality in AP[46]. Obese individuals pose significant challenges in bedside clinical care and these issues are not reported in literature. For example, there is added difficulty in intravenous cannulation, insertion of intra-arterial and central venous lines, mobilisation and interpretation of chest X-ray findings. Use of ultrasonography is also limited by the increased abdominal fat and reduces sensitivity in diagnosis of gallstones. To add on, obese individuals are at increased risk of ventilatory problems and have higher risk of abdominal compartment syndrome[47]. Individual units must locally audit various scoring systems and use the most accurate system to guide clinical decisions.

MANAGEMENT OF MILD AP

Mild AP is self-limiting and emphasis should be placed on symptom control and managing the aetiology to prevent future recurrences. Pain control has been emphasised in several guidelines[48,49]. Use of non-steroidal anti-inflammatory drugs (NSAIDs) has been shown to be equally effective as opioids in reducing the need for rescue analgesia in mild AP[50]. In our opinion, analgesia should be administered and escalated according to the World Health Organization pain ladder[51], and patient's co-morbidities (*e.g.* elderly patients with renal impairment should not be given NSAIDs). Patients with ABP should be advised index admission (or within 2 wk) laparoscopic cholecystectomy, provided there is no suspicion of bile duct stone[19]. Patients with alcohol abuse should be provided psychological support and enrolled in de-addiction initiatives alongside social support. Lifestyle modifications (*e.g.* diet control, weight loss) should be made in hypertriglyceridemia-induced AP[4]. First-line medications with fibrates should also be started with an aim for triglyceride level to be < 500 mg/dL (5.65 mmol/L)[52]. Patients with idiopathic AP belong to a special group where a discussion for EUS and/or laparoscopic cholecystectomy for possibility of underlying microlithiasis is important for informed decision making[19,53]. In patients with pancreas divisum, multidisciplinary team collaboration is essential to discuss the role of sphincterotomy to ameliorate intraductal hypertension and recurrent AP[54].

MANAGEMENT OF NON-MILD AP

In patients with non-mild AP, radiological changes and/or organ dysfunction are evident. Some patients with moderately-SAP may clinically improve and potentially can qualify for index admission cholecystectomy. The remaining moderately-SAP patients are managed according to SAP due to inherent risk of mortality and unpredictable natural disease course[15,16]. We shall discuss the controversies related to fluid management, role of antibiotics, indications for intensive care unit (ICU) admission, mode of nutrition, role of ERCP, and indications for invasive (endoscopic and/or surgical) interventions.

Fluid management

The inflammatory cascade in AP may result in persistent organ dysfunction lasting > 48 h, resulting in SAP. Patients with SAP often present with cardiovascular compromise *e.g.* hypotension and are kept nil by mouth during the acute presentation (refer to sub-section on mode of nutrition for further discussion). Prompt intravenous fluid resuscitation is key for initial cardiovascular support in SAP. Two common questions need to be addressed: (1) Choice of fluid; and (2) Amount/rate of fluid administration.

While colloids have the advantage of more efficient replacement of intravascular loss (1:1 replacement compared to 3:1 replacement for crystalloids), there is risk of acute kidney injury requiring renal replacement therapy (RRT) with starch, and risk of allergic reactions. A Cochrane review on the use of crystalloids and colloids in critically ill patients (69 studies with 30020 patients) found no difference in all-cause mortality[55]. However, there was moderate certainty evidence of slight increase in need for RRT when starches were used. Use of hydroxyethyl starch (HES) in severe sepsis has also been shown to increase mortality compared to ringer's lactate[56]. The American Gastroenterological Association (AGA) guidelines on the initial management of AP similarly recommends against the use of HES due to the lack of mortality benefits[57], and a study which showed increased multi-organ failure with HES[58]. In our opinion, in a condition like SAP which already bears high mortality on its own, measures should be taken to minimise further insult. Crystalloids should be the choice of fluids. When comparing between type of crystalloids, the IAP/APA guidelines recommend ringer's lactate due to reduced incidence of systemic inflammatory response syndrome compared to normal saline in AP[19,59]. However, the AGA guidelines make no recommendations on whether ringer's lactate or normal saline should be used as clinical outcomes such as organ failure, necrosis or mortality were not investigated[57]. In patients with AP secondary to hypercalcemia, normal saline should be used instead as ringer's lactate contains 3 mEq/L calcium. While different guidelines make conflicting recommendations over the choice of crystalloids, normal saline is considered "less physiological" due to high sodium and lack of potassium[60]. Over-administration of normal saline may also lead to normal anion gap hyperchloremic acidosis in cases of persistent hypotension. Therefore, we believe that ringer's lactate should be considered first.

Secondly, how fast and how much fluids should be given? Like any resuscitation, this should be goal-directed with an initial rate of 5-10 mL/kg/h[19,61]. However, excessive fluid replacement *i.e.* over-resuscitation may do more harm than good *e.g.* dilutional coagulopathy, fluid overload and re-perfusion mediated injury. Additionally, in AP, faster rate of infusion at 10-15 mL/kg/h has been shown to increase the need for mechanical ventilation, abdominal compartment syndrome, sepsis and mortality [61]. The definition of "goal-directed" is similar to the management of hypotension or shock, where vital parameters are used to trend clinical response, such as fall in heart rate, mean arterial pressure ≥ 65 mmHg and urinary output > 0.5 mL/kg/h. Invasive methods may also be used, but clinicians are to be

cognisant that central venous pressure monitoring is a static marker. Stroke volume variation is a better marker of fluid responsiveness as it allows dynamic monitoring of fluid responsiveness.

Role of antibiotics in SAP

Sequelae of SAP include (peri) pancreatic necrosis with or without infection. A meta-analysis by Werge *et al*[62] on 71 studies with 6970 patients showed that patients with infected necrosis had higher mortality than those with sterile necrosis [Odds ratio (OR): 2.57, 95% confidence interval (CI): 2.00-3.31] [62]. Organ dysfunction with concomitant infection in SAP was also associated with higher mortality compared to organ dysfunction with sterile necrosis (35.2% *vs* 19.8%). This raises the question on the role of antibiotics in SAP and its impact on clinical outcomes: (1) Prophylactic antibiotics in SAP *vs* antibiotics for infected necrosis only; and (2) Choice and/or duration of antibiotics.

Older guidelines, for instance the Japanese Guidelines 2015, recommend prophylactic antibiotics administration in SAP and acute necrotizing pancreatitis (ANP) as its use may improve prognosis if carried out early within 72 h from onset of disease (level 2B evidence)[63]. However, the 2019 World Society of Emergency Surgery (WSES) guidelines do not recommend the routine use of prophylactic antibiotics for all AP as there is no significant reduction in morbidity or mortality[49].

There have been several systematic reviews and meta-analyses on this topic. Ukai *et al*[64] in 2015 analysed 6 randomized controlled trials (RCTs) with 397 ANP patients and showed that early prophylactic antibiotics (within 72 h from onset of symptoms or 48 h after admission) was associated with lower mortality (prophylactic antibiotics: 7.4% *vs* no antibiotics: 14.4%, OR: 0.48, 95%CI: 0.25-0.94) and reduced incidence of infected pancreatic necrosis (prophylactic antibiotics: 16.3% *vs* no antibiotics: 25.1%, OR: 0.55, 95%CI: 0.33-0.92) compared to no antibiotics use[64]. However, a recent meta-analysis on the use of prophylactic carbapenem antibiotics by Guo *et al*[65] on 6 studies (5 RCTs, 1 retrospective observational study) showed similar mortality (prophylactic antibiotics: 11.0% (n = 29/264) *vs* no prophylactic antibiotics: 15.4% (n = 38/246), OR: 0.69, 95%CI: 0.41-1.16, P = 0.17) and incidence of infected pancreatic necrosis [prophylactic antibiotics: 12.5% (n = 33/264) *vs* no prophylactic antibiotics: 15.9% (n = 39/246), OR: 0.74, 95%CI: 0.44-1.23, P = 0.24][65]. Guo *et al*[65] included studies with heterogeneity in the timing of prophylactic antibiotics administration: One study started antibiotics within 48 h of symptom onset[66], three studies within 72 h of symptom onset[67-69] and one study within 120 h of symptom onset[70]. Unlike Guo *et al*[65] who analysed only patients with prophylactic carbapenem, Ukai *et al*[64] included studies with cefuroxime[71], and ciprofloxacin[72]. In addition, while the populations examined are similar between the two studies, ANP (study by Ukai *et al*[64]) is not synonymous with SAP (study by Guo *et al*[65]). Moderately-SAP is defined as presence of local complications which include acute necrotic collection (ANC), peri-pancreatic collection, or walled-off necrosis (WON). SAP is defined as presence of persistent organ dysfunction > 48 h. While ANP may result in systemic inflammation, infection, and subsequent organ dysfunction, not all cases of ANP qualify for SAP as determined by the revised Atlanta classification. Though Guo *et al*[65] did not show any statistically significant improvement in mortality or reduced infected pancreatic necrosis[65], there was an absolute unadjusted difference of 4.4% in mortality, which in our opinion is clinically meaningful and should not be dismissed as insignificant.

In our opinion, the role of antibiotics is absolute in patients with concomitant acute cholangitis (AC) (biliary sepsis) and in selected patients where intestinal bacterial translocation has ensued due to prolonged duration of hypoperfusion. Future studies should consider evaluating the role of prophylactic antibiotics in high-risk patients *e.g.* elderly with multiple co-morbidities. If prophylactic antibiotics are started, then one must titrate according to the results of fluid cultures and clinical response to reduce risk of resistant strains or fungal superinfection in vulnerable SAP patients.

Apart from prophylactic antibiotics, other adjuncts have been considered in improving outcomes of SAP. Selective decontamination of the digestive tract (SDD) is a prophylactic strategy to reduce exogenous and endogenous infection consisting of a course of parenteral and enteral antibiotics, topical antibiotics (for patients on tracheostomy), good hygiene and surveillance throat and rectal cultures[73]. SDD has been shown to reduce multi-organ dysfunction in critically ill patients (meta-analysis on 7 RCTs with 1270 patients)[74]. Mortality was also shown to be reduced in another meta-analysis[75]. However, evidence is scarce on the utility of SDD in SAP. To date, only 1 RCT in 1995 reported reduction in mortality[76], while 1 retrospective study in 2007 reported non-statistically significant reduction in organ dysfunction (70% to 59%) and mortality (40% to 28%) with SDD[77]. Further studies are required to validate these findings before definitive conclusion can be made on recommendations. In contrary, probiotics have been shown to have no benefits in preventing infections in AP[78].

Until more evidence is reported, we endorse the 2019 WSES and the IAP/APA that there should not be a recommendation for the use of prophylactic antibiotics nor probiotics in SAP[19,49]. SDD may have benefits in reducing organ dysfunction and mortality in SAP. However, further well-designed RCTs are required to fill in this knowledge gap. This also draws attention for the need of an umbrella review to summarize findings from existing systematic reviews and meta-analysis on the use of prophylactic antibiotics in SAP.

Indications for ICU admission

By definition, all cases of SAP will require at least high dependency unit (HDU) monitoring in view of persistent organ failure lasting > 48 h. This aids continuous vital chart assessment, invasive haemodynamic monitoring, accurate fluid balance charts documentation, round the clock nursing and medical attention for timely escalation of care in event of deterioration. The escalation of care is determined by clinical judgement and use of surrogate markers to assess the severity of AP and physiological disturbance. Prediction and prognostic scores serve as useful adjuncts to guide clinicians, but do not replace the need for continuous vigilant monitoring and reliance on one's judgment to detect early warning signs of clinical deterioration so as not to miss the golden window of opportunity for timely care. Point of care tests like arterial blood gas analysis are integral to early recognition of deterioration. The 2021 joint guidelines by the French Society of Anaesthesia and Intensive Care Medicine also strongly recommends for intra-abdominal pressure monitoring for diagnosis and rapid treatment of intra-abdominal hypertension (IAH)[79]. SAP and large administration of fluids are risk factors for IAH [80], which bears significantly higher mortality than those without[81]. In rare instances, an astute family member may highlight certain cues which suggest patient's clinical deterioration, and those should not be dismissed. For example, they may highlight to medical staff "today he/she looks more tired", "yesterday he/she could open eyes and could talk to me for xx minutes, but not today" *etc.* The HDU team should have a seamless access to the ICU team. Communication or personal egos have no place in timely escalation and expeditious transfer for airway management or ventilatory support. It is our view that even patients with non-invasive ventilation should be under the care of the ICU outreach team even though they are physically nursed in HDU. In our institution, HDU is able to support continuous vitals monitoring, invasive lines (*e.g.* arterial line and central venous pressure line), support patients on one vasopressor (*e.g.* noradrenaline); and has a nurse to patient ratio of 1 to 2 or 1 to 3.

Furthermore, various tiers of ICU have also been defined: (1) Level 1 ICU: Capable of providing oxygen, non-invasive monitoring, and more intensive nursing care than in normal ward; (2) Level 2 ICU: Capable of providing invasive monitoring and basic life support for a short period; and (3) Level 3 ICU: Capable of providing full spectrum of monitoring and life support[82]. Ohbe *et al*[83] defined ICU as availability of physician on-site 24 h *per* day, at least 2 intensivists working full-time, around-the-clock nursing and nurse-to-patient ratio of 1 to 2. HDU was defined as similar capabilities compared to ICU, without requirement for intensivists and reduced nurse-to-patient ratio of 1 to 4 or 1 to 5[83]. In our institution, ICU has capabilities of supporting patients on mechanical ventilation, invasive life support *e.g.* extracorporeal membrane oxygenation and support dual or triple vasopressors and/or inotropes. Interestingly, Ohbe *et al*[83] showed that ICU (*i.e.* with availability of intensivists and better nurse-to-patient ratio) decreased 30-d mortality by 7.2% in patients with pneumonia on mechanical ventilation[83]. The authors attributed this to better nurse-to-patient ratio, especially in the context of high workload with critically ill patients[84]. Patients with SAP may also present with acute respiratory distress syndrome or severe metabolic acidosis requiring mechanical ventilation[85,86]. Such patients should be directly admitted to an ICU.

Additionally, the IAP/APA guidelines state that all patients with SAP should be managed at a specialist centre (defined as a high-volume centre)[19]. Improved morbidity and/or mortality have been reported for pancreas resection (pancreatectomy or pancreaticoduoenectomy) when performed at high-volume centres[87,88]. However, what is defined as "high-volume"? Even for oncological surgeries, "high-volume" has been variable, with studies reporting 20-35 cases annually as cut-off for pancreas resection[89,90]. In contrary, studies which reported on outcomes of out-of-hospital cardiac arrest defined high-volume as ≥ 40-100 cases annually[91]. For AP, there is no literature on what defines "high-volume". In our opinion, there is no real "cut-off" for what defines a high-volume centre in AP. We believe that SAP should be managed in a specialist centre, which should be defined as the availability of specialised round-the-clock services for radiological imaging, interventional radiology, endoscopic interventions and surgical capabilities.

Mode of nutrition

While almost all patients with mild AP will be allowed to maintain oral nutrition, patients with SAP may have associated nausea or vomiting, gastrointestinal ileus with nasogastric tube in-situ, or are on mechanical ventilatory support. The traditional belief that feeding stimulates the release of cholecystokinin, causing the secretion of proteolytic enzymes that results in autodigestion and further damage to the pancreas is unfounded[92]. Furthermore, enteral feeding has been shown to maintain bowel mucosa integrity and prevents intestinal bacterial translocation, thus reducing risk of pancreatic necrosis with superadded infection and systemic sepsis[93]. Evidence has also shown that early oral feeding reduces length of stay (LOS)[94]. To add on, SAP is a catabolic process which results in loss of nutrients, water, electrolytes and protein[95,96]. Thus, early and optimal caloric formula feeds considering "stress factor multiplication" should be commenced early in the journey of SAP.

Enteral nutrition has been recommended over total parenteral nutrition (TPN) in SAP; Yi *et al*[97] in 2012 who analyzed 8 RCTs (381 patients) showed reduced infective complications [Risk ratio (RR): 0.46, 95%CI: 0.27-0.78], organ failure (RR: 0.44, 95%CI: 0.22-0.88) and mortality (RR: 0.37, 95%CI: 0.21-0.68) with enteral nutrition[97]. However, evidence is lacking regarding the mode of enteral nutrition: Per-

oral *vs* naso-enteric feeding tube. As mentioned above, patients with SAP have physiological compromise and may not be able to tolerate per-oral intake. A RCT comparing early nasoenteric tube feeding (within 24 h from randomization) and delayed oral feeding (initiated 72 h after presentation) did not show superiority of early nasoenteric tube feeding in reducing infections and mortality[98]. Another RCT (110 patients) compared hunger-based feeding (commencement of oral feeding once patients felt hungry) *vs* conventional feeding (commencement of oral feeding after normalization of biochemical parameters and resolution of symptoms) in moderate AP and SAP[99]. Compared to conventional feeding, hunger-based feeding allowed for earlier feeding (mean fasting duration 1.6 d *vs* 2.7 d, $P = 0.001$) and was also associated with shorter LOS (6.3 d *vs* 7.3 d, $P = 0.041$). However, incidence of infection and mortality was comparable between both feeding regimes. Results from this study suggest that "hunger" reflects recovery of gastrointestinal dysfunction. Benefits of earlier feeding and ensuring return to their baseline status therefore allows for earlier discharge.

The type of diet is also an important consideration. The revised Clinical Practice Guidelines of the Korean Pancreatobiliary Association for Acute Pancreatitis recommend for low-fat diet as long as tolerated in AP (level B evidence)[48]. High fat diet has been shown to increase oxidative stress and enhance inflammation in animal studies[100]. Human studies also show increase in pancreatic secretion after fat-rich diet[101], which may worsen pain. Use of low-fat diet has been shown to be safe compared to clear liquid diet with provision of more calories[102]. Tolerating low-fat diet and solid diet early may expedite discharge and reduce LOS.

Apart from the timing of feeding, the mode of nasoenteral (NG) feeding *i.e.* nasogastric *vs* nasojejunal (NJ) feeding should also be considered. Insertion of NJ tube requires fluoroscopic guidance and technical expertise, while NG tube insertion is a simple bedside procedure. It has been postulated that NJ tube reduces pancreatic stimulation and risk of aspiration pneumonitis[103,104]. A Cochrane review on 5 RCTs (220 patients) showed similar mortality between NJ and NG feeding, and no studies reported any incidence of aspiration pneumonia[105]. After review of all the above evidence, per-oral or nasoenteric feeding should be used over TPN unless contraindicated. The mode of feeding, per-oral *vs* feeding tube, should be determined by clinical wisdom and earlier enteral nutrition should be advocated, especially if it is driven by "hunger" sensation. If enteral feeding is planned, NG tube insertion should be attempted first due to ease of insertion and lack of benefits of NJ tube insertion.

Role of ERCP for gallstone pancreatitis

Gallstone is the most common cause of AP and it is possibly lodged into the common bile duct for it to cause AP. Thus, ERCP for biliary decompression and/or stone removal is an integral consideration in AP management. The 2019 WSES guidelines recommend against routine ERCP for acute gallstone pancreatitis (AGP) (Level 1A evidence)[49]. However, the American College of Gastroenterology guidelines recommend urgent ERCP within 24 h for severe AGP complicated by organ failure[106], and the United Kingdom practice guidelines similarly advocate early ERCP (within 72 h) for predicted or severe AGP[107]. The 2012 Cochrane review which compared early routine ERCP *vs* conservative management in AGP (5 studies with predicted mild AP, 7 studies with predicted SAP) showed comparable mortality and local complications[108]. Subgroup analysis was also performed for studies with predicted mild AP and SAP; similarly there was no significant differences in outcomes: (1) Mortality (early routine ERCP in mild AP: RR: 4.53, 95%CI: 0.22-92.88, $P = 0.33$; early routine ERCP in SAP: RR: 0.64, 95%CI: 0.20-2.04, $P = 0.45$); and (2) Local complications (early routine ERCP in mild AP: RR: 0.99, 95%CI: 0.52-1.90, $P = 0.99$; early routine ERCP in SAP: RR: 0.70, 95%CI: 0.36-1.39, $P = 0.31$).

While ERCP is minimally invasive compared to surgery, ERCP still bears the risk of sedation and post-ERCP complications. This is added onto the physiological insult during AP. Hence, there needs to be a clear benefit before attempting ERCP in AGP. No benefit has been shown for early ERCP compared to conservative management for both mild AP and SAP in AGP[108]. However, in the same meta-analysis, the authors showed significantly lower local complications in patients who had biliary obstruction (without cholangitis)[108]. No analysis was done for mortality. For patients with concomitant cholangitis, there was reduced mortality, local and systemic complications in patients who received early ERCP compared to conservative management[108].

Biliary obstruction leads to bile stasis and in presence of stone, this is considered infected until proven otherwise. Bactibilia in patients with biliary obstruction leads to cholangio-venous reflux and spillover of gram negative endotoxins into systemic circulation with downstream injury to organ systems[109]. ERCP reverses the pathophysiology of cholangitis and thus the maximal utility is in SAP patients with concomitant cholangitis[108].

However, diagnosis of concomitant AC is challenging in AP. Both AC and AP present with acute epigastric and/or right hypochondrium pain and fever; AP may present with jaundice in the presence of biliary obstruction. This essentially fulfils the Charcot's triad, the traditional method of diagnosis for AC. Commonly used biochemistry markers includes white blood cell count, C-reactive protein (CRP) and liver function test. Both AC and AP result in systemic inflammation and subsequent leukocytosis and raised CRP. Presence of biliary obstruction will result in an "obstructive pattern" of liver function test, with raised alkaline phosphatase and γ-glutamyl transferase. The Tokyo Guidelines 2018 (TG18) guidelines require the presence of (1) Systemic inflammation: Fever and/or chills, laboratory data with evidence of inflammatory response; (2) Cholestasis: Jaundice, abnormal liver function tests; and (3)

Biliary dilatation and evidence of etiology on imaging (*e.g.* stricture or stone)[110]. AP with biliary obstruction without AC will fulfil all the criteria for the diagnosis of AC. A study by Weiland *et al*[111] showed that the TG18 fairs poorly in the diagnosis of AC with suspected biliary obstruction (sensitivity 82%, 95%CI: 74-88%; specificity 60%, 95%CI: 56-63%)[111].

Procalcitonin (PCT) is a trending biomarker which may be used to distinguish between AP alone *vs* AP with concomitant AC. PCT has higher sensitivity (88% *vs* 75%) and specificity (81% *vs* 67%) than CRP for discriminating bacterial infections from non-infective causes of inflammation[112]. Alberti *et al* [113] did a prospective study on 152 patients on the use of PCT and showed that PCT > 0.68 mg/dL had higher incidence of AC, infected necrosis and need for urgent ERCP in patients with AP[113]. Similarly, a RCT on 260 patients with AP was conducted to compare PCT-guided care (antibiotics administration if PCT ≥ 1.0 μg/L, and to withhold antibiotics if PCT < 1.0 μg/L) *vs* standard care (as *per* IAP/APA guidelines *i.e.* antibiotics administration if clinical suspicion of infection or proven infected WON)[114]. They showed that PCT-guided care resulted in fewer administration of antibiotics (risk difference: -15.6%, 95%CI: -27.0, -4.2, P = 0.0071), with similar number of clinical infections, hospital-acquired infections, mortality and adverse events. While PCT may not be able to differentiate infected pancreatic necrosis *vs* AC, its use is promising and may prove as a useful adjunct alongside other investigations for starting empirical antibiotics.

After review of the above evidence, early ERCP should not be performed for all AGP. However, in the presence of biliary obstruction and/or AC, early ERCP should be performed. There is difficulty in the differentiating AC *vs* biliary obstruction in AP. Nevertheless, early ERCP should still be performed in biliary obstruction as benefits have been shown compared to conservative management alone.

Indications for invasive (endoscopic and/or surgical) intervention in SAP

In general, interventions in SAP patients should be performed on-demand and not by-the-clock. Also, interventions should be delayed as much as possible and the least invasive modality should be selected due to the high physiological insult in SAP. Open necrosectomy (ON) is rarely performed due to high morbidity and mortality[115-119]. Advances in endoscopic and minimally invasive techniques have shifted the approach towards minimally invasive necrosectomy (MIN). Several meta-analyses showed no difference in short-term mortality, but has reduced incidence of serious adverse events (rate ratio: 0.41, 95%CI: 0.25-0.68, only 1 study was included) and multiple organ failures (OR: 0.16, 95%CI: 0.06-0.39, P < 0.0001) in MIN patients compared to ON[120,121].

The 2019 WSES guidelines recommend a step-up approach for infected pancreatic necrosis with initial treatment with percutaneous drainage (Level 1A evidence)[49]. The TENSION (Transluminal endoscopic step-up approach *vs* minimally invasive surgical step-up approach in patients with infected necrotising pancreatitis) trial is a RCT which was published in 2018 (Endoscopic step-up approach n = 51, surgical step-up approach n = 47)[122]. They compared the use of endoscopic step-up approach (initial treatment with EUS-guided transluminal drainage (EUS-TD) with placement of two stents, with subsequent endoscopic transluminal necrosectomy if no clinical improvement) *vs* surgical step-up approach (initial treatment with radiologically-guided percutaneous drainage through the left retroperitoneum, with subsequent video-assisted retroperitoneal debridement (VARD) if drainage was clinically unsuccessful) in patients with high suspicion of infected pancreatic or extra-pancreatic necrosis. Endoscopic step-up approach was associated with reduced LOS {median 35 [interquartile range (IQR) 19-85] d *vs* median 65 (IQR: 40-90) d, P = 0.014} and reduced pancreatic fistula [5% *vs* 32%, RR: 0.15 (95%CI: 0.04-0.62), P = 0.0011] compared to surgical step-up approach. Major complications and mortality were comparable between endoscopic and surgical step-up approach. Similar results were noted in a meta-analysis comparing endoscopic *vs* minimally invasive techniques (laparoscopic cystogastrostomy, VARD, or step-up approach to VARD following radiologically guided percutaneous drainage); incidence of pancreatic fistula, new-onset multiple organ failure (5.2% *vs* 19.7%, RR: 0.34, P = 0.045) and LOS were lower in endoscopic techniques[123]. However, mortality was comparable. Percutaneous drainage and surgical step-up approach may cause external extravasation of pancreatic exocrine exudates resulting in pancreatic fistula[124]. To add on, pro-inflammatory response of pancreatic enzymes may result in systemic inflammation resulting in new-onset organ failure[125]. These result in longer LOS for surgical step-up approach compared to the endoscopic step-up approach.

Apart from the advantages endoscopic approach offers, it is however important to consider the technical challenges of endoscopic drainage. Endoscopic techniques include conventional direct transluminal drainage (CTD) by forward viewing endoscopy, transpapillary drainage (TPD) and EUS-TD. CTD offers drainage *via* a blind approach (identified through luminal bulging of peripancreatic collection) which presents risk of bleeding, perforation, and oversight of main pancreatic duct (MPD) abnormality. TPD requires communication between the peripancreatic collection with the MPD to allow for drainage. EUS-TD is the safest with visual guidance, but fluid collections must be within 1cm of gastric or duodenal walls[126]. Anatomical location of ANC or WON may render difficulty for endoscopic drainage and hence, radiologically guided percutaneous drainage should still be considered first in these circumstances.

Apart from short-term outcomes, studies have evaluated long-term patient-related outcome measures. A recent systematic review by Psaltis *et al*[127] in 2022 included 11 articles which assessed the quality of life (QOL) after endoscopic and/or surgical management of SAP[127]; literature was hetero-

genous which rendered inability for pooled analysis. However, the authors suggested that endoscopic management may confer better QOL compared to surgical management based on current literature. A RCT comparing endoscopic *vs* MIN showed significantly higher physical component scores for endoscopic necrosectomy at 3 mo following intervention (P = 0.039)[128]. Mental health was also reported to be better following minimally invasive drainage (consisting of percutaneous catheter drainage, negative pressure irrigation and endoscopic necrosectomy *via* an artificial sinus tract) compared to ON[129]. It is noteworthy that the studies included in the review did not include laparoscopic or minimally invasive retroperitoneal pancreatic necrosectomy.

Considering all available evidence on endoscopic, MIN and ON, there is no mortality benefits between the choice of intervention. This is in line with the WSES 2019 guidelines[49]. However, endoscopic step-up approach confers additional benefits such as reduced incidence of pancreatic fistula, lower new-onset organ failure, and shorter LOS compared to surgical step-up approach. It is important to note that while mortality has been shown to be comparable, existing studies did not evaluate long-term mortality. Organ failure has been demonstrated to be an important case of long-term morbidity and mortality[15,130]. Therefore, endoscopic step-up approach should be used for infected ANP if technically feasible.

Summary of the management of SAP

While there are several controversies surrounding the abovementioned areas discussed, there are also several guidelines, such as the IAP/APA guidelines, 2019 WSES guidelines and the revised Clinical Practice Guidelines of the Korean Pancreatobiliary Association for Acute Pancreatitis[19,48,49]. Guidelines serve as recommendations for clinical practice. However, compliance is equally, if not more important. Results however have been disappointing. A large multi-center international audit showed poor compliance to clinical guidelines in the management of ABP[131]. For instance, there were 53.4% of patients who received prophylactic antibiotics for mild ABP, and 83.4% who received prophylactic antibiotics for severe ABP. Similarly, only 44.7% with ABP (all severity) had early enteral feeding, and 47.7% with mild ABP had early enteral feeding. An international survey on 1054 participants from 94 countries similarly showed that 15.5% of participants administer routine prophylactic antibiotics for AP, and only 26.6% will start patients who did not vomit on early enteral feeding[132]. As discussed above, there are currently no recommendations for prophylactic antibiotics, and early enteral feeding is recommended due to its protective effect on bowel mucosa integrity and prevents intestinal bacterial translocation. Possible explanations for the lack of compliance may be due to traditional beliefs clinicians have, reluctance for compliance to guidelines or a delay of translation of evidence into personal or institutional protocols[133]. Hirota *et al*[134] in 2014 extracted 10 statements from the Japanese guidelines on AP and classified them into 10 AP bundles for SAP; they showed that patients who had ≥ 8 bundles implemented had lower mortality compared to < 8 bundles (overall 505 patients with SAP, mortality 13.7% *vs* 7.6%, P = 0.042)[134]. This reinforces that while guidelines help shape clinical practice, what is more important is compliance to guidelines and not more guidelines. Clinicians need to be up-to-date with evidence and guidelines, and integrate them into personal and/or institutional practices and protocols to optimise clinical outcomes.

MANAGEMENT OF RECURRENT AP

In some patients, AP recurs or relapses, especially when the initial aetiology is not treated or removed. In patients with AGP, this means that cholecystectomy is essential. In patients with hypercalcemia or hyperlipidemia, appropriate management of underlying aetiology is essential. In patients with drug-induced pancreatitis, the culprit drug should be avoided and substituted with an alternative medication [9]. However, sometimes the underlying etiology may be multifactorial or idiopathic. The International State-of-the-Science conference defined recurrent AP as two or more well-documented separate attacks of AP with complete resolution for more than 3 mo between attacks[135]. Recurrent AP is a complex pathology with possible anatomic, environmental, and genetic causal interplay. Thus, the diagnostic work-up should include EUS, autoimmune serological tests, and genetic studies. In rare situations, ERCP during the acute episode of abdominal pain may be necessary to identify and treat the causative aetiology[136]. Biliary and pancreatic ductal manometry and biliary sphincterotomy can potentially reduce recurrent AP rates in patients with anomalous pancreato-biliary junction, choledochocele, ampullary neoplasms, biliary parasitosis, and sphincter of Oddi dysfunction[137]. Empiric trial of steroids without compelling evidence of autoimmune pancreatitis is not advised[135]. Similarly, empiric cholecystectomy is not advised in patients with no evidence of gallbladder disease on EUS and other imaging modalities and with normal liver function tests[135]. About one-quarter of patients with recurrent AP may progress to chronic pancreatitis, and a diagnosis of chronic pancreatitis does not preclude a future diagnosis of AP or recurrent AP[138]. It is essential that patients with recurrent AP are managed by physicians with special interest in pancreatology and its management should be guided by local multidisciplinary teams to not only reduce progression to chronicity, but also to maintain good QOL in patients.

CONCLUSION

AP is a disease spectrum where majority of patients present with mild disease. However, in the minority with non-mild AP, mortality is high. Proper risk stratification using a conglomerate of clinical judgement and predictive scores for proper resource allocation and care is integral of any health system to deliver good outcomes. Early goal-directed fluid resuscitation with crystalloids should be carried out. Prophylactic antibiotics have yet to show any clear morbidity or mortality benefits in SAP. Enteral nutrition is recommended over parenteral nutrition, if not contraindicated. Timing of starting enteral nutrition is still unclear, but should not be delayed until complete resolution of disease. Decision for higher intensity monitoring should also be based on clinical status and ICU capabilities of respective institutions. Early ERCP should be performed for concomitant biliary obstruction or AC. Endoscopic step-up approach is the preferred choice in the management of infected pancreatic necrosis.

FOOTNOTES

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Abstract

In recent years, natural orifice specimen extraction surgery (NOSES), a novel minimally invasive surgical technique, has become a focus in the surgical field, and has been initially applied in gastric surgery in many national medical centers worldwide. In addition, this new surgical technique was launched in major hospitals in China. With an increasing number of patients who have accepted this new surgical technique, NOSES has provided new prospects for the treatment of gastric cancer (GC), which may achieve a better outcome for both patients and surgeons. More and more experts and scholars from different countries and regions are currently paying close attention to NOSES for the treatment of GC. However, there are only a few reports of its use in GC. This review focuses on the research progress in NOSES for radical gastrectomy in recent years. We also discuss the challenges and prospects of NOSES in clinical practice.

Key Words: Gastrectomy; Gastric cancer; Laparoscopic surgery; Minimally invasive surgery; Natural orifice specimen extraction surgery; Radical gastrectomy

Core Tip: Gastric cancer (GC) is a very common malignancy worldwide. Natural orifice specimen extraction surgery (NOSES), an emerging minimally invasive surgical technique, has gradually become a new modality for the treatment of GC. NOSES has gained more and more attention as well as recognition from experts and scholars nationally and internationally. We herein discuss the research progress and application prospects of NOSES.

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INTRODUCTION

Gastric cancer (GC) is a very common malignancy worldwide. It is reported that the incidence rate of GC ranks fourth among all malignancies in the world and is the second most common cause of cancer-related death[1]. GC has been a focus of research in the field of gastrointestinal tumor surgery, as surgery is considered to be the most important part of GC treatment plans, especially in advanced GC. With the rapid development of surgical techniques, minimally invasive surgery has played an important role in the development of surgery. In 1994, Kitano *et al*[2] performed laparoscopic distal gastrectomy for early GC for the first time. Thereafter, with the development of laparoscopic surgical techniques over the next 20 years, treatment for GC has gone through a series of stages from laparotomy to laparoscopy, porous laparoscopic surgery (mostly five holes), and single hole laparoscopic surgery[3-5]. In terms of minimally invasive surgery and aesthetics, natural orifice specimen extraction surgery (NOSES) has the advantages of combined traditional laparoscopic techniques and minimally invasive surgery, including minimal cutaneous trauma and postoperative pain, fast postoperative recovery, short hospital stay, and a positive psychological impact[6]. Technical innovation of NOSES has resulted in better treatments for patients.

It is worth mentioning that all the natural orifice transluminal endoscopic surgery (NOTES) procedures are performed through a natural cavity, without any visible scars on the surface of the body. The abdominal incision is completely eliminated as it is a minimally invasive surgical technique. However, it is difficult to perform this surgical technique using current medical technology[6,7]. It requires surgeons to be skilled in laparoscopic techniques, especially in laparoscopic reconstruction of the digestive tract. For this reason, NOTES is carried out on a relatively modest scale.

NOSES makes full use of the latest laparoscopic instruments and techniques, and specimen extraction is achieved by taking specimens from a natural cavity (mouth, rectum, and vagina) of the human body, followed by complete reconstruction of the digestive tract. This avoids abdominal incision for specimen extraction. Technically, it is easily performed by skilled surgeons. NOSES is a bridge between conventional laparoscopic surgery and NOTES[8]. Compared with traditional laparoscopic surgery, the minimally invasive effect of NOSES is much more significant, and postoperative recovery is faster[9,10]. It can eliminate the risk of abdominal incision-related complications, relieve pain, and achieve a better abdominal cosmetic effect.

CURRENT SITUATION OF NOSES

NOSES can complete various conventional surgical techniques (resection and reconstruction) in the abdomen and pelvis using laparoscopic instruments, robots, transanal endoscopic micro-surgery or soft endoscopy and other equipment platforms. Specimens are extracted from a natural cavity (rectum, vagina, or oral cavity)[6]. This is an emerging minimally invasive surgery without an abdominal incision[6]. NOTES is a type of NOSES. In the early 1990s, a few cases with specimen extraction through a natural cavity were reported[11,12]. In 2008, the first attempt of transvaginal specimen extraction during laparoscopic colorectal cancer surgery in seven female patients was carried out by Palanivelu *et al*[13], which resulted in a new era of minimally invasive gastrointestinal surgery. In 2011, Wang *et al*[14] reported two female patients who underwent radical resection of rectal cancer using the transvaginal approach. There were no visible scars on the abdomen or incision-related complications. This is the first report of the operation and specimen extraction performed *via* a vaginal approach in China. In 2012, the robot platform was used in the radical resection of rectal cancer for the first time in China, and specimen extraction was also performed through a natural cavity (anus)[15]. Over the next few years, NOSES gained more interest from Chinese experts and scholars. This new surgical technique was also performed in major hospitals in China. There are now increasing numbers of related reports and patients undergoing this operation. Tang *et al*[16] found that the NOSES group had advantages in terms of reducing postoperative complications and postoperative pain, faster recovery of gastrointestinal function, and shorter postoperative hospital stay. Most notably, the physical function, role function, emotional function, and overall health status in the NOSES group were significantly better than those in the conventional laparoscopic surgery group. In addition, body image scores were significantly higher in the NOSES group. However, there was no significant difference in long-term survival between the two groups. This operation may lead to the leakage of digestive fluid, abdominal infection, as well as local, rectal, and vaginal incision recurrence[17-20].

RESEARCH PROGRESS AND APPLICATION PROSPECTS OF NOSES IN GC

In 2011, Jeong *et al*[21] began to apply NOSES in early GC. Following traditional laparoscopic subtotal gastrectomy with regional lymph node dissection, a posterior colpotomy was performed by an experienced gynecologist, who placed the specimen retrieval bag in the abdominal cavity. The specimen and the retrieval bag were then removed *via* the transvaginal route. The authors pointed out that this new surgical method may be feasible and safe for elderly female patients with early GC. In 2015, a 72-year-old female patient underwent total laparoscopic subtotal gastrectomy, regional lymph node dissection, and Roux-en-Y gastrojejunostomy[22]. Similarly, the specimen was extracted through the colpotomy incision. In this case, the diameter of the adenocarcinoma located in the gastric antrum was only 2 cm, thus the extraction was not difficult. Postoperative histopathology of the adenocarcinoma was pT3pN0. During the next 10 mo, the patient received conventional adjuvant chemoradiotherapy, with no postoperative complications. This is the first time that transvaginal extraction was used for an advanced gastric tumor after total laparoscopic gastrectomy. This study demonstrated that NOSES is a safe and feasible procedure for advanced GC. In 2015, the *World Journal of Gastroenterology* reported for the first time, the application of robotic gastrectomy in eight female patients (aged between 42 and 69 years) using the Da Vinci Robotic System, and transvaginal specimen extraction. The patients were divided into two groups according to the location of the tumor; two cases received robotic total gastrectomy and six underwent robotic distal gastrectomy, with transvaginal specimen extraction in both groups using the same method[23]. The mean total operation time was 224 min, and the mean postoperative stay was 3.6 d. Postoperative gastrointestinal stenosis, anastomotic leakage, and re-admission were not reported during the follow-up period. To some extent, this study proved the feasibility and safety of robotic radical gastrectomy with transvaginal specimen extraction for female patients with GC. In 2019, Liu *et al*[24] reported a case of early gastric angular adenocarcinoma (cT1bN0M0). After total laparoscopic distal gastrectomy and a modified delta-shaped anastomosis, the specimen was extracted from the anus *via* the anterior rectal wall incision. During this procedure, the rectum was disinfected with iodine water, and iodophor gauze was placed in the anus for full dilation. A 6 cm incision was made on the anterior wall of the upper rectum. The specimen in the retrieval bag was slowly pulled out of the abdominal cavity through the anus to complete the extraction process. After the operation, the patient's vital signs were stable and there were no complications. The patient recovered and was discharged from hospital after 14 d. In December of the same year, Sun *et al*[25] reported on NOSES gastrectomy in a 64-year-old male patient. After laparoscopic distal gastrectomy, the surgeon placed the retrieval bag in the abdominal cavity to retrieve the specimen, and then performed a modified gastroduodenal triangle anastomosis to complete the reconstruction of the digestive tract. The anorectum was repeatedly rinsed with iodine water, and the anorectal intestinal wall was supported by iodophor gauze after sufficient anal dilation. A 4 cm incision was made in the upper rectum, an oval clamp was inserted through the anorectum, and the specimen bag was pulled out from the incision through the anorectum to complete the removal of the surgical specimens. On the tenth day, the patient recovered and was discharged without any complications or tumor recurrence. Wang *et al*[26] performed both total laparoscopic subtotal gastrectomy and radical anterior resection in a 65-year-old man, and the extraction of specimens was completed through the anus. The postoperative pathology confirmed that both tumors were moderately differentiated adenocarcinoma, and the lymph node in each specimen was negative. After six cycles of adjuvant chemotherapy, no recurrence was observed during the follow-up period.

The number of patients in the above case reports on GC-NOSES is limited. However, it is the only way for the NOSES technique to become popular in central hospitals and the use of this technique is only beginning. If the surgeon masters this new technique, a stable surgical team can be established. A single center clinical study on GC-NOSES has been launched in recent years.

In 2017, Hüscher *et al*[27] conducted a prospective, non-randomized single center clinical study of laparoscopic NOSES radical gastrectomy, which was only performed in patients with early GC. After laparoscopic gastrectomy, a 3 cm incision was made on the gastric stump. The specimen was then cut into three small segments, and stitched one by one. Finally, the specimens were removed through the oral cavity. A total of 14 patients with early GC were included in this study and they were followed for 18 mo. One patient died of postoperative pneumonia (mortality 7.14%), and the remaining patients had no serious complications or wound infection. The mean postoperative hospital stay was 4.7 ± 1.0 d. To some extent, this study indicated that the safety and feasibility of NOSES radical gastrectomy for early GC were similar to those of traditional laparoscopic surgery, but the NOSES technique did reduce the mortality and postoperative hospital stay. In the same year, a retrospective study was reported in Polski Przeglad Chirurgiczny, which included 50 patients with gastrointestinal stromal tumors[28]. In this study, 12 patients' specimens were retrieved through the oral cavity and the remaining 38 *via* a conventional abdominal incision. The statistical results of 12 patients showed that the mean operation time was 92.5 min, the tumor size ranged from 14 mm to 40 mm, and the mean length of hospital stay was 3.2 d. Postoperative pathology confirmed that all the cases showed radical excision. One patient developed a surgical site infection and one patient had fluid collection at the suture site which prolonged hospital stay to 8 d. Following a comparative analysis, the researchers believe that the NOSES technique is a promising, safe, and effective minimally invasive surgery. Recently, Tang *et al*[16] used a type of NOSES

Table 1 Natural orifice specimen extraction surgery for gastric cancer

Abbreviations	Full name	Orifice
GC-NOSES I	Laparoscopic distal gastrectomy (Billroth I) with transrectal specimen extraction	Rectum
GC-NOSES II	Laparoscopic distal gastrectomy (Billroth I) with transvaginal specimen extraction	Vagina
GC-NOSES III	Laparoscopic distal gastrectomy (Billroth II) with transrectal specimen extraction	Rectum
GC-NOSES IV	Laparoscopic distal gastrectomy (Billroth II) with transvaginal specimen extraction	Vagina
GC-NOSES V	Laparoscopic proximal gastrectomy with transrectal specimen extraction	Rectum
GC-NOSES VI	Laparoscopic proximal gastrectomy with transvaginal specimen extraction	Vagina
GC-NOSES VII	Laparoscopic total gastrectomy with transrectal specimen extraction	Rectum
GC-NOSES VIII	Laparoscopic total gastrectomy with transvaginal specimen extraction	Vagina
GC-NOSES IX	Laparoscopic partial gastrectomy with transoral specimen extraction	Mouth

GC: Gastric cancer; NOSES: Natural orifice specimen extraction surgery.

to perform Roux-en-Y reconstruction after laparoscopic total gastrectomy with two circular staplers (one of which was oval). The advantage of this technique is that it can be applied to the tumor located very close to the cardia. Thus, it could obtain a high-quality anastomosis effect, and a laparoscopic suture is not required to close the intestinal common opening. Consequently, the operation time could be significantly shortened and the patient's gastrointestinal function would recover more quickly.

NOSES, a new surgical technique, is now carried out in more and more hospitals. However, there is still a lack of standardization in this novel minimally invasive surgery. In June 2017, Professor Xi-Shan Wang and other experts initiated the China NOSES Alliance and the NOSES Special Committee of Colorectal Surgeons Branch of Chinese Medical Doctor Association. In 2019, the NOSES Special Committee issued the International Consensus on NOSES for GC[29]. The consensus systematically named and standardized the NOSES procedure for GC. According to three factors related to the resection range, as well as the type of digestive reconstruction and specimen extraction route, the method of NOSES for GC can be divided into nine types (Table 1)[6]. In addition, the consensus described in detail the indications and contraindications, precautions and approach of surgery, and solutions to the difficulties in specimen extraction of GC-NOSES, which would be instructive for the development of NOSES in clinical practice. In general, there are seven steps in the NOSES procedure: (1) Preoperative course; (2) Positioning and placement of trocars; (3) Localization of the tumor; (4) Laparoscopic subtotal gastrectomy; (5) Trans-natural cavity (mouth, rectum, and vagina) specimen extraction; (6) Digestive tract reconstruction; and (7) Postoperative course. More significantly, the resection range of gastrectomy cannot be intentionally reduced due to specimen extraction through a narrow orifice. Based on different tumor locations, the methods of gastrectomy and reconstruction should be carefully selected to preserve gastrointestinal function. In addition, the anastomosis should be provided with sufficient blood supply and no tension or stenosis[21].

CONCLUSION

NOSES is better than traditional laparoscopic assisted radical gastrectomy for GC in some aspects. For example, it avoids abdominal surgical incision, and eliminates incision-related complications such as incision site infection, difficult or non-healing incision, wound dehiscence, incisional hernia, abdominal incision tumor implantation, and even the pain and scarring caused by the incision[30]. In addition, it can eliminate the incision scar related psychological impact, psychological burden, and psychological trauma of surgery[8]. NOSES for GC also reflects the doctor's pursuit of people-oriented principle, by prioritizing the interests of the patients. However, we should also pay attention to the shortcomings and potential complications of NOSES for GC. For example, due to the unique intraluminal anastomosis and the approach of specimen extraction in NOSES for GC, there are potential risks, such as intraperitoneal exposure and dissemination of tumor cells, intraperitoneal bacterial infection, structural or functional damage of natural lumen, abscission and implantation of tumor cells. Due to the lack of relevant reports on NOSES for GC, we can only learn from other literature reports on gastrointestinal surgery using this technique.

In recent years, specimen extraction *via* a natural orifice, an emerging minimally invasive surgical technique, has become one of the research hotspots in the surgical field nationally and internationally. This technique has been preliminarily applied to gastroenterological surgery in many national medical centers around the world. With the increasing number of surgical cases, NOSES has gradually become a

novel modality for GC treatment, which not only provides a better treatment choice for patients and operators, but has also gained more and more attention and recognition from experts and scholars worldwide.

However, we should also be aware that the clinical development of GC-NOSES is still in its infancy. Research on GC-NOSES has mainly focused on single-center, small sample and retrospective analyses [22,23], indicating a lack of large sample and multi-center prospective studies to support the extensive development of GC-NOSES in evidence-based medicine. In addition, GC-NOSES related complications deserve further investigation, such as abdominal infection, natural orifice injury, tumor implantation metastasis, anastomotic leakage, prognosis and recurrence in patients, and its long-term efficacy.

FOOTNOTES

Author contributions: Zhang ZC and Luo QF performed the majority of the writing, and prepared the table; Luo QF, Wang WS, Chen JH, and Wang CY performed data acquisition and manuscript writing; Ma D designed the outline and coordinated the writing of the paper; and all authors have read and approved the final version to be published.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Clinical value of extended lymphadenectomy in radical surgery for pancreatic head carcinoma at different T stages

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Abstract

BACKGROUND

As the lymph-node metastasis rate and sites vary among pancreatic head carcinomas (PHCs) of different T stages, selective extended lymphadenectomy (ELD) performance may improve the prognosis of patients with PHC.

AIM

To investigate the effect of ELD on the long-term prognosis of patients with PHC of different T stages.

METHODS

We analyzed data from 216 patients with PHC who underwent surgery at our hospital between January 2011 and December 2021. The patients were divided into extended and standard lymphadenectomy (SLD) groups according to extent of lymphadenectomy and into T1, T2, and T3 groups according to the 8th edition of the American Joint Committee on Cancer's staging system. Perioperative data and prognoses were compared among groups. Risk factors associated with prognoses were identified through univariate and multivariate analyses.

RESULTS

The 1-, 2- and 3-year overall survival (OS) rates in the extended and SLD groups were 69.0%, 39.5%, and 26.8% and 55.1%, 32.6%, and 22.1%, respectively (P = 0.073). The 1-, 2- and 3-year disease-free survival rates in the extended and SLD groups of patients with stage-T3 PHC were 50.3%, 25.1%, and 15.1% and 22.1%, 1.7%, and 0%, respectively (P = 0.025); the corresponding OS rates were 65.3%, 38.1%, and 21.8% and 36.1%, 7.5%, and 0%, respectively (P = 0.073). Multivariate analysis indicated that portal vein invasion and lymphadenectomy extent were risk factors for prognosis in patients with stage-T3 PHC.

CONCLUSION
ELD may improve the prognosis of patients with stage-T3 PHC and may be of benefit if performed selectively.

Key Words: Pancreatic head carcinoma; Extended lymphadenectomy; T stage; Surgical treatment; Risk factor; Long-term prognosis

Core Tip: Since the lymph node metastasis rate and site differ in pancreatic head carcinoma(PHC) patients at different T stage, we hypothesized that selectively performing extended lymphadenectomy (ELD) can improve the outcome of surgical treatment in PHC patients. The result confirmed that proceeding ELD in T3 stage PHC patients can increase long-term prognosis, providing a new idea to optimized the surgical procedure of PHC. Therefore we concluded that it may be beneficial to perform ELD in PHC patients at T3 stage and potentially increase the clinical outcome of these patients.

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INTRODUCTION

Pancreatic carcinoma, a common digestive system pathology, is a highly malignant cancer and the third leading cause of cancer-related death, according to the American Cancer Society[1]. Its morbidity rate has increased recently[2-4]. Pancreatic head carcinoma (PHC) is located at the head and uncinate process of the pancreas, and radical surgery is currently the only potential curative therapy for it[5]. However, the postoperative long-term prognosis of patients with PHC is unsatisfactory due to local and distant recurrence in the early postoperative stage.

Lymph-node metastasis is an important PHC transfer pathway, and radical lymph-node dissection is mandatory following anti-tumor treatment[6]. Fortner[7] first proposed extended lymphadenectomy (ELD) in 1973, and this technique has been adopted increasingly widely with its improvement. However, randomized controlled trials have shown that although this procedure increases the lymph-node count, it does not improve the metastatic lymph-node count or long-term prognosis, and thus is of limited clinical value[8]. Variations in the lymph-node metastasis rate and sites among PHC stages may explain this phenomenon. Song *et al*[9] reported that patients with higher T-stage gastric cancer tend to have higher lymph-node metastasis rates, and confirmed the potential beneficial effect of extensive station-7 lymph-node resection. Considering the positive correlation between the lymph-node metastasis rate and tumor size in patients with PHC, as well as the tendency for distant lymph-node metastasis in advanced PHC[10,11], the selective performance of ELD in patients with PHC of higher T stages may improve the PHC prognosis. In this study, we evaluated the effect of ELD on the long-term prognoses of patients with PHC of different T stages, and the potential clinical value of this procedure.

MATERIALS AND METHODS

Sample and ethical considerations

We retrospectively analyzed data from patients with PHC who received surgical treatment in the Hepatobiliary Surgery Department of Beijing Chaoyang Hospital between January 2011 and December 2021. The application of the inclusion and exclusion criteria yielded a sample of 216 patients as shown in Figure 1. The inclusion criteria were: (1) Age 20-85 years; (2) No distant metastasis on preoperative evaluation; (3) No celiac axis, common hepatic artery, or superior mesenteric artery invasion on preoperative evaluation; (4) Surgical treatment including successful *en-bloc* resection; (5) Postoperative pathological confirmation of the diagnosis of pancreatic ductal adenocarcinoma; and (6) Completeness of clinical and follow-up information. The exclusion criterion was postoperative loss to follow-up.

All surgical procedures and treatment strategies examined in this study were performed with the informed consent of the patients and their family members. The Ethics Committee of Beijing Chaoyang Hospital approved the study and granted access to the patients' clinical information (No. 2020-D.-302).

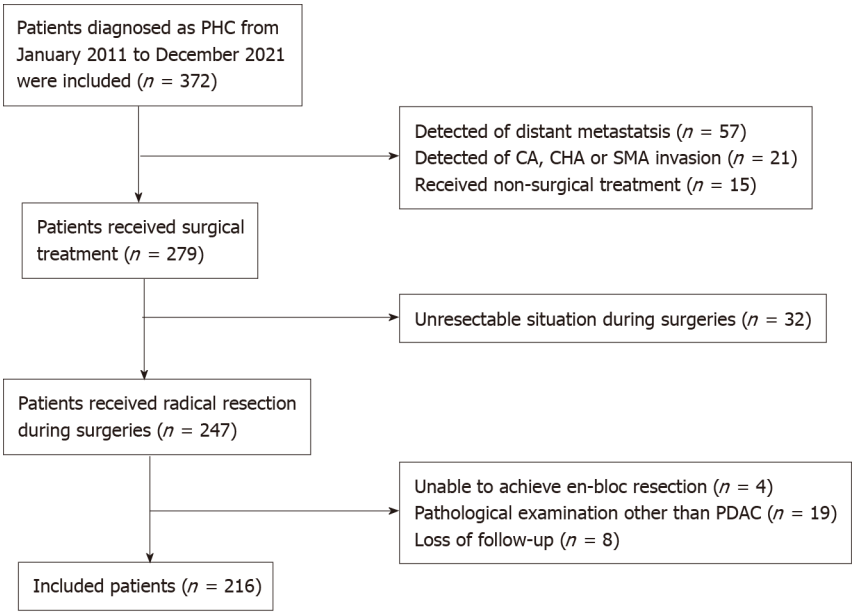

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Figure 1 Flow of patient selection. PHC: Pancreatic head carcinoma; CA: Celiac axis; CHA: Common hepatic artery; SMA: Superior mesenteric artery; PDAC: Pancreatic ductal adenocarcinoma.

Sample characteristics

The sample of 216 patients comprised 124 males and 92 females (male:female ratio, 1.3:1) with a mean age of 63.6 ± 10.4 (range: 29-84) years. The patients' initial symptoms included jaundice (n = 110), abdominal pain (n = 78), and atypical gastrointestinal symptoms (n = 9); PHC was detected by physical examination in 19 patients. Sixty-eight (34.5%) patients had diabetes. Sixty-one of the patients exhibiting jaundice received preoperative jaundice-reducing treatment, consisting of endoscopic retrograde cholangiopancreatography (n = 10) and percutaneous transhepatic biliary drainage (n = 51).

Patient grouping and definitions

The patients were divided according to T stage, based on the 8th edition of the American Joint Committee on Cancer manual, into T1 (tumor diameter ≤ 2 cm, n = 44), T2 (2 cm < tumor diameter ≤ 4 cm, n = 127), and T3 (tumor diameter > 4 cm, n = 45) groups. They were divided into standard and ELD groups according to the extent of lymphadenectomy intraoperatively as shown in Table 1, with lymph-node stations designated using the Japan Pancreas Society's nomenclature for peripancreatic lymph nodes[12]. The standard lymphadenectomy (SLD) group (Figure 2A) consisted of cases in which station-5 (suprapyloric), station-6 (infrapyloric), station-8a (anterosuperior along the common hepatic artery), station-12b and c (along the bile duct and around the cystic duct), station-13a and p (on the posterior aspect of the superior and inferior portions of pancreas head), and station-17a and p (on the anterior surface of the superior and inferior portions of the pancreas head) lymph nodes were removed. The ELD group (Figure 2B) consisted of cases not only involving the above-mentioned lymph nodes, but also in which station-8p (posterior along the common hepatic artery), station-9 (around the celiac artery), station-12a and p (along the proper hepatic artery and posterior to the portal vein), station-14a and b (on the right side of the superior mesenteric artery), station-14c and d (on the left side of the superior mesenteric artery), and station-16 (around the abdominal aorta) lymph nodes were removed.

Portal vein invasion was categorized as type I (≤ 1/4 of the superior mesenteric-portal vein circumference), type II (> 1/4 of the superior mesenteric-portal vein circumference), type III (superior mesenteric/splenic vein junction), and type IV (superior mesenteric-portal vein including the portal vein trunk and superior mesenteric vein branches), according to the Chaoyang vascular classification proposed by our center[13]: Patients with type I invasion underwent partial venous excision and direct closure, those with type II invasion underwent direct end-to-end anastomosis or allogenic vein reconstruction after segmental venous excision, those with type III invasion underwent allogenic vein reconstruction after segmental venous excision, and those with type IV invasion underwent phleboplasty of the superior mesenteric vein branch ends and allogenic vein reconstruction after segmental venous excision.

Index analysis and follow-up

General preoperative data and intraoperative and postoperative recovery data were obtained from the patients' medical records. The perioperative data were compared among different groups. The patients

Table 1 Extent of extended lymphadenectomy and standard lymphadenectomy in pancreatic head carcinoma

Location	Standard lymphadenectomy	Extended lymphadenectomy
Superior pyloric (No.5)	O	O
Inferior pyloric (No.6)	O	O
Anterior CHA (No.8a)	O	O
Posterior CHA (No.8p)	X	O
Celiac axis (No.9)	X	O
Proper hepatic artery (No.12a)	X	O
Bile duct (No.12b)	O	O
Cystic duct (No.12c)	O	O
Portal vein (No.12p)	X	O
Posterior pancreaticoduodenal (No.13a-b)	O	O
Origin and right side of SMA (No.14a-b)	X	O
Left side of SMA(No.14c-d)	X	O
Celiac axis to IMA (No.16a2, No.16b1)	X	O
Anterior pancreaticoduodenal (No.17a-b)	O	O

O: Dissected; X: Not dissected; CHA: Common hepatic artery; SMA: Superior mesenteric artery; IMA: Inferior mesenteric artery.

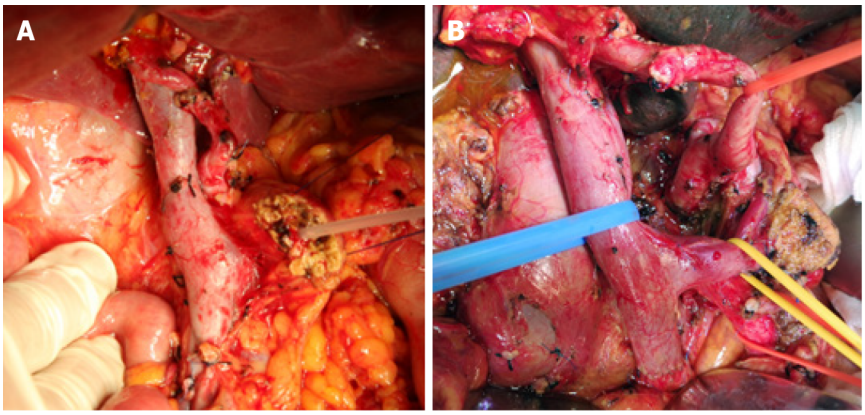

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Figure 2 Extent of lymphadenectomy in different groups. A: An intraoperative picture shows the extent of standard lymphadenectomy; B: An intraoperative picture shows the extent of extended lymphadenectomy.

underwent follow-up evaluations in the first and third months after surgery, and then every 3 mo until 2 years postoperatively and every 6 mo thereafter. The follow-up evaluations consisted of blood testing [routine bloodwork, blood biochemistry, and carbohydrate antigen (CA)19-9 level measurement], imaging examinations (pulmonary and enhanced abdominal computed tomography), postoperative treatment, and the assessment of tumor recurrence and survival. Tumor recurrence and death were follow-up visit endpoints. The long-term prognoses of patients in different groups were analyzed and compared.

Statistical analysis

The data are presented as means ± standard errors of the mean. Nominal and continuous data were compared using the chi-squared and student's *t* tests, respectively. Survival outcomes were calculated using the Kaplan-Meier method and compared using the log-rank test. Variables that were significant in univariate analysis were included in a multivariate Cox proportional-hazards regression model. All statistical analyses were performed using SPSS (version 24.0; IBM Corporation, Armonk, NY, United States), with two-sided P values < 0.05 considered to be significant.

RESULTS

Perioperative characteristics

All surgeries were successful, and no intraoperative death occurred. Seven patients died in the perioperative period, of abdominal hemorrhage secondary to pancreatic fistula, pulmonary infection (n = 2 each), abdominal infection, renal failure, and heart failure (n = 1 each); the perioperative mortality rate was 3.2%. The SLD group consisted of 88 patients and the ELD group consisted of 128 patients. Portal vein invasion was observed in 116 patients; 83 of these patients underwent allogenic vascular replacement, 27 underwent end-to-end anastomosis after vascular resection, while 6 patients underwent direct suturing after wedge vascular resection. The average volume of intraoperative blood loss was 500 mL (400, 800), and 103 (47.7%) patients received blood transfusions. The average operative time was 11.0 ± 2.9 h (range: 6-20 h).

Postoperative complications were observed in 69 (31.9%) cases, comprising 26 (12.0%) cases of postoperative diarrhea, 24 (11.1%) cases of gastric emptying disturbance, 22 (10.2%) cases of abdominal infection, 9 (4.2%) cases of biochemical fistula, 7 (3.2%) cases of abdominal hemorrhage, 6 (2.8%) cases of level-C pancreatic fistula, 5 (2.3%) cases of pulmonary infection, 4 (2.8%) cases of level-B pancreatic fistula, 4 (1.9%) cases of biliary fistula, 4 (1.9%) cases of gastrointestinal hemorrhage, 4 (1.9%) cases of lymphorrhagia, 3 (1.4%) cases of wound infection, 2 (0.9%) cases of intestinal fistula, 1 (0.5%) case of portal vein thrombosis, 1 (0.5%) case of renal failure, and 1 (0.5%) case of heart failure.

All patients were diagnosed with pancreatic ductal adenocarcinoma, confirmed by postoperative pathological examination. The numbers of cases of highly, moderately, and poorly differentiated adenocarcinoma were 18 (8.3%), 126 (58.3%), and 72 (33.3%), respectively. The average tumor diameter was 3.5 ± 1.5 cm. Postoperative pathological examination led to the detection of an average of 24.2 ± 13.5 lymph nodes per patient and 145 metastatic lymph nodes overall; the lymph-node metastasis rate was 67.1%. Radical resection (R0) was achieved in 201 (93.1%) cases, and R1 resection was achieved in the remaining cases [5 (2.3%) cases each with positive pancreatic and peripancreatic excision margins, 3 (1.4%) cases with positive portal-vein excision margins, and 2 (0.9%) cases with positive uncinate-process excision margins].

Overall long-term prognoses

The study follow-up period ended in March 2022. During this period, 109 (50.5%) patients received 1-12 cycles of postoperative adjuvant chemotherapy. The median disease-free survival (DFS) period in the total sample was 15 mo, and the 1-, 2-, and 3-year postoperative DFS rates were 56.3%, 33.1%, and 18.3%, respectively (Figure 3A). The median overall survival (OS) period was 17 mo, and the 1-, 2-, and 3-year postoperative OS rates were 60.7%, 35.3%, and 23.9%, respectively (Figure 3B). The median DFS periods for patients with stage-T1-, -T2, and -T3 PHC were 23, 15, and 11 mo, respectively; the 1-, 2-, and 3-year postoperative DFS rates for these patients were 75.6%, 47.7%, and 31.9%; 56.3%, 32.8%, and 16.6%; and 36.4%, 18.7%, and 9.3%, respectively (P = 0.002, Figure 3C). The median OS periods for patients with stage-T1-, -T2, and -T3 PHC were 26, 15, and 13 mo, respectively; the 1-, 2-, and 3-year postoperative OS rates for these patients were 74.0%, 51.8%, and 36.7%; 59.2%, 33.0%, and 23.1%; and 51.0%, 24.1%, and 12.1%, respectively (P = 0.005, Figure 3D).

Comparisons of perioperative and survival data

More lymph nodes were detected postoperatively in the extended than in the SLD group (P < 0.05; Table 2). The incidence rates of postoperative complications and the mortality rate did not differ between the extended and SLD groups, except that more patients in the former had postoperative diarrhea (P < 0.05; Table 3).

The median DFS periods for patients in the extended and SLD groups were 16 and 14 mo, respectively; the 1-, 2-, and 3-year postoperative DFS rates in these groups were 59.9%, 32.1%, and 20.7% and 53.8%, 34.6%, and 16.7%, respectively (P = 0.227, Figure 4A). The median OS periods for patients in the extended and SLD groups were 18 and 15 mo, respectively; the 1-, 2-, and 3-year postoperative OS rates in these groups were 69.0%, 39.5% and 26.8% and 55.1%, 32.6%, and 22.1%, respectively (P = 0.073, Figure 4B).

Comparisons of perioperative and survival data according to T stage and lymphadenectomy extent

ELD increased the numbers of lymph nodes detected in patients with stage-T1- and -T3 disease (P < 0.05; Table 4). Patients in the ELD group were younger than those in the SLD group (P < 0.05). ELD increased the incidence rate of postoperative diarrhea in patients with stage-T2- and -T3 disease (P < 0.05) without affecting the incidence rates of other perioperative complications or the mortality rate (Table 5).

The median DFS periods for patients with stage-T1 PHC in the extended (n = 16) and standard (n = 28) lymphadenectomy groups were 21 and 23 mo, respectively; the 1-, 2-, and 3-year DFS rates in these groups were 74.0%, 47.1%, and 39.3% and 76.4%, 47.6%, and 26.5%, respectively (P = 0.797, Figure 5A). The OS periods for patients with stage-T1 disease in the extended and SLD groups were 41 and 26 mo, respectively; the 1-, 2-, and 3-year OS rates in these groups were 79.3%, 50.5% and 50.5% and 70.8%,

Table 2 General data between extended and standard lymphadenectomy group in pancreatic head carcinoma patients

Variables	ELD group (*n* = 88)	SLD group (*n* = 128)	*P* value
Gender (male/female)	51/37	73/55	0.893
Age (yr)	62.1 ± 11.0	64.6 ± 10.0	0.080
TB (μmol/L)	62.6 (15.3, 144.6)	57.7 (12.7, 143.4)	0.679
CA19-9 (U/ml)	161.8 (38.5, 544.9)	202.1 (44.9, 773.2)	0.342
Intraoperative blood loss (mL)	500 (400, 800)	600 (400, 800)	0.332
Operation time (h)	11.1 ± 2.8	11.0 ± 2.9	0.693
Tumor size (cm)	3.5 ± 1.4	3.5 ± 1.7	0.790
Tumor differentiation (poorly/ modrately& highly)	25/63	47/81	0.203
Portal vein invasion (yes/no)	47/41	69/59	0.943
Lymph node metastasis (yes/no)	54/34	91/37	0.135
Retrieved lymph node count	25 (18, 35)	19 (14, 28)	0.001
Positive lymph node count	1 (0, 4)	2 (0, 3)	0.614
Resection margin (R0/R1)	83/5	118/10	0.545
Postoperative chemotherapy (yes/no)	48/40	61/67	0.320

ELD: Extended lymphadenectomy; SLD: Standard lymphadenectomy; TB: Total bilirubin; CA19-9: Carbohydrate antigen 199; R: Resection margin.

Table 3 Perioperative complications between extended and standard lymphadenectomy group in pancreatic head carcinoma patients

Variables	ELD (*n* = 88)	SLD (*n* = 128)	*P* value
Perioperative death	2	5	0.783
Postoperative complications	27	42	0.741
Biochemical fistula	3	6	0.908
Pancreatic fistula (grade B/C)	4	6	0.779
DGE	9	15	0.732
Diarrhea	22	4	< 0.001
Abdominal infection	9	13	0.987
Abdominal hemorrhage	3	4	0.783

ELD: Extended lymphadenectomy; SLD: Standard lymphadenectomy; DGE: Delayed gastric emptying.

53.1%, and 29.0%, respectively (P = 0.322, Figure 5B).

The median DFS periods for patients with stage-T2 PHC in the extended (n = 51) and standard (n = 76) lymphadenectomy groups were 15 and 13 mo, respectively; the 1-, 2-, and 3-year DFS rates in these groups were 59.5%, 29.9%, and 16.8% and 54.0%, 35.0%, and 16.6%, respectively (P = 0.549, Figure 5C). The OS periods for patients with stage-T2 disease in the extended and SLD groups were 17 and 13 mo, respectively; the 1-, 2-, and 3-year OS rates in these groups were 67.2%, 36.7%, and 21.5% and 54.1%, 30.7%, and 24.2%, respectively (P = 0.411, Figure 5D).

The median DFS periods for patients with stage-T3 PHC in the extended (n = 21) and standard (n = 24) lymphadenectomy groups were 14 and 9 mo, respectively; the 1-, 2-, and 3-year DFS rates in these groups were 50.3%, 25.1%, and 15.1% and 22.1%, 1.7%, and 0%, respectively (P = 0.025, Figure 5E). The OS periods for patients with stage-T3 disease in the extended and SLD groups were 18 and 12 mo, respectively; the 1-, 2-, and 3-year OS rates in these groups were 65.3%, 38.1%, and 21.8% and 36.1%, 7.5%, and 0%, respectively (P = 0.005, Figure 5F).

Risk factors associated with the postoperative prognosis in patients with stage-T3 PHC

In the univariate analysis, the postoperative long-term prognosis served as the dependent variable and preoperative data (sex, age, CA19-9 level), intraoperative data (operation time, blood loss), pathological

Table 4 General data between extended and standard lymphadenectomy group in pancreatic head carcinoma patients at different T stages

Variables	T1 stage			T2 stage			T3 stage		
	ELD group (*n* = 16)	SLD group (*n* = 28)	*P* value	ELD group (*n* = 51)	SLD group (*n* = 76)	*P* value	ELD group (*n* = 21)	SLD group (*n* = 24)	*P* value
Gender (male/female)	10/6	14/14	0.423	32/19	46/30	0.801	9/12	13/11	0.449
Age (yr)	62.8 ± 12.4	64.1 ± 9.7	0.696	64.2 ± 9.8	64.7 ± 10.3	0.801	56.2 ± 10.9	64.8 ± 9.7	0.001
TB (μmol/L)	58.1 (16.8, 107.5)	72.3 (28.1, 149.0)	0.742	80.8 (14.6, 149.3)	60.6 (12.7, 168.7)	0.885	44.4 (13.0, 137.7)	29.4 (10.3, 96.8)	0.285
CA19-9 (U/mL)	115.9 (24.0, 262.8)	92.5 (38.7, 312.5)	0.817	152.7 (53.7, 545.9)	207.0 (43.5, 1058.9)	0.507	180.2 (39.6, 556.4)	424.5 (77.8, 1285.6)	0.270
Intraoperative blood loss (mL)	500 (400, 600)	500 (400, 650)	0.788	500 (400, 800)	600 (400, 800)	0.310	500 (400, 1000)	550 (400, 1000)	0.741
Operation time (h)	10.8 ± 3.5	9.5 ± 2.9	0.194	10.9 ± 2.5	11.3 ± 2.7	0.404	11.9 ± 3.0	11.6 ± 3.2	0.746
Tumor size (cm)	1.7 ± 0.4	1.8 ± 0.3	0.274	3.2 ± 0.5	3.4 ± 0.5	0.193	5.4 ± 1.0	6.1 ± 2.0	0.155
Tumor differentiation (poorly/moderately-highly)	2/14	11/17	0.126	14/37	24/52	0.619	9/12	12/12	0.632
Portal vein invasion (yes/no)	4/12	6/22	0.919	28/23	45/31	0.630	15/6	18/6	0.787
Lymph node metastasis (yes/no)	10/6	15/13	0.565	31/20	55/21	0.171	15/6	23/5	0.587
Retrieved lymph node count	21 (18, 32)	15 (12, 19)	0.004	26 (21, 33)	23 (16, 31)	0.509	25 (15, 40)	20 (15, 30)	0.030
Positive lymph node count	2 (0, 2)	1 (0, 2)	0.373	1 (0, 4)	2 (0, 4)	0.513	1 (0, 3)	4 (1, 5)	0.022
Resection margin (R0/R1)	16/0	28/0	-	48/3	68/8	0.555	19/2	22/2	0.700
Postoperative chemotherapy (yes/no)	6/10	15/13	0.305	29/22	36/40	0.294	13/8	10/14	0.175

ELD: Extended lymphadenectomy; SLD: Standard lymphadenectomy; TB: Total bilirubin; CA19-9: Carbohydrate antigen 199; R: Resection margin.

data (tumor differentiation, lymph-node metastasis, metastatic lymph node count, portal vein invasion, excision margin condition, lymphadenectomy extent), and postoperative adjuvant therapy data served as independent variables. The univariate analysis results are shown in Table 6. Lymph-node metastasis, portal vein invasion, and lymphadenectomy extent were significant risk factors in the univariate analysis and were included in the Cox proportional-hazard model. Portal vein invasion [relative risk (RR) = 2.471, 95% confidence interval (CI): 1.028-5.942] and the extent of lymphadenectomy (RR = 2.395, 95%CI: 1.065-5.383) were independent risk factors associated with the long-term prognosis of patients with stage-T3 PHC (Table 7). Among these patients, those with no portal vein invasion who underwent ELD tended to have better long-term prognoses.

DISCUSSION

Pancreatic carcinoma is a highly malignant cancer originating from the pancreatic ductal epithelial cells. It is usually characterized by early local invasion and distant metastasis, leading to poor long-term prognosis[14]. Although radical surgery remains the only potential curative therapy for PHC[5,15], the long-term postoperative prognosis remains unsatisfactory, emphasizing the importance and necessity of optimizing surgical procedures for PHC, especially that of advanced T stages.

Lymph-node metastasis is an important pancreatic carcinoma transfer pathway; it is confirmed by postoperative pathological examination in about 60% of patients[16]. It has also been recognized as an independent predictor of postoperative recurrence[17-19] and a factor affecting the long-term prognosis of patients with pancreatic carcinoma[20]. The International Study Group on Pancreatic Surgery has published recommendations for the extent and minimum number of retrieved lymph nodes for SLD [21]. However, Nakao *et al*[22] observed in resected PHC specimens lymph-node metastasis rates of 23% and 26% at stations 14 and 16, reflecting incomplete removal of involved lymph nodes by SLD. Imamura *et al*[23] found that the lymph-node recurrence rate was as high as 21% and that recurrence was seen most commonly at stations 14 and 16, contributing to 11% and 10% of all recurrence, in patients. Thus, expansion of the lymphadenectomy extent may be beneficial[24].

Table 5 Perioperative complications between extended and standard lymphadenectomy group in pancreatic head carcinoma patients at different T stages

Variable	T1 stage			T2 stage			T3 stage		
	ELD group (*n* = 16)	SLD group (*n* = 28)	*P* value	ELD group (*n* = 51)	SLD group (*n* = 76)	*P* value	ELD group (*n* = 21)	SLD group (*n* = 24)	*P* value
Perioperative death	0	1	1.000	2	4	0.938	0	0	-
Postoperative complications	4	12	0.391	14	25	0.514	9	5	0.111
Biochemical fistula	1	3	0.961	1	3	0.912	1	0	0.467
Pancreatic fistula (grade B/C)	0	3	0.463	4	3	0.585	0	0	-
DGE	2	4	0.771	4	10	0.349	3	1	0.506
Diarrhea	3	1	0.254	12	2	< 0.001	7	1	0.031
Abdominal infection	1	3	0.961	5	8	0.895	3	2	0.874
Abdominal hemorrhage	0	1	1.000	3	3	0.938	0	0	-

ELD: Extended lymphadenectomy; SLD: Standard lymphadenectomy; DGE: Delayed gastric emptying.

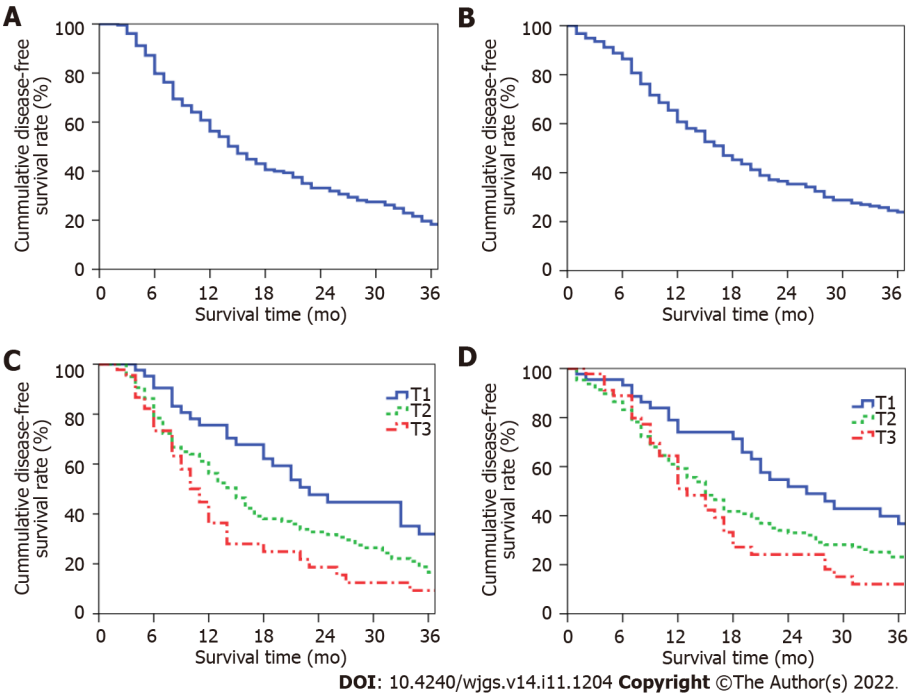

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Figure 3 Long-term prognosis of patients. A: The cumulative overall disease-free survival (DFS) curve of patients; B: The cumulative overall survival (OS) curve of patients; C: The cumulative DFS curves of patients at different T stages; D: The cumulative OS curves of patients at different T stages.

According to the 2021 Chinese guidelines for the diagnosis and treatment of pancreatic cancer[25], ELD in patients who have undergone pancreaticoduodenectomy for PHC should involve the excision of station-8p, -9, -12a, -12p, -14p, -14d, -16a2, and -16b1 lymph nodes in addition to those excised in SLD. However, recent research has shown that ELD not only prolongs the operation time, but increases intraoperative blood loss, the incidence rate of perioperative complications, and the perioperative mortality rate[8,26,27], Thus, the safety of ELD remains controversial. In contrast to these findings, the operation time, intraoperative blood loss, perioperative mortality rate, and incidence rates of perioperative complications except postoperative diarrhea did not differ between the extended and SLD groups in this study. The circumferential dissection of lymphatic and connective tissue around the root of the superior mesenteric artery in ELD may explain the higher incidence of postoperative diarrhea in patients who have undergone this procedure[26,27]. Farnell *et al*[28] reported that the incidence rates of

Table 6 Univariate analysis of long-term prognosis in pancreatic head carcinoma patients at T3 stage

Variables	Number (n = 45)	yr OS (%)	3-yr OS (%)	χ^2	P value
Gender				0.004	0.949
Male	22	46.8	13.7		
Female	23	54.1	10.8		
Age (yr)				2.192	0.139
≤ 60	22	60.2	20.1		
> 60	23	43.6	5.5		
CA19-9 (U/mL)				1.504	0.220
≤ 37	9	59.3	29.6		
> 37	36	48.9	7.5		
Operation time (h)				2.647	0.104
≤ 10	18	63.2	19.0		
> 10	27	42.5	6.1		
Intraoperative blood loss (mL)				0.253	0.615
≤ 800	30	49.2	16.5		
> 800	15	55.9	0		
Tumor differentiation				0.996	0.318
Poorly	21	39.3	8.2		
Moderately-highly	24	59.9	15.0		
Lymph node metastasis				5.542	0.019
Yes	34	42.9	7.9		
No	11	77.8	25.9		
Positive lymph node count				0.569	0.451
≤ 3	33	52.9	8.2		
> 3	12	46.3	23.1		
Portal vein invasion				4.141	0.042
Yes	33	42.3	7.7		
No	12	72.7	24.2		
Resection margin				0.035	0.852
R0	41	48.1	13.9		
R1	4	75.0	0		
Extent of lymphadenectomy				7.843	0.005
ELD	21	65.3	21.8		
SLD	24	36.1	0		
Postoperative chemotherapy				0.027	0.869
Yes	23	41.5	11.9		
No	22	61.2	12.4		

TB: Total bilirubin; CA19-9: Carbohydrate antigen 19-9; R: Resection margin; ELD: Extended lymphadenectomy; SLD: Standard lymphadenectomy; OS: Overall survival.

postoperative diarrhea at 4, 8, and 14 mo postoperatively in patients with PHC who underwent extended and SLD were 42%, 11%, and 15% and 8%, 11%, and 0%, respectively, with no difference between groups at 8 and 14 mo. Nimura *et al*[27] found that the influence of diarrhea on the quality of

Table 7 Cox multivariate regression analysis of long-term prognosis in pancreatic head carcinoma patients at T3 stage

Variables	RR	95%CI	*P* value
Lymph node metastasis	1.915	0.724-5.063	0.190
Portal vein system invasion	2.471	1.028-5.942	0.043
Extent of lymphadenectomy	2.395	1.065-5.383	0.035

RR: Relative risk; CI: Confidence interval.

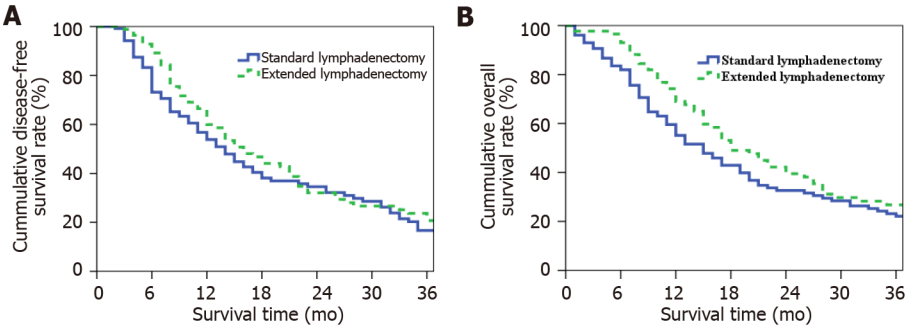

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Figure 4 Long-term prognosis of patients in extended lymphadenectomy group and standard lymphadenectomy group. A: The cumulative disease-free survival curve of patients in two groups; B: The cumulative overall survival curve of patients in two groups.

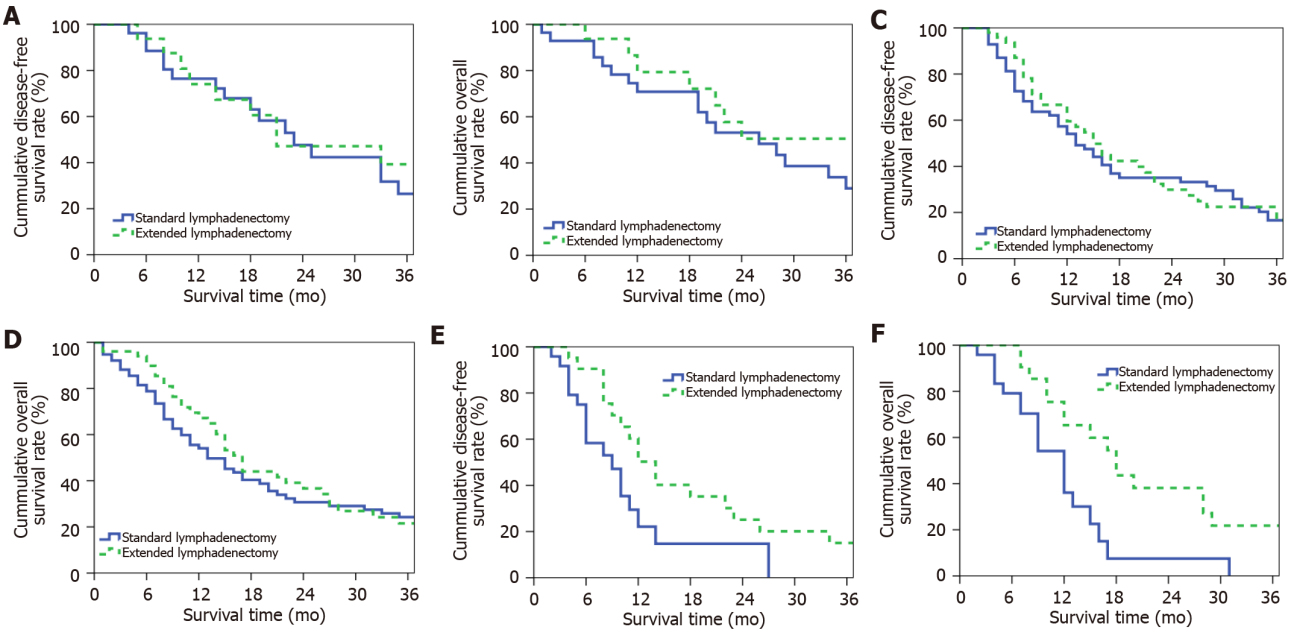

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Figure 5 Long-term prognosis of patients at different T stages in extended lymphadenectomy group and standard lymphadenectomy group. A: The cumulative disease-free survival (DFS) curve of patients at T1 stage in two groups; B: The cumulative overall survival (OS) curve of patients at T1 stage in two groups; C: The cumulative DFS curve of patients at T2 stage in two groups; D: The cumulative OS curve of patients at T2 stage in two groups; E: The cumulative DFS curve of patients at T3 stage in two groups; F: The cumulative OS curve of patients at T3 stage in two groups.

life of patients with PHC who had undergone ELD gradually decreased, with no significant difference from patients who had undergone SLD at 1 year postoperatively. Thus, postoperative diarrhea secondary to ELD is a controllable and temporary complication with no long-term patient effect. Considering that ELD did not increase the incidence rate of postoperative complications or the perioperative mortality rate, we believe that it can be performed feasibly and safely.

Radical surgery that reduces the tumor load *via* complete removal of the tumor and lymph nodes is currently considered to be a precondition for a promising prognosis for patients with PHC and to lay a foundation for postoperative adjuvant chemoradiotherapy[6]. ELD, which enables the removal of potentially invaded lymph nodes, can be used to achieve radical resection and, theoretically, improve the prognosis of patients with PHC[29]. However, recent research indicates that although this procedure increases the number of lymph nodes retrieved for postoperative pathological examination, it does not increase the positive lymph-node count or improve the long-term PHC prognosis[8,28,30-33]. Notably, little attention has been paid in this research to differences in the lymph-node metastasis rate and sites according to the PHC stage or the clinical value of the selective performance of ELD in patients with PHC at certain stages. Our previous study confirmed that ELD improved the OS and DFS rates in patients with borderline resectable PHC[34], emphasizing the potential clinical value of the selective performance of ELD in patients at greater risk of lymph-node metastasis and local invasion (in whom radical resection may not be achieved with SLD). Muralidhar *et al*[35] reported that lymph-node metastasis was more likely to occur in patients with larger pancreatic tumors at advanced T stages, illustrating the potential correlation between the T stage and lymph-node metastasis. Pu *et al*[10] found that the lymph-node metastasis rate reached a plateau of 70%-80% in patients with pancreatic tumors of > 40 mm diameter, and that about 50% of patients with stage-T3 pancreatic carcinoma and lymph-node metastasis were categorized as stage N2. After researching the mode of lymph node metastasis in pancreatic carcinoma patients, Kanda *et al*[11] reported that distant lymph-node metastasis was seen only in stage-T3- and -T4 pancreatic carcinoma, with station-16 metastasis observed in 10.7% and 33.3% of cases, respectively. These findings shows that patients with advanced T-stage pancreatic carcinoma tend to have higher lymph-node metastasis rates and distant lymph-node metastasis, and thus that SLD is insufficient to achieve radical resection in these patients. Hence, we hypothesized that the selective performance of ELD in patients with PHC of advanced T stages would improve these patients' long-term prognosis. Our results showed that ELD increased the retrieved and positive lymph node counts and improved the long-term prognosis of patients with stage-T3 PHC, supporting our hypothesis.

PHC usually invades the peri-pancreatic plexus and vessels, and the perivascular region and lymph nodes are the most common sites of local recurrence after surgical treatment[26]. Kovač *et al*[36] reported that ELD with the achievement of R0 resection reduced the local recurrence rate in patients with PHC. The peripancreatic connective tissue and nerve plexus are excised during ELD, constituting the radical removal of potential invasion and recurrence sites, which may explain the ability of this procedure to improve the prognosis of patients with stage-T3 PHC. In our study, the positive lymph node count and long-term prognosis after ELD were not improved in patients with stage-T1 and -T2 disease. Radical resection can be achieved with SLD in these patients due to the relatively low lymph-node metastasis rate and absence of distant lymph-node metastasis[10,11], which may explain the limited benefit of ELD in these cases. The clinical value of ELD in patients with stage-T1 and -T2 PHC needs to be analyzed further.

As ELD inevitably causes complications such as diarrhea, delayed gastric emptying, and malnutrition [27,37], surgeons must balance the pros and cons of performing it[6]. Due to technical limitations, the N stage of pancreatic carcinoma cannot be determined precisely[38], the T stage is the only accessible preoperative index. The selective performance of ELD based on the T stage can help surgeons not only to make reasonable surgical plans and radically excise potentially invaded lymph nodes, but also to avoid severe postoperative complications secondary to extensive surgical excision. Thus, our results have certain clinical value.

With rapid progress in medical technology, the treatment of PHC is becoming more comprehensive and surgically focused. Perioperative chemotherapy, especially preoperative neoadjuvant chemotherapy, has gained popularity as a part of PHC treatment due to its ability to improve the R0 resection rate[39,40]. Currently, neoadjuvant chemotherapy is considered to be the first-line treatment for patients with borderline resectable pancreatic carcinoma, according to the National Comprehensive Cancer Network's guidelines. Postoperative chemotherapy, most commonly mFORFILRINOX, has been widely adopted in PHC treatment[41]. Molecular targeting agents are currently suitable only for patients confirmed to have related gene mutations. Despite the progress in perioperative adjuvant chemotherapy, surgery remains the focus of PHC treatment, and radical surgery with comprehensive perioperative chemotherapy is understood to improve long-term patient survival. Thus, determination of the relationships between ELD and perioperative chemotherapeutic parameters is of clinical value. Only a few patients who received neoadjuvant chemotherapy were included in this retrospective study, making the statistical assessment of such relationships difficult. Whether patients benefit from ELD combined with perioperative chemotherapy remains unknown. With the popularity of perioperative therapy, our department began to perform ELD with postoperative neoadjuvant chemotherapy and additional follow-up chemotherapy for patients with PHC. The accumulation of data on such cases and cooperation among departments and medical centers are needed to further explore the clinical value of ELD in comprehensive PHC treatment.

Our study has several limitations. First, it had a single-center retrospective design. Second, the ELD group was younger than the SLD group, which may have confounded the results due to selection bias. However, as age has not been identified as an independent prognostic factor for the postoperative prognosis of patients with PHC, any such bias effect was likely slight. A multicenter prospective study

is needed to verify our findings. Third, as we found that ELD increases the retrieved and positive lymph-node counts, it may enable more accurate postoperative N staging. The selective provision of postoperative chemoradiotherapy based on the postoperative N and tumor stages may be of benefit to patients with PHC; additional research on this possibility is needed.

CONCLUSION

ELD can be performed in patients with PHC feasibly and safely. Its performance may improve the long-term prognosis of patients with stage-T3 PHC through the expansion of the lymphadenectomy extent and elimination of potentially invaded lymph nodes.

ARTICLE HIGHLIGHTS

Research background

Pancreatic head carcinoma (PHC) is a highly malignant tumor, and radical surgery is the only potential curative treatment. However, the long-term postoperative prognosis remains unsatisfactory. As lymph-node metastasis is commonly seen in patients with PHC and has been identified as an independent prognostic factor for postoperative prognosis, extended lymphadenectomy (ELD) has been proposed for the resection of potentially invaded lymph nodes and improvement of the surgical outcome. However, no such improvement in prognosis has been observed. The PHC lymph-node metastasis rate correlates with the T stage, and selective ELD performance for advanced T-stage cases may improve the long-term prognosis.

Research motivation

Given the increases in the lymph-node metastasis rate and sites in patients with PHC, particularly that of advanced T stage, selective ELD performance for patients with advanced T-stage PHC may enable the elimination of more potentially invaded lymph nodes and improvement of the postoperative prognosis.

Research objectives

The objective of this study was to assess the therapeutic effect of ELD in patients with PHC of different T stages.

Research methods

We retrospectively analyzed data from 216 patients diagnosed with pancreatic ductal adenocarcinoma who underwent surgical treatment at Beijing Chaoyang Hospital between January 2011 and December 2021. The patients were allocated to T1, T2, and T3 groups according to the 8th edition of the American Joint Committee on Cancer's staging manual and divided into ELD and standard lymphadenectomy (SLD) groups according to the intraoperative extent of lymphadenectomy. Perioperative data and prognoses were compared between the ELD and SLD groups at the T1, T2, and T3 stages, and univariate and multivariate analyses were performed to identify risk factors.

Research results

The 1-, 2-, and 3-year disease-free survival (DFS) rates in the ELD and SLD groups were 59.9%, 32.1%, and 20.7% and 53.8%, 34.6%, and 16.7%, respectively (P = 0.227); corresponding overall survival (OS) rates were 69.0%, 39.5%, and 26.8% and 55.1%, 32.6%, and 22.1%, respectively (P = 0.073). The 1-, 2-, and 3-year DFS rates for patients with stage-T3 PHC in the ELD and SLD groups were 50.3%, 25.1%, and 15.1% and 22.1%, 1.7%, and 0%, respectively (P = 0.025); corresponding OS rates were 65.3%, 38.1%, and 21.8% and 36.1%, 7.5%, and 0%, respectively (P = 0.005). Multivariate analysis indicated that portal vein invasion and lymphadenectomy extent were risk factors affecting the prognosis of patients with stage-T3 PHC.

Research conclusions

Our research confirmed that ELD can be performed safely for PHC. Although ELD may not improve the overall prognosis of patients with PHC, its selective performance in patients with stage-T3 PHC may improve the long-term postoperative prognosis.

Research perspectives

Several limitations of this study must be recognized. First, it was a single-center retrospective study; our findings need to be verified in multicenter prospective studies. Second, the stage-T3 SLD and ELD groups differed in age, which may have confounded our results; further research with more balanced samples is needed. As ELD increases the retrieved land positive lymph node counts, it may enable more

accurate N staging, which may aid decision making about postoperative adjuvant therapy; further research on this possibility is needed.

FOOTNOTES

Author contributions: Lyu SC, Wang HX, and Liu ZP are equal coauthors of this article; Lyu SC, Wang HX, Liu ZP, and Wang J contributed to the study design; Lang R and He Q provided administrative support; Lyu SC and Lang R provided study materials and/or patients; Lyu SC, Wang HX, and Huang JC contributed to data collection and assembly; Lyu SC, Wang HX, and Liu ZP contributed to data analysis and interpretation; and all authors contributed to manuscript writing and final approval.

Institutional review board statement: This study complied with the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Chaoyang Hospital (no. 2020-D.-302). The study design was approved by the appropriate ethics review board. All allogeneic vessels applied during surgery were obtained during organ procurement undertaken by the OPO and were approved for clinical application by our hospital's Ethics Committee and Committee for Clinical Application of Medical Technology.

Informed consent statement: All study participants or their legal guardians provided informed written consent to the collection of personal and medical data prior to study enrollment.

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

Data sharing statement: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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

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ORIGINAL ARTICLE

Retrospective Cohort Study

Comparison of clinicopathological characteristics between resected ampullary carcinoma and carcinoma of the second portion of the duodenum

Kohei Nishio, Kenjiro Kimura, Akihiro Murata, Go Ohira, Hiroji Shinkawa, Shintaro Kodai, Ryosuke Amano, Shogo Tanaka, Sadatoshi Shimizu, Shigekazu Takemura, Akishige Kanazawa, Shoji Kubo, Takeaki Ishizawa

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Abstract

BACKGROUND

Few studies compared the oncological and biological characteristics between ampullary carcinoma (AC) and cancer of the second portion of the duodenum (DC-II), although both tumors arise from anatomically close locations.

AIM

To elucidate differences in clinicopathological characteristics, especially the patterns of lymph node metastasis (LNM), between AC and DC-II.

METHODS

This was a retrospective cohort study of 80 patients with AC and 27 patients with DC-II who underwent pancreaticoduodenectomy between January 1998 and December 2018 in two institutions. Clinicopathological factors, LNM patterns, and prognosis were compared between the two groups.

RESULTS

The patients with AC and DC-II did not exhibit significant differences in 5-year overall survival (66.0% and 67.1%, respectively) and 5-year relapse-free survival (63.5% and 62.2%, respectively). Compared to the patients with DC-II, the rate of preoperative biliary drainage was higher (P = 0.042) and the rates of digestive symptoms (P = 0.0158), ulcerative-type cancer (P < 0.0001), large tumor diameter (P < 0.0001), and advanced tumor stage (P = 0.0019) were lower in the patients with AC. The LNM rates were 27.5% and 40.7% in patients with AC and DC-II,

respectively, without significant difference (P = 0.23). The rates of LNM to hepatic nodes (N-He) and pyloric nodes (N-Py) were significantly higher in patients with DC-II than in those with AC (metastasis to N-HE: 18.5% and 5% in patients with DC-II and AC, respectively; P = 0.0432; metastasis to N-Py: 11.1% and 0% in patients with DC-II and AC, respectively; P = 0.0186)

CONCLUSION
Although there were no significant differences in the prognosis and recurrence rates between the two groups, metastases to N-He and N-Py were more frequent in patients with DC-II than in those with AC.

Key Words: Ampulla of Vater; Duodenum; Lymphatic metastasis pattern; Lymphatic metastasis station; Lymph node excision; Neoplasm; Pancreaticoduodenectomy

Core Tip: Few studies compared the oncological and biological characteristics between ampullary carcinoma (AC) and cancer of the second portion of the duodenum (DC-II), although both tumors arise from anatomically close locations. Here, we found that the rate of preoperative biliary drainage was significantly higher and the rates of digestive symptoms, ulcerative-type cancer, large tumor diameter, and advanced tumor stage were significantly lower in AC than in DC-II. There were no significant differences in prognosis, recurrence, and lymph node metastasis rates between the two groups, although hepatic and pyloric lymph node metastases were more frequent in DC-II than in AC.

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INTRODUCTION

Ampullary carcinoma (AC) accounts for 0.2% of all gastrointestinal cancers and 7% of all periampullary cancers[1]. In contrast to other periampullary carcinomas, AC is associated with higher resection rates and better prognosis because of its earlier presentation due to the anatomical characteristics[2]. The reported rates of resection and 5-year survival after resection of AC are approximately 50%[3] and 30%-52%[4,5], respectively, whereas primary duodenal cancer (DC) accounts for approximately 0.3% of all gastrointestinal cancers[6] and 30%-45% of all small intestinal cancers[7]. The reported rates of resection and 5-year survival after resection of DC are 39%[8] and 37%-67%[9-12], respectively. The only curative treatment for both AC and DC, especially DC located in the second portion of the duodenum (DC-II), is surgical resection with regional lymph node dissection using pancreaticoduodenectomy. The National Comprehensive Cancer Network (NCCN) guidelines recommend pancreaticoduodenectomy with *en bloc* removal of regional lymph nodes for resectable DC-II and state that pyloric preservation is acceptable in the absence of a hereditary condition[13]. In contrast, there are no NCCN guidelines for AC. The lymph node metastasis (LNM) patterns and the optimal range of lymph node dissection in DC-II and AC remain controversial. The present study aimed to compare the oncological and biological characteristics between DC-II and AC.

MATERIALS AND METHODS

Eighty-four patients with AC and thirty-six patients with DC-II who underwent surgical resection in Osaka City University Hospital or Osaka City General Hospital between January 1, 1998 and December 31, 2018. After the exclusion of patients who underwent duodenal partial resection (n = 9) and papillectomy (n = 4), the remaining 80 patients with AC and 27 patients with DC-II who underwent pancreaticoduodenectomy were included in the present retrospective cohort study (Figure 1). All patients were followed for survival, and the median follow-up period was 36.5 (range, 2.3-227.3) months. Recurrence was defined when the tumor was detected again by imaging modalities, such as enhanced CT. Surgical approaches included classical pancreaticoduodenectomy (Whipple procedure) in

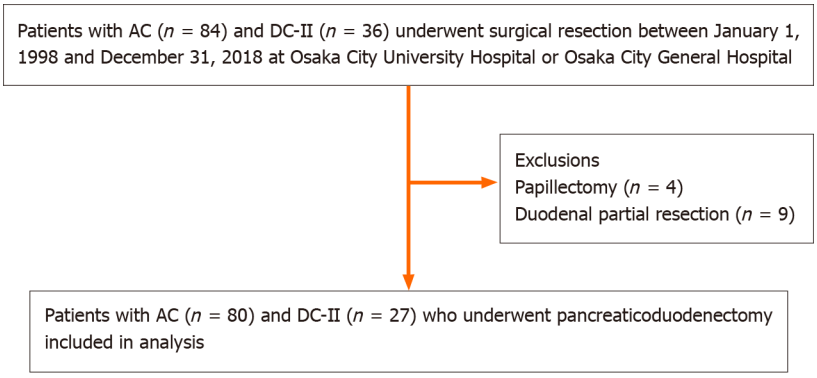

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Figure 1 Patient flowchart. AC: Ampullary carcinoma; DC-II: Cancer of the second portion of the duodenum.

50 patients (12 patients with DC-II and 38 patients with AC), subtotal stomach-preserving pancreaticoduodenectomy in 49 patients (14 patients with DC-II and 35 patients with AC), and pylorus-preserving pancreaticoduodenectomy in 8 patients (1 patient with DC-II and 7 patients with AC). As adjuvant chemotherapy, 33 patients, including 8 patients with DC-II and 25 patients with AC, received S-1 (4 patients with DC-II and 14 patients with AC), tegafur-uracil (3 patients with DC-II and 8 patients with AC), and gemcitabine (1 patient with DC-II and 3 patients with AC). There were no definitive criteria for the administration of adjuvant chemotherapy.

The demographic and clinical variables included age, sex, preoperative body mass index, preoperative modified Glasgow prognostic score, tumor size, gross appearance, preoperative biliary drainage, preoperative symptoms, preoperative serum carbohydrate antigen level, preoperative serum carcinoembryonic antigen level, operative procedure, duration of operation, volume of intraoperative blood loss, histological grade, Union for International Cancer Control (UICC) classification, LNM, lymphatic invasion, venous invasion, postoperative complications, and adjuvant chemotherapy.

The TNM classification and the pathological stage of all tumor specimens were determined using the 7th edition of the UICC TNM classification[14]. Tumor differentiation was classified into well differentiated, moderately differentiated, poorly differentiated, and undifferentiated adenocarcinoma, according to the World Health Organization classification[15]. Regional lymph nodes were classified into superior pancreaticoduodenal lymph nodes (N-SP), inferior pancreaticoduodenal lymph nodes (N-IP), pyloric lymph nodes (N-Py), hepatic lymph nodes (N-He), and superior mesenteric lymph nodes (N-SM) according to AJCC Cancer Staging 7th edition[16]. The initial recurrent sites were classified into liver, lungs, distant lymph nodes, peritoneum, local, and others.

Statistical analysis

The clinicopathological factors were compared between the patients with DC-II and AC. Categorical variables were compared using the χ^2 or Fisher's exact test. Continuous variables were compared using Mann–Whitney U tests. Survival was calculated using the Kaplan–Meier method, and comparisons between the groups were performed using the log-rank test. P values of < 0.05 were considered to indicate statistical significance. All statistical analyses were performed using JMP® version 12 (SAS Institute, Cary, NC, United States).

RESULTS

Comparison of overall survival and relapse-free survival between the patients with DC-II and AC

The 5-year overall survival (OS) rate was 66.0% in the patients with AC and 67.1% in those with DC-II ($P = 0.80$) (Figure 2A). The 5-year RFS rate was 63.5% in the patients with AC and 62.2% in those with DC-II ($P = 0.88$) (Figure 2B).

Comparison of the clinicopathological factors between the patients with DC-II and AC

Table 1 shows the results of the comparative analysis of the clinicopathological factors between the patients with DC-II and AC. Briefly, the rate of preoperative biliary drainage was significantly higher in the patients with AC than in those with DC-II ($P = 0.042$). Conversely, the rates of digestive symptoms *i.e.*, vomiting, nausea or abdominal pain ($P = 0.0158$), ulcerative-type tumor ($P < 0.0001$), large tumor diameter ($P < 0.0001$), and advanced tumor invasion ($P = 0.0019$) were significantly higher in the patients with DC-II than in those with AC. The LNM rate was 27.5% in the patients with AC and 40.7% in those with DC-II, without significant difference ($P = 0.23$).

Table 1 Comparative analysis of clinicopathological factors between patients with resected cancer of the second portion of the duodenum and ampullary carcinoma

Variable	Comparison	DC-II (*n* = 27), %		AC (*n* = 80)	*P* value
Sex	Male	15 (55.6)	49 (61.3)	0.65	
	Female	12 (44.4)	31 (38.7)		
Age	Median (range)	69 (41-85)	64 (37-84)	0.35	
Preoperative BMI (kg/m^2)	Median (range)	22.1 (16.9-27.3)	21.7 (15.8-31.3)	0.59	
Preoperative mGPS	0	17	47	-	
	1	5	18	-	
	2	5	14	-	
	0	17 (63.0)	47 (58.8)	0.82	
	1-2	10 (37.0)	32 (40.0)		
Preoperative biliary drainage	No	21 (77.8)	44 (55.0)	**0.042**	
	Yes	6 (22.2)	36 (45.0)		
Preoperative symptoms	Absent	8 (29.6)	31 (38.7)	0.49	
	Present	19 (70.4)	49 (61.3)		
Digestive symptoms	Absent	13 (48.1)	60 (75.0)	**0.0158**	
	Present	14 (51.9)	20 (25.0)		
Anemia or tarry stool	Absent	23 (85.2)	77 (96.3)	0.06	
	Present	4 (14.8)	3 (3.7)		
Preoperative CA19-9 (U/mL)	Normal	19 (70.4)	56 (70.0)	1	
	Elevated	8 (29.6)	24 (30.0)		
Preoperative CEA (ng/mL)	Normal	25 (92.6)	66 (82.5)	0.35	
	Elevated	2 (7.4)	13 (16.3)		
Surgery	PD	12	38	-	
	SSPPD	14	35	-	
	PpPD	1	7	-	
Operation time (min)	Median (range)	451 (287-837)	446.5 (266-736)	**0.44**	
Intraoperative blood loss volume (mL)	Median (range)	685 (80-4110)	652 (150-9015)	**0.48**	
Gross appearance	Protruding type	8 (29.6)	59 (73.8)	**< 0.0001**	
	Ulcerative-type	19 (70.4)	21 (26.2)		
Histological grade	Pap	1	3	-	
	Well	10	42	-	
	Mod	13	31	-	
	Por	1	4	-	
	Muc	2	0	-	
	Pap/well	11 (40.7)	45 (56.3)	0.19	
	Mod/por/muc	16 (59.3)	35 (43.7)		
Tumor diameter (mm)	Median (range)	35 (14-65)	18 (5-84)	**< 0.0001**	
T category[1]	Tis	5	23	-	
	T1 (1a, 1b)	5 (4, 1)	9	-	
	T2	1	28	-	

	T3	5	16	-
	T4	11	4	-
	T0–T2	11 (40.7)	60 (75.0)	**0.0019**
	T3–T4	16 (59.3)	20 (25.0)	
N factor	N0	16	58	-
	N1	5	22	-
	N2	6	x	-
Lymph node metastasis	Absent	16 (59.3)	58 (72.5)	0.23
	Present	11 (40.7)	22 (27.5)	
Number of lymph nodes with metastasis	Median (range)	0 (0–6)	0 (0–12)	0.13
M factor	M0	24	78	0.1
	M1	3	2	-
Stage	0	5	22	-
	I (A, B)	6	29 (11, 18)	-
	II A	2	4	-
	II B	3	19	-
	III (A, B)	8 (5, 3)	4	-
	IV	3	2	-
Lymphatic invasion	0	15	50	-
	1	4	12	-
	2	7	15	-
	3	1	2	-
	X	0	1	-
	0	15 (55.6)	50 (62.5)	0.5
	1-3	12 (44.4)	29 (36.3)	
Venous invasion	0	20	69	-
	1	5	8	-
	2	2	2	-
	3	0	0	-
	X	0	1	-
	0	20 (74.1)	69 (86.3)	0.13
	1-3	7 (25.9)	10 (12.5)	
Postoperative complication (≥ CD III)	No	18 (66.7)	42 (52.5)	0.26
	Yes	9 (33.3)	38 (47.5)	
Adjuvant chemotherapy	No	19 (70.4)	55 (68.8)	1
	Yes	8 (29.6)	25 (31.2)	

[1]7th edition of the Union for International Cancer Control TNM classification.

AC: Ampullary carcinoma; BMI: Body mass index; CA19-9: Carbohydrate antigen 19-9; CD: Clavien–Dindo classification; CEA: Carcinoembryonic antigen; DC-II: Carcinoma of the second portion of the duodenum; mGPS: Modified Glasgow prognostic score; mod: moderately differentiated adenocarcinoma; muc: mucinous adenocarcinoma; pap: papillary adenocarcinoma; PD: Pancreaticoduodenectomy; poor: Poorly differentiated adenocarcinoma; PpPD: Pylorus-preserving pancreaticoduodenectomy; SSPPD: Subtotal stomach-preserving pancreatoduodenectomy; well: Well-differentiated adenocarcinoma.

Comparison of the affected sites and the frequency of LNM between the patients with DC-II and AC

Table 2 shows the results of the comparative analysis of the affected sites and the frequency of LNM to specific sites between the patients with DC-II and AC. In summary, the rates of LNM to the N-He and

Table 2 Comparison of the sites and the frequency of lymph node metastasis between the patients with cancer of the second portion of the duodenum and ampullary carcinoma

Variable	Comparison	DC-II (*n* = 27), %	AC (*n* = 80), %	*P* value
N-Py[a]	present	3(11.1)	0 (0)	**0.0186**
	absent	23 (85.2)	73 (100)	
N-He	present	5 (18.5)	4 (5)	**0.0432**
	absent	22 (81.5)	76 (95)	
N-SP	present	7 (25.9)	14 (17.5)	0.40
	absent	20 (74.1)	66 (82.5)	
N-IP	present	3 (11.1)	10(12.5)	1.00
	absent	24 (88.9)	70 (87.5)	
N-SM	present	2 (7.4)	5 (6.2)	1.00
	absent	25 (92.6)	75 (93.8)	

[a]Pylorus-preserving pancreaticoduodenectomy excluded.

AC: Ampullary carcinoma; DC-II: Carcinoma of the second portion of the duodenum; N-He: Hepatic lymph nodes; N-IP: Inferior pancreaticoduodenal lymph nodes; N-Py: Pyloric lymph nodes; N-SM: Superior mesenteric lymph nodes; N-SP: Superior pancreaticoduodenal lymph nodes.

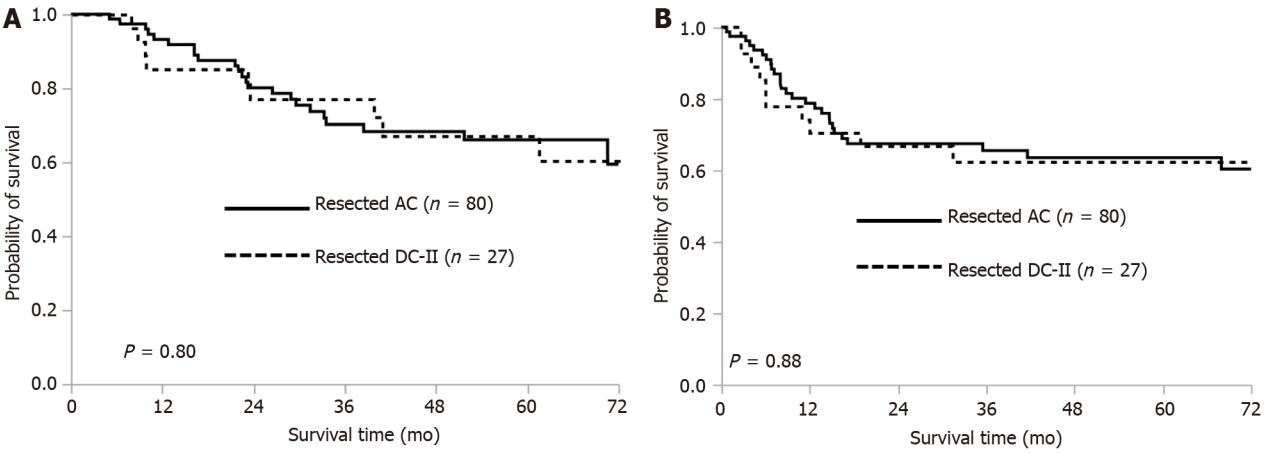

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Figure 2 Survival curves of patients with cancer of the second portion of the duodenum (*n* = 27) and ampullary carcinoma (*n* = 80). A: Overall survival of patients with cancer of the second portion of the duodenum (DC-II) and ampullary cancer (AC); B: Relapse-free survival of patients with DC-II and AC.

the N-Py were significantly higher in the patients with DC-II than in those with AC (metastasis to N-He: 18.5% and 5% in patients with DC-II and AC, respectively; $P = 0.0432$; metastasis to N-Py: 11.1% and 0% in patients with DC-II and AC, respectively; $P = 0.0186$). There were no significant differences in the rates of metastases to the N-SP, N-IP, and N-SM between the patients with DC-II and AC.

Figure 3 shows the LNM distribution in patients with DC-II and AC. Briefly, LNM was found in 11 of the 27 patients (40.7%) with DC-II, including metastases to N-SP, N-He, N-Py, N-IP, and N-SM in 7 (63.6%), 5 (45.5%), 3 (27.3%), 3 (27.3%), and 2 (18.2%) patients, respectively. Meanwhile, LNM was found in 22 of the 80 patients (27.5%) with AC, including metastases to N-SP, N-IP, N-SM, and N-He in 14 (63.6%), 10 (45.5%), 5 (22.7%), and 4 (18.2%) patients, respectively. Metastasis to N-Py was not found in any of the patients with AC (0%).

Analysis of the initial recurrent sites in patients with DC-II and AC

Table 3 shows the comparison of the initial recurrent sites of DC-II and AC. Initial recurrence was observed in 28 patients with AC and 10 patients with DC-II. Specifically, 10 (35.7%), 6 (21.4%), 6 (21.4%), and 5 patients (17.9%) with AC experienced recurrence in distant lymph nodes, lungs, liver, and local sites, respectively. Meanwhile, 5 (50%), 3 (30%), and 2 (20%) patients with DC-II experienced recurrence in distant lymph nodes, lungs, and liver, respectively, with no local recurrence observed in any of the

Table 3 Analysis of initial recurrent sites in patients with cancer of the second portion of the duodenum and ampullary carcinoma

Initial recurrent site	DC-II (*n* = 10), %	AC (*n* = 28), %	*P* value
Liver	2 (20.0)	6 (21.4)	1.00
Lungs	3 (30.0)	6 (21.4)	0.67
Distant lymph nodes	5 (50.0)	10 (35.7)	0.47
Peritoneal dissemination	1 (10.0)	3 (10.7)	1.00
Local	0 (0)	5 (17.9)	0.29
Others	1 (10.0)	2 (7.1)	1.00

AC: Ampullary carcinoma; DC-II: Carcinoma of the second portion of the duodenum.

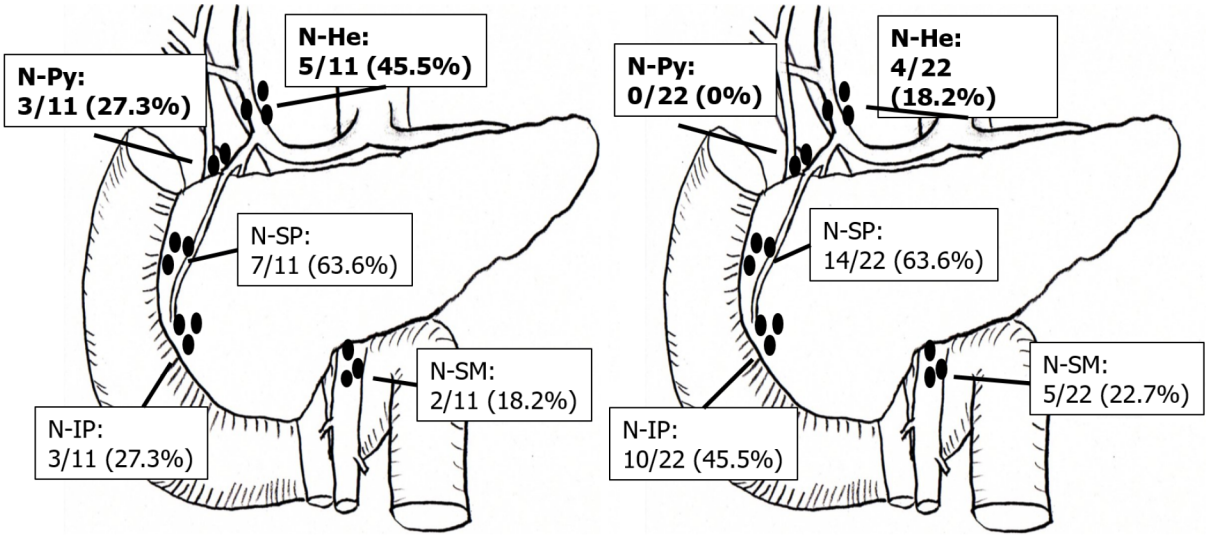

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Figure 3 The distribution of lymph node metastasis in patients with cancer of the second portion of the duodenum (*n* = 11) and ampullary carcinoma (*n* = 22). A: Metastasis to specific lymph nodes in 11 patients with DC-II; B: Metastasis to specific lymph nodes in 22 patients with AC. N-He: Hepatic lymph nodes; N-IP: Inferior pancreaticoduodenal nodes: N-Py: Pyloric lymph nodes; N-SM: Mesenteric nodes; N-SP: Superior pancreaticoduodenal nodes

patients with DC-II. There was no significant difference in the recurrence pattern between the patients with AC and DC-II.

DISCUSSION

The present study results indicated that metastases to N-He and N-Py were more frequent in patients with DC-II than in those with AC. The NCCN guidelines indicate that pancreatoduodenectomy with *en bloc* removal of regional lymph nodes, including retropancreatic, hepatic artery, inferior pancreaticoduodenal, and superior mesenteric lymph nodes, should be performed for resectable DC-II [13]. Furthermore, the guidelines state that pyloric preservation is acceptable in the absence of a hereditary condition[13]. The 7th edition of the UICC TNM classification of malignant tumors include N-Py as regional lymph nodes[14]. Sakamoto *et al*[17] indicated that the rate of metastasis to N-Py and N-He was significantly higher in patients with duodenal bulbs tumors and DC-II than in those with tumors in the third or fourth portion of the duodenum. Kato *et al*[18] reported that metastasis was detected in infrapyloric lymph nodes in 11.4% of patients with DC in the 1st-4th portion, and the location of the LNM did not exhibit a significant correlation with the primary site of DC. In the present study, metastasis to N-Py was found in 11.1% of patients with DC-II. In contrast, there are no NCCN guidelines for AC, and the 7th edition of the UICC TNM classification of malignant tumors include N-Py in the regional lymph nodes in patients with AC[14]. The General Rules for Clinical and Pathological Studies on Cancer of the Biliary Tract (6th edition) by the Japanese Society of Hepato-Biliary-Pancreatic Surgery include N-Py in the list of regional lymph nodes in patients with AC, although N-Py dissection is not mandatory[19]. Kayahara *et al*[20] reported that metastasis to N-Py was absent in patients with resected AC. Similarly,

no patient with resected AC had metastasis to N-Py in the present study cohort. Mu *et al*[21] reported that the rate of metastasis to N-Py was 2.5% in patients with AC. Lee *et al*[22] also reported that LNM of AC first spread to the posterior pancreaticoduodenal lymph nodes followed by spread to the anterior pancreaticoduodenal nodes, and metastasis to N-Py and N-He was limited in patients with AC. Several studies on AC reported that lymphatic spread mainly extended from the posterior pancreaticoduodenal region to the superior mesenteric lymph nodes[20,23,24]. Furthermore, another study suggested that the papilla of Vater was derived from the ventral pancreas with not many communicating lymphatic vessels between the ventral and dorsal pancreas[25]; therefore, it was speculated that most of the LNM of AC moved toward N-SM *via* the inferior pancreaticoduodenal artery. However, we also speculated that lymphatic spread not only extended from the posterior pancreaticoduodenal region to the superior mesenteric node but also from the anterior pancreaticoduodenal region to N-Py and N-He *via* the gastric duodenal artery in DC-II. These anatomical considerations might be associated with the higher rates of metastases to N-He and N-Py in patients with DC-II than in those with AC.

In the current study, the rates of cases with large tumor diameter and advanced tumor invasion were higher in patients with DC-II than in those with AC. These differences might be due to the earlier appearance of symptoms, such as jaundice, in patients with AC than in those with DC-II, leading to the earlier diagnosis of AC. We did not observe significant differences in OS and RFS between the patients with AC and DC-II despite the more advanced tumor invasion observed in the patients with DC-II. These results might suggest that even in DC with more advanced tumor invasion than AC, the prognosis equivalent to AC could be obtained if pancreaticoduodenectomy with regional lymph node dissection as well as AC was performed. Riall *et al*[26] reported that the 5-year overall survival rate after pancreaticoduodenectomy was 37% in patients with AC and 51% in those with DC and that the prognosis of DC was significantly better than that of AC. Other studies reported that there was no significant difference in OS between the patients with resected AC and DC[27,28]. However, these studies were small in scale and retrospective in design; therefore, large-scale cohort studies are warranted for the accurate comparison of prognosis between the patients with DC and AC.

The present study results also revealed that distant lymph nodes were the most common sites of initial recurrence in both DC-II and AC. Several studies reported that the most common site of recurrence was liver in patients with AC undergoing curative resection[29,30]. Conversely, Cecchini *et al*[31] reported that 45% of the patients with resected DC had recurrence and that the first sites of recurrence were distant, locoregional, and both in 21%, 19%, and 5% of the patients. Onkendi *et al*[32] reported that approximately 60% of all recurrences were locoregional of paients with resected DC. However, these studies included segmental resection in addition to pancreaticoduodenectomy, which were considered as the cause of the high locoregional recurrence rate. In a study including patients undergoing pancreaticoduodenectomy for AC or DC, Bowitz *et al*[33] reported that the recurrence patterns of AC and DC were similar, with first recurrence to isolated distant sites in most patients with AC and DC (73.9%; AC, 69.2%; DC, 80.6%); the authors also reported that liver was the most affected distant site of recurrence (33.8%; AC, 28.8%; DC, 36.1%). In the present study, pancreaticoduodenectomy with regional lymph node dissection was performed in both the patients with AC and DC-II and the rate of recurrence at local sites such as the regional lymph nodes was lower than the rate of recurrence in distant lymph nodes. These results suggested that pancreaticoduodenectomy with regional lymph node dissection was effective not only in AC but also in DC-II.

The major limitations of the present study were the small sample size and the retrospective study design. Additionally, standard surgical procedures were not performed in some patients and the adjuvant chemotherapy indications and regimens were not standardized. Multicenter prospective studies with larger cohorts are necessary to clarify the prognosis and the LNM patterns in patients with DC-II and AC for the selection of appropriate surgical procedures with the best outcomes.

CONCLUSION

There were no significant differences in prognosis and recurrence rate between the patients with DC-II and AC despite the more advanced tumor invasion in patients with DC-II than in those with AC. Metastases to N-He and N-Py were more frequent in patients with DC-II than in those with AC.

ARTICLE HIGHLIGHTS

Research background

Few studies have compared the oncological and biological characteristics between ampullary carcinoma (AC) and cancer of the second portion of the duodenum (DC-II), although both tumors arise from anatomically close locations.

Research motivation

The lymph node metastasis (LNM) patterns and the optimal range of lymph node dissection in DC-II and AC remain controversial.

Research objectives

The present study aimed to elucidate differences in clinicopathological characteristics, especially the patterns of LNM, between AC and DC-II.

Research methods

This was a retrospective cohort study of 80 patients with AC and 27 patients with DC-II who underwent pancreaticoduodenectomy between January 1998 and December 2018 in two institutions. Clinicopathological factors, LNM patterns, and prognosis were compared between the two groups.

Research results

The rate of preoperative biliary drainage was significantly higher and the rates of digestive symptoms, ulcerative-type cancer, large tumor diameter, and advanced tumor stage were significantly lower in patients with AC than DC-II. There were no significant differences in prognosis, recurrence, and lymph node metastasis rates between the two groups, although hepatic and pyloric lymph node metastases were more frequent in DC-II than in AC.

Research conclusions

Although there were no significant differences in the prognosis and recurrence rates between the two groups, metastases to N-He and N-Py were more frequent in patients with DC-II than in those with AC.

Research perspectives

Lymph node dissection to N-He and N-Py may be omitted for AC, that is unlikely for DC-II.

FOOTNOTES

Author contributions: Nishio K designed the study and wrote the draft of the article. Kimura K and Kubo S contributed to interpretation of the data and the critical revision of the article content. All the other authors (Murata A, Ohira G, Shinkawa H, Kodai S, Amano R, Takemura S, Shimizu S, Kanazawa A and Ishizawa A) contributed to the data collection and interpretation and critically reviewed the article; All the authors have read and agreed to the article.

Institutional review board statement: This study was approved by the Ethics Committees of Osaka City University (approval No. 2020-198) and Osaka City General Hospital (approval No. 1910076) and was performed in compliance with the Declaration of Helsinki.

Informed consent statement: All patients provided informed consent for using their data in this study according to the institutional regulations of the study sites.

Conflict-of-interest statement: All authors declare that they have no competing interests related to the manuscript.

Data sharing statement: No additional data are available.

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

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ORIGINAL ARTICLE

Retrospective Study

Metastatic lymph nodes and prognosis assessed by the number of retrieved lymph nodes in gastric cancer

Hao Wang, Xin Yin, Sheng-Han Lou, Tian-Yi Fang, Bang-Ling Han, Jia-Liang Gao, Yu-Fei Wang, Dao-Xu Zhang, Xi-Bo Wang, Zhan-Fei Lu, Jun-Peng Wu, Jia-Qi Zhang, Yi-Min Wang, Yao Zhang, Ying-Wei Xue

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Abstract

BACKGROUND

The prognostic value of quantitative assessments of the number of retrieved lymph nodes (RLNs) in gastric cancer (GC) patients needs further study.

AIM

To discuss how to obtain a more accurate count of metastatic lymph nodes (MLNs) based on RLNs in different pT stages and then to evaluate patient prognosis.

METHODS

This study retrospectively analyzed patients who underwent GC radical surgery and D2/D2+ LN dissection at the Cancer Hospital of Harbin Medical University from January 2011 to May 2017. Locally weighted smoothing was used to analyze the relationship between RLNs and the number of MLNs. Restricted cubic splines were used to analyze the relationship between RLNs and hazard ratios (HRs), and X-tile was used to determine the optimal cutoff value for RLNs. Patient survival was analyzed with the Kaplan-Meier method and log-rank test. Finally, HRs and 95% confidence intervals were calculated using Cox proportional hazards models to analyze independent risk factors associated with patient outcomes.

RESULTS

A total of 4968 patients were included in the training cohort, and 11154 patients were included in the validation cohort. The smooth curve showed that the number of MLNs increased with an increasing number of RLNs, and a nonlinear

relationship between RLNs and HRs was observed. X-tile analysis showed that the optimal number of RLNs for pT1-pT4 stage GC patients was 26, 31, 39, and 45, respectively. A greater number of RLNs can reduce the risk of death in patients with pT1, pT2, and pT4 stage cancers but may not reduce the risk of death in patients with pT3 stage cancer. Multivariate analysis showed that RLNs were an independent risk factor associated with the prognosis of patients with pT1-pT4 stage cancer ($P = 0.044$, $P = 0.037$, $P = 0.003$, $P < 0.001$).

CONCLUSION

A greater number of RLNs may not benefit the survival of patients with pT3 stage disease but can benefit the survival of patients with pT1, pT2, and pT4 stage disease. For the pT1, pT2, and pT4 stages, it is recommended to retrieve 26, 31 and 45 LNs, respectively.

Key Words: Gastric cancer; Metastatic lymph nodes; Number of retrieved lymph nodes; Prognosis

Core Tip: The prognostic value of quantitative assessments of the number of retrieved lymph nodes (RLNs) in gastric cancer (GC) patients needs further study. The purpose of this study was to discuss how to obtain a more accurate count of metastatic LNs based on RLNs according to different pT stages and then to evaluate the prognosis of patients. Our results showed that the optimal number of RLNs for pT1-pT4 stage GC patients were 26, 31, 39 and 45, respectively. A greater number of RLNs can reduce the risk of death in patients with pT1, pT2, and pT4 stage cancers but may not pT3 stage.

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INTRODUCTION

Gastric cancer (GC) is the sixth most common malignant tumor in the world, with more than 860000 deaths each year[1]. The depth of tumor invasion - lymph node (LN) metastasis - distant metastasis (TNM) staging system issued by the Union for International Cancer Control and the American Joint Committee on Cancer (AJCC) is the global standard for GC staging[2,3]. LN metastasis of tumor cells is one of the most common forms of GC metastasis[4,5]. Therefore, surgeons performed LN dissection based on the perigastric lymphatic pathways to control metastasis. Karpeh *et al*[6] found that compared with the location of LN metastasis, the number of metastatic LNs (MLNs) was more important in determining the prognosis of GC patients. The AJCC 8th edition staging system divided GC patients into stages pN3a and pN3b according to MLNs based on pN3 stage, which was effective in clinical applications for evaluating patient prognosis. Therefore, accurate assessment of MLNs is critical for determining the prognosis of GC patients.

Radical gastrectomy and LN dissection are necessary for the long-term survival of GC patients[7]. For the evaluation of MLNs, sufficient numbers of retrieved LNs (RLNs) need to be acquired during surgery and confirmed by postoperative pathological examination[8]. At present, D2/D2 + LN dissection is the standard lymphadenectomy for GC[9]. Compared with D1, expanded LN dissection may effectively control LN metastasis to prolong patient survival[10,11] and clear potential metastatic LNs[12]. Smith *et al*[13] found that for pT1/2N0 patients, every 10 additional RLNs may be associated with a 7.6% increase in overall survival (OS). However, the linear relationship shows that MLNs are positively correlated with RLNs[14-17], indicating that insufficient RLNs may lead to stage migration. The pN stage determined by RLNs might thus be affected and differ from the actual pN stage, which causes errors in subsequent treatment and assessment of prognosis[18]. Furthermore, a previous study showed that evaluating the optimal number of RLNs based on pT staging can not only enhance the accuracy of staging but also better predict patient prognosis[13]. In this context, we analyzed RLNs according to a more accurate pT stage based on clinical application and discussed how to obtain accurate MLNs through RLNs for precise staging and the influence of RLNs on patient prognosis.

This study retrospectively analyzed patients who underwent radical GC surgery in the Gastrointestinal Surgery Department of the Cancer Hospital Affiliated to Harbin Medical University from January 2011 to May 2017. We analyzed the suitable RLNs in pT1-pT4 stages based on pT stage and explored their relationship with long-term patient survival.

MATERIALS AND METHODS

Patients

This study retrospectively analyzed patients who underwent radical GC surgery and D2/D2 + LN dissection at the Affiliated Tumor Hospital of Harbin Medical University from January 2011 to May 2017. The diagnosis of GC was based on tissue samples obtained from preoperative gastroscopy, which were further confirmed by professional pathologists through tissue collected during surgery. The surgical method and LN dissection were performed in accordance with the Japanese GC Treatment Guidelines (Fifth Edition)[19].

The exclusion criteria for this study were as follows: (1) Tumor located in the whole stomach; (2) Preoperative chemotherapy; (3) Patients with a history of other malignant tumors; and (4) Remnant GC. The clinicopathological data of the patients were stored in the GC information management system v1.2 of the Affiliated Tumor Hospital of Harbin Medical University (copyright number 2013SR087424, http://www.sgihmu.com), including sex, age, tumor location, tumor size, histological type, pT stage, pN staging, *etc*. The above content was in compliance with the eighth edition of AJCC regulations[3].

Oxaliplatin + capecitabine (XELOX) or oxaliplatin + S-1 (SOX) are the primary treatment options for patients in pathological stages II to III. Due to the long time span, to ensure the accuracy of this study, we included only patients who received complete chemotherapy at our institution, for a total of 1119 patients. The remaining patients were not included in the postoperative chemotherapy patient group because these patients did not complete all postoperative chemotherapy regimens in our institution, and most of the patients returned to local hospitals for treatment after surgery and did not have complete chemotherapy records.

All patients were followed up after surgery: Stage I patients every 12 mo, stage II patients every 6 mo, and stage III patients every 3-6 mo. Follow-up was conducted by telephone, fax, e-mail, or in the outpatient complex building of the Affiliated Tumor Hospital of Harbin Medical University. Follow-up included complete blood cell analysis, biochemical examination, tumor markers, gastroscopy, and abdominal ultrasonography, and some patients underwent computed tomography (CT)/positron emission tomography-CT examination according to their condition.

Validation cohort

Data for the validation cohort were obtained from the National Cancer Institute Surveillance, Epidemiology, and End Results Program (http://seer.cancer.gov/) provided by SEER*Stat software. We included patients diagnosed with GC between 2010 and 2016 to ensure a minimum follow-up of 5 years. Patients with incomplete or missing records of tumor invasion depth, LNs status, and distant metastasis status were excluded, and then pT staging and pN staging were reverified according to the eighth edition of the AJCC staging manual. The screening process is shown in Figure 1.

Statistical methods

OS was defined as the follow-up time from the time of operation to the time of death or the last date of follow-up. If the patient was alive at the last follow-up, it was included in this study, expressed by the mean ± SD and the 5-year survival rate. The relationship between RLNs and MLNs at each stage was analyzed using locally weighted smoothing (LOESS)[19]. The relationship between RLNs and hazard ratios (HRs) at each stage, pT1-pT4, was assessed by a restricted cubic spline model[20]. X-tile software was used to calculate the optimal cutoff value of RLNs for the prognosis of pT1-pT4 GC (X-Tile version 3.6.1 Yale University, New Haven, CT)[21], and then the Kaplan-Meier method and log-rank test were used to evaluate the effect of the best cutoff value of the number of RLNs in each stage, pT1-pT4, on prognosis. The chi-square test was used to analyze the relationship between the optimal cutoff value of RLNs in each stage, pT1-pT4, and the clinicopathological characteristics of patients. HRs and 95% confidence intervals were calculated using a Cox proportional hazards model. In all analyses, $P < 0.05$ was considered statistically significant. All analyses were performed using R software (version 4.1.2) and SPSS (version 25 for Windows).

RESULTS

Patient characteristics

Ultimately, at our institution, a total of 4968 patients were included in the study as a training cohort (Table 1). Among them, there were 1106 patients in the pT1 stage, 745 patients in the pT2 stage, 1583 patients in the pT3 stage, and 1534 patients in the pT4 stage. In the entire cohort, the median number of RLNs was 27 (range 1-95), with 2062 pN0 stage patients, 927 pN1 stage patients, 893 pN2 stage patients, and 1086 pN3 stage patients according to postoperative pathological examinations.

For the Surveillance, Epidemiology, and End Results (SEER) database, after excluding patients according to the exclusion criteria, 11154 patients were finally included in the study as a validation cohort (Figure 1). Among them, there were 2746 pT1 patients, 1534 pT2 patients, 4570 pT3 patients, and

Table 1 Clinical and pathological characteristics of patients in the training cohort and validation cohort

Characteristics	Training cohort	Validation cohort	*P* value
	n = 4968	*n* = 11154	
Sex			< 0.001
Male	3634 (73.1)	7214 (64.7)	
Female	1334 (26.9)	3940 (35.3)	
Age (yr)			< 0.001
≤ 60	2845 (57.3)	3418 (30.6)	
> 60	2123 (42.7)	7736 (69.4)	
Tumor location			< 0.001
Upper third	552 (11.1)	3954 (35.4)	
Middle third	811 (16.3)	1248 (11.2)	
Lower third	3605 (72.6)	5952 (53.4)	
Tumor size (mm)			< 0.001
≤ 50	3225 (64.9)	6813 (61.1)	
> 50	1743 (35.1)	4341 (38.9)	
Histological type			< 0.001
Well -moderately differentiated	2056 (41.4)	3402 (30.5)	
Poorly-undifferentiated	2204 (44.4)	4197 (37.6)	
Signet ring cell	397 (8.0)	1899 (17.0)	
Others	311 (6.3)	1656 (14.8)	
pT stage			< 0.001
pT1	1106 (22.3)	2746 (24.6)	
pT2	745 (15.0)	1534 (13.8)	
pT3	1583 (31.9)	4570 (41.0)	
pT4	1534 (30.9)	2304 (20.7)	
pN stage			< 0.001
pN0	2062 (41.5)	5411 (48.5)	
pN1	927 (18.7)	2039 (18.3)	
pN2	893 (18.0)	1768 (15.9)	
pN3	1086 (21.9)	1936 (17.4)	
pTNM			< 0.001
I	1445 (29.1)	3476 (31.2)	
II	1383 (27.8)	3821 (34.3)	
III	2140 (43.1)	3857 (34.6)	
RLNs, median (range)	27 (1-95)	16 (1-90)	
Chemotherapy			< 0.001
No/unknown	3769 (75.9)	5191 (46.5)	
Yes	1199 (22.5)	5963 (53.5)	

Tumor location, tumor size, pTNM stage, histological type and the number of removed lymph nodes were determined according to the postoperative pathology report. Statistically significant *P* values are in bold ($P < 0.05$).
RLNs: Retrieved lymph nodes.

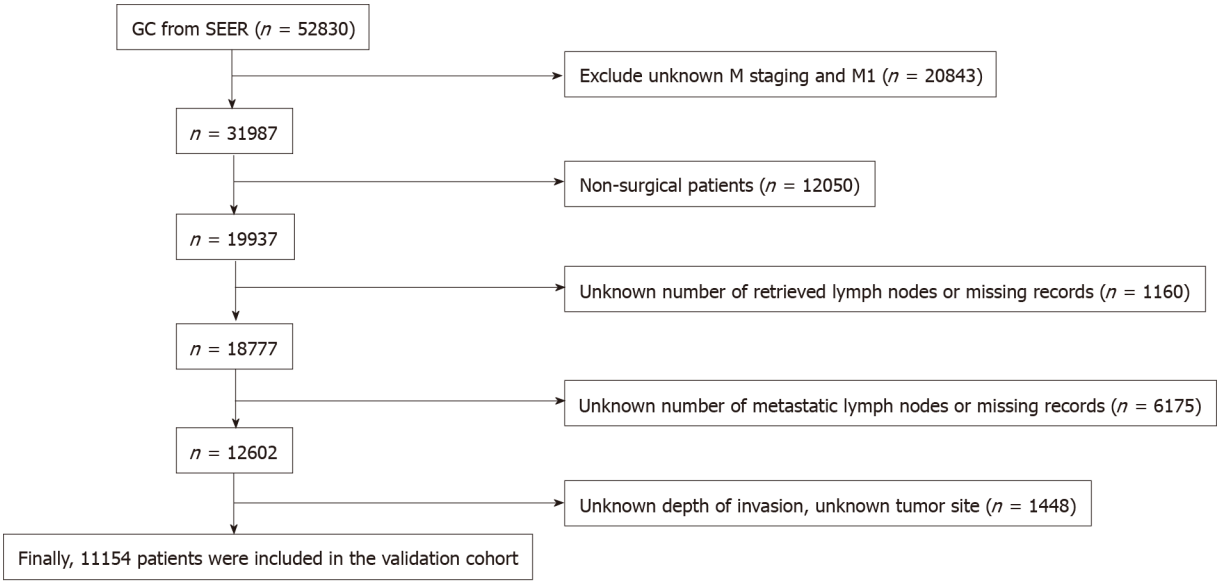

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Figure 1 Flow chart of Surveillance, Epidemiology, and End Results database screening process based on exclusion criteria. GC: Gastric cancer; SEER: Surveillance, Epidemiology, and End Results.

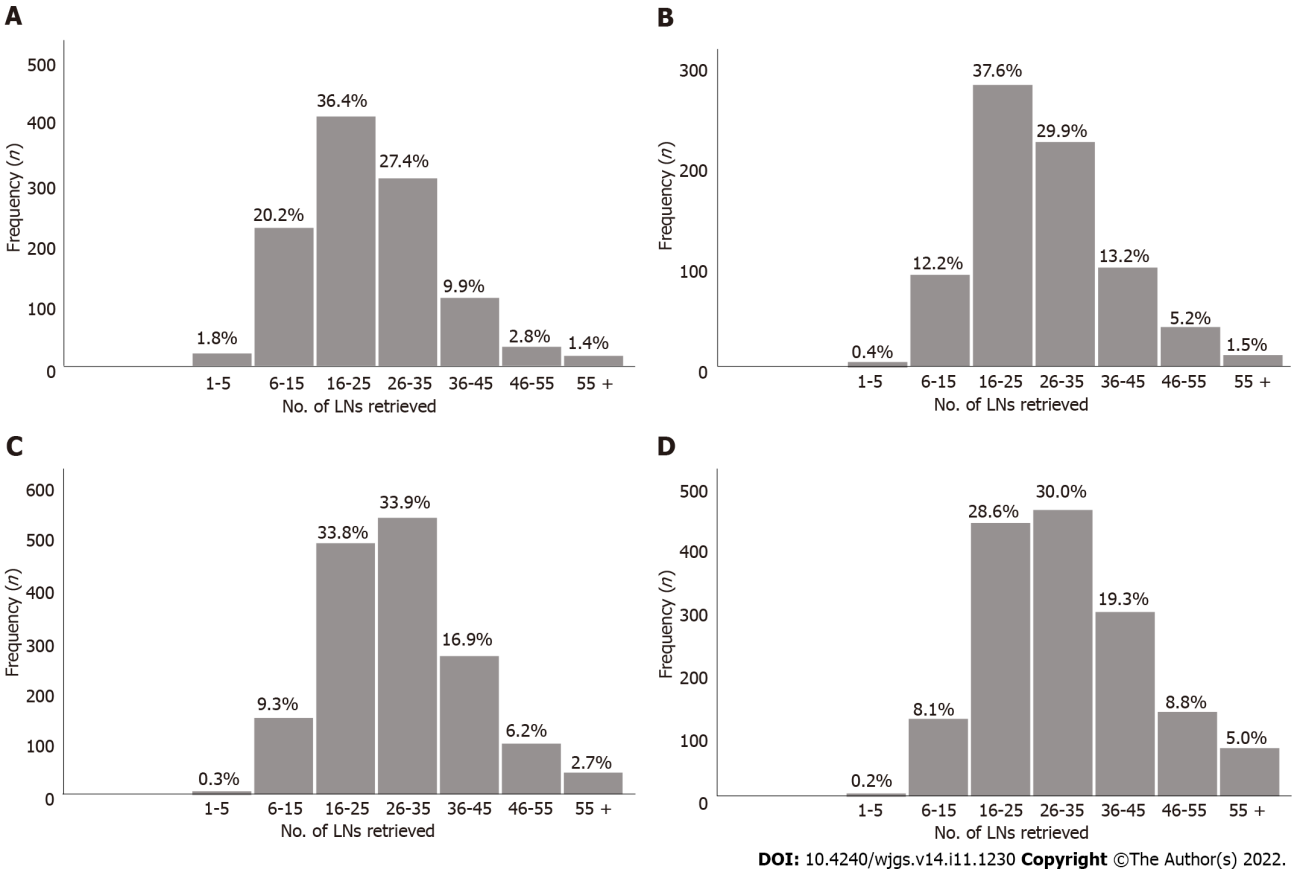

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Figure 2 Number of lymph nodes examined for each stage subgroup in the training cohort. A: pT1; B: pT2; C: pT3; D: pT4. LNs: Lymph nodes.

2304 pT4 patients. In the entire validation cohort, the median number of RLNs was 16 (range 1-90), with 5411 pN0 stage patients, 2039 pN1 stage patients, 1768 pN2 stage patients, and 1936 pN3 stage patients according to postoperative pathological examinations (Table 1).

Analysis of the number of LNs retrieved in the pT1-pT4 stage subgroups

The absolute and relative frequencies of RLNs in each subgroup at the pT1-pT4 stages in the training

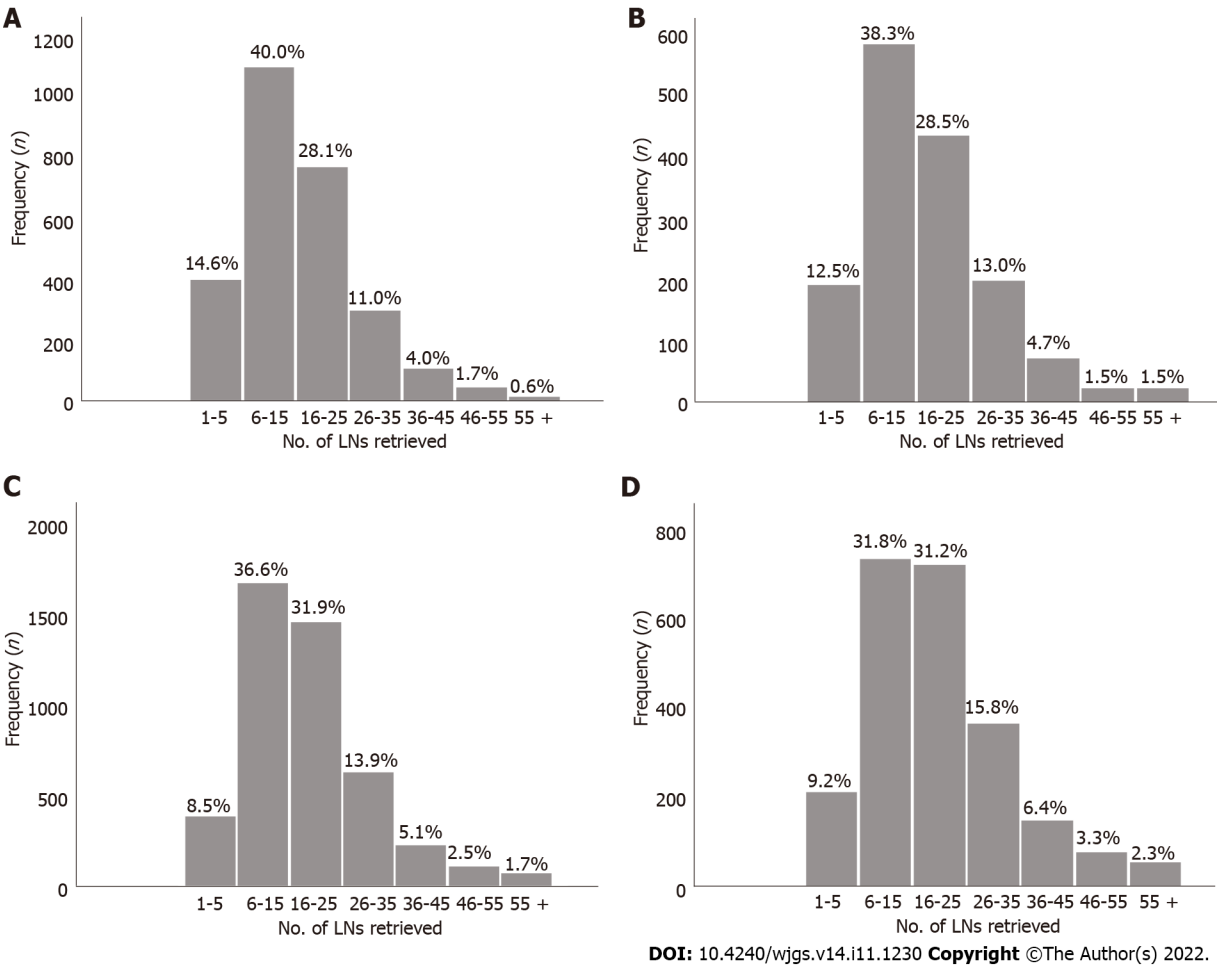

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Figure 3 Number of lymph nodes examined for each stage subgroup in the validation cohort. A: pT1; B: pT2; C: pT3; D: pT4. LNs: Lymph nodes.

cohort are shown in Figure 2, and the absolute and relative frequencies of RLNs in each subgroup at the pT1-pT4 stages in the validation cohort are shown in Figure 3. In the training cohort, for pT1, 16 or more LNs were enucleated in 77.9% of patients, with a median of 23 (range 1-79) of 26862 RLNs, for pT2, 16 or more LNs were enucleated in 87.4% of patients, with a median of 25 (range 4-95) of 20193 RLNs, for pT3, 16 or more LNs were enucleated in 90.4% of patients, with a median of 28 RLNs of 46501(range 4-84), for pT4, 91.7% of patients had 16 or more enucleated LNs, there were 47936 RLNs, and the median was 29 (range 2-86). The LOESS nonlinear trend showed that MLNs in each subgroup showed an upward trend with increasing RLNs (Figures 4A-D), whereas for the pT1 stage, the nonlinear trend indicated that when the number of RLNs exceeded approximately 50, the MLNs decreased with increasing RLNs.

Evaluation of the effect of the number of LNs retrieved on patient survival

To assess the relationship between RLNs and mortality risk, we performed a restricted cubic spline model analysis (Figures 5A-D). For pT1, pT2, and pT4 stages, the smooth curve shows that HRs decrease with the increase in RLNs. For pT3, the smooth curve shows that HRs increase with the increase in RLNs. The results showed that the number of LNs retrieved may affect patient survival. However, the trend in HRs and RLNs in the pT3 stage was opposite that in the pT1 stage, pT2 stage, and pT4 stage. To further verify the effect of RLNs on patient survival, every 10 LNs was taken as the cutoff point. That is, fewer than 5 LNs were removed, and 6-15 LNs were removed until more than 55 LNs were retrieved. Table 2 lists the 5-year survival rates based on RLNs in each subgroup, increasing at intervals of every 10 LNs. For patients with pT1, pT2, and pT4 stage cancers, adding RLNs prolonged the 5-year patient survival rate, but for patients with pT3 stage cancer, adding RLNs did not prolong the 5-year patient survival rate.

Influence of the optimal cutoff value of LNs retrieved in each pT1-pT4 stage subgroup on the survival of patients

Since a nonlinear relationship between RLNs and HRs was observed in each subgroup at the pT1-pT4 stages, we analyzed survival differences among these patients by X-tile software (Figure 6). The results

Table 2 Five-year overall survival by the number of retrieved lymph nodes in the training cohort

pT stage	No. of retrieved lymph nodes														*P* value
	1-5 (No., %)		6-15 (No., %)		16-25 (No., %)		26-35 (No., %)		36-45 (No., %)		46-55 (No., %)		55 + (No., %)		
pT1	20	90.0	223	89.1	403	92.5	303	94.4	110	91.0	31	100.0	16	100.0	0.210
pT2	3	66.7	86	82.1	280	84.3	223	86.4	98	91.3	39	87.1	11	100.0	0.371
pT3	4	50.0	148	70.0	486	64.8	531	61.7	267	60.3	98	62.4	42	48.5	0.172
pT4	3	33.3	124	45.9	439	51.0	460	58.3	296	55.2	135	67.4	77	56.1	0.005

No: The number of patients. The five-year overall survival rate is presented as %.

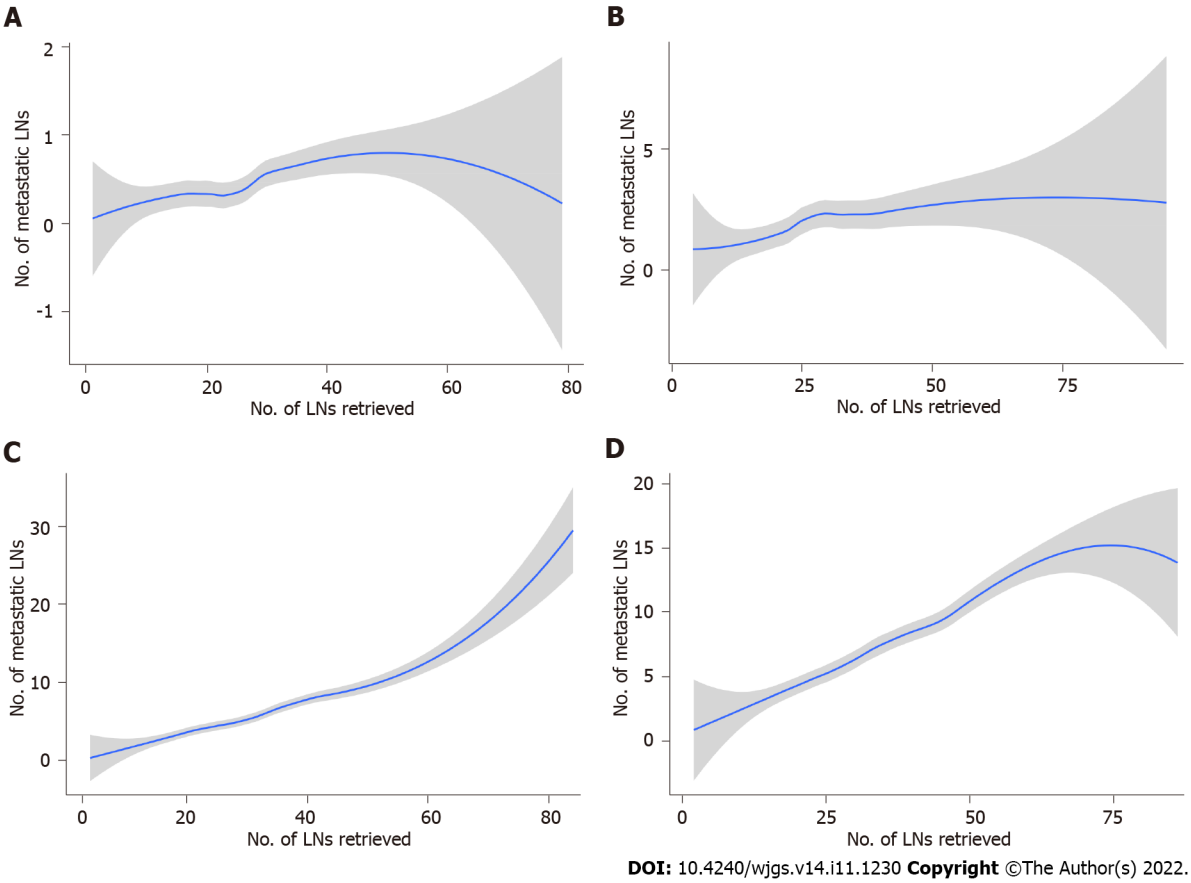

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Figure 4 The association between the number of examined lymph nodes and the number of metastatic lymph nodes locally weighted smoothing in the Chinese training cohort. A: pT1; B: pT2; C: pT3; D: pT4. The shaded area is the 95% confidence interval. LNs: Lymph nodes.

showed that for the pT1 stage, the best cutoff values for RLNs were 12 and 26, for the pT2 stage, the best cutoff values for RLNs were 17 and 31, or pT3, the best cutoff values for RLNs were 19 and 39, and for pT4, the best cutoff values for RLNs were 16 and 45. After that, subgroup survival analysis was performed according to the best cutoff alue of RLNs in each substage. Increasing RLNs can improve prognosis of patients with pT1, pT2, and pT4 stages hile may not improve prognosis of patients with pT3 stage. In addition, chi-square analysis showed that for pT1 stage and pT3 stage cancers, with the increase in RLNs, the proportion of patients younger than 60 years old gradually increased, and there was a statistically significant correlation ($P < 0.001$, $P = 0.002$). For stages pT1, pT3, pT4, pN stage increased with the optimal cutoff value of the number of removed LNs, and there was a statistically significant association ($P < 0.001$, $P < 0.001$, $P < 0.001$) (Table 3).

To verify the relationship between the optimal cutoff value of RLNs in this study and the long-term survival of patients, we used the SEER validation cohort to validate the pT1-pT4 subgroup (Figure 7). Increasing RLNs can improve prognosis of patients with pT1-pT4 stages. Chi-square analysis found that for pT1-pT4, with the increase in RLNs, the proportion of patients less than 60 years old gradually increased, and pN stage increased with the optimal cutoff value for the number of removed LNs, and

Table 3 Chi-square analysis of the number of removed lymph nodes and patient characteristics in the pT1-pT4 subgroups in the Chinese training cohort

Characteristics	pT1 (1106), RLNs			*P* value	pT2 (745), RLNs			*P* value	pT3 (1583), RLNs			*P* value	pT4 (1534), RLNs			*P* value
	≤ 12	13-25	≥ 26		≤ 17	18-30	≥ 31		≤ 19	20-38	≥ 39		≤ 16	17-44	≥ 45	
Sex				0.114				0.803				0.006				0.132
Male	112	353	320		109	274	188		230	677	240		119	851	161	
Female	31	150	140		32	80	62		73	295	68		43	286	74	
Age (yr)				< 0.001				0.699				0.002				0.273
≤ 60	74	302	323		80	214	152		137	523	183		82	637	138	
> 60	69	201	137		61	140	98		166	449	125		80	500	97	
Tumor location				0.003				0.216				0.036				0.025
Upper third	17	24	19		17	34	15		54	139	36		34	137	26	
Middle third	14	59	68		17	40	37		63	164	68		25	211	45	
Lower third	112	420	373		107	280	198		186	669	204		103	789	164	
Tumor size (mm)				0.005				0.004				< 0.001				< 0.001
≤ 50	139	477	417		129	287	196		202	514	147		87	549	81	
> 50	4	26	43		12	67	54		101	458	161		75	588	154	
Histological type				0.008				0.689				0.878				0.145
Well-moderately differentiated	67	273	229		67	160	104		125	378	116		73	391	73	
Poorly-undifferentiated	39	153	158		63	148	113		122	426	141		75	631	135	
Signet ring cell	14	36	43		6	24	17		36	113	32		7	57	12	
Others	23	41	30		5	22	16		20	55	19		7	58	15	
pN stage				< 0.001				0.128				< 0.001				< 0.001
pN0	125	43	374		85	195	127		112	241	62		54	220	37	
pN1	15	49	45		32	80	57		86	206	54		41	240	22	
pN2	3	22	28		21	50	40		68	237	64		42	275	43	
pN3	0	2	13		3	29	26		37	288	128		25	402	133	
pTNM				0.014				0.045				< 0.001				0.003
I	140	479	419		85	195	127		0	0	0		0	0	0	

II	3	24	40	53	130	97	198	447	116	43	201	31
III	0	0	1	3	29	26	105	525	192	119	936	204

Tumor location, tumor size, pTNM stage, histological type and the number of removed lymph nodes were determined according to the postoperative pathology report. Statistically significant *P* values are in bold ($P < 0.05$). RLNs: Retrieved lymph nodes.

there was a statistically significant association (Table 4).

Stage migration

For the pT1-pT4 stages, a scatter plot and linear regression showed that the number of positive LNs detected by pathology increased with the number of LNs removed during surgery, and this result was statistically significant ($P = 0.0001$, $R^2 = 0.0135$; $P = 0.0011$, $R^2 = 0.0142$; $P < 0.0001$, $R^2 = 0.1118$; $P < 0.0001$, $R^2 = 0.1364$) (Figures 8A-D).

Multivariate analysis of the prognosis of patients with pT1-pT4 stage cancer

Finally, multivariate analysis showed that age, tumor location, MLNs, and RLNs were independent risk factors associated with the prognosis of patients with pT1 stage cancer. Age, MLNs, and RLNs were independent risk factors associated with the prognosis of patients with pT2 stage cancer. Age, tumor size, MLNs, and RLNs were independent risk factors associated with the prognosis of patients with pT3 stage cancer. Age, tumor size, MLNs, and RLNs were independent risk factors associated with the prognosis of patients with pT4 stage cancer (Table 5).

In the SEER validation cohort, sex, age, tumor location, MLNs, and RLNs were associated with prognosis in patients with pT1 stage independent risk factors. Age, tumor location, tumor size, MLNs, RLNs and chemotherapy were independent risk factors associated with the prognosis of patients with pT2 stage cancer. Age, tumor size, MLNs, and RLNs were independent risk factors associated with the prognosis of patients with pT3 stage cancer. Age, tumor location, tumor size, MLNs, and RLNs were independent risk factors associated with the prognosis of patients with pT4 stage cancer (Table 6).

DISCUSSION

In clinical practice, pT stage according to the depth of tumor invasion can effectively assess patient prognosis, and the risk of LN metastasis increases as pT stage increases[13,22,23]. Smith *et al*[13] analyzed the optimal number of RLNs by pT staging and found that for the pN0 and pN1 stages of different pT stages, increasing RLNs could prolong prognosis and improve stage migration, and when RLNs reached 40, prognosis could be significantly improved. Chinese GC patients are mostly in the advanced stage, and the frequency of LN metastasis is high. For different pT stages, RLNs ≤ 15 cannot achieve accurate staging of pN0 and pN1 stages[24]. However, for patients with extensive LN metastasis (pN2-pN3), the appropriate number of RLNs cannot be effectively determined. In addition, although the LN metastasis rate can help to avoid stage migration, it is suitable for the removal of less

Table 4 Chi-square analysis of the number of removed lymph nodes and patient characteristics in the pT1-pT4 subgroups in the Surveillance, Epidemiology, and End Results validation cohort

Characteristics	pT1 (2746), RLNs			*P* value	pT2 (1534), RLNs			*P* value	pT3 (4570), RLNs			*P* value	pT4 (2304), RLNs			*P* value
	≤ 12	13-24	≥ 25		≤ 17	18-30	≥ 31		≤ 19	20-38	≥ 39		≤ 16	17-44	≥ 45	
Sex				0.521				0.263				0.033				0.668
Male	727	678	288		584	305	121		1988	1012	223		576	630	82	
Female	428	439	186		316	138	70		775	469	103		448	511	57	
Age (yr)				0.018				0.049				0.006				0.054
≤ 60	278	305	145		252	133	64		869	499	130		306	384	53	
> 60	877	810	329		648	410	127		1894	982	196		718	757	86	
Tumor location				0.008				0.001				< 0.001				< 0.001
Upper third	354	382	140		348	168	54		1391	709	93		159	143	13	
Middle third	134	139	81		93	59	39		188	146	54		109	172	34	
Lower third	667	596	253		459	216	98		1184	626	179		756	826	92	
Tumor size (mm)				0.575				0.009				< 0.001				0.002
≤ 50	966	934	387		695	314	132		1581	749	149		443	417	46	
> 50	189	183	87		205	129	59		1182	432	177		581	724	93	
Histological type				0.648				0.945				0.951				0.193
Well-moderately differentiated	538	502	217		304	138	67		782	427	86		169	147	25	
Poorly-undifferentiated	316	314	141		304	158	62		1212	628	144		397	469	52	
Signet ring cell	187	193	64		123	58	26		406	228	51		238	288	37	
Others	114	108	52		169	89	36		363	198	45		220	237	25	
pN stage				< 0.001				< 0.001				< 0.001				< 0.001
pN0	1008	885	369		547	255	96		1196	526	94		253	166	16	
pN1	115	148	53		216	91	39		664	275	48		236	135	19	
pN2	28	63	30		106	52	31		561	311	55		298	212	21	
pN3	4	21	22		31	45	25		342	369	129		237	628	83	
pTNM				< 0.001				< 0.001				< 0.001				< 0.001
I	1123	1033	422		547	255	96		0	0	0		0	0	0	

II	32	82	46	322	143	70	1860	801	142	180	130	13
III	0	2	6	31	45	25	903	680	184	844	1011	126

Tumor location, tumor size, pTNM stage, histological type and the number of removed lymph nodes were determined according to the postoperative pathology report. Statistically significant *P* values are in bold ($P < 0.05$).
RLNs: Retrieved lymph nodes.

than 15 LNs or D1 resection[22,25], whereas our study mostly focuses on D2 resection of 16 LNs. Therefore, pT stage was used as the basis to assess the number of RLNs in this study, which could be used to accurately assess patient prognosis. For patients with few RLNs, we suggest that more attention is needed, and active treatment may improve the prognosis of such patients.

Although early GC has a better prognosis, patient prognosis of patients still differs significantly. When accompanied by lymphatic and vascular invasion, the prognosis of early GC is still poor, and the risk of LN metastasis is high[26,27]. Osumi *et al*[26] found that the frequency of LNs also increased with increasing macroscopic tumor diameter. In addition, Choi *et al*[28] performed a more detailed grouping of pN staging according to the location of LN metastasis and achieved good applicability. In this study, we found that 16% of pT1 stage GC patients developed LN metastasis, and 18% of pT1 stage GC patients in the SEER validation cohort developed LN metastasis. This proportion is also consistent with the proportion of LN metastases found in 11% of pT1 GC patients by Yoshikawa *et al*[29]. For pT2 stage cancer, 45.4% of the patients in the database of this study had LN metastasis, and 41.9% of the patients in the SEER validation cohort had LN metastasis, which indicates that pT1 and pT2 GC are in earlier stages. The smooth curve shows that for pT1 stage and pT2 stage cancer, MLNs and RLNs have a positive trend, but for pT1 stage cancer, when RLNs are approximately 50, the number of MLNs shows a downward trend, which may be related to the lower risk of LN metastasis in early GC. This finding also means that increasing the numbers of RLNs may not result in more MLNs. It is still necessary to accurately evaluate LN status.

Minimally invasive surgeries, such as laparoscopy, are mostly used in early GC, which is beneficial to enhance patients' postoperative recovery. In a laparoscopy-related study, Lee *et al*[30] found no significant difference in OS between laparoscopic surgery and traditional open surgery for early GC and no significant difference in the number of LNs removed (laparotomy: 36.4 *vs* laparoscopy: 36). An *et al*[31] found no significant difference in disease-free survival between laparoscopic and open surgery for early-stage GC, whereas there was still no significant difference in the number of LNs removed (laparotomy: 24 *vs* laparoscopic: 26). These results support the hypothesis that, regardless of the indications for minimally invasive treatment, sufficient LNs still need to be removed in patients with early-stage GC, independent of the technique employed. Our smooth curve findings also support this hypothesis, which is consistent with previous studies[12-14]. For early-stage GC, we found that removal of more than 26 LNs can significantly improve patient prognosis, and the 5-year survival rate of patients when RLNs were appropriately increased to 46 was 100%. The applicability of the cutoff values of our RLNs has been well validated in the SEER database, which also includes people of different races, such as white, black, and Asian individuals. This finding also shows that the cutoff value of RLNs in this study had good applicability and clinical potential.

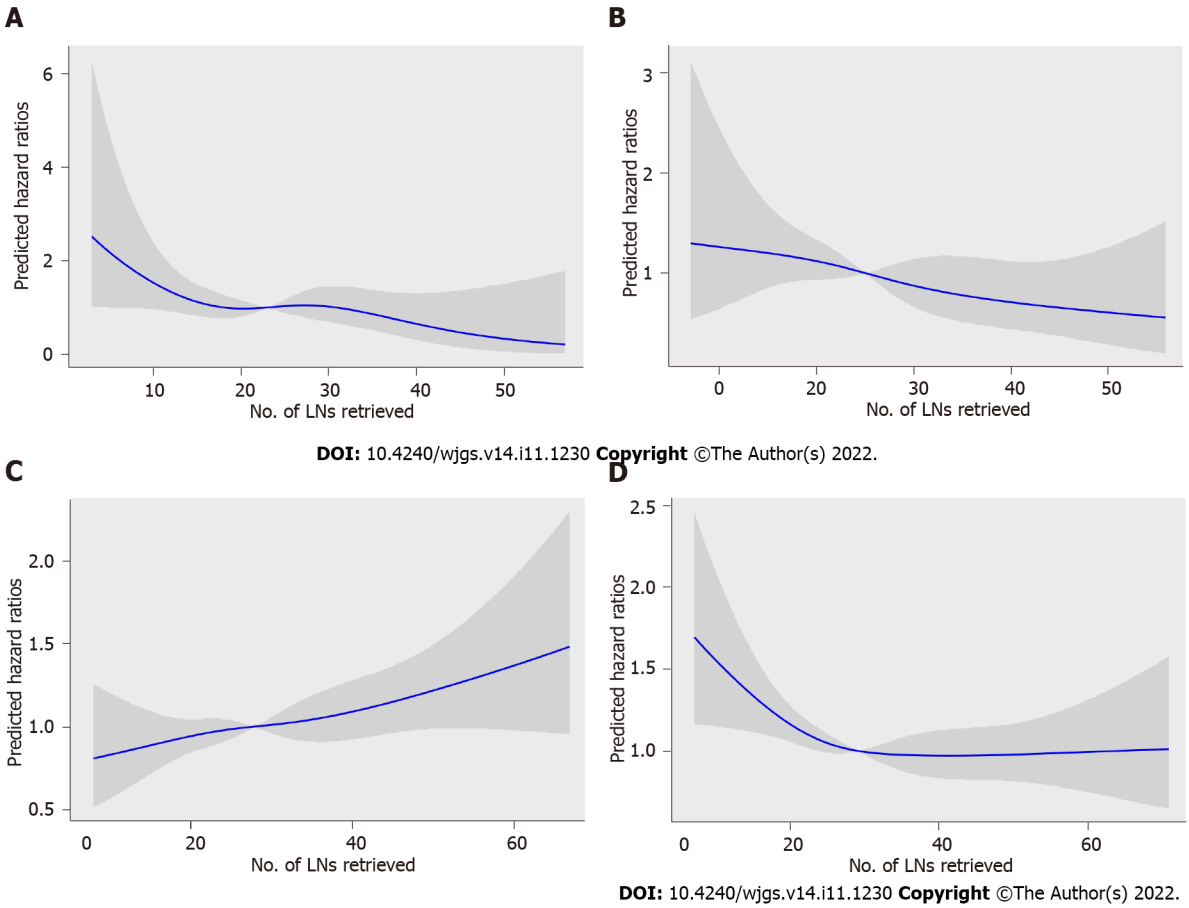

Figure 5 Association between the number of examined lymph nodes and the hazard ratios in the Chinese training cohort. A: pT1; B: pT2; C: pT3; D: pT4. The blue line represents the estimated hazard ratios, and the shaded area is the 95% confidence interval. LNs: Lymph nodes; HRs: Hazard ratios.

For GC patients at the pT3 stage, both the smooth curve and the survival curve indicate that increasing numbers of RLNs may not prolong patient long-term survival, and the 5-year survival rate of cases with more than 39 RLNs is lower than those with less than 19 RLNs (57.7% *vs* 68.3%), which is contrary to the conclusion of the SEER database validation cohort. Chi-square analysis of the difference between the database in this study and the SEER database found that for pT3 stage patients, regardless of the training cohort or validation cohort, there was a statistically significant correlation between the number of RLNs and age. In the training cohort, the proportion of young GC patients increased significantly with the number of RLNs, whereas the opposite was true in SEER. Relevant studies have shown that GC is more aggressive among young patients and that the prognosis is worse[32,33]. In addition, a large number of perigastric LNs are associated with antitumor immunity. When tumors are detected by the immune system, it can lead to local LN enlargement[34,35], and extensive LN dissection may compromise the patients' immune system function[36]. In addition, there is stage migration in patients in pT3, and we cannot determine whether the poorer prognosis of patients with higher RLNs is because the discovery of more MLNs masks the actual therapeutic benefit of LN dissection. Therefore, both of the above factors may be responsible for this opposite survival trend.

For GC patients at the pT4 stage, both the smooth curve and the survival curve indicate that increasing numbers of RLNs may prolong patients' long-term survival, which is consistent with previous studies on RLNs[37,38]. However, we found that the survival rate of patients with RLNs ≥ 55 was lower than that of patients with RLNs ≤ 55. Since only 77 patients had RLNs ≤ 55, we think this finding may be due to the small sample size, which also needs to be expanded for verification. Nevertheless, the trend in the survival curves suggested that an increase in RLNs can improve prognosis, and it was well validated in SEER, which also suggested that the increase in RLNs could help improve the prognosis of patients with pT4 stage disease. Clearly, increasing the number of RLNs is particularly important for local control in advanced stages of the disease. In the AJCC 8th edition staging system, when patients with pT4a or pT4b stage have LN metastases, the final pTNM stage is classified as stage III. Although treatment methods have been improved, the prognosis of stage III GC is still poor [39]. Zhang *et al*[40] found that for patients in the T4 stage, if the number of MLNs was ≥ 21, the prognosis was similar to that at stage IV. In this study, the smooth curve shows that MLNs increase with RLNs, which also means that there may be high-risk patients in pT4 stage with a similar prognosis to stage IV. Therefore, increasing the number of RLNs may guarantee accurate TNM staging and can help

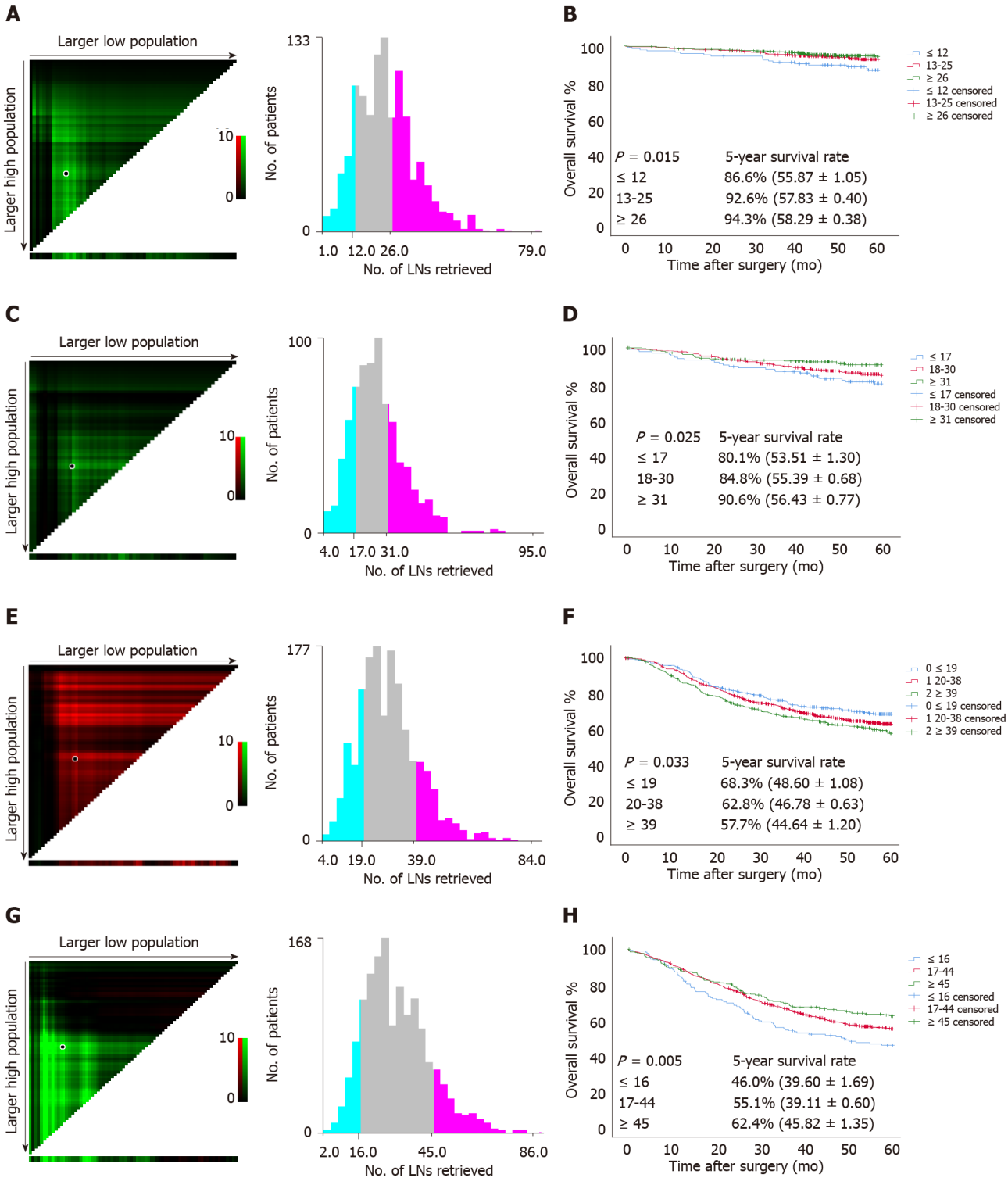

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Figure 6 Estimation of the cutoff value of retrieved lymph nodes using X-tile software and overall survival curves of pT1-pT4 patients stratified by the estimated cutoff value in the Chinese training cohort. A and B: pT1; C and D: pT2; E and F: pT3; G and H: pT4. LNs: Lymph nodes.

differentiate such high-risk patients. We also found that if 45 LNs are removed, the long-term survival may be prolonged significantly, which is also suitable for GC patients of different regions and races in the SEER database. However, the cutoff value for RLNs is different from that in Zhang *et al*[38] (45 *vs* 31). Zhang *et al*[38] included only patients without LN metastasis, and we think that it may have caused the difference found in the included samples. Chi-square analysis found that when RLNs were ≥ 45, the proportion of patients in pN3 stage increased significantly, and linear regression showed that there was a significant correlation between RLNs and MLNs, all of which indicated that some patients in pT4 stage had low to high TNM stage. Therefore, the increase in RLNs is helpful for accurate staging and local control of LNs, but this finding also needs to be confirmed by follow-up studies.

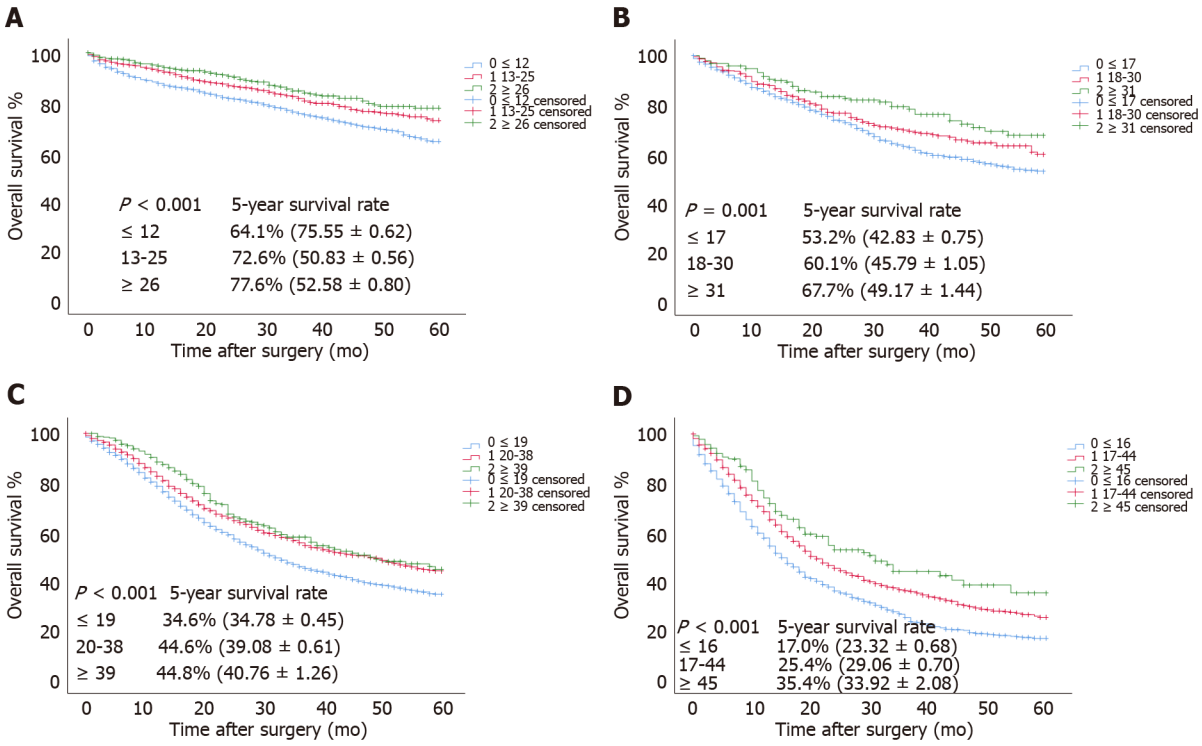

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Figure 7 The overall survival curves of pT1-pT4 patients in the validation cohort stratified according to the estimated cutoff value. A: pT1; B: pT2; C: pT3; D: pT4.

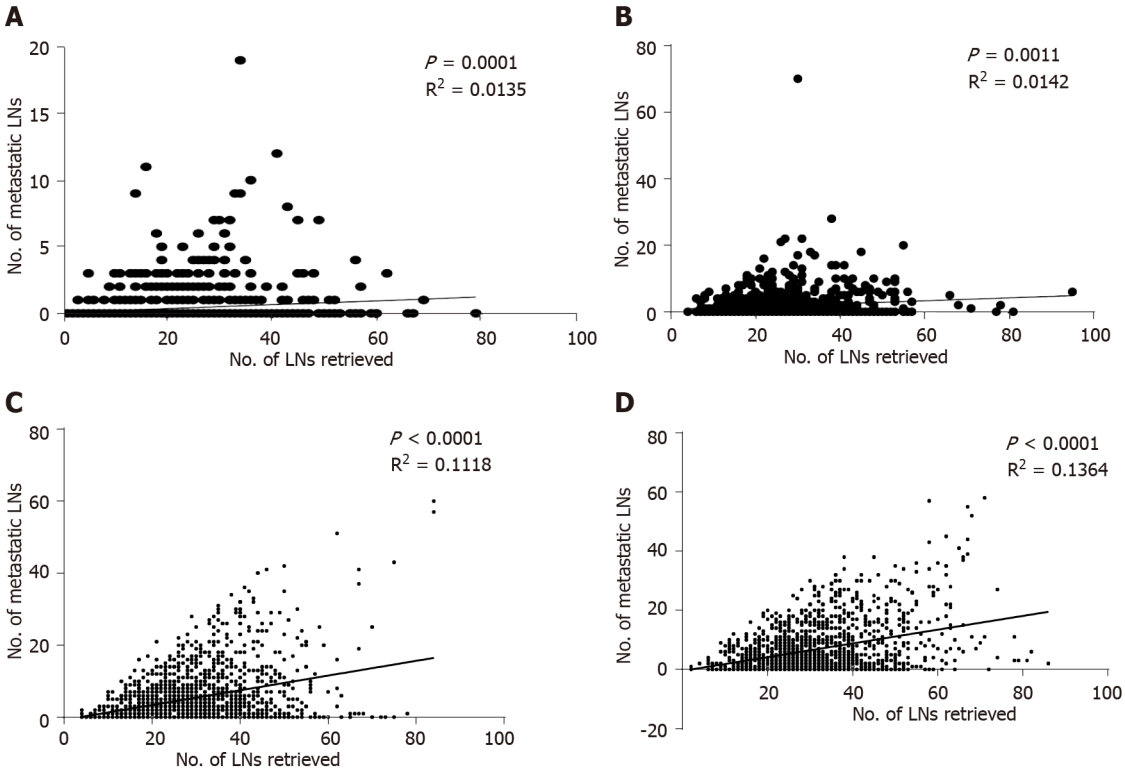

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Figure 8 Scatter plot and linear regression analysis of the number of metastatic lymph nodes and the number of positive lymph nodes in the overall patient population. A: pT1; B: pT2; C: pT3; D: pT4. LNs: Lymph nodes.

Table 5 Prognostic factors of patients with gastric cancer by univariate and multivariate analyses based on Cox regression analysis in the Chinese validation cohort

Characteristics	Multivariate analysis, pT1		Multivariate analysis, pT2		Multivariate analysis, pT3		Multivariate analysis, pT4	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Sex		-		-		-		-
Male								
Female								
Age	1.056 (1.030-1.082)	< 0.001	1.048 (1.024-1.072)	< 0.001	1.016 (1.007-1.025)	< 0.001	1.021 (1.013-1.029)	< 0.001
Tumor location		0.034		-		0.122		-
Upper third	1				1			
Middle third	0.384 (0.151-0.972)	0.043			0.828 (0.623-1.100)	0.192		
Lower third	0.413 (0.209-0.815)	0.011			0.783 (0.619-0.989)	0.040		
Tumor size (mm)		-		-		< 0.001		< 0.001
≤ 50					1		1	
> 50					1.435 (1.201-1.715)		1.422 (1.209-1.671)	
Histological type		-		-		0.260		-
Well-moderately differentiated					1			
Poorly-undifferentiated					1.133 (0.934-1.374)	0.204		
Signet ring cell					1.305 (0.993-1.374)	0.056		
Others					1.037 (0.993-1.716)	0.851		
MLNs	1.224 (1.133-1.322)	< 0.001	1.067 (1.049-1.086)	< 0.001	1.063 (1.052-1.073)	< 0.001	1.053 (1.044-1.063)	< 0.001
RLNs	0.976 (0.954-0.999)	0.044	0.979 (0.960-0.999)	0.037	0.988 (0.979-0.996)	0.003	0.974 (0.967-0.981)	< 0.001
Chemotherapy		-		-		-		-
Yes								
No/unknown								

-: Univariate analysis was not statistically significant; RLNs: Retrieved lymph nodes; MLNs: Metastatic lymph nodes.

There were some limitations in this study. First, as a retrospective study, we included patients from 2011 to 2017. Due to the longer time span, some clinical information was missing from our study, such as carcinoembryonic antigen, programmed cell death-1, and other clinical information, and it may be difficult to assess the connection between clinicopathological features and RLNs. Second, assessing patient sensitivity to chemotherapy using RLNs also deserves further study. Therefore, we will supply clinical information in future clinical studies.

CONCLUSION

Our study shows that RLNs are an independent risk factor associated with the prognoses of pT1-pT4 stage GC patients. The mortality risk of patients with an increasing number of RLNs is not constant. For patients with pT1, pT2, and pT4 stage cancers, increasing the number of RLNs can prolong patient long-term survival. However, for patients with pT3 stage cancer, adding RLNs may not improve their long-term survival. For pT1 stage patients, it is recommended to retrieve at least 26 LNs. For pT2 stage patients, it is recommended to retrieve at least 31 LNs. For pT4 stage patients, it is recommended to

Table 6 Prognostic factors of patients with gastric cancer by univariate and multivariate analyses based on Cox regression analysis in the Surveillance, Epidemiology, and End Results validation cohort

Characteristics	Multivariate analysis, pT1		Multivariate analysis, pT2		Multivariate analysis, pT3		Multivariate analysis, pT4	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Sex		0.001		-		-		-
Male	1							
Female	0.712 (0.596-0.851)							
Age	1.044 (1.035-1.052)	< 0.001	1.032 (1.024-1.040)	< 0.001	1.018 (1.014-1.022)	< 0.001	1.018 (1.014-1.022)	< 0.001
Tumor location		< 0.001		< 0.001		-		0.007
Upper third	1		1				1	
Middle third	0.491 (0.364-0.661)	< 0.001	0.671 (0.496-0.908)	0.010			0.883 (0.718-1.085)	0.235
Lower third	0.636 (0.534-0.758)	< 0.001	0.603 (0.501-0.726)	< 0.001			1.122 (0.963-1.308)	0.140
Tumor size (mm)		-		0.004		< 0.001		< 0.001
≤ 50			1		1		1	
> 50			1.323 (1.091-1.604)		1.172 (1.079-1.274)		1.285 (1.157-1.427)	
Histological type		-		-		-		-
Well-moderately differentiated								
Poorly-undifferentiated								
Signet ring cell								
Others								
MLNs	1.111 (1.088-1.135)	< 0.001	1.022 (1.013-1.030)	< 0.001	1.024 (1.021-1.027)	< 0.001	1.035 (1.030-1.039)	< 0.001
RLNs	0.978 (0.969-0.986)	< 0.001	0.981 (0.973-0.990)	< 0.001	0.986 (0.983-0.990)	< 0.001	0.973 (0.969-0.978)	< 0.001
Chemotherapy		-		0.002		-		-
Yes			1					
No/unknown			1.323 (1.110-1.577)					

-: Univariate analysis was not statistically significant; RLNs: Retrieved lymph nodes; MLNs: Metastatic lymph nodes; HR: Hazard ratio; CI: Confidence interval.

retrieve 45 LNs.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer (GC) is the sixth most common malignant tumor in the world. The number of metastatic lymph nodes (MLNs) was more important in determining the prognosis of GC patients. For the evaluation of MLNs, sufficient numbers of retrieved lymph nodes (RLNs) need to be acquired during surgery and confirmed by postoperative pathological examination. RLNs based on pT staging can not only enhance the accuracy of staging but also better predict patient prognosis. However, the prognostic value of quantitative assessments of the number of RLNs in GC patients needs further study.

Research motivation
Assessing whether RLNs have prognostic significance for GC of different pT stages will provide a basis for clinicians to treat and predict the prognosis of GC patients.

Research objectives
To discuss how to obtain a more accurate count of MLNs based on RLNs in different pT stages and then to evaluate patient prognosis.

Research methods
This study retrospectively analyzed patients who underwent GC radical surgery and D2/D2 + LN dissection at the Cancer Hospital of Harbin Medical University from January 2011 to May 2017. Locally weighted smoothing was used to analyze the relationship between RLNs and the number of MLNs. Restricted cubic splines were used to analyze the relationship between RLNs and hazard ratios (HRs), and X-tile was used to determine the optimal cutoff value for RLNs. Patient survival was analyzed with the Kaplan-Meier method and log-rank test. Finally, HRs and 95% confidence intervals were calculated using Cox proportional hazards models to analyze independent risk factors associated with patient outcomes.

Research results
A total of 4968 patients were included in the training cohort, and 11154 patients were included in the validation cohort. The smooth curve showed that the number of MLNs increased with an increasing number of RLNs, and a nonlinear relationship between RLNs and HRs was observed. X-tile analysis showed that the optimal number of RLNs for pT1-pT4 stage GC patients was 26, 31, 39, and 45, respectively. A greater number of RLNs can reduce the risk of death in patients with pT1, pT2, and pT4 stage cancers but may not reduce the risk of death in patients with pT3 stage cancer. Multivariate analysis showed that RLNs were an independent risk factor associated with the prognosis of patients with pT1-pT4 stage cancer ($P = 0.044$, $P = 0.037$, $P = 0.003$, $P < 0.001$).

Research conclusions
A greater number of RLNs may not benefit the survival of patients with pT3 stage disease but can benefit the survival of patients with pT1, pT2, and pT4 stage disease. For the pT1, pT2, and pT4 stages, it is recommended to retrieve 26, 31 and 45 LNs respectively.

Research perspectives
Due to the longer time span, some clinical information was missing from our study, such as tumor markers and other clinical information. Therefore, we focused on the relationship between RLNs and some clinicopathological features in the future, as well as the evaluation of the sensitivity of RLNs to different chemotherapy regimens.

FOOTNOTES

Author contributions: Wang H and Yin X designed and conceived the project together, and they made the same contribution to the work; Wang H, Yin X, Lou SH, Fang TY, Han BL, and Gao JL interpreted and analyzed the data; Professor Xue YW revised the important key content of the manuscript; Wang H, Yin X, Lou SH, Fang TY, Han BL, Gao JL, Wang YF, Zhang DX, Wang XB, Lu ZF, Wu JP, Zhang JQ, Wang YM, and Zhang Y participated in patient information collection; and the final manuscript was read and approved by all authors.

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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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Data sharing statement: Patients' data were saved in the Gastric Cancer Information Management System v1.2 of Harbin Medical University Cancer Hospital (Copyright No. 2013SR087424, http:www.sgihmu.com).

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ORIGINAL ARTICLE

Retrospective Study

Comprehensive abdominal composition evaluation of rectal cancer patients with anastomotic leakage compared with body mass index-matched controls

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Abstract

BACKGROUND

Anastomotic leakage (AL) is a fatal complication in patients with rectal cancer after undergoing anterior resection. However, the role of abdominal composition in the development of AL has not been studied.

AIM

To investigate the relationship between abdominal composition and AL in rectal cancer patients after undergoing anterior resection.

METHODS

A retrospective case-matched cohort study was conducted. Complete data for 78 patients with AL were acquired and this cohort was defined as the AL group. The controls were matched for the same sex and body mass index (± 1 kg/m^2). Parameters related to abdominal composition including visceral fat area (VFA), subcutaneous fat area (SFA), subcutaneous fat thickness (SFT), skeletal muscle area (SMA), skeletal muscle index (SMI), abdominal circumference (AC), anterior to posterior diameter of abdominal cavity (APD), and transverse diameter of abdominal cavity (TD) were evaluated based on computed tomography (CT) images using the following Hounsfield Unit (HU) thresholds: SFA: -190 to -30, SMA: -29 to 150, and VFA: -150 to -20. The significance of abdominal composition-related parameters was quantified using feature importance analysis; an artificial intelligence method was used to evaluate the contribution of each included variable.

RESULTS

Two thousand two hundred and thirty-eight rectal cancer patients who underwent anterior resection from 2010 to 2020 in a large academic hospital were investigated. Finally, 156 cases were enrolled in the study. Patients in the AL

group showed longer operative time (225.03 ± 55.29 *vs* 207.17 ± 40.80, P = 0.023), lower levels of preoperative hemoglobin (123.32 ± 21.17 *vs* 132.60 ±1 6.31, P = 0.003) and albumin (38.34 ± 4.01 *vs* 40.52 ± 3.97, P = 0.001), larger tumor size (4.07 ± 1.36 *vs* 2.76 ± 1.28, P < 0.001), and later cancer stage (P < 0.001) compared to the controls. Patients who developed AL exhibited a larger VFA (125.68 ± 73.59 *vs* 97.03 ± 57.66, P = 0.008) and a smaller APD (77.30 ± 23.23 *vs* 92.09 ± 26.40, P < 0.001) and TD (22.90 ± 2.23 *vs* 24.21 ± 2.90, P = 0.002) compared to their matched controls. Feature importance analysis revealed that TD, APD, and VFA were the three most important abdominal composition-related features.

CONCLUSION

AL patients have a higher visceral fat content and a narrower abdominal structure compared to matched controls.

Key Words: Anastomotic leakage; Abdominal composition; Rectal cancer; Body mass index-matched; Anterior to posterior diameter; Transverse diameter

Core Tip: We investigated the association between abdominal composition and anastomotic leakage in rectal cancer patients who underwent anterior resection in a large academic hospital from 2010 to 2020. The data revealed that patients who developed anastomotic leakage had a higher visceral fat content and a narrower abdominal structure, despite body mass index matching.

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INTRODUCTION

Compelling evidence demonstrates that total mesorectal resection (TME) successfully reduces the local recurrence rate of rectal cancer and is the gold standard for managing mid- and low-lying rectal cancer [1-3]. However, the morbidity of anastomotic leakage (AL), a worrisome complication of TME, is on the rise[4]. Once AL develops, it often requires reintervention and can lead to perioperative death and adverse oncology outcomes[5-7]. Early identification of patients at high risk of AL is critical to AL prevention and reduction of the reoperation rate, and will guide intraoperative decisions (for instance on whether to choose a diverting ileostomy or not) and improve perioperative management.

Numerous studies have explored the risk factors associated with AL in rectal cancer patients who underwent anterior resection[8,9]. However, there is no effective approach for predicting AL, implying that potential predictors should be identified. Recent studies show that some abdominal composition related factors are key contributors to AL in patients with colorectal cancer after undergoing surgery [10]. Theoretically, a less visceral fat content and a bigger abdominal volume are more favorable for surgeons to perform anterior resection procedure and thus leads to less technical difficulty, shorter operation time, and lower probability of AL[11]. Computed tomography (CT) images have been employed to assess the possible effects of abdominal composition related parameters, including visceral fat area (VFA) and skeletal muscle index (SMI), on patient surgical outcome[10,12-15]. Large VFA, for instance, is potentially effective in predicting AL in patients with colorectal cancer who received anterior resection despite reports to the contrary[9]. Additionally, SMI, measured by a CT scan of the lower margin of the third lumbar spine, is a reliable indicator of the systemic nutritional status and is associated with perioperative complications[16]. Additional indicators, including abdominal circumference (AC), anterior to posterior diameter of abdominal cavity (APD), and transverse diameter of abdominal cavity (TD), are suggested to exert potential effects on perioperative complications but their roles in AL is unknown.

Considering the impact of abdominal composition on the surgeons and patients, it was hypothesized that the abdominal composition of rectal cancer patients who developed AL after anterior resection may be different from that of individuals with similar body mass index (BMI) who did not develop AL. Here, we compared the abdominal composition between AL patients and sex- and BMI-matched controls.

MATERIALS AND METHODS

Patients

A total of 2238 medical records of rectal cancer patients who underwent anterior resection at our center from January 1, 2010 to January 1, 2020 were reviewed. Of note, 173 patients were excluded due to non-primary rectal adenocarcinoma (n = 32) and missing clinical data (n = 141). All patients underwent a 90-d follow-up. Of the 2065 subjects, 107 (5.18%) developed clinical AL (*i.e.*, grades B and C). Among the AL patients, 29 were excluded for missing CT images, and the remaining 78 were included in the final analysis and defined as the AL group. The control group was matched 1:1 for the same sex and BMI (± 1 kg/m^2) from patients who did not develop AL. A flowchart of this study is shown in Figure 1.

Definition and variables

In this study, rectal cancer was defined as a tumor located between the dentate line and sacral promontory. AL refers to clinical AL, including grade B and grade C, defined as disruption and defect in intestinal wall integrity at the anastomosis site, making the internal and external compartments communicate with each other[17]. AL diagnosis is contingent on the fecal fluid from pelvic draining or water-soluble contrast agent enema and extra-rectal imaging. Alternatively, when AL was suspected, perianastomotic abscess or effusion detected by CT was examined to diagnose AL. Because water-soluble contrast agent enema is not performed routinely at our center, AL of grade A was not included. The clinical variables gender, age, height, weight, BMI, ASA score, previous abdominal history, hypertension, diabetes, cigarette smoking, alcohol use, tumorous obstruction, preoperative cleansing enema, preoperative antibiotic use, distance between tumor and anal margin, neoadjuvant, preoperative hemoglobin, preoperative albumin, type of operation, tumor size, clinical tumor stage, operation time, number of linear stapler firings, indwelling pelvic drainage tube, indwelling trans-anal tube, and stoma were also considered. Abdominal composition-related parameters assessed included BMI, AC, subcutaneous fat area (SFA), subcutaneous fat thickness (SFT), skeletal muscle area (SMA), SMI, VFA, APD, and TD.

Assessment of abdominal composition associated parameters

Data of BMI and AC were acquired from medical records, whereas other indicators were examined at the lower margin of the third lumbar (L3) plane of the unenhanced CT image using Slice-O-Matic software (version 5.0; Tomovision, Montreal, Canada). CT images were saved in DICOM (Medical Digital Imaging and Communication) format and retrieved from the institutional database. SFA, SMA, and VFA were measured by setting Hounsfield Unit (HU) thresholds (SFA: -190 to -30, SMA: -29 to 150 and VFA: -150 to -20)[18]. SFT refers to the vertical distance from the linear alba to the skin. SMI was calculated as SMA/hight^2 (cm^2/m^2)[19,20]. APD refers to the vertical distance from the linear alba to the anterior edge of the L3 spine. TD refers to the transverse diameter of the abdominal cavity through the anterior edge of the L3 spine.

Statistical analysis

Continuous variables are presented as the mean and standard deviation (SD), whereas categorical variables are presented as numerical values (percentages). Student's t-test and chi-square test were used to compare continuous variables and categorical variables, respectively. A P value of < 0.05 denoted statistical significance. All statistical analyses were performed using IBM SPSS 24.0 (SPSS for Windows, IBM Corporation, Armonk, NY, United States).

Feature importance analysis

Feature importance analysis is an artificial intelligence method used for examining the importance of each included feature. This approach is based on some ensemble learning algorithms, such as random forest and XGboost. In this study, we used the random forest analysis to calculate the importance of each abdominal composition related parameter. Random forest is an ensemble classifier based on a combination of multiple decision trees which are generated through sampling from the original data set and the final predictions are voted by integrating all the trees. Mean decrease accuracy was calculated by randomly permuting a variable to reassess the predictions. If a variable is important, the mean decrease accuracy will show a large change. Therefore, the random forest algorithm could compute the importance of each included variable. This procedure was conducted using Scikit-learn package (version 0.24.1) in Python 3.8.5.

RESULTS

Demographic and clinical characteristics

A total of 156 patients were included in the final analysis. Table 1 shows the comparison of the clinical characteristics between the AL group and the control group. Compared to the controls, the patients in

Table 1 Comparison of demographic and clinicopathologic characteristics in patients with anastomotic leakage and controls, *n* (%)

Variable	Controls (*n* = 78)	AL patients (*n* = 78)	*P* value
Male sex	57 (71.3)	57 (71.3)	1.000
Age, mean (SD), yr	58.23 (9.46)	56.82 (10.54)	0.380
Height, mean (SD), cm	166.23 (7.92)	166.87 (7.34)	0.601
Weight, mean (SD), kg	63.41 (11.62)	65.40 (11.39)	0.282
Operative time, mean (SD), min	207.17 (40.80)	225.03 (55.29)	0.023
Laparoscopic surgery	77 (98.7)	76 (97.4)	1.000
Location of tumor, mean (SD), cm	7.86 (3.39)	8.22 (3.59)	0.507
Intraperitoneal chemotherapy	50 (64.1)	54 (69.2)	0.497
Cleansing enema	57 (73.1)	60 (76.9)	0.579
Indwelling trans-anal tube	73 (93.6)	68 (87.2)	0.174
Indwelling drainage tube	72 (92.3)	74 (94.9)	0.746
Tumorous obstruction	1 (1.3)	6 (7.7)	0.053
Cigarette smoking	24 (30.8)	35 (44.9)	0.098
Alcohol use	14 (17.9)	21 (26.9)	0.249
Hypertension	20 (25.6)	19 (24.4)	1.000
Diabetes	10 (12.8)	11 (14.1)	1.000
Previous abdominal surgery	11 (14.1)	5 (6.4)	0.186
Preoperative antibiotics	75 (76.2)	72 (92.3)	0.303
Hemoglobin, mean (SD), g/L	132.60 (16.31)	123.32 (21.17)	0.003
Albumin, mean (SD), g/L	40.52 (3.97)	38.34 (4.01)	0.001
Neoadjuvant therapy	1 (1.3)	3 (3.8)	0.620
Tumor size, mean (SD), cm	2.76 (1.28)	4.07 (1.36)	< 0.001
ASA score			0.049
1	17 (21.86)	9 (11.5)	
2	56 (71.8)	56 (71.8)	
3	5 (6.4)	13 (16.7)	
Stage			< 0.001
1	67 (85.9)	19 (24.4)	
2	5 (6.4)	33 (42.3)	
3	6 (7.7)	26 (33.3)	
Number of linear stapler firings			0.393
1	38(48.7)	37 (47.4)	
2	39 (50.0)	37 (47.4)	
3	1 (1.3)	4 (5.1)	
Stoma	20 (25.6)	18 (23.1)	0.852

SD: Standard deviation; ASA: American Society of Anesthesiologists; AL: Anastomotic leakage.

the AL group had longer operative time (225.03 ± 55.29 *vs* 207.17 ± 40.80, $P = 0.023$). Patients in the AL group exhibited lower levels of preoperative hemoglobin (123.32 *vs* 132.60, $P = 0.003$) and albumin (38.34 *vs* 40.52, $P = 0.001$), larger tumor size (4.07 *vs* 2.76, $P < 0.001$), and later cancer stage ($P < 0.001$) compared to the controls. The ASA score had a marginal effect ($P = 0.049$). No statistical difference was found between the AL group and the control group for other features.

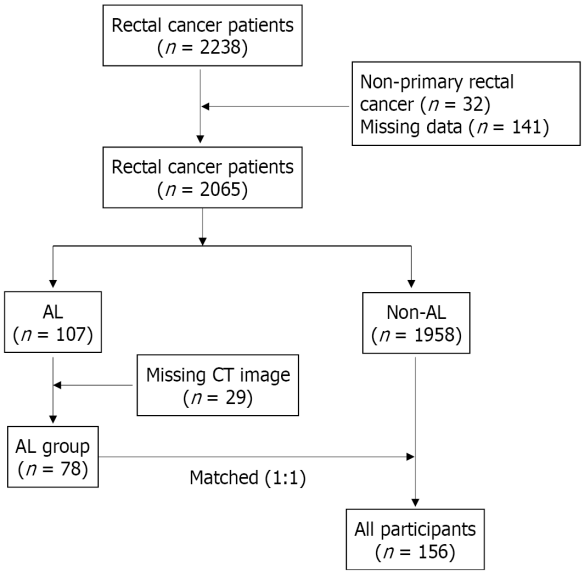

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Figure 1 Flow chart of patient inclusion and exclusion.

Comparison of abdominal composition related parameters

Table 2 shows the difference in abdominal composition related parameters between the AL group and the control group. Patients in the AL group had a larger VFA (125.68 *vs* 97.03, $P = 0.008$), a smaller APD (77.30 *vs* 92.09, $P < 0.001$), and a smaller TD (22.90 *vs* 24.21, $P = 0.002$) compared to those in the control group. These results are intriguing and suggest a potential contribution of a narrower abdominal cavity to AL development. Differences in other indicators were not statistically significant. A radar plot demonstrated the comparison of these indicators between the AL group and the control group (Figure 2).

Feature importance analysis

Although determination of statistical significance of abdominal composition-related indicators can be used to prove correlations, it is not sufficient. Feature importance analysis was conducted to quantify the contribution of each abdominal composition related indicator in AL development. Results demonstrated that TD, APD, and VFA were the three most important features (Figure 3). Additionally, we performed univariate and multivariate logistic regression analyses to investigate whether the VFA, APD, and TD were independent risk factors for AL. The data indicated that the VFA, APD, and TD were independent risk factors ($P < 0.05$) (Supplementary Table 1).

DISCUSSION

The mechanism underlying AL occurrence involves several factors. The present work compared the clinical characteristics and abdominal composition in rectal cancer patients who received anterior resection and developed AL to controls who were matched for sex and BMI. This study was conducted in a large academic hospital in which more than 4000 gastrointestinal operations were performed annually. Analysis revealed a 5.18% incidence of clinical AL, which concur with previous reports[21-23]. In this study cohort, when comparison was conducted in clinical characteristics, lower levels of preoperative hemoglobin and albumin, longer operative time, larger tumor size, and later cancer stage were associated with AL. In addition, when comparing abdominal composition related parameters, it is interesting to find that a higher visceral fat content and a narrower abdominal structure were associated with AL. This work provides evidence that the occurrence of AL is not only associated with patient related factors, but also with the underlying factors that may affect surgical technique.

Related studies have demonstrated that BMI, an easily available and most commonly used index of obesity, is a risk factor for AL in rectal cancer patients who received anterior resection. However, other studies have reported contrary reports[24,25]. Considering that BMI cannot distinguish between the content and distribution of fat and skeletal muscle, it is imperative to explore whether fat and skeletal muscle content or distribution potentially impacts the development of AL. Verduin *et al*[9] investigated the role of VFA on AL in 2370 colon cancer patients and the results implicated VFA as an independent risk factor for AL in the elective colon resection patients (odds ratio = 1.026, $P = 0.035$). Elsewhere, a study employed CT images to quantify the fat distribution and proposed the association of high adipose

Table 2 Comparison of abdominal parameters in patients with anastomotic leakage and controls

Variables	Controls (*n* = 78)	AL patients (*n* = 78)	*P* value
BMI (SD), kg/m^2	23.05 (3.05)	23.17 (2.88)	0.797
AC, mean (SD), cm	87.00 (10.94)	89.71 (14.20)	0.120
SFA, mean (SD), cm^2	108.72 (54.12)	113.72 (55.87)	0.571
SFT, mean (SD), mm	18.68 (8.20)	18.03 (7.31)	0.601
SMA, mean (SD), cm^2	127.89 (29.57)	132.06 (33.40)	0.410
SMI, mean (SD), cm^2/m^2	46.00 (8.81)	47.10 (10.57)	0.482
VFA, mean (SD), cm^2	97.03 (57.66)	125.68 (73.59)	0.008
APD, mean (SD), mm	92.09 (26.40)	77.30 (23.23)	< 0.001
TD, mean (SD), cm	24.21 (2.90)	22.90 (2.23)	0.002

BMI: Body mass index; SD: Standard deviation; AC: Abdominal circumference; SFA: Subcutaneous fat area; SFT: Subcutaneous fat thickness; SMA: Skeletal muscle area; SMI: Skeletal muscle index (SMA/height^2); VFA: Visceral fat area; APD: Anterior to posterior diameter of abdominal cavity; TD: Transverse diameter of abdominal cavity; AL: Anastomotic leakage.

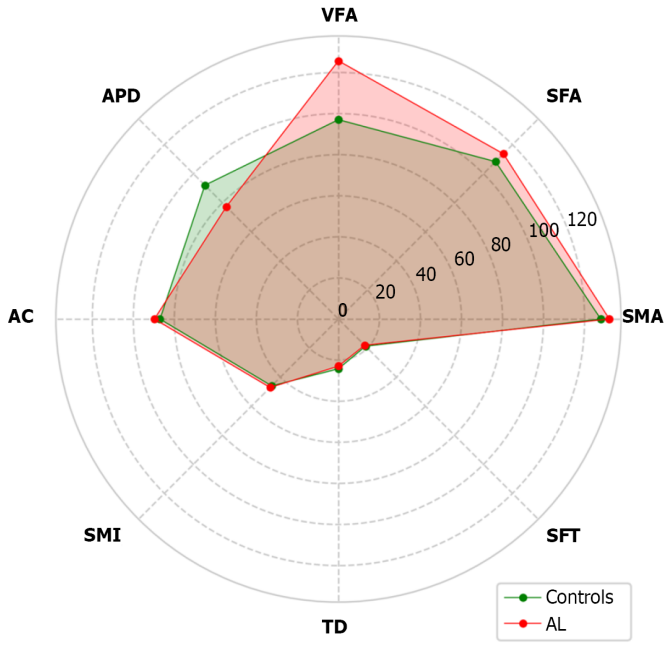

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Figure 2 Radar plot for comparison of abdominal composition related parameters between the anastomotic leakage group and the control group. AC: Abdominal circumference; SFA: Subcutaneous fat area; SFT: Subcutaneous fat thickness; SMA: Skeletal muscle area; SMI: Skeletal muscle index (SMA/height^2); VFA: Visceral fat area; APD: Anterior to posterior diameter of abdominal cavity; TD: Transverse diameter of abdominal cavity; AL: Anastomotic leakage.

tissue with higher risk AL in rectal cancer patients[26]. However, whether VFA and other abdominal composition parameters potentially influence the occurrence of AL in patients with a similar BMI remains to be further evaluated. In addition, owing to the narrow pelvic structure, the male sex is widely accepted as an independent risk factor for AL in rectal cancer patients who received anterior resection, and some evidence has demonstrated the role of pelvic related parameters on AL[27]. Theoretically, a narrow pelvic structure is associated with the increased difficulty of the operation and prolonged operation time. All these features may increase the risk of AL. However, whether a narrow abdominal structure plays a similar role in AL occurrence is not known.

By comparing the differences in abdominal composition between AL and non-AL patients through sex and BMI matching, we found a higher VFA (125.68 *vs* 97.03, P = 0.008) and smaller narrow abdominal cavity structure (APD, 77.30 *vs* 92.09, P < 0.001; TD, 22.90 *vs* 24.21, P = 0.002) in AL patients than in the controls. The differences in skeletal muscle-related parameters, including SMA and SMI,

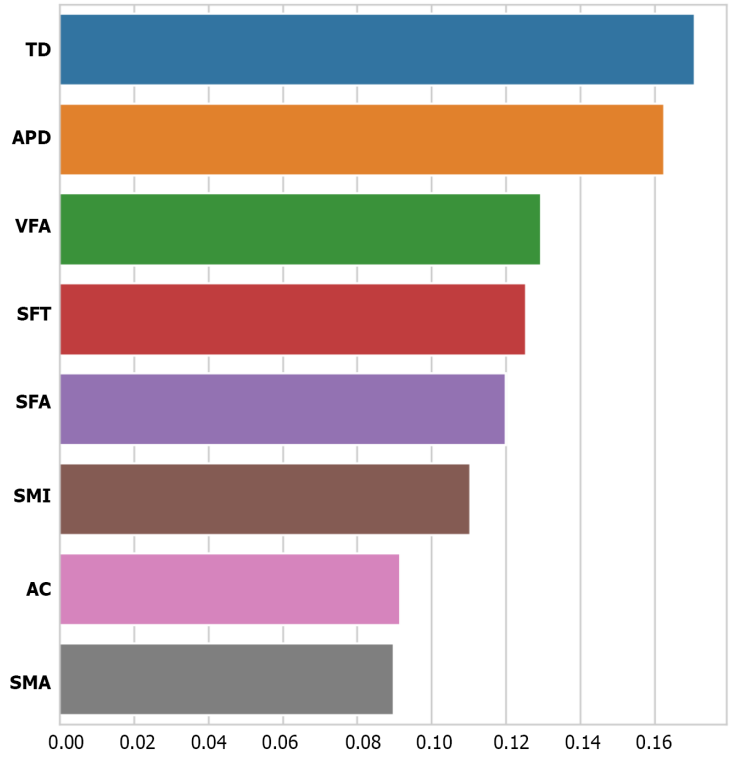

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Figure 3 Importance of each feature in the development of anastomotic leakage. AC: Abdominal circumference; SFA: Subcutaneous fat area; SFT: Subcutaneous fat thickness; SMA: Skeletal muscle area; SMI: Skeletal muscle index (SMA/height^2); VFA: Visceral fat area; APD: Anterior to posterior diameter of abdominal cavity; TD: Transverse diameter of abdominal cavity; AL: Anastomotic leakage.

were not significant, which may be ascribed to the unbalanced matching of other variables between the AL patients and controls, because various variables are associated with muscle content and density. This study provides support to the hypothesis that even with a similar BMI, AL patients are characterized by a higher VFA and a narrower abdominal structure.

This study has several limitations. First, as a single-center case-matched study, selection bias cannot be completely ignored. Second, although standard and strict screening and matching criteria were employed, the large initial sample size and the small sample size for analysis may imply that the research results need to be further validated on a larger cohort. Third, some variables impacting abdominal composition were not collected, including whether subjects are athletes, metabolic syndrome, *etc*. Lastly, this study was performed based on abdominal CT images, and as such, some indicators such as muscle density and intermuscular fat could not be evaluated in detail. Given the retrospective nature of this study and the small sample size, future longitudinal investigations with large samples are advocated to provide reliable data to determine causality for the correlation of abdominal components and AL.

CONCLUSION

The present analysis demonstrates the difference in abdominal components between AL patients and controls matched for sex and BMI. The contribution of each indicator to the development of AL was demonstrated. Intriguingly, in addition to the differences in VFA, the negative effects of APD and TD on AL were observed. This study adds considerable value to the field of AL preoperative risk assessment in rectal cancer patients. VFA, APD, and TD are potential indicators for predicting the risk of AL and can guide surgical decision-making (for example, performing a temporary ileostomy for high-risk patients).

ARTICLE HIGHLIGHTS

Research background

Compelling evidence demonstrates the relationship of abdominal composition and postoperative complications. Anastomotic leakage (AL) is a fatal complication in patients with rectal cancer who have

received anterior resection. However, the roles of abdominal composition on AL have not been studied.

Research motivation

To study the characteristics of abdominal components in patients who received rectal cancer surgery and developed AL.

Research objectives

To add risk factors for AL prediction in rectal cancer patients undergoing anterior resection for guiding surgical decision-making, *e.g.*, performing a temporary ileostomy or not.

Research methods

A retrospective case-matched cohort study was conducted. The abdominal composition was quantified based on computed tomography images by setting Hounsfield Unit thresholds. The abdominal composition related parameters were compared and the importance of these indicators was quantified using feature importance analysis.

Research results

A total of 156 cases were included in this study. Comparing the abdominal composition related parameters demonstrated that patients who developed AL exhibited a larger visceral fat area (VFA, 125.68 ± 73.59 *vs* 97.03 ± 57.66, $P = 0.008$) and a smaller anterior to posterior diameter of abdominal cavity (APD, 77.30 ± 23.23 *vs* 92.09 ± 26.40, $P < 0.001$) and transverse diameter of abdominal cavity (TD, 22.90 ± 2.23 *vs* 24.21 ± 2.90, $P = 0.002$). Feature importance analysis revealed TD, APD, and VFA to be the three most important abdominal composition related parameters.

Research conclusions

Rectal cancer patients who have a higher visceral fat content and a narrower abdominal structure might be at a higher risk of developing AL.

Research perspectives

A narrow abdominal structure is associated with the increased difficulty of the operation and prolonged operation time. In addition, the association of abdominal composition related parameters and postoperative complications was reported. But, whether abdominal composition is associated with AL is not known.

FOOTNOTES

Author contributions: Liu L and Shao SL contributed to conceptualization and design of the study; Shao SL and Li YK contributed to acquisition of the data; Li YK, Shao SL, and Qin JC contributed to methodology; Liu L, Li YK, and Shao SL contributed to formal analysis; Liu L contributed to software; Qin JC contributed to supervision; Shao SL and Liu L contributed to manuscript writing, review, and editing; all authors contributed to final approval of the version of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Local Ethical Committee of Tongji Hospital of Huazhong University of Science and Technology (Approval No. TJ-IRB20210719).

Informed consent statement: The patients' consent was waived due to the retrospective nature of the study.

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

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ORIGINAL ARTICLE

Retrospective Study

Recombinant human thrombopoietin treatment in patients with chronic liver disease-related thrombocytopenia undergoing invasive procedures: A retrospective study

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Abstract

BACKGROUND

Chronic liver disease (CLD) related thrombocytopenia increases the risk of bleeding and poor prognosis. Many liver disease patients require invasive procedures or surgeries, such as liver biopsy or endoscopic variceal ligation, and most of them have lower platelet counts, which could aggravate the risk of bleeding due to liver dysfunction and coagulation disorders. Unfortunately, there is no defined treatment modality for CLD-induced thrombocytopenia. Recombinant human thrombopoietin (rhTPO) is commonly used to treat primary immune thrombocytopenic purpura and thrombocytopenia caused by solid tumor chemotherapy; however, there are few reports on the use of rhTPO in the treatment of CLD-related thrombocytopenia.

AIM

To evaluate the efficacy of rhTPO in the treatment of patients with CLD-associated thrombocytopenia undergoing invasive procedures.

METHODS

All analyses were based on the retrospective collection of clinical data of patients with CLD who were treated in the Department of Infectious Diseases at The First Affiliated Hospital of Soochow University between June 2020 and December 2021. Fifty-nine male and 41 female patients with liver disease were enrolled in this study to assess the changes in platelet counts and parameters before and after the use of rhTPO for thrombocytopenia. Adverse events related to treatment, such as bleeding, thrombosis, and disseminated intravascular coagulation, were also investigated.

RESULTS

Among the enrolled patients, 78 (78%) showed a platelet count increase after rhTPO use, while 22 (22%) showed no significant change in platelet count. The mean platelet count after rhTPO treatment in all patients was 101.53 ± 81.81 × 10^9/L, which was significantly improved compared to that at baseline (42.88 ± 16.72 × 10^9/L), and this difference was statistically significant (P < 0.001). In addition, patients were further divided into three subgroups according to their baseline platelet counts (< 30 × 10^9/L, 30-50 × 10^9/L, > 50 × 10^9/L). Subgroup analyses showed that the median platelet counts after treatment were significantly higher (P < 0.001, all). Ninety (90%) patients did not require platelet transfusion partially due to an increase in platelet count after treatment with rhTPO. No serious adverse events related to rhTPO treatment were observed. Overall, rhTPO demonstrated good clinical efficacy for treating CLD-associated thrombocytopenia.

CONCLUSION

rhTPO can improve platelet count, reduce the risk of bleeding, and decrease the platelet transfusion rate, which may promote the safety of invasive procedures and improve overall survival of patients with CLD.

Key Words: Recombinant human thrombopoietin; Invasive procedures; Chronic liver disease; Liver cirrhosis; Thrombocytopenia; Platelet transfusion

Core Tip: Recombinant human thrombopoietin (rhTPO), commonly used to treat primary immune thrombocytopenic purpura and thrombocytopenia caused by solid tumor chemotherapy, has not been extensively investigated in the treatment of chronic liver disease (CLD)-related thrombocytopenia, where there is an increased risk of bleeding and a poor prognosis, especially in patients undergoing invasive procedures or surgery. Our retrospective study evaluates the efficacy of rhTPO in the treatment of patients with CLD-associated thrombocytopenia undergoing invasive procedures. Overall, rhTPO demonstrated good clinical efficacy by improving platelet count, reducing bleeding risk and decreasing the platelet transfusion rate, which can promote the probability of tolerance to receive invasive management and improve overall survival of patients with CLD.

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INTRODUCTION

A platelet count of < 150 × 10^9/L in circulation is defined as thrombocytopenia[1]. The major causes of thrombocytopenia include hematological diseases, bone marrow suppression after chemotherapy for malignant tumors, drug-induced thrombocytopenia, and chronic liver disease (CLD). The incidence rate of thrombocytopenia caused by CLD varies in different studies, with the average morbidity ranging from 6%-78%[2]. As CLD progresses, the degree of thrombocytopenia worsens. Patients with end-stage liver disease often experience serious complications. An extremely low platelet count aggravates the risk of bleeding and has a poor prognosis[3]. Many patients with CLD require invasive procedures or surgeries, such as liver biopsy, endoscopic variceal ligation, endoscopic injection sclerotherapy and transjugular intrahepatic portosystemic shunt for varices, splenectomy for hypersplenism, hepatectomy for liver cancer, and non-liver surgery. The risk of bleeding during invasive procedures in patients with CLD is associated with platelet count, coagulopathy status, and the type of procedure. An increased risk of bleeding with invasive procedures has been reported in patients with CLD[3], and there is no defined treatment modality for CLD-induced thrombocytopenia. Re-combinant human thrombopoietin (rhTPO) is commonly used to treat primary immune thrombocytopenic purpura (ITP) and thrombocytopenia caused by solid tumor chemotherapy; however, there are few reports on the use of rhTPO in the treatment of CLD-related thrombocytopenia. We aimed to analyze the efficacy of rhTPO for the treatment of CLD-related thrombocytopenia to provide a reference for clinical treatment.

MATERIALS AND METHODS

Inclusion and exclusion criteria

Clinical data of 100 patients with CLD treated in the Department of Infectious Diseases at The First Affiliated Hospital of Soochow University between June 2020 and December 2021 were retrospectively collected. The inclusion and exclusion criteria were based on consensus and guidelines[4,5] for the diagnosis and treatment of chronic viral hepatitis, alcoholic liver disease, autoimmune hepatitis, cirrhosis, and hepatocellular carcinoma. The inclusion criteria were as follows: (1) Patients over 18 years of age with CLD, cirrhosis, or liver cancer caused by different factors; (2) Platelet count < 50×10^9/L or requiring increase based on clinical judgment; and (3) an rhTPO dose of 300 U/kg per day with a medication duration of at least five days. The exclusion criteria were as follows: (1) Thrombocytopenia caused by platelet inhibitors, linezolid, chloramphenicol, vancomycin, sulfonamides, fluoroquinolones, or other drugs; (2) Thrombocytopenia caused by tumor chemotherapy; (3) Thrombocytopenia caused by severe infection; (4) Thrombocytopenia caused by hematological diseases; (5) Tseudothrombocytopenia and idiopathic thrombocytopenia, such as when blood samples are collected in ethylenediaminetetraacetic acid tubes; and (6) Thrombotic disease in the past six months, including pulmonary embolism, portal vein thrombosis, and deep venous thrombosis. The study was reviewed by the ethics committee of The First Affiliated Hospital of Soochow University, and ethical approval was obtained (2020 Ethics Approval No. 216).

Data collection

Clinical data were collected retrospectively, including sex; age; etiology of liver diseases; routine blood tests, such as hemoglobin levels, platelet (PLT) count, platelet crit (PCT), platelet volume (MPV), and platelet distribution width (PDW); routine biochemical tests such as for total bilirubin (TBIL), serum albumin; routine blood coagulation tests, such as prothrombin time (PT), fibrinogen; other indicators, such as changes in vital signs during treatment; complications such as hepatic encephalopathy and ascites; and platelet transfusion rate. Adverse events related to treatment such as bleeding, thrombosis, and disseminated intravascular coagulation were also collected. All patients underwent Child-Pugh scoring according to laboratory examination results, imaging data, and clinical manifestations. We also performed subgroup analyses according to different baseline platelet levels, Child-Pugh grades, and medication duration.

Statistical methods

All data were analyzed using SPSS version 25.0. Normally distributed data are expressed as mean ± SD. Non-normally distributed data are expressed as median and quartile ranges. To compare measurement data between two groups, the *t*-test or Wilcoxon rank sum test was used depending on whether data conformed to a normal distribution. The paired *t*-test or Wilcoxon signed rank test was used to compare changes in intra-group variables. Counting data are expressed as frequency and percentage, and the Pearson χ^2 test or Fisher's exact probability test was used for comparison between two groups. Unless otherwise stated, all treatment effect tests were performed at a bilateral significance level of 0.05. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 100 patients were reviewed in this study, including 59 men and 41 women, with a mean age of 58.48 ± 13.90 years. Analysis of the etiology of CLD among the patients were shown in Table 1. Ninety-five patients had already been diagnosed with liver cirrhosis (LC) before enrollment. The mean duration of CLD was 11.54 years. Among the enrolled patients, the mean hemoglobin and serum albumin levels were 93.44g/L and 30.23 g/L, and the median of TBIL, fibrinogen and PT levels were 61 μmol/L, 1.50 g/L and 16.20 s, respectively, suggesting that CLD patients always accompany with liver dysfunction. As for complications related to liver disease, 21 (21%) patients had hepatic encephalopathy and 56 (56%) had ascites. During the treatment period, 90 (90%) patients did not receive PLT transfusions. From baseline to post-treatment, 4 (4%) patients had anorexia and fatigue and 2 (2%) had low-grade fever (temperature < 38 °C). No serious adverse events related to rhTPO treatment, such as infection, bleeding, or thromboembolism were observed (Table 1).

Routine blood test results at baseline and post-treatment (within 10 d after drug withdrawal) were analyzed. PLT count increased significantly after treatment compared with that at baseline (42.88 ± 16.72 *vs* 101.53 ± 81.81 × 10^9/L, Table 2), and PLT count increased on average by 58.65 ± 79.24 × 10^9/L. Among the enrolled patients, 78 (78%) showed PLT count increased after rhTPO, and 22 (22%) showed no significant change in PLT count. The paired sample *t*-test was used to further analyze the data of the two groups. The PLT count and PCT levels increased significantly after treatment ($P < 0.001$, Table 2).

Subgroup analysis was performed based on baseline PLT counts. The overall population was divided into three groups according to the baseline PLT count, with 25 patients with PLT counts < 30×10^9/L in group I, 43 with PLT counts of 30-50 × 10^9/L in group II, and 32 with PLT counts of > 50×10^9/L in

Table 1 Patient baseline characteristics

Characteristic	Count (%)
Male	59 (59.00)
Age	58.48 ± 13.90
Etiology	
Hepatitis B related CLD	38 (38.00)
Hepatitis C related CLD	3 (3.00)
Schistosome related CLD	16 (16.00)
Autoimmune liver disease	14 (14.00)
Alcoholic liver disease	5 (5.00)
Liver tumors	14 (14.00)
Drug induced CLD	2 (2.00)
Liver abscess	1 (1.00)
Chronic liver failure	1 (1.00)
Budd Chiari syndrome	1 (1.00)
CLD of unknown origin	5 (5.00)
Child-Pugh grades	
Grade A (5-6 points)	8 (8.00)
Grade B (7-9 points)	48 (48.00)
Grade C (10-15 points)	44 (44.00)
Different platelet counts ($\times 10^9$/L)	
Group I (< 30)	25 (25.00)
Group II (30-50)	43 (43.00)
Group III (> 50)	32 (32.00)
Medication duration	
Group A (7 d)	31 (31.00)
Group B (8-14 d)	38 (38.00)
Group C (15-21 d)	22 (22.00)
Group D (22-28 d)	9 (9.00)
No platelet transfusion	90 (90.00)
Side effect	
Fever	2 (2.00)
Fatigue and anorexia	4 (4.00)

CLD: Chronic liver disease.

group III. Changes in PLT count and PCT before and after treatment were analyzed (Tables 3 and 4, Figure 1A). Regardless of baseline PLT count, the overall PLT count increased in post-treatment compared to that before treatment, and the difference was statistically significant ($P < 0.05$).

The efficacy of treatment was evaluated according to the different Child-Pugh Grades. The PLT count after rhTPO treatment was higher than that before treatment, regardless of the Child-Pugh grades (Table 5, Figure 1B). The average medication duration of Child-Pugh grade A, B and C patients were 6.75 ± 1.99, 11.81 ± 5.84, and 13.14 ± 6.73 d, respectively. All patients were grouped according to the medication duration, with 31 patients with seven days in group A, 38 patients with 8-14 d in group B, 22 patients with 15-21 d in group C and 9 patients with 22-28 d in group D. The mean treatment duration with rhTPO was 12 d in all enrolled patients. Patients in each group were analyzed at baseline, during treatment, and post-treatment periods (Table 6-9, Figure 1C), focusing on PLT count and treatment-related adverse events. The PLT count of patients with CLD showed an overall upward trend following

Table 2 Changes in routine blood test results of the total population from baseline to post-treatment

	Baseline	Post-treatment	Change	95%CI	*P* value[3]
PLT (× 10^9/L)	42.88 ± 16.72	101.53 ± 81.81	58.65 ± 79.24	42.93, 74.37	< 0.001
PCT (%)	0.05 ± 0.02	0.14 ± 0.10	0.08 ± 0.09[1]	0.06, 0.11	< 0.001
MPV (fL)	11.61 ± 1.48	11.76 ± 1.26	0.14 ± 1.50[2]	-0.27, 0.55	0.498
PDW (%)	16.01 ± 2.55	15.16 ± 3.09	-0.77 ± 3.99[2]	-1.85, 0.32	0.162

[1]Data were analyzed in 58 patients.
[2]This was an analysis of 54 patients.
[3]Paired sample *t*-test.
PLT: Platelet count; PCT: Platelet crit; MPV: Platelet volume; PDW: Platelet distribution width.

Table 3 Comparison of platelet counts at baseline and post-treatment in the different platelet count groups

	Baseline (× 10^9/L)	Post-treatment (× 10^9/L)	Change (× 10^9/L)	*P* value[1]
Group I (*n* = 25)				< 0.001
mean ± SD	21.60 ± 7.22	68.28 ± 57.52	46.68 ± 56.77	
Median	21.00	55.00	35.00	
IQR	16.50-28.00	30.50-82.50	4.50-56.50	
Min, max	6.00, 30.00	7.00, 235.00	-4.00, 214.00	
Group II (*n* = 43)				< 0.001
mean ± SD	41.19 ± 5.81	96.23 ± 80.58	55.05 ± 79.80	
Median	41.00	76.00	35.00	
IQR	35.00-46.00	54.00-133.00	12.00-93.00	
Min, max	31.00, 50.00	9.00, 489.00	-31.00, 448.00	
Group III (*n* = 32)				< 0.001
mean ± SD	61.78 ± 8.28	141.53 ± 86.99	79.75 ± 87.04	
Median	61.00	127.50	70.00	
IQR	55.00-67.00	53.25-214.25	-4.75-146.50	
Min, max	51.00, 86.00	7.00, 307.00	-53.00, 255.00	

[1]Wilcoxon rank sum test.

rhTPO treatment (Figure 2).

DISCUSSION

A common complication of CLD in the blood is thrombocytopenia. The incidence of thrombocytopenia caused by CLD varies across different studies. The average prevalence of thrombocytopenia in CLD is about 6%; however, when the disease progresses to LC, the morbidity can reach 78%[2]. Apart from viral hepatitis, the incidence of alcoholic liver disease and non-alcoholic fatty liver disease are gradually increasing, and immune hepatitis and drug-induced liver dysfunction also account for some cases of CLD. In this study, the mean duration of liver disease in enrolled patients was 11.54 years, and 95% of them had already progressed from CLD to LC. Viral hepatitis is the most common cause of cirrhosis-induced thrombocytopenia. In our study, 41 (41%) cases of CLD with thrombocytopenia were caused by hepatitis B or C viral infection.

CLD-associated thrombocytopenia has complicated mechanisms, and the reduced production, excessive destruction, and abnormal distribution of PLT are all involved. A decrease in thrombopoietin (TPO) levels is the leading cause of thrombocytopenia. TPO is a hematopoietic growth factor that exerts its biological effects by binding to specific c-Mpl receptors on the surface of megakaryocytes and PLT; it

Table 4 Comparison of platelet crit at baseline and post-treatment in the different platelet count groups

	Baseline (%)	Post-treatment (%)	Change (%)	*P* value[1]
Group I (*n* = 25)				0.018[2]
mean ± SD	0.02 ± 0.01	0.08 ± 0.06	0.06 ± 0.05	
Median	0.02	0.08	0.05	
IQR	0.01-0.03	0.02-0.12	0.01-0.10	
Min, max	0.01, 0.03	0.01, 0.18	0.00, 0.15	
Group II (*n* = 43)				< 0.001[3]
mean ± SD	0.05 ± 0.04	0.13 ± 0.09	0.08 ± 0.11	
Median	0.05	0.09	0.05	
IQR	0.04-0.05	0.07-0.16	0.03-0.11	
Min, max	0.03, 0.26	0.01, 0.51	-0.19, 0.46	
Group III (*n* = 32)				< 0.001[4]
mean ± SD	0.07 ± 0.01	0.17 ± 0.09	0.10± 0.10	
Median	0.07	0.17	0.07	
IQR	0.06-0.08	0.09-0.25	0.01-0.18	
Min, max	0.05, 0.09	0.04, 0.36	-0.04, 0.29	

[1]Wilcoxon rank sum test.
[2]Data were analyzed by 8 patients.
[3]PThis was an analysis of 31 patients.
[4]Date were analyzed by 19 patients.

Table 5 Comparison of platelet counts at baseline and post-treatment in patients with different Child-Pugh grades

	Baseline (× 10^9/L)	Post-treatment (× 10^9/L)	Change (× 10^9/L)
Child-Pugh A (*n* = 8)			
mean ± SD	41.75 ± 21.68	53.63 ± 34.13	11.88 ± 33.00
Median	47.00	48.50	3.00
IQR	23.00-55.75	39.25-62.25	-6.00-38.50
Min, max	6.00, 73.00	7.00, 127.00	-34.00, 71.00
Child-Pugh B (*n* = 48)			
mean ± SD	44.08 ± 17.01	105.88 ± 73.34	61.79 ± 69.53
Median	46.50	82.00	50.50
IQR	30.00-55.75	49.25-175.00	5.00-124.75
Min, max	10.00, 80.00	7.00, 266.00	-53.00, 214.00
Child-Pugh C (*n* = 44)			
mean ± SD	42.00 ± 16.36	105.52 ± 94.30	63.52 ± 91.48
Median	40.50	72.50	37.50
IQR	33.25-51.75	47.00-139.75	6.25-104.00
Min, max	9.00, 86.00	15.00, 489.00	-36.00, 448.00

regulates the proliferation, differentiation, and internal replication of megakaryocytes and modulates PLT-specific proteins and circulating PLT concentration[6]. Thus, TPO can stimulate PLT production and increase peripheral blood PLT count. In addition, TPO acts on hematopoietic stem cells to protect and regulate the hematopoietic stem cell pool. It cooperates with erythropoietin, stem cell factor, interleukin-3, and granulocyte colony stimulating factor to promote the proliferation of erythroid and

Table 6 Changes in platelet counts in group A (7 d of treatment)

	Baseline	Day 2	Day 5	Post-treatment	Change
n	31	10	26	31	31
mean ± SD (× 10^9/L)	41.87 ± 17.40	42.90 ± 29.41	42.04 ± 27.39	67.74 ± 62.81	25.87 ± 57.67
Median (× 10^9/L)	45.00	41.50	42.00	54.00	10.00
IQR (× 10^9/L)	33.00-55.00	17.25-54.00	19.75-54.25	28.00-80.00	-7.00-44.00
Min, max (× 10^9/L)	6.00, 73.00	15.00,111.00	9.00, 127.00	7.00, 303.00	-34.00, 244.00

Table 7 Changes in platelet counts in group B (8-14 d of treatment)

	Baseline	Day 2	Day 5	Day 9	Post-treatment	Change
n	38	20	29	26	38	38
mean ± SD (× 10^9/L)	45.42 ± 16.27	46.10 ± 14.34	60.79 ± 33.18	108.19 ± 65.18	133.85 ± 103.23	81.97 ± 90.29
Median (× 10^9/L)	43.00	43.50	55.00	96.00	95.00	55.00
IQR (× 10^9/L)	33.50-55.50	33.75-57.75	37.00-70.00	49.00-166.75	58.00-190.00	21.25-127.25
Min, max (× 10^9/L)	9.00, 80.00	25.00, 71.00	18.00, 170.00	28.00, 261.00	21.00, 489.00	-27.00, 448.00

Table 8 Changes in platelet counts in group C (15-21 d of treatment)

	Baseline	Day 5	Day 9	Day 14	Post-treatment	Change
n	22	17	18	18	22	22
mean ± SD (× 10^9/L)	43.36 ± 19.23	47.47 ± 19.60	69.50 ± 33.25	107.61 ± 65.53	106.32 ± 65.97	62.95 ± 64.96
Median (× 10^9/L)	45.00	51.00	78.50	92.50	90.50	47.50
IQR (× 10^9/L)	27.75-59.25	31.00-54.50	32.50-85.75	55.25-181.25	55.25-148.00	16.5-128.25
Min, max (× 10^9/L)	10.00, 86.00	19.00, 95.00	20.00, 138.00	7.00, 235.00	7.00, 222.00	-53.00, 179.00

Table 9 Changes in platelet counts in group D (22-28 d of treatment)

	Baseline	Day 5	Day 14	Day 24	Post-treatment	Change
n	9	9	7	8	9	9
mean ± SD (× 10^9/L)	35.56 ± 11.72	41.22 ± 17.41	50.29 ± 33.76	83.88 ± 34.87	90.89 ± 71.85	55.33 ± 63.15
Median (× 10^9/L)	34.00	37.00	42.00	84.50	79.00	45.00
IQR (× 10^9/L)	27.50-38.00	33.00-51.50	39.00-45.00	47.75-118.00	36.50-126.50	5.50-93.00
Min, max (× 10^9/L)	25.00, 64.00	16.00, 78.00	18.00, 124.00	42.00, 127.00	29.00, 254.00	-12.00, 190.00

granulocyte progenitor cells and stem cells to enter the proliferation cycle[7,8]. TPO is mainly synthesized in liver parenchymal and sinusoidal cells and also in the bone marrow and kidney[9]. TPO level in peripheral blood decreases with liver malfunction persists, which is particularly manifested in CLD and LC[2,10]. Hypersplenism is another classic cause of thrombocytopenia in patients with LC. The larger the spleen, the more blood cells are retained in the spleen and the more obvious the decrease in blood cell count in peripheral circulation.

In patients with CLD and LC, mild (50-100 × 10^9/L) thrombocytopenia is often not complicated by serious bleeding risk. Treatment may be suspended temporarily without the need for invasive operations or the occurrence of complications, such as esophagogastric varices. Moderate (20-50 × 10^9/L) and severe (< 20 × 10^9/L) thrombocytopenia are independent risk factors for poor prognosis in advanced CLD[11]. Oliver *et al*[12] compared the mortality of patients with CLD undergoing non-liver surgery to that of patients without CLD, and found that the odds of mortality were 1.8–3.3 times higher in patients with CLD [odds ratio of bleeding 2.0 (1.8-2.3)]. Owing to the high risk of bleeding, symptomatic treatment, such as PLT transfusion and the use of TPO analogs and TPO receptor agonists,

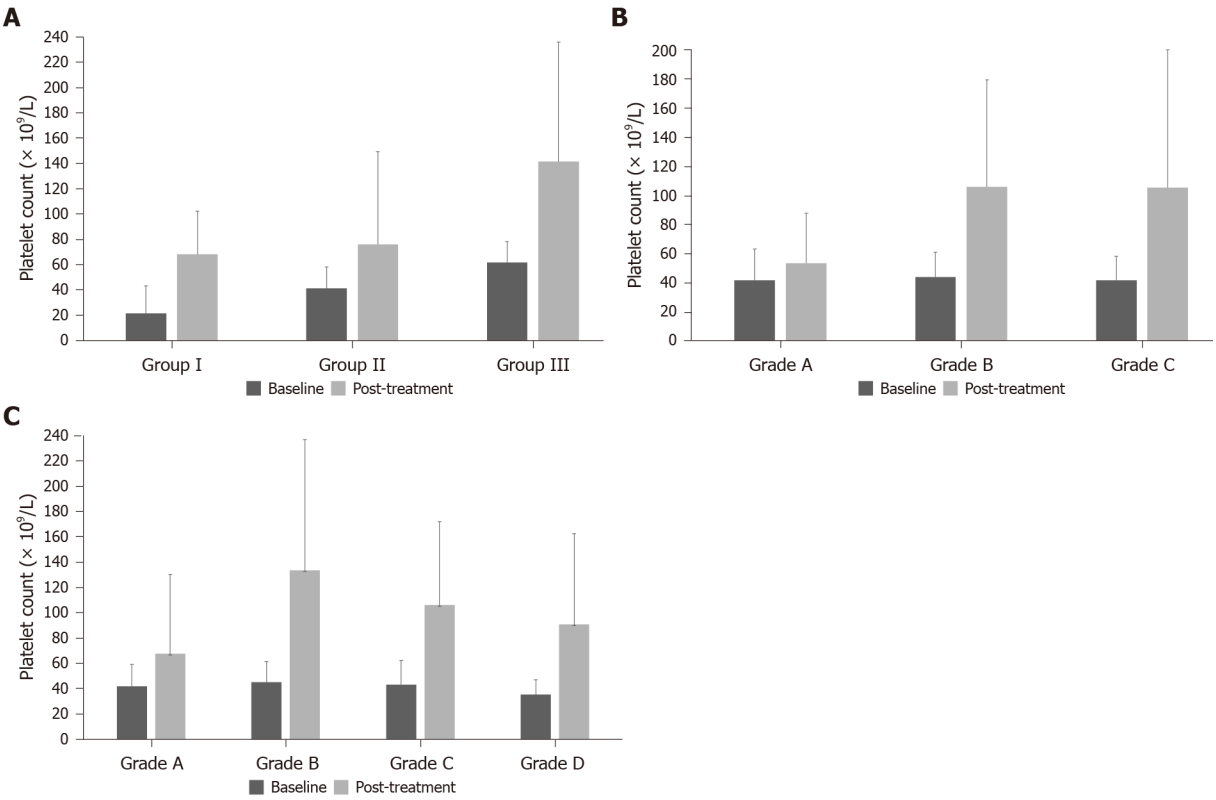

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Figure 1 Platelet count for chronic liver disease-patients treated with recombinant human thrombopoietin. A: Platelet count in different baseline platelet count groups; B: Platelet count in different Child-Pugh grades groups; C: Platelet count in different medication durations groups.

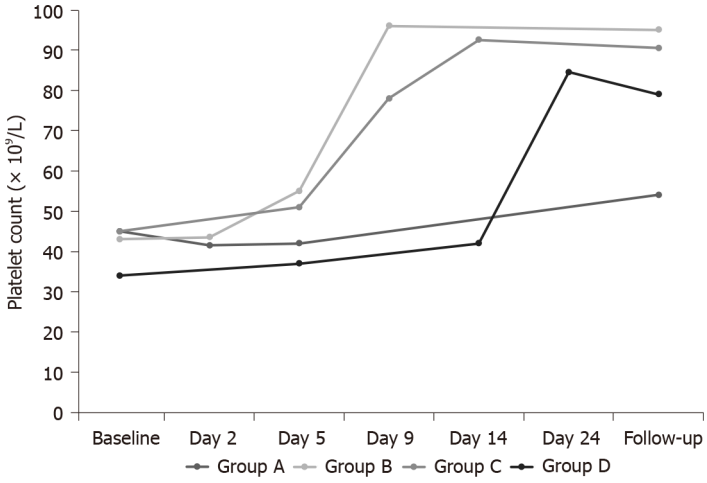

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Figure 2 Variation trend of platelet count with different medication durations.

is often required according to the etiology and changes in the patient's condition. PLT transfusion carries the risk of PLT antibody production, which results in resistance to subsequent PLT transfusion [13]. Moreover, PLT transfusion still has potential risks[14], such as infectious diseases caused by blood transfusion, fever, allergic reactions, and hemolytic reactions. Besides, PLT transfusion has a limited effect on CLD, with PLT counts increasing by approximately 10 × 10^9/L after transfusion[15,16], while PLT transfusion can increase PLT count by 30 × 10^9/L in healthy patients[17]. In this study, 90% patients did not receive PLT transfusion, partially due to an increase in their PLT count after rhTPO treatment. Romiplostim and eltrombopag are widely used TPO receptor agonists. However, owing to the risk of thromboembolic adverse events[18], these drugs are not suitable for patients with CLD. rhTPO is a full-length glycosylated TPO expressed by Chinese hamster ovary cells and purified *via* gene recombination

technology. Because its characteristics are similar to those of endogenous TPO, rhTPO has similar pharmacological effects on PLT levels. The drug was approved for use in China for the treatment of thrombocytopenia caused by chemotherapy for solid tumors and ITP. In our study, rhTPO had a positive effect on CLD associated thrombocytopenia, and no serious adverse effects were observed. The results suggest that rhTPO could improve the platelet count and reduce the risk of bleeding in patients with CLD, also increase the probability of tolerance to receive invasive management, such as liver surgery, liver biopsy, and artificial extracorporeal liver support, to improve clinical benefits in patients. The PLT count increased in 78 patients after treatment with rhTPO, and there was no significant change in the PLT count of 22 patients, including 13 with end-stage LC, six with liver cancer, and three with severe liver dysfunction. Due to the ineffectiveness of rhTPO in these patients, specific mechanisms were speculated: (1) Bone marrow suppression caused by CLD. CLD caused by hepatitis viruses [such as the hepatitis C virus (HCV)] inhibits PLT production in the bone marrow, resulting in thrombocytopenia[2]. In a study by Zhang *et al*[19], the core envelope of HCV was highly homologous with the PLT membrane glycoprotein GPIIIa49-66 and induced thrombocytopenia in the form of molecular modeling, which may be the reason for HCV-related LC associated thrombocytopenia. Recently, a retrospective analysis[20] also showed a significant increase in PLT count after virus elimination in patients with HCV-related CLD or LC. In addition, alcohol inhibits the formation of hematopoietic cells, increases damage, and changes the morphology and function of hematopoietic cells through direct toxicity to the bone marrow and peripheral blood[21]; (2) CLD-induced production of PLT antibodies, such as PLT-associated immunoglobulin G (IgG) antibodies and autoantibodies against PLT membrane proteins. PLT-associated IgG and PLT glycoprotein autoantibody levels are increased in patients with LC[22]. In patients with liver disease, autoantibodies against PLT surface antigens accelerate the consumption of PLTs in the spleen and trigger rapid destruction[23]. Kajihara *et al*[24] found that patients with LC or ITP had similar anti-PLT membrane Glycoprotein IIb IIIa (GP IIb IIIa) antibody responses. The frequency of stimulation of GP IIb IIIa antibody to produce B cells in patients with LC is even higher than that in patients with ITP, suggesting that autoantibody-mediated PLT destruction is partly involved in LC-related thrombocytopenia. Similarly, Wada *et al*[23] found that B cells produced by anti-GP IIb IIIa antibodies may predict the efficacy of TPO agonists in patients with CLD or LC; and (3) thrombocytopenia caused by CLD is complicated by infection. Decreased platelet count produced by megakaryocytes in the bone marrow is the main cause in CLD-related thrombocytopenia[2]. Patients with CLD exhibit impaired immune function and are immunocompromised. Various factors, such as liver dysfunction, intestinal bacterial translocation, and increased portal and systemic shunt, increase the risk of infection[25], especially with tumors and end-stage LC, making patients prone to severe infection and even sepsis. Moreover, infection can promote disease progression and increase mortality in patients with CLD. Bone marrow suppression caused by infectious agents is common in clinics. Sepsis accounts for approximately 50% of all cases of thrombocytopenia in severe patients[26]. In patients with sepsis, the pathogenesis of thrombocytopenia is often related to an imbalance in the host response[27], such as an increase in cytokine levels, enhancement of vascular endothelial cell activity, and serious loss of vascular integrity. PLTs are activated by inflammatory factors and bacterial products, causing a cascade reaction of coagulation and promoting the excessive consumption of PLTs.

Additionally, this study showed that rhTPO significantly improved PLT counts and PCT levels in enrolled patients compared with the values at baseline levels, regardless of the duration of medication or the Child-Pugh grade. PCT level can be used as a parameter to predict advanced fibrosis and cirrhosis. It mainly refers to the percentage of PLT in the peripheral blood volume[28,29]. In this study, PCT levels increased after rhTPO administration compared to those before administration. A possible reason is that PCT can be expressed as the product of PLT count and MPV and increases with PLT count. MPV and PDW reflect PLT size and function, respectively. They can be used as indicators of inflammatory responses *in vivo* and reflect PLT activation. Large PLTs are more likely to produce inflammatory factors and prethrombotic substances, which promote inflammatory reactions and thrombosis in the body. In this study, the differences of MPV and PDW between baseline and post-treatment were not statistically significant, suggesting that rhTPO mainly affected PLT counts and had little effect on MPV and PDW indices.

CONCLUSION

In conclusion, rhTPO was effective in the treatment of CLD-associated thrombocytopenia, with no serious adverse events related to treatment, suggesting good medication safety and providing a new approach for the treatment of CLD-related thrombocytopenia. As such, rhTPO can prevent hemorrhagic events and provide opportunities for safer invasive procedures or other non-liver surgeries, which can improve the overall survival for patients with CLD. Moreover, the administration of rhTPO could reduce the need for PLT transfusion and the risks associated with it[30]. This study has some limitations. Firstly, it was a retrospective study. The sample size was small and limited to one region. The follow-up duration was short; thus, we could not assess the long-term effects. Owing to the generally low PLT count in the enrolled patients, there was a lack of data on the collection of PLT

parameters. In future studies, more comprehensive data are needed, including body mass index, medication history, and long-term follow-up evaluation after treatment, to further prove the efficacy and safety of rhTPO in CLD-related thrombocytopenia.

ARTICLE HIGHLIGHTS

Research background

Thrombocytopenia is a common complication in chronic liver disease (CLD), promoting a high risk of bleeding and a poor prognosis, especially in patients undergoing invasive procedures or surgeries.

Research motivation

Recombinant human thrombopoietin (rhTPO) is commonly used to treat primary immune thrombocytopenic purpura and thrombocytopenia caused by solid tumor chemotherapy, and has not been extensively investigated in the treatment of CLD-related thrombocytopenia.

Research objectives

This study aimed to evaluate the efficacy of rhTPO in the treatment of patients with CLD-associated thrombocytopenia undergoing invasive procedures.

Research methods

This retrospective analysis of clinical data of patients with CLD assessed the changes in platelet counts and parameters before and after the use of rhTPO for thrombocytopenia. Subgroup analysis was performed according to different characteristics, such as baseline platelet count levels. Adverse events related to treatment were investigated.

Research results

Among the enrolled patients, 78 (78%) showed an elevation in platelet count after rhTPO use. The mean platelet count after rhTPO treatment in all patients was 101.53 ± 81.81 × 10^9/L, which was significantly improved compared to that at baseline (42.88 ± 16.72 × 10^9/L), and this difference was statistically significant ($P < 0.001$). Subgroup analysis also showed the same result. Ninety (90%) patients did not require platelet transfusion partially due to an increase in platelet count after treatment with rhTPO.

Research conclusions

rhTPO was effective in the treatment of CLD-associated thrombocytopenia with good medication safety, promoting the safety of invasive procedures and improving overall survival of patients with CLD.

Research perspectives

rhTPO could be a new approach for the treatment of CLD-related thrombocytopenia that will promote clinical benefits in patients with CLD who are undergoing invasive procedures.

FOOTNOTES

Author contributions: All the authors solely contributed to this paper. Ding JN, Feng TT and Zhao WF designed the research study; Ding JN, Feng TT, Sun W, Cai XY, Zhang Y and Zhao WF performed the research; Ding JN, Cai XY and Zhang Y analyzed the data and wrote the manuscript; Feng TT, Sun W and Zhao WF revised the manuscript; all authors have read and approve the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Assessment of tumor markers CA 19-9, CEA, CA 125, and CA 242 for the early diagnosis and prognosis prediction of gallbladder cancer

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Abstract

BACKGROUND

Gallbladder cancer (GBC) is one of the leading and aggressive cancers in this region of India. It is very difficult to diagnose in the early stage, as it lacks typical early signs and symptoms; thus, the diagnosis is often in the advanced stage, which ultimately leads to a poor 5-year survival outcome. Tumor markers including carbohydrate antigen 19-9 (CA 19-9), carcinoembryonic antigen (CEA), CA 125, CA 242, and alpha fetoprotein are used as indicators in the diagnosis and prognosis of GBC.

AIM

To compare tumor marker levels between GBC and benign GB diseases (GBDs) and to assess the combined use of tumor markers to increase the diagnostic accuracy for GBC.

METHODS

Patients of either sex aged ≥ 18 years, with suspected GBC (GB polyp, irregular thick GB wall, GB mass, porcelain GB) on the basis of radiological imaging were included in this study. GB wall thickness using ultrasonography and tumor markers CEA, CA 125, CA 19-9, and CA 242 in all patients were recorded. All cases after surgical intervention were divided into two groups, GBC and benign GBD, according to histopathological examination findings. The cases were

followed up and clinical findings, radiological findings, and levels of tumor markers were assessed.

RESULTS

A total of 200 patients were included in this study, of whom 80 patients had GBC and 120 patients had benign GBD. The median (interquartile range) age was 52.0 (41.0-60.0) years and the majority of patients (132, 66.0%) were women. Tumor markers including CA 19-9, CA 125, CEA, and CA 242 were significantly elevated in patients with GBC ($P < 0.001$). There was a significant reduction in tumor markers at 3 and 6 mo from baseline ($P < 0.001$). The mean survival of patients with normal and elevated levels of tumor markers CA 125, CA 19-9, and CEA was comparable; however lymph node metastasis and CA 242 expression level were independent prognostic factors.

CONCLUSION

Serum levels of tumor markers including CA 19-9, CA 125, CEA, and CA 242 were significantly associated with GBC. However, no significant association was observed between the presence of elevated levels of any tumor marker with respect to survival. Tumor marker assessment during follow-up may represent a treatment response.

Key Words: Benign gallbladder; Tumor markers; Survival; Benign lesions; Sensitivity; Specificity

Core Tip: Gallbladder cancer (GBC) is one of the leading and aggressive cancers, which is often diagnosed in the advanced and metastatic stage as it lacks typical early signs and symptoms. This study assessed the different tumor markers separately and in combination, to determine the diagnostic accuracy of these markers and prognostic significance in GBC. The level of tumor markers was significantly elevated in GBC. There was no association between the presence of elevated levels of any marker and survival; however, it showed response to treatment with a significant reduction in tumor markers at 3 mo and 6 mo.

Citation: Sinha SR, Prakash P, Singh RK, Sinha DK. Assessment of tumor markers CA 19-9, CEA, CA 125, and CA 242 for the early diagnosis and prognosis prediction of gallbladder cancer. *World J Gastrointest Surg* 2022; 14(11): 1272-1284

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INTRODUCTION

Gallbladder cancer (GBC) is one of the leading and most aggressive cancers in the north and north-east region of India. There is a high prevalence of GBC in the northern region of India, especially in women (11.8/100000 population) and the north-east region (17.1/100000 population)[1].

It is very difficult to diagnose GBC in the early stage as it lacks typical clinical early manifestations leading to poor 5-year survival outcomes[2-4]. It is critical to diagnose GBC as early as possible, as most patients present in the advanced stage and thus have a low chance of radical treatment and prolonged survival.

Presently, the diagnosis of GBC mainly depends on radiological imaging such as ultrasonography (USG), computed tomography (CT) scan, magnetic resonance imaging, positron emission tomography scan, and invasive examination such as fine-needle aspiration cytology, core biopsy, and laparoscopy. In spite of these, there is no single tumor marker that can be used to diagnose and prognosticate GBC[5-7].

Tumor markers such as carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA 125), CA 242, and CA 19-9 have been widely used for the diagnosis of various types of cancer. CEA and CA 19-9 have traditionally been used as tumor markers for GBC, although they are not very sensitive. Despite their low sensitivity, it has been found that when these markers are used individually to diagnose GBC, inconsistent results are obtained[8-11]. Currently, only one study from China has reported the combined use of these tumor markers to increase the diagnostic specificity and sensitivity for GBC[12].

The present study compared tumor marker levels between GBC and benign GB diseases (GBDs) and assessed the combined use of tumor markers to increase the diagnostic sensitivity and specificity for GBC.

MATERIALS AND METHODS

This was an observational study conducted at the Department of Biochemistry in collaboration with the Department of General Surgery, Surgical Gastroenterology, and the State Cancer Institute, Indira Gandhi Institute of Medical Sciences, Patna from September 2018 to August 2020. The study was approved by the institutional ethics committee (Vide Letter No. 479/IEC/2018/IGIMS), and the study procedure was in accordance with the principles of the Declaration of Helsinki.

Patients of either sex aged ≥ 18 years and patients with high suspicion of GBC (irregular thick GB wall, GB mass, GB polyp, porcelain GB) on the basis of radiological imaging were included in this study. Patients with a GB mass with surgical obstructive jaundice, disseminated GBC, those already receiving chemotherapy or radiotherapy, and those who presented with synchronous second primary cancer were excluded from the study. A venous blood sample was collected from each patient in the fasting state. The data of all patients regarding age at presentation, weight, body mass index, biochemical parameters such as complete blood count, liver function test, kidney function test, tumor markers CEA, CA 125, CA 19-9, CA 242, and GB wall thickness using USG were recorded. All patients who were included in the study underwent surgical management and the surgical specimen was sent for histopathological examination (HPE). Cancer staging was performed according to the 8th edition of the American Joint Committee on Cancer TNM staging system for GBC (8th ed, 2017). All cases were divided into the GBC group and the benign GBD group according to HPE findings. Patients in the GBC group were evaluated at 3 and 6 mo. During each follow-up, clinical findings, radiological findings, the level of tumor markers, and other laboratory parameters were recorded.

Tumor markers including CA 125, CA 19-9, and CEA were estimated by the chemiluminescence immunoassay principle using the Beckman-Coulter Access 2 Immunoassay System, maintaining all quality control precautions using the Calibrator and Reagent Kit provided by Beckman Coulter with reference range (CA 125, 0-35 U/mL; CA19-9, 0-35 U/mL; CEA, 0-3 ng/mL). Tumor marker CA 242 was estimated with an enzyme-linked immunosorbent assay kit with reference range 0-20 U/mL.

Definition

The survival time for each patient was defined as the interval between the date of definitive resection and the date of last follow-up or death. Disease-free interval was defined as the interval between completion of surgical resection and diagnosis of recurrence.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences software, version 23.0. Qualitative data are presented as numbers and percentages, whereas quantitative data are presented as the mean ± standard deviation or median (range), depending on the normal or skewed distribution of data. The normal distribution of quantitative data was assessed by the Shapiro-Wilk test. The independent sample *t*-test or the Mann-Whitney *U*-test was used for the continuous variables and the chi-square (χ^2) test for the categorical variables. The Cox regression model was used to determine the correlation between mortality and liver function test. Hazards ratios (HRs) and 95% confidence intervals (CIs) were computed. Kaplan-Meier event-free survival was computed and plotted. $P < 0.05$ was considered statistically significant.

RESULTS

Overall characteristics of patients

A total of 200 patients were included in this study, of whom 80 patients had GBC and 120 patients had benign GBD. The median (interquartile range [IQR]) age was 52.0 (41.0-60.0) years and 132 (66.0%) patients were women. The laboratory parameters are summarized in Table 1.

Although, IQR indirect bilirubin was significantly higher in patients with GBC compared to patients with benign GBD (0.6 mg/dL *vs* 0.4 mg/dL; $P = 0.015$), and the median levels of serum glutamic oxaloacetic transaminase (SGOT) ($P = 0.001$) and serum glutamic pyruvic transaminase (SGPT) ($P = 0.012$) were significantly higher in the GBC group than in the benign group, all values were within the normal range in both groups. GB wall thickness on USG was increased by twofold in patients from the GBC group (Table 1). The majority of patients ($n = 71$) had a stone size between 0.5 and 1 cm. In patients with benign GBD, the majority of patients had a stone size in the range of < 0.5-2.0 cm compared to the patients with GBC. However, the majority of patients with GBC had a stone size > 2 cm compared to the patients with benign GBD (Figure 1).

Association of tumor markers with benign GBD and GBC

Tumor markers including CA 19-9, CA 125, CEA, and CA 242 were significantly elevated in patients with GBC ($P < 0.001$). CA 19-9 was elevated in 71.3%, CEA in 64.4%, and CA 242 in 86.3% of patients with GBC (Table 2).

Table 1 Demographic characteristics

Parameters	GBC, *n* = 80	Benign GB disease, *n* = 120	Total, *n* = 200	*P* value
Age, yr (*n* = 200)	57.0 (50.2-66.5)	47.0 (34.0-56.0)	52.0 (41.0-60.0)	< 0.001
Sex (*n* = 200), *n* (%)				0.951
Men	27 (33.8)	41 (34.2)	68 (34.0)	
Women	53 (66.3)	79 (65.8)	132 (66.0)	
BMI in kg/m^2, (mean)	27.06 ± 4.46	26.50 ± 5.6	26.8 ± 4.98	0.229
Hemoglobin in g/dL	11.8 (10.8-12.6)	11.6 (10.2-12.8)	11.75 (10.6-12.70)	0.523
TLC in cells/μL	8075.0 (6759.0-9801.0)	7830.0 (6705.0-8800.0)	7846.0 (6745.0-9440.0)	0.094
Lymphocytes in cells/μL	27.4 (21.2-31.0)	26.9 (22.0-31.0)	27.0 (22.0-31.0)	0.421
Monocytes in cells/mm^3	5.7 (3.4-7.9)	6.0 (4.0-7.0)	6.0 (4.0-7.30)	0.604
Neutrophils in cells/mm^3	63.1 (58.2-69.6)	63.0 (59.0-67.0)	63.0 (58.92-67.77)	0.816
Eosinophils, %	3.0 (1.2-4.0)	3.5 (2.0-4.4)	3.0 (2.0-4.10)	0.023
Basophils in cells/μL	0.5 (0.3-1.0)	0.4 (0.1-1.0)	0.50 (0.20-1.0)	0.351
Bilirubin in mg/dL				
Total	0.9 (0.6-1.2)	0.8 (0.6-1.1)	0.87 (0.64-1.12)	0.251
Direct	0.3 (0.2-0.5)	0.3 (0.2-0.5)	0.30 (0.20-0.52)	0.621
Indirect	0.6 (0.4-0.7)	0.4 (0.3-0.6)	0.50 (0.36-0.65)	0.015
ALP in IU/L	119.5 (80.5-163.2)	109.0 (76.2-136.2)	111.0 (78.0-146.50)	0.019
SGOT in U/L	34.0 (27.2-43.0)	28.0 (24.0-34.0)	31.0 (25.0-36.0)	0.001
SGPT in U/L	27.0 (21.0-36.5)	23.0 (21.0-30.5)	24.0 (21.0-34.0)	0.012
INR	1.1 (1.0-1.1)	1.1 (1.0-1.1)	1.12 (1.10-1.12)	0.158
Serum creatinine in mg/dL	0.8 (0.7-0.9)	0.8 (0.7-0.9)	0.80 (0.68-0.97)	0.459
BUN in mg/dL	12.3 (9.0-14.4)	12.3 (9.9-14.5)	12.30 (5.0-12.0)	0.479
GB wall thickness in mm	12.0 (9.2-15.1)	6.0 (4.0-8.0)	8.0 (5.0-12.0)	< 0.001

Data shown as median (interquartile range), unless otherwise specified. Qualitative data between benign and carcinoma groups were analyzed using Mann-Whitney *U*-test and quantitative data were compared with the χ^2 test. ALP: Alkaline phosphate; BUN: Blood urea nitrogen; INR: International normalized ratio; IQR: Interquartile range; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; TLC: Total leukocyte count; GB: Gallbladder; GBC: Gallbladder cancer.

Association between tumor markers and clinical characteristics

Serum levels of CA 19-9, CA 125, and CA 242 were significantly associated with age ($P < 0.05$). However, there was no significant association of tumor markers with presence of gallstones and sex of the patient (Table 3).

Sensitivity and specificity analyses of tumor markers

The sensitivity of CA 19-9 and CA 242 was comparatively higher than CEA and CA 125 in different stages of GBC (Table 4).

The sensitivity was 3.8% when all four markers exceeded the critical values. These results suggested that diagnosis of GBC based on combined detection of the tumor markers could increase the specificity, but not the sensitivity of diagnosis (Table 5). CA 242 had the highest sensitivity of 86.3%, and CA 125 had the highest specificity of 93.3% for the diagnosis of GBC (Table 6). Receiver operating characteristic curves are shown in Figure 2.

A combination of CA 19-9 and CA 242 had the highest sensitivity of 83.2%, and a combination of ≥ 3 markers had the highest specificity of 100.0% for the diagnosis of GBC (Table 7).

Correlation between tumor markers and lymph node metastasis

Serum CEA, CA 125, CA 19-9, and CA 242 levels in GBC patients with and without lymph node metastasis (LNM) were compared. Serum CA 125, CA 19-9, CEA, and CA 242 levels were comparable between patients with LNM and patients without LNM (Table 8).

Table 2 Association of tumor markers with benign gallbladder disease and gallbladder cancer

All parameters	Benign, *n* = 120	Carcinoma, *n* = 80	*P* value
CA 19-9 in U/mL	3.1 (1.4-19.4)	112.9 (23.3-318.8)	< 0.001
CA 19-9, *n* (%)			
Normal	108 (90.0)	23 (28.7)	< 0.001
Elevated	12 (10.0)	57 (71.3)	
CA 125 in U/mL	8.6 (3.1-15.1)	24.5 (12.0-53.3)	< 0.001
CA 125, *n* (%)			
Normal	112 (93.3)	49 (61.3)	< 0.001
Elevated	8 (6.7)	31 (38.8)	
CEA in μg/L	2.3 (1.2-3.1)	3.1 (1.8-4.5)	< 0.003
CEA, *n* (%)			
Normal	114 (94)	60 (75)	< 0.003
Elevated	6 (5.9)	20 (25)	
CA 242 in U/mL	2.8 (1.5-9.8)	55.5 (32.7-96.5)	< 0.001
CA 242, *n* (%)			
Normal	108 (90.0)	11 (13.7)	< 0.001
Elevated	12 (10.0)	69 (86.3)	

Data shown as median (interquartile range). Qualitative data between benign and carcinoma groups were analyzed using Mann-Whitney *U*-test and quantitative data were compared with the χ^2 test. CA 19-9: Carbohydrate antigen 19-9; CA 125: Carbohydrate antigen 125; CA 242: Carbohydrate antigen 242; CEA: Carcinoembryonic antigen.

Multivariate regression analyses

Multivariate survival analyses using the Cox proportional hazards model showed that LNM and CA 242 expression level were independent prognostic factors (Table 9).

Comparison of tumor markers before and after surgical management of GBC

The CA 19-9 marker showed a significant reduction from baseline at the 3- and 6-mo follow-up (P < 0.001 and P = 0.029, respectively). CA 125 marker levels were also significantly reduced at 3 mo (P = 0.012) and 6 mo (P = 0.011). The CEA marker showed a significant reduction at 3 mo (P = 0.042); however, reduction from baseline at the 6-mo follow-up was insignificant (P = 0.196). CA 242 showed a significant reduction, both at the 3- and 6-mo follow-up (P < 0.001 and P = 0.001, respectively) (Figure 3).

Survival outcomes

The mean survival of patients between normal and elevated levels for CA 125, CA 19-9, and CEA markers were comparable. There was no significant difference in terms of survival in patients with different levels of tumor markers, suggesting no significant association of the elevated levels of any marker and survival (Figure 4). Overall, there were 6 cases of recurrence with a mean disease-free interval of 9.2 mo.

DISCUSSION

This study was conducted in patients with suspected GBC to assess different tumor markers separately and in combination, to determine their diagnostic accuracy and prognosis of GBC. The key findings indicated that the IQR age was 52.0 (41.0-60.0) years and 132 (66.0%) patients were women. Although median levels of SGOT (P = 0.001) and SGPT (P = 0.012) were significantly higher in the GBC group than in the benign GBD group, they were within the normal range in both groups. GB wall thickness was increased twofold in patients with GBC. Tumor markers including CA 19-9, CA 125, CEA, and CA 242 were significantly elevated in patients with GBC (P < 0.001). Serum levels of CA 19-9, CA 125, and CA 242 were significantly associated with age (P < 0.05). The sensitivity of CA 19-9 and CA 242 was comparatively higher than CEA and CA 125 in different stages of GBC. The sensitivity was 3.8% when

Table 3 Association between tumor markers and clinical characteristics

Characteristics	CA 19-9		*P* value	CA 125		*P* value	CEA		*P* value	CA 242		*P* value
	Normal, *n* = 131	Elevated, *n* = 69		Normal, *n* = 161	Elevated, *n* = 39		Normal, *n* = 181	Elevated, *n* = 19		Normal, *n* = 119	Elevated,*n* = 81	
Age, yr	49.0 (39.0-59.0)	55.0 (45.0-63.5)	0.009	50.0 (39.0-59.0)	56.0 (50.0-69.0)	0.001	50.0 (40.0-59.5)	56.0 (45.0-65.0)	0.093	48.0 (34.0-56.0)	56.0 (47.5-64.5)	< 0.001
Sex												
Male	46 (35.1)	22 (31.9)	0.754	51 (31.7)	17 (43.6)	0.112	62 (34.3)	6 (31.6)	> 0.05	41 (34.5)	27 (33.3)	0.881
Female	85 (64.9)	47 (68.1)		110 (68.3)	22 (56.4)		119 (65.7)	13 (68.4)		78 (65.5)	54 (66.7)	
Gallstones												
Absent	12 (9.2)	10 (14.5)	0.181	19 (11.8)	3 (7.7)	0.578	21 (11.6)	1 (5.3)	0.701	7 (5.9)	15 (18.5)	0.010
Present	119 (90.8)	59 (85.5)		142 (88.2)	36 (92.3)		160 (88.4)	18 (94.7)		112 (94.1)	66 (81.5)	

Data shown as *n* (%). Test used: χ^2 test. CA 19-9: Carbohydrate antigen 19-9; CA 125: Carbohydrate antigen 125; CA 242: Carbohydrate antigen 242; CEA: Carcinoembryonic antigen.

all four markers exceeded the critical values. CA 242 had the highest sensitivity of 86.3%, and CA 125 had the highest specificity of 93.3% for the diagnosis of GBC. There was a significant reduction in tumor markers at 3 and 6 mo from baseline ($P < 0.001$).

A total of 200 patients were included in this study, of whom 80 patients had GBC and 120 patients had benign GBD. Tumor markers CEA, CA 19-9, CA 125 and CA 242 have been used for the diagnosis and prognosis of various types of cancer including liver, gastric, colorectal, and pancreatic[9,13]. In this study, the serum levels of tumor markers CA 19-9, CA 125, CEA, and CA 242 were significantly higher in patients with GBC ($P < 0.001$) than in patients with benign GBD. This is in accordance with previous studies where all these tumor markers were evaluated as therapeutic and diagnostic markers[12-15].

In the present study, it was observed that CA 242 had the highest sensitivity of 86.3% and CA 125 had the highest specificity of 93.3% for the diagnosis of GBC. A recent study of 71 patients diagnosed with GBC showed that CA 19-9 had the highest sensitivity of 85% and CA 125 had the highest specificity of 81.8%[16]. A prospective study by Sachan *et al*[17] reported that CA 19-9 had better sensitivity and specificity (52% and 80%, respectively) than CEA (51% and 72%, respectively) for the prediction of tumor burden in patients with GBC. Another study by Wang *et al*[12] reported that CA 19-9 and CA 242 had the highest sensitivity and specificity of 71.7% and 98.7%, respectively. GBC can be detected using serum CA 19-9, which had moderate sensitivity and good specificity[18]. In a meta-analysis by Zhou [18], it was noted that GBC can be detected using serum CA 19-9, which had moderate sensitivity and good specificity. These findings suggest that the sensitivity and specificity of tumor markers were inconsistent when used individually for the diagnosis of GBC; however, better sensitivity was observed when the markers were used in combination[19-21]. In the current study, sensitivity was 3.8% when all four markers exceeded the critical values. This is in accordance with a previous study with a sensitivity of 8.9% and a diagnostic accuracy that was better when CA 19-9, CA 125, and CA 242 were used in combination. These results suggest that the diagnosis of GBC based on combined detection of the tumor

Table 4 Analyses of the sensitivity of tumor markers in different stages of gallbladder cancer

Clinical stages	Patients, *n* = 80	CA 19-9	CEA	CA 125	CA 242
I	15 (18.6)	10 (66.7)	1 (6.7)	5 (33.3)	13 (86.7)
IIA	13 (16.3)	12 (92.3)	1 (7.7)	5 (38.5)	12 (92.3)
IIB	4 (5.0)	4 (100.0)	0	2 (50.0)	4 (100.0)
IIIA	4 (5.0)	4 (100.0)	0	2 (50.0)	4 (100.0)
IIIB	44 (55.0)	27 (61.3)	8 (18.1)	17 (38.6)	36 (81.8)

Data shown as *n* (%). CA 19-9: Carbohydrate antigen 19-9; CA 125: Carbohydrate antigen 125; CA 242: Carbohydrate antigen 242; CEA: Carcinoembryonic antigen.

Table 5 Analyses of different combinations of markers in gallbladder cancer diagnosis

Group	*n*	1 marker	2 markers	3 markers	4 markers
Benign GB disease	120	29 (24.2)	6 (5.0)	1 (0.8)	0
GBC	80	14 (17.5)	27 (33.7)	25 (31.3)	3 (3.8)
Positive likelihood rate		0.5%	4.5%	25%	100%

GB: Gallbladder; GBC: Gallbladder cancer.

Table 6 Performance of markers for predicting gallbladder cancer

Variable	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC (95%CI); *P* value
CA 19-9 (cutoff: 39.21 by ROC)	71.3	90.0	82.6	82.4	0.849 (0.791-0.907); < 0.001
CA 125 (cutoff: 36.00 by ROC)	38.8	93.3	79.5	69.6	0.758 (0.686-0.831); < 0.001
CEA (cutoff: 10.36 by ROC)	12.5	92.5	52.6	61.3	0.623 (0.542-0.703); 0.003
CA 242 (cutoff: 15.10 by ROC)	86.3	90.0	85.2	90.8	0.925 (0.881-0.969); < 0.001

AUC: Area under the curve; CA 19-9: Carbohydrate antigen 19-9; CA 125: Carbohydrate antigen 125; CA 242: Carbohydrate antigen 242; CEA: Carcinoembryonic antigen; NPV: Negative predictive value; PPV: Positive predictive value; ROC: Receiver operating characteristic.

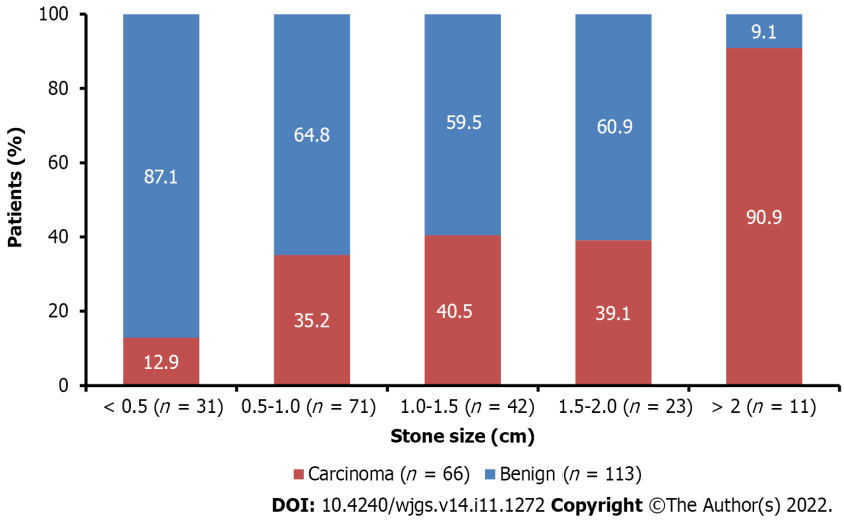

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Figure 1 Stone size between patients with benign gallbladder disease and gall bladder cancer.

Table 7 Performance of combination of markers for predicting gallbladder cancer

Variable	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Combination of any 2 markers	63.5	95.0	84.6	85.7
Combination of markers CA 19-9 and CA 242, n = 26	83.2	93.3	96.2	83.5
Combination of ≥ 3 markers	35.0	100.0	100.0	69.8

Any two markers: CA 19 -9 and CA 242 (n = 26); CA 19-9 and CEA (n = 3); CA 19-9 and CA 125 (n = 2); CEA and CA 242 (n = 7); CA 125 and CA 242 (n = 1). CA 19-9: Carbohydrate antigen 19-9; CA 125: Carbohydrate antigen 125; CA 242: Carbohydrate antigen 242; CEA: Carcinoembryonic antigen; NPV: Negative predictive value; PPV: Positive predictive value.

Table 8 Correlations between carbohydrate antigen 19-9, carcinoembryonic antigen, carbohydrate antigen 125, and carbohydrate antigen 242 expression and lymph node metastasis

Marker level	No LNM, n = 36	LNM, n = 44	P value
CA 19-9 in U/mL	110.5 (54.2- 176.7)	221.8 (14.9-753.0)	< 0.05
CEA in μg/L	3.2 (1.4-4.0)	3.37 (1.9-6.2)	> 0.05
CA 125 in U/mL	23.0 (21.5-47.3)	33.0 (7.4-64.2)	> 0.05
CA 242 in U/mL	48.5 (36.1-84.7)	92.0 (25.8-112.0)	< 0.05

Data shown as median (interquartile range). Test: Independent sample t-test. CA 19-9: Carbohydrate antigen 19-9; CA 125: Carbohydrate antigen 125; CA 242: Carbohydrate antigen 242; CEA: Carcinoembryonic antigen; LNM: Lymph node metastasis.

Table 9 Cox proportional hazards model for multivariate regression analysis

Prognostic factor	Parameter estimate	Wald χ^2	P value	Hazard ratio	95% CI
CA 19-9	0	0.152	0.697	1	0.999-1.001
CEA	-0.137	1.415	0.234	0.872	0.696-1.093
CA 125	0.001	0.211	0.464	1.001	0.995-1.008
CA 242	0.017	10.422	0.001	1.017	1.007-1.027
LNM	-2.06	6.001	0.014	0.127	0.024-0.662
Age	-0.05	2.814	0.093	0.951	0.897-1.009
Sex	-0.264	0.098	0.755	0.768	0.146-4.027
BMI	0.038	0.478	0.489	1.038	0.933-1.155
GB wall thickness	-0.076	2.096	0.148	0.927	0.837-1.027
Stone size	-0.318	2.114	0.146	0.728	0.474-1.117

95%CI: 95% confidence interval; BMI: Body Mass Index; CA 19-9: Carbohydrate antigen 19-9; CA 125: Carbohydrate antigen 125; CA 242: Carbohydrate antigen 242; CEA: Carcinoembryonic antigen; GB: Gallbladder; LNM: Lymph node metastasis.

markers could increase the sensitivity and specificity of the diagnosis.

Serum levels of CA 19-9, CA 125, and CA 242 were significantly associated with age (P < 0.05). However, there was no association of tumor markers with the presence of gallstones and sex of the patient. In accordance with this, a prospective exploratory study conducted at a tertiary care center in Lucknow, did not find any association of CA 242 with tumor stage, presence of jaundice, gallstones and sex of the patient[14].

The difference between mean survival with respect to normal *vs* elevated levels of tumor markers was not significant in this study. These findings may be explained by the inclusion criteria, as in the present study, only early and suspicious cases of GBC were included. In accordance with this, a previous study by Agarwal *et al*[14] explained that CA 19-9 and CA 242 are not recommended as prognostic markers. By contrast, Agarwal *et al*[16] reported the prognostic role of tumor markers in terms of overall survival

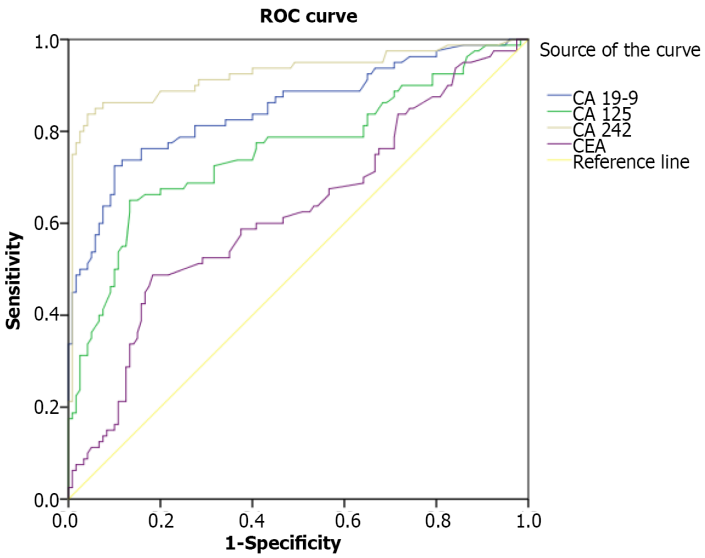

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Figure 2 Receiver operating characteristic curve analysis showing diagnostic performance of carbohydrate antigen 19-9 (U/mL), carbohydrate antigen 125 (U/mL), carcinoembryonic antigen (μg/L), and carbohydrate antigen 242 (U/mL) in predicting gallbladder cancer *vs* benign gallbladder disease. ROC: Receiver operating characteristic curve.

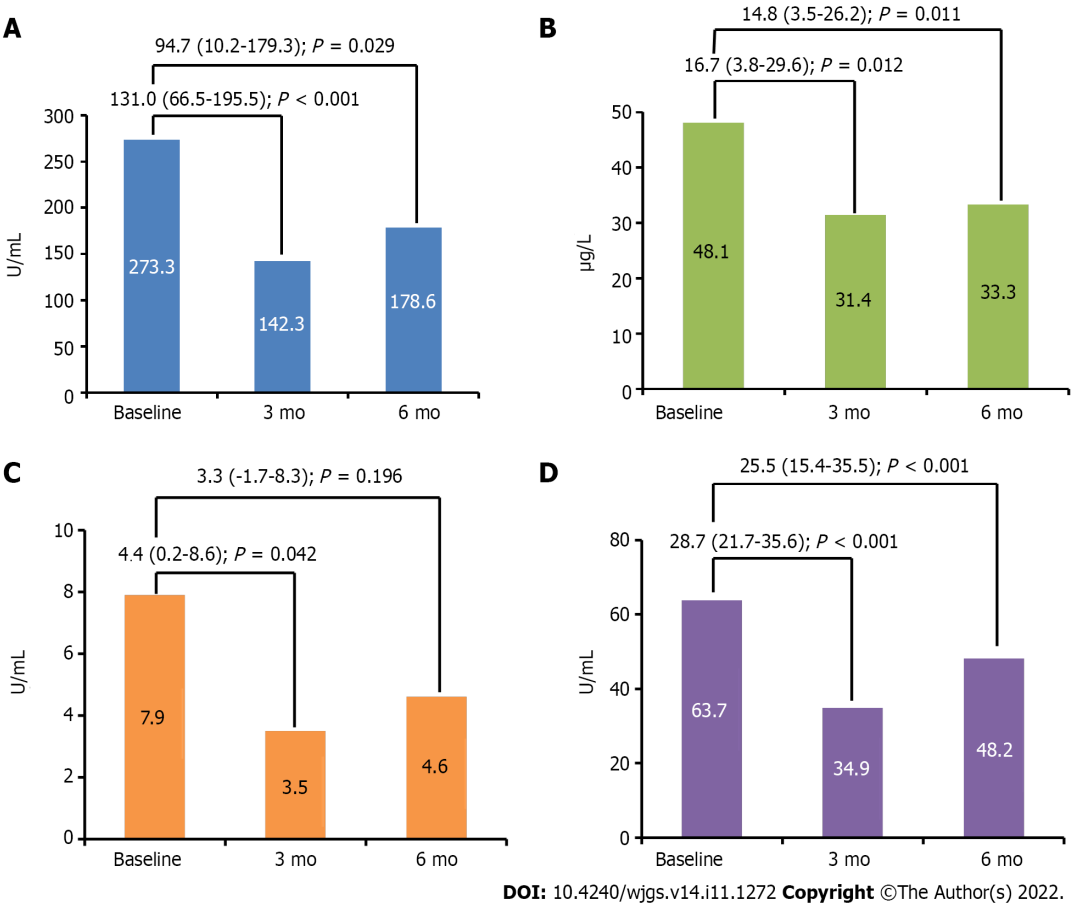

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Figure 3 Comparison of tumor marker levels of carbohydrate antigen 19-9, carbohydrate antigen 125, carcinoembryonic antigen, and carbohydrate antigen 242 before and after surgical management of gallbladder cancer. A: Carbohydrate antigen 19-9; B: Carbohydrate antigen 125; C: Carcinoembryonic antigen; D: Carbohydrate antigen 242.

rate.

The present study had a few limitations. It was a non-randomized observational study with a relatively small sample size and a short follow-up duration of only 6 mo. The study included only operable and suspicious cases of GBC to determine early indications of malignancy by assessing different tumor markers in resource-constrained countries. Further studies with a large number of patients with longer duration of follow-up are required to validate our results.

CONCLUSION

The present study suggested that serum levels of tumor markers including CA 19-9, CA 125, CEA and CA 242 were significantly associated with GBC. Significant reductions in tumor markers during follow-up show their importance as one of the criteria for assessment of treatment response. However, no significant association was observed between the presence of elevated levels of any marker and survival.

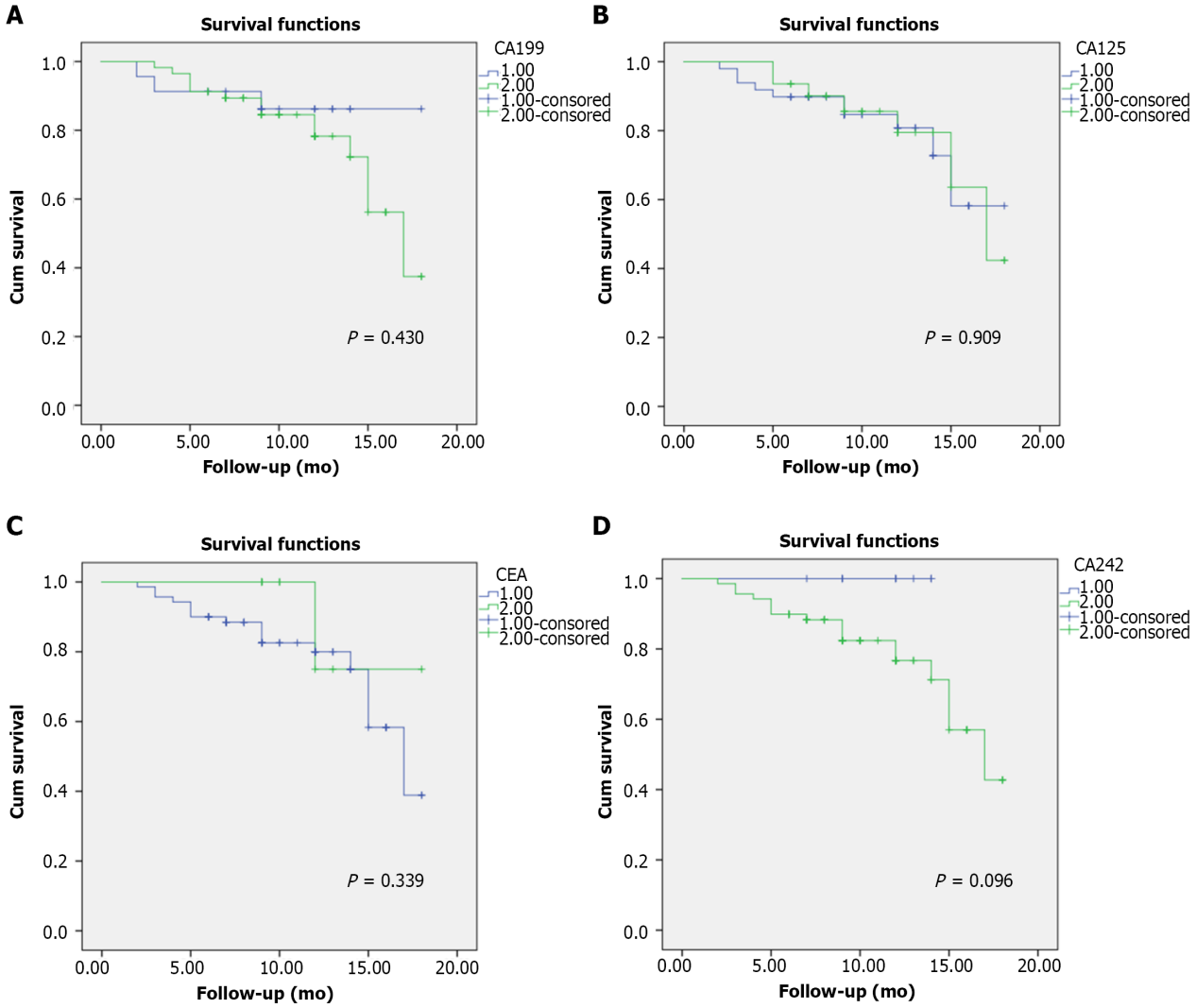

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Figure 4 Survival of patients with gallbladder cancer according to elevated *vs* normal marker levels of serum carbohydrate antigen 19-9 (U/mL), serum carbohydrate antigen 125 (U/mL), serum carcinoembryonic antigen (μg/L), and serum carbohydrate antigen 242 (U/mL) levels. A: Serum carbohydrate antigen 19-9 (U/mL); B: Serum carbohydrate antigen 125 (U/mL); C: Serum carcinoembryonic antigen (μg/L); D: Serum carbohydrate antigen 242 (U/mL).

ARTICLE HIGHLIGHTS

Research background

Tumor markers such as carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA 125), CA 242, and CA 19-9 have been widely used for the diagnosis of various types of cancer. Many researchers have focused on gallbladder cancer (GBC) and CEA or CA125, but no research has been carried out on all four markers together, especially in India.

Research motivation

This study focuses on the assessment of tumor markers CA 19-9, CEA, CA 125, and CA 242 for the early diagnosis and prognosis prediction of GBC.

Research objectives

The present study included patients with suspected GBC to assess different tumor markers separately and in combination, to determine their diagnostic accuracy and prognosis of GBC.

Research methods

This observational study was conducted in patients of either sex aged ≥ 18 years, with suspected GBC (GB polyp, irregular thick GB wall, GB mass, porcelain GB) on the basis of radiological imaging. All cases after surgical intervention were divided and grouped into two groups, the GBC group and benign GB disease group, according to histopathological examination findings. The cases were followed up and clinical findings, radiological findings, and tumor markers were assessed.

Research results

The key findings indicated that the median (interquartile range) age was 52.0 (41.0-60.0) years and 132 (66.0%) patients were women. The median levels of serum glutamic oxaloacetic transaminase (SGOT) (P = 0.001) and serum glutamic pyruvic transaminase (SGPT) (P = 0.012) were significantly higher in the GBC group than in the benign GBD group but were within the normal range in both groups. GB wall thickness was increased twofold in patients with GBC. Tumor markers including CA 19-9, CA 125, CEA, and CA 242 were significantly elevated in patients with GBC (P < 0.001). Serum levels of CA 19-9, CA 125, and CA 242 were significantly associated with age (P < 0.05). The sensitivity of CA 19-9 and CA 242 was comparatively higher than CEA and CA 125 in different stages of GBC. The sensitivity was 3.8% when all four markers exceeded the critical values. CA 242 had the highest sensitivity of 86.3%, and CA 125 had the highest specificity of 93.3% for the diagnosis of GBC. There was a significant reduction in tumor markers at 3 and 6 mo from baseline (P < 0.001).

Research conclusions

All four markers were important but in this study, CA 242 followed by CA 19-9 was most sensitive for the detection of GBC while CA125 was most specific for the diagnosis of GBC; however, CA 242 and CA 19-9 in combination were more specific and sensitive.

Research perspectives

Currently, there is only one study from China that has reported the combined use of these tumor markers to increase the diagnostic specificity and sensitivity for GBC. This study was conducted to make an early diagnosis of GBC on the basis of tumor markers, which itself will lead to better survival outcomes.

FOOTNOTES

Author contributions: Sinha DK was the guarantor and designed the study; Sinha SR, Prakash P, and Singh RK participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript; Sinha SR, Prakash P, Singh RK, and Sinha DK revised the article critically for important intellectual content.

Institutional review board statement: The study was reviewed and approved by Institutional Ethics Committee vide letter (Approval No. 479/IEC/2018/IGIMS).

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ORIGINAL ARTICLE

Observational Study

Disturbed passage of jejunal limb near esophageal hiatus after overlapped esophagojejunostomy following laparoscopic total gastrectomy

Hirokazu Noshiro, Keiichiro Okuyama, Yukie Yoda

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Abstract

BACKGROUND

Overlapped esophagojejunostomy (OEJ) is a secure purely laparoscopic reconstruction after laparoscopic total gastrectomy (LTG). However, long-term surgical results have not been documented well.

AIM

In this paper, we report unusual patients who manifested jejunal limb stricture near the esophageal hiatus without anastomotic stenosis during long-term observation after surgery.

METHODS

From April 2009 until May 2020, we retrospectively reviewed 211 patients underwent LTG following by OEJ for gastric carcinoma and took a standard surveillance program. We aimed to characterize a novel complicated disorder observed in these patients to assist treatment and prevention.

RESULTS

Five patients (2.4%) had unusual jejunal limb stricture after LTG and OEJ, occurring at a mean of 10 mo after initial radical LTG. All five patients had disturbed oral intake and marked weight loss, and two had aspiration pneumonia. Various diagnostic modalities and intraoperative findings in each patient revealed an intact anastomosis, bent or tortuous jejunal limb resulting from loose fibrous adhesions on the left crus at the esophageal hiatus and no cancer recurrence. All five patients were successfully treated by reoperation for adhesiolysis, division of the left crus and rearrangement of the jejunal limb.

CONCLUSION
Disturbed passage through the jejunal limb near the hiatus can occur after some types of OEJ following LTG. We speculate that it may result from a short remnant esophagus, excessive mobilization of the jejunal limb that permits bending or tortuosity and adhesions on the left crus at the hiatus. Prevention for this complication is possible during the original LTG procedure.

Key Words: Laparoscopic total gastrectomy; Overlapped esophagojejunostomy; Anastomotic stenosis; Adhesiolysis; Gastric carcinoma

Core Tip: Overlapped esophagojejunostomy (OEJ) is a secure purely laparoscopic reconstruction after laparoscopic total gastrectomy (LTG). However, disturbed passage through the jejunal limb near the esophageal hiatus can occur. In this paper, mechanisms and prevention for this complication are described. Five patients (2.4%) had disturbed oral intake and marked weight loss, all had unusual jejunal limb stricture after LTG and OEJ. Reoperation for adhesiolysis and division of the left crus and rearrangement of the jejunal limb was required. Prevention for this complication is possible during the original LTG procedure.

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INTRODUCTION

Since the development of safe and feasible intracorporeal anastomosis under laparoscopy[1,2], purely laparoscopic total gastrectomy (LTG) has been widely used to treat gastric carcinoma occupying the upper third of the stomach[3-7]. Overlapped esophagojejunostomy (OEJ) is a secure purely laparoscopic side-to-side reconstruction method that uses an endoscopic linear stapler after LTG[2]. Very few cases of postoperative anastomotic leakage or stenosis have been reported in patients treated with OEJ after LTG [8,9]. In addition, this technique is applicable even to patients treated by LTG with long esophageal excision[10]. However, we have experienced five unusual cases of jejunal limb stricture near the esophageal hiatus without anastomotic stenosis during long-term observation after LTG with OEJ. All five patients required reoperation for this complication. In this report, we sequentially analyzed these five patients and describe the characteristics of this complication to assist treatment and prevention.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Saga University Hospital (2020-07-06). All data and clinical findings were obtained retrospectively from the medical charts and videos, which were stored in our department library.

Patients

Since April 2009, all patients with curable gastric carcinoma at Saga University Hospital have been treated basically with laparoscopic surgery. Open surgery was performed in one patient for systemic para-aortic lymphadenectomy and in four patients who underwent other open surgery concomitantly. From April 2009 until May 2020, 925 patients underwent laparoscopic gastrectomy with at least 5 years of follow-up. During the study period, no patient had conversion to open surgery and only four patients missed postoperative surveillance appointments. Among the 925 patients, six had intrathoracic OEJ through a thoracoscopic approach because they required excision of over 4 cm of the esophagus. In one patient who underwent proximal gastrectomy, OEJ was performed as a part of double-tract reconstruction. After exclusion of these seven patients, 211 patients who underwent LTG following by OEJ for reconstruction of the alimentary tract were enrolled in this study.

Surgery

To provide information that allows speculation about the mechanisms of the complication, we summarize the detailed surgical procedures below. Five abdominal ports were placed during robotic surgery and laparoscopic surgery. Lymph node dissection extended to the stations along the hepatic, splenic and celiac arteries[11], and splenectomy was occasionally performed for complete dissection around the splenic hilum[12]. The esophago-cardiac branch of the subphrenic artery was divided, but the main artery was generally preserved. The esophageal hiatus was enlarged to a variable extent in the ventral direction in the tendinous portion of the diaphragm for the subsequent OEJ procedure. When further enlargement of the hiatus was requested for operative views and procedures, division of the left crus of the diaphragm was added. We intentionally transected the isolated esophagus vertically, using an endoscopic linear stapler, to create the OEJ on the posterior side on the esophageal stump. However, the transection often seemed to be horizontal after division. The jejunum was transected with a stapler 15 cm to 20 cm from the ligament of Treitz, and the mesentery was divided up to the bifurcation of the jejunal arteries and veins. If the approximation between the jejunal limb and the esophageal stump needed improvement, a combined jejunal artery and vein were divided after a clamp test to confirm blood supply. The jejunal limb was raised through the antecolic route as the first choice; the retrocolic route was used when the antecolic route was not possible. A small hole for insertion of the stapler fork was created on the posterior portion of the esophageal stump when the esophagus was transected vertically. Otherwise, the right portion was selected in most patients because of facilitation of the procedures and proper arrangement of the jejunal limb. A small enterotomy was also created on the antimesenteric side of the jejunal limb 45 mm from the stump. A 45-mm endoscopic linear stapler was used to create an overlapped side-to-side anastomosis. The stapling device for creation of the anastomosis was commonly introduced through the left abdominal port by the assistant's left hand. After adjusting, approximating and firing of the linear stapler, the entry hole was closed with continuous hand-sewing with absorbable 4-0 monofilament suture so that the V-shaped anastomosis was maximally widened. Barbed 3-0 suture was often available in more recent procedures[13]. The esophagus was generally not fixed at the hiatus. The jejunal limb was rarely fixed to the hiatus or to the other structures unless arrangement of the limb looked tortuous. When the jejunal limb passed *via* the retrocolic route, it was always fixed to the transverse mesocolon with a couple of nonabsorbable sutures. Prevention of Petersen's internal hernia was carefully performed with nonabsorbable sutures. A drainage tube was placed when there were concerns about anastomotic leakage, massive accumulation of lymphorrhea or pancreatic fistula.

Postoperative clinical course

Postoperative management after LTG was carried out according to the regular critical care protocol. Patient without postoperative complications usually left the hospital on POD 10 to 14. After discharge, patients who were diagnosed with pathological stage II or higher received adjuvant chemotherapy[14]. Postoperative surveillance was performed every 2 to 3 mo for patients with advanced-stage gastric cancer and every 6 to 12 mo for patients with early-stage cancer, for at least 5 years after surgery. During the observation period, body weight measurement, blood sampling and computed tomography (CT) examination were routinely performed. Endoscopic examination or upper gastrointestinal X-ray series was added for patients with any unusual complaints.

RESULTS

Characteristics of patients

Among the 211 patients who underwent LTG following by OEJ, the mean age was 69 years (range 25–88 years), and the female-to-male ratio was 42:169. The clinical stages according to the 8th edition of the TNM classification system[15] were as follows: 94 patients were stage I, 46 were stage II, 55 were stage III and 16 were stage IV. Five patients (2.4%) had unusual jejunal limb stricture after LTG and OEJ. The characteristics of these five patients at the first radical LTG are listed in Table 1. The group included one woman and four men. The age range at first LTG was 65 to 80 years. Three patients had gastric carcinoma located in the upper stomach, and one had Siewert type III esophagogastric junctional carcinoma invading 1 cm of the esophagus. The fifth patient had remnant gastric carcinoma after open distal gastrectomy and Billroth I reconstruction 13 years prior to LTG. The clinical depth of invasion was T1 in three patients and T2 in two patients; all patients were diagnosed as free from lymph node metastasis preoperatively, corresponding to clinical stage I in all patients. Therefore, none of the patients was treated with neoadjuvant chemotherapy. After pathological examination of the excised stomach specimens, one patient was diagnosed with pathological T3 and two had lymph node metastasis. One patient diagnosed with pathological stage IIB with T3 and N1 disease was treated with oral adjuvant chemotherapy for 1 year.

Table 1 Characteristics of the five patients at the first laparoscopic total gastrectomy

Case	1	2	3	4	5
Sex	M	M	M	M	F
Age	69	67	80	74	65
Original disease					
Location	Upper	Remnant stomach	Upper	EGJ	Upper
Histological type	Well	Well	Moderately	Well	Poorly
Clinical Stage[1]	I	I	I	I	I
Pathological Stage[1]	IA	IA	IIB	IA	IB
Neoadjuvant chemotherapy	-	-	-	-	-
Adjuvant chemotherapy	-	-	+	-	-
Type of gastrectomy	Total	Total (Complete)	Total	Total	Total
Approach	Laparoscopic	Laparoscopic	Laparoscopic	Laparoscopic	Robotic
Operation time (min)	336	475	339	438	368
Blood loss (mL)	130	76	93	35	34
Splenectomy	-	-	-	-	-
Lymph node dissection	D2	D2	D2	D2	D2
Length of excised esophagus (cm)	1.5	1.5	1.5	3.5	2.0
Direction of esophageal transection	Horizontal	Vertical	Horizontal	Horizontal	Horizontal
Site of esophagostomy	Right	Posterior	Right	Right	Right
Enlarged hiatus	Large	Large	Small	Large	Small
Direction	Ventral	Ventral	Ventral	Ventral	Ventral
Closure of enlarged hiatus	-	-	-	-	-
Route of jejunum	Antecolic	Retrocolic	Antecolic	Retrocolic	Antecolic
Insertion of stapler	Left	Left	Left	Left	Left
Fixation of esophagus	-	-	-	-	-
Fixation of jejunum	-	-	-	+	-
Anastomosis site (common channel level)	at hiatus	above hiatus	below hiatus	above hiatus	below hiatus
Drainage	+	+	+	+	+
Resume of oral intake	3	1	3	4	3
Length of hospital stay	11	49	12	17	19
Postoperative complications	-	-	-	-	-

[1]TNM classification, 8th edition.
EGJ:Esophagogastric junction.

Summary of initial laparoscopic total gastrectomy

A summary of the initial radical LTG in the five patients is shown in Table 1. All five patients had LTG without splenectomy; four patients were treated with laparoscopic surgery and one with robotic surgery. The mean length of excised esophagus was 2.0 cm (range 1.5–3.5 cm). The direction of the esophageal transection was horizontal in four patients and vertical in one. In the four patients with horizontal transection, the entry hole was created on the right side of the esophageal stump. The esophageal hiatus was slightly enlarged toward the ventral side in the tendinous portion of the diaphragm in two patients and was greatly enlarged in the same portion in three patients. After the reconstructive procedures, the enlarged hiatus was not closed in any patient. The jejunal limb was raised to the esophageal stump *via* the antecolic route in three patients and *via* the retrocolic route in two patients. In all patients, a stapling device was introduced through the left abdominal port as usual for the anastomosis. At surgery, the level of the closed entry hole was above the hiatus in two patients, at

the hiatus in one patient and below the hiatus in two patients. No patient had fixation of the esophagus to the hiatus. One patient whose anastomotic level was high had fixation of the jejunal limb using absorbable sutures around the hiatus to achieve proper positioning. A drainage tube was placed in all patients.

Postoperative clinical course after LTG

None of the five patients had abnormal findings on postoperative upper gastrointestinal X-ray series with contrast medium at the first admission for LTG. Four of the five patients had a typical postoperative clinical course and were discharged from the hospital. The patient who was treated for remnant gastric cancer had persistent anorexia resulting from a feeling of abdominal fullness and had a prolonged hospital stay.

Severe symptoms developed within nine months after LTG in all patients. After a mean interval of 10 mo (range 5–21 mo), the five patients underwent reoperation to treat ongoing complications. Clinical findings and surgical procedures for reoperation are summarized in Table 2. All patients had disturbed oral intake. X-ray examination showed poor passage of contrast medium at the hiatus, jejunal stenosis (approximately 1 cm in length) at the hiatus and dilatation of the distal esophagus (Figure 1A). Bending of the jejunal limb was also suggested or suspected in all patients. Body weight decreased markedly after the first LTG in all patients (Table 3). The mean weight loss was 26% (range 14%–33%) at the time of reoperation. Two patients experienced aspiration pneumonia, which was confirmed with CT examination. In all five patients, endoscopy showed intact anastomosis, but the jejunal limb was bent and sometimes seemed to be tortuous (Figure 1B). However, the 1-cm diameter endoscope could be passed through the bent portion in all patients. Endoscopic balloon dilatation was tried in all cases but did not achieve permanent results. No cancer recurrence was observed in any patient in any of several diagnostic modalities.

Laparoscopic adhesiolysis

Laparoscopic adhesiolysis around the hiatus was planned. Adhesiolysis was performed *via* the previous five port sites, except for one patient who could be treated *via* four ports. In all patients, adhesions between the liver and suprapancreatic portion were very strong, and adhesiolysis at the esophageal stump was also challenging because of scar formation at the staple line. However, adhesions at other locations were released easily in four patients, who had all undergone previous surgery by laparoscope. In the one patient who had undergone prior open distal gastrectomy before LTG, adhesiolysis was challenging in the upper abdominal cavity. However, adhesions were mild around the hiatus, which had been newly manipulated during LTG. On the left crus of the diaphragm, the jejunal limb was bent and had fibrous adhesions (Figure 2A and B). The anastomosis was elevated far above the hiatus after adhesiolysis up to the level of anastomosis in all cases. The jejunal limb above the hiatus was slightly shifted to the left side in the mediastinum. As shown in Figure 3, a schema based on these findings, the jejunal limb stricture resulted from the shortened remnant esophagus and jejunal bending resulted from loose and fibrous adhesions on the left crus at the esophageal hiatus. This was confirmed by the presence of a pressure mark on the jejunum after completion of adhesiolysis (Figure 2C). During reoperation, the hiatus was enlarged by dividing the left crus in all patients to obtain a better operative view and to prevent jejunal stricture. The jejunal limb was fixed to the right side of the hiatus or other abdominal structures to achieve a straight line after intraoperative endoscopic luminal examination (Figure 4A).

Postoperative clinical course after adhesiolysis

Postoperative X-ray examinations after reoperation showed no disturbed passage or bending of the jejunal limb in any of the five patients (Figure 4B). There were no operative morbidities after the reoperation for adhesiolysis. All patients gained body weight after the reoperation (Table 3). After a mean duration of 47 mo (range 11–82 mo) after reoperation for adhesiolysis, all patients were well and had usual oral intake.

DISCUSSION

In this report, we describe unusual disturbed passage through the jejunal limb near the esophageal hiatus that occurred in five patients (2.4%) after purely LTG following by OEJ. This serious complication did not result from anastomotic stenosis after alimentary tract reconstruction or from hiatal stenosis caused by scar formation; the jejunal limb stenosis was caused by a shortened remnant esophagus and excessive mobilization of the jejunal limb, which produced bending or tortuosity and loose fibrous adhesions on the left crus at the hiatus. Because balloon dilatation did not successfully resolve this disorder, surgical treatment for adhesiolysis, division of the left crus and rearrangement of the jejunal limb were performed.

Table 2 Summary of clinical findings and procedures in the five patients at the reoperation

Case	1	2	3	4	5
Age	69	67	80	76	66
Interval from the 1st operation (mo)	7	9	8	5	21
Preoperative endoscopy					
Anastomotic stricture	-	-	-	-	-
Recurrence	-	-	-	-	-
Efferent scope passage	+	+	+	+	+
Bending or tortuous	+	+	+	+	+
Preoperative UGI series					
Esophagus dilatation	+	+	+	+	+
Length of jejunal stricture	1.5 cm	0.8 cm	occluded	1.0 cm	1.0 cm
Bending or tortuous	+	+	+	+	+
Preoperative CT					
Recurrence	-	-	-	-	-
Pneumonia	+	-	-	+	-
Approach	Laparoscopic	Laparoscopic	Laparoscopic	Laparoscopic	Laparoscopic
Operation time (min)	66	255	118	203	113
Blood loss (mL)	3	223	45	36	10
Number of ports	4	5	5	5	5
Adhesiolysis	+	++	+	+	+
Intraoperative endoscopy	+	+	+	-[1]	+
Fixation of jejunum	-	+	+	+	+
Left crus cutting	+	+	+	+	+
Resume of oral intake (POD)	1	3	2	2	1
Length of hospital stay (d)	5	7	22	9	6
Postoperative complications	-	-	-	-	-

[1]Air insufflation through the nasogastric tube.
UGI: Upper gastrointestinal; CT: Computed tomography; POD: Postoperative day.

Anastomotic stenosis is a well-known postoperative complication after esophagojejunostomy following total gastrectomy. In early reports, Tsujimoto *et al*[8] summarized that the complication occurred in 0% to 3.8% of patients undergoing LTG following by OEJ; this rate was lower than that after circular-stapled anastomosis and the functional end-to-end method. In recent reports, the rate of anastomotic stenosis is similarly low, ranging from 0% to 4.6%[3,9,16-18]. However, little is known about disturbed passage of the jejunal limb near the esophageal hiatus. In our series, 2.4% of patients had this uncommon disorder. Huang *et al*[19] reported difficulty with solid food intake in some patients after LTG and OEJ, according to clinical queries of constituent items of pain on the European Organisation for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire (EORTC-QLQ-C30) and dysphagia on the EORTC-QLQ 22-item Stomach assessment tool. Therefore, it is possible that this postoperative change might happen to some extent in every patient after LTG and OEJ. In that case, this disorder might not be an independent category of postoperative complications. We initially thought that we encountered the five patients in whom severe symptoms developed. However, the patients' serious complaints would not have improved without surgical treatment. Therefore, we summarize below the characteristics of this complicated disorder in our five patients to help others avoid missing the timing for reoperation.

First, severe symptoms developed in the relatively early period after LTG. Next, oral intake was seriously disturbed and weight loss was severe. Aspiration pneumonia developed in some patients. Disturbed oral intake could be verified by X-ray examination, which showed poor passage of contrast medium resulting from jejunal stenosis and bending of the jejunal limb near the hiatus, in addition to

Table 3 Changes in body weight of the five patients

Case	1	2	3	4	5	mean
Height (cm)	169.4	164.0	171.5	154.7	145.2	161.0
BW before the first LTG (kg)	66.3	71.3	65.1	57.5	54.8	63.0
BWLR at the discharge of the first LTG (%)	-8.0%	-7.0%	-4.6%	-4.2%	-6.9%	-6.1%
BWLR before the reoperation (%)	-25.3%	-25.5%	-13.8%	-33.0%	-32.3%	-26.0%
BWLR at the discharge of the reoperation (%)	-24.0%	-23.6%	-13.2%	-28.9%	-32.5%	-24.4%
Maximal BWLR from the reoperation (%)	-17.0%	-23.6%	-5.7%	-21.7%	-21.5%	-17.9%

LTG: Laparoscopic total gastrectomy; BW: Body weight; BWLR: Body weight loss rate compared to BW before laparoscopic total gastrectomy.

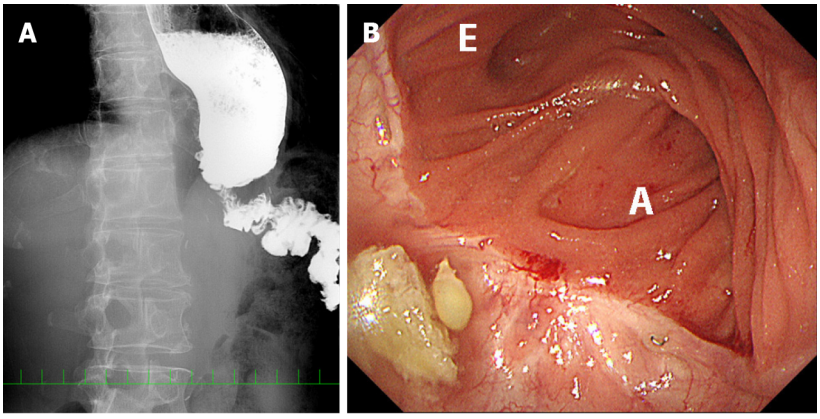

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Figure 1 Stricture of the jejunal limb before reoperation in case 5. A: Preoperative X-ray examination with contrast medium shows poor passage of contrast medium at the hiatus, jejunal stenosis (approximately 1 cm in length) and jejunal bending at the hiatus, in addition to distal esophageal dilatation; B: Endoscopic luminal examination shows an intact anastomosis and a bent or tortuous efferent jejunal limb, but the scope could be passed through this portion. E: Efferent side; A: Afferent side.

dilatation of the distal esophagus. No anastomotic stenosis was seen on endoscopic luminal examination. Moreover, the scope could be passed through the bent jejunal limb and endoscopic balloon dilatation was unsuccessful in permanently resolving the disorder. Finally, several cancer surveillance processes revealed no recurrence of gastric carcinoma.

We think that disturbed oral intake, continued weight loss or aspiration pneumonia suggest the need for surgical treatment of this disorder after LTG. Total gastrectomy is often associated with reduced oral intake and weight loss. Okabe *et al*[3] reported that the patients had lost 7.2% of initial body weight at 2 years after laparoscopic distal gastrectomy and 13.9% at 2 years after laparoscopic total gastrectomy. In our five patients, weight loss reached 26% of body weight, which was much greater compared with the 13.9% reported by Okabe *et al*[3]. Moreover, LTG is not directly associated with aspiration pneumonia. Two patients in our series developed aspiration pneumonia, which should be considered a serious sign for the advanced stage of this disorder. Because endoscopic balloon dilatation was unsuccessful in all patients, surgical treatment for adhesiolysis should be considered as soon as possible. We did not hesitate to perform laparoscopic surgical treatment because postoperative intraabdominal adhesions are relatively easy to release when the prior surgery has been performed by laparoscopy[20]. One patient previously had an open distal gastrectomy before LTG, which should be called laparoscopic complete gastrectomy. Even in this patient, adhesions at the newly manipulated surgical sites around the hiatus were not very strong at reoperation for adhesiolysis.

Commonly observed findings in our series enable us to speculate on the mechanisms of disturbed passage through the jejunal limb near the hiatus after LTG. Dense and tough adhesions were not observed around the esophageal hiatus, except on the staple line at the esophageal stump, even if the esophageal hiatus had been divided and enlarged. Therefore, uncommon severe scar formation was an unlikely cause of jejunal stricture near the hiatus. It is also unlikely to the drainage tube placed during LTG was responsible for these strictures. Our speculations are described below.

First, the remnant esophagus was short, and the anastomotic site was elevated at reoperation in all patients. Approximately 5 cm of the remnant esophagus had to be isolated to perform the overlapped method. A prepared and isolated esophagus easily shrinks[21]. Because the remnant esophagus was not

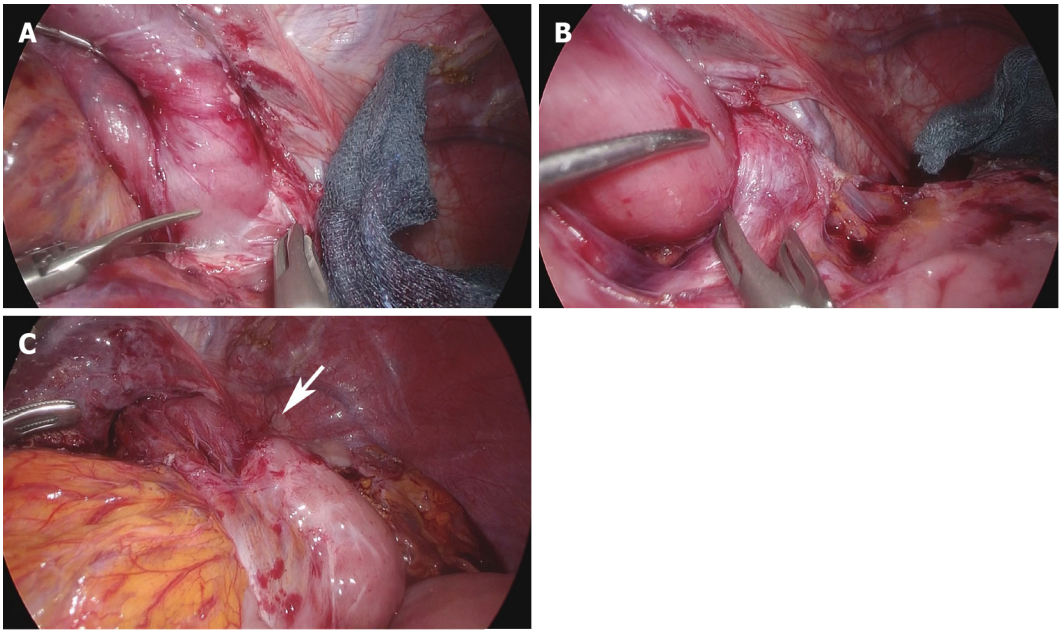

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Figure 2 Stricture of the jejunal limb during reoperation in case 5. A: Fibrous adhesions are observed around the hiatus; B: Loose adhesions are present on the left crus; C: A pressure mark (white arrow) is identified on the jejunal limb after completion of adhesiolysis up to the anastomosis.

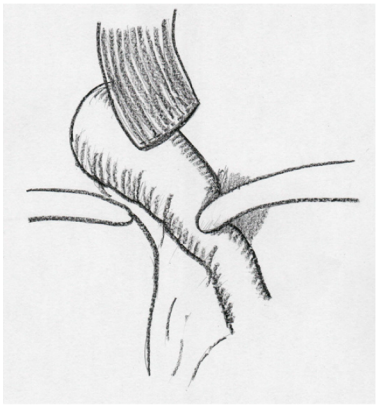

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Figure 3 Schema of the complicated disorder after overlapped esophagojejunostomy following laparoscopic total gastrectomy. The jejunal limb stricture was resulted from the shortened remnant esophagus and jejunal bending resulting from loose and fibrous adhesions on the left crus at the esophageal hiatus.

fixed at the hiatus, the anastomotic site moved upward into the mediastinum, elevating the jejunal limb to the level of the hiatus.

Next, bending or tortuosity of the jejunal limb and adhesions on the left crus at the hiatus might play an important role. Generally, the jejunal limb is prepared so that it is easily approximated to the esophageal stump during LTG. This is because the tension is not easily assessed because of the decreased tactile sensation using laparoscopic forceps and high tension is associated with anastomotic leakage. Excessive mobilization of the raised jejunal limb might result in higher elevation of the anastomosis when the anastomosis is not fixed. Bending of the jejunal limb might occur at the hiatus because of excessive mobilization of the jejunal limb. The left crus of the diaphragm, which is a left side component of the esophageal hiatus, is commonly prepared to isolate the esophagus or dissect the left paraesophageal lymph nodes during total or proximal gastrectomy for gastric or esophagogastric junctional cancer. Therefore, this portion generally is stripped of serosa after total or proximal gastrectomy, resulting in some adhesion formation even after laparoscopic surgery. Finally, jejunal limb stricture at the hiatus might be produced through this process. As the operative findings showed, fibrous adhesions were always observed at this portion and were suspected to be responsible for bending of the jejunal limb. The jejunal stricture length of approximately 1 cm was consistent with the thickness of the crus which sometimes made a pressure mark on the jejunal limb. To prevent these

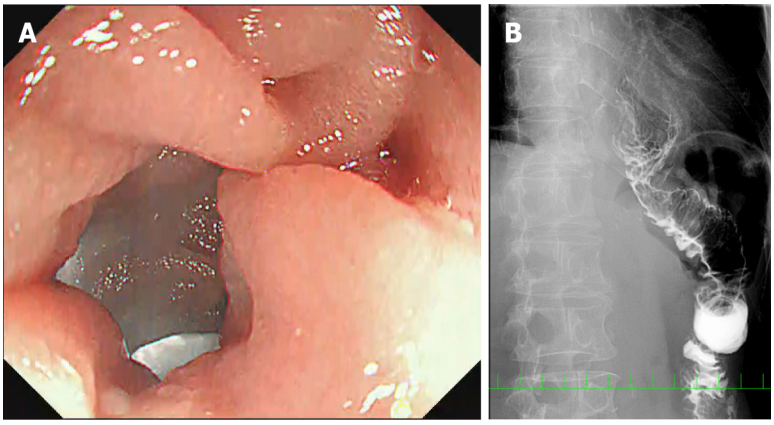

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Figure 4 No stricture of the jejunal limb on intra- or postoperative examinations in case 5. A: Intraoperative endoscopic luminal examination showed a straight efferent jejunal limb; B: Postoperative X-ray examination with contrast medium showed good passage at the hiatus, as well as improvement of jejunal limb bending and distal esophageal dilatation.

conditions, the anastomosis must be fixed firmly around the hiatus; however, fixation cannot always be performed if the remnant esophagus is short. In this case, arrangement of the jejunal limb may help to avoid adhesions between the jejunal limb and the left crus that cause bending. We consider that the jejunal limb, except for the mesenteric component, should be fixed to the right side of the hiatus or other abdominal structures by a couple of stitches using nonabsorbable sutures to achieve a linear alimentary tract near the hiatus.

The direction of the esophageal transection and the anastomotic side on the esophageal stump did not account for this complication. We considered that the flexible organs would move easily with gravity to the wide left subphrenic space after total gastrectomy. Laparoscopic surgery results in few postoperative adhesions, which facilitates this movement[20]. If anastomosis is made on the left side of the esophageal stump that is transected horizontally[3,4,9,16,17,22,23], the jejunal limb will fall into the left subphrenic space after the anastomosis. The jejunal limb could then become largely tortuous unless the limb is fixed to other abdominal structures to avoid torsion. However, we previously believed that flexibility of the jejunal limb should not be disturbed by fixation to promote better peristalsis. Indeed, this concern was consistent with a previous report that jejunal elevation could cause intractable stenosis after LTG with circular-stapled esophagojejunostomy, depending on the side of the afferent loop[24].To prevent stenosis, the anastomosis should be created on the right side[8,18] or the posterior side[13,25] of the esophageal stump. In these cases, torsion will be minimal, even if the jejunal limb falls into the vacant space under the left diaphragm. We now consider it important to arrange the jejunal limb in a straight line without excessive mobilization after OEJ, regardless of where the anastomosis is created on the esophageal stump. In addition, enlargement of the hiatus by division of the left crus might be useful. In all five of our patients, the left crus was cut to arrange the jejunal limb in a straight-line during reoperation.

CONCLUSION

In conclusion, disturbed passage through the jejunal limb near the esophageal hiatus can occur in the relatively early period after OEJ following LTG, and surgical treatment for adhesiolysis, division of the left crus and rearrangement of the jejunal limb is required to treat this complication. Depending on the speculated cause of jejunal limb stricture, prevention of this complication may be possible during the original LTG procedure.

ARTICLE HIGHLIGHTS

Research background

Overlapped esophagojejunostomy (OEJ) is a secure purely laparoscopic reconstruction after laparoscopic total gastrectomy (LTG). Very few cases of postoperative anastomotic leakage or stenosis have been reported in patients treated with OEJ after LTG.

Research motivation
We have experienced five unusual cases of jejunal limb stricture near the esophageal hiatus without anastomotic stenosis during long-term observation after LTG with OEJ.

Research objectives
The objectives in this paper are mechanisms and prevention for this complication are described.

Research methods
From April 2009 until May 2020, 211 patients who underwent LTG following by OEJ for reconstruction of the alimentary tract were enrolled in this study.

Research results
We describe the characteristics of this complication to assist treatment and prevention.

Research conclusions
We had experienced five cases, all patients needed reoperation. We needed to know the mechanism of this complication.

Research perspectives
LTG was widely used for gastric carcinoma. OEJ is a secure purely laparoscopic reconstruction method. Postoperative complications were very low. However, we had experienced unusual cases of jejunal limb stricture.

FOOTNOTES

Author contributions: Noshiro H contributed to conceptualization, methodology, formal analysis, investigation, writing-original draft, writing-review & editing; Okuyama K contributed to writing-review & editing; Yoda Y contributed to investigation; All authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Development of a warning score for early detection of colorectal anastomotic leakage: Hype or hope?

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Abstract

BACKGROUND

Colorectal anastomotic leakage (CAL), a severe postoperative complication, is associated with high morbidity, hospital readmission, and overall healthcare costs. Early detection of CAL remains a challenge in clinical practice. However, some decision models have been developed to increase the diagnostic accuracy of this event.

AIM
To develop a score based on easily accessible variables to detect CAL early.

METHODS
Based on the least absolute shrinkage and selection operator method, a predictive classification system was developed [Early ColoRectAL Leakage (E-CRALL) score] from a prospective observational, single center cohort, carried out in a colorectal division from a non-academic hospital. The score performance and CAL threshold from postoperative day (POD) 3 to POD5 were estimated. Based on a precise analytical decision model, the standard clinical practice was compared with the E-CRALL adoption on POD3, POD4, or POD5. A cost-minimization analysis was conducted, on the assumption that all alternatives delivered similar health-related effects.

RESULTS
In this study, 396 patients who underwent colorectal resection surgery with anastomosis, and 6.3% (n = 25) developed CAL. Most of the patients who developed CAL (n = 23; 92%) were diagnosed during the first hospital admission, with a median time of diagnosis of 9.0 ± 6.8 d. From POD3 to POD5, the area under the receiver operating characteristic curve of the E-CRALL score was 0.82, 0.84, and 0.95, respectively. On POD5, if a threshold of 8.29 was chosen, 87.4% of anastomotic failures were identified with E-CRALL adoption. Additionally, score usage could anticipate CAL diagnosis in an average of 5.2 d and 4.1 d, if used on POD3 and POD5, respectively. Regardless of score adoption, episode comprehensive costs were markedly greater (up to four times) in patients who developed CAL in comparison with patients who did not develop CAL. Nonetheless, the use of the E-CRALL warning score was associated with cost savings of €421442.20, with most (92.9%) of the savings from patients who did not develop CAL.

CONCLUSION
The E-CRALL score is an accessible tool to predict CAL at an early timepoint. Additionally, E-CRALL can reduce overall healthcare costs, mainly in the reduction of hospital costs, independent of whether a patient developed CAL.

Key Words: Anastomotic leakage; Colorectal; Surgery; Biomarkers; Score; Costs

Core Tip: Colorectal anastomotic leakage, a severe postoperative complication, is associated with high morbidity, hospital readmission, and overall healthcare costs. Early detection of colorectal anastomotic leakage remains a challenge in clinical practice. Some decision models have been developed to increase the diagnostic accuracy of this event. A score designed with easily accessible variables could have a positive impact on timely diagnosis of colorectal anastomotic leakage and could minimize healthcare costs.

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INTRODUCTION

Anastomotic leakage, a severe postoperative complication, remains the Achilles' heel of colorectal surgery, despite the technical advances in this field. Colorectal anastomotic leakage (CAL) is associated with high morbidity, mortality, increased length of hospital stay (LOHS), reoperation rate, and healthcare costs[1-5]. It is worth mentioning that CAL has a major impact on the patient's quality of life and oncological outcomes, including cancer recurrence[6-8].

Nonspecific signs and symptoms often precede the acute and rapid clinical deterioration of a patient with CAL. Late diagnosis and management increase the likelihood of an undesirable outcome. Therefore, timely CAL diagnosis is crucial[4,9,10]. Decision models have been designed to assess the risk of CAL development[4,10-13]. These models use regular scores of combined clinical, imaging, and laboratorial parameters, but the relevance of the models in early detection is still uncertain. The limited

sensitivity (SS) of computed tomography (CT) in detecting CAL is a particular cause for concern and should be considered to avoid CAL diagnostic and management delays[14]. Furthermore, it has been reported that an early minimally invasive reoperation should be considered in all patients with CAL suspicion because it is associated with low conversion, mortality, and morbidity rates[15].

The occurrence of CAL has a significant negative influence on medical resource utilization. Thus, its early identification is critical to generate favorable economic outcomes while avoiding downstream economic impacts of CAL development[1,2,16]. Use of diverting stomas, accurate scores, and attempted reoperation has been demonstrated to decrease LOHS, overall morbidity and readmissions[16].

The purpose of this study was to develop a classification system capable of assisting clinicians in detecting CAL early and accurately. In addition, we aimed to assess the cost-effectiveness of using this classification system in daily clinical practice.

MATERIALS AND METHODS

Prospective monocentric study design

A prospective, observational, single center study was conducted in a colorectal division of a non-academic hospital. The study included patients undergoing urgent or elective colorectal resection, regardless of the approach (open or laparoscopic), indication (benign or malignant), and creation of a protective stoma. Data was collected between March 1, 2017 and August 31, 2019 and recorded in a database according to the study protocol previously published[17]. CAL, the main endpoint, was defined in accordance with clinical, imaging, and surgical criteria[5,17,18]. Patients were excluded from the study if under 18-years-old, pregnant, unable to give written informed consent, had not received R0 resection with anastomosis, or had inflammatory bowel disease. A 90-d follow-up included data of postoperative complications (including CAL), LOHS and readmissions.

Development of the classification system

We aimed to establish clear and simple rules that can be used in daily clinical practice for recognizing patients at higher risk of CAL early. A predictive classification system was developed from patient-centered data and based on the least absolute shrinkage and selection operator method[19]. The least absolute shrinkage and selection operator method is a classification technique for variable selection and regularization that results in balanced classifiers in terms of predictive ability and model interpretability [19]. The classifier was named Early ColoRectAL Leakage (E-CRALL), and logo registration trademark was performed (Figure 1).

The first step to build the classifier included the estimation of conditional probability for developing CAL from the prospective study dataset and sorted into demographic, intraoperative and postoperative classes (Supplementary Table 1). The postoperative category was grouped into three levels (clinical condition, abdominal pain, and biomarker plasma values) from postoperative day (POD) 3 to POD5. The least absolute shrinkage and selection operator *Probit* and *Logit* models, suitable for binary dependent outcomes, were applied.

Further, the risk of overfitting was managed and reduced by splitting the sample. A training sample (70% of total) was used to estimate the models and build alternative classifiers for each POD (3, 4, and 5), and a testing sample (30% of total) was adopted to assess the performance of the classifier and the ability to predict CAL. The classifier with the best predictive performance was selected using cross-validation and minimizing the deviance and deviance ratio statistics. The performance of alternative classifiers was also evaluated using the area under the receiver operating characteristic curve. Finally, the red flag threshold indicative of CAL was settled, maximizing both the SS and specificity (SP) of the classifier. Three different optimal classifiers were developed, one for each POD (3, 4, and 5).

Cost-minimization analysis

A cost-minimization analysis was conducted to compare the standard clinical practice (no use of E-CRALL) with the adoption of E-CRALL on POD3, POD4, or POD5, assuming that all alternatives delivered similar health-related effects[20]. The time horizon of the decision problem was the 1st postoperative month, the target population was the prospective study patients, and the analysis perspective was that of the National Health Service. This cost-minimization analysis was based on the analytical decision model (Figure 2) presenting six possible patient pathways after application of E-CRALL[20,21]. The patient can be CAL positive or negative (observed ex-post but based on known ex-ante probabilities). In both branches, patients were divided by the optimal classifier, as E-CRALL positive or negative. All E-CRALL positive patients received an abdominal and pelvic CT scan. If the CT scan detected CAL, patients underwent proper management (Figure 2, pathways 1 and 4). Otherwise, if CT scan was negative or doubtful of CAL, patients were re-operated and managed accordingly (Figure 2, pathways 2 and 5). Finally, E-CRALL negative patients maintained appropriate clinical surveillance until CAL diagnosis (Figure 2, pathway 3) or discharge (Figure 2, pathway 6).

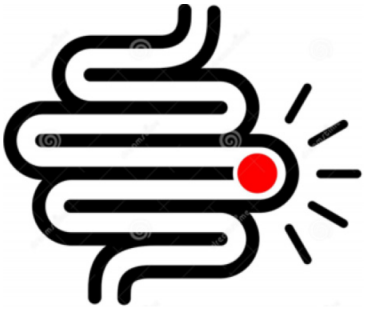

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Figure 1 Early ColoRectAL Leakage score logotype.

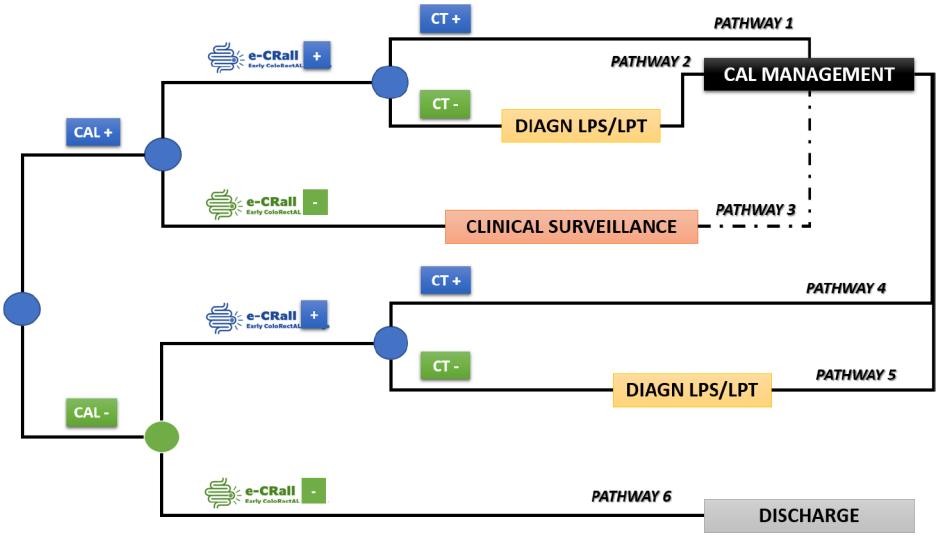

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Figure 2 The decision tree model scenario with adoption of the Early ColoRectAL Leakage score, considering postoperative days 3, 4, or 5 independently). CAL: Colorectal anastomotic leakage; CT: Computed tomography; Diagn: Diagnosis; E-CRALL: Early ColoRectAL Leakage score; LPS: Laparoscopy; LPT: Laparotomy (open surgery).

The branch probabilities to feed the tree came from several sources. The probabilities of CAL were estimated from the prospective study dataset, and the SS and SP of the E-CRALL score on a specific POD were estimated from the models. The predictive effect of abdominal and pelvic CT scan was drawn from relevant studies[14,22-24].

The estimation of costs to populate the model (Figure 2) were obtained from the Portuguese National Health Service reimbursement, used as a surrogate indicator for full hospital costs. Costs were based on the Ministerial Order nº 254/2018 of September 7, 2018 (Addendum III). The final costs of each of the six possible pathways were estimated under some assumptions, as presented in Table 1. The expected costs of each alternative were computed by the roll-back method[20].

The estimation of costs for standard clinical practice were obtained as follow: iCAL x Cost_CAL + (1-iCAL) x Cost_NoCAL, where iCAL was the incidence of CAL in the prospective study dataset and Cost_CAL (Cost_NoCAL) was the cost of treatment of a CAL (No CAL) patient. Costs were based on the Ministerial Order nº 254/2018 of September 7, 2018 (Addendum III). For each patient, the Diagnosis Related Group 221 and 223, respective degree of severity and comprehensive costs, were identified.

All statistical analysis was conducted using Stata Statistical software (Release 16; StataCorp, College Station, TX, United States).

RESULTS

Patients and outcomes

During the study period, we included 396 patients who underwent colorectal resection. Among them, 25 (6.3%) developed CAL. Age, the Charlson Comorbidity Index, and the American Society of

Table 1 Description of assumptions, values, and probabilities for final cost estimation in the decision tree model scenario with adoption of Early ColoRectAL Leakage score on postoperative day

Patient pathway	Assumptions/Observations	€ value	Probability, %
P1	SS and SP of E-CRALL score (Table 5); SS and SP of CT scan[13,21,22]; Full Hospital costs - Ministerial Order nº 254/2018 (Addendum III); Additional Reoperations/CT scan - Ministerial Order nº 254/2018 (Addendum III and IV); LOHS adjustment (reoperation; discharge in advance)	525.10	4.2
P2		1269.70	1.8
P3		379.00	0
P4		499.10	5.3
P5		1243.70	7.9
P6		353.00	80.8

CT: Computed tomography; E-CRALL: Early ColoRectAL Leakage score; LOHS: Length of hospital stay; SP: Specificity; SS: Sensitivity.

Anesthesiologists grade affected the onset of CAL (Table 2). A laparoscopic approach was used in 82% of patients. The surgical approach ($P < 0.001$), the volume of blood loss ($P < 0.001$), the occurrence of intraoperative complications ($P < 0.001$), and the duration of the procedure ($P = 0.011$) were significantly related to the development of CAL (Table 2).

In this study, 92% of patients who developed CAL ($n = 23$) were diagnosed during the first hospital admission. The mean (± standard deviation) and median time for CAL diagnosis were 9.0 ± 6.8 d and 8 d (interquartile range = 7), respectively. Anastomotic leakage was significantly associated with a longer hospital stay [median of 21 d (patients who developed CAL) *vs* 7 d (patients without complications) *vs* 13 d (patients with other complications); $P < 0.001$]. The 90-d mortality rate was 0.8%, representing 3 patients who developed CAL (Table 2).

E–CRALL score

Table 3 displays the variables and their respective weight on the score to determine the E-CRALL score for POD3-POD5. Many of the variables were statistically significant with predictive power to detect CAL. The predictive ability of this warning score had an AUROC for POD3 to POD5 of 0.82, 0.84 and 0.95, respectively (Figure 3 and Table 4). The score applied on POD5 had the best predictive power [0.95 (95% confidence interval: 0.90-0.99)].

The cutoff value for applying the E-CRALL score was calculated, defining the threshold for signaling a "patient who developed CAL". Setting the optimal cutoff as the one that maximizes both SS and SP of the classifier was established for POD3 and POD5 at 0.0551 and 0.0829, respectively. Considering a discriminant threshold of 5.51 (0.0551 × 100), the E-CRALL score on POD3 had a SS, SP, positive predictive value, and negative predictive value of 85.7%, 66.1%, 13.8%, and 98.7%, respectively. On POD5, if a threshold of 8.29 (0.0829 × 100) was chosen, then 87.4% of anastomotic failures were identified (Table 4).

Time to CAL diagnosis

The E-CRALL score adoption from POD3 to POD5 allowed the estimation of different lengths of time to detect CAL and the respective benefits in terms of time saving (Table 5). The E-CRALL score usage could anticipate CAL diagnosis in an average of 5.2 d if used on POD3 and in 4.1 d if used on POD5. CAL diagnosis was possible on the same day of E-CRALL score application on POD4 and POD5.

Cost analysis

Prospective monocentric study: In standard clinical practice, the patients who developed CAL had index admission comprehensive costs markedly greater (286%) than patients who did not develop CAL (€9096.00 *vs* €3177.00, respectively) (Table 6).

E-CRALL score application: In the model setting (Figure 2) after applying the E-CRALL score (on POD5), the adjusted comprehensive costs for each endpoint (pathway 1 to 6) were estimated and summarized in Table 6. In patients who developed CAL, episode comprehensive costs were markedly greater (four times) in comparison with patients who did not develop CAL (€8176.88 *vs* €1946.84, respectively).

Cost-minimization analysis

Regardless of CAL status, a cost comparison of the two approaches (standard clinical practice *vs* E-CRALL score application) from POD3 to POD5 was performed (Table 7). Greater cost savings were observed when the E-CRALL score was applied on POD5. Overall, the use of the E-CRALL warning

Table 2 Patient demographics and clinical and operative characteristics

Characteristic	Group 1, *n* = 277	Group 2, *n* = 94	Group 3, *n* = 25	*P* value
Age, mean ± SD	68.8 ± 11.3	72.2 ± 14.5	73.6 ± 13.6	0.02[a]
Sex, *n* (%)				0.505
Male	161 (58.1)	59 (62.7)	17 (68.0)	
Female	116 (41.9)	35 (37.3)	8 (32.0)	
BMI, mean ± SD	26.8 ± 3.99	26.3 ± 4.05	26.0 ± 3.97	0.33
CCI, mean ± SD	5.12 ± 1.83	5.55 ± 2.38	6.04 ± 2.15	0.03[a]
ASA score, *n* (%)				0.018[a]
I–II	187 (67.5)	47 (50.0)	13 (45.8)	
III–IV	90 (32.5)	47 (50.0)	12 (54.2)	
Type of surgery, *n* (%)				0.071
Elective	238 (86.0)	72 (76.6)	19 (75.0)	
Urgent	39 (14.0)	22 (23.4)	6 (25.0)	
Surgical approach, *n* (%)				< 0.001[a]
Open	25 (9.0)	15 (16.0)	2 (8.0)	
Laparoscopic	238 (86.0)	72 (77.0)	15 (60.0)	
Conversion	14 (5.0)	7 (7.4)	8 (32.0)	
Procedure, *n* (%)				0.739
Right colectomy[1]	138 (49.8)	47 (50.0)	11 (44.0)	
Left colectomy	17 (6.1)	7 (7.4)	1 (4.0)	
Sigmoid/RS resection	55 (19.8)	15 (15.9)	4 (16.0)	
Low anterior resection	48 (17.3)	16 (17.0)	8 (32.0)	
Other	19 (6.8)	9 (9.6)	1 (4.0)	
Level of anastomosis, *n* (%)				0.66
Ileocolic	150 (54.1)	50 (53.2)	11 (44.0)	
Colocolic	23 (8.3)	5 (5.3)	1 (4.0)	
≥ 6 cm from AV	67 (24.2)	25 (26.6)	10 (40.0)	
< 6 cm from AV	37 (13.4)	14 (14.9)	3 (12.0)	
Covering stoma, *n* (%)	23 (8.3)	8 (8.51)	2 (8.0)	0.99
Blood loss in mL, mean ± SD	51.6 ± 36.6	58.8 ± 47.7	104.0 ± 191.1	< 0.001[a]
Intraoperative complications, *n* (%)	3 (1.1)	5 (5.3)	4 (16.0)	< 0.001[a]
Operative time in min, mean ± SD	141.9 (48.3)	146.2 (50.0)	172.8 (57.2)	0.011[a]
LOHS in d				< 0.001[a]
mean ± SD	7.4 ± 2.1	14.3 ± 7.4	24.0 ± 14.0	
Median	7	13	21	
90-d mortality, *n* (%)	0 (0)	0 (0)	3 (12.0)	< 0.001[a]

[a]$P < 0.05$.

[1]Included ileocecal resection/extended right-sided colectomy.

Group 1: No complications; Group 2: Complications not related to colorectal anastomotic leakage; Group 3: Colorectal anastomotic leakage. ASA: American Society of Anesthesiologists; AV: Anal verge; BMI: Body mass index; CCI: Charlson Classification Index; LOHS: Length of hospital stay; RS: Rectosigmoid; SD: Standard deviation.

Table 3 Items weighted for the early ColoRectAL leakage score from postoperative day 3 to 5

E-CRALL score	POD3	POD4	POD5
Body mass index	-0.05142	-0.02927	Not included
Charlson Comorbidity Index score	0.1403	Not included	Not included
Open surgery	Not included	-0.0196	Not included
ASA score III or IV	0.0764	Not included	Not included
Blood loss (in mL)	0.2418	0.2044	0.1426
Operative time (in min)	0.0070	0.0074	0.0041
Anastomosis colocolic	-0.1065	-0.0297	Not included
Intraoperative complications	1.1731	1.378	0.7685
Plasma level of CRP (in mg/L)	0.0099	0.0089	0.0066
Plasma level of CLP (in μg/mL)	0.1333	0.1809	0.4548
Plasma level of ECC (in cell/μL)	Not included	-0.0007	-0.0038
Clinical condition: improved	Not included	-0.6075	-2.199
Abdominal pain (absent/low)	Not included	-1.1150	-0.2843
Abdominal pain (at wound)	-1.19011	-1.845	-1.5299
Abdominal pain (localized)	Not included	Not included	1.2566

ASA: American Society of Anesthesiologists; CLP: Calprotectin; CRP: C-reactive protein; ECC: Eosinophil cell count; E-CRALL: Early ColoRectAL Leakage score; POD: Postoperative day.

Table 4 Sensitivity, specificity, positive predictive value, and negative predictive value for the Early ColoRectAL Leakage score according to the postoperative day

E-CRALL score	POD3	POD4	POD5
Threshold	5.51	2.56	8.29
Sensitivity, %	85.7	100	100
Specificity, %	66.1	69.6	86.6
PPV	13.8	17.2	32.1
NPV	98.7	100	100
CAL diagnosis, %	67.2	71.4	87.4
AUROC (95%CI)	0.82 (0.67-0.96)	0.84 (0.74-0.94)	0.95 (0.90-0.99)

AUROC: Area under the receiver operating characteristic curve; CAL: Colorectal anastomotic leakage; CI: Confidence interval; E-CRALL: Early ColoRectAL Leakage score; NPV: Negative predictive value; POD: Postoperative day; PPV: Positive predictive value.

score was associated with a cost savings of €421442.20, with most (92.9%) of the savings from patients who did not develop CAL (Table 8).

DISCUSSION

One strategy to anticipate CAL diagnosis included pooling clinical and laboratory variables in a weighted scoring system to improve the diagnostic accuracy measures of these variable when used separately. Design complexity, the need for external validation, and the difficulties in implementation in daily clinical practice are some of the challenges of score systems. So far, four scores have been developed for early CAL diagnosis; these are the Dutch leakage (DULK) score[11], its modified version (the modified DULK)[4], the Diagnostic Leakage (DIACOLE) score[10], and those based on artificial intelligence methods[13]. Each score has aimed to identify patients early, with suggestive CAL findings based on a cutoff point (discriminant threshold) to establish a management plan that includes additional

Table 5 Time to CAL diagnosis and time savings by adopting the Early ColoRectAL Leakage from postoperative day 3 to postoperative day 5

E-CRALL score	POD3	POD4	POD5
Time to CAL diagnosis in d	3.9	4.0	5.0
Expected time saving in d	5.2	5.1	4.1

CAL: Colorectal anastomotic leakage; E-CRALL: Early ColoRectAL Leakage score; POD: Postoperative day.

Table 6 Inpatient episode cost and length of stay based on standard clinical practice vs Early ColoRectAL Leakage score adoption on postoperative day 5

	Non-CAL patients		CAL patients	
Cost	Standard	E-CRALL	Standard	E-CRALL
Index costs in €	3177.00	1946.84	9096.00	8176.88
Index LOHS in d	9.1	5.0	24.0	20.0

CAL: Colorectal anastomotic leakage; E-CRALL: Early ColoRectAL Leakage score; LOHS: Length of hospital stay; POD: Postoperative day.

Table 7 Inpatient episode cost analysis adjusted to postoperative day 3 to postoperative day 5

POD	Baseline setting	Model setting
POD3	3532.14	2533.44
POD4		2493.25
POD5		2320.64

POD: Postoperative day.

Table 8 Cost minimization analysis

Cost	Non-CAL patients	CAL patients	All patients
E-CRALL score costs, € (%)	722277.79 (77.9)	204422.00 (22.1)	926699.79
Standard practice costs, € (%)	1143720.00 (82.9)	236496.00 (17.1)	1380216.00
Cost savings, € (%)	421442.20 (92.9)	32074.00 (7.1)	453516.20

CAL: Colorectal anastomotic leakage; E-CRALL: Early ColoRectAL Leakage score.

exams or reoperation[4,10].

The E-CRALL score, proposed and tested in our study, demonstrated a substantial reduction in time to CAL detection (from 3.9 to 5.0 d) and expected time savings (from 4.1 to 5.2 d), depending on the day of its application. The use of the DULK score showed several benefits, namely the decrease in the delay to CAL detection (median 1.5 d compared to 4.0 d) and a reduction in CAL mortality (from 39% to 24%) compared to standard surveillance[11]. The modified version of the DULK aimed to simplify the original version of the score. It was accomplished through the reduction of the number of parameters necessary to compute the score, becoming user-friendly for clinicians in daily clinical practice[4]. With an exception for respiratory rate, the other three parameters were included in the E-CRALL warning score. The predictive ability of both the DULK modified version and E-CRALL score was quite similar. However, both score systems were developed based on distinct methodological approaches. Both tools aimed to recognize CAL early and seem to be useful as warning scores for further investigation (for example, CT scan with rectal contrast or reoperation).

The E-CRALL score has the benefits of a high AUROC after POD3, good predictive performance, and the inclusion of variables from the preoperative and intraoperative stages. However, our observations should be confirmed in a different cohort before their full clinical application. After external validation,

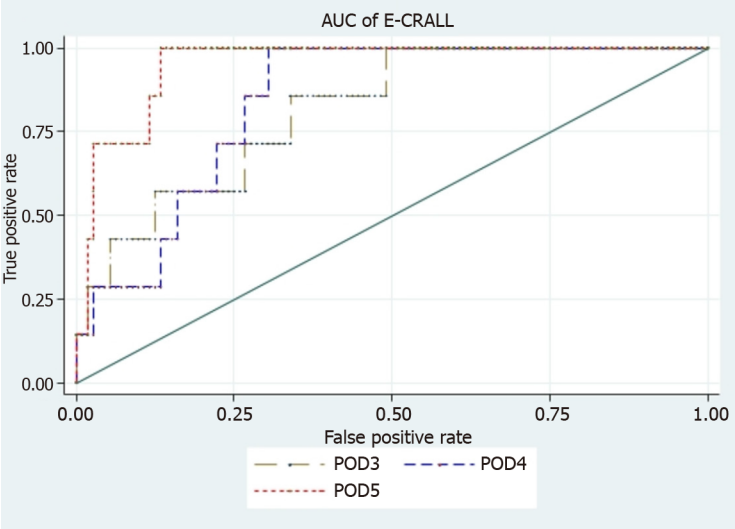

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Figure 3 Area under the receiver operating characteristic curve of colorectal anastomotic leakage for the Early ColoRectAL Leakage score for postoperative day 3 to postoperative day 5. AUC: Area under the curve; CAL: Colorectal anastomotic leakage; E-CRALL: Early ColoRectAL Leakage score; POD: Postoperative day.

E-CRALL may be useful for standardizing postoperative monitoring and aiding less experienced clinicians in the early detection of CAL, similar to the modified DULK score[4]. Martin *et al*[12], concluded that the DULK score was the most reliable instrument for early diagnosis of CAL. They also suggested its integration into risk management health policies to improve the quality of care according to the failure to rescue concept[12,18].

Artificial intelligence methods [*i.e.* artificial neural networks (ANNs)] were used by Adams *et al*[13] to create a tool capable of accurately identifying patients at risk of developing CAL. They developed an ANN-based score and then trained and validated the score on a retrospective cohort. The score included 19 input variables from the three phases of the surgical process, similar to the E-CRALL score. Internal validation produced an AUROC, SS, and SP of 0.89, 85.0%, and 82.1 %, respectively. External validation was estimated in a small prospective consecutive cohort (12 patients), presenting an SP of 83.3%. These results suggest good generalizability and effective prevention of overfitting by the ANN model. The authors concluded that models based on ANNs can assist in early detection of clinical CAL based on daily clinical data but not measuring this reduction to CAL detection, as E-CRALL score does.

The DIACOLE score was built from the results of a systematic review of the literature. At the onset, the potential laboratorial and clinical postoperative signs and symptoms of CAL were identified and complemented by a binary meta-analysis of those variables previously identified. Based on meta-analysis data, the weight of each identified factor was estimated. The DIACOLE diagnostic index showed an AUROC of 0.91, which was comparable with the E-CRALL score on POD5 (AUROC of 0.95) and was considered a good warning score for CAL diagnosis[10]. The diagnostic threshold of the DIACOLE score was established using the cutoff point that optimizes SS and SP. This estimation process was identical in both scores, even though the E-CRALL score delivered higher SS and SP (> 90%) than the DIACOLE score (82.9%)[10]. The authors of the DIACOLE score defined two discriminant thresholds: a lower level (> 3.065) advising daily clinical and laboratorial (with complete blood count) re-evaluation; and a higher level (> 5.436), recommending imaging (CT scan or water-soluble contrast enema)[10]. On the other hand, the E-CRALL score established just one threshold, dependent on the POD and recommending imaging (CT scan) or early reoperation (if equivocal or negative imaging). Because both score calculations seem to be burdensome due to assessment concerns, the authors developed a user-friendly free software to compute the score value[10]. Table 9 summarizes the distinctive aspects of the four scores available for CAL diagnosis.

This study has validated that the overall cost increases markedly for patients who develop CAL, being significantly greater (286.3%) than for patients who did not develop CAL. This result is in line with other reports. Ashraf *et al*[16] found an increase of 154% in the mean in-patient hospital cost for 20 patients with anastomotic leakage after anterior resection (£6233 ± £965 *vs* £9605 ± £6908 for non-CAL and CAL patients, respectively). Similar results were observed by other studies[2,25,26].

One of the aims of this study was to assess the economic value of the use of the E-CRALL score. When comparing expected costs of E-CRALL application with those of standard practice, the results clearly pointed to the economic advantage of E-CRALL. We assumed that the health outcomes with and without the E-CRALL score were similar. Overall costs decreased after E-CRALL use, revealing a reduction of 32.0% and 13.6% in non-CAL and CAL patients, respectively, compared with standard

Table 9 Distinctive aspects of the Dutch Leakage, Adams, Diagnostic Score Leakage, and E-CRALL scores

Aspect	DULK	Adams *et al*[12]	DIACOLE	E-CRALL
Preoperative parameters		X		X
Intraoperative parameters		X		X
Postoperative parameters	X	X	X	X
Method: Points (P)/Threshold (T)/AAN (A)	P	A	T (single)	T (daily)
Predictive ability (AUROC)	NA	0.89	0.91	0.95 (POD5)
Validation: Internal (I)/External (E)	I + E	I+E[1]	I	I
Early CAL detection	X			X

[1]External validation was obtained from 12 consecutive pilot prospective patients. AUROC: Area under the receiver operating characteristic curve; CAL: Colorectal anastomotic leakage; DIACOLE: Diagnostic Score Leakage; DULK: Dutch Leakage score; E-CRALL: Early ColoRectAL Leakage score; NA: Not available; POD: Postoperative day.

clinical practice. These overall savings were first and foremost explained by the reduction in LOHS, as evidenced by the high proportion of savings that were seen in the non-CAL group (92.9%). Decision support systems based on inaccurate data are a source of false positive and false negative results, with possible adverse impacts on health and financial outcomes. Both potential false positives (*i.e.* excessive investigations) and false negatives (*i.e.* missed diagnoses) were incorporated in this analysis. However, in this study, costs related to false positive and false negative results had a lower impact than the benefits of the reduction in the LOHS. Moreover, reducing the time to CAL diagnosis had a smaller positive economic effect, accounting for 7.1% of cost savings (€32074.00). So far, a cost minimization analysis has not been performed in any of the similar scores mentioned above, but these tools may provide useful real-world information for improving financial outcomes.

A strength of the E-CRALL score is the combination of preoperative, intraoperative, and postoperative variables, emphasizing the clinical method because it incorporates technology (three biomarkers: calprotectin, C-reactive protein, and eosinophil cell count) and information from clinical data and physical examination (preoperative and intraoperative aspects, abdominal pain, and clinical condition).

Another strength of the E-CRALL score is defined as a single warning threshold, depending on the POD, and then recommending imaging (CT scan) or early reoperation (if equivocal or negative imaging). This simplifies the CAL detection approach. Additionally, an early operation in cases of dubious or negative imaging, helps reduce the time to CAL detection and consequently starts CAL treatment promptly. Other authors concluded that early reoperation, namely re-laparoscopy, for managing complications following colorectal surgery appears to be safe and effective in highly selected patients[27-29]. The key approach for this selection can involve the adoption of the E-CRALL score. In addition, a policy of early reoperation in patients with suspected complications enables timely management with expedient resolution, saving time to CAL diagnosis and to discharge[29].

This study has several limitations. First, it is noteworthy that the E-CRALL score was developed and tested on only one dataset. Therefore, these findings should be considered with caution and should be validated externally, which is planned for a future multicentric, prospective study. Another limitation is related to the E-CRALL complexity for daily clinical implementation. It includes 13 diverse variables, which may increase the workload for healthcare staff.

Furthermore, this study addressed the economic burden of CAL in routine practice if all alternatives deliver equivalent health outcomes. This assumption is based on a conservative estimation since health outcomes improve with the early diagnosis[29,30]. In addition, there was a large divergence in the cost estimation of CAL, depending on the method of its calculation. This prospective study adopted comprehensive costs as there is the usual practice of public (National Health Service) reimbursement paid to the hospital. These methods may inadvertently underestimate costs due to under-coding or in contrast raise the practice of 'gaming' to receive more revenue. The estimation of personalized cost (tailored approach) by the aggregate of the index costs would be a more appropriate method[16,31].

Finally, it is crucial to estimate costs related to a delayed diagnosis as well as costs related to a high rate of false positive cases, unjustified reoperations, or frequent readmissions. Consequences of false negative cases on LOHS are difficult to accurately assess. A conservative policy was applied with the adoption of a cutoff with a SS around 100% to minimize the impact of false negatives on LOHS and the consequences of inappropriate early discharge.

CONCLUSION

The E-CRALL score demonstrated a high predictive ability, with SS and a negative predictive value of 100% after POD4 and a significant SP (86.6%) on POD5. This study internally validated the E-CRALL score for the early diagnosis of CAL and will integrate the local risk management policy, improving the quality of colorectal surgical healthcare. The routine adoption of the E-CRALL score may help prioritize CAL detection, supporting the policy of early reoperation in patients with suspected anastomotic failure. Even though the reduced time to CAL diagnosis had a smaller positive economic effect, overall costs decreased after E-CRALL use, revealing a noteworthy reduction of in-hospital costs, independent of CAL status, which was primarily due to the reduction in the LOHS in patients who did not develop CAL.

ARTICLE HIGHLIGHTS

Research background

Colorectal anastomotic leakage (CAL) is a surgical complication with a huge impact on morbidity and mortality. Early diagnosis of CAL can reduce these complications as well as hospital readmission and overall healthcare costs.

Research motivation

Decision models have been developed to increase the diagnostic accuracy of CAL. A user-friendly score applied in routine clinical practice can have a positive impact on the timely diagnosis of CAL and minimize healthcare costs.

Research objectives

To develop a score capable of assisting clinicians in early and accurate detection of CAL. In addition, we aimed to assess the cost-effectiveness of using this classification system in daily clinical practice.

Research methods

From March 1, 2017 to August 31, 2019, 396 patients who underwent colorectal resection with anastomosis were enrolled in a prospective, observational, single center study. A score based on the least absolute shrinkage and selection operator method developed and named the Early ColoRectAL Leakage (E-CRALL) score. The score performance and CAL threshold from postoperative day (POD) 3 to POD5 were estimated. A cost-minimization analysis was also conducted.

Research results

This study included 396 patients who underwent colorectal resection with anastomosis. Among them, 6.3% (n = 25) developed CAL. The median time to CAL diagnosis was 9.0 ± 6.8 d. From POD3 to POD5, the area under the receiver operating characteristic curve of the E-CRALL score was 0.82, 0.84, and 0.95, respectively. The score anticipated CAL diagnosis in an average of 5.2 d and 4.1 d if used on POD3 and POD5, respectively. Overall costs in patients who developed CAL were markedly higher in comparison with patients who did not develop CAL. The E-CRALL warning score was associated with a cost savings of €421442.20.

Research conclusions

The E-CRALL score demonstrated a high predictive ability, with sensitivity and a negative predictive value of 100% on POD4 and a significant specificity (86.6%) on POD5. The routine adoption of the E-CRALL score may help prioritize CAL detection. Overall costs decreased after E-CRALL use, revealing a noteworthy reduction of in-hospital costs, independent of CAL status, which was primarily from the reduction in the LOHS for patients who did not develop CAL.

Research perspectives

A prospective, multicentric study will be conducted to test the warning score and promote external validation of our research.

FOOTNOTES

Author contributions: Rama NJM, Guarino MPS, and Lourenço Ó designed the study; Lourenço Ó performed the data analyses; Rama NJM, Motta Lima PC and Guarino MPS prepared the manuscript; Rama NJM, Rocha A, Castro-Poças F, andPimentel J revised the paper critically; All authors read and approved the final manuscript.

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CASE REPORT

Preoperative blood circulation modification prior to pancreaticoduodenectomy in patients with celiac trunk occlusion: Two case reports

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Abstract

BACKGROUND

Celiac trunk stenosis or occlusion is a common condition observed in patients undergoing pancreaticoduodenectomy (PD). The risk of upper abdominal organ ischemia or failure increases if the blood circulation in the celiac arterial system is not maintained after the surgery.

CASE SUMMARY

We present two cases of elderly patients with distal cholangiocarcinoma and celiac trunk occlusion who underwent PD. We performed blood circulation modification preoperatively with transcatheter coil embolization of the arterial arcades of the pancreatic head *via* the superior mesenteric artery to develop collateral communication between the superior mesenteric artery and the common hepatic or splenic arteries to ensure arterial blood flow to the upper abdominal organs. The postoperative course was marked by delayed gastric emptying, but no major surgical complications, such as biliary or pancreatic fistula, or clinical, biochemical, or radiological evidence of ischemic disease, was observed.

CONCLUSION

Preoperative blood circulation modification may be a valid alternative procedure for elderly patients with celiac trunk occlusion who are ineligible for interventional or surgical revascularization.

Key Words: Preoperative blood circulation modification; Cholangiocarcinoma; Pancreaticoduodenectomy; Whipple procedure; Celiac trunk occlusion; Atherosclerosis; Transcatheter coil embolization; Case report

Core Tip: Celiac trunk stenosis or occlusion is a common condition observed in patients undergoing pancreaticoduodenectomy (PD). Celiac trunk occlusion may increase the risk of upper abdominal organ ischemia or failure. In this case report, we present two elderly patients who underwent PD for distal cholangiocarcinoma with celiac trunk occlusion. We performed blood circulation modification preoperatively with transcatheter coil embolization of the arterial arcades of the pancreatic head to develop collateral communication between the superior mesenteric and the common hepatic or splenic artery.

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INTRODUCTION

Celiac trunk stenosis is a common condition observed in up to 10% of patients undergoing pancreaticoduodenectomy (PD)[1,2]. If undiagnosed, it can lead to fatal ischemia of the upper abdominal organs after the surgery because the blood supply *via* the pancreatic head arcades is sacrificed intraoperatively due to the ligation of the gastroduodenal artery (GDA)[1-4]. Herein we describe two elderly patients who underwent PD following a novel blood circulation modification with transcatheter coil embolization of the arterial arcades of the pancreatic head.

CASE PRESENTATION

Chief complaints

Case 1: In June 2019, an 83-year-old man with a history of hypertension, chronic kidney disease, and chronic obstructive pulmonary disease was referred to our hospital for liver dysfunction during a blood test, fever, and anorexia.

Case 2: An 84-year-old man with a history of cervical spondylosis, chronic obstructive pulmonary disease, and atrial fibrillation was admitted to our institution in August 2019 with a 1-mo history of epigastric pain, weight loss, and dyspepsia.

History of present illness

Case 1: A computed tomography (CT) scan revealed celiac artery (CeA) occlusion due to atherosclerosis, with thickening of the extrahepatic bile duct wall and luminal stenosis, resulting in mild upstream bile duct dilatation, and the possibility of cholangitis or distal cholangiocarcinoma was enlightened.

Distal cholangiocarcinoma was suspected following magnetic resonance cholangiopancreatography (MRCP), which revealed a stricture of the extrahepatic bile duct and mild dilatation of the intrahepatic bile duct (Figure 1A and B). An ERCP with brushing cytology was performed to confirm the diagnosis, and a plastic stent was placed.

Case 2: CT revealed dilatation of the entire bile duct system, with 15-mm tissue obstructing the wall and lumen of the pancreatic tract of the common bile duct without pancreatic duct dilatation. Additionally, a small lymph node was observed around the hepatic hilum and abdominal aorta (Figure 1C and D). Distal bile duct cancer was suspected, and the patient underwent MRCP and ERCP with brushing cytology, which confirmed the diagnosis.

Laboratory examinations

Case 1: Distal cholangiocarcinoma cT2N0M0 stage IIA was diagnosed according to the American Joint Committee on Cancer (AJCC) 8th classification, and PD was scheduled.

Case 2: According to the AJCC 8th edition classification, a diagnosis of distal cholangiocarcinoma cT2N1M0 stage IIB was made, and PD was scheduled. A plastic stent was placed in the common hepatic duct preoperatively.

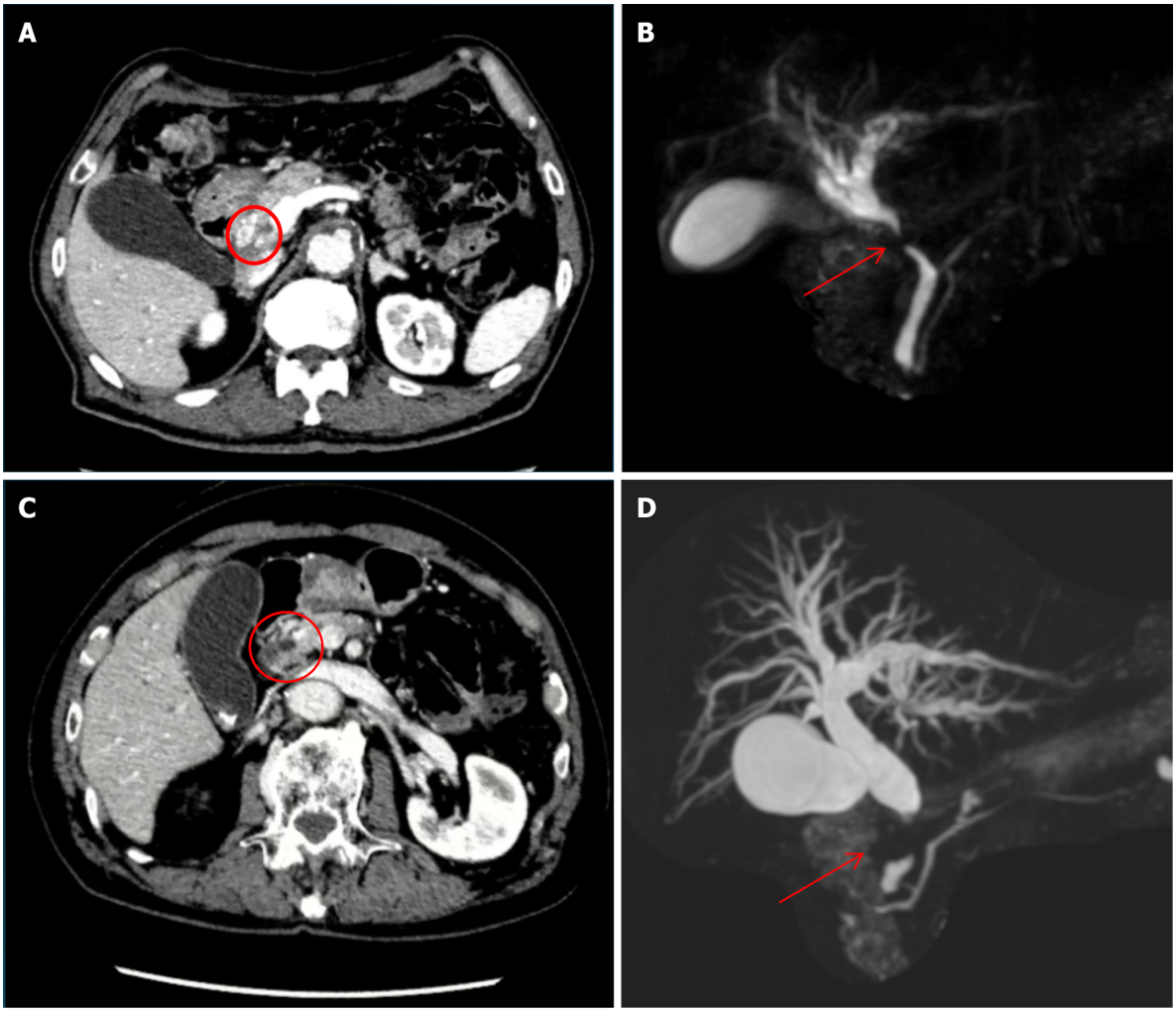

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Figure 1 Imaging examinations. A: Dynamic computed tomography (case 1) showing common bile duct wall thickening at the ductal confluence (circle) and mild dilatation of the intrahepatic bile duct; B: Magnetic resonance cholangiopancreatography showing stricture of common bile duct (arrow) and dilatation of the intrahepatic bile duct; C: Dynamic computed tomography (case 2) showing bile duct wall thickening at the upper pancreatic margin level (circle) with dilatation of the entire bile duct system without pancreatic duct dilatation; D: Magnetic resonance cholangiopancreatography showing stenosis of the distal common hepatic duct (arrow) and dilatation of the intrahepatic bile duct.

Imaging examinations

Case 1: An angiographic study and CT with 3D reconstruction were performed; complete occlusion of the CeA and complex anomalous arterial anatomy were observed (Figure 2). The inferior pancreaticoduodenal artery (IPDA), which branches from the superior mesenteric artery (SMA), supplied the celiac arterial system's primary blood supply, while the dorsal pancreatic artery (DPA) supplied the right hepatic arteries (RHA) and splenic arteries (SPA). Preoperatively, we embolized the arterial arcades of the pancreatic head using a coil to increase blood flow *via* the SMA to the RHA and SPA (Figure 3). Both post-procedural CT and angiography confirmed the development of blood flow sustained by the DPA, and no radiological signs of ischemic complications were observed.

Case 2: On preoperative CT, complete CeA obstruction due to atherosclerosis and a well-developed collateral pathway between the SMA and CeA were observed (Figure 4). Angiography revealed complete celiac trunk occlusion, maintenance of the major backflow to the celiac arterial system by two main pathways (the pancreatic head arcades), and linkage of the DPA to the common hepatic artery (CHA). We speculated that celiac arterial blood flow could be supplied *via* the DPA; however, ligating the GDA would cause blood flow reduction. Hence, there was a high risk of severe ischemia of the upper abdominal organs.

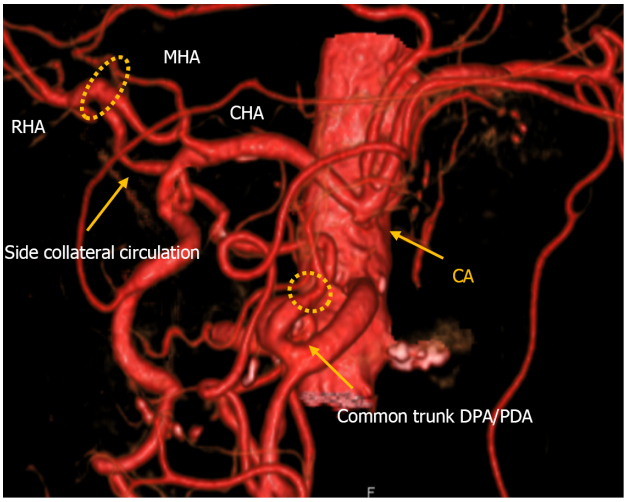

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Figure 2 Computed tomography with 3D reconstruction of the vascular anatomy in case 1. Computed tomography showed a right hepatic artery (RHA) and middle hepatic artery originating from the common hepatic artery, the usual pancreaticoduodenal arcade originating from the gastroduodenal artery, a common trunk between the dorsal pancreatic artery and pancreaticoduodenal artery originating from the superior mesenteric artery, an additional arcade originating from the common trunk and passing through the dorsal surface of the pancreatic head and linking directly to the RHA, and a replaced left hepatic artery originating from the left gastric artery. RHA: Right hepatic artery; MHA: Middle hepatic artery; CHA: Common hepatic artery; PDA: Pancreaticoduodenal artery; SMA: Superior mesenteric artery.

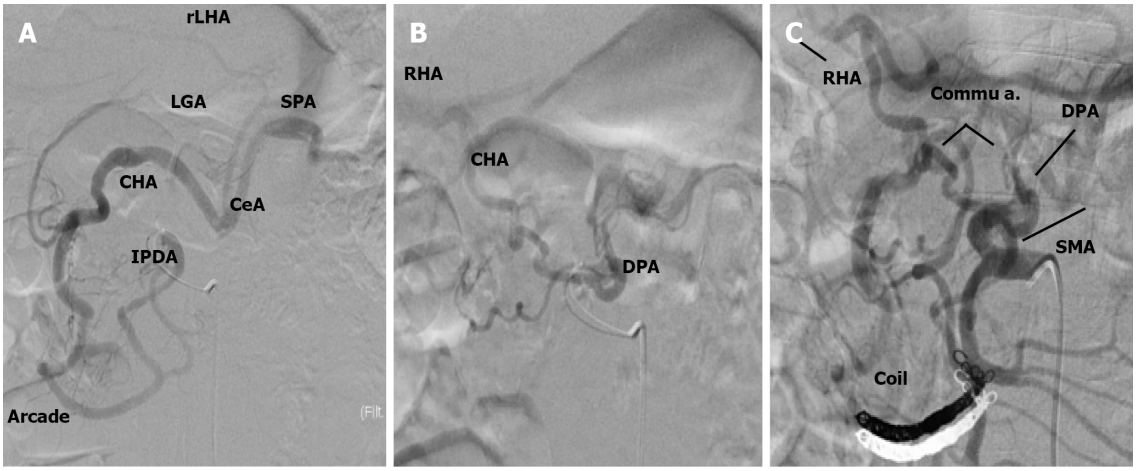

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Figure 3 Angiographic study. A: The inferior pancreaticoduodenal artery was responsible for the main back flow to the celiac artery; B: The dorsal pancreatic artery (DPA) was responsible for the blood flow of the right hepatic artery; C: Blood re-flow post embolization and the DPA was responsible for the main flow to the celiac artery. IPDA: Inferior pancreaticoduodenal artery; DPA: Dorsal pancreatic artery; SPA: Splenic arteries; RHA: Right hepatic artery; MHA: Middle hepatic artery; CHA: Common hepatic artery; GDA: Gastroduodenal artery; SMA: Superior mesenteric artery; LHA: Left hepatic artery; LGA: Left gastric artery; CeA: Celiac artery.

FINAL DIAGNOSIS

Case 1

Pathological diagnosis identified pT3apN1pM0, stage IIB, poorly differentiated biliary tract cancer. Of the 24 lymph nodes retrieved, only one was involved, and the lesion was completely included in the resection margin (R0 resection). The operative time was 7 h and 55 min, and the estimated blood loss was 700 mL.

Case 2

Pathological diagnosis identified pT2pN1pM0, stage IIB, intermediate-grade biliary tract cancer, which involved 3 of 20 lymph nodes retrieved.

The nodes and the lesion were completely included in the resection margin (R0 resection). The operation time was 6 h and 32 min, and the estimated blood loss was 200 mL.

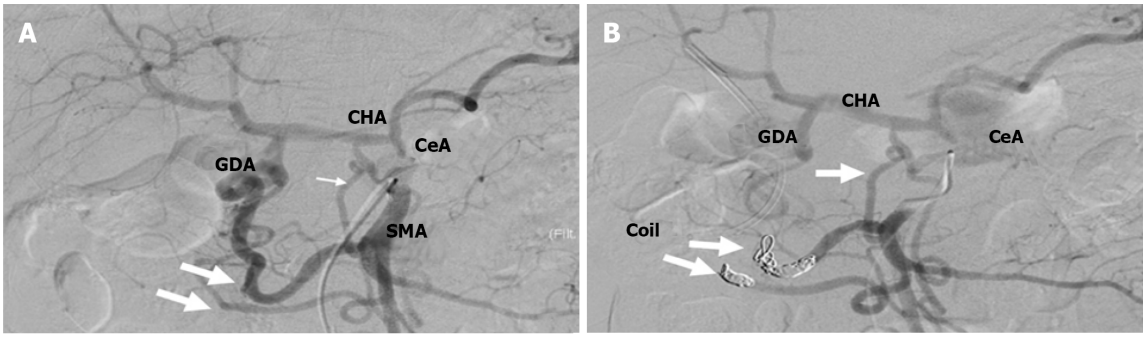

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Figure 4 Angiographic study. A: Pre-embolization angiography showed that the main backflow to the celiac artery was granted from the GDA; B: Post embolization angiography showed that after blood flow modification, the main backflow was granted from the dorsal pancreatic artery (arrow). CHA: Common hepatic artery; GDA: Gastroduodenal artery; SMA: Superior mesenteric artery; CeA: Celiac artery.

TREATMENT

Case 1

An open-approach Whipple procedure with D2 lymphadenectomy was performed in August 2019 (10 d after the TAE). During lymph node dissection around the hepatoduodenal ligament, the collateral artery from the DPA to RHA was successfully preserved.

Case 2

To reduce this risk, we decided to embolize the arterial arcades of the pancreatic head using a coil to increase the blood flow from the DPA to the CHA preoperatively. After embolization, angiography and CT confirmed blood re-flow from the DPA through the entire celiac arterial system, and no radiological signs of parenchyma or bowel ischemia were found. A standard open-approach Whipple procedure with D2 Lymphadenectomy was performed in September 2019 (10 d after the TAE). During the operation, the DPA was identified and preserved (Figure 5).

OUTCOME AND FOLLOW-UP

Case 1

Postoperatively, the patient developed blue toe syndrome and delayed gastric emptying but did not show any major surgical complications, such as biliary or pancreatic fistula; additionally, there was no clinical, biochemical, or radiological evidence of ischemic disease. The patient was discharged on postoperative day (POD) 56. The patient was not followed up; hence, no evidence of recurrence or delayed complications was obtained on the scheduled 6-mo CT scan.

Case 2

Postoperatively, the patient developed pneumonia, pulmonary embolism, and delayed gastric emptying but did not show any major surgical complications and was discharged on POD 41. No evidence of recurrence was observed at the 3-year follow-up.

DISCUSSION

Stenosis of the celiac trunk is a frequent occlusive vascular disease that can be observed in 2%-11% of patients who undergo PD[2-5]. Occlusion of the celiac axis is a rare situation encountered in 1%-3% of patients and is associated with a higher risk of ischemic consequences on the liver and both hepaticojejunal and pancreatico-jejunal anastomoses[6].

The main causes of stenosis or total occlusion of the celiac trunk are compression by the medial arcuate ligament (MAL) followed by atherosclerosis, which accounts for nearly 90% of the causes, including aortic dissection, congenital causes, inflammatory disease, invasion of malignancy, and iatrogenicity[7].

The typical symptoms of celiac trunk stenosis include postprandial abdominal pain, nausea, vomiting, and weight loss; nevertheless, clinically significant ischemic disease is rarely encountered owing to the development of rich collateral vessels from the SMA[8]. The diagnosis of CeA stenosis can be easily accessed through CT and arteriography, with a detection rate of 91.5%[4]; evaluation of all the

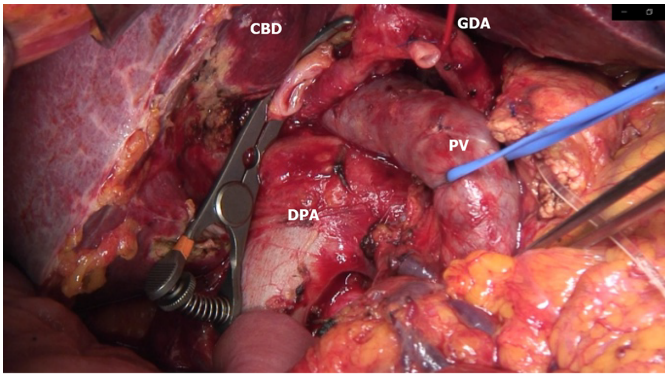

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Figure 5 Intraoperative image. The common bile duct was clipped with a bulldog, the gastroduodenal artery was ligated, and the portal vein was surrounded by a vessel loop at the bottom of the dorsal pancreatic artery hypertrophy. DPA: Dorsal pancreatic artery; CBD: Common bile duct; PV: Portal vein; GDA: Gastroduodenal artery.

collateral pathways is essential for any preoperative planning. When considering PD, any anatomical variant that may affect surgical planning should be evaluated using CT along with 3D reconstruction[9] and, in selective cases, angiographic studies. However, most surgeons do not routinely perform angiographic studies, and while preoperative imaging is often diagnostic, if an angiographic study is not performed in case of doubt, vascular sufficiency can be assessed intraoperatively.

Bull *et al*[3] endorsed a well-known maneuver that tested the pulsation of the hepatic artery before GDA ligation to ensure adequate patency of the collateral pathways. GDA ligation at its origin is an essential step during PD, and in the event of celiac trunk stenosis, the procedure can lead to ischemia of the liver, stomach, spleen, and residual pancreas, resulting in complications such as organ failure, abscess, and anastomotic leakage[4,5]. Berney *et al*[9] reported two cases of postoperative transient ischemic liver dysfunction and two cases of disruption of the pancreatic jejunal anastomosis in patients with CeA stenosis without preoperative or intraoperative revascularization procedures. Gaujoux *et al*[4] reported 545 patients who underwent PD and identified 23 CeA compressions by MAL, 2 CeA, and 2 SMA atherosclerotic stenoses. After PD, ischemic complications accounted for one-third of the 2.6% postoperative mortality, suggesting that ischemic complications account for significant morbidity and mortality after PD. Zhou *et al*[10] retrospectively analyzed the risk for biliary fistula in 508 patients who underwent PD, of which 84 had CeA stenosis due to atherosclerotic disease. The incidence of biliary fistulas was 2.1% in patients with mild CeA stenosis (1/47) and 27% in those with severe stenosis.

Different options have been proposed to treat CeA stenosis encountered during PD, majorly depending on the underlying disease. In cases of extrinsic compression caused by MAL, division of the median arcuate ligament can be performed intraoperatively[11]. In cases of atherosclerotic stenosis, percutaneous transcatheter angioplasty or stenting can be performed[12]. In cases of severe stenosis or complete occlusion, percutaneous revascularization with angioplasty or stenting of the CeA was not possible. Therefore, endovascular treatment *via* arcades of the pancreatic head[13] or surgical treatment with vascular reconstruction should be considered. Several surgical revascularization methods have been reported in the literature: Bypass grafting using autologous or prosthetics graft[14,15], end-to-end or end-to-side arterial anastomosis method[14-16] (Table 1), *etc*. Vascular reconstruction with PD increases the risk of thromboembolism and postoperative bleeding (caused by pancreatic fistula) and carries an intrinsic risk of thrombosis and leakage of the vascular anastomosis.

In our study, we treated two elderly patients with severe comorbidities and atherosclerotic diseases. In such cases, arterial bypass could be technically difficult because of diffuse atherosclerotic disease, and the risk of thrombosis and leakage of vascular anastomoses could be very high.

Considering the patients' advanced age and risk of comorbidities as well as to avoid the risk of fatal ischemic complications after PD, we decided to embolize the arterial arcades of the pancreatic head before the operation to increase the blood flow from the SMA to the celiac arterial system.

This expedient minimizes the risk of fatal ischemic complications after PD, ensuring that the entire collateral pathway and hypertrophy of the collateral vessels are preserved during the operation. We observed delayed gastric emptying, which was correlated with slight transient gastric ischemia. Repetitive postoperative CT showed strong hypertrophy of the collateral vessels, with good blood flow of the celiac arterial system and no vascular complications.

In elderly patients with severe stenosis or complete occlusion who are not eligible for interventional revascularization or surgical reconstruction, this technique is simple, feasible, repeatable in case of failure, and less prone to complications than any previous vascular reconstruction method. However, the use of CT and angiographic studies to evaluate vascular anatomy and eventually plan blood flow modification prior to the surgical procedure is crucial.

Table 1 Outcome of treatment in case of CA stenosis due to atherosclerosis

Ref.	Number of cases	Age, yr	Disease	Degree of CA stenosis	Treatment	Time between vascular reconstruction and surgery	Outcome	Discharged POD
Berney *et al* [9], 1999	13	69 median ages	Pancreatic adenocarcinoma	9 occlusion, 5 subtotal stenosis, 1 partial stenosis	2 GDA preservation	IO	Pancreatic fistula	N/A
			Pancreatic adenocarcinoma		1 aortohepatic bypass	IO	No complications	
			2 Pancreatic adenocarcinoma, 5 chronic pancreatitis, 1 ampullary cancer, 1 duodenal adenoma		9 no reconstruction	IO	2 liver ischemia3 pancreatic fistulas	
			Pancreatic adenocarcinoma		1 CeA reimplantation	IO	No complications	
Nara *et al*[2], 2005	2	57	Duodenal cancer	Occlusion	Middle colic right gastroepiploic anastomosis	IO	Transient liver ischemia	35 d
		61	Duodenal cancer	Occlusion	Preservation of replaced RHA	IO	Pancreatic fistula	128 d
Hayashibe *et al*[17], 2005	1	75	Duodenal cancer	Occlusion	Aorta-CHA venous bypass	IO	No complications	35 d
Halazun *et al* [16], 2006	1	65	CCA	50%	Preoperative stent	1 d	No complications	N/A
Soonawalla *et al*[5], 2007	1	60	Pancreatic adenocarcinoma	Occlusion	CeA reimplantation into aorta	IO	No complications	N/A
Smith *et al* [18], 2007	10	76 median ages (73-86)	Adenocarcinoma, ampullary tumor, islet cell tumor, papillary tumor	3 pt 30%; 1 pt 20%; 2 pt 50%; 1 pt 25%; 2 pt 60%; 1 pt occlusion	10 no reconstruction	IO	1 death for MOF, 1 GI bleeding	N/A
Gaujoux *et al* [4], 2009	3	72	Malignant ampulloma	N/A	Aortohepatic bypass	IO	Pancreatic fistula	N/A
	59	Pancreatic adenocarcinoma	N/A	Preoperative CeA stent	3 wk	Pancreatic fistula	N/A	
	77	Malignant ampulloma	N/A	Postoperative CeA stent	0 POD	Pancreatic fistula	N/A	
El-Ghazaly *et al*[19], 2009	1	70	Pancreatic adenocarcinoma	Occlusion	Anterior pancreaticoduodenal arcade resected and anastomosed end-to-end	IO	No complications	10 d
Berselli *et al* [20], 2010	1	72	Branch type IPMN	Occlusion	Side to side anastomosis SPPDA to the IPPDA	IO	Pancreatic fistula, GI bleeding, Splenic artery pseudoaneurysm	97 d
Yi *et al*[21], 2014	1	51	NET	N/A	Preoperative angioplasty and stent of CA	1 mo	No complications	7 d

Beane *et al* [22], 2017	1	69	Pancreatic cancer	Occlusion	SMA to HA venous bypass	IO	Pancreatic fistula, GI bleeding, pseudoaneurysm of graft; hepatic abscess (4 mo after discharge)	30 d
Zhou *et al*[10], 2018	84	73 median ages (61-88)	N/A	47 pt (mild 1%-49%); 37 pt (substantial 50%-99%)	No treatment	IO	2 deaths, 2 GI bleeding, 11 biliary fistulas, 8 pancreatic fistulas	21 d median (8-21 POD)
Tagkalos *et al* [23], 2018	1	64	Pancreatic adenocarcinoma	Occlusion (postoperative diagnosis)	Heparinization	3 POD	Transient liver ischemia	14 d
Oikawa *et al* [7], 2022	1	80	CCA	Occlusion	No reconstruction	IO	Pancreatic fistula	41 d

IO: Intraoperative; CCA: Cholangiocarcinoma; N/A: Not applicable; POD: Postoperative day.

CONCLUSION

In elderly patients with celiac trunk occlusion, PD can lead to a severe risk of postoperative complications, and preoperative blood circulation modification can reduce the risk of ischemic accidents. Precise preoperative anatomical studies of the vascular pathway and an optimal surgical or radiological technique must be chosen on a case-by-case basis to avoid unfavorable postoperative outcomes.

FOOTNOTES

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MINIREVIEWS

Timing of individualized surgical intervention in Crohn's disease

Kai Xia, Ren-Yuan Gao, Xiao-Cai Wu, Lu Yin, Chun-Qiu Chen

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Abstract

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract with an increasing incidence worldwide. Comprehensive therapy for CD focuses on symptom control and healing the intestinal mucosa to improve the quality of life and prevent complications. Surgical intervention plays a vital role in comprehensive therapy. However, deciding the optimal timing for surgical intervention has long been a focus of controversy. This review provides insights into the timing of surgery for CD and guides clinicians in daily treatment.

Key Words: Crohn's disease; Surgical intervention; Timing of surgery; Individualization; Therapy

Core Tip: Surgical intervention plays an important role in the comprehensive treatment of Crohn's disease (CD). However, the timing of surgery has always been a major controversial point. This review focuses on the main surgical indications for CD and the clinical factors that may influence surgical timing decisions. We also emphasize the value of early surgery in treating CD.

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease that can affect the entire digestive tract, especially the terminal ileum and proximal colon[1,2]. The course of CD is protracted, characterized by alternating active and remission stages. The epidemiologic patterns of CD depict that the prevalence and hospitalization rates are currently rising gradually worldwide, contributing to an increasing burden on healthcare systems[3-6]. The underlying cause of CD is still unknown but includes a variety of factors, including genetic susceptibility, environmental triggers, immune regulation, and gut microbial imbalance[7-9]. CD is prone to various complications due to penetrating and chronic intestinal inflammatory response, including intestinal obstruction, bowel perforation, fistula, or intra-abdominal abscess [10,11]. After diagnosis, approximately 50% and 70% of CD patients develop complications within 5 or 10 years, respectively[12,13].

Recently, the launch of new biological agents has breathed new life into the clinical treatment of CD, while surgical intervention still plays an indispensable role[14-16]. The cumulative surgery rate for CD patients is 16.6%, 35.4%, 53%, and 94.5% for 1, 5, 10, and 30 years, respectively, after the onset of the disease[17]. The choice of optimal timing for surgical intervention has always been a focus of controversy. Some scholars advocate for early surgical intervention if drugs fail to achieve good results. Nevertheless, the recurrence after surgery is almost inevitable, and approximately 40% of CD patients require reoperation[18]. Other scholars prefer to avoid early surgery only if it is necessary to resect the intestinal segments that cause complications following the principle of intestinal conservation. However, postoperative complications significantly increase due to poor nutritional status and severe abdominal infection[19]. This review mainly focuses on the choice of individualized surgical intervention timing for CD patients.

SURGICAL INDICATIONS FOR CD

According to the relevant literature and clinical experience, we summarize the main surgical indications for CD, which involve serious complications of CD (Figure 1), failure of medical therapy, and growth retardation in children.

Serious complications of CD

Intestinal obstruction: Intestinal obstruction is a common and serious complication of CD, especially fibrosis-associated intestinal stricture[20]. Lin *et al*[21] revealed that approximately 70% of CD patients inevitably develop fibrosis-associated intestinal stricture a decade following diagnosis. Medical treatment is frequently ineffective in patients who develop intestinal obstruction, and surgical resection is primarily required in that case[22,23]. Certainly, with the development of endoscopic technology, endoscopic balloon dilation is also an appropriate treatment option when the length of strictures is ≤ 5 cm, non-angulated, and with a sizeable intestinal cavity large enough to allow balloon dilators in the absence of contraindications such as the presence of fistula, abscess, or malignancy[24,25]. Furthermore, acute inflammatory obstruction can be frequently relieved by medical therapy. If conservative therapy is ineffective, surgical intervention should be considered to relieve the obstruction.

Intra-abdominal abscess: Intra-abdominal abscess is an important clinical complication of CD, the cause of which may be spontaneous or secondary to surgery[26,27]. The current first-line therapy for CD complicated by intra-abdominal abscess, is percutaneous abscess drainage with systemic antibiotics[28,29]. However, surgical intervention should be considered actively if the symptoms of sepsis do not improve after drainage, abscess ruptures with severe peritonitis, or multiple abscesses cannot be drained. Intestine resection appears to be inevitable in most CD patients presenting intra-abdominal abscess[30,31].

Fistula: Therapy for fistula has always been a complex clinical challenge. Simple enteral fistula without infection and clinical symptoms can be healed by a medical treatment such as enteral nutrition or biological agents[32,33]. For other complex enteral fistulae, including spontaneous enteroenteral or enteroexternal fistula formed after abscess drainage, the possibility of self-healing is low, and surgery should be adopted[34,35]. CD patients with severe fistula are often accompanied by loss of digestive fluid, resulting in disturbance of internal environmental balance, secondary infection, and malnutrition. Therefore, the infection should be readily controlled, and adequate nutritional support provided before elective surgery[36,37]. Yzet *et al*[38] recently reported successful cases of endoscopic treatment for enteroexternal fistula, which was feasible with short-term effectiveness.

Perianal lesions: Perianal lesions are common complications of CD, with perianal fistula and abscess being one of the most common[39,40]. The management of symptomatic simple perianal fistula and complex perianal fistula employs a multidisciplinary approach, which includes antibiotics, biological therapies, and surgery[41,42]. Furthermore, stem cell therapy is also an effective option for complex perianal fistula in CD patients[43,44]. As for the treatment of perianal abscess, surgical drainage and

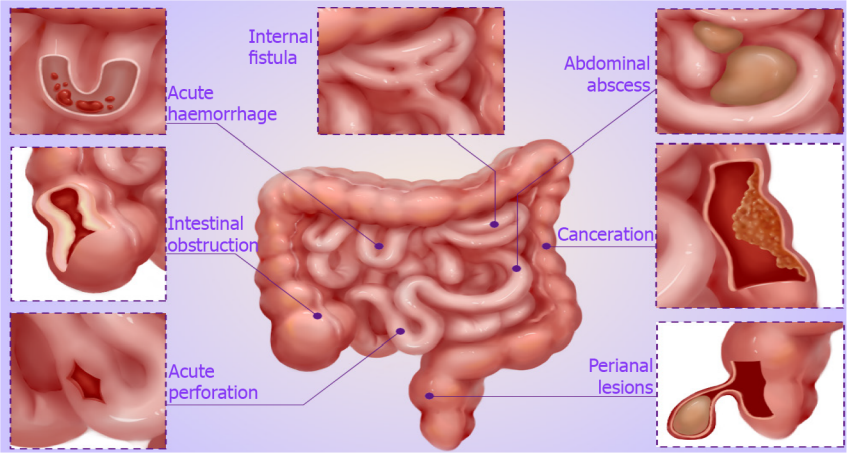

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Figure 1 Major categories of Crohn's disease complications, including intestinal obstruction, fistula, intra-abdominal abscess, perianal lesions, massive bleeding, perforation, and canceration.

antibiotic therapy are preferred.

Perforation, massive bleeding, or canceration: The incidence of CD complicated by acute perforation is low. However, emergency surgical intervention is often required if it occurs[45]. When complicated by massive bleeding, the location of bleeding should be identified, and treatments such as drug, endoscopic, or interventional hemostasis should be actively adopted. Emergency surgery is required if the above treatments fail and massive bleeding continues[46,47]. In addition, CD complicated by canceration is an absolute indication for surgery[48].

Failure of medical therapy: Surgical intervention may be considered when drug therapy fails, and symptoms such as intolerance to severe side effects and ineffectiveness to various biological agents are difficult to control.

Growth retardation in children: Pediatric CD often presents as a triad of abdominal pain, diarrhea, and weight loss, characterized by growth retardation[49,50]. Therefore, the pediatric treatment of CD induces and maintains clinical remission of the disease and optimizes nutrition and growth as soon as possible[51]. Surgery should be performed before puberty for prepubertal or early pubertal patients with severe malnutrition resulting in growth arrest[52]. Since the rate of postoperative recurrence is still high, drug therapy is required to maintain remission after surgery[53].

CLINICAL FACTORS AFFECTING TIMING OF SURGERY

Surgical intervention for CD aims to deal with complications and improve the quality of life of patients, as they tend to be in poor general conditions. Therefore, except for emergencies such as massive bleeding and acute perforation, adequate preoperative preparation should be completed to improve the efficacy of surgery. As a clinician, more attention should be paid to following the clinical factors to minimize perioperative complications.

Nutritional support

Malnutrition is one of the prominent clinical manifestations of CD. Our team recently published a study indicating that CD patients were at higher nutritional risk than healthy people[54]. It can hinder wound healing and increase the risk of incision infection, hernia, and anastomotic leak[55]. Therefore, nutritional status is recognized as an independent risk factor for postoperative complications. Yamamoto *et al*[56] revealed that patients with preoperative low albumin levels (< 30 g/L) had a 2.6-fold increased incidence of postoperative complications, similar to that reported by Shah *et al*[57]. Another study indicated that preoperative optimization with nutritional support reduced the overall rate of postoperative complications of CD[58]. Thus, perioperative nutritional support is vital for CD patients, while enteral nutrition should be adopted when the intestinal state permits. Appropriate enteral nutrition can improve the nutritional status, protect the intestinal mucosal barrier, and induce clinical remission[59,60]. It is a well-established and recommended first-line induction therapy in pediatric CD with remission rates of up to 80%[61].

Table 1 Correlations between drug factors and surgical complications of Crohn's disease

Ref.	Drugs	Type of study	Number of patients	Observations	Conclusion
Cohen *et al*[68], 2022	TNFis	Prospective study	947	Postoperative infection rate	No correlation
Uchino *et al*[69], 2022	TNFis	Retrospective study	305	Surgical mortality	No correlation
Abd El Aziz *et al*[70], 2022	TNFis	Prospective study	274	Intra-abdominal septic complications	No correlation
Azzam *et al*[71], 2022	Azathioprine	Retrospective study	105	Endoscopic recurrence rate	Negative correlation
Cosnes *et al*[72], 2005	Azathioprine	Retrospective study	2573	Intestinal complications	No correlation
Nguyen *et al*[73], 2014	Steroids	Retrospective study	15495	Postoperative sepsis and VTE	Positive correlation

TNFis: Tumor necrosis factor inhibitors; VTE: Venous thromboembolism.

Infection control

A recent study by Bachour *et al*[62] revealed that abdominal infection was associated with an increased risk of surgical postoperative recurrence of CD. Tzivanakis *et al*[63] indicated that the presence of preoperative abdominal abscess formation was identified as an independent predictor of anastomotic-associated complications. If the risk factor is present before surgery, the risk of anastomotic complications can be increased to 14%. Therefore, CD patients with abdominal abscesses can often be first managed with antibiotics and percutaneous drainage, while definitive surgical intervention should be performed after the infection has been controlled[64].

Effects of drugs

Whether preoperative CD treatment with tumor necrosis factor inhibitors (TNFis) increases the risk of postoperative complications remains controversial. TNFis may compromise immunity, collagen production, and angiogenesis, resulting in postoperative infective complications and altered wound healing[65,66]. In addition, TNF-α is a key cytokine in collagen production and angiogenesis, with animal studies confirming its role in wound healing[67]. However, previous studies have confirmed that preoperative TNFis exposure was not correlated with postoperative infectious complications[68-70] (Table 1).

Azathioprine is commonly used as an immunosuppressant for treating CD and may not increase the risk of postoperative complications. Although azathioprine has demonstrated efficacy in preventing postoperative recurrence, there is no significant decrease in the need for surgery or intestinal complications from CD[71,72] (Table 1). Furthermore, CD patients are frequently treated with steroids before surgery. Nguyen *et al*[73] indicated that preoperative steroids were correlated with a higher risk of postoperative sepsis (Table 1). Therefore, steroids should be minimized or discontinued 6 mo before surgery.

VALUE OF EARLY SURGICAL INTERVENTION IN TREATMENT OF CD

Early surgery for CD is commonly performed within a short time after diagnosis, while the time frame is still inconclusive[74,75]. An *et al*[76] defined early surgery as patients who had undergone upfront surgery for CD due to an acute complication and those who underwent surgery within 6 mo of diagnosis. Interestingly, this study revealed that patients with ileocolonic CD may have a better prognosis if undergoing early surgical intervention, with fewer admissions to the hospital and reduced overall operation rates. Aratari *et al*[77] also defined early surgery when performed at the time of CD diagnosis, when these patients underwent surgery for the acute or subacute presentation of CD. Meanwhile, late surgery was defined as patients with an established diagnosis of CD who underwent surgery during the course of the disease on account of intestinal complications or refractoriness to medical therapy. Early surgery may significantly prolong the time of clinical recurrence of CD compared to late surgery. Considering the lack of evidence from these retrospective studies, the conclusions warrant further verification.

Early surgical intervention may benefit patients with localized CD, which refers to intestinal CD affecting < 30 cm in extent. This usually applies to an ileocaecal location but also isolated colonic disease, or conceivably to proximal small intestinal disease[78]. Ponsioen *et al*[79] indicated that early laparoscopic surgery for localized CD could improve the overall quality of life of patients and reduce the rate of recurrence and reoperation. A long-term follow-up study by Stevens *et al*[80] during the LIR! C-trial revealed that most patients with localized CD who underwent early surgery were free of anti-TNF treatment, and none required a second surgery. Conversely, almost half of the patients who underwent anti-TNF treatment moved on to a Crohn-related resection. Furthermore, de Groof *et al*[81]

revealed that mean CD total direct healthcare costs per patient at 1 year were lower in the group who underwent early surgery compared with the anti-TNF group. Early surgical intervention is a reasonable and cost-effective treatment option for patients with localized CD.

China has a high incidence of hepatitis and tuberculosis. However, anti-TNF treatment may increase the risk of opportunistic infections[82,83]. Early surgery instead of anti-TNF treatment can reduce opportunistic infections. Additionally, early surgical resection of localized lesions may improve the response to postoperative anti-TNF treatment, the curative effect of which is better than that of the initial therapy[84,85].

CONCLUSION

CD is a refractory disease with a high misdiagnosis rate, a tendency for lifelong recurrence, and a high rate of operation and reoperation. Surgical intervention is a key part of the comprehensive treatment of CD. Inappropriate timing of surgery may lead to catastrophic postoperative complications, increasing the risk of surgery and prolonging hospital stays. Therefore, clinicians need to evaluate the severity and type of CD as well as the effectiveness of medical therapy and choose the timing of surgical intervention based on individual circumstances to ensure the maximum benefit for CD patients. Maybe in the future, with the deepening of multi-omics researches such as radiomics, metabolomics, and microbiomics, it will provide a more favorable basis for individualized timing of CD surgery and identify the early changes of CD related acute lesions.

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ORIGINAL ARTICLE

Basic Study

Hydrogen gas and preservation of intestinal stem cells in mesenteric ischemia and reperfusion

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Abstract

BACKGROUND

Patients with mesenteric ischemia frequently suffer from bowel necrosis even after revascularization. Hydrogen gas has showed promising effects for ischemia-reperfusion injury by reducing reactive oxygen species in various animal and clinical studies. We examined intestinal tissue injury by ischemia and reperfusion under continuous initiation of 3% hydrogen gas.

AIM

To clarify the treatment effects and target cells of hydrogen gas for mesenteric ischemia.

METHODS

Three rat groups underwent 60-min mesenteric artery occlusion (ischemia), 60-min reperfusion following 60-min occlusion (reperfusion), or ischemia-reperfusion with the same duration under continuous 3% hydrogen gas inhalation (hydrogen). The distal ileum was harvested. Immunofluorescence staining with caspase-3 and leucine-rich repeat-containing G-protein-coupled 5 (LGR5), a specific marker of intestinal stem cell, was conducted to evaluate the injury location and cell types protected by hydrogen. mRNA expressions of LGR5, olfactomedin 4 (OLFM4), hairy and enhancer of split 1, Jagged 2, and Neurogenic locus notch homolog protein 1 were measured by quantitative polymerase chain reaction. Tissue oxidative stress was analyzed with immunostaining for 8-hydroxy-2'-deoxyguanosine (8-OHdG). Systemic oxidative stress was evaluated by plasma 8-OHdG.

RESULTS

Ischemia damaged the epithelial layer at the tip of the villi, whereas reperfusion induced extensive apoptosis of the cells at the crypt base, which were identified as intestinal stem cells with double immunofluorescence stain. Hydrogen mitigated such apoptosis at the crypt base, and the LGR5 expression of the tissues was higher in the hydrogen group than in the reperfusion group. OLFM4 was also relatively higher in the hydrogen group, whereas other measured RNAs were comparable between the groups. 8-OHdG concentration was high in the reperfusion group, which was reduced by hydrogen, particularly at the crypt base. Serum 8-OHdG concentrations were relatively higher in both reperfusion and hydrogen groups without significance.

CONCLUSION

This study demonstrated that hydrogen gas inhalation preserves intestinal stem cells and mitigates oxidative stress caused by mesenteric ischemia and reperfusion.

Key Words: Hydrogen molecule; Intestinal ischemia; Ischemia-reperfusion injury; Tissue protection; Non-operative management; Leucine-rich repeat-containing G-protein-coupled 5

Core Tip: Distal ileum of rats was observed after 60-min mesenteric artery occlusion (ischemia), 60-min reperfusion following 60-min occlusion (reperfusion), or ischemia-reperfusion with the same duration under continuous 3% hydrogen gas inhalation (hydrogen). Immunofluorescence staining with caspase-3 and leucine-rich repeat-containing G-protein-coupled 5 (LGR5) (a specific marker of intestinal stem cell) identified ischemia damaged the epithelial layer at the tip of the villi, whereas reperfusion induced extensive apoptosis of intestinal stem cells that was mitigated by hydrogen. In addition, quantitative polymerase chain reaction revealed the LGR5 expression of the tissues was higher in rats with hydrogen inhalation than in those with reperfusion injury.

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INTRODUCTION

Mesenteric ischemia is caused by insufficient blood flow in the mesenteric artery to meet the metabolic demand of the visceral organs[1]. Despite the relatively low incidence of mesenteric ischemia, delayed diagnosis caused by vague symptoms sometimes results in devastating complications, such as intestinal necrosis, abdominal sepsis, and mortality[1-3]. While rapid recirculation of mesenteric vessels by endovascular or surgical intervention has been critical, increasing the arterial flow would be the only method of preserving the intestines when hemodynamic instability causes mesenteric ischemia[1,4,5]. Notably, some patients develop bowel necrosis even after revascularization of the mesenteric artery[6].

In the last decades, hydrogen gas (molecular hydrogen) has emerged as an attractive medicinal agent for various diseases, specifically for ischemic diseases that require revascularization[7-9]. Some animal studies have shown that hydrogen had anti-inflammatory effects and reduced the reactive oxygen species (ROS) that are produced during ischemia-reperfusion injury[7,8,10,11]. Hydrogen inhalation was associated with the reduction of necrotic tissues in the animal model of cerebral and myocardial ischemia[7,8]. Moreover, several clinical investigations have reported that hydrogen gas inhalation was beneficial on acute myocardial infarction and out-of-hospital cardiac arrest, which are typical ischemia-reperfusion injuries[12,13].

Furthermore, studies on the safety of hydrogen gas have identified that hydrogen can be supplied to patients using a simple device without any adverse events, suggesting its high feasibility for clinical use [12-14]. Although the physiological mechanisms of the possible therapeutic benefits remain unclear, recent studies have suggested that the antioxidant effects of hydrogen would be introduced by cell signal transduction, preventing cellular apoptosis[15,16]. Another study reported that oxidation-reduction reactions that involve molecular hydrogen occur only with strong fatal ROS rather than with weak or beneficial ROS[14].

Accordingly, as mesenteric ischemia with revascularization is an ischemia-reperfusion injury, we aimed to clarify the favorable effects of hydrogen gas inhalation for mesenteric ischemia as a novel

noninvasive treatment. In this study, we examined the degree of tissue damage in the intestines following ischemia and reperfusion and the tissue-protective effects of continuous initiation of 3% hydrogen gas. Moreover, several cell markers were substantially measured for the differentiation of hydrogen-target cells to elucidate the pathophysiological mechanisms of hydrogen.

MATERIALS AND METHODS

Animals

The protocol used in this study was approved by the Research Council and Animal Care and Use Committee of the Research Institute of Keio University in Tokyo, Japan (approval number 21013-0) and was performed in accordance with the guidelines for the care and use of laboratory animals established by the Japanese Pharmacological Society and the National Institutes of Health.

Eight-week-old male Sprague-Dawley rats (250-270 g) were purchased from Sankyo Labo Service Corporation, Inc. (Tokyo, Japan) and kept in a temperature- and light-controlled room (20 °C, 12-h light/dark cycle). The rats had free access to food and water. Before the procedure, they were intraperitoneally anesthetized with a combination of 0.3 mg/kg medetomidine, 2.0 mg/kg midazolam, and 2.5 mg/kg butorphanol. They were appropriately anesthetized throughout the procedure.

Hydrogen gas preparation

Hydrogen gas (3%) was prepared using a hydrogen gas supply device (Nihon Kohden Co., Tokyo, Japan)[14] and administered to rats at a rate of 0.2 L/min. The hydrogen gas stored in the device was mixed with air, and the targeted concentration was measured inside the supply device. The gas flow rate was adjusted at the output port of the device and validated with a flow meter attached to the respiratory circuit.

Experimental protocol

The rats were allocated to three groups: ischemia (control 1), reperfusion (control 2), and hydrogen groups. The ischemia group (n = 10) underwent a median laparotomy and dissection of the superior mesenteric artery. The artery was then occluded at the root by a double microclamp for 60 min. The marginal arteries of the intestines were also ligated at the ileocolic junction and at 15 cm proximal from the junction to achieve complete ischemia of the terminal ileum. The reperfusion group (n = 11) similarly underwent 60-min occlusion of the superior mesenteric artery and ligation of the marginal arteries. The occlusion was then released by declamping of the mesenteric artery, and reperfusion of the intestine was observed for 60 min without closing the abdomen[17,18]. The hydrogen group (n = 9) was connected to the respiratory circuit using a gas supply hood that covered the face and head of the rats, in which spontaneous respiration was maintained without using mechanical ventilation[14]. After hydrogen gas inhalation, the rats underwent the same surgical procedures as those in the reperfusion group.

In each rat, intestinal ischemia was confirmed by the paleness of the distal ileum and pulselessness of the mesenteric artery. The procedures of the tree groups were conducted simultaneously to reduce potential confounders by procedures. All animals were sacrificed immediately after the aforementioned procedures. A 2-cm-long ileum was then excised at 6 cm proximal from the ileocolic junction, which was processed for histological evaluation and ribonucleic acid (RNA) extraction. Blood samples were also obtained directly from the left ventricle[19]. Details of study protocol were not pre-registered nor published.

Histological evaluation

Tissues were fixed in 4% neutral-buffered paraformaldehyde, and 4 μm paraffin-embedded sections were prepared. Hematoxylin and eosin (H&E) staining was performed to evaluate histopathological changes that were visually compared between the three groups (ischemia, ischemia-reperfusion, and ischemia-reperfusion under hydrogen gas inhalation).

For immunostaining, samples were deparaffinized and rehydrated, and endogenous peroxidase activity was then suppressed using 0.3% hydrogen peroxide (H_2O_2) in methanol. Nonspecific binding was blocked with bovine serum albumin (BSA) for 30 min. Primary rabbit antirat antibody against active caspase-3 (CST 9661S; Cell Signaling Technology, Beverly, MA, United States) or against 8-hydroxy-2'-deoxyguanosine (8-OHdG) that is an oxidized nucleoside of DNA induced by ROS (N45.1; Japan Institute for the Control of Aging, Fukuroi, Shizuoka, Japan) was applied with 1:200 dilution and then incubated overnight at 4 °C. After washing, sections were incubated with biotinylated antirabbit antibodies (Vector Laboratories, Burlingame, CA, United States) diluted to 1:200 in a blocking serum for 30 min. Sections were subjected to peroxidase along with 3,3'-diaminobenzidine-tetrahydrochloride and H_2O_2 (Elite ABC Kit and DAB Substrate Kit; Vector Laboratories). Slides were washed and counter-stained with Gill's hematoxylin (Accustain; Sigma-Aldrich, St. Louis, MO, United States), and samples were microphotographed at Zeiss Axioscope2 (Carl Zeiss, Oberkochen, Germany).

Frozen sections of the harvested tissues were incubated with one of the following primary antibodies diluted in 0.1% BSA/phosphate-buffered saline (PBS): LGR5 as an intestinal stem cell marker[20] (1:200, bs-1117R Bioss Antibodies Inc., MA, United States) and active caspase-3 (1:200). After washing with PBS/0.1% Tween 20 (Wako Pure Chemical Industries, Japan), sections were incubated with secondary antibodies for 1 h at room temperature using Alexa Fluor 488-conjugated (1:500, Invitrogen, CA, United States) or TAS fluorescence systems (NEL 702, PerkinElmer Life Sciences Inc., MA, United States). After counterstaining with Hoechst 33258 (94403, Sigma-Aldrich, MO, United States) to visualize nuclei, images were obtained with a BZ9000 (Keyence, Osaka, Japan).

RNA extraction, cDNA synthesis, polymerase chain reaction, and real-time polymerase chain reaction

Total RNA was isolated using a miRNeasy Mini Kit (Qiagen, Valencia, CA, United States) and converted to cDNA using the High-Capacity Reverse Transcription Kit (Applied Biosystems, Carlsbad, CA, United States), according to the manufacturer's instructions. Real-time polymerase chain reaction (PCR) was performed using a QuantiFast SYBR Green PCR Kit (Qiagen), according to the manufacturer's instructions. The PCR primers used in this study were as follows: LGR5 forward, 5'-TGTCATGTGAGCTGGATGG-3' and reverse, 5'-ATGCAGGAGACTGGCAGGTA-3'; OLFM4 forward, 5'-GTGGACAGAAGGTGGTACTCTG-3' and reverse, 5'- GCTGGACATACTCCTTCACCTTA-3'; Hes1 forward, 5'-ATAAACCCTCAACTGCTCCGT-3' and reverse, 5'-CCATGATAGGCTTTGATGACTTTCT-3'; Jag2 forward, 5'-CCACACCAGATGAGGAGCTG-3' and reverse, 5'-CAGAACTTGTTGCAGGTGGC-3'; Notch1 forward, 5'-TGGTCTCAACTGCCAGAACC-3' and reverse, 5'-CACTCGCAGTG-GTACTGTGT-3'; and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) forward, 5'-TTGTGCAGT-GCCAGCCTC-3' and reverse, 5'-GGTAACCAGGCGTCCGATAC-3'. Expression levels were calculated using the $2^{-\Delta\Delta Ct}$ method and normalized to levels of the internal control GAPDH[19,21,22]. Real-time PCR was performed by a researcher who was blinded to the group allocation.

Evaluation of systemic oxidative injury

Serum samples were prepared from blood using Nanosep® Centrifugal Devices with Omega™ Membrane 10K (Pall Corporation, NY, United States), according to the manufacturer's instructions. The supernatant was used to determine 8-OHdG by a competitive enzyme-linked immunosorbent assay (Highly Sensitive 8-OHdG Check; Japan Institute for the Control of Aging, Fukuroi, Shizuoka, Japan) [20].

Statistical analysis

Descriptive statistics are presented as median (interquartile range) or number (percentage). Intergroup comparisons of mRNA expressions and 8-OHdG concentrations were performed using analysis of variance with Tukey-Kramer as post-hoc test and/or Kruskal-Wallis tests, as appropriate. All statistical tests used a α error rate of 0.05 and were two-sided. All statistical analyses were conducted using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, United States), and Microsoft Excel (Microsoft, Redmond, WA, United States).

RESULTS

Intestinal mucosal injury

Histological sections with H&E staining showed morphologic changes in the intestinal mucosa of the ischemia group (Figure 1A), in which pyknosis was observed in the epithelial layer. Mucosa was more severely injured in the reperfusion group (Figure 1B), and extensive pyknosis in the epithelial layer, denudation of the tip of the villi, and capillary congestion were observed. Conversely, the hydrogen groups showed similar degree of injury to the ischemia group (Figure 1C), with mild epithelial pyknosis and denudation of the villi.

Intestinal stem cell injury by ischemia-reperfusion injury

Immunofluorescence analyses with caspase-3 antibodies revealed that the intestinal mucosa of the ischemia group was mainly injured at the epithelial layer closed to the tip of the villi (Figure 2A). In the reperfusion group, apoptosis was extensively identified at the crypt base, where intestinal stem cells exist[23,24], in addition to injuries at the whole epithelial layer (Figure 2B). Apoptosis at the crypt base was limited in the hydrogen group (Figure 2C), whereas epithelial injury was observed at the villi with a half side of the digestive tract.

In the ischemia group, immunofluorescence analyses using simultaneous staining of caspase-3 and LGR5, a specific protein for intestinal stem cell, revealed that LGR5-positive cells at the crypt base did not undergo apoptosis [caspase-3 (red) and LGR5 (green) were separately stained; Figure 3A]. Conversely, multiple LGR5-positive cells underwent apoptosis after reperfusion (there were double-stained cells with caspase-3 and LGR5; Figure 3B).

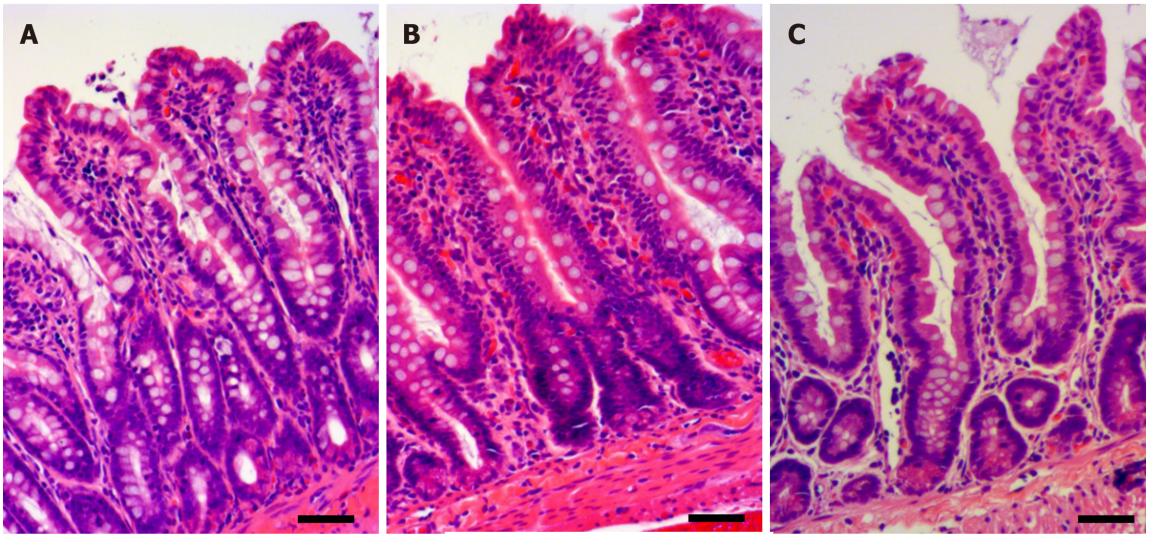

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Figure 1 Intestinal mucosal injury with ischemia-reperfusion injury. A: Histological sections with H&E stain showed pyknosis in the epithelial layer in the ischemia group; B: Extensive pyknosis in the epithelial layer, denudation of the tip of the villi, and capillary congestion in the reperfusion group; C: Mild epithelial pyknosis and denudation of the villi in the hydrogen group. Scale bar: 50 μm.

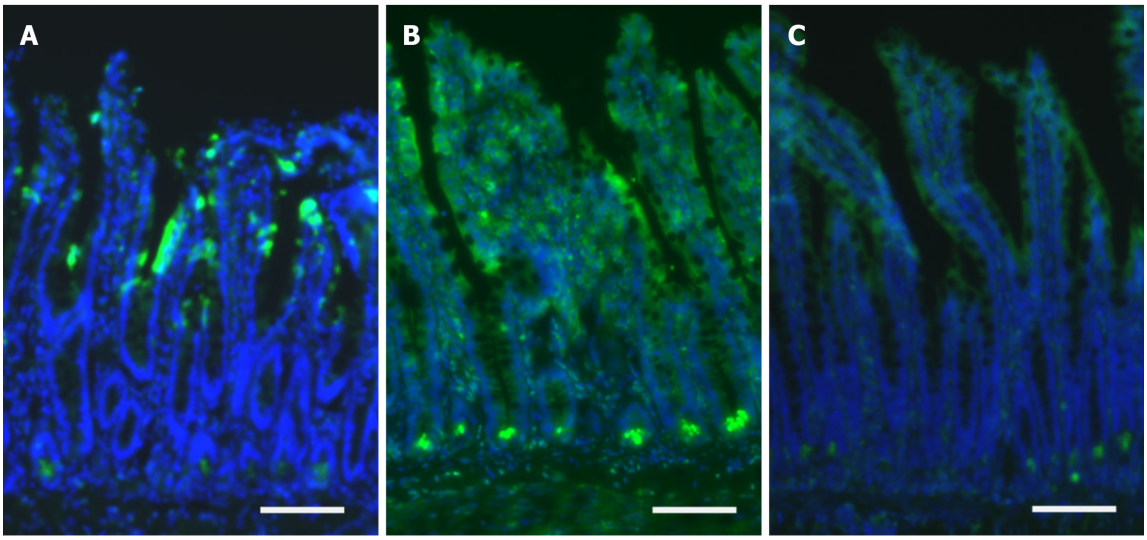

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Figure 2 Intestinal stem cell injury by ischemia-reperfusion injury. A: Immunofluorescence staining with caspase-3 (green) revealed mucosal injury at the epithelial layer closed to the tip of the villi in the ischemia group; B: Extensive apoptosis was identified at the crypt base and the whole epithelial layer in the reperfusion group; C: Apoptosis at the crypt base was limited in the hydrogen group. Scale bar: 100 μm.

Quantitative analysis of RNA with RT-PCR

Quantitative analyses of RNA in the homogenized intestinal tissues were conducted on LGR5, OLFM4, Hes1, Jag2, and Notch1, and Figure 4 summarizes these RNA expressions in the ischemia, reperfusion, and hydrogen groups. The expression of LGR5 was significantly lower in the reperfusion group than in the ischemia group, whereas the expression of LGR5 was higher in the hydrogen group than in the reperfusion group (Figure 4A). In addition, the expression of OLFM4 was relatively higher in the hydrogen group than in the reperfusion group, although the differences were not significant.

Conversely, the expression of Hes1, a transcriptional repressor of genes, was relatively high in the reperfusion group than in the ischemia and hydrogen groups (Figure 4B). Expressions of Jag2 (a ligand in Notch signaling for cell fate decision) and Notch1 (a transmembrane receptor in Notch signaling) were comparable among the ischemia, reperfusion, and hydrogen groups (Figure 4B).

Mucosal and systemic oxidative injuries

Immunostaining for 8-OHdG of intestinal tissue showed that the ischemia group had limited oxidative

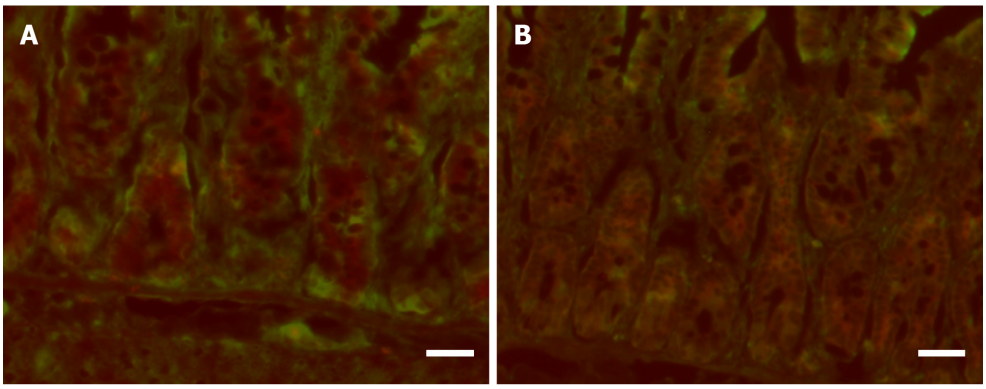

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Figure 3 Intestinal stem cell with double immunofluorescence staining. A: Double immunofluorescence staining with caspase-3 (red) and leucine-rich repeat-containing G-protein-coupled 5 (LGR5) (green) showed that LGR5-positive cells at the crypt base did not undergo apoptosis in the ischemia group (caspase-3 and LGR5 were separately stained); B: Multiple LGR5-positive cells underwent apoptosis after reperfusion (there were double-stained cells with caspase-3 and LGR5). Scale bar: 50 μm.

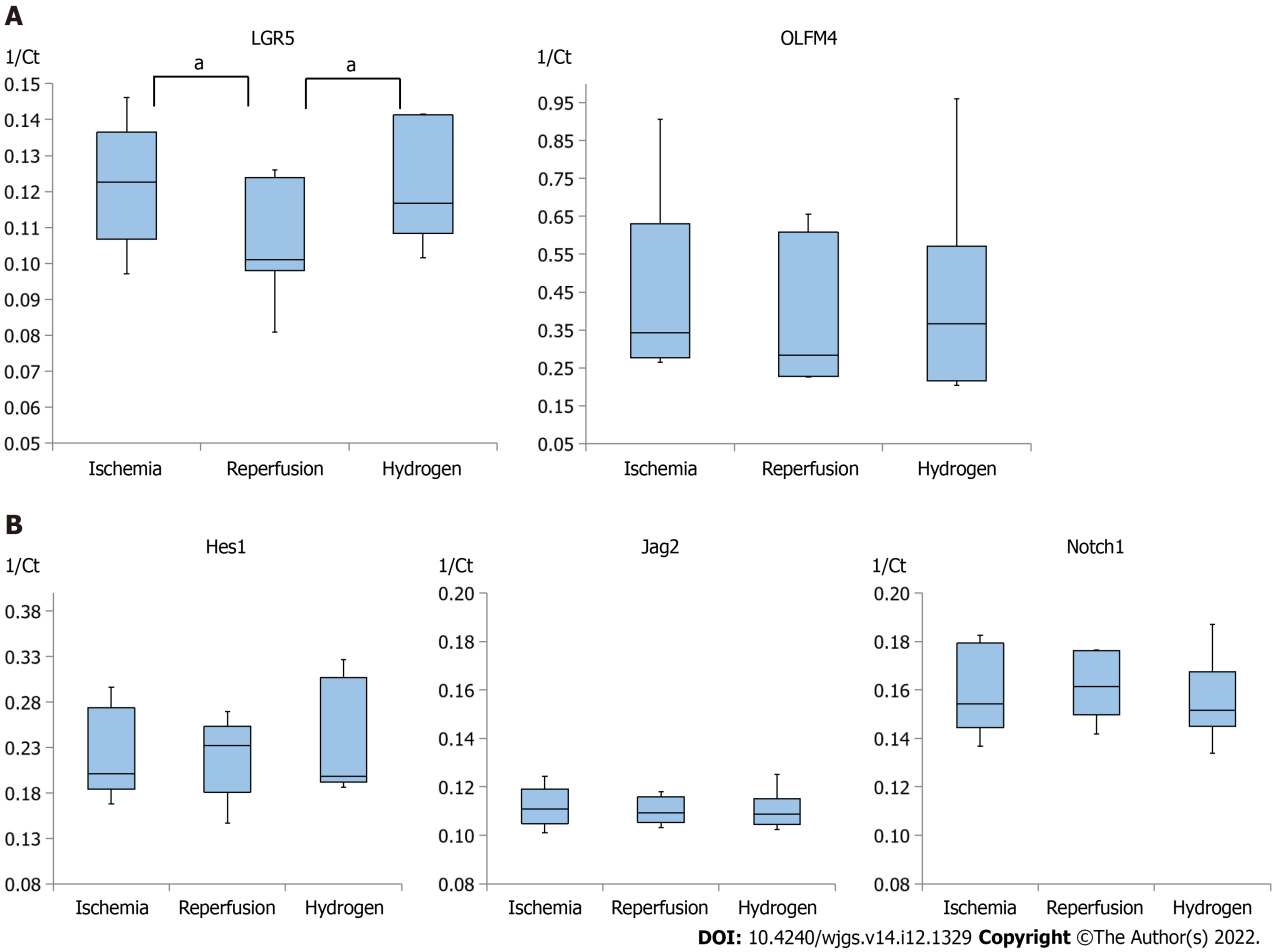

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Figure 4 Quantitative analysis of RNA. A: Leucine-rich repeat-containing G-protein-coupled 5 expression was significantly lower in the reperfusion group than in the ischemia group, but it was significantly higher in the hydrogen group than in the reperfusion group. Olfactomedin 4 expression was also relatively higher in the hydrogen group than in the reperfusion group, although the differences were not significant; B: Hes1 expression was relatively high in the reperfusion group than in the ischemia and hydrogen groups, whereas Jag2 and Notch1 expressions were comparable between the ischemia, reperfusion, and hydrogen groups. $^{a}P < 0.05$. LGR5: Leucine-rich repeat-containing G-protein-coupled 5; OLFM4: Olfactomedin 4; Hes1: Hairy and enhancer of split 1; Jag2: Jagged 2; Notch1: Neurogenic locus notch homolog protein 1.

stress at the intestinal mucosa, although considerable pyknosis occurred in the epithelial layer, particularly at the tip of the villi (Figure 5A). Conversely, the reperfusion group had extensive oxidative injury throughout the epithelium, including at the crypt base (Figure 5B). The hydrogen group had

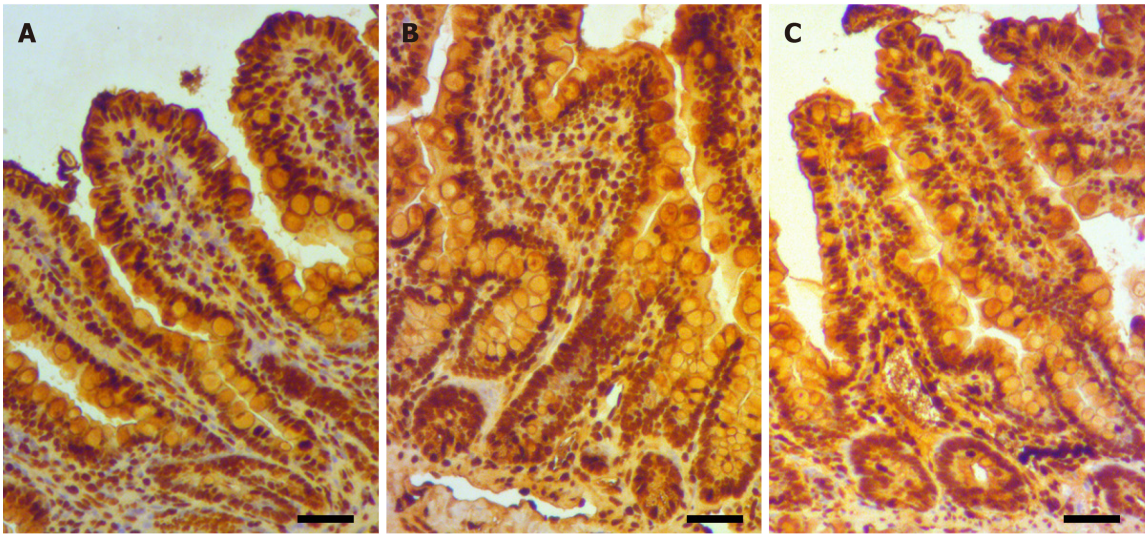

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Figure 5 Mucosal oxidative injury in the ischemia-reperfusion model. A: Immunostaining for 8-hydroxy-2'-deoxyguanosine showed limited oxidative stress at the mucosa in the ischemia group, although there was considerable pyknosis at the tip of the villi; B: Extensive oxidative injury throughout the epithelium, including the crypt base, in the reperfusion group; C: Mild-to-moderate oxidative injury at the mucosa of the crypt base, along with pyknosis with the denudation at the tip of the villi, in the hydrogen group. Scale bar: 50 μm.

mild-to-moderate oxidative injury at the mucosa of the crypt base, along with pyknosis with the denudation at the tip of the villi (Figure 5C).

Regarding systematic oxidative injury, the serum 8-OHdG concentrations immediately after the intervention in each group (ischemia, ischemia and reperfusion, and ischemia and reperfusion under hydrogen gas inhalation) are summarized in Figure 6. Despite the lack of significance, 8-OHdG concentration was higher in the reperfusion and hydrogen groups than in the ischemia group.

DISCUSSION

In this study, the tissue-protective effects of continuous hydrogen gas inhalation were histologically identified in the model of ischemic-reperfusion injury at mesentery. In addition, hydrogen protected intestinal stem cells from oxidative stress following ischemia-reperfusion injury, which has not been reported as therapeutic effect of hydrogen in previous studies. Notably, the intestinal stem cells were not injured by ischemia alone (ischemia without reperfusion), and therefore, hydrogen would provide tissue-protective effect only when reperfusion happens, rather than only ischemic injury exists.

Previous clinical and animal studies have suggested that hydrogen gas has anti-oxidative and anti-inflammatory effects on several critical diseases, such as cerebral infarction, myocardial infarction, and post-cardiac arrest syndrome[7,10,12]. Although pathophysiological mechanisms underlying these therapeutic effects remain unclear, hydrogen would attenuate excessive neutrophil activation and reduce hydroxyl radicals produced following an ischemia-reperfusion injury[25,26]. In this study, fewer oxidized nucleosides of DNA (8-OHdG) were observed at the crypt base of the intestines during continuous inhalation of hydrogen gas, which suggests that hydrogen mitigated ROS toxicity.

Immunofluorescence assay using LGR5 suggested that the intestinal stem cells would be a target of the therapeutic effects of hydrogen, at least under mesenteric ischemia and reperfusion. Stem cells have unique features, one of which is self-proliferation under adequate ischemic stimuli, whereas differentiated enterocytes undergo apoptosis because of ischemia-induced energy depletion[23,27]. In a study on the association between ROS and intestinal stem cells, modest ROS following ischemia would signal proliferation and differentiation of stem cells[27]. However, the same study suggested that high levels of ROS can induce intestinal stem cell apoptosis, which is similar to the observations in this study. We showed relative preservation of intestinal stem cells with ischemic stress alone and extensive apoptosis of stem cells with reperfusion that would have introduced massive ROS. Therefore, our results might indicate that hydrogen reduces excessive ROS caused by ischemia-reperfusion stimuli and prevents apoptosis of intestinal stem cells.

The protective effects of hydrogen on intestinal stem cells are also indicated by the higher LGR5 expression with hydrogen gas inhalation in the quantitative measurement of RNA. OLFM4 is a robust marker of LGR5-positive stem cells[28], and in this study, its expression was relatively higher in the hydrogen group than in the reperfusion group. Jag2/Notch1/Hes1 expressions have been reported to increase with epithelial cell proliferation following ischemia-reperfusion injury in the intestines[19].

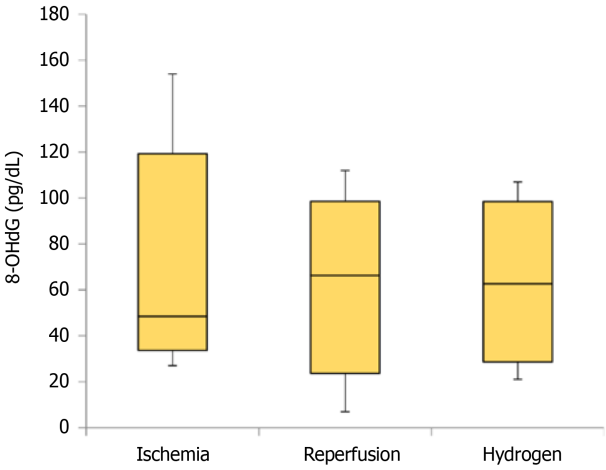

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Figure 6 Systematic oxidative injury in the ischemia-reperfusion model. Serum 8-hydroxy-2'-deoxyguanosine (8-OHdG) concentration immediately after each intervention (ischemia, ischemia-reperfusion, and ischemia-reperfusion under hydrogen gas inhalation) was measured. Although not significant, the 8-OHdG concentration was higher in the reperfusion and hydrogen groups than in the ischemia group. 8-OHdG: 8-hydroxy-2'-deoxyguanosine.

Expressions of Jag2 and Notch1 were comparable between the three groups, and the expression of Hes1 was slightly high in the reperfusion group, suggesting that proliferation signals at the epithelium under ischemia would be similar regardless of reperfusion or hydrogen inhalation.

Systemic oxidative stress was not different between the reperfusion and hydrogen groups. Therefore, hydrogen would not systematically affect the total amount of ROS in the body. Although hydrogen may reduce ROS in other tissues or organs in addition to the intestinal mucosa, such possible effects were not examined in this study. Moreover, the mechanisms of the reduction of ROS toxicity by hydrogen were not assessed. Future studies should focus on these topics to develop a noninvasive novel therapy using hydrogen gas.

CONCLUSION

This study reported on the tissue-protective effects of continuous hydrogen gas inhalation in ischemia-reperfusion injury in the intestines. The target cells of hydrogen might be intestinal stem cells, which are injured by excessive ROS caused by reperfusion following ischemia rather than by ischemic stress alone. The pathophysiological mechanisms for ROS reduction by hydrogen in stem cells should be further clarified in future studies.

ARTICLE HIGHLIGHTS

Research background

Mesenteric ischemia introduces unfavorable clinical outcomes particularly when bowel necrosis is diagnosed, and it can happen even after revascularization. However, promising treatment has not been developed to prevent bowel necrosis after revascularization.

Research motivation

Hydrogen gas inhalation has showed tissue preserving effects for several ischemia-reperfusion injuries by reducing reactive oxygen species (ROS) in various animal and clinical studies. In addition, the safety of hydrogen gas was shown by clinical studies that examined the efficacy of hydrogen on myocardial infarction and post-cardiac arrest syndrome. Therefore, hydrogen gas for mesenteric ischemia can be a novel noninvasive treatment.

Research objectives

This study aimed to clarify the favorable effects of hydrogen gas inhalation for mesenteric ischemia and reperfusion. We hypothesized that the degree of tissue damage in the intestines following ischemia and reperfusion would be mitigated by continuous initiation of 3% hydrogen gas.

Research methods

Rats were allocated to three groups: ischemia (control 1) that underwent 60-min occlusion of mesenteric artery by clamping under laparotomy, reperfusion (control 2) that underwent the ischemia procedure and 60-min release of occlusion, and hydrogen that underwent the ischemia and reperfusion under 0.3% hydrogen gas inhalation at a rate of 0.2 L/min. Then, the tissue damages at the ileum were histologically evaluated, using immunostaining against caspase-3, 8-hydroxy-2'-deoxyguanosine, and leucine-rich repeat-containing G-protein-coupled 5 (LGR5). Several mRNA, including LGR5, were quantitatively measured with RT-PCR.

Research results

The reperfusion procedure introduced intestinal tissue destruction, which was mitigated by hydrogen gas inhalation. In addition, the intestinal tissue injury by the reperfusion involved intestinal stem cell that was marked by LGR5, whereas the ischemia without reperfusion did not affect the stem cell. The expression of LGR5 was significantly lower in the reperfusion group than in the ischemia group, whereas the expression of LGR5 was higher in the hydrogen group than in the reperfusion group.

Research conclusions

This study reported on the tissue-protective effects of continuous hydrogen gas inhalation in the ischemia and reperfusion injury at the intestine. The target cells of hydrogen might be intestinal stem cells that are injured by excessive ROS caused by reperfusion following ischemia.

Research perspectives

Hydrogen may reduce ROS in other tissues in addition to the intestinal mucosa, which should be examined in the future study. Moreover, the mechanisms of the reduction of ROS toxicity by hydrogen should be revealed to validate the hydrogen as a noninvasive novel treatment.

FOOTNOTES

Author contributions: Yamamoto R, Suzuki S, Homma K, Yamaguchi S, and Sujino T designed the experiment; Yamamoto R, Suzuki S, and Homma K performed the experiment and analyzed the data; Sasaki J supervised the experiment; Yamamoto R and Suzuki S wrote the original manuscript; Yamamoto R, Suzuki S, and Homma K revised the manuscript; all authors reviewed the manuscript.

Institutional animal care and use committee statement: The protocol used in this study was approved by the Research Council and Animal Care and Use Committee of the Research Institute of Keio University in Tokyo, Japan (approval number 21013-0) and was performed in accordance with the guidelines for the care and use of laboratory animals established by the Japanese Pharmacological Society and the National Institutes of Health.

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

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ORIGINAL ARTICLE

Retrospective Study

Microbial spectrum and drug resistance of pathogens cultured from gallbladder bile specimens of patients with cholelithiasis: A single-center retrospective study

Xiao-Ming Huang, Zong-Jin Zhang, Nan-Rong Zhang, Jian-Dong Yu, Xiang-Jun Qian, Xian-Hua Zhuo, Jia-Yu Huang, Wei-Dong Pan, Yun-Le Wan

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Abstract

BACKGROUND

Bacterial infection is an important cause of cholelithiasis or gallstones and interferes with its treatment. There is no consensus on bile microbial culture profiles in previous studies, and identified microbial spectrum and drug resistance is helpful for targeted preventive and therapeutic drugs in the perioperative period.

AIM

To analyze the bile microbial spectrum of patients with cholelithiasis and the drug susceptibility patterns in order to establish an empirical antibiotic treatment for cholelithiasis-associated infection.

METHODS

A retrospective single-center study was conducted on patients diagnosed with cholelithiasis between May 2013 and December 2018.

RESULTS

This study included 185 patients, of whom 163 (88.1%) were diagnosed with gallstones and 22 (11.9%) were diagnosed with gallstones and common bile duct stones (CBDSs). Bile culture in 38 cases (20.5%) was positive. The presence of CBDSs (OR = 5.4, 95%CI: 1.3-21.9, P = 0.03) and longer operation time (> 80 min) (OR = 4.3, 95%CI: 1.4-13.1, P = 0.01) were identified as independent risk factors for positive bile culture. Gram-negative bacteria were detected in 28 positive bile specimens, and *Escherichia coli* (*E. coli*) (19/28) and *Klebsiella pneumoniae* (5/28) were the most frequently identified species. Gram-positive bacteria were present in 10 specimens. The resistance rate to cephalosporin in *E. coli* was above 42% and varied across generations. All the isolated *E. coli* strains were sensitive to carbapenems, with the exception of one imipenem-resistant strain. *K. pneumoniae* showed a similar resistance spectrum to *E. coli*. *Enterococcus* spp. was largely sensitive to glycopeptides and penicillin, except for a few strains of *E. faecium*.

CONCLUSION

The presence of common bile duct stones and longer operation time were identified as independent risk factors for positive bile culture in patients with cholelithiasis. The most commonly detected bacterium was *E. coli*. The combination of β-lactam antibiotics and β-lactamase inhibitors prescribed perioperatively appears to be effective against bile pathogens and is recommended. Additionally, regular monitoring of emerging resistance patterns is required in the future.

Key Words: Bacterial infection; Drug resistance; Cholelithiasis; Gallbladder bile culture

Core Tip: In this work, we analyzed the microbial spectrum of the bile of cholelithiasis patients, and their drug susceptibility pattern. We found that the presence of common bile duct stones and longer operative duration were independent risk factors for positive bile culture for patients complicated with cholelithiasis. The most commonly detected bacterium was *Escherichia coli*. In addition, the combination of β-lactam antibiotics and β-lactamase inhibitors prescribed perioperatively appears to be effective against bile pathogens secondary to carbapenems or glycopeptides and is recommended, but its resistance should also be noted.

Citation: Huang XM, Zhang ZJ, Zhang NR, Yu JD, Qian XJ, Zhuo XH, Huang JY, Pan WD, Wan YL. Microbial spectrum and drug resistance of pathogens cultured from gallbladder bile specimens of patients with cholelithiasis: A single-center retrospective study. *World J Gastrointest Surg* 2022; 14(12): 1340-1349

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INTRODUCTION

Bacteria can easily enter the biliary system from the duodenum; however, continuous bile secretion in the biliary system prevents their growth and colonization. Despite this, the presence of bacteria in bile has been reported in 9.5%-54.0% of patients with cholelithiasis or gallstones[1-3], and up to 70.2%-78.0% of patients with common bile duct stones (CBDSs)[4,5]. As the presence of bacteria in the biliary tract may increase the risk of postoperative septic complications[6-8], it is essential to identify the risk factors for positive bile culture during cholecystectomy and, accordingly, design a suitable antibiotic prophylaxis regimen[6,8].

The indiscriminate use of antibiotics in the last few decades has led to the emergence of multidrug-resistant (MDR) pathogenic bacteria[9], which have also been isolated from bile specimens[10]. Such

MDR microbes reduce the efficacy of empirical drugs[11,12]. Therefore, it is essential to identify the species of pathogenic bacteria found in the bile of cholelithiasis patients, as well as their drug susceptibility profile, in order to develop effective antibiotic regimens for biliary tract infections. To this end, we analyzed the distribution and drug resistance patterns of pathogens isolated from bile samples obtained from patients with cholelithiasis on the basis of bile culture and drug susceptibility test results.

MATERIALS AND METHODS

Study population

This study included patients with bile culture results who underwent cholecystectomy with or without common bile duct exploration, stone extraction, and T tube drainage between May 2013 and December 2018 at the Department of Hepatobiliary Surgery at The Sixth Affiliated Hospital of Sun Yat-sen University. The indications for surgical treatment were cholelithiasis and its complications. Most patients had presented with right upper abdominal pain or other discomfort at the time of admission. In all the included patients, a gallstone with acute or chronic cholecystitis was preoperatively diagnosed based on abdominal ultrasound and computed tomography (CT) imaging and confirmed after cholecystectomy. Each surgical procedure was performed by a professional hepatobiliary surgical team. Access to clinical data was approved by the Institutional Review Board of the Sixth Affiliated Hospital of Sun Yat-sen University (2022ZSLYEC-352).

Inclusion and exclusion criteria

Inclusion criteria were patients aged ≥ 18 years, who underwent cholecystectomy indicated by cholelithiasis and its complications. All included patients had complete clinicopathological and bile culture results. Exclusion criteria were cholecystectomy indicated by other reasons (n = 12), lack of bacterial culture results (n = 64), and contaminated bile culture sample (n = 2). Demographic characteristics, microbial spectrum and drug resistance of pathogens in patients were assessed. A total of 185 patients were included, and the clinicopathological and microbiological data were retrospectively collected from the medical record system. The research flow chart is outlined in Figure 1.

Bile culture, identification of bacteria, and drug sensitivity tests

Bile samples (5 μL) were extracted during cholecystectomy and promptly transported in sterile containers to a microbiology laboratory for bacterial culture as per standard protocols. Bacterial identification and drug susceptibility tests were performed using the French Bio-Merieux ATB-Expression Automatic Bacterial Identification and Drug Susceptibility Test instrument. The results were evaluated according to the 2010 recommendations of the American Society for Clinical Laboratory Standardization.

Statistical analysis

Data analysis was performed using SPSS 24.0 for Windows (SPSS Inc., Chicago, IL, United States). Continuous variables that followed Gaussian distribution were expressed as mean ± SD, and those with non-normal distribution were expressed as the median with interquartile range. Categorical variables were described using frequencies. Data were compared using the two-tailed student t-test, chi-square test, Fisher's exact test, or Mann-Whitney U-test, as appropriate. Significant covariates identified by univariate analysis were further analyzed by multivariate logistic regression analysis to determine the independent risk factors for positive bile culture. A P value < 0.05 was considered to indicate statistical significance.

RESULTS

Patient characteristics

Out of a total of 285 patients who underwent cholecystectomy between May 2013 and December 2018, 185 fulfilled the inclusion criteria and were included in this study. The cohort comprised 80 (43.2%) male and 105 (56.8%) female patients, and their mean age was 54.3 years (SD = 15). Twenty-two patients were diagnosed with gallstones accompanied by CBDSs, and bile cultures were positive for 17 (77.3%) of these patients. In contrast, only 12.9% (21/163) of the patients who did not have CBDSs had bacterial colonization in their bile samples. In addition, 155 (83.8%) patients had right upper abdominal discomfort. Laparoscopic cholecystectomy is the most common procedure used for removing gallstones, but four patients with calculous cholecystitis underwent open surgery due to severe adhesions. In addition, one patient with CBDSs underwent complete laparoscopic surgery. The median operative time was 80 (59-120) min, and cefotaxime/sulbactam sodium and cefamandole were the main preventive or therapeutic antibiotics used preoperatively. The overall rate of septic complications was 5.4% (10/185), and the incidence of septic complications was similar in the culture-positive and culture-negative

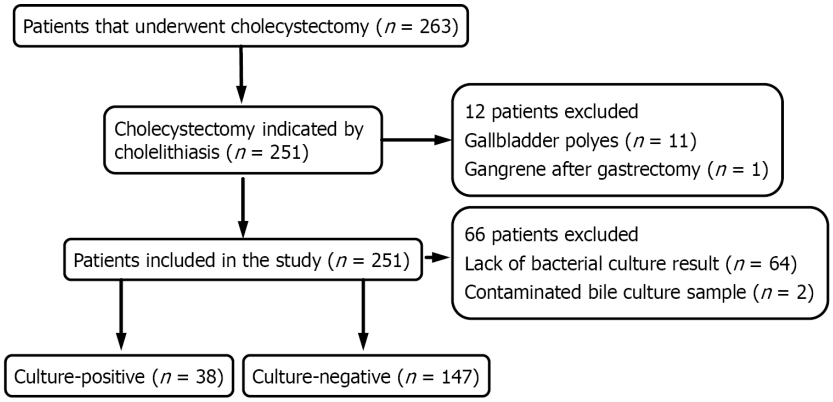

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Figure 1 Flowchart of the patient selection process.

patients [4.1% (6/147) *vs* 10.5% (4/38)]. The detailed demographic characteristics of both groups are summarized in Table 1, and they show significant differences in age, BMI, presence of CBDSs, previous endoscopic retrograde cholangiopancreatography (ERCP), previous use of antibiotics, presence of multiple stones, open surgery, operation time, and preoperative therapeutic antibiotics. Multivariate logistic regression analysis of these significant variables indicated that the presence of CBDSs (OR = 5.4, 95%CI: 1.8-21.9, P = 0.029) and longer operation time (OR = 4.3, 95%CI: 1.4-13.1, P = 0.01) were independent risk factors for bacterial colonization of bile samples (Table 2).

Microbial spectrum of bile specimens

Of the 38 (20.5%) patients with positive bile culture results, 28 (73.7%) harbored gram-negative bacteria that were predominantly from the family *Enterobacteriaceae*, including *Escherichia coli* (19 cases), *Klebsiella pneumoniae* (5 cases), *Enterobacter cloacae* (2 cases), *Enterobacter aerogenes* (1 case), and *Enterobacter mirabilis* (1 case). Gram-positive bacteria were detected in 10 (26.3%) patient samples and included *Enterococcus faecalis* (6 cases), *Enterococcus faecium* (3 cases), and *Staphylococcus aureus* (1 case) as the predominant species. No fungal species were detected, as shown in Table 3.

Antibiotics susceptibility test results

Based on the antibiotics susceptibility test results, the pathogens were divided into sensitive, intermediate resistant, and resistant groups, and pathogens assigned to the latter two groups were included in the resistance rate analysis. Due to differences in test strips, the results of the susceptibility tests differed across the patients. The resistance rate of *E. coli* against cephalosporins decreased with more advanced generations, and the rates were 68.4%, 57.9%, 52.6%, and 47.3% for cefuroxime, cefotaxime, ceftazidime, and cefepime, respectively. The resistance rate against ciprofloxacin was similar to that against cefoxitin (42.1%). *E. coli* also displayed a high level of resistance against broad-spectrum penicillins, that is, 78.9% and 63.2% against ticarcillin and piperacillin, respectively. Furthermore, *E. coli* exhibited a resistance rate of 83.3% against amoxicillin in 12 of the specimens tested. The combination of piperacillin and the β-lactamase inhibitor tazobactam was effective against *E. coli*, as it was associated with a low resistance rate of 15.8%. In addition, almost all the isolated bacteria were sensitive to carbapenems, with the exception of one that was resistant to imipenem. *K. pneumoniae* showed a similar resistance spectrum to *E. coli*, except that it had lower resistance against amikacin and ciprofloxacin. *Enterococcus* spp. exhibited a high resistance rate of 88.9% against aminoglycosides (gentamicin and streptomycin), while *E. faecalis* exhibited 100% sensitivity to glycopeptide. In contrast, several strains of *E. faecium* were resistant to glycopeptides (1/3) and penicillins (2/3). The results are summarized in Tables 4 and 5. Finally, 24 of the 38 patients harbored MDR strains, with 10 (52.6%) *E. coli* strains and 1 (20%) *K. pneumoniae* strain producing extended spectrum β-lactamases (ESBLs).

DISCUSSION

The gallbladder is a sterile organ, but pathological conditions, such as gallstones, polyps, and tumors, create favorable conditions for bacterial colonization by blocking bile circulation, which results in cholestasis[5,13]. Bacterial colonization can lead to inflammation of the biliary tract and even sepsis in severe cases. The main sources of biliary tract infection are the blood and duodenum[10]. In our study, bacteria were detected in the bile specimens of 20.5% cholelithiasis patients, and *Enterobacteriaceae* (73.7%; mainly *E. coli* and *K. pneumoniae*) and *Enterococcus* spp. (23.7%; *E. faecium* and *E. faecalis*) were the dominant species. Consistent with previous studies, most of the bacteria detected here were

Table 1 Baseline characteristics of the bile culture-positive group and culture-negative group

Parameter	Total	Culture-negative	Culture-positive	*P* value
Number	185	147	38	-
Age (yr; mean ± SD)	54.3 ± 15.0	52.4 ± 14.7	61.3 ± 14.2	0.001
BMI (kg/m^2; mean ± SD)	23.1 ± 3.4	23.4 ± 3.2	22.1 ± 3.8	0.040
Male (%)	80 (43.2)	61 (33.0)	19 (10.3)	0.346
Combined with CBDS (%)	22 (11.9)	5 (2.7)	17 (9.2)	< 0.001
Right upper abdominal pain (%)	155 (83.8)	120 (64.9)	35 (18.9)	0.118
Positive Murphy sign (%)	27 (14.6)	24 (13.0)	3 (1.6)	0.189
Diabetes mellitus (%)	11 (5.9)	8 (4.3)	3 (1.6)	0.699
Hypertension (%)	41 (22.2)	32 (17.3)	9 (4.9)	0.800
History of ERCP (%)	7 (3.7)	1 (0.5)	6 (3.2)	< 0.001
Previous intake of antibiotics (%)	44 (23.8)	29 (15.7)	15 (8.1)	0.011
WBC count (> 10 × 10^9/L)	16 (8.6)	11 (5.9)	5 (2.7)	0.267
Multiple stones (%)	132 (71.3)	99 (53.5)	33 (17.8)	0.018
Max diameter of stone (cm; mean ± SD)	1.2 ± 0.8	1.1 ± 0.8	1.3 ± 0.7	0.177
Non-laparoscopic surgery (%)	41 (22.2)	19 (10.3)	22 (11.9)	< 0.001
Operative time (min), median (IQR)	80 (59-120)	70 (56.5-93.8)	124 (95.0-188.8)	< 0.001
Septic complications (%)	10 (5.4)	6 (3.2)	4 (2.2)	0.125

CBDS: Common bile duct stone; ERCP: Endoscopic retrograde cholangiopancreatography; BMI: Body mass index; WBC: White blood cell.

Table 2 Multivariate analysis results of risk factors for positive bile culture

Variables	OR (95%CI)	*P*
Operation time > 80 min	4.3 (1.4-13.1)	0.01
Combined with CBDS	5.4 (1.3-21.9)	0.02

95%CI: 95% confidence interval; OR: Odds ratio; CBDS: Common bile duct stone.

endogenous and of intestinal origin[12,14,15]. Unlike other studies, however, we did not detect *Pseudomonas aeruginosa* or any fungal species[15,16]; this could probably be explained by our limited sample size.

The risk of bacterial invasion of the bile is associated with biliary obstruction, older age (> 70 years), acute cholecystitis, CBDSs, cholangitis, ERCP before cholecystectomy, and dysfunctional gallbladder[8,15,17]. In our study, the presence of CBDSs and longer operation time were identified as independent risk factors for positive bile culture. In the case of positive bile culture, postoperative antibiotic use needs to be adjusted in order to minimize the risk of infection after surgery. Studies have shown a higher incidence of postoperative septic complications in patients with positive bile culture than in those without bile infection[6,8,18], with the overall rates varying from 0.9% to 20.0%[6,8,19]. In contrast to these studies, in the present study, the rate of septic complications was 3.2% in the negative culture group and 2.2% in the positive culture group. This indicates that there was no significant correlation between the presence of bacteria and biliary sepsis. The differences in the findings may be associated with the empirical use of cefotaxime/sulbactam sodium and the smaller sample size in our cohort.

According to the definition of MDR proposed by the European Centre for Disease Prevention and Control Advisory Forum in 2010, it is described as resistance to one agent of at least three or more classes of antibiotics, but it does not cover intrinsic resistance or resistance against a key antimicrobial agent[9]. In the present study, although the antibiotic sensitivity tests did not include all the relevant antibiotics, the lowest incidence of MDR was 63.2%, which indicates that the rate of MDR is high in pathogens that infect bile. Cephalosporins and quinolones are commonly used to treat biliary tract infections, and the concentration of these drugs increases in bile after their absorption and metabolism [20,21]. However, as a result of the emergence of drug-resistant bacteria, the efficacy of conventional

Table 3 Composition of bile isolated bacteria

Isolated microbes	Total strains	Frequency
Gram-negative	28	73.7%
Escherichia coli	19	50.0%
Klebsiella pneumoniae	5	13.2%
Enterobacter cloacae	2	5.3%
Enterobacter aerogenes	1	2.6%
Enterobacter mirabilis	1	2.6%
Gram-positive	10	26.3%
Enterococcus faecalis	6	15.8%
Enterococcus faecium	3	7.9%
Staphylococcus aureus	1	2.6%
Fungus	0	0

Table 4 Antibiotics susceptibility test results for *Enterococcus spp*

	Enterococcus faecalis (6)		*Enterococcus faecium* (3)	
Antimicrobial agents	AST	Resistance (%)	AST	Resistance (%)
Gentamicin	1S + 5I	5 (83.3)	3I	3 (100)
Streptomycin	1S + 4I + 1R	5 (83.3)	2I + 1R	3 (100)
Ciprofloxacin	3S + 3I	3 (50)	2S + 1R	1 (33.3)
Levofloxacin	5S + 1I	1 (16.7)	2S + 1R	1 (33.3)
Vancomycin	6S	0	2S + 1I	1 (33.3)
Teicoplanin	6S	0	3S	0
Ampicillin	6S	0	1S + 1I + 1R	2 (66.7)
Penicillin	6S	0	1S + 2R	2 (66.7)
Quinupristin-dalfopristin	1S + 5R	5 (83.3)	2S + 1I	1 (33.3)
Tetracycline	3S + 3R	3 (50)	2S + 1R	1 (33.3)
Rifampin	1S + 1I + 4R	5 (83.3)	2S + 1R	1 (33.3)
Erythromycin	4I + 2R	6 (100)	1S + 2R	2 (66.7)

AST: Aspartate aminotransferase.

antibacterial drugs has begun to decline[9,10]. In this study, the gram-negative bacteria showed nearly 100% sensitivity to meropenem and imipenem, while 40% of the strains were resistant to cephalosporins and quinolones and over 50% were resistant to second- or third-generation cephalosporins. This high rate of resistance is mainly attributed to the emergence of ESBL-producing bacteria, which accounted for 52.6% of the *E. coli* strains isolated from our cohort. Therefore, the empirical treatment of biliary infections should take into account ESBL-producing bacteria. Treatment with multiple drug combinations, including β-lactamase inhibitors, has been highly effective against gram-negative bacilli[21-23]. This was confirmed by the high sensitivity of *E. coli* to piperacillin and tazobactam in the present study; however, *E. coli* exhibits a fairly high resistance rate against ticarcillin/clavulanic acid or amoxicillin/clavulanic acid. Aminoglycosides are also used to treat biliary infections[20], and the resistance rates of *E. coli* against gentamicin and amikacin were found to be 36.8% and 15.8%, respectively.

MDR *Enterococcus* spp. has been increasingly detected in recent years, and these species exhibit intrinsic resistance to most cephalosporins and carbapenems[9,24]. The overall prevalence of vancomycin-resistant *Enterococcus*, one of the major nosocomial pathogens worldwide[25], is 5%-20% [25,26]. In this study, *Enterococcus* spp., especially *E. faecalis*, were highly sensitive to ampicillin and penicillin. Interestingly, while only 14.7% of *E. faecalis* strains isolated in Japan are resistant to *β*-lactam

Table 5 Antibiotics susceptibility test results for *Enterobacteriaceae*

Antimicrobial agents	*Escherichia coli* (*n* = 19)		*Klebsiella pneumoniae* (5)		*Enterobacter cloacae* (2)	*Enterobacter aerogenes* (1)	*Enterobacter mirabilis* (1)
	AST	Resistance (%)	AST	Resistance (%)	AST	AST	AST
Amikacin	16S + 3R	3 (15.8)	5S	0	2S	1S	1S
Gentamicin	12S + 7R	7 (36.8)	4S + 1R	1 (20)	2S	1S	1S
Amoxicillin	2S + 10R	-	5R	5 (100)	1R	1R	-
Amoxicillin/clavulanic acid	11S + 3I + 5R	8 (42.1)	3S + 1I + 1R	2 (40)	1R	1I	1S
Ticarcillin	4S + 15R	15 (78.9)	5R	5 (100)	2S	1S	1S
Ticarcillin/clavulanic acid	4S + 8R	-	3S + 1R	-	1S + 1R	1S	1S
Piperacillin	7S + 12R	12 (63.2)	1S + 3I + 1R	4 (80)	2S	1S	1S
Piperacillin/tazobactam	16S + 3R	3 (15.8)	5S	0	2S	1S	1S
Cefazolin-1st	1S + 5R	-	1R	-	-	-	1R
Cefoxitin	11S + 8R	8 (42.1)	3S + 2R	2 (40)	1R	1R	1R
Cefuroxime-2nd	6S + 13R	13 (68.4)	2S + 3R	3 (60)	2S	1R	1S
Cefotaxime-3rd	8S + 1I + 10R	11 (57.9)	4S + 1I	1 (25)	2S	1S	1S
Ceftazidime-3rd	9S + 10R	10 (52.6)	4S + 1R	1 (25)	2S	1S	1R
Cefepime-4th	10S + 1I + 8R	9 (47.3)	4S + 1R	1 (25)	2S	1S	1S
ESBLs (+)	10	10 (52.6)	1	-	-	-	-
Ciprofloxacin	11S + 8R	8 (42.1)	4S + 1R	1 (20)	2S	1R	1I
Imipenem	18S + 1R	1 (5.3)	5S	0	2S	1S	1R
Meropenem	19S	0	5S	0	2S	1S	1S

AST: Aspartate aminotransferase; ESBLs: Extended spectrum β-lactamases.

antibiotics, 85.7% of the *E. faecium* strains are resistant to ampicillin and all strains of both species are resistant to penicillin[26]. In addition, *Enterococcus* spp. were found to be highly resistant to aminoglycosides and sensitive to teicoplanin, and only one vancomycin-resistant *Enterococcus* strain was detected in our study. All these results indicate that the antibiotic regimen against biliary infections should be based on both the antibacterial spectrum of the drugs and the resistance patterns. Therefore, clinicians should routinely test bile samples collected during cholecystectomy in order to monitor the pathogenic species and drug susceptibility. This will not only provide a definite guide for postoperative treatment, but also provide data for future empirical use of antimicrobial agents.

This single-center retrospective study is based on data from hospital medical records, and several limitations should be noted. This study is limited by its retrospective design, that is, a heterogeneous population and the possibility of a type II error. In particular, owing to the small number of patients included, further studies are required to validate our findings.

CONCLUSION

The risk of biliary infection increases in patients with cholelithiasis, and the risk is higher in patients with CBDSs and longer operation time. The dominant pathogens detected in this study were *E. coli*, *K. pneumoniae*, *E. faecium*, and *E. faecalis*. In addition, the combination of *β*-lactam antibiotics and *β*-lactamase inhibitors was found to be an effective first-line treatment against bile pathogens. However, we must also be aware of the emergence of resistance to certain types of drugs.

ARTICLE HIGHLIGHTS

Research background

Bacterial infection is an important cause of cholelithiasis or gallstones and interferes with its treatment.

Research motivation

Identified microbial spectrum and drug resistance of pathogens cultured from gallbladder bile specimens is helpful for targeted preventive and therapeutic drugs in the perioperative period.

Research objectives

Investigate the bile microbial spectrum of patients with cholelithiasis and the drug susceptibility patterns in order to establish an empirical antibiotic treatment for cholelithiasis-associated infection.

Research methods

A retrospective single-center study was conducted on patients diagnosed with cholelithiasis between May 2013 and December 2018.

Research results

The presence of common bile duct stones (OR = 5.4, 95%CI: 1.3-21.9, P = 0.03) and longer operation time (> 80 min) (OR = 4.3, 95%CI: 1.4-13.1, P = 0.01) were identified as independent risk factors for positive bile culture. Gram-negative bacteria were detected in 28 positive bile specimens, and *Escherichia coli* (*E. coli*) (19/28) and *Klebsiella pneumoniae* (5/28) were the most frequently identified species. Gram-positive bacteria were present in 10 specimens. All the isolated *E. coli* strains were sensitive to carbapenems, with the exception of one imipenem-resistant strain. *K. pneumoniae* showed a similar resistance spectrum to *E. coli*. *Enterococcus* spp. was largely sensitive to glycopeptides and penicillin, except for a few strains of *E. faecium*.

Research conclusions

The presence of common bile duct stones and longer operation time were identified as independent risk factors for positive bile culture in patients with cholelithiasis. The most commonly detected bacterium was *E. coli*. The combination of β-lactam antibiotics and β-lactamase inhibitors prescribed perioperatively appears to be effective against bile pathogens and is recommended.

Research perspectives

To explore the characteristics of patients infected with drug-resistant bacteria and the prevention and treatment of drug-resistant bacteria.

FOOTNOTES

Author contributions: Huang XM, Zhang ZJ, and Zhang NR contributed equally to this study; Huang XM, Zhang ZJ, and Zhang NR contributed to study design, patient inclusion and exclusion, data collection, data analysis and interpretation, and manuscript writing; Yu JD, Qian XJ, Zhuo XH, and Huang JY contributed to data collection; Pan WD and Wan YL contributed equally to the work; Pan WD and Wan YL contributed to critical revision of the manuscript for important intellectual content and study supervision; all authors read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of the Sixth Affiliated Hospital of Sun Yat-sen University (Approval No. 2022ZSLYEC-352).

Informed consent statement: The informed consent was waived in these patients.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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ORIGINAL ARTICLE

Retrospective Study

Low preoperative skeletal muscle index increases the risk of mortality among resectable pancreatic cancer patients: A retrospective study

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Abstract

BACKGROUND

The only potential curative treatment for patients with pancreatic cancer is surgery; however, the prognosis remains poor. Measures of body composition based on computed tomography (CT) have been established as a reliable predictor of the prognosis of cancer patients after surgery.

AIM

To elucidate the associations of body composition measures derived from preoperative CT scans with the prognosis of patients with pancreatic cancer.

METHODS

One hundred fifteen patients undergoing pancreatic resection with curative intent for pancreatic cancer were retrospectively enrolled. A preoperative CT scan at the third lumbar vertebral level was performed to measure the skeletal muscle index (SMI), mean skeletal muscle radiodensity, subcutaneous adipose tissue index, and visceral to subcutaneous adipose tissue area ratio. The clinical and pathological data were collected. The effects of these factors on long-term survival were evaluated.

RESULTS

Among the five body composition measures, only low SMI independently predicted overall survival (OS) [hazard ratio (HR): 2.307; 95% confidence interval (CI): 1.210-4.402] and recurrence-free survival (HR: 1.907; 95%CI: 1.147-3.171). Furthermore, patients with low SMI (*vs* high SMI) were older (68.8 ± 9.3 years *vs* 63.3 ± 8.4 years); low SMI was present in 27 of 56 patients (48.2%) aged 65 years

and older and in 11 of 59 younger patients (18.6%). In addition, subgroup analyses revealed that the correlation between low SMI and OS was observed only in patients aged 65 years and older.

CONCLUSION
Low preoperative SMI was more prevalent in elderly patients and was associated with a poor prognosis among pancreatic cancer patients, especially elderly patients.

Key Words: Pancreatic cancer; Body composition; Elderly; Skeletal muscle index; Prognosis

Core Tip: Measures of body composition have been regarded as a reliable prognostic predictor for cancer patients after surgery, but further research is needed. In this study, we showed that low preoperative skeletal muscle index (SMI) potentially predicts the prognosis of pancreatic cancer patients. We also revealed that low SMI was more prevalent in elderly patients and was associated with a poor prognosis among elderly patients after pancreatic cancer resection.

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INTRODUCTION

Pancreatic cancer is among the most aggressive malignancies, representing one of the leading causes of cancer-related deaths worldwide[1,2]. The only potential curative treatment modality for patients with pancreatic cancer currently available is surgery. However, approximately 80% of patients are estimated to present with either unresectable or metastatic disease at the time of the first admission[3]. In addition, the prognosis remains poor even for the small subset of patients with a localized, resectable tumor, with only 20% surviving for 5 years following surgery[4]. In this context, multiple factors, such as the tumor status, administration of adjuvant chemotherapy, and surgical radicality, have been recognized as tumor-related prognostic factors. Therefore, the characterization of these prognostic factors may help stratify patients for better individualized treatment and improve long-term survival outcomes.

According to the literature, body mass index (BMI) calculated from height and weight is a valuable indicator of body size. Recently, the relationship between obesity and pancreatic cancer has been extensively studied[5]. Data derived from clinical trials and meta-analyses have consistently shown that obesity (BMI > 25 kg/m^2) is associated with poor survival outcomes, but some studies have reported inconsistent associations with overweight or lower levels of obesity[6-8]. This discrepancy may be explained by the fact that BMI measures the relation of weight to height without assessing individual components of the body, such as muscle and adipose tissue, or components of weight with differing associations with survival.

Currently, a paucity of studies have explored measures of body composition mainly in patients with resectable pancreatic cancer[9-11]. Sarcopenia, an age-dependent decrease in skeletal muscle volume, was initially described in 1989[12]. Based on the recent consensus from the European Working Group on Sarcopenia in Older People and the Asian Working Group for Sarcopenia, computed tomography (CT) imaging at the level of the third lumbar vertebra is an effective imaging modality for the clinical detection of sarcopenia[13,14]. Several previous studies have documented that sarcopenia, which is mainly established by the presence of low muscle quantity and quality, is significantly associated with a poor prognosis for advanced pancreatic cancer patients[15-20].

Furthermore, numerous epidemiological and fundamental studies have provided evidence to support a possible link between obesity and pancreatic cancer[8,21,22]. Measures of body composition reflecting obesity, including visceral obesity [namely, a high visceral adipose tissue index (VATI)] and low skeletal muscle radiodensity (SMD) (a measure of muscle quality indicative of adipose tissue deposition in muscle fibers and reduced function), have been established as useful prognostic indicators[9-11,23]. Sarcopenia was recently identified as an independent prognostic factor, especially for elderly patients with esophageal cancer[24]. However, at present, no similar studies have been performed in patients with resectable pancreatic cancer. Therefore, we examined associations between cancer prognosis and the measures of body composition, including muscle mass, muscle radiodensity, and adiposity, in a retrospective cohort. Specifically, we analyzed the effects of measures of body composition on the

prognosis of patients in different age groups.

MATERIALS AND METHODS

Patient selection and data collection

A retrospective review was performed on the records from all patients who underwent pancreatectomy for resectable pancreatic ductal adenocarcinoma (PDAC) at a single institution from January 2015 to December 2019. Patients with abdominal CT scans captured within 1 wk before surgery that were available for analysis were included. Patients who had a history of abdominal surgery were excluded from the study. A total of 115 patients were finally enrolled in this study. Preoperative demographics, body weight, height, and laboratory data, including leukocytes, neutrophils, lymphocytes, platelets, albumin, and carbohydrate antigen 19-9 levels, were obtained from the electronic media database. Systemic inflammatory indicators were defined as follows: neutrophil-lymphocyte ratio (absolute neutrophil count divided by absolute lymphocyte count), platelet-to-lymphocyte ratio (absolute platelet count divided by absolute lymphocyte count), and systemic immune-inflammation index (SIII, platelet count × neutrophil-lymphocyte ratio). Tumor size, tumor location, pathological TNM staging (according to AJCC 8th edition), tumor differentiation grade, presence of perineural invasion, status of the resection margin, lymph node metastasis, and adjuvant chemotherapy were also recorded for analysis. This study was approved by the Institutional Review Board of Huadong Hospital Affiliated to Fudan University.

CT-based body composition assessment

Cross-sectional CT images of the third lumbar vertebra were analyzed using Slice-O-Matic software (v.5. Tomovision, Montreal, Quebec, Canada)[17,25]. In detail, various body composition parameters were measured, including subcutaneous adipose tissue area, visceral adipose tissue area, and skeletal muscle area. The following tissue Hounsfield unit (HU) thresholds were employed: -190 to -30 for subcutaneous adipose tissue, -150 to -50 for visceral adipose tissue, and -29 to 150 for skeletal muscle. As described previously, the body composition evaluation included the subcutaneous adipose tissue index (SATI), VATI, and skeletal muscle index (SMI), which were named and calculated from subcutaneous adipose tissue area, visceral adipose tissue area, and skeletal muscle area divided by height in meters squared (cm^2/m^2), respectively[9]. The visceral to subcutaneous adipose tissue area ratio (VSR) was calculated to assess the abdominal adipose tissue distribution, and skeletal muscle radiodensity was measured from the mean CT value (HU) of the whole skeletal muscle area to assess muscle quality. This procedure was performed by two experienced investigators who were blinded to the clinical characteristics of the participants.

Cutoff values and classification settings

Based on the considerable differences in body composition between sexes, sex-specific cutoff values were established using receiver operating characteristic curves for each body composition parameter[10,26]. The cutoff values were selected based on the best accuracy of 1-year mortality; thus, the cutoff value for SMI (cm^2/m^2) in males was 45.16 [area under the curve (AUC) = 0.650] and 34.65 (AUC = 0.698) in females. The cutoff values for mean muscle radiodensity (HU) in males and females were 35.8 (AUC = 0.538) and 30.47 (AUC = 0.793), respectively. The SMI and mean muscle radiodensity cutoff points possessing the maximum absolute value of the log-rank statistic were used to establish the incidence of low SMI and low SMD. In addition, the cutoff values were 0.86 (AUC = 0.574) and 1.06 (AUC = 0.639) for the VSR, 28.70 (AUC = 0.639) and 49.72 (AUC = 0.691) for the VATI (cm^2/m^2), and 43.99 (AUC = 0.599) and 48.76 (AUC = 0.635) for the SATI (cm^2/m^2) in males and females, respectively. The classifications of underweight, normal weight, and obesity were based on definitions applied to Asian populations[9]. The analyses were performed using the following BMI categories: < 20.0 kg/m^2, underweight; 20.0-24.9 kg/m^2, normal weight; and ≥ 25.0 kg/m^2, obese. According to the World Health Organization, 65 years was the established cutoff to define people as elderly[27].

Statistical analysis

Patient characteristics were summarized as counts and percentages for categorical variables and means and standard deviations for continuous variables. Differences in variables between groups were analyzed using Pearson's χ^2 test for categorical variables or the independent t test for continuous variables. Overall survival (OS) was defined as the interval from the first diagnosis until death, and recurrence-free survival (RFS) was calculated from the date of surgery to the date of recurrence or metastasis. Cumulative OS and RFS were estimated using the Kaplan-Meier method, and differences between groups were calculated using the log-rank test. The optimal high *vs* low values of inflammatory indicators were defined by examining a grid of cutoff values and choosing the cutoff value with the lowest -2 log-likelihood[28]. The effects of body composition parameters and clinicopathological factors on OS or RFS were evaluated using a Cox proportional hazards model. All variables with P < 0.05 in the univariate analysis were included in the multivariate analysis. The results were presented as

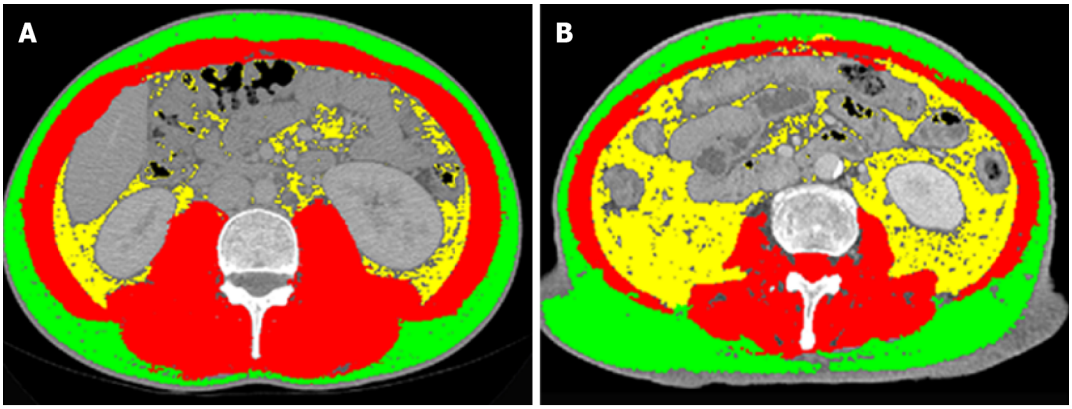

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Figure 1 Selective representative computed tomography images with tag overlay at the third lumbar vertebra level from two individual patients with pancreatic cancer presenting with similar body mass index (21.45 kg/m² in patient A and 21.48 kg/m² in patient B). The red, yellow and green shadows indicate the skeletal muscle area (SMA), visceral adipose tissue area (VATA), and subcutaneous adipose tissue area (SATA), respectively. Skeletal muscle index, subcutaneous adipose tissue index and visceral adipose tissue index were calculated from SATA, VATA, and SMA divided by height in meters squared, respectively. The visceral to subcutaneous adipose tissue area ratio was calculated by dividing VATA by SATA. Skeletal muscle density indicates the mean computed tomography value (HU) of SMA. A: Body mass index (BMI): 21.45; B: BMI: 21.48. SMI: Skeletal muscle index; SATI: Subcutaneous adipose tissue index; VATI: Visceral adipose tissue index; VSR: Visceral to subcutaneous adipose tissue area ratio; SMD: Skeletal muscle density; HU: Hounsfield unit.

hazard ratios (HRs) with 95% confidence intervals (CIs). All statistical analyses were conducted using SPSS (SPSS 25.0, IBM Inc., Chicago, IL, United States) and GraphPad Prism (GraphPad Software 8.0.1, San Diego, CA, United States). P values < 0.05 were considered statistically significant.

RESULTS

Demographic characteristics of the patients

The clinicopathological characteristics of the 115 enrolled patients were summarized (Table 1). According to the sex-specific cutoff values, 38 (33.3%) patients were characterized by low SMI, whereas 26 (22.6%) patients were characterized by low SMD. Patients with low SMI were older, more likely to be male, had poorly differentiated carcinoma, and had a tumor located in the pancreatic head compared to those with high SMI. Additionally, patients with low SMI more frequently had lower albumin levels. In addition, an older age and perineural invasion were highly predominant among patients with low SMD. Notably, we observed that neither SMI nor SMD was significantly associated with the TNM stage or indicators of systemic inflammation, such as the neutrophil-lymphocyte ratio, platelet-to-lymphocyte ratio, and SIII.

Prognostic value of body composition for patients with resectable pancreatic cancer

First, the prognostic value of the widely used measurement BMI was assessed. Both obesity and underweight were related to a worse prognosis for pancreatic cancer patients than normal weight; however, a significant difference in survival was not observed between the obese and underweight groups (Supplementary Figure 1). Notably, two normal weight patients with similar BMIs showed rather different body composition parameters from CT-based measurements, including SMI, SMD, VATI, SATI, and VSR (Figure 1). These findings indicated that BMI may not be an appropriate indicator to assess the correlation between body composition and the prognosis. Thus, the correlation between body composition parameters based on CT scans and the survival prognosis was further evaluated. Patients with low preoperative SMI and low SMD experienced a shorter OS than those with high SMI (P < 0.001; Figure 2A) and high SMD (P = 0.006; Figure 2B). Shorter RFS was also observed among patients with low SMI (P = 0.021; Figure 2C) but not among those with low SMD (P = 0.119; Figure 2D). Meanwhile, high VATI, high SATI, and high VSR were not related to either poor OS or RFS outcomes (Supplementary Figure 2).

Table 1 Patient and tumor characteristics comparing low and high skeletal muscle index or radiodensity

Characteristics	Total (*n* = 115)	Low SMI (*n* = 38)	High SMI (*n* = 77)	*P* value	Low SMD (*n* = 26)	High SMD (*n* = 89)	*P* value
Age	65.1 (9.0)	68.8 (9.3)	63.3 (8.4)	0.002[b]	70.8 (7.0)	63.5 (8.9)	< 0.001[c]
Male sex	71 (61.7)	29 (76.3)	42 (54.5)	0.024[a]	13 (50.0)	58 (65.2)	0.162
BMI in kg/m^2	22.7 (3.3)	20.9 (3.1)	23.6 (3.0)	< 0.001[c]	24.0 (4.0)	22.3 (2.9)	0.016[a]
< 20.0	21(18.3)	14 (36.8)	7 (9.1)		5 (19.2)	16 (18.0)	
20.0-24.9	69 (60.0)	20 (52.6)	49 (63.6)		10 (38.5)	59 (66.3)	
≥ 25.0	25 (21.7)	4 (10.5)	21 (27.3)	0.001[b]	11 (42.3)	14 (15.7)	0.01[a]
Albumin in g/dL	42.5 (5.6)	40.6 (4.1)	43.5 (6.1)	0.01[a]	41.7 (7.7)	42.8 (4.9)	0.393
Tumor location							
Head	67 (58.3)	29 (76.3)	38 (49.4)		18 (69.2)	49 (55.1)	
Body + tail	48 (41.7)	9 (23.7)	39 (50.6)	0.006[b]	8 (30.8)	40 (44.9)	0.197
Tumor size in cm	3.6 (1.4)	3.7 (1.7)	3.3 (1.2)	0.942	3.3 (1.3)	3.6 (1.4)	0.602
Differentiation							
Well	5 (4.3)	1 (2.7)	4 (5.3)		3 (12.0)	4 (4.6)	
Moderate	100 (87.0)	31 (83.8)	69 (92.0)		19 (76.0)	81 (93.1)	
Poor	7 (6.1)	5 (13.5)	2 (2.7)	0.04[a]	3 (12.0)	2 (2.3)	0.774
Nodal metastases	64 (55.7)	20 (52.6)	44 (57.1)	0.647	12 (46.2)	52 (58.4)	0.268
Perineural invasion[1]	81 (86.2)	27 (87.1)	54 (85.7)	0.855	25 (100)	56 (81.2)	0.046[a]
R1 resection	13 (11.3)	3 (7.9)	10 (13.2)	0.602	3 (11.5)	10 (11.4)	1.000
Adjuvant therapy	84 (73.0)	24 (63.2)	60 (77.9)	0.093	18 (69.2)	66 (74.2)	0.618
TNM stage							
I	43 (37.4)	14 (36.8)	29 (37.7)		14 (53.8)	29 (32.6)	
II	57 (49.6)	19 (50.0)	38 (49.4)		10 (38.5)	47 (52.8)	
III	15 (13.0)	5 (13.1)	10 (13.0)	0.996	2 (7.6)	13 (14.6)	0.135
CA19-9 > 200 KU/L	71 (61.7)	24 (66.7)	47 (63.5)	0.746	21 (84.0)	50 (58.8)	0.021[a]
SMA in cm^2	123.0 (30.6)	108.4 (19.9)	130.2 (32.4)	< 0.001[c]	113.2 (28.4)	125.9 (30.7)	0.056
SMD in HU	39.4 (8.6)	38.5 (10.0)	39.8 (7.8)	0.462	28.5 (5.1)	42.6 (6.5)	< 0.001[c]
SMI in cm^2/m^2	44.6 (9.8)	38.1 (5.3)	47.7 (10.0)	< 0.001[c]	41.1 (9.0)	45.6 (9.9)	0.033[a]
VAT in cm^2	113.4 (66.5)	89 (50.2)	125.4 (70.5)	< 0.001[c]	151.0 (60.2)	102.4 (64.5)	0.001[b]
SAT in cm^2	121.4 (64.6)	100.5 (45.4)	131.7 (70.2)	0.014[a]	160.0 (89.3)	110.1 (50.7)	< 0.001[c]
NLR > 2.6	44 (38.3)	16 (42.1)	28 (36.4)	0.551	13 (50.0)	31 (34.8)	0.162
PLR > 108	77 (67.0)	27 (71.1)	50 (64.9)	0.512	21 (80.8)	56 (62.9)	0.089
SIII > 400	68 (59.1)	24 (63.2)	44 (57.1)	0.537	17 (65.4)	51 (57.3)	0.461

[1]Data were available for 94 patients. Statistics are presented as the means (standard deviations) for age, body mass index, albumin, tumor size, and body composition parameters and *n* (%) for the other parameters.

[a]*P* < 0.05.

[b]*P* < 0.01.

[c]*P* < 0.001.

SMA: Skeletal muscle area; SMD: Skeletal muscle radiodensity; HU: Hounsfield units; SMI: Skeletal muscle index; VAT: Visceral adipose tissue; SAT: Subcutaneous adipose tissue; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SIII: Systemic immune-inflammation index; BMI: Body mass index; CA19-9: Carbohydrate antigen 19-9.

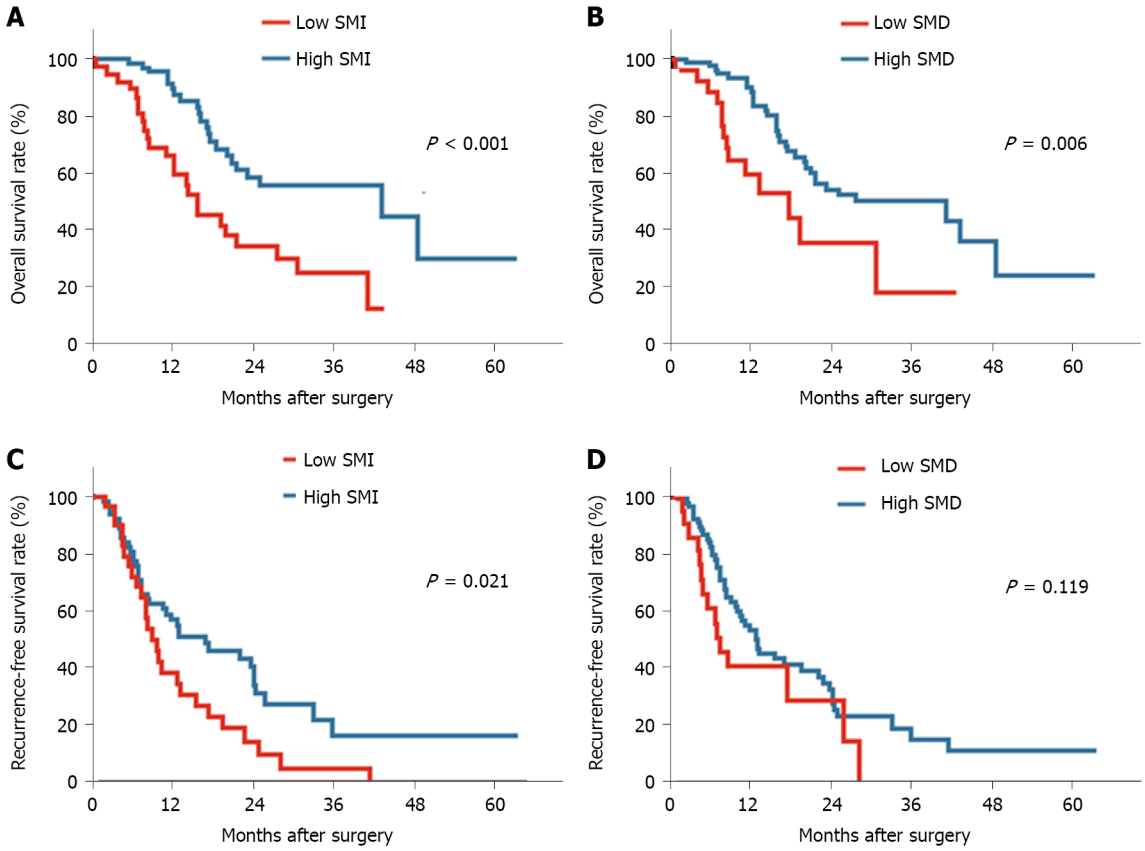

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Figure 2 Kaplan Meier survival curves for overall survival and recurrence-free survival based on skeletal muscle index and skeletal muscle density. A and C: Overall survival (OS) and recurrence-free survival (RFS) curves for patients with low and high skeletal muscle index; B and D: OS and RFS curves for patients with low and high skeletal muscle density. SMI: Skeletal muscle index; SMD: Skeletal muscle density.

Risk factors for mortality and tumor recurrence after resection

In the univariate risk analysis of factors associated with mortality (Table 2), low SMI, low SMD, high carbohydrate antigen 19-9 levels, high platelet-to-lymphocyte ratio, high SIII, lymph node metastasis, and absence of adjuvant chemotherapy were identified as risk factors for mortality after tumor resection. Remarkably, low SMI remained an independent risk factor for mortality in the multivariate analysis (HR: 2.307; 95%CI: 1.210-4.402; P = 0.011), indicating that a low muscle quantity was a significant risk factor for mortality. We also observed higher mortality among patients with low SMD, although this finding was not significant (HR: 2.093; 95%CI: 1.000-4.379; P = 0.050).

Furthermore, low SMI, lymph node metastasis, and high SIII, but not low SMD, were identified as risk factors based on the univariate analysis of risk factors associated with RFS (Table 3). The multivariate analysis showed that low SMI continued to be independently associated with tumor recurrence (HR: 1.907; 95%CI: 1.147-3.171; P = 0.013).

Effects of body composition on mortality and recurrence among elderly patients

A significant difference in age was observed between the groups with and without low SMI or SMD. We performed subgroup analyses based on age and body composition to further elucidate the potential effect of body composition on the prognosis of elderly patients with PDAC. First, we identified that 48.2% (n = 27) of elderly patients and 18.6% (n = 11) of young patients were characterized by low SMI. In addition, 35.7% (n = 20) of elderly patients and 10.2% (n = 6) of young patients were identified as having low SMD. Compared to young patients, a larger proportion of patients aged 65 years and older had a low SMI or SMD. Moreover, among elderly patients, the presence of low SMI was associated with a significantly decreased OS compared with those with high SMI (P = 0.005; Figure 3A). Furthermore, an almost comparable OS was observed between groups with a high and low SMI among patients younger than 65 years (P = 0.432; Figure 3B). Meanwhile, among the different age groups, the OS and RFS rates in the low SMD group did not differ significantly from those in the high SMD group (P = 0.110 and P = 0.320, respectively; Figure 3C and D). These findings indicated that a low preoperative SMI was more prevalent in elderly patients and was associated with a poor prognosis among pancreatic cancer patients, especially elderly patients.

Table 2 Univariate and multivariate analyses of risk factors for overall survival following pancreatic cancer resection

Factor	Univariate analysis	*P* value	Multivariate analysis	*P* value
	HR (95%CI)		HR (95%CI)	
Age ≥ 65 yr	1.661 (0.905-3.051)	0.102		
Male sex	0.686 (0.371-1.267)	0.228		
BMI < 20.0 underweight	0.534 (0.262-1.085)	0.083		
BMI ≥ 25.0 obesity	0.631 (0.322-1.233)	0.178		
Albumin < 3.8 g/dL	1.146 (0.550-2.388)	0.716		
Low SMI	2.805 (1.559-5.045)	0.001[b]	2.307 (1.210-4.402)	0.011[a]
Low SMD	2.395 (1.261-4.550)	0.008[b]	2.093 (1.000-4.379)	0.05
Tumor location, head	1.620 (0.870-3.019)	0.128		
Tumor size > 2 cm	1.107 (0.494-2.480)	0.805		
Differentiation poor	3.102 (0.947-10.158)	0.061		
Nodal metastases	1.853 (1.022-3.358)	0.042[a]	2.308 (1.200-4.442)	0.012[a]
Perineural invasion	2.303 (0.701-7.564)	0.169		
R1 Resection	1.165 (0.415-3.267)	0.772		
TNM stage III	1.515 (0.673-3.414)	0.316		
Adjuvant therapy	0.528 (0.284-0.980)	0.043[a]	0.480 (0.242-0.952)	0.036[a]
CA19-9 > 200 KU/L	1.891 (1.021-3.504)	0.043[a]	0.851 (0.428-1.689)	0.644
NLR > 2.6	1.630 (0.911-2.916)	0.099		
PLR > 108	2.208 (1.150-4.238)	0.017[a]	1.296 (0.517-3.250)	0.58
SIII > 400	1.911 (1.044-3.500)	0.036[a]	1.338 (0.586-3.057)	0.489

[a]$P < 0.05$.
[b]$P < 0.01$.
HR: Hazard ratio; BMI: Body mass index; CA19-9: Carbohydrate antigen 19-9; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SIII: Systemic immune-inflammation index; SMI: Skeletal muscle index; SMD: Skeletal muscle radiodensity; CI: Confidence interval.

DISCUSSION

In this retrospective study, we assessed preoperative body composition measures from clinically acquired CT scans and comprehensively analyzed the effects of these measures on mortality and cancer recurrence in our single cohort of patients undergoing surgical resection for PDAC. Our findings revealed that low SMI was highly prevalent and associated with a significantly increased risk of death and cancer recurrence among pancreatic cancer patients. We also identified that elderly patients exhibited a higher risk of low SMI than younger patients. Based on the results of the subgroup analysis of mortality and recurrence stratified by age, we noted that low SMI was a valuable predictor of mortality, specifically in the elderly patient subgroup. Thus, prognostic measures may be easily integrated into routine clinical care using new software to generate a highly accurate measure of SMI from clinically collected CT scans.

Results from our cohort and some other cohorts of patients with resectable pancreatic cancer indicated that elderly patients are more vulnerable to sarcopenia (usually defined by a low SMI) than young patients[15,23,29]. Most experts believe that age-related sarcopenia is an inevitable part of aging [30]. The aging-related denervation process exerts a strong effect on quantitative changes in muscle, such as loss of muscle fibers and atrophy, and qualitative changes in muscle affecting protein function, the repair process, and coordinated contractility and resilience to stress, leading to a loss of muscle volume and function in older age[31]. However, our results were inconsistent with some findings from previous studies that no significant difference in age was observed between the subgroups with and without sarcopenia[10,32]. This difference may be attributed to the cutoff values used for low SMI. In addition, the cutoff value for sarcopenia in previous studies that showed between-cohort age-related differences were considerably lower than the corresponding value in studies that did not show any significant difference in age between sarcopenia and non-sarcopenia cohorts. Currently, no established consensus value is available for CT-based sarcopenia (namely, low SMI) in Asian populations.

Table 3 Univariate and multivariate analysis of risk factors for recurrence-free survival following pancreatic cancer resection

Factor	Univariate analysis	*P* value	Multivariate analysis	*P* value
	HR (95%CI)		HR (95%CI)	
Age > 65 yr	1.661 (0.905-3.051)	0.102		
Male sex	0.631 (0.382-1.041)	0.071		
BMI < 20.0 underweight	1.216 (0.660-2.240)	0.530		
BMI ≥ 25.0 obesity	1.823 (0.969-3.430)	0.062		
Albumin < 3.8 g/dL	0.871 (0455-1.668)	0.677		
Low SMI	1.784 (1.083-2.939)	0.023[a]	1.907 (1.147-3.171)	0.013[a]
Low SMD	1.567 (0.885-2.773)	0.123		
Tumor location, head	1.327 (0.795-2.215)	0.278		
Tumor size > 2 cm	1.611 (0.767-3.382)	0.208		
Differentiation poor	0.978 (0.238-4.022)	0.976		
Nodal metastases	1.897 (1.134-3.174)	0.015[a]	1.922 (1.129-3.272)	0.016[a]
Perineural invasion	1.886 (0.841-4.231)	0.124		
R1 Resection	1.593 (0.754-3.365)	0.222		
TNM stage III	1.703 (0.833-3.483)	0.144		
Adjuvant therapy	0.866 (0.479-1.567)	0.635		
CA19-9 in Ku/L > 200	1.439 (0.855-2.421)	0.170		
NLR > 2.6	1.071 (0.648-1.769)	0.789		
PLR > 108	1.612 (0.955-2.722)	0.074		
SIII > 400	1.827 (1.097-3.043)	0.021[a]	1.655 (0.984-2.785)	0.058
Platelets > 310 × 10^9	1.245 (0.533-2.910)	0.613		

[a]$P < 0.05$.

HR: Hazard ratio; BMI: Body mass index; CA19-9: Carbohydrate antigen 19-9; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SIII: Systemic immune-inflammation index; SMI: Skeletal muscle index; SMD: Skeletal muscle radiodensity; CI: Confidence interval.

Therefore, more large-scale studies are needed in the future to establish a consensus cutoff value for sarcopenia in Asian populations and confirm these observations.

We further identified that low preoperative SMI was an independent prognostic factor for mortality and cancer recurrence for PDAC patients after pancreatectomy. These findings are consistent with previous reports describing the effect of low SMI on PDAC patients[10,15,32,33]. More importantly, we found that low SMI exerted a greater adverse effect on the prognosis among elderly patients. In contrast, no remarkable association between low SMI and mortality was identified among nonelderly patients. Likewise, Nakashima *et al*[24] revealed that low SMI was significantly associated with patients with esophageal cancer aged 65 years and older but not with those younger than 65 years[24].

Furthermore, comparable OS and RFS rates were observed among both elderly and young patients with low SMI. Additionally, low SMI contributes to a long-term prognosis that is similar to that of lymph node metastasis in elderly patients. Several studies have reported that sarcopenia is associated with insulin resistance, vitamin D deficiency, increased inflammatory cytokine levels, such as tumor necrosis factor-α and interleukin-6, and decreased concentrations of myokines, such as interleukin-15 [34-37]. Notably, all of the aforementioned inflammatory cytokines are related to the progression of pancreatic cancer[38-42]. Thus, the quantity of skeletal muscle may be linked to the prognosis of patients with PDAC through various mechanisms.

Recently, with the gradual increase in the incidence of PDAC among elderly patients and the aging population, the number of pancreatic cancer patients with sarcopenia is estimated to increase steadily [43]. Therefore, an early preoperative diagnosis of low SMI/sarcopenia coupled with early intervention is essential for elderly patients to extend their OS and simultaneously promote a good quality of life, which would also conserve large amounts of medical resources.

In this study, we did not observe a relationship between survival and SMD (a surrogate of muscle quality) in patients with pancreatic cancer. To our knowledge, only one previous study of patients with unresectable pancreatic cancer and distal cholangiocarcinoma reported a significant relationship

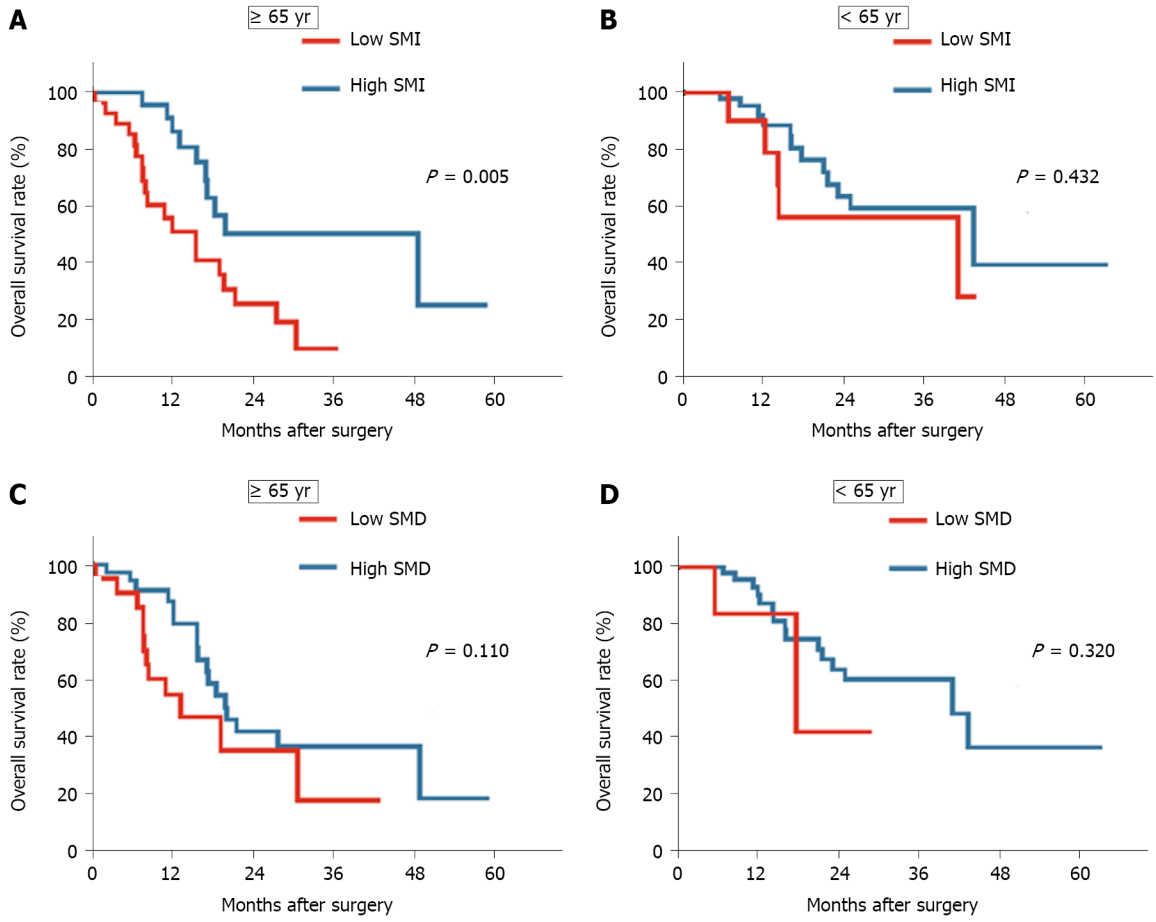

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Figure 3 Kaplan Meier overall survival curves of the cohort stratified by age. A and C: Overall survival (OS) curves for patients aged 65 and older stratified according to skeletal muscle index (SMI) (A) and skeletal muscle density (SMD) (C); B and D: OS curves for patients aged younger than 65 yr stratified by SMI (B) and SMD (D). SMI: Skeletal muscle index; SMD: Skeletal muscle density.

between SMD and the tumor prognosis[11]. In that study, low SMD was defined operationally as a mean skeletal muscle radiodensity of < 33 HU in patients with a BMI ≥ 25 kg/m² and < 41 HU in patients with a BMI < 25 kg/m² across the orthogonal view. Moreover, the prevalence of low SMD (55.3%) was much higher among patients in the previous study than among patients in the present study (22.6%). These results imply that fatty infiltration into muscle may be a hallmark of more advanced cancer but is not as predominant in cancer at an earlier stage.

However, despite these promising results, we acknowledge several limitations of the present study. First, this study was performed retrospectively at a single center with a relatively small sample size; hence, the potential for selection bias exists. Therefore, larger prospective cohort studies are needed to confirm these findings. Second, we must consider whether our cutoff values are adequate to define low SMI or sarcopenia. Although the cutoff value must be determined from a normal population of people of different ages, a unified standard is unavailable for the general Asian populations. Moreover, no specific cutoff values for pancreatic cancer were available to identify patients with sarcopenia. Here, we determined the cutoff values in this population using receiver operating characteristic curves, which is considered a more accurate method than the use of standard deviations to set cutoff values. However, more studies are still needed to explore more specific indicators that may reflect muscle function and are not limited by race or region.

CONCLUSION

In summary, low preoperative SMI, which is simply diagnosed through routine staging CT scans, was associated with a poor prognosis, especially among elderly patients with pancreatic cancer. Thus, the early identification of aging-specific factors, such as SMI, enables early interventions to ameliorate clinical outcomes in elderly patients with pancreatic cancer.

ARTICLE HIGHLIGHTS

Research background

The only potential curative treatment for patients with pancreatic cancer is surgery; however, the prognosis remains poor.

Research motivation

Measures of body composition based on computed tomography (CT) scans have been established as reliable predictors of the prognosis of cancer patients after surgery, but further research focusing on pancreatic cancer is needed.

Research objectives

To elucidate the associations of body composition measures derived from preoperative CT scans with the prognosis of patients with pancreatic cancer.

Research methods

One hundred fifteen patients undergoing pancreatic resection with curative intent for pancreatic cancer were retrospectively enrolled. The preoperative CT scan at the third lumbar vertebral level was measured for skeletal muscle index (SMI), mean skeletal muscle radiodensity, subcutaneous adipose tissue index, visceral adipose tissue index, and subcutaneous adipose tissue area ratio. The clinical and pathological data were collected. The effects of these factors on long-term survival were evaluated.

Research results

Among the five body composition measures, only low SMI independently predicted overall survival (OS) [hazard ratio (HR): 2.307; 95% confidence interval (CI): 1.210-4.402] and recurrence-free survival (HR: 1.907; 95%CI: 1.147-3.171). Furthermore, patients with low SMI (*vs* high SMI) were older (68.8 ± 9.3 years *vs* 63.3 ± 8.4 years); low SMI was present in 27 of 56 patients (48.2%) aged 65 years and older and in 11 of 59 younger patients (18.6%). In addition, subgroup analyses revealed that the correlation between low SMI and OS was observed only in patients aged 65 years and older.

Research conclusions

Low preoperative SMI was more prevalent in elderly patients and was associated with a poor prognosis among pancreatic cancer patients, especially elderly patients.

Research perspectives

The early identification of aging-specific factors, such as low SMI, allows for the possibility to facilitate early interventions to ameliorate clinical outcomes in elderly patients with pancreatic cancer.

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FOOTNOTES

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ORIGINAL ARTICLE

Observational Study

Development of a prediction model for enteral feeding intolerance in intensive care unit patients: A prospective cohort study

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Abstract

BACKGROUND

Enteral nutrition (EN) is essential for critically ill patients. However, some patients will have enteral feeding intolerance (EFI) in the process of EN.

AIM

To develop a clinical prediction model to predict the risk of EFI in patients receiving EN in the intensive care unit.

METHODS

A prospective cohort study was performed. The enrolled patients' basic information, medical status, nutritional support, and gastrointestinal (GI) symptoms were recorded. The baseline data and influencing factors were compared. Logistic regression analysis was used to establish the model, and the bootstrap resampling method was used to conduct internal validation.

RESULTS

The sample cohort included 203 patients, and 37.93% of the patients were diagnosed with EFI. After the final regression analysis, age, GI disease, early feeding, mechanical ventilation before EN started, and abnormal serum sodium were identified. In the internal validation, 500 bootstrap resample samples were performed, and the area under the curve was 0.70 (95%CI: 0.63-0.77).

CONCLUSION

This clinical prediction model can be applied to predict the risk of EFI.

Key Words: Enteral feeding intolerance; Critical care medicine; Clinical prediction model; Nutrition assessment; Nutritional support; Critical care nursing

Core Tip: Enteral nutrition (EN) is an essential piece of providing care to critically ill patients. However, some patients will experience complications related to EN and become intolerant to this nutritional support. In this study, we developed a model to predict patients who are at high risk of enteral feeding intolerance. In the future when an intensive care unit patient requires EN, nurses can distinguish whether the patient is a high-risk patient. Then, they can allocate their time to more observation of the high-risk patient to discover the patient's complications and administer effective measures in advance. In the long-term, this strategy will reduce the workload of the nursing staff and will achieve more accurate care.

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INTRODUCTION

Enteral nutrition (EN) is a preferred and cost-effective approach to nutritional support[1,2]. When EN is provided, nutrients in the gastrointestinal (GI) tract activate intestinal endocrine cells and lymphoid tissues, which positively contributes to GI function (*e.g.*, movement, digestion, and immunity)[3,4]. However, during the provision of EN, many complications can develop that have an adverse impact on nutritional support[5]. Enteral feeding intolerance (EFI) is a common and primary manifestation among many GI complications.

EFI is the inability to deliver adequate energy or nutrients to patients due to GI symptoms in the absence of mechanical obstruction[6]. EFI develops in 2%-75% of enteral feeding patients in intensive care units (ICUs)[7]. When EFI occurs, prokinetic agents and post-pyloric feeding are recommended[8]. If EFI cannot be attenuated by medications or other feeding access, then EN is reduced or suspended[9, 10]. This may result in an inability to attain nutritional goals or in malnutrition.

Therefore, distinguishing high-risk patients before EFI occurs is very important and has a guiding role in clinical practice. Many studies have explored the mechanics and causes for the development of EFI in clinical practice. A review summarized some of the main reasons: (1) Admission diagnosis of burns, head injuries, sepsis, and multi-trauma; (2) Premorbid conditions of disordered glucose metabolism, age, and sex; (3) Electrolyte disorders; and (4) Use of drugs such as sedatives, analgesics, and catecholamines[9]. A recent review of a multicenter and multiyear database indicated that EFI was more likely to occur in burn, cardiovascular/vascular disease, GI disease, and sepsis patients in the ICU [11]. However, in recent years, assessment of EFI at the bedside was driven by clinician opinion, which is still subjective to some extent. This may result in misjudgment of EFI occurrence and have an adverse effect on nutrition delivery and clinical recovery.

A clinical prediction model (CPM) is built upon the use of mathematical formulas to estimate the probability that a particular individual will have a disease or an outcome in the future[12,13]. CPM can assist clinicians in decision-making and developing therapy programs in complex clinical situations and may help patients have better outcomes. Many studies have identified variables associated with EFI, such as diabetes, abdominal surgery, and head injury. This study aimed to analyze different risk factors for EFI occurrence in the ICU and to construct a CPM that would screen high-risk ICU patients to implement early prevention and intervention methods.

MATERIALS AND METHODS

Study design, setting, and participants

A prospective cohort study was conducted with patients in the ICU at a college hospital, which is a general teaching hospital with 116 ICU beds at the northern and southern campuses. This study was performed in three of the five ICU departments, which included comprehensive ICU, emergency ICU, and neurosurgery ICU. This study was performed between November 2020 and May 2021.

Patients in the ICU were included in the study when EN was started. Patients who received EN for less than 24 h were not included in the model-construction dataset. Eligible patients received the standard nutrition protocol on medical advice (continuous infusion *via* nutrition pump at rates between 20 mL/h to 150 mL/h). Depending on the patient's condition, different feeding tubes and formulas were chosen. Exclusion criteria included the following: (1) Age < 18 years; (2) Oral intake; (3) Pregnancy or breastfeeding; (4) Occlusive ileus; and (5) Informed consent not obtained from the patient or their next of kin.

Variables

Outcome measure: According to the results of the literature review and discussion with experts, the primary outcome was patients diagnosed with EFI, including GI symptoms and reduction or suspension of EN. A patient was diagnosed with EFI if one or more listed GI symptoms occurred and resulted in the reduction or suspension of EN within 2 wk of starting EN[7,14]. When patients had several symptoms, one symptom was determined to be the main symptom rather than recording several duplicate symptoms.

GI symptoms included the following: (1) Moderate gastric residual volume (defined as GRV, reaching 200 mL)[7,15,16]. Ultrasonography was adopted once a day 4 h after completion of EN using the following formula: GRV = 27.0 + 14.6 × gastric antral cross-sectional area - 1.28 × age, where gastric antral cross-sectional area = (anteroposterior diameter × craniocaudal diameter × II)/4[17]; (2) Diarrhea, which was defined as having three or more loose or liquid stools within 24 h with a stool weight greater than 200–250 g/day (estimated by assistant nurses)[18]; (3) Vomiting, which was defined as the expulsion of gastric contents from the oropharynx or nasopharynx one or more times a day[19]; (4) Aspiration, which referred to the entry of oropharyngeal food, secretions, or gastroesophageal reflux into the subglottic airway[20]; (5) Regurgitation, which referred to the reflux of gastric contents into the oropharynx without nausea, retching, or straining[21]; (6) Constipation, which was considered a reduction in the frequency of defecation to less than three times a week and difficulty defecating or dry stools[22]; and (7) Abdominal distention, which was considered an uncomfortable feeling of fullness and distension of the abdomen, and abdominal ultrasound showed gas or dilation of the bowel[21].

Predictor selection: We searched databases and consulted with medical experts in GI surgery and critical care medicine (see Supplementary Tables 1 and 2, which demonstrates the literature screening and factor coding results). Eligible studies had a primary endpoint of EFI occurring when diagnosed with GI symptoms. After expert group discussion, the predictor of proton-pump inhibitor use was excluded. The following 14 predictors were selected: age[23-29]; trauma (including blunt trauma, penetrating trauma, and burns)[30-32]; head injury (including postoperative neurosurgery and brain trauma)[33]; sepsis[34]; abdominal surgery[23,31,32]; GI disease (including GI surgery, GI inflammation, *etc.*)[11,23,28]; blood glucose[35,36]; serum albumin (hypoproteinemia or abnormal content level of albumin)[37]; electrolyte disorders (abnormal content level of K, Na, Cl, Mg, Ca, and P)[38]; mechanical ventilation (had or having mechanical ventilation)[5,23,26]; sedative and analgesic medicine (fentanyl, dexmedetomidine, propofol, and so on)[39]; catecholamine medicine (epinephrine, norepinephrine, and dopamine)[40,41]; early feeding (feeding initiated within 48 h after admission to the ICU)[40]; and tube feeding protocol (feeding formulas, largest feeding speeds, and largest total volume).

Data sources/measurement

A structured form was prospectively used to obtain baseline data for the enrolled patients. When a patient began to receive EN, the nurses responsible for that patient recorded EN and GI symptoms daily. Doctors measured ultrasonographic results daily using a Doppler ultrasound diagnostic apparatus (GE Venue; GE Healthcare, Chicago, IL, United States). The follow-up endpoint was: (1) A diagnosis of EFI; (2) EN for more than 2 wk; (3) Transfer out of the ICU (including to home, to another hospital, and to another department in the hospital); (4) Gastric tube removal; or (5) Death.

Study size

Fourteen predictors were identified based on a literature analysis and expert consultation. The sample size of the case group was calculated to be 10 times greater than the predictors. Considering a 10% drop-off rate, we planned to include at least 155 patients.

Statistical analyses

We searched for predictors of EFI that were repeatedly reported in studies or systematic reviews and could be easily ascertained in different settings by those with various clinical experience. These data were recorded by researchers for many days in the cohort and checked by 2 people.

Data analyses were conducted using IBM SPSS Statistics (version 25.0. Armonk, NY: IBM Corp) and R software (version 4.0.3; R Core Team). Descriptive data, including mean and standard deviation, frequency, percentage, median, and quartile, were used for the univariate analysis. When univariate analysis showed that independent variables were associated with intolerance ($P < 0.15$), they were included in the multiple logistic regression model. Variables were entered into the logistic regression

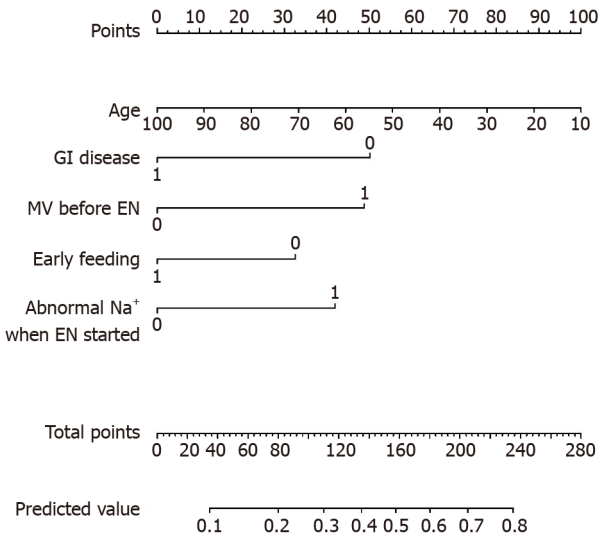

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Figure 1 Nomogram for predicting enteral feeding intolerance in intensive care unit patients. 0: No; 1: Yes. EN: Enteral nutrition; GI: Gastrointestinal; MV: Mechanical ventilation.

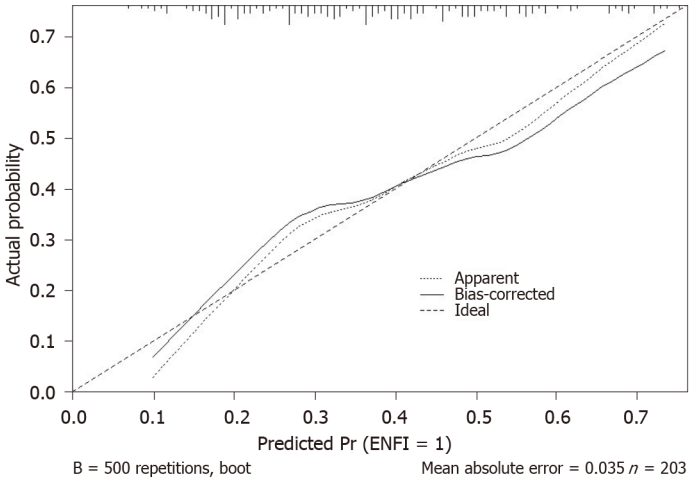

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Figure 2 Calibration curve of the prediction model performance during internal validation.

analysis, and we used the stepwise approach to perform the multivariable selection. Finally, we displayed the model using a nomogram because this format is more convenient.

Internal validation was performed using bootstrap validation. We assessed the predictive accuracy of the prognostic instrument with discrimination and calibration. Discrimination was calculated using the area under the curve, ranging from 0.5 (no discrimination) to 1.0 (perfect discrimination). Calibration was assessed using a calibration plot.

RESULTS

Participants

The three ICUs had 74 beds, and 684 patients were treated in the three ICUs during the study period. The cohort included 203 EN participants for the final analysis, including 153 patients from the comprehensive ICU, 34 patients from the neurosurgery ICU, and 16 patients from the emergency ICU. Overall, EFI occurred in 37.93% of ICU patients. The baseline characteristics of the enrolled patients are shown in Table 1.

Table 1 Baseline characteristics of the participants included in the analysis

Variables	EFI group, *n* = 77	Non-EFI group, *n* = 126	Statistics	*P* value
Age in yr	64.55 ± 15.86	69.06 ± 14.31	t = 2.091	0.038
Sex, *n* (%)			χ^2 = 1.919	0.166
Male	55 (71.4)	78 (61.9)		
Female	22 (28.6)	48 (38.1)		
BMI in kg/m^2	23.64 ± 3.41	23.91 ± 4.70	t = 0.030	0.672
APACHE II	15.0 (9.0, 23.0)	15.0 (9.5, 21.0)	Z = -0.117	0.907
SOFA	6.0 (3.0, 10.0)	5.0 (1.0, 8.0)	Z = -1.533	0.125
Diagnosis, *n* (%)			χ^2 = 1.574	0.986
Respiratory disease	15 (19.5)	26 (20.6)		
Circulatory disease	6 (7.8)	9 (7.1)		
Neurological disease	12 (15.6)	25 (19.8)		
Digestive disease	11 (14.3)	18 (14.3)		
Post-surgery	22 (28.6)	30 (23.8)		
Sepsis	5 (6.5)	7 (5.6)		
Multiple trauma	3 (3.9)	4 (3.2)		
Other	3 (3.9)	7 (5.6)		
Endpoint event, *n* (%)				
Diagnosis of EFI	77 (100)			
EN for more than 2 wk		35 (27.8)		
Transfer out of the ICU		65 (51.6)		
Gastric tube removal		18 (14.3)		
Death		8 (6.3)		

APACHE II: Acute physiology and chronic health evaluation II; BMI: Body mass index; EFI: Enteral feeding intolerance; EN: Enteral nutrition; ICU: Intensive care unit; SOFA: Sepsis-related organ failure assessment.

EFI occurrence

A total of 77 patients were included in the case group. EFI occurred more often in the first 7 d after EN started, and more than 90% of EFI cases lasted less than 3 d. Diarrhea, distention, and regurgitation were the most common GI symptoms among patients with EFI. The EFI occurrence in the case group is shown in Table 2.

Selected factors for the model

Univariate analysis of the cohort (Table 3) identified an association between EFI and seven predictors that have been consistently reported in the literature; these include age, GI disease, medical history of mechanical ventilation, mechanical ventilation occupied, sedatives, early feeding, and feeding formula. Four novel potential predictors were also identified, including abnormal serum sodium and serum phosphorus before EN was started and abnormal serum sodium and serum chlorine when EN was started. These variables were entered into a multivariate model. Sepsis was also included in the model because clinical experts strongly recommended it.

Model fitting

We applied the stepwise approach to perform multivariable selection, and five variables were included for the final analysis. Age, GI disease, and early feeding decreased the risk of EFI in the ICU. Mechanical ventilation started before EN and abnormal serum sodium when EN was started increased the risk of EFI in the ICU. We fitted the model using the final variables to obtain the final CPM (Table 4).

Predictive nomogram for the probability of EFI

The nomogram illustrated the strength of the association of the predictors with the outcome (Figure 1).

Table 2 Enteral feeding intolerance occurrence in the case group, *n* (%)

Variables	Case group, *n* = 77
EN tube	
Nasogastric	72 (93.5)
Nasal jejunal	3 (3.9)
Jejunostomy	2 (2.6)
When EFI occurred after EN started	
1-3 d	20 (26.0)
4-7 d	32 (41.6)
8-14 d	25 (32.5)
Number of days EFI lasted	
1 d	46 (59.7)
2-3 d	28 (36.4)
≥ 4 d	3 (3.9)
GI symptoms	
Diarrhea	31 (40.3)
Abdominal distention	22 (28.6)
Regurgitation	14 (18.2)
Vomiting	5 (6.5)
Aspiration	2 (2.6)
Large GRV	2 (2.6)
Constipation	1 (1.3)

EFI: Enteral feeding intolerance; EN: Enteral nutrition; GI: Gastrointestinal; GRV: Gastric residual volume.

The "0" indicated "NO" (*i.e.* the patient had no history of GI disease, did not receive mechanical ventilation before EN, did not receive early feeding, and/or had no abnormal serum sodium when EN was started), and the "1" indicated "YES" (*i.e.* the patient had a history of GI disease, received mechanical ventilation before EN, received early feeding, and/or had abnormal serum sodium when EN was started). The variable of "age" was a continuous variable. On the point scale axis, each variable was given a point based on the value. A total score could be easily calculated by adding every single point. By projecting the total points to the lower total point scale, we were able to estimate the probability of EFI. According to statistical standards, if 1 patient's predictive probability was more than 0.5, then there was a higher possibility that EFI will occur.

Performance of the nomogram

We did the bootstrap validation, and model performance showed an area under the curve of 0.70. The calibration curve of the model's performance is demonstrated in Figure 2.

DISCUSSION

We developed a novel practical prognostic instrument for predicting the risk of EFI in the ICU that may support clinicians when making treatment recommendations for patients receiving EN. Development of the model followed established recommendations. We identified three protective predictors, namely age, GI disease, and early feeding. Moreover, two risk factors were determined, namely mechanical ventilation before EN started and abnormal serum sodium. The internally validated area under the curve was 0.70 for the model to predict EFI outcomes.

We developed the CPM using an assembled population from three different ICU departments at one center. We made every effort to enroll patients with different diseases. Therefore, our model could apply to most situations in the ICU. To control for potential bias, the data of every patient were divided into three parts. The basic information was recorded by a researcher, the daily EN data were recorded

Table 3 Univariate analysis of predictors associated with enteral feeding intolerance

Variables	EFI group, *n* = 77	Non-EFI group, *n* = 126	Statistics	*P* value
Age in yr, mean ± SD	64.55 ± 15.86	69.06 ± 14.31	t = 2.091	0.038
Sex, *n* (%)			χ^2 = 1.919	0.166
Male	55 (71.4)	78 (61.9)		
Female	22 (28.6)	48 (38.1)		
Diabetes, *n* (%)	20 (26.0)	33 (26.2)	χ^2 = 0.001	0.973
Abdominal surgery, *n* (%)	9 (11.7)	21 (16.7)	χ^2 = 0.941	0.332
GI disease, *n* (%)	15 (19.5)	37 (29.4)	χ^2 = 2.451	0.117
Head injury, *n* (%)	14 (18.2)	18 (14.3)	χ^2 = 0.546	0.460
Sepsis, *n* (%)	5 (6.5)	12 (9.5)	χ^2 = 0.572	0.449
Trauma, *n* (%)	3 (3.9)	8 (6.3)		0.539
Analgesic, *n* (%)	33 (42.9)	49 (38.9)	χ^2 = 0.313	0.576
Sedative, *n* (%)	49 (63.6)	58 (46.0)	χ^2 = 5.942	0.015
Catecholamines, *n* (%)	22 (28.6)	26 (20.6)	χ^2 = 1.667	0.197
Early feeding, *n* (%)	42 (54.5)	88 (69.8)	χ^2 = 4.856	0.028
Feeding volume in mL	1000 (500, 1500)	1000 (500, 1400)	Z = -0.495	0.620
Feeding speed in mL/h	80 (50, 100)	80 (50, 100)	Z = -0.220	0.826
Mechanical ventilation, *n* (%)				
Before EN started	54 (70.1)	60 (47.6)	χ^2 = 9.837	0.002
When EN started	54 (70.1)	64 (50.8)	χ^2 = 7.342	0.007
Abnormal level of albumin, *n* (%)				
Diagnosis with hypoproteinemia	1 (1.3)	4 (3.2)		0.652
Albumin before EN	14 (18.2)	21 (16.7)	χ^2 = 0.077	0.782
Albumin when EN started	1 (1.3)	6 (4.8)		0.257
Abnormal level of electrolytes, *n* (%)				
Diagnosis with electrolyte disorders	5 (6.5)	12 (9.5)	χ^2 = 0.572	0.449
Before EN started, *n* (%)				
Potassium	32 (41.6)	45 (35.7)	χ^2 = 0.693	0.405
Sodium	38 (49.4)	49 (38.9)	χ^2 = 2.136	0.144
Chlorine	54 (70.1)	88 (69.8)	χ^2 = 0.002	0.965
Magnesium	53 (68.8)	81 (64.3)	χ^2 = 0.440	0.507
Calcium	69 (89.6)	118 (93.7)	χ^2 = 1.075	0.300
Phosphorus	55 (71.4)	77 (61.1)	χ^2 = 2.237	0.135
When EN started, *n* (%)				
Potassium	14 (18.2)	22 (17.5)	χ^2 = 0.017	0.896
Sodium	32 (41.6)	33 (26.2)	χ^2 = 5.186	0.023
Chlorine	55 (71.4)	76 (60.3)	χ^2 = 2.578	0.108
Magnesium	38 (49.4)	59 (46.8)	χ^2 = 0.122	0.727
Calcium	69 (89.6)	113 (89.7)	χ^2 = 0.000	0.987
Phosphorus	43 (55.8)	63 (50.0)	χ^2 = 0.654	0.419
Feeding formula, *n* (%)			χ^2 = 10.861	0.048
Rice soup	10 (13.0)	5 (4.0)		

Peptisorb	14 (18.2)	39 (31.0)
Nutrison Fibre	15 (19.5)	33 (26.2)
TPF-D[1]	24 (31.2)	32 (25.4)
TPF-T[2]	3 (3.9)	2 (1.6)
Water	11 (14.3)	15 (11.9)

[1]TPF-D: Enteral Nutritional Emulsion "RuiDai," suitable for diabetics.
[2]TPF-T: Enteral Nutritional Emulsion "RuiNeng", rich in fat and calorie.
EN: Enteral nutrition; EFI: Enteral feeding intolerance; GI: Gastrointestinal.

Table 4 Final clinical prediction model of enteral feeding intolerance in the intensive care unit

Variable	OR (95%CI)	*Z* statistic	*P* value
Age in yr	0.98 (0.96, 1.00)	-1.881	0.060
GI disease	0.41 (0.18, 0.86)	-2.254	0.024
Early feeding	0.56 (0.28, 1.11)	-1.652	0.099
MV before EN	2.39 (1.27, 4.58)	2.682	0.007
Abnormal Na^+ when EN started	2.11 (1.11, 4.07)	2.262	0.024

EN: Enteral nutrition; GI: Gastrointestinal; MV: Mechanical ventilation; OR: Odds ratio.

by clinical nurses, and the ultrasonographic data were recorded by ICU doctors trained in performing ultrasonography. The researcher was unable to obtain the other data before the follow-up ended. In addition, we utilized the quantitative method of content analysis to guarantee the scientific rationality of our study.

Alternative predictors were found from the literature and clinical experts. When we performed univariate analysis, we included predictors with *P* values smaller than 0.15 with the aim that no possible significant factors were omitted. We determined the potential effective predictors based on the *P* value and by considering those predictors recommended by experts or that were highly suspected. These predictors were well-defined, easily measured, and routinely available. In internal validation, we used the bootstrap validation to assess discrimination and calibration and repeated the validation 500 times for accuracy.

In our study, we found that older patients were less likely to develop EFI. This result is similar to the results of existing studies[28,29] but contrary to conventional wisdom. After a literature review, expert consultation, and clinical observation, we identified some reasons that explain this counterintuitive result. Older patients are given less EN because of their energy requirements and physical condition. In our study, patients aged 60 years or older received on average less EN per day than younger patients [900 (500, 1200) *vs* 1000 (500, 1500), respectively]. Critically ill elderly patients have many chronic diseases, such as diabetes, chronic gastroenteritis, and hepatic dysfunction. To promote GI motility and regulate water balance, nutrition teams often use water or rice soup as the initial nutrition for the elderly. Water or rice soup is used for a period of time to facilitate a later transition to an EN emulsion, which may reduce stimulation of the GI tract in elderly patients[42]. The direct relationship between age and EFI requires further experimental analysis to completely understand the relationship.

Similarly, we found that ICU patients with GI disease (*e.g.*, pancreatitis, post-gastrectomy, or upper GI hemorrhage) were less likely to experience EFI. In our study, patients with GI disease were likely given less feed to avoid worsening their health issues [patients with GI disease: 575 (275, 975) *vs* patients without GI disease: 1000 (725, 1500), $P < 0.000$]. In clinical practice, the intention of a small volume of EN is not to meet energy requirements but to maintain the structural and functional integrity of the GI tract [43]. Therefore, GI symptoms may be slight and difficult to observe in this circumstance. In addition, medical interventions (*e.g.*, metoclopramide, probiotics, acupuncture, and enema) are administered to patients diagnosed with GI disease[44-46]. This advance treatment may lead to a decreased occurrence of EFI.

A previous attempt to develop a prediction model yielded promising results but had limited applicability because its target population was patients with gastrectomy for gastric cancer rather than ICU patients[47]. Some preventive measures have been implemented to reduce EFI occurrence in ICU patients, such as fat-modified enteral formula and bolus enteral feeding methods[48-50]. However, there is a gap in the knowledge of distinguishing patients at high risk of EFI. Medical workers can apply our model when it is recommended that a patient receives EN. By analyzing the conditions between the

period of being admitted to the ICU and receiving EN, patients at high risk are determined and are given a set of preventive measures, which is an effective measure for reducing the occurrence of EFI. Notably, experienced clinical workers already have some knowledge of which patients will be high risk for EFI and have put protective measures into clinical practice. Based on the current nutritional management practices in our center, the predictive model should be used knowing that high-risk patients may have already received preventive measures.

There are potential limitations to our study. Because of time and manpower, we developed the model using a small sample size in a single center. The effect of sepsis, trauma, electrolytes could not be properly addressed because of the small sample size. The differences between these factors between the two groups may be overlooked. Due to the actual situation, the effect of various formula feeds could not be ascertained because of use of several feeding formulas. In addition, the representativeness and predictive performance of our model may have limitations. However, this limit may be slight because the final model includes only five variables. Moreover, the delivery strategy of intermittent or continuous feeding and the temperature of the nutrient solution contribute to EFI occurrence[51]. Our study did not consider these effects because all included patients received room temperature continuous feeding in our medical center. During the study, there may have been some confounding factors that we did not consider, including etiology, medications, and fluids. For future research, these factors should be considered, and we suggest external validation in different centers over additional time periods. In the future, we hope to be able to analyze the effect of individual factors on EFI on the basis of expanding the sample size. In addition, applying our prediction model to additional interventional studies as a tool to optimize clinical management is a long-term goal.

CONCLUSION

We have developed and internally validated a CPM for predicting the risk of EFI in patients receiving EN in the ICU. The developed nomogram is easy to use and might help clinicians make individualized predictions of each patient's probability of experiencing EFI. Early identification of patients at high risk of EFI can greatly help doctors and nurses better manage clinical care. Clinical nurses can implement different nursing measures according to each patient's risk. These measures will ultimately help ICU patients achieve better nutritional support and a quicker recovery.

ARTICLE HIGHLIGHTS

Research background

Enteral nutrition (EN) is essential for critically ill patients, but some patients develop enteral feeding intolerance (EFI). Intolerance can hinder a patient's energy intake and recovery. Therefore, predicting EFI is of vital importance in clinical practice.

Research motivation

Determining which patients are at high risk of developing EFI based on their current physical condition and medical treatment will allow physicians and nurses to individualize medical care and begin EFI preventative measures for the high-risk patients.

Research objectives

To develop a clinical prediction model (CPM) to predict the risk of EFI in patients receiving EN in the intensive care unit (ICU). We currently know that many factors can influence the development of EFI.

Research methods

A prospective cohort study was performed, and we prospectively recorded enrolled patients' data. Prospective cohort studies can more realistically document patient data and clinical responses, reducing human intervention. We used ultrasound measurement of the antrum cross-sectional area to measure gastric residual volume, which can effectively reduce the occurrence of complications and increase the efficiency of feeding.

Research results

We developed and internally validated a CPM for predicting the risk of EFI in patients receiving EN in the ICU. After univariate and multivariate analyses, five factors were used for the CPM, including age, gastrointestinal disease, early feeding, mechanical ventilation before EN started, and abnormal serum sodium when EN started.

Research conclusions

This model can help clinical workers to identify patients at high risk for EFI earlier, which will allow these patients to receive preventative measures in advance.

Research perspectives

In the future, an increased sample size and analyzing more variables will develop a more accurate clinical predictive model. Prospective cohort studies and randomized control studies are the best methods for the future research.

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FOOTNOTES

Author contributions: Lu XM contributed to conceptualization, methodology, formal analysis, investigation, data curation, writing the original draft, and project administration; Jia DS contributed to conceptualization, methodology, investigation, and writing the original draft; Wang R and Yang Q contributed to methodology, investigation, and resources; Jin SS contributed to investigation and resources; Chen L contributed to conceptualization, methodology, resources, review and editing of the manuscript, supervision, and project administration; All authors read and approved the final manuscript.

Institutional review board statement: The study protocol was approved (numbered 2020KY230) by the appropriate ethics committee (Medical Ethics Committee of Shanghai General Hospital) on December 23, 2020.

Informed consent statement: Before we enrolled patients, informed consent was obtained from the patient or next of kin. Since we needed to complete daily ultrasonography of patients, we needed to obtain their informed consent.

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

Data sharing statement: If there is a need to get the dataset, please contact Xue-Mei Lu (lu_xm1118@163.com). The information of the patients in the dataset is anonymized.

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

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ORIGINAL ARTICLE

Prospective Study

Real-time *in vivo* distal margin selection using confocal laser endomicroscopy in transanal total mesorectal excision for rectal cancer

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Abstract

BACKGROUND

Transanal total mesorectal excision (TaTME) allows patients with ultralow rectal cancer to be treated with sphincter-saving surgery. However, accurate delineation of the distal resection margin (DRM), which is essential to achieve R0 resection for low rectal cancer in TaTME, is technically demanding.

AIM

To assess the feasibility of optical biopsy using probe-based confocal laser endomicroscopy (pCLE) to select the DRM during TaTME for low rectal cancer.

METHODS

A total of 43 consecutive patients who were diagnosed with low rectal cancer and scheduled for TaTME were prospectively enrolled from January 2019 to January 2021. pCLE was used to determine the distal edge of the tumor as well as the DRM during surgery. The final pathological report was used as the gold standard. The diagnostic accuracy of pCLE examination was calculated.

RESULTS

A total of 86 pCLE videos of 43 patients were included in the analyses. The sensitivity, specificity and accuracy of real-time pCLE examination were 90.00%

[95% confidence interval (CI): 76.34%-97.21%], 86.96% (95%CI: 73.74%-95.06%) and 88.37% (95%CI: 79.65%-94.28%), respectively. The accuracy of blinded pCLE reinterpretation was 86.05% (95%CI: 76.89%-92.58%). Furthermore, our results show satisfactory interobserver agreement (κ = 0.767, standard error = 0.069) for the detection of cancer tissue by pCLE. There were no positive DRMs (≤ 1 mm) in this study. The median DRM was 7 mm [interquartile range (IQR) = 5-10 mm]. The median Wexner score was 5 (IQR = 3-6) at 6 mo after stoma closure.

CONCLUSION

Real-time *in vivo* pCLE examination is feasible and safe for selecting the DRM during TaTME for low rectal cancer (clinical trial registration number: NCT04016948).

Key Words: Transanal total mesorectal excision; Probe-based confocal laser endomicroscopy; Optical biopsy; Distal resection margin; Low rectal cancer

Core Tip: Transanal total mesorectal excision (TaTME) allows patients even with ultra-low rectal cancer to be treated with sphincter-saving surgery. However, low rectal cancer resection with sphincter preservation may lead to a positive distal resection margin (DRM), with a high risk for local recurrence. Confocal laser endomicroscopy (CLE) enables the real-time, *in vivo* optical biopsy of living tissue. Real-time *in vivo* probe-based CLE examination can provide optical biopsy and is feasible and safe for selecting the DRM during TaTME for low rectal cancer.

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INTRODUCTION

Colorectal cancer is the third most prevalent type of cancer and the second primary cause of cancer-related mortality worldwide[1]. Low rectal carcinoma often requires abdominoperineal resection and permanent abdominal colostomy, and it places major economic and psychological burdens on patients [2]. Transanal total mesorectal excision (TaTME) is increasingly adopted by colorectal surgeons in the treatment of patients with low rectal cancer[3,4]. This technique gives patients, even those with ultralow rectal cancer, the opportunity to undergo sphincter-saving surgery. However, low rectal cancer resection with sphincter preservation may lead to a positive distal resection margin (DRM), with a high risk for local recurrence[5-7]. To date, no devices have been used in the surgical field to guide resection margin selection. Frozen biopsy is recommended during surgery for low rectal cancer to confirm a negative DRM. However, it cannot be used to guide selection of the resection margin in real time, and it is a time-consuming, irreversible, and traumatic process. Accordingly, accurate delineation of the DRM is essential to achieve R0 resection for low rectal cancer.

Recently, several studies have reported that confocal laser endomicroscopy (CLE) enables the real-time, *in vivo* optical biopsy of living tissue[8-12]. It has the potential to fundamentally change the role of biopsy in the gastrointestinal field, and a state-of-the-art classification system (Miami classification) has been proposed for normal and pathological states in gastrointestinal diseases based on probe-based CLE (pCLE)[13]. However, no studies have investigated the feasibility of optical biopsy using pCLE in the real-time *in vivo* selection of the DRM during TaTME for low rectal cancer. We hypothesize that real-time *in vivo* pCLE examination can help surgeons select the DRM accurately and might contribute to improving the oncological and functional prognosis of low rectal cancer after treatment with TaTME. The aim of this study was to evaluate the feasibility of optical biopsy using pCLE for selecting the DRM during TaTME in the treatment of low rectal cancer.

MATERIALS AND METHODS

Study design

This was a prospective, single-center study that was approved by the Institutional Review Board of Nanfang Hospital of Southern Medical University. The study protocol was registered at ClinicalTrials.gov (No. NCT04016948).

Patients

Patients who were diagnosed with low rectal cancer by preoperative endoscopic biopsy and scheduled for TaTME were prospectively enrolled in this study. Written informed consent was obtained from each patient prior to participation. Inclusion criteria were as follows: Diagnosis of low rectal cancer (tumor lying within 5 cm from the anal verge) and planned treatment with TaTME; age of at least 18 years; and American Society of Anesthesiologists class 1-3. The exclusion criteria were as follows: (1) T4b cancer as determined by computed tomography, magnetic resonance imaging or endoscopic examination; (2) Emergent case with obstruction or perforation; (3) Coagulopathy (international normalized ratio > 1.5 or prothrombin time < 50%); (4) Impaired renal function (creatinine level > 1.2 mg/dL); (5) Pregnancy; (6) Breastfeeding; and (7) Past history of allergies.

Equipment and procedure

During surgery, pCLE was used to determine the distal edge of the tumor as well as to examine the preselected DRM. pCLE was performed using the Cellvizio Endomicroscopy System [Mauna Kea Technologies (MKT), Paris, France]. The ColoFlex UHD probe, a flexible mini-probe with a lateral resolution of 1 μm, was used in our study. The pCLE imaging data were collected at a scan rate of 12 frames/s. The probe has a field of view of 240 μm and can image at a depth of 60 μm below the mucosal surface, and it allows optical biopsies with 1000 times magnification.

Before image acquisition, fluorescein sodium was injected intravenously. The fluorescent agent used was 10% fluorescein sodium (Baiyunshan Mingxing Pharmaceutical Company, Guangzhou, China). The fluorescein sodium (0.5 mL) hypersensitivity test was implemented 20 min before pCLE examination. Then, 2.5 mL of fluorescein sodium diluted with 2.5 mL of 0.9% sodium chloride was injected intravenously 5 min prior to pCLE imaging. After strict sterilization, one end of the probe was connected to the laser outlet of Cellvizio, and the other end was placed on the surgical table. Adequate exposure of the tumor lesion was achieved using a colorectal retractor (CooperSurgical Lone Star colorectal retractor, Beijing Xinya S&T Co., Ltd., Beijing, China), and pCLE imaging was performed by the surgeon under direct vision by using the probe in direct contact with the tissues (Figure 1). The pCLE video recording was initiated when the probe contacted the lesion, and it terminated when the probe moved away from the lesion. The pathologist analyzed the pCLE videos and evaluated the margin between the abnormal tissue of the lesion and the surrounding normal mucosa in real time. A dot was marked with an electric scalpel at the distal edge of the tumor as determined by pCLE (Figure 1B and 1C). If the pathologist could not determine the distal edge of the tumor, then the dot was marked at a nontumor site identified by pCLE imaging as the closest healthy tissue below the macroscopic lesion. Then, the DRM was located 5-10 mm below the marked dot (Figure 1B). Finally, pCLE examination was performed preceding the surgical resection to ensure a negative DRM. Conventional samples were collected for histology at the marked dot and the DRM (Figure 1D). Histopathological analysis of the samples and the final resection specimen was performed as the gold standard, and the diagnosis made by pCLE was compared with that of the final pathological reports. All pCLE videos were stored on a personal computer in the form of MKT files (proprietary format, MKT Software, Paris, France).

pCLE optical biopsy diagnostic criteria

The pCLE optical biopsy diagnostic criteria were according to the "Miami criteria"[13] and Kuiper *et al* [14]'s diagnostic classification. Briefly, the diagnostic criteria include the crypt architecture and vessel architecture classification. The crypt architecture was divided into three types. Normal mucosa was scored as crypt type 1 and presented normal regular luminal openings, size, and distribution of crypts covered by a homogeneous layer of epithelial cells, including goblet cells. Hyperplastic polyps and inflammatory lesions were scored as crypt type 2 and presented regular-shaped or star-shaped luminal crypt openings with normal or reduced goblet cells. Neoplastic lesions were scored as crypt type 3, which included variable width of epithelial lining with tubular-shaped crypts and loss of goblet cells (striped dark epithelium) and irregular and decreased volume of lamina propria. For vessel architecture, normal mucosa was scored as vessel type 1 and presented a hexagonal, honeycomb appearance that presented a network of capillaries outlining the luminal openings of the crypts. Hyperplastic polyps and inflammatory lesions were scored as vessel type 2, presented hexagonal, honeycomb appearance with mild (or no) increase in the number of capillaries or increased amounts of normal vessels without leakage. Neoplasia was scored as vessel type 3, presenting dilated and distorted vessels with elevated leakage and irregular architecture with little or no orientation to adjunct tissue. We analyzed the pCLE imaging features and made relative diagnoses according to the above categories.

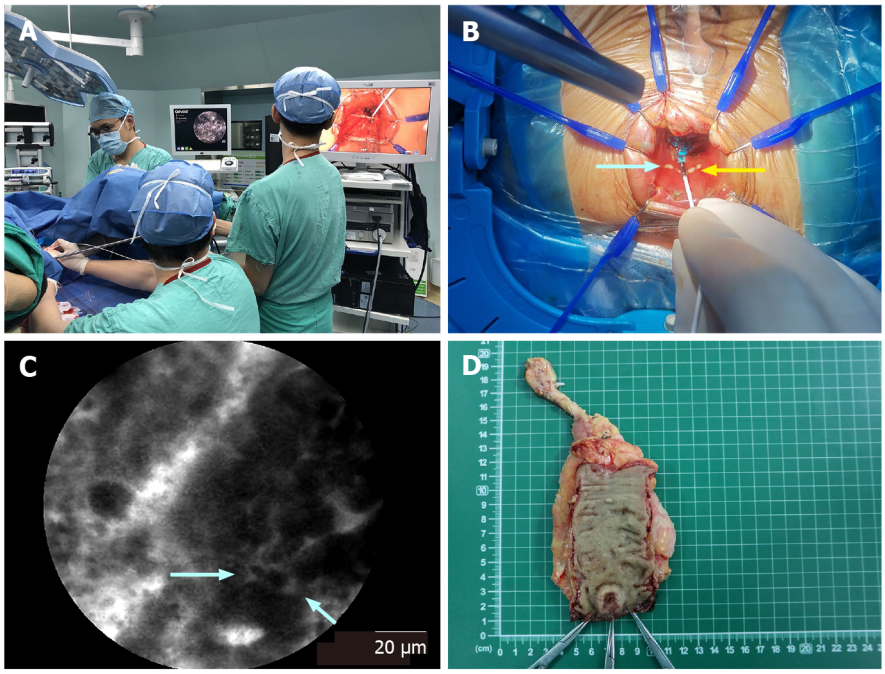

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Figure 1 Selection of the distal resection margin guided by probe-based confocal laser endomicroscopy. A: During transanal total mesorectal excision, the surgeon used the tip of the probe in direct contact with the tissues. In the meantime, the pathologist analyzed the real-time probe-based confocal laser endomicroscopy (pCLE) videos; B: A dot (white arrow) was marked by an electric scalpel at the distal edge of the tumor, which was determined by pCLE optical biopsy. Then, the distal resection margin (DRM) (yellow arrow) was marked 5-10 mm below the marked dot; C: In pCLE videos, the distal edge of the tumor (white arrow) was determined at the end of the distorted structures (dark, irregularly thickened epithelium); D: Conventional samples were collected for histology at the marked dot and DRM after surgery.

For the patients who received neoadjuvant chemoradiotherapy, we adopted a pCLE scoring classification system created by Safatle-Ribeiro *et al*[15], assigning one point to the presence of each feature as follows: Vascular features including fluorescein leakage and an increased vessel/crypt ratio; and epithelial features including dark irregular crypts, intratumoral budding, back-to-back glands, and a cribriform pattern. Hence, in our study, patients with 0-1 points were diagnosed with complete response (no residual neoplasia), and those with 2-6 points were diagnosed with partial response (residual neoplasia). Consequently, we analyzed the diagnostic accuracy of pCLE in patients with neoadjuvant chemoradiotherapy according to the above classification.

Evaluation of pCLE videos

During the surgery, one pathologist (observer A) made a real-time interpretation of the findings of the pCLE examination. Then, reinterpretation of the same pCLE videos was performed by another pathologist (observer B) who was blinded to the real-time diagnosis and final histopathology report. Finally, the real-time and blinded interpretations of the pCLE videos were compared with the final pathological report. Both observers had been trained in the pCLE system and image interpretation and had read more than 100 pCLE images of the colorectum. The quality of all videos was evaluated, and the diagnosis was made according to the "Miami criteria"[13]. We also adopted the colonic crypt architecture and vessel architecture classification for pCLE established by Kuiper *et al*[14]. The sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV) and interobserver agreement of pCLE optical biopsy in distinguishing between normal and cancerous tissue were calculated.

Specimen quality assessment

The TME specimen quality should be assessed based on the following features. Grade 1 represents low quality: Incomplete mesorectum; mesorectum fascia defects deeper than 5 mm; conical gross specimen. Grade 2 represents moderate quality: Relatively intact mesorectum; mesorectum fascia defects deeper than 5 mm; no visible muscularis propria with adequate resection margin; approximately conical gross specimen. Grade 3 represents high quality: Intact mesorectum; no mesorectum fascia defects deeper than 5 mm; no visible muscularis propria; cylindrical specimen. A circumferential resection margin (CRM) was defined as positive when it was less than 1 mm, and a positive CRM or positive DRM was considered R1 resection. All TME specimens were evaluated by pathologists after surgery.

Sample size calculation

From January 2019 to June 2019, the average time for intraoperative diagnosis by frozen section was 25 ± 10 min in our hospital. We hypothesized that the average time of intraoperative diagnosis by pCLE would be 20 min, and 43 cases were determined. With this number of cases, the study would have 90% power to detect a difference between the two techniques to prove the superiority of pCLE (two-sided type I error = 0.05).

Statistical analysis

Patient demographic and clinical data and pCLE image characteristics were evaluated by descriptive statistics. The data of continuous variables are represented as the mean ± SD or median [interquartile range (IQR)], and the data of categorical variables are presented as numbers and frequencies. The intraobserver agreement was calculated by means of intraclass correlation coefficients (ICCs). Based on the 95% confidence interval (CI) of the ICC estimate, values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 are indicative of poor, moderate, good, and excellent reliability, respectively. Cohen's kappa (κ) was calculated to assess the interobserver agreement of the two observers. The κ value was graded as follows: Poor (0.01-0.20); fair (0.21-0.40); moderate (0.41-0.60); substantial (0.61-0.80); and excellent (0.81-1.00). Statistical Package for the Social Sciences software (Release 22.0, SPSS, Inc., 2012) was applied for statistical analyses.

RESULTS

Patient demographics and tumor characteristics

From January 2019 to January 2021, a total of 43 consecutive patients were enrolled according to the predefined inclusion and exclusion criteria. Patient demographics and tumor characteristics are shown in Table 1. There were 29 males (67.4%) and 14 females (32.6%), with a median age of 57 (IQR = 47-65) years. The median tumor height (the height from the anal verge to the distal edge of the tumor) was 4 cm (IQR = 3.6-4.6 cm). Preoperative neoadjuvant chemoradiotherapy was administered to 21 patients (48.8%), three of whom showed a complete response (no viable cancer cells). Finally, 43 marked dots and 43 DRMs were analyzed by comparing the pCLE diagnosis with the pathological reports. All pCLE procedures were performed successfully and safely, and no adverse reactions were observed following fluorescein injection.

pCLE optical biopsy

In total, 43 patients underwent pCLE examination, including 21 patients who underwent neoadjuvant chemoradiotherapy. Representative pCLE images and matched images of hematoxylin and eosin-stained rectal tissues are shown in Figure 2. In normal rectal tissues, pCLE images presented normal round crypt structures with regular luminal openings, covered by a homogeneous single-cell-layered epithelium with dark goblet cells, and regular narrow vessels with hexagonal, honeycomb appearance surrounding crypts (Figure 2A). In rectal neoplastic tissues, pCLE images presented dark and irregularly thickened epithelium with decreased volume of lamina propria and dilated, distorted vessels with elevated leakage (Figure 2C). We analyzed the tissue features in 86 pCLE videos and made relative diagnoses. The intraoperative real-time pCLE imaging correctly diagnosed 36 tumor lesions and 40 normal lesions in 40 pathological tumor lesions and 46 pathological normal lesions.

In 21 patients who underwent neoadjuvant chemoradiotherapy, 3 patients had a complete response, while 18 had a partial response after neoadjuvant chemoradiotherapy according to the pathological reports after surgery. Representative endoscopic images and corresponding pCLE images are shown Figure 3. All patients received endoscopic examination before surgery to evaluate the residual lesions. Seven patients' endoscopic reports showed a complete response, presenting a residual scar (Figure 3A). Fourteen patients' endoscopic reports showed a partial response, presenting a residual tumor lesion (Figure 3C). In complete response rectal tissues (no neoplastic features), the typical pCLE images showed regular crypts with thickening epithelium and enlarged vessels with fibrotic stroma (Figure 3B). The pCLE images of residual neoplasia showed atypical glands with dark and irregular crypts and enlarged twisty vessels (Figure 3D). The pCLE imaging correctly diagnosed 15 cases of residual neoplasia (scored in range 2-6 points) in 18 cases of pathological partial response.

pCLE diagnostic accuracy

A total of 86 pCLE videos from 43 patients were included in the analyses. The sensitivity, specificity, PPV, and NPV of real-time pCLE examination (observer A) in distinguishing between cancerous and normal tissue were 90.00% (95%CI: 76.34%-97.21%), 86.96% (95%CI: 73.74%-95.06%), 85.71% (95%CI: 71.46%-94.57%), and 90.91% (95%CI: 78.33%-97.47%), respectively (Table 2). The overall rate of accuracy was 88.37% (95%CI: 79.65%-94.28%). In the blinded pCLE reinterpretation after surgery (observer B), the sensitivity, specificity, PPV, NPV and accuracy of the pCLE examination were 87.50% (95%CI: 73.20%-95.81%), 84.78% (95%CI: 71.13%-93.66%), 83.33% (95%CI: 68.64%-93.03%), 88.64% (95%CI: 75.44%-

Table 1 Patient demographics and tumor characteristics

Variable	*n* = 43
Age: Median (IQR), yr	57 (47-65)
Sex: Male/female, *n*	29/14
BMI: Median (IQR), kg/m^2	22.40 (19.50-23.95)
ASA class, *n* (%)	
1	8 (18.6)
2	30 (69.8)
3	5 (11.6)
4	0
Tumor size: Median (IQR), cm	2.5 (2.0-3.8)
Tumor height[1]: Median (IQR), cm	4.0 (3.6-4.6)
Histological subtype, *n* (%)	
Adenocarcinoma	39 (90.7)
Mucinous adenocarcinoma/signet ring cell carcinoma	4 (9.3)
Differentiation grade, *n* (%)	
Well	7 (16.3)
Moderate	32 (74.4)
Poor	4 (9.3)
Neoadjuvant chemoradiotherapy, *n* (%)	21 (48.8)
TRG[2], *n* (%)	
Grade 0	3 (7.0)
Grade 1	10 (23.3)
Grade 2	7 (14.0)
Grade 3	1 (2.3)
T stage, *n* (%)	
T0	5 (11.6)
T1	4 (9.3)
T2	17 (39.5)
T3	13 (30.2)
T4	4 (9.3)
N stage, *n* (%)	
N0	30 (69.8)
N1	10 (23.3)
N2	3 (7.0)
M stage, *n* (%)	
M0	43 (100)
M1	0

[1]Height of the distal edge of the tumor from the anal verge.
[2]Tumor regression grade.
BMI: Body mass index; ASA: American Society of Anesthesiologists; TRG: Tumor Regression Grade; IQR: Interquartile range.

Table 2 Probe-based confocal laser endomicroscopy diagnostic accuracy considering pathology as the standard reference

	Observer A (real-time interpretation)		Observer B (blinded interpretation)	
	%	95%CI	%	95%CI
Sensitivity	90.00	76.34-97.21	87.50	73.20-95.81
Specificity	86.96	73.74-95.06	84.78	71.13-93.66
Accuracy	88.37	79.65-94.28	86.05	76.89-92.58
PPV	85.71	71.46-94.57	83.33	68.64-93.03
NPV	90.91	78.33-97.47	88.64	75.44-96.21
Interobserver agreement	κ = 0.767, standard error = 0.069			

CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value.

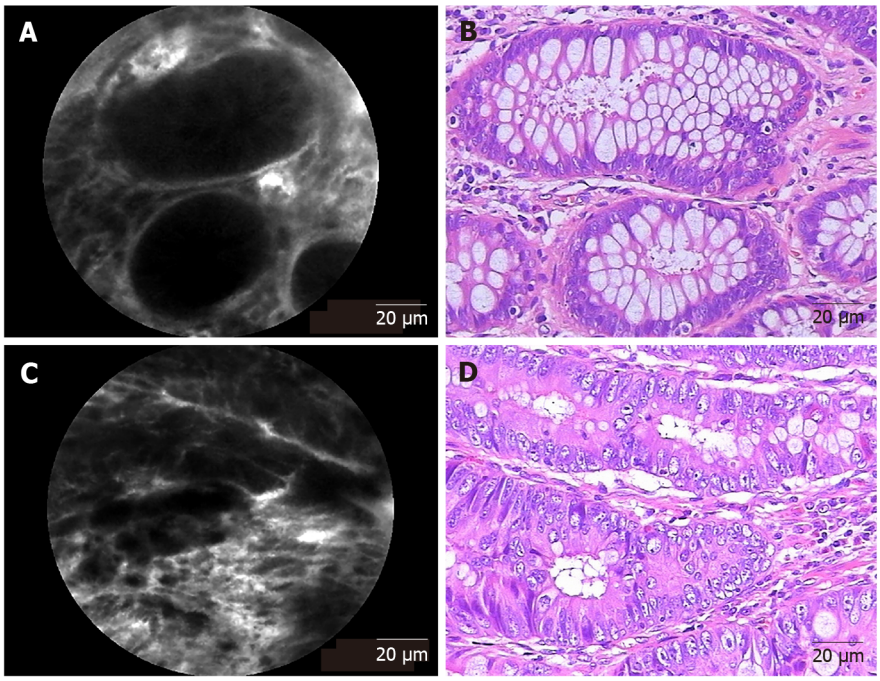

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Figure 2 Representative probe-based confocal laser endomicroscopy images and corresponding hematoxylin and eosin-stained images of rectal tissues. A: Probe-based confocal laser endomicroscopy (pCLE) image of normal tissue presenting normal round crypt structures with regular luminal openings covered by a homogeneous single-cell-layered epithelium with dark goblet cells and regular narrow vessels with hexagonal, honeycomb appearance surrounding crypts; B: Corresponding image of normal rectal tissue stained by hematoxylin and eosin (H&E); C: pCLE image of rectal neoplastic tissues manifesting as dark and irregularly thickened epithelium with decreased volume of lamina propria and dilated, distorted vessels with elevated leakage. The epithelium was dark and irregularly thickened, and the vessels were dilated; D: Corresponding image of H&E-stained rectal adenocarcinoma tissue.

96.21%), and 86.05% (95%CI: 76.89%-92.58%), respectively (Table 2).

The neoadjuvant chemoradiotherapy group showed a lower sensitivity (83.33% *vs* 95.45%, P = 0.485), specificity (77.27% *vs* 95.83%, P = 0.153), accuracy (80.00% *vs* 95.65%, P = 0.055), and PPV (75.00% *vs* 95.45%, P = 0.147) than the nonneoadjuvant treatment group (Table 3). In our study, the mean ICC was 0.839 (95%CI: 0.763-0.892), which means that the intraobserver agreement was good. The interobserver agreement was substantial for the detection of rectal cancer, with a mean κ of 0.767 (standard error = 0.069).

Surgical and functional outcomes

The surgical and functional outcomes are shown in Table 4. No positive DRMs were detected in our study. All TME specimens were evaluated by pathologists after surgery. There were 40 specimens defined as grade 3 and 3 specimens defined as grade 2. The median distance from the lowest edge of the tumor to the DRM was 7 mm (IQR = 5-10 mm). The median operative duration was 240 min (IQR = 202-265 min), while the median intraoperative pCLE examination duration was 17 min (IQR = 15-18 min).

Table 3 Comparison of real-time probe-based confocal laser endomicroscopy diagnostic accuracy between the neoadjuvant group and the nonneoadjuvant group

	Neoadjuvant group (*n* = 42)		Nonneoadjuvant group (*n* = 44)		*P* value
	%	95%CI	%	95%CI	
Sensitivity	83.33	58.58-96.42	95.45	77.16-99.88	0.458
Specificity	77.27	54.63-92.18	95.83	78.88-99.89	0.153
Accuracy	80.00	64.35-90.95	95.65	85.16-99.47	0.055
PPV	75.00	50.90-91.34	95.45	77.16-99.88	0.147
NPV	85.00	62.11-96.79	95.83	78.88-99.89	0.473

CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value.

Table 4 Surgical and functional outcomes

Variable	
Operative duration: Median (IQR), min	240 (202-265)
pCLE examination duration: Median (IQR), min	17 (15-18)
Estimated blood loss: Median (IQR), mL	27 (20-50)
DRM distance: Median (IQR), mm	7.0 (5.0-10.0)
Anastomotic leakage, *n* (%)	2 (4.7)
Positive DRM, *n* (%)	0 (0)
Wexner score[1], median (IQR)	5 (3-6)
Anastomotic stenosis, *n* (%)	1 (2.3)
Recurrence, *n* (%)	1 (2.3)
Metastasis, *n* (%)	2 (4.7)

[1]An incontinence score designed by Wexner, determined at 6 mo after stoma closure.
pCLE: Probe-based confocal laser endomicroscopy; DRM: Distal resection margin; IQR: Interquartile range.

The time required to select the DRM decreased over time.

The median Wexner score was 5 (IQR = 3-6), as evaluated at six months after stoma closure. The median follow-up period was 24 (range, 22-46) mo. One patient had anastomotic stenosis. Two patients had liver metastasis at 6 mo and 13 mo after surgery. One patient died one year after metastasis, and another died 18 mo after metastasis. Notably, one patient had cancer recurrence 18 mo after surgery.

DISCUSSION

Sphincter-saving low rectal cancer resection is technically challenging, especially in obese patients with large tumors. The narrow pelvis and the forward angle of the distal rectum restrict the laparoscopic view, making it difficult to perform laparoscopic procedures. TaTME provides an open approach from the anus to cancerous lesions and provides an excellent view of the surgical field, allowing the tumor to be seen directly from the bottom to the top. In our study, the transanal approach allowed the pCLE probe to directly contact the tissues without endoscopy. Therefore, pCLE can provide continuous and stable imaging of the tissue architecture and cellular morphology in the mucosal layer during TaTME. The pCLE analysis evaluated both epithelial and vascular patterns of malignancy, including the Cannizzaro-Spessotto scale, vessel/crypt ratio, stroma, dark crypts, budding, back-to-back glands and cribriform pattern[15]. To our knowledge, this is the first study of optical biopsy using pCLE to select the DRM in TaTME for low rectal cancer.

To date, surgeons only "experientially" determine the DRM using surgical instruments or macroscopic examination of the tumor margin, which may lead to an insufficient or excessive DRM. de Lacy *et al*[6] reported that patients with low rectal cancer treated with TaTME had a positive DRM rate of 7.8%. pCLE can provide *in vivo* microscopic imaging of the colorectal mucosa and submucosa,

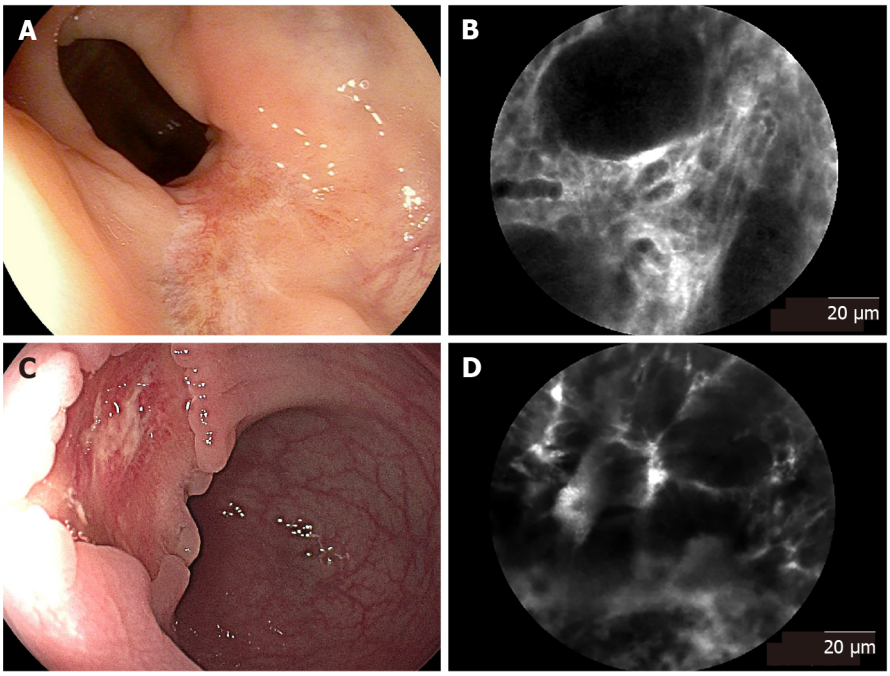

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Figure 3 Endoscopic images and corresponding probe-based confocal laser endomicroscopy images of rectal tissues after neoadjuvant chemoradiotherapy. A: Endoscopic image of rectal tissue with complete response, presenting a residual scar; B: Corresponding probe-based confocal laser endomicroscopy (pCLE) image showed regular crypts with thickening epithelium and enlarged vessels with fibrotic stroma; C: Endoscopic image of rectal tissue with partial response, presenting a residual tumor lesion; D: Corresponding pCLE image showed atypical glands with dark and irregular crypts and enlarged twisty vessels.

enabling the real-time histological diagnosis of superficial and submucosal cancer infiltration[8,10]. In some studies, pCLE showed high agreement with true histopathology, reaching an accuracy of 88%-94.44%[8,10,16]. In our study, the accuracy of real-time pCLE examination was 88.37% (95%CI: 79.65%-94.28%). A direct and stable plane can be provided in TaTME for pCLE examination without the use of endoscopy.

Our study demonstrates that pCLE examination can be useful for detecting cancer infiltration and selecting the DRM. In our study, the diagnosis made by pCLE showed a good correlation with that made by histopathology as the gold standard. Real-time pCLE examination could differentiate between cancerous and normal tissue with a favorable accuracy of 88.37%. In particular, the sensitivity (90.00%) and NPV (90.91%) were high, resulting in high accuracy in not selecting a positive DRM. Wijsmuller *et al*[17] reported that neoadjuvant chemoradiotherapy could significantly alter pCLE rendering due to subsequent inflammation, edema, fibrosis and crypt distortion. Our results show a lower sensitivity (83.33% *vs* 95.45%, $P = 0.458$), specificity (77.27% *vs* 95.83%, $P = 0.153$), accuracy (80.00% *vs* 95.65%, $P = 0.055$), and PPV (75.00% *vs* 95.45%, $P = 0.147$) in the neoadjuvant chemoradiotherapy group than in the nonneoadjuvant treatment group. However, these differences between the two groups were not statistically significant. Therefore, pCLE examination is suitable for patients with or without neoadjuvant chemoradiotherapy. It is undeniable that the response to neoadjuvant chemoradiotherapy may lead to crypt distortion with epithelial irregularities due to inflammation, edema and fibrosis (Figure 2C), and these may increase the incidence of diagnostic errors. Therefore, awareness of neoadjuvant chemoradiotherapy before pCLE examination may be helpful to improve the diagnostic accuracy.

Several studies have reported that a DRM of 1 cm or less did not compromise oncological safety[18,19]. Therefore, we were relatively liberal with the selection of the DRM as long as it was confirmed to be negative intraoperatively by pCLE. There were no positive DRMs in our study, confirming the feasibility of optical biopsy using pCLE as an accurate method to select a tumor-free DRM in TaTME. As reported in a recent study[20], the mean DRM distance of patients who underwent TaTME for the treatment of low rectal cancer was 17.7 mm, which was much longer than our result of 7 mm. Previous studies investigating anorectal function after anterior resection for rectal cancer have suggested that a shorter remaining rectum might contribute to more disordered postoperative anorectal function because the rectal anal inhibitory reflex is generally preserved with higher levels of anastomosis and a longer residual rectum[21,22]. In this study, the median Wexner score was 5 (range, 3-6) at 6 mo after stoma closure, which means that patients in our study had satisfactory anorectal function after surgery. In summary, real-time pCLE examination may help reduce the tumor-free DRM and potentially contribute to the postoperative restoration of anorectal function in patients with low rectal cancer.

In this study, we first used pCLE to evaluate the tumor margin and select the DRM with satisfactory accuracy. We recommend pCLE examination as a routine test to help surgeons select the DRM in TaTME and perform "tailored surgery" for low rectal cancer patients. The limitation of this study was based on a single center, and the sample size was relatively small, which might limit the power of the study. Therefore, a large-scale multicenter, prospective, randomized controlled trial needs to be performed. The cancer cells sometimes crawl mainly submucosa rather than the mucosal layer, such as poorly differentiated adenocarcinomas. Due to the limitation of current technology, the pCLE imaging depth is restricted to 60 μm. Therefore, in our experience, patients who have been diagnosed with poorly differentiated adenocarcinoma preoperatively should receive submucosal intraoperative frozen biopsy to ensure distal margin safety.

CONCLUSION

In conclusion, real-time *in vivo* pCLE examination is feasible and safe for selecting the DRM during TaTME for low rectal cancer, with high accuracy and a particularly high NPV. The pCLE examination is convenient, timesaving and easy for surgeons to perform and could thus be promoted as a regular examination for selecting the DRM during TaTME for low rectal cancer.

ARTICLE HIGHLIGHTS

Research background

Transanal total mesorectal excision (TaTME) allows patients even with ultra-low rectal cancer to be treated with sphincter-saving surgery. However, accurate delineation of the distal resection margin (DRM), which is essential to achieve R0 resection for low rectal cancer in TaTME, is technically demanding. Probe-based confocal laser endomicroscopy (pCLE) enables the real-time, *in vivo* optical biopsy of living tissue, which means it might help making intraoperative real-time diagnosis for suspicious tumor lesions. Therefore, we investigated whether pCLE can provide optical biopsy for DRM selection and help tailored surgery in low rectal cancer.

Research motivation

No studies have investigated the feasibility of optical biopsy using pCLE in the real-time *in vivo* selection of the DRM during TaTME for low rectal cancer. This study aimed to explore whether real-time *in vivo* pCLE examination can help surgeons select the DRM accurately and contribute to improving the surgical outcome and oncological and functional prognosis of low rectal cancer after treatment with TaTME. To our knowledge, this is the first study of optical biopsy using pCLE to select the DRM in TaTME for low rectal cancer.

Research objectives

This study investigated whether real-time *in vivo* pCLE examination is feasible and safe for selecting the DRM during TaTME for low rectal cancer.

Research methods

The pCLE exaination was used to determine the distal magin during surgery. The final pathological report was used as the gold standard. The diagnostic accuracy of pCLE examination was calculated.

Research results

Real-time *in vivo* pCLE examination is feasible and safe for selecting the DRM during TaTME for low rectal cancer, with high accuracy and a particularly high negative predictive value. The pCLE examination is convenient, timesaving and easy for surgeons to perform and could thus be promoted as a regular examination for selecting the DRM during TaTME for low rectal cancer.

Research conclusions

Real-time *in vivo* pCLE examination can provide optical biopsy for distal margin selecting in TaTME for low rectal cancer.

Research perspectives

Real-time *in vivo* pCLE can be used to determine the distal margin in TaTME surgical procedure for low rectal cancer.

FOOTNOTES

Author contributions: J Yan and Tan J designed the research study; Tan J, Ji HL, Hu YW, Li ZM, Zhuang BX, Deng HJ, Wang YN, Zheng JX, Wang T, Jiang W, Han ZL, and Yan J performed the research; Tan J, Ji HL, Hu YW, Li ZM, Zhuang BX, Deng HJ, Wang YN, Zheng JX, Wang T, Jiang W, Han ZL, and Yan J analyzed the data and wrote the manuscript; and all authors have read and approve the final manuscript.

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Clinical trial registration statement: This study is registered at Clinical Trial. The registration identification number is NCT04016948.

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

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META-ANALYSIS

Short- and long-term outcomes of laparoscopic *vs* open surgery for T2 gallbladder cancer: A systematic review and meta-analysis

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Abstract

BACKGROUND

With the development of laparoscopic techniques, gallbladder cancer (GBC) is no longer a contraindication to laparoscopic surgery (LS). Although LS is recommended for stage T1 GBC, the value of LS for stage T2 GBC is still controversial.

AIM

To evaluate the short- and long-term outcomes of LS in comparison to those of open surgery (OS) for stage T2 GBC.

METHODS

We searched the PubMed, Embase, Cochrane Library, Ovid, Google Scholar, and Web of Science databases for published studies comparing the efficacy of LS and OS in the treatment of stage T2 GBC, with a cutoff date of September 2022. The Stata 15 statistical software was used for analysis. Relative risk (RR) and weighted mean difference (WMD) were calculated to assess binary and continuous outcome indicators, respectively. Begg's test and Egger's test were used for detecting publication bias.

RESULTS

A total of five studies were included, with a total of 297 patients, 153 in the LS group and 144 in the OS group. Meta-analysis results showed that the LS group was better than the OS group in terms of operative time [WMD = -41.29, 95% confidence interval (CI): -75.66 to -6.92, P = 0.02], estimated blood loss (WMD = -261.96, 95%CI: -472.60 to -51.31, P = 0.01), and hospital stay (WMD = -5.67, 95%CI:

-8.53 to -2.81, P = 0.0001), whereas there was no significant difference between the two groups in terms of blood transfusion (RR = 0.60, 95%CI: 0.31-1.15, P = 0.13), complications (RR = 0.72, 95%CI: 0.39-1.33, P = 0.29), number of lymph nodes retrieved (WMD = –1.71, 95%CI: -4.27 to -0.84, P = 0.19), recurrence (RR = 0.41, 95%CI: 0.06-2.84, P = 0.36), 3-year and 5-year overall survival (RR = 0.99, 95%CI: 0.82-1.18, P = 0.89 and RR = 1.02, 95%CI: 0.68-1.53, P = 0.92; respectively), and 3-year and 5-year disease-free survival (RR = 1.01, 95%CI: 0.84-1.21, P = 0.93 and RR = 1.15, 95%CI: 0.90-1.46, P = 0.26; respectively).

CONCLUSION

The long-term outcomes of LS for T2 GBC are similar to those of OS, but LS is superior to OS in terms of operative time, intraoperative bleeding, and postoperative hospital stay. Nevertheless, these findings should be validated *via* high-quality randomized controlled trials and longer follow-ups.

Key Words: Gallbladder cancer; T2 stage; Laparoscopic cholecystectomy; Oncological outcome; Meta-analysis

Core Tip: This study evaluated the safety and efficacy of laparoscopic surgery in comparison to those of open surgery for stage T2 gallbladder cancer. A total of five studies were included after retrieving various literature databases, with a cutoff date of September 2022. Meta-analysis results showed that the laparoscopic surgery group was better than the open surgery group in terms of operative time, estimated blood loss, and hospital stay, whereas there was no significant difference between the two groups in terms of blood transfusion, complications, number of lymph nodes retrieved, recurrence, and 3-year and 5-year overall and disease-free survival rates.

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INTRODUCTION

Gallbladder cancer (GBC) is one of the most common malignancies of the biliary system and has the sixth highest incidence among gastrointestinal tumors[1]. Radical resection is the only potentially curative treatment for GBC[2-4]. Traditional open extended cholecystectomy, including regional lymph node dissection and wedge resection of the gallbladder bed, is the standard radical surgery for stage T2 GBC[5,6]. Since the late 1980s, laparoscopic surgery (LS) has been widely used to treat benign gallbladder disease, and GBC has been considered a contraindication to LS[7,8]. With the continuous improvement of devices and techniques in recent years, curative resection of gastrocolic cancer and liver cancer in difficult sites and even pancreaticoduodenectomy can be conducted laparoscopically. Additionally, LS is increasingly employed in radical resection of stage T1a GBC, and thus GBC is no longer a contraindication to LS[9]. However, the short- and long-term outcomes of LS for stage T2 GBC are still controversial.

Although there are still concerns about the efficacy of laparoscopic radical surgery of stage T2 GBC, LS has already been exploratively applied to treat patients with T2 GBC, and even T3 GBC, at several large medical institutes. There has been a rapid increase in incidental GBC with the widespread use of laparoscopic techniques in benign gallbladder disease, especially in patients with T2 GBC[10,11]. It has become a point of debate whether LS is safe for the treatment of T2 GBC and whether open surgery (OS) is required.

Previous studies on T2 GBC have been limited to case reports or small sample retrospective single arm case series on the technical feasibility, safety, and oncological outcomes. Several recent studies have reported long-term outcomes of laparoscopic treatment of stage T2 GBC[12-16]. As there is still a lack of evidence from high-quality multicenter randomized controlled trials (RCTs), we believe that it is necessary to conduct a meta-analysis to provide an evidence-based reference for laparoscopic radical surgery of T2 GBC.

MATERIALS AND METHODS

This meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[17]. The data used in this study were derived from published studies and are anonymous. This study did not need informed consent from patients or a review by an institutional ethics committee. This meta-analysis was registered under the registration number CRD42022367334 on the systematic review registration platform PROSPERO (https://www.crd.york.ac.uk/PROSPERO/). We also cited high-quality articles in *Reference Citation Analysis* (https://www.referencecitation-analysis.com).

Search strategy

The PubMed, Medline, Cochrane Library, Ovid, Google Scholar, and Web of Science databases were searched with a cutoff date of September 2022. The search topics were "laparosco*", "open", "extended cholecystectomy", "open surgery" and "T2 gallbladder cancer". The search strategy for each database is described in the Supplementary material. We also conducted an expanded search based on the references of the retrieved publications. Table 1 lists the basic characteristics of the included studies.

Inclusion criteria

(1) Population: Stage T2 GBC; (2) Intervention: LS; (3) Comparison: OS; (4) Study sample size: Unlimited; (5) Type of studies: RCTs and prospective or retrospective cohort studies; (6) Follow-up time: Unlimited; (7) Language type of the publications: Unlimited; (8) Study type: Human studies; and (9) Primary outcomes: Overall survival, disease-free survival, recurrence, and the number of lymph nodes removed. Secondary outcomes: Operative time, intraoperative blood loss, hospital stay, and postoperative complications.

Exclusion criteria

(1) Studies with unknown follow-up times or incomplete data and no response from the contact author and those not peer-reviewed; (2) Single arm studies with LS or OS; and (3) Robots, reviews, case reports, and animal studies.

Quality assessment

The quality of the cohort studies (retrospective or prospective) was assessed using the Newcastle-Ottawa Scale, which specifically included study population selection, comparability, and exposure evaluation or outcome evaluation. The RCTs were conducted for the risk assessment according to the "risk assessment tool" recommended by the Cochrane Collaboration Network[18-20].

Statistical analysis

The meta-analysis was performed using the STATA SE 13 software. Relative risk (RR) and weighted mean difference (WMD) were used to calculate the pooled statistics for binary and continuous data, respectively, and the 95% confidence interval (CI) was reported for each. Heterogeneity was assessed using the χ^2 test, with the significance level set at $P = 0.05$. This meta-analysis was carried out using a random effects model. $P < 0.05$ was considered to indicate statistical significance[21]. Begg's test and Egger's test were performed using the Stata 15 software to quantitatively assess each outcome for publication bias. Funnel plots were drawn to qualitatively and visually assess the outcomes for publication bias.

RESULTS

Search results and study selection

After searching the publication databases and excluding duplications, 47 articles remained. We then excluded the reviews (including systematic reviews), case reports, and meta-analyses as well as the studies that were not relevant based on their titles or abstracts, finally leaving five publications to be employed in this meta-analysis. The detailed steps of the publication retrieval are shown in Figure 1. These five publications involved one study from Japan and four studies from South Korea. The basic characteristics of the included studies are shown in Table 1. The included studies were all cohort studies, and the quality was evaluated using the Newcastle-Ottawa Scale. The Newcastle-Ottawa Scale scores are attached to Supplementary Table 1.

Results of the meta-analysis

We compared LS and OS for T2 GBC in 11 postoperative outcomes, each of which was analyzed for sensitivity. The results of the meta-analysis are summarized in Table 2. Random effects models were used to obtain the effect sizes.

Table 1 Basic characteristics of the included studies

Ref.	Country	Type	Period	Case	Age		Sex (M/F)		Liver resection[1]		Quality
				LS *vs* OS	LS	OS	LS	OS	LS	OS	
Lee *et al*[12], 2022	Korea	R	2011-2018	20 *vs* 24	71.85 ± 9.11	68.08 ± 10.64	5/15	11/13	1/4/15	1/13/10	7
Cho *et al*[13], 2022	Korea	R (PSM)	2010-2017	19 *vs* 19	69.9 ± 9.1	66.7 ± 7.8	8/11	12/7	NA	NA	6
Navarro *et al*[14], 2020	Korea	R (PSM)	2005-2017	43 *vs* 43	66.7 ± 10.3	65.4 ± 7.6	25/18	28/15	38/5/0	23/12/8	6
Jang *et al*[15], 2019	Korea	R	2004-2017	55 *vs* 44	70.1 ± 8.1	65.5 ± 10.5	19/36	23/21	38/16/1	9/32/3	8
Itano *et al*[16], 2015	Japan	R	2003-2013	16 *vs* 14	68.1 ± 19.9	71.5 ± 13.2	9/7	5/9	NA	NA	7

[1]No/wedge/S4b or 5.

F: Female; R: Retrospective comparative studies; LS: Laparoscopic surgery; M: Male; NA: Not available; OS: Open surgery; PSM: Propensity score matching.

Table 2 Meta-analysis results of all available studies in measured outcomes

Measured outcomes	Studies, *n*	Heterogeneity test		Model	RR/WMD	95%CI	*P* value
		*I*² (%)	*P* value				
Operative time	5	62	0.03	Random	-41.29	-75.66, -6.92	0.02[a]
Intraoperative blood loss	4	86	0.0001	Random	-261.96	-472.60, -51.31	0.01[a]
Hospital stays	5	76	0.002	Random	-5.67	-8.53, -2.81	0.0001[a]
Lymph nodes retrieved	5	79	0.0008	Random	-1.71	-4.27, 0.84	0.19
Transfusion	3	0	0.57	Random	0.60	0.31, 1.15	0.13
Complication	5	0	0.5	Random	0.72	0.39, 1.33	0.29
Recurrence	2	50	0.16	Random	0.41	0.06, 2.84	0.36
3-yr OS	3	40	0.19	Random	0.99	0.82, 1.18	0.89
5-yr OS	3	80	0.006	Random	1.02	0.68, 1.53	0.92
3-yr DFS	3	29	0.24	Random	1.01	0.84, 1.21	0.93
5-yr DFS	3	55	0.11	Random	1.15	0.90, 1.46	0.26

[a]Indicates statistical significance.

CI: Confidence interval; DFS: Disease-free survival; OS: Overall survival; RR/WMD: Relative risk/weighted mean difference.

Operative time, intraoperative blood loss, and hospital stay: Five studies reported the operative time with moderate heterogeneity (WMD = -41.29, 95%CI: -75.66 to -6.92, P = 0.02)[12-16]. Four studies reported the intraoperative blood loss with moderate heterogeneity (WMD = -261.96, 95%CI: -472.60 to -51.31, P = 0.01)[12,14-16]. Five studies reported the hospital stays with high heterogeneity (WMD = -5.67, 95%CI: -8.53 to -2.81, P = 0.0001)[12-16]. Operative time (min), intraoperative blood loss (mL), and length of hospital stay (d) were significantly lower in LS than in OS (Figure 2A and 2B).

Number of lymph nodes retrieved, recurrence, blood transfusion, and complications: Five studies reported the number of lymph nodes retrieved with high heterogeneity (WMD = -1.71, 95%CI: -4.27 to 0.84, P = 0.19). Three studies reported the intraoperative blood transfusion with low heterogeneity (RR = 0.56, 95%CI: 0.29-1.09, P = 0.09)[12,14,15]. Five studies reported the complication rate with low heterogeneity (RR = 0.72, 95%CI: 0.39-1.33, P = 0.29)[12-16]. Two studies reported the recurrence rate with moderate heterogeneity (RR = 0.41, 95%CI: 0.06-2.84, P = 0.36)[12,16]. There was no significant difference between the LS and OS groups in the number of lymph nodes retrieved, recurrence, blood transfusion, or complications (Figure 2B and 2C).

3-year and 5-year overall and disease-free survival rates: Three studies reported the 3-year overall survival rate with moderate heterogeneity (RR = 0.99, 95%CI: 0.82-1.18, P = 0.89)[12-14]. Three studies reported the 5-year overall survival rate with high heterogeneity (RR = 1.02, 95%CI: 0.68-1.53, P = 0.92)[12,14,15]. Three studies reported the 3-year disease-free survival rate with low heterogeneity (RR =

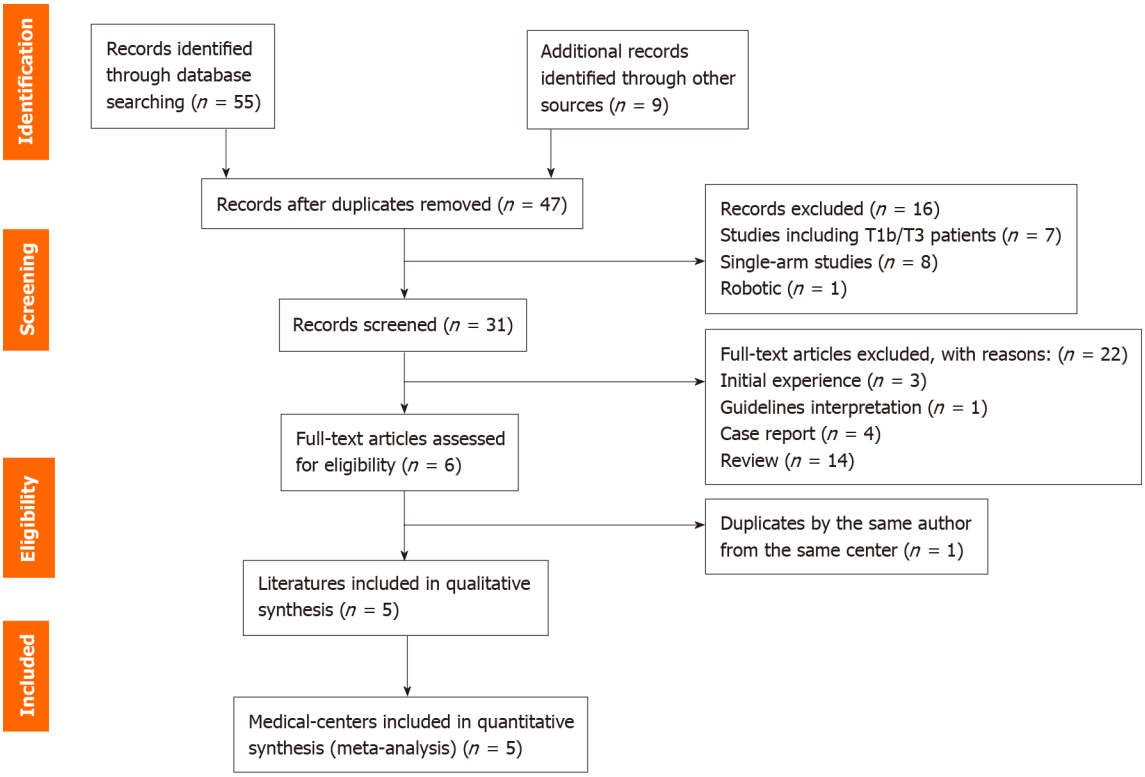

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Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for the literature search.

1.01, 95%CI: 0.84-1.21, P = 0.93)[12-14]. Three studies reported the 5-year disease-free survival rate with moderate heterogeneity (RR = 1.15, 95%CI: 0.90-1.46, P = 0.26)[12,14,15]. There was no statistical difference between the LS and OS groups in terms of 3-year and 5-year overall and disease-free survival rates (Figure 2D).

Sensitivity analysis and publication bias

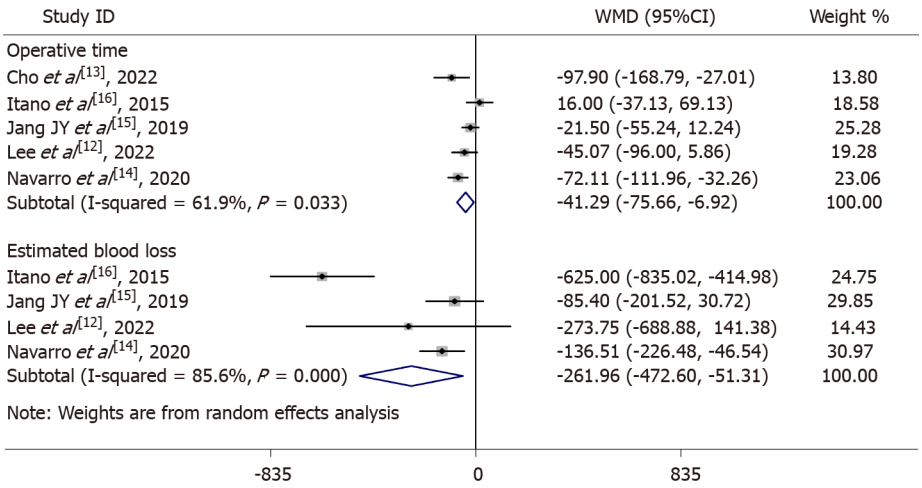
The sensitivity analysis showed that our meta-analysis was stable, and no reversal of the meta-analysis results was found. Publication bias was qualitatively assessed using funnel plots. The funnel plots were largely symmetrically distributed, with no significant extreme values (Supplementary Figure 1). Neither Begg's test nor Egger's test revealed any significant publication bias (Supplementary Table 2).

DISCUSSION

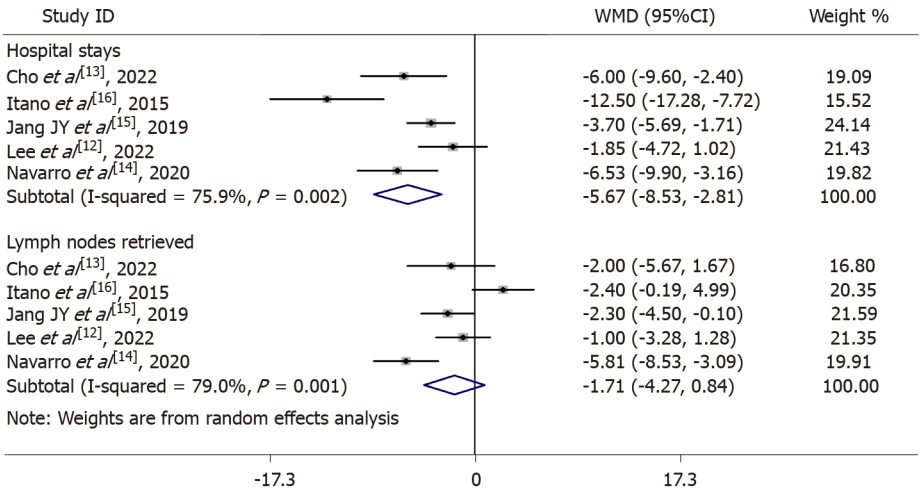
Recently, LS for patients with stage T2 GBC has become feasible in high-volume medical centers and has shown similar outcomes to those of OS[16,22-25]. However, the value of LS for T2 GBC remains controversial. The current guidelines, such as those of the National Comprehensive Cancer Network and the Japanese Society of Hepatobiliary and Pancreatic Surgery, do not recommend LS for T2 GBC[9]. Previous studies referenced by the guidelines have shown that LS is associated with a higher risk of tumor spread and incisional recurrence than OS[7,26,27]. However, tumor spread is not a complication specific to LS and can also occur in OS[28]. Currently, since specimens are often intraoperatively obtained using plastic internal bags, which can prevent tumor spread and incision site recurrence in GBC[29,30], there is no statistically significant difference in the incidence of incisional implants between LS and OS[31].

LS follows the principles of OS. Lymph node dissection and R0 rate are two important indicators to evaluate radical surgery for GBC. Studies found that the rate of lymph node metastasis in stage T2 GBC was 46%[32,33]. It has been suggested that LS is superior to OS for lymph node dissection because of the unique magnified surgical field of view[22]. However, the results of this meta-analysis showed no significant difference between the two procedures. R0 resection is also an important prognostic factor for postoperative patients. Among the analyzed studies, only the study by Lee *et al*[12] reported the R0 resection rate to be similar between the LS and OS groups, with no statistical difference.

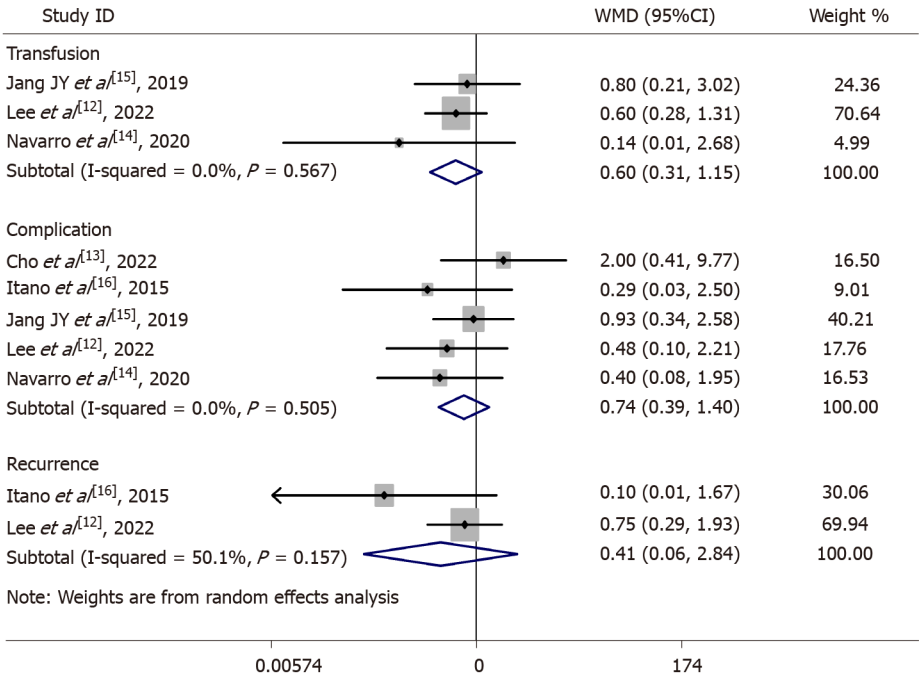
A


Study ID
WMD (95%CI)
Weight %
Operative time
Cho et al[13], 2022
-97.90 (-168.79, -27.01)
13.80
Itano et al[16], 2015
16.00 (-37.13, 69.13)
18.58
Jang JY et al[15], 2019
-21.50 (-55.24, 12.24)
25.28
Lee et al[12], 2022
-45.07 (-96.00, 5.86)
19.28
Navarro et al[14], 2020
-72.11 (-111.96, -32.26)
23.06
Subtotal (I-squared = 61.9%, P = 0.033)
-41.29 (-75.66, -6.92)
100.00
Estimated blood loss
Itano et al[16], 2015
-625.00 (-835.02, -414.98)
24.75
Jang JY et al[15], 2019
-85.40 (-201.52, 30.72)
29.85
Lee et al[12], 2022
-273.75 (-688.88, 141.38)
14.43
Navarro et al[14], 2020
-136.51 (-226.48, -46.54)
30.97
Subtotal (I-squared = 85.6%, P = 0.000)
-261.96 (-472.60, -51.31)
100.00
Note: Weights are from random effects analysis
-835
0
835

B


Study ID
WMD (95%CI)
Weight %
Hospital stays
Cho et al[13], 2022
-6.00 (-9.60, -2.40)
19.09
Itano et al[16], 2015
-12.50 (-17.28, -7.72)
15.52
Jang JY et al[15], 2019
-3.70 (-5.69, -1.71)
24.14
Lee et al[12], 2022
-1.85 (-4.72, 1.02)
21.43
Navarro et al[14], 2020
-6.53 (-9.90, -3.16)
19.82
Subtotal (I-squared = 75.9%, P = 0.002)
-5.67 (-8.53, -2.81)
100.00
Lymph nodes retrieved
Cho et al[13], 2022
-2.00 (-5.67, 1.67)
16.80
Itano et al[16], 2015
-2.40 (-0.19, 4.99)
20.35
Jang JY et al[15], 2019
-2.30 (-4.50, -0.10)
21.59
Lee et al[12], 2022
-1.00 (-3.28, 1.28)
21.35
Navarro et al[14], 2020
-5.81 (-8.53, -3.09)
19.91
Subtotal (I-squared = 79.0%, P = 0.001)
-1.71 (-4.27, 0.84)
100.00
Note: Weights are from random effects analysis
-17.3
0
17.3

C


Study ID
WMD (95%CI)
Weight %
Transfusion
Jang JY et al[15], 2019
0.80 (0.21, 3.02)
24.36
Lee et al[12], 2022
0.60 (0.28, 1.31)
70.64
Navarro et al[14], 2020
0.14 (0.01, 2.68)
4.99
Subtotal (I-squared = 0.0%, P = 0.567)
0.60 (0.31, 1.15)
100.00
Complication
Cho et al[13], 2022
2.00 (0.41, 9.77)
16.50
Itano et al[16], 2015
0.29 (0.03, 2.50)
9.01
Jang JY et al[15], 2019
0.93 (0.34, 2.58)
40.21
Lee et al[12], 2022
0.48 (0.10, 2.21)
17.76
Navarro et al[14], 2020
0.40 (0.08, 1.95)
16.53
Subtotal (I-squared = 0.0%, P = 0.505)
0.74 (0.39, 1.40)
100.00
Recurrence
Itano et al[16], 2015
0.10 (0.01, 1.67)
30.06
Lee et al[12], 2022
0.75 (0.29, 1.93)
69.94
Subtotal (I-squared = 50.1%, P = 0.157)
0.41 (0.06, 2.84)
100.00
Note: Weights are from random effects analysis
0.00574
0
174

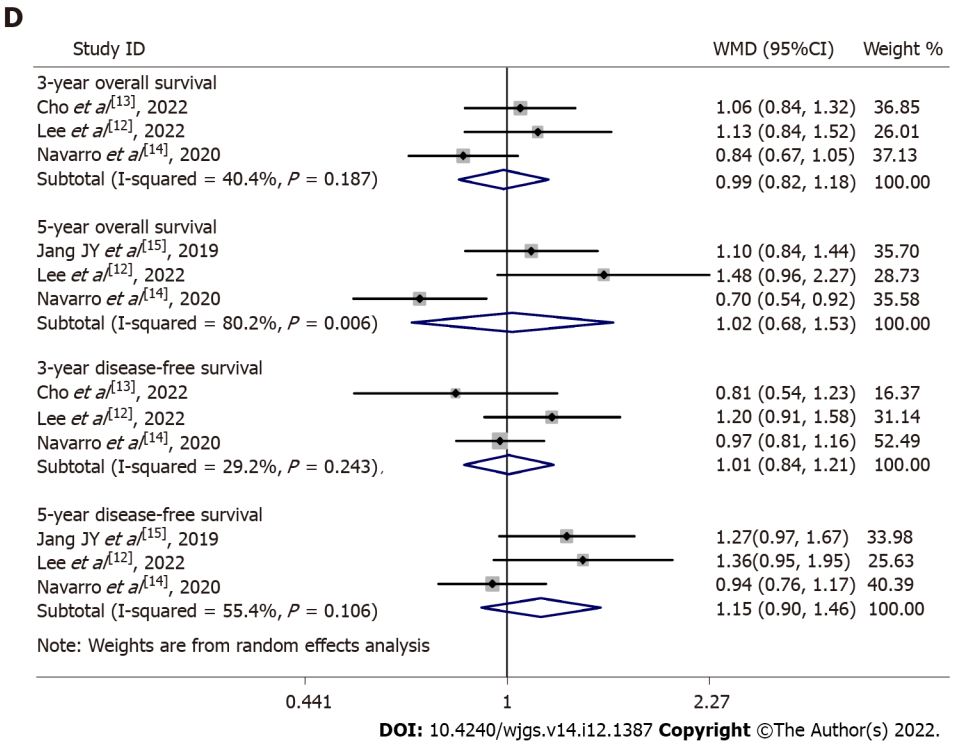


Figure 2 Forest plot. A: Operative time and intraoperative blood loss; B: Hospital stay and number of lymph nodes retrieved; C: Blood transfusion, complications, and recurrence; D: 3-year overall survival, 5-year overall survival, 3-year overall survival, and 5-year overall survival. CI: Confidence interval; RR: Relative risk; WMD: Weighted mean difference.

Although oncological outcomes based on surgical procedures, such as R0 rates and number of lymph nodes removed, were not significantly different between the LS and OS groups, the therapeutic effect should be based on more direct clinical evidence, such as improved survival, improved quality of life, or reduced tumor-related symptoms. These clinical benefits sometimes cannot be assessed based on intraoperative or short-term outcomes. Therefore, we explored long-term survival and found that postoperative recurrence and 3-year and 5-year overall and disease-free survival rates are not significantly different between the LS and OS groups.

In addition, our findings suggest that LS is associated with lower operation time, intraoperative blood loss, and length of hospital stay than OS. Although a random effects model was used to combine the effect sizes, there was a high degree of heterogeneity in operative time, intraoperative bleeding, and length of hospital stay, which significantly weakens the explanatory effect of the results and may cause confounding bias. The high heterogeneity may be explained by the fact that surgeons are still at the learning curve stage. As these results are prone to bias, they need to be validated *via* high-quality RCTs.

CONCLUSION

LS for T2 GBC has similar long-term survival outcomes to those of OS but is superior to OS in terms of operative time, intraoperative bleeding, and length of hospital stay. Additional high-quality RCTs and long follow-ups are needed to further evaluate the effectiveness of LS for stage T2 GBC.

ARTICLE HIGHLIGHTS

Research background

Although laparoscopic surgery (LS) is recommended for stage T1 gallbladder cancer (GBC), the value of LS for stage T2 GBC is still controversial.

Research motivation

This study evaluated the short- and long-term outcomes of LS in comparison to those of open surgery (OS) for stage T2 GBC.

Research objectives

As there is still a lack of evidence from high-quality multicenter randomized controlled trials, we believe that it is necessary to conduct a meta-analysis to provide an evidence-based reference for laparoscopic radical surgery of T2 GBC.

Research methods

We searched the PubMed, Embase, Cochrane Library, Ovid, Google Scholar, and Web of Science databases for published studies, with a cutoff date of September 2022.

Research results

A total of 5 studies were included with a total of 297 patients, 153 in the LS group and 144 in the OS group. Meta-analysis results showed that the LS group was better than the OS group in terms of operative time, estimated blood loss, and hospital stay, whereas there was no significant difference between the two groups in terms of blood transfusion, complications, number of lymph nodes retrieved, recurrence, and 3-year and 5-year overall and disease-free survival.

Research conclusions

The long-term outcomes of LS for T2 GBC are similar to those of OS, but LS is superior to OS in terms of operative time, intraoperative bleeding, and postoperative hospital stay.

Research perspectives

Our meta-analysis is the first to assess the efficacy of the laparoscopic approach in the treatment of stage T2 GBC and to provide a reference for clinical management.

FOOTNOTES

Author contributions: Zhang W and Ouyang DL equally contributed to this work; Zhang W and Ouyang DL drafted the manuscript and acquired and interpreted the data; Che X designed the study and revised the manuscript.

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META-ANALYSIS

Meta-analysis of transanal *vs* laparoscopic total mesorectal excision of low rectal cancer: Importance of appropriate patient selection

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Abstract

BACKGROUND

Achieving a clear resection margins for low rectal cancer is technically challenging. Transanal approach to total mesorectal excision (TME) was introduced in order to address the challenges associated with the laparoscopic approach in treating low rectal cancers. However, previous meta-analyses have included mixed population with mid and low rectal tumours when comparing both approaches which has made the interpretation of the real differences between two approaches in treating low rectal cancer difficult.

AIM

To investigate the outcomes of transanal TME (TaTME) and laparoscopic TME (LaTME) in patients with low rectal cancer.

METHODS

A comprehensive systematic review of comparative studies was performed in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards. Intraoperative and postoperative complications, anastomotic leak, R0 resection, completeness of mesorectal excision, circumferential resection margin (CRM), distal resection margin (DRM), harvested lymph nodes, and operation time were the investigated outcome measures.

RESULTS

We included twelve comparative studies enrolling 969 patients comparing TaTME (n = 969) and LaTME (n = 476) in patients with low rectal tumours. TaTME was associated with significantly lower risk of postoperative complications (OR: 0.74, P = 0.04), anastomotic leak (OR: 0.59, P = 0.02), and conversion to an open procedure (OR: 0.29, P = 0.002) in comparison with LaTME. Moreover, the rate of R0 resection was significantly higher in the TaTME group (OR: 1.96, P = 0.03). Nevertheless, TaTME and LaTME were comparable in terms of rate of intraoperative complications (OR: 1.87; P = 0.23), completeness of mesoractal excision (OR: 1.57, P = 0.15), harvested lymph nodes (MD: -0.05, P = 0.96), DRM (MD: -0.94; P = 0.17), CRM (MD: 1.08, P = 0.17), positive CRM (OR: 0.64, P = 0.11) and procedure time (MD: -6.99 min, P = 0.45).

CONCLUSION

Our findings indicated that for low rectal tumours, TaTME is associated with better clinical and short term oncological outcomes compared to LaTME. More randomised controlled trials are required to confirm these findings and to evaluate long term oncological and functional outcomes.

Key Words: Total mesorectal excision; Laparoscopic; Transanal; Rectal cancer

Core Tip: The meta-analysis of best available evidence demonstrated that for low rectal tumours, Transanal total mesorectal excision (TaTME) is associated with better clinical and short term oncological outcomes compared to Laparoscopic TME. More randomised controlled trials with adequate power and high quality are required to not only confirm these findings, but also to evaluate long term oncological and functional outcomes.

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INTRODUCTION

The incidence of rectal cancer is increasing making it one of the most common cancers worldwide[1]. Rapidly evolving use of total mesorectal excision (TME) and neoadjuvant chemotherapy have led to considerable improvements in the outcomes of rectal cancer surgery[2]. A clear resection margin associated with a high quality TME is important for an ideal oncological resection, reducing the incidence of local or regional recurrence, and increasing survival from cancer[3,4].

Achieving a negative resection margins during resection of low rectal tumours can be challenging due to existence of diminishing gap between the wall of the rectum and mesorectal fascia towards the anal canal[5]. This has resulted in worse oncological outcomes associated with resection of lower rectal tumours, in comparison with resection of middle or high rectal tumours, because of greater incidence of local recurrence and positive resection margin[6]. Transanal approach to TME was introduced in order to address the challenges associated with the laparoscopic and even open TME in surgical management of low rectal cancers[7].

In 2020, in a comprehensive meta-analysis of comparative studies, we reported that Transanal TME (TaTME) led to higher R0 resection rate and number of harvested lymph nodes while decreasing rates of positive circumferential resection margin (CRM) and conversion to open procedure when compared to laparoscopic TME (LaTME)[8]. Moreover, our findings indicated that TaTME and LaTME may have similar risk of perioperative morbidity[8]. Nevertheless, most of the evaluated studies in the aforementioned meta-analysis compared TaTME and LaTME in patients with middle and low rectal tumours subjecting the findings to bias. Considering the existence of new studies focusing on the clinical outcomes of TaTME and LaTME in management of low rectal cancer, conduction of another meta-analysis is worthwhile in order to help defining more appropriate patient selection.

This study aimed to systematically evaluate the best available comparative evidence surrounding TaTME and LaTME in surgical management of low rectal cancer only and compare the outcome so both approaches using meta-analytical model.

MATERIALS AND METHODS

Study design and selection of eligible studies

In our review protocol, we highlighted the inclusion and exclusion criteria, our methodology, and evaluated outcome measures. This study was carried out in line with standards of Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[9].

All comparative studies investigating the outcomes of transanal and laparoscopic TME in patients with low cancer were considered for inclusion. A rectal tumour within 6 cm of anal verge was considered as a low rectal tumour. We considered all adult (aged > 18 years) patients undergoing TaTME or LaTME for low rectal cancer. TaTME was the intervention of interest and LaTME was the comparison of interest.

The primary outcome measures were intraoperative and postoperative complications, and anastomotic leak. The investigated primary oncological outcome measures were R0 resection, CRM, positive CRM, distal resection margin (DRM), completeness of mesorectal excision, and number of harvested lymph nodes. Moreover, conversion to open and operative time were defined as secondary outcome measures.

Literature search strategy

Following sources: MEDLINE, Web of Science, and CENTRAL were searched by two independent authors. Appendix 1 outlines the used search strategy (Supplementary Table 1). The most recent literature search was carried out on 08 July, 2022. Moreover, we screened the reference lists of the included studies and previous review articles in order to identify more relevant articles.

Study selection

Two independent review authors screened the title and abstract of the identified studies. This was followed by retrieval of the full-texts of the related studies and their assessment in line with our inclusion and exclusion criteria. Discrepancies in this stage were addressed by discussion among the reviewers.

Extraction and management of data

We created a data extraction tool and extracted details of study-related data, data regarding demographic characteristics of the included patients in each study and outcome data. Two independent reviewers were involved in this process. Disagreements between the authors were resolved following discussion. In case of no resolution, an additional reviewer was consulted.

Assessment of risk of bias

The methodological quality of the included studies was assessed by 2 review authors who determined their associated risk of bias using the Newcastle-Ottawa scale[10] for observational studies and Cochrane's tool[11] for randomized controlled trials (RCTs). We resolved disagreements in methodological quality assessment by discussion between the reviewers. However, if disagreement remained unresolved, a third reviewer was consulted as an adjudicator.

Summary measures and synthesis

For dichotomous outcome measures the odds ratio (OR) was calculated as the summary measures. For continuous outcome parameters, the mean difference (MD) between the two groups was calculated. If mean values were not reported, we extracted data on median and interquartile range and converted those to mean and standard deviation using Hozo *et al*[12]'s equation.

The unit of analysis for all of the analyzed outcome measures in this study was an individual participant. We did not require contacting the authors of the included studies to ask for any potential missing information.

Data analysis was carried out *via* Review Manager 5.4 software[11]. One author extracted and entered the data into the software and another author cross-checked the data. Random-effects modelling were used for analysis of all outcomes. We reported outcome of analyses in Forest plots with 95% confidence intervals (CIs).

The Cochran Q test (χ^2) was used to assess between-study heterogeneity. We calculated I^2 and used the following guide for interpreting the degree of heterogeneity: 0% to 50% might not be important; 50% to 75%: May represent moderate heterogeneity; 75% to 100% may represent substantial heterogeneity. Moreover, we constructed funnel plots for any outcome synthesis involving more than 10 studies.

We performed sensitivity analyses to assess for potential sources of heterogeneity and evaluate the robustness of our findings. Finally, we conducted leave-one-out sensitivity analysis to assess the effect of each study on the overall effect size and heterogeneity.

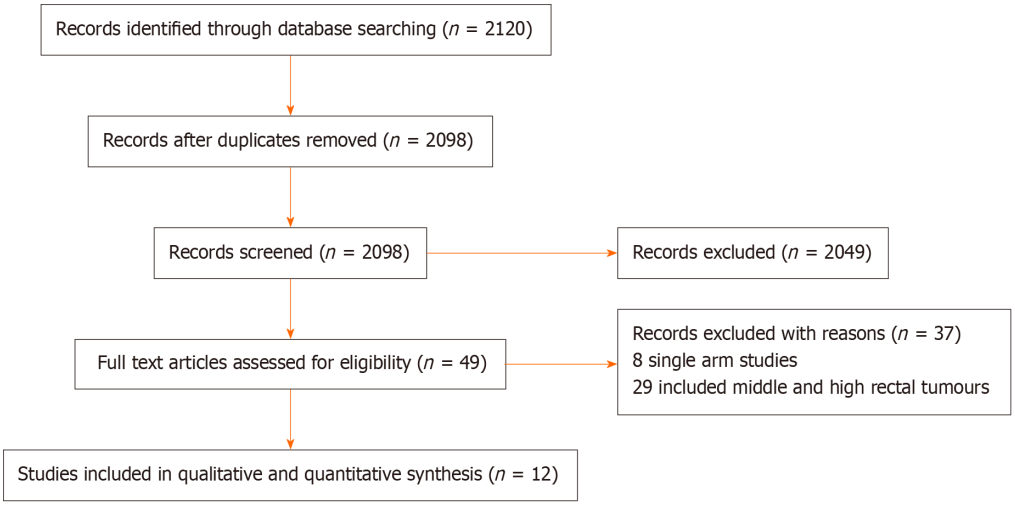

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Figure 1 Study flow diagram.

RESULTS

The literature search resulted in 2120 articles. Following further assessment of the aforementioned articles, 12 comparative studies (2 randomised and 10 observational studies)[13-24] met the inclusion criteria (Figure 1). The included studies enrolled 969 patients of whom 493 underwent TaTME and the remaining 476 patients had LaTME for rectal cancer.

Table 1 presents the included studies related data. Table 2 presents baseline demographic and clinical characteristics of the included patients. The patients in the transanal and laparoscopic groups were of similar age (P = 0.53), gender (P = 0.19), and BMI (P = 0.68). No significant difference was found between the TaTME and LaTME groups in rectal cancer stages I (P = 0.29), II (P = 0.30) and III (P = 0.95). Furthermore, the mean distance of the tumour to the anal verge in the TaTME and LaTME groups were 3.4 cm ± 1.4 cm and 3.6 cm ± 1.5 cm, respectively, which was not significantly different (P = 0.07). Neoadjuvant chemotherapy was carried our similarly between two groups (P = 0.22).

Methodological appraisal

The methodological assessment of 10 observational studies is presented in Table 3. In 7 studies, the risk of bias was low and in 3 studies it was moderate. Moreover, the outcome of methodological assessment of the included randomized controlled trials is demonstrated by Figure 2.

Data synthesis

Outcomes are summarised in Figures 3 and 4.

Intraoperative complications: Six studies (382 patients) reported intraoperative complications as an outcome. The rate of intraoperative complications in the TaTME and LaTME were 7.3% and 4.2%, respectively. There was no significant difference in intraoperative complications between TaTME and LaTME (OR: 1.87; 95%CI: 0.68-5.18, P = 0.23). There was low between-study heterogeneity (I^2 = 6%, P = 0.36).

Postoperative complications: Eleven studies (923 patients) reported postoperative complications as an outcome. The rate of overall postoperative complications in the TaTME and LaTME were 30.0% and 35.9%, respectively. TaTME significantly reduced postoperative complications when compared to LaTME (OR: 0.74; 95%CI: 0.56-0.99, P = 0.04). There was moderate heterogeneity among the included studies (I^2 = 2%, P = 0.42).

Anastomotic leak: This outcome was reported by eleven studies (896 patients). Anastomotic leak occurred in 10.1% and 15.5% of patients in the TaTME and LaTME groups, respectively. TaTME was associated with a significantly lower rate of anastomotic leak compared with LaTME (OR: 0.59; 95%CI: 0.38-0.91, P = 0.02). Heterogeneity among the included studies was low (I^2 = 0%, P = 0.49).

R0 resection: Nine studies (609 patients) reported R0 resection as an outcome. An R0 resection was achieved in 93.5% and 87.8% of patients in the TaTME and LaTME groups, respectively. The rate of R0 resection was significantly higher in the TaTME group (OR: 1.96; 95%CI: 1.07-3.58, P = 0.03). Low between-study heterogeneity was detected (I^2 = 0%, P = 0.51).

Table 1 Included studies related data

Ref.	Publication year	Journal	Country	Study design	TaTME	LaTME
de'Angelis *et al*[13]	2015	*Langenbecks Arch Surg*	France	Retrospective observational study	32	32
Kanso *et al*[14]	2015	*Dis Colon Rectum*	France	Retrospective observational study	51	34
Pontallier *et al*[15]	2016	*Surg Endosc*	France	RCT	38	34
Marks *et al*[16]	2016	*Tech. Coloproctol*	United States	Retrospective observational study	17	17
Lelong *et al*[17]	2017	*J Am Coll Surg*	France	Retrospective observational study	34	38
Denost *et al*[18]	2018	*Surg Endosc*	France	RCT	50	50
Mege *et al*[19]	2018	*Colorectal Dis*	France	Retrospective observational study	34	34
Rubinkiewicz *et al*[20]	2018	*Cancer Manag Res*	Poland	Retrospective observational study	35	35
Roodbeen *et al*[21]	2019	*Surg Endosc*	Netherlands	Retrospective observational study	41	41
Rubinkiewicz *et al*[22]	2019	*BMC Surg*	Poland	Prospective observational study	23	23
Ren *et al*[23]	2021	*Asian J Surg*	China	Prospective observational study	32	32
Li *et al*[24]	2022	*Gastroenterol Res Pract*	China	Prospective observational study	106	106

TaTME: Transanal total mesorectal excision, LaTME: Laparoscopic total mesorectal excision; RCT: Randomised controlled trial.

Completeness of mesorectal excision: This outcome was reported by nine studies (766 patients). The rate of completeness of mesorectal excision in the TaTME and LaTME groups were 81.4% and 74.0%, respectively. The pooled analysis did not demonstrated similar rate of completeness of mesorectal excision between two groups (OR: 1.57; 95%CI: 0.85-2.90, $P = 0.15$). There was moderate between-study heterogeneity ($I^2 = 60\%$, $P = 0.01$).

Number of harvested lymph nodes: Eight studies (747 patients) reported the number of harvested lymph nodes in the TaTME and LaTME groups. The mean number of harvested lymph nodes in the TaTME was 16.1 ± 2.1, while it was 16.3 ± 3.2 in the LaTME group. The pooled analysis demonstrated no significant difference in the number of harvested lymph nodes between two groups (MD: -0.05; 95%CI: -1.98-1.89, $P = 0.96$). The between-study heterogeneity was moderate ($I^2 = 71\%$, $P = 0.001$).

DRM: Eight studies (745 patients) reported DRM in their study groups. The mean DRM in the TaTME group was 15.8 mm ± 3.9 mm whereas it was 17.6 mm ± 3.8 mm in the LaTME group. The pooled analysis found no significant difference in DRM between two groups (MD: -0.94; 95%CI: -2.26-0.39, $P = 0.17$). There was low heterogeneity among the included studies ($I^2 = 0\%$, $P = 0.53$).

CRM: Six studies (465 patients) reported CRM in their study groups. The mean CRM in the TaTME group was 8.5 mm ± 1.2 mm and it was 8.1 mm ± 2.9 mm in the LaTME group. The pooled analysis did not identify any significant difference in CRM between two groups (MD: 1.08; 95%CI: -0.46-2.61, $P = 0.17$). There was moderate between-study heterogeneity ($I^2 = 71\%$, $P = 0.004$).

Positive CRM: Eight studies (717 patients) reported the rate of positive CRM in their study groups. The rate of positive CRM in the TaTME group was 9.0% and it was 13.3% in the LaTME group. There was no significant difference in the rate of positive CRM between two groups (OR: 0.64; 95%CI: 0.37-1.10, $P = 0.11$). Between-study heterogeneity was low ($I^2 = 0\%$, $P = 0.59$).

Procedure time: Ten studies (889 patients) reported the procedure time as an outcome. The mean procedure time in the TaTME and LaTME groups were 274.1 min ± 91.8 min and 282.4 min ± 103.0 min, respectively. There was no significant difference in procedure time between two groups (MD: -6.99 min; 95%CI: -25.28-11.30, $P = 0.45$). Heterogeneity among the studies was significant ($I^2 = 86\%$, $P < 0.00001$).

Conversion to open: This outcome was reported by eleven studies (923 patients). The rate of conversion to an open procedure in the TaTME group was 1.5% and it was 7.5% in the LaTME group. The conversion rate was significantly lower in the TaTME group compared to the LaTME group (OR: 0.29; 95%CI: 0.13-0.64, $P = 0.002$). There was low between-study heterogeneity ($I^2 = 0\%$, $P = 0.54$).

Considering that the included study inadequately reported length of hospital stay as an outcome, we were unable to conduct an analysis on this outcome.

Sensitivity analysis

There was no change in the direction of pooled effect size when the risk ratio, or risk difference was

Table 2 Included studies related data

Ref.	Publication year	Age	Gender	BMI	Neoadjuvant therapy	Tumour stage	Tumour location	Distance of tumour to anal verge
de'Angelis[13]	2015	64.91 ± 10.05 *vs* 67.16 ± 9.61	66% *vs* 66%	25.19 ± 3.52 *vs* 24.53 ± 3.19	100% *vs* 100%	I: 65.6% *vs* 56.3%; II: 31.3% *vs* 40.6%; III: 3.1% *vs* 3.1%	Low rectum	4 (2.5-5.0) *vs* 3.7 (2.5-5.0)
Kanso *et al*[14]	2015	59 ± 11 (32-79) *vs* 59 ± 11 (33-82)	71% *vs* 77%	24 ± 4 (17-32) *vs* 24 ± 4 (15-34)	80% *vs* 79%	NR	Lower rectum	1.6 ± 0.8 (0-3.5) *vs* 1.8 ± 0.9 (0-3.5)
Pontallier *et al*[15]	2016	62 (39-81) *vs* 62 (35-82)	68% *vs* 62%	25.5 *vs* 24.8	79% *vs* 88%	I: 21% *vs* 21%; II: 19% *vs* 14%; III: 60% *vs* 65%	Low rectum	4 (2-6) *vs* 4 (2-6)
Marks *et al*[16]	2016	60 *vs* 59	NR	25.9 *vs* 26.4	NR	I: 29.4% *vs* 23.5%; II: 70.6% *vs* 76.5%	Low rectum	< 4 *vs* < 4
Lelong *et al*[17]	2017	NR	68% *vs* 58%	24 (18.6-45.0) *vs* 24.2(17.7-32.7)	88.2% *vs* 92.1%	I: 17.6% *vs* 23.7%; II: 70.6% *vs* 71.0%; III: 11.8% *vs* 5.3%	Low rectum	NR
Denost *et al*[18]	2018	64 (39-82) *vs* 63 (31-90)	74% *vs* 64%	25.1 (17.3-33.2) *vs* 25.6 (18.3-38.3)	78% *vs* 84%	NR	Low rectum	4 (2-6) *vs* 4 (2-6)
Mege *et al*[19]	2018	58 ± 14 *vs* 59 ± 13	68% *vs* 68%	25 ± 4 *vs* 25 ± 3	85% *vs* 85%	I: 29.4% *vs* 11.8%; II: 67.6% *vs* 82.3%; III: 43.5% *vs* 47.8%; IV: 2.9% *vs* 5.9%	Low rectum	NR
Rubinkiewicz *et al*[20]	2018	64.3 ± 10.1 *vs* 60.3 ± 10.2	69% *vs* 69%	26.10 ± 4.09 *vs* 27.10 ± 4.71	88.6% *vs* 88.6%	I: 42.9% *vs* 45.7%; II: 57.1% *vs* 54.3%	Low rectum	2.90 ± 1.17 *vs* 3.19 ± 1.47
Roodbeen *et al*[21]	2019	62.5 ± 10.7 *vs* 66.0 ± 9.2	82.9% *vs* 78%	26.7 ± 1.9 *vs* 26.1 ± 4.0	43.9% *vs* 43.9%	I: 22.0% *vs* 19.5%; II: 36.6% *vs* 39%; III: 31.7% *vs* 31.7%; IV: 9.8% *vs* 9.8%	Low rectum	2.0 (0.0-4.0) *vs* 1.5 (0.0-3.0)
Rubinkiewicz *et al*[22]	2019	60 (51-67) *vs* 64 (58-67)	69% *vs* 69%	26 (22.8-29.7) *vs* 26.5 (23.8-30.6)	78.2% *vs* 82.6%	NR	Low rectum	3(2-4) *vs* 4 (3-5)
Ren *et al*[23]	2021	65.78 ± 12.37 *vs* 67.16 ± 10.03	59.3% *vs* 56.2%	22.87 ± 2.66 *vs* 23.05 ± 2.70	71.8% *vs* 65.6%	I: 34.3% *vs* 37.5%; II: 28.1% *vs* 31.2%; III: 31.2% *vs* 21.8%	Low rectum	5.53 ± 0.98 *vs* 5.78 ± 0.94
Li *et al*[24]	2022	55 ± 12 (23-78) *vs* 56 ± 12 (26-79)	100% *vs* 100%	23:0 ± 2.9 *vs* 22:9 ± 3.2	100% *vs* 100%	NR	Low rectum	3.6 ± 0.9 (2.0-5.0) *vs* 3.8 ± 0.9 (1.4-5.0)

Transanal total mesorectal excision *vs* Laparoscopic total mesorectal excision. BMI: Body mass index; NR: Not reported.

calculated or during leave-one-out sensitivity analysis.

DISCUSSION

In view of ongoing debates regarding the best surgical approach for resection of low rectal cancer, we conducted a comprehensive systematic review and meta-analysis to evaluate comparative outcomes of transanal *vs* laparoscopic TME in management of low rectal cancer. We identified two RCTs and 10 observational studies[13-24] enrolling 969 patients of whom 493 had TaTME and 476 patients had LaTME for low rectal tumour. The subsequent outcome synthesis showed that TaTME significantly reduced rate of postoperative complications, anastomotic leak, and conversion to open in comparison to LaTME. Moreover, TaTME resulted in significantly higher rate of R0 resection. However, no significant difference was found in intraoperative complications, completeness of mesoractal excision, harvested lymph nodes, DRM, CRM, positive CRM and procedure time between TaTME and LaTME

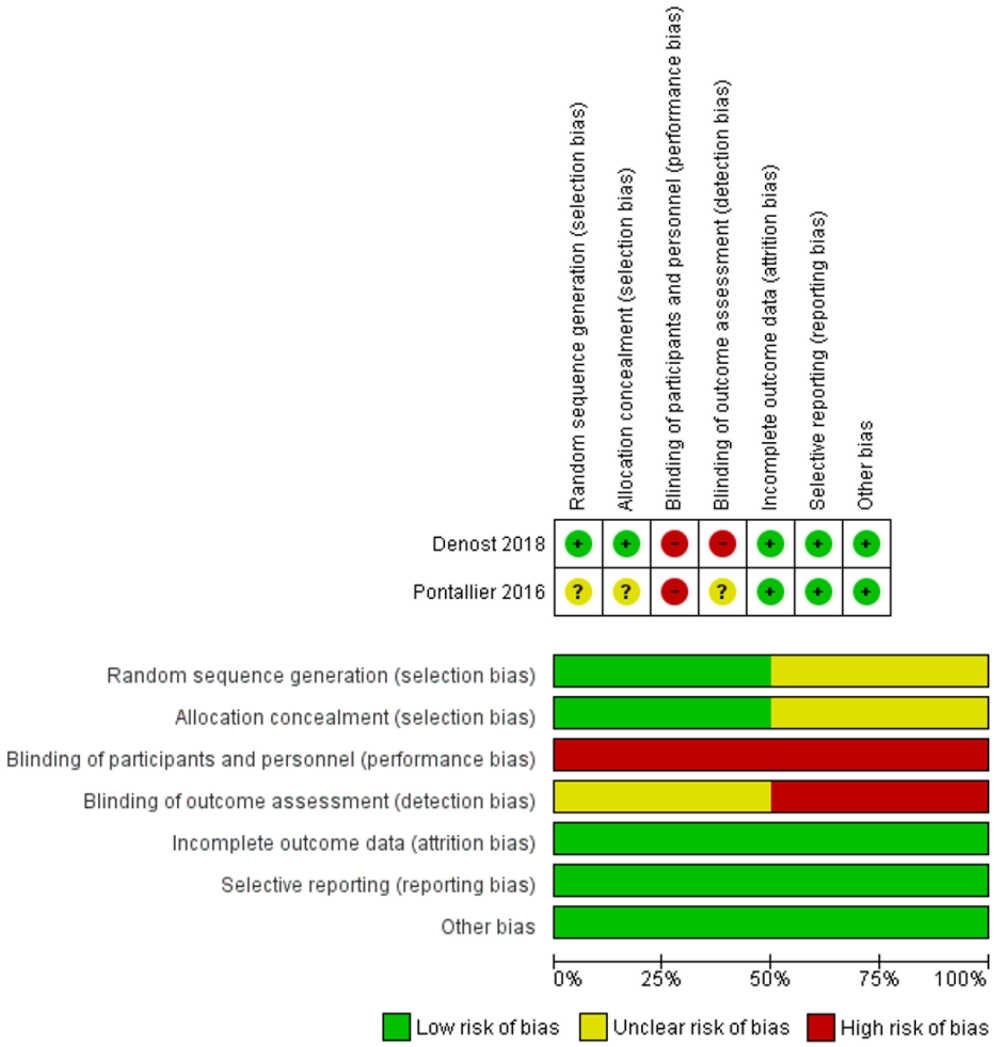
The between-study heterogeneity in the analyses of intraoperative and postoperative complications, anastomotic leak, R0 resection, DRM, positive CRM, and conversion to open were low suggesting that the reported findings with respect to these outcomes can be considered robust. Moderate heterogeneity

Table 3 Methodological quality of the observational studies assessed with the Newcastle-Ottawa scale

Author	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total score
de'Angelis[13], 2015	*	*	*	*	**	*	*	*	9
Kanso *et al*[14], 2015	*	*	*	*	**	*	*	*	9
Marks *et al*[16], 2016	*	*	*	*	-	*	*	*	7
Lelong *et al*[17], 2017	*	*	*	*	*	*	*	*	8
Mege *et al*[19], 2018	*	*	*	*	**	*	*	*	9
Rubinkiewicz *et al*[20], 2018	*	*	*	*	**	*	*	*	9
Roodbeen *et al* [21], 2019	*	*	*	*	**	*	*	*	9
Rubinkiewicz *et al*[22], 2019	*	*	*	*	*	*	*	*	8
Ren *et al*[23], 2021	*	*	*	*	**	*	*	*	9
Li *et al*[24], 2022	*	*	*	*	**	*	*	*	9

among the included studies in the analyses of completeness of mesorectal excision, and number of harvested lymph nodes may suggest variation of reporting in the included studies on these outcomes. There was high between-study heterogeneity regarding procedure time suggesting that our findings about procedure time may be less robust.

The findings of our meta-analysis are not consistent with some of the findings of our previous meta-analysis on this topic published in 2020[8]. The simple explanation for such disagreement is the difference in the inclusion criteria of the two studies with regards to the location of the rectal cancer. We only included low rectal cancer patients in this meta-analysis while previously we included both middle and low rectal cancer patients. In fact, as a direction for future research, in our previous meta-analysis we encouraged future studies to consider patients with low rectal cancer only when comparing TaTME and LaTME to evaluate a more realistic comparison between these two management approaches[8]. This is indeed reassuring to observe growing evidence in the context of comparative outcomes of TaTME and LaTME in management of low rectal cancer. The appropriate patient selection in this context is of great importance as inappropriate patient selection for TaTME has been demonstrated to result in



DOI: 10.4240/wjgs.v14.i12.1397

Figure 2 Risk of bias summary and graph showing authors' judgments about each risk of bias item.

unfavourable outcomes of TaTME leading to suspension of TaTME in some countries. Wasmuth *et al*[25] reported high rate of anastomotic leak and local recurrence associated with TaTME, the findings that led to suspicion of TaTME in Norway. However, only 5% of their included patients had low rectal tumours with the remaining patients having middle or high rectal cancers. Moreover, the study lacked a control group, hence low level of evidence.

In the current meta-analysis, we independently evaluated the baseline characteristics of the study population to assess if the patients in the TaTME and LaTME groups were comparable. We found no significant difference in age, gender, BMI, rate of neoadjuvant chemotherapy, and stage of cancer between two groups. Moreover, we demonstrated similar distance between the distal tumour and anal verge between the TaTME and LaTME patients. This is of a cardinal importance as TaTME has been introduced to address the challenges associated with open and laparoscopic approaches in resecting very low rectal cancers, particularly in male patients with narrow pelvis[8]. Therefore, comparability of our included populations in both groups makes our findings more robust.

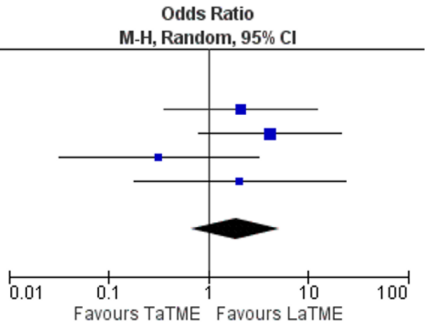
We were not able to conduct any analyses on comparative functional outcomes of TaTME and LaTME considering that only two of the included studies reported such outcomes. Lelong *et al*[17] compared functional outcomes of TaTME and LaTME and demonstrated no significant difference in urinary complications and faecal incontinence between two groups. Rubinkiewicz *et al*[22] also investigated functional outcomes in patients undergoing TaTME and LaTME for low rectal tumours and reported no significant differences in risk of low anterior resection syndrome between two groups and its severity. The authors found comparable median Wexner score in both groups[22]. Considering the current limited evidence in the context of functional outcomes of TaTME compared with LaTME, no definitive conclusions can be made.

Although we were not able to analyse long term oncological outcomes including disease recurrence, the findings of one of our included RCTs in this context is important. After 5 years follow-up, Denost *et al*[18] reported no significant differences in long-term outcomes between TaTME and LaTME. Although

A

Study or Subgroup	TaTME Events	TaTME Total	LaTME Events	LaTME Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
de'Angelis 2015	0	32	0	32		Not estimable	2015
Marks 2016	0	17	0	17		Not estimable	2016
Rubinkiewicz 2018	4	35	2	35	30.5%	2.13 [0.36, 12.46]	2018
Mege 2018	7	34	2	34	34.5%	4.15 [0.79, 21.66]	2018
Roodbeen 2019	1	41	3	41	18.5%	0.32 [0.03, 3.18]	2019
Ren 2020	2	32	1	32	16.5%	2.07 [0.18, 24.01]	2020
Total (95% CI)		**191**		**191**	**100.0%**	**1.87 [0.68, 5.18]**	
Total events	14		8				

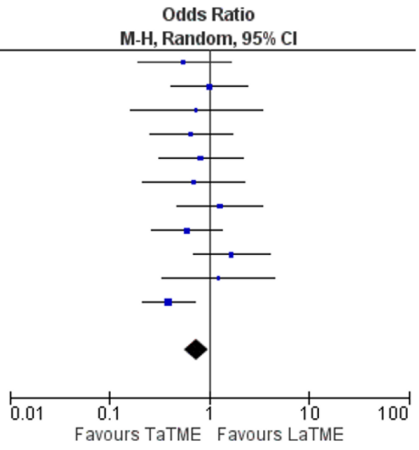
Heterogeneity: Tau² = 0.07; Chi² = 3.20, df = 3 (*P* = 0.36); I² = 6%
Test for overall effect: Z = 1.21 (*P* = 0.23)



B

Study or Subgroup	TaTME Events	TaTME Total	LaTME Events	LaTME Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
de'Angelis 2015	8	32	12	32	7.0%	0.56 [0.19, 1.63]	2015
Kanso 2015	24	51	16	34	10.6%	1.00 [0.42, 2.39]	2015
Marks 2016	4	17	5	17	3.5%	0.74 [0.16, 3.41]	2016
Pontallier 2016	12	38	14	34	8.6%	0.66 [0.25, 1.73]	2016
Lelong 2017	11	34	14	38	8.5%	0.82 [0.31, 2.17]	2017
Rubinkiewicz 2018	6	35	8	35	5.8%	0.70 [0.21, 2.28]	2018
Mege 2018	14	34	12	34	8.4%	1.28 [0.48, 3.42]	2018
Denost 2018	16	50	22	50	12.0%	0.60 [0.27, 1.35]	2018
Roodbeen 2019	19	41	14	41	10.1%	1.67 [0.68, 4.06]	2019
Ren 2020	6	32	5	32	4.8%	1.25 [0.34, 4.59]	2020
Li 2022	21	106	41	106	20.6%	0.39 [0.21, 0.73]	2022
Total (95% CI)		**470**		**453**	**100.0%**	**0.74 [0.56, 0.99]**	
Total events	141		163				

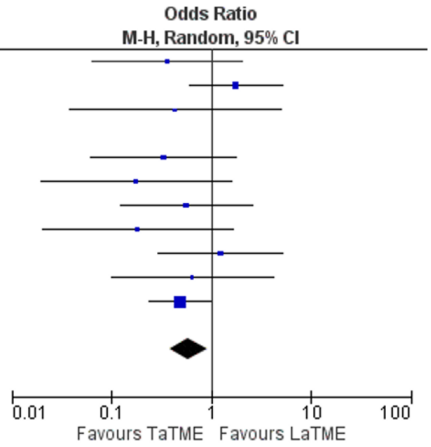
Heterogeneity: Tau² = 0.00; Chi² = 10.19, df = 10 (*P* = 0.42); I² = 2%
Test for overall effect: Z = 2.03 (*P* = 0.04)



C

Study or Subgroup	TaTME Events	TaTME Total	LaTME Events	LaTME Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
de'Angelis 2015	2	32	5	32	6.3%	0.36 [0.06, 2.01]	2015
Kanso 2015	14	51	6	34	16.0%	1.77 [0.60, 5.17]	2015
Pontallier 2016	1	38	2	34	3.1%	0.43 [0.04, 4.99]	2016
Marks 2016	0	17	0	17		Not estimable	2016
Lelong 2017	2	34	6	38	6.6%	0.33 [0.06, 1.78]	2017
Mege 2018	1	34	5	34	3.8%	0.18 [0.02, 1.59]	2018
Rubinkiewicz 2018	3	35	5	35	8.1%	0.56 [0.12, 2.56]	2018
Denost 2018	1	50	5	50	3.9%	0.18 [0.02, 1.63]	2018
Roodbeen 2019	5	28	4	27	9.0%	1.25 [0.30, 5.26]	2019
Ren 2020	2	32	3	32	5.4%	0.64 [0.10, 4.14]	2020
Li 2022	15	106	27	106	37.9%	0.48 [0.24, 0.97]	2022
Total (95% CI)		**457**		**439**	**100.0%**	**0.59 [0.38, 0.91]**	
Total events	46		68				

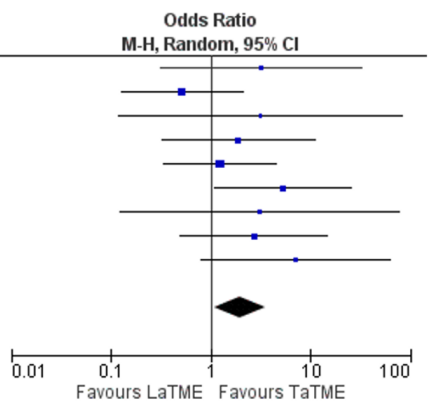
Heterogeneity: Tau² = 0.00; Chi² = 8.47, df = 9 (*P* = 0.49); I² = 0%
Test for overall effect: Z = 2.41 (*P* = 0.02)



D

Study or Subgroup	TaTME Events	TaTME Total	LaTME Events	LaTME Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
de'Angelis 2015	31	32	29	32	6.8%	3.21 [0.32, 32.60]	2015
Kanso 2015	43	51	31	34	18.4%	0.52 [0.13, 2.12]	2015
Marks 2016	17	17	16	17	3.4%	3.18 [0.12, 83.76]	2016
Lelong 2017	32	34	34	38	11.7%	1.88 [0.32, 10.99]	2017
Mege 2018	29	34	28	34	21.7%	1.24 [0.34, 4.54]	2018
Denost 2018	48	50	41	50	14.4%	5.27 [1.08, 25.78]	2018
Rubinkiewicz 2018	35	35	34	35	3.5%	3.09 [0.12, 78.41]	2018
Roodbeen 2019	39	41	36	41	12.6%	2.71 [0.49, 14.84]	2019
Ren 2020	31	32	26	32	7.6%	7.15 [0.81, 63.30]	2020
Total (95% CI)		**326**		**313**	**100.0%**	**1.96 [1.07, 3.58]**	
Total events	305		275				

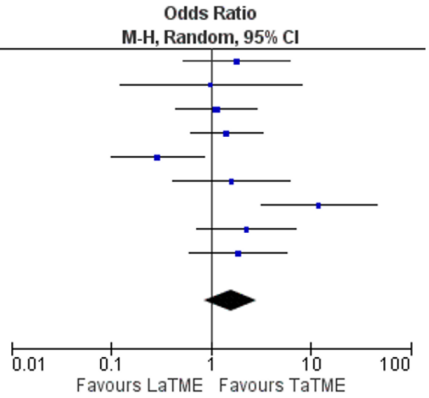
Heterogeneity: Tau² = 0.00; Chi² = 7.24, df = 8 (*P* = 0.51); I² = 0%
Test for overall effect: Z = 2.19 (*P* = 0.03)



E

Study or Subgroup	TaTME Events	TaTME Total	LaTME Events	LaTME Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
de'Angelis 2015	27	32	24	32	10.8%	1.80 [0.52, 6.25]	2015
Marks 2016	15	17	15	17	6.0%	1.00 [0.12, 8.06]	2016
Lelong 2017	19	34	20	38	13.4%	1.14 [0.45, 2.89]	2017
Denost 2018	35	50	31	50	14.3%	1.43 [0.62, 3.29]	2018
Mege 2018	18	34	27	34	12.2%	0.29 [0.10, 0.85]	2018
Rubinkiewicz 2018	31	35	29	35	9.9%	1.60 [0.41, 6.26]	2018
Roodbeen 2019	38	41	21	41	10.2%	12.06 [3.21, 45.40]	2019
Ren 2020	26	32	21	32	11.5%	2.27 [0.72, 7.16]	2020
Li 2022	101	106	97	106	11.7%	1.87 [0.61, 5.79]	2022
Total (95% CI)		**381**		**385**	**100.0%**	**1.57 [0.85, 2.90]**	
Total events	310		285				

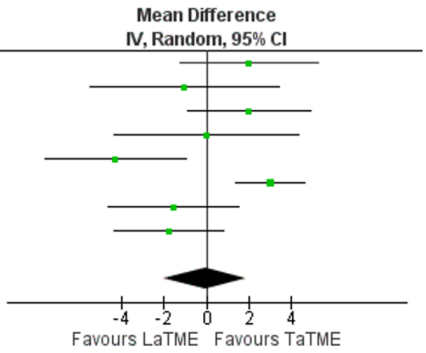
Heterogeneity: Tau² = 0.50; Chi² = 19.79, df = 8 (*P* = 0.01); I² = 60%
Test for overall effect: Z = 1.44 (*P* = 0.15)



F

Study or Subgroup	TaTME Mean	TaTME SD	TaTME Total	LaTME Mean	LaTME SD	LaTME Total	Weight	Mean Difference IV, Random, 95% CI	Year
Kanso 2015	15	8	51	13	7	34	12.3%	2.00 [-1.22, 5.22]	2015
de'Angelis 2015	17.6	7.14	32	18.63	10.7	32	9.4%	-1.03 [-5.49, 3.43]	2015
Lelong 2017	14	7	34	12	5.25	38	13.2%	2.00 [-0.88, 4.88]	2017
Mege 2018	14	10	34	14	8	34	9.7%	0.00 [-4.30, 4.30]	2018
Denost 2018	16.5	8	50	20.75	8.9	50	12.1%	-4.25 [-7.57, -0.93]	2018
Roodbeen 2019	18.75	3.75	41	15.75	3.76	41	16.5%	3.00 [1.37, 4.63]	2019
Ren 2020	19.5	6.54	32	21.06	5.94	32	12.7%	-1.56 [-4.62, 1.50]	2020
Li 2022	13.75	7.8	106	15.5	10.9	106	14.1%	-1.75 [-4.30, 0.80]	2022
Total (95% CI)			**380**			**367**	**100.0%**	**-0.05 [-1.98, 1.89]**	

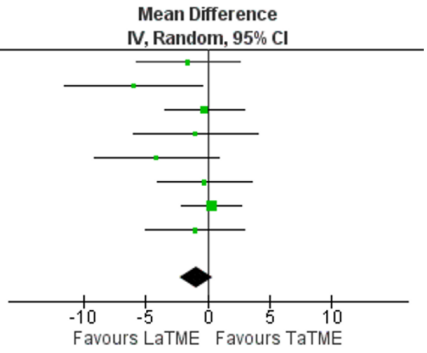
Heterogeneity: Tau² = 5.22; Chi² = 23.96, df = 7 (*P* = 0.001); I² = 71%
Test for overall effect: Z = 0.05 (*P* = 0.96)



G

Study or Subgroup	TaTME Mean	TaTME SD	TaTME Total	LaTME Mean	LaTME SD	LaTME Total	Weight	Mean Difference IV, Random, 95% CI	Year
de'Angelis 2015	21.32	8.59	32	22.92	8.44	32	10.1%	-1.60 [-5.77, 2.57]	2015
Kanso 2015	12	9	51	18	15	34	5.6%	-6.00 [-11.61, -0.39]	2015
Denost 2018	12.5	8	50	12.75	8.38	50	17.0%	-0.25 [-3.46, 2.96]	2018
Mege 2018	13	9	34	14	12	34	6.9%	-1.00 [-6.04, 4.04]	2018
Rubinkiewicz 2018	15.7	9.2	35	19.8	12.2	35	6.8%	-4.10 [-9.16, 0.96]	2018
Roodbeen 2019	22.5	8.66	41	22.77	9.1	41	11.9%	-0.27 [-4.12, 3.58]	2019
Ren 2020	17.7	3.4	32	17.4	6	32	30.7%	0.30 [-2.09, 2.69]	2020
Li 2022	12	9	106	13	19	106	11.0%	-1.00 [-5.00, 3.00]	2022
Total (95% CI)			**381**			**364**	**100.0%**	**-0.94 [-2.26, 0.39]**	

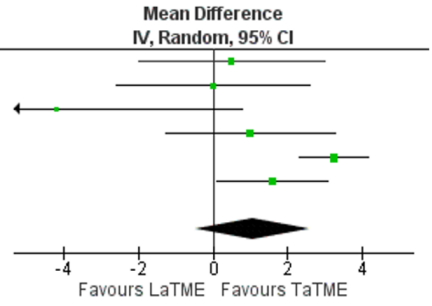
Heterogeneity: Tau² = 0.00; Chi² = 6.04, df = 7 (*P* = 0.53); I² = 0%
Test for overall effect: Z = 1.39 (*P* = 0.17)



H

Study or Subgroup	TaTME Mean	TaTME SD	TaTME Total	LaTME Mean	LaTME SD	LaTME Total	Weight	Mean Difference IV, Random, 95% CI	Year
de'Angelis 2015	9.68	4.57	32	9.19	5.55	32	15.6%	0.49 [-2.00, 2.98]	2015
Kanso 2015	7	6	51	7	6	34	15.1%	0.00 [-2.60, 2.60]	2015
Rubinkiewicz 2018	9.9	7.8	35	14.1	12.9	35	7.0%	-4.20 [-9.19, 0.79]	2018
Denost 2018	8.5	5.8	50	7.5	5.8	50	16.8%	1.00 [-1.27, 3.27]	2018
Roodbeen 2019	9	2.29	41	5.75	2.02	41	24.2%	3.25 [2.32, 4.18]	2019
Ren 2020	6.81	2.99	32	5.22	3.05	32	21.3%	1.59 [0.11, 3.07]	2020
Total (95% CI)			**241**			**224**	**100.0%**	**1.08 [-0.46, 2.61]**	

Heterogeneity: Tau² = 2.31; Chi² = 17.38, df = 5 (*P* = 0.004); I² = 71%
Test for overall effect: Z = 1.37 (*P* = 0.17)



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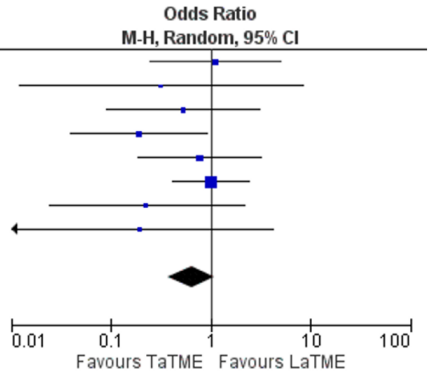
Study or Subgroup	TaTME Events	TaTME Total	LaTME Events	LaTME Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Kanso 2015	5	51	3	34	13.1%	1.12 [0.25, 5.04]	2015
Marks 2016	0	17	1	17	2.8%	0.31 [0.01, 8.27]	2016
Lelong 2017	2	34	4	38	9.5%	0.53 [0.09, 3.10]	2017
Denost 2018	2	50	9	50	11.7%	0.19 [0.04, 0.93]	2018
Mege 2018	4	34	5	34	14.8%	0.77 [0.19, 3.17]	2018
Roodbeen 2019	19	41	19	41	39.2%	1.00 [0.42, 2.38]	2019
Ren 2020	1	32	4	32	5.8%	0.23 [0.02, 2.14]	2020
Li 2022	0	106	2	106	3.2%	0.20 [0.01, 4.14]	2022
Total (95% CI)		**365**		**352**	**100.0%**	**0.64 [0.37, 1.10]**	
Total events	33		47				

Heterogeneity: Tau² = 0.00; Chi² = 5.56, df = 7 (*P* = 0.59); I² = 0%
Test for overall effect: Z = 1.62 (*P* = 0.11)



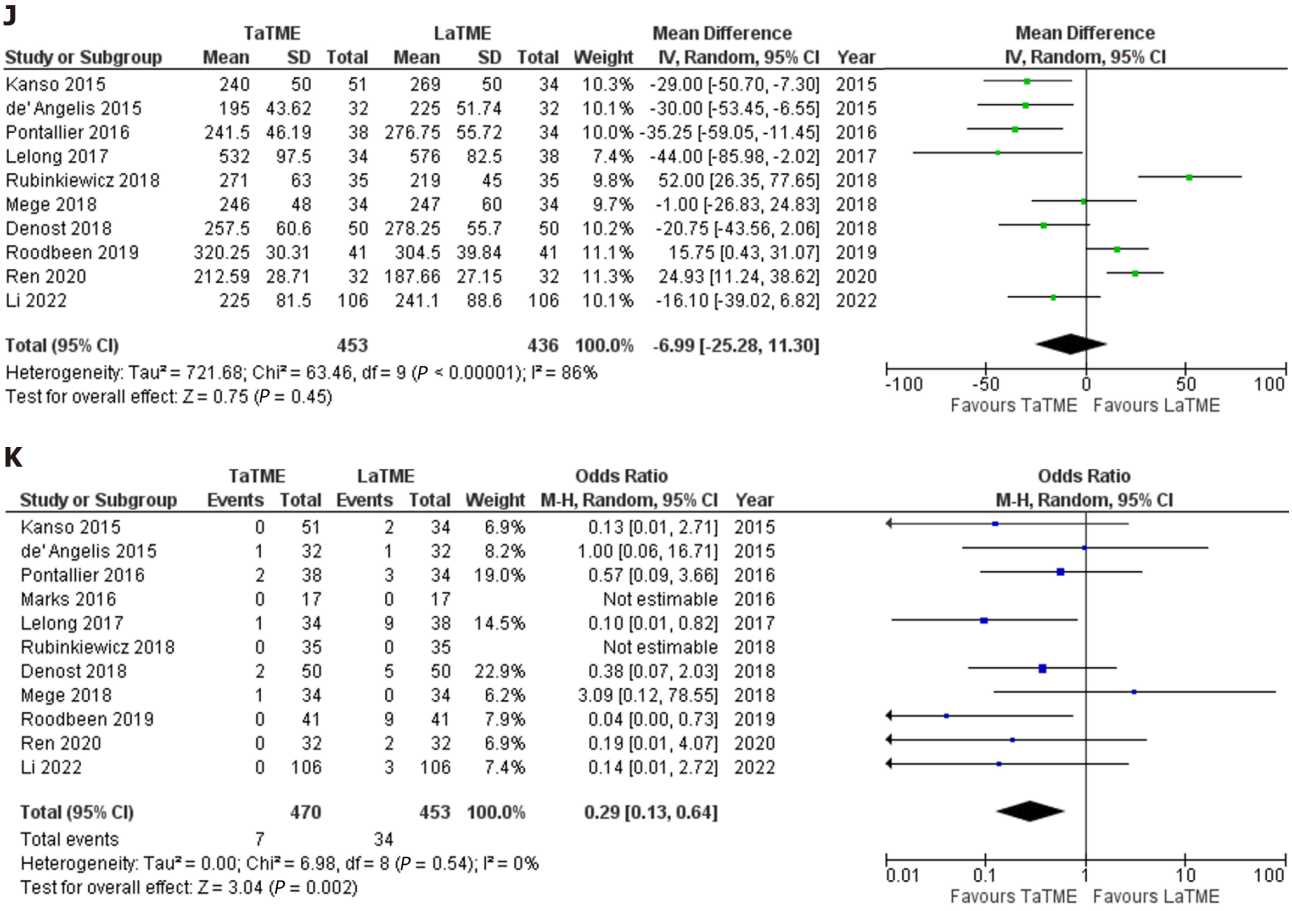


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Figure 3 Forest plots of comparison. A: Intraoperative complications; B: Postoperative complications; C: Anastomotic leak; D: R0 resection; E: Completeness of mesorectal excision; F: Number of harvested lymph nodes; G: Distal resection margin; H: Circumferential resection margin; I: Positive circumferential resection margin; J: Procedure time; K: Conversion to an open procedure. The solid squares denote the odds ratios or mean difference. The horizontal lines represent the 95% confidence intervals, and the diamond denotes the pooled effect size. M-H: Mantel Haenszel test.

the authors found a significant association between CRM involvement and local recurrence (P = 0.011), the 5-year local recurrence rate was similar between two groups (3% *vs* 5%, P = 0.30). Moreover, the authors reported similar 5-year disease-free survival between two groups (72% *vs* 74%, P = 0.351). The rate of local recurrence in the aforementioned RCT is comparable with the recurrence rate of 4% reported in a review by Deijen *et al*[26]. Undoubtedly, futures high quality randomized studies with adequate follow-up periods are required to investigate long term oncological outcomes of transanal and laparoscopic approaches to TME.

This study has a number of limitations. Only two of the considered studies were RCTs. Most of the included studies were observational studies with their inherited selection bias. Some of the included studies had small sample sizes which might have introduced Type 2 error to our findings. We were unable to conduct independent analyses on length of hospital stay, functional outcomes or long term oncological outcomes as the data provided by the included studies on such outcomes was inadequate. Finally, there was moderate risk of bias in 3 of our included studies.

CONCLUSION

Our meta-analysis demonstrated that for low rectal tumours, TaTME is associated with better clinical and short term oncological outcomes compared to LaTME. More randomised controlled trials with adequate power and high quality are required to not only confirm these findings, but also to evaluate long term oncological and functional outcomes.

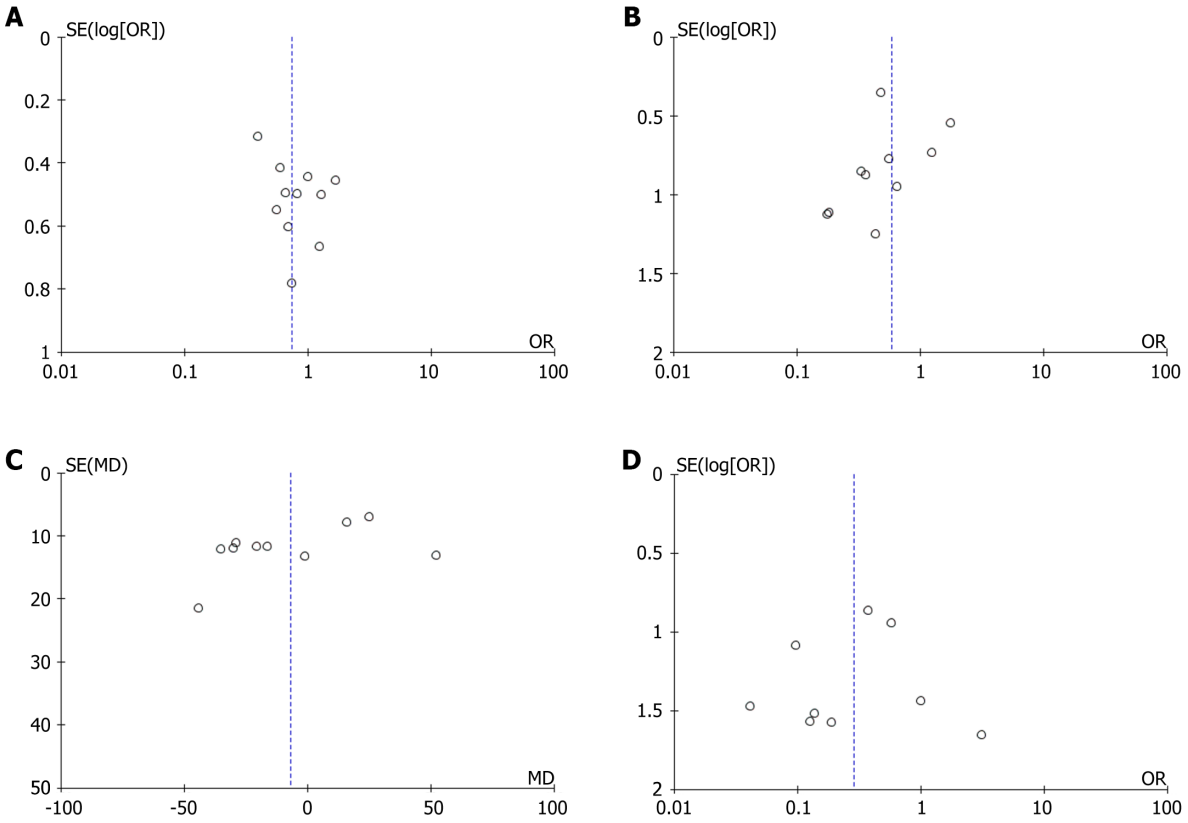

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Figure 4 Funnel plots of comparison. A: Postoperative complications; B: Anastomotic leak; C: Procedure time; D: Conversion to open procedure.

ARTICLE HIGHLIGHTS

Research background

Achieving a clear resection margins for low rectal cancer is technically challenging. Transanal TME (TaTME) has been introduced in order to address the chalenges associated with the open and laparoscopic TME (LaTME) in resecting low rectal tumours.

Research motivation

Previous meta-analyses have included mixed patients with mid and low rectal tumours when comparing TaTME and LaTME which has made the interpretation of the real differences between two approaches in treating low rectal cancer difficult.

Research objectives

To investigate the outcomes of transanal TaTME and LaTME in patients with low rectal cancer.

Research methods

A comprehensive systematic review of comparative studies were conducted according to the standards of Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Intraoperative and postoperative complications, anastomotic leak, completeness of mesorectal excision, R0 resection, distal (DRM) and circumferential resection margin (CRM), number of harvested lymph nodes, and procedure time were the evaluated outcome parameters.

Research results

We identified twelve comparative studies enrolling a total of 969 patients comparing the outcomes of TaTME (n = 969) and LaTME (n = 476) in patients with low rectal cancer. The meta-analysis demonstrated that TaTME was associated with significantly lower rate of postoperative complications (OR: 0.74, P = 0.04), anastomotic leak (OR: 0.59, P = 0.02), and conversion to an open procedure (OR: 0.29, P = 0.002) compared with LaTME. Moreover, it was associated with significantly higher rate of R0 resection (OR: 1.96, P = 0.03). However, there was no significant difference in intraoperative complications (OR: 1.87; P = 0.23), completeness of mesoractal excision (OR: 1.57, P = 0.15), harvested lymph nodes (MD: -0.05, P = 0.96), DRM (MD: -0.94; P = 0.17), CRM (MD: 1.08, P = 0.17), positive CRM (OR:

0.64, P = 0.11) and procedure time (MD: -6.99 minutes, P = 0.45) between TaTME and LaTME.

Research conclusions

Our findings indicated that for low rectal tumours, TaTME is associated with better clinical and short term oncological outcomes compared to LaTME.

Research perspectives

The available evidence does not allow evaluation of long term oncological and functional outcomes. More randomized controlled trials are required to confirm the findings of this meta-analysis regarding clinical and short term oncological outcomes and to evaluate long term oncological and functional outcomes.

FOOTNOTES

Author contributions: Shahi H designed the research study; Patel I, Bhattacharya P, and Fazili N collected the data for the meta-analysis; Hajibandeh S and Hajibandeh S analysed and interpreted the data, did the statistical analysis, and wrote the article; all authors critically revised the article and provided final approval for the article.

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CASE REPORT

Secondary sclerosing cholangitis in a young COVID-19 patient resulting in death: A case report

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Abstract

BACKGROUND

With the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019 in Wuhan, China, liver injury in patients with coronavirus disease 2019 (COVID-19) due to SARS-CoV-2 infection has been regularly reported in the literature. There are a growing number of publications describing the occurrence of secondary sclerosing cholangitis (SSC) after SARS-CoV-2 infection in various cases. We present a case of sudden onset SSC in a critically ill patient (SSC-CIP) following COVID-19 infection who was previously healthy.

CASE SUMMARY

A 33-year old female patient was admitted to our University Hospital due to increasing shortness of breath. A prior rapid antigen test showed a positive result for SARS-CoV-2. The patient had no known preexisting conditions. With rapidly increasing severe hypoxemia she required endotracheal intubation and developed the need for veno-venous extracorporeal membrane oxygenation in a setting of acute respiratory distress syndrome. During the patient´s 154-d stay in the intensive care unit and other hospital wards she underwent hemodialysis and extended polypharmaceutical treatment. With increasing liver enzymes and the development of signs of cholangiopathy on magnetic resonance cholangiopancreatography (MRCP) as well as endoscopic retrograde cholangiopancreatography (ERCP), the clinical setting was suggestive of SSC. At an interdisciplinary meeting, the possibility of orthotopic liver transplantation and additional kidney transplantation was discussed due to the constant need for hemodialysis. Following a deterioration in her general health and impaired respiratory function with a reduced chance of successful surgery and rehabilitation, the plan for transplantation was discarded. The patient passed away due to multiorgan failure.

CONCLUSION
SSC-CIP seems to be a rare but serious complication in patients with SARS-CoV-2 infection, of which treating physicians should be aware. Imaging with MRCP and/or ERCP seems to be indicated and a valid method for early diagnosis. Further studies on the effects of early and late SSC in (post-) COVID-19 patients needs to be performed.

Key Words: Secondary sclerosing cholangitis; COVID-19; Liver failure; Critically ill patients; Magnetic resonance cholangiopancreatography; Endoscopic retrograde cholangiopancreatography; Case report

Core Tip: Secondary sclerosing cholangitis in critically ill patients is an important complication in patients requiring intensive care treatment. With the ongoing coronavirus disease 2019 pandemic we will see increasing complications regarding the liver and the biliary system. Our case report hopes to aid other surgeons, radiologists and intensive care physicians in their decision making.

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INTRODUCTION

With the emergence of an unknown respiratory virus of the corona group in late 2019 in Wuhan, China, an undetected spread of the newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been observed, which was declared a pandemic by the WHO in March 2020.

Common signs of SARS-CoV-2 infection include flu-like symptoms, dyspnea, fatigue, anosmia, headache and fever, with potentially life-threatening acute respiratory distress syndrome (ARDS) developing in some cases, requiring intensive medical care. During this ongoing crisis, and due to the nature of a novel virus infection, the scientific community has been able to identify a wide range of different symptoms and features attributable to the later and rarer hyperinflammatory phase in some cases. In particular, the diffuse inflammatory phase appears to be a multiorgan problem that is not limited to the lungs or upper respiratory tract[1,2].

Liver injury in patients with SARS-CoV-2 infection has been regularly reported in the literature during the course of the ongoing coronavirus disease 2019 (COVID-19) pandemic. The occurrence of elevated and abnormal liver parameters has been demonstrated in 14% to 76% of patients. Recent case reports and series have investigated and discussed the probability of increased risk for permanent damage to the hepatobiliary system[1-4].

There are a growing number of publications in the literature describing the occurrence of secondary sclerosing cholangitis (SSC) after SARS-CoV-2 infection in various cases, particularly after severe COVID-19-associated ARDS with a reported incidence of up to 2.6% of intensive care unit (ICU) patients [5].

We report the sudden onset of SSC in a critically ill patient (SSC-CIP) following severe COVID-19 infection ultimately resulting in death.

CASE PRESENTATION

Chief complaints

A 33-year-old female patient was admitted to our University Hospital by emergency medical services (EMS) due to shortness of breath.

History of present illness

According to her relatives, she had been feeling ill for a week, and her general health deteriorated rapidly and she developed a high fever. She had tested positive for the novel coronavirus (SARS-CoV-2) 7 d prior to admission.

History of past illness

The patient had an elevated body mass index of 34 (1.68 m/95 kg), and was previously healthy with no preexisting conditions, particularly no known liver damage or respiratory problems.

Personal and family history

No relevant personal or family history was recorded.

Physical examination

On arrival of the EMS, respiratory function was already compromised by severe hypoxemia requiring endotracheal intubation and mechanical ventilation onsite, which did not improve on admission with high ventilation pressure and poor O_2 saturation. Veno-venous extracorporeal membrane oxygenation (vvECMO) was administered, which provided acceptable oxygenation in the setting of severe acute respiratory distress syndrome (COVID-19-ARDS) with a persistent need of continuous catecholamines. During the patient´s 154-d stay in the ICU and other hospital wards, hemodialysis was initiated on day 4, ECMO was removed on day 14, and successful weaning was achieved on day 15 (Figure 1).

Laboratory examinations

During the patient's treatment for severe COVID-19-associated ARDS in the ICU, impaired liver function with elevated liver and cholestasis parameters (bilirubin, gamma-glutamyl transferase (GGT) and alkaline phosphatase (AP)) was detected. Due to the polypharmaceutical therapy regime with additional ECMO treatment, toxic/ischemic liver injury was initially suspected.

Following ECMO removal and reduction of sedation (particularly ketamine), elevated liver enzymes persisted indicating SSC-CIP. Laboratory parameters continued to show slightly elevated bilirubin (1.4 mg/dL), GGT (1299 U/L), AP (1883 U/L), aspartate aminotransferase (AST) (162 U/L) and alanine aminotransferase (ALT) (119 U/L).

Treatment for SSC-CIP with Ursofalk® 1000 mg was initiated.

Imaging examinations

A computed tomography of the abdomen on day 10 showed no signs of parenchymal damage or cholestasis (Figure 2A).

After prolonged treatment in the ICU, the patient underwent magnetic resonance cholangiopancreatography (MRCP) on day 47 after admission, which revealed no signs of liver injury or intrahepatic cholestasis but mild stenosis of the distal common bile duct (CBD) and suspected stricture of prepapillary CBD main.

Endoscopic retrograde cholangiopancreatography (ERCP) was performed on day 60 and showed rarefication of intrahepatic bile ducts, suggesting SSC-CIP (Figure 2C). An additional MRCP follow-up on day 105 after the initial admission confirmed SSC-CIP with worsening of multiple diffuse stricture of the CBD and entire intrahepatic biliary tree compared to the initial MRCP. Round T2-signal changes with restricted diffusion were identified, suggestive of additional cholangetic abscess formation (Figure 2B and D).

Magnetic resonance imaging (MRI) follow-up on day 129 depicted progressive encapsulated intrahepatic fluid accumulation with restricted diffusion and rim-contrast enhancement, associated with progressive intrahepatic abscess.

MULTIDISCIPLINARY EXPERT CONSULTATION

In the following weeks, our patient suffered from persistent and undulating elevated inflammatory parameters [especially C-reactive protein (CRP), peak 217 mg/L] and overall worsening of her general condition. Due to renal failure, hemodialysis was performed three times a week. Liver parameters remained elevated (*e.g.*, bilirubin peak 17.29 mg/dL on day 139).

At an interdisciplinary meeting, the possibility of orthotopic liver transplantation and additional kidney transplantation was discussed due the constant need for hemodialysis. As a result of a deterioration in general health and impaired respiratory function with a reduced chance of successful surgery and rehabilitation, the plan for transplantation was discarded.

FINAL DIAGNOSIS

Due to the rapid acceleration and worsening of SSC-CIP, we strongly suspected the presence of post-COVID-19 cholangiopathy with the development of SSC-CIP.

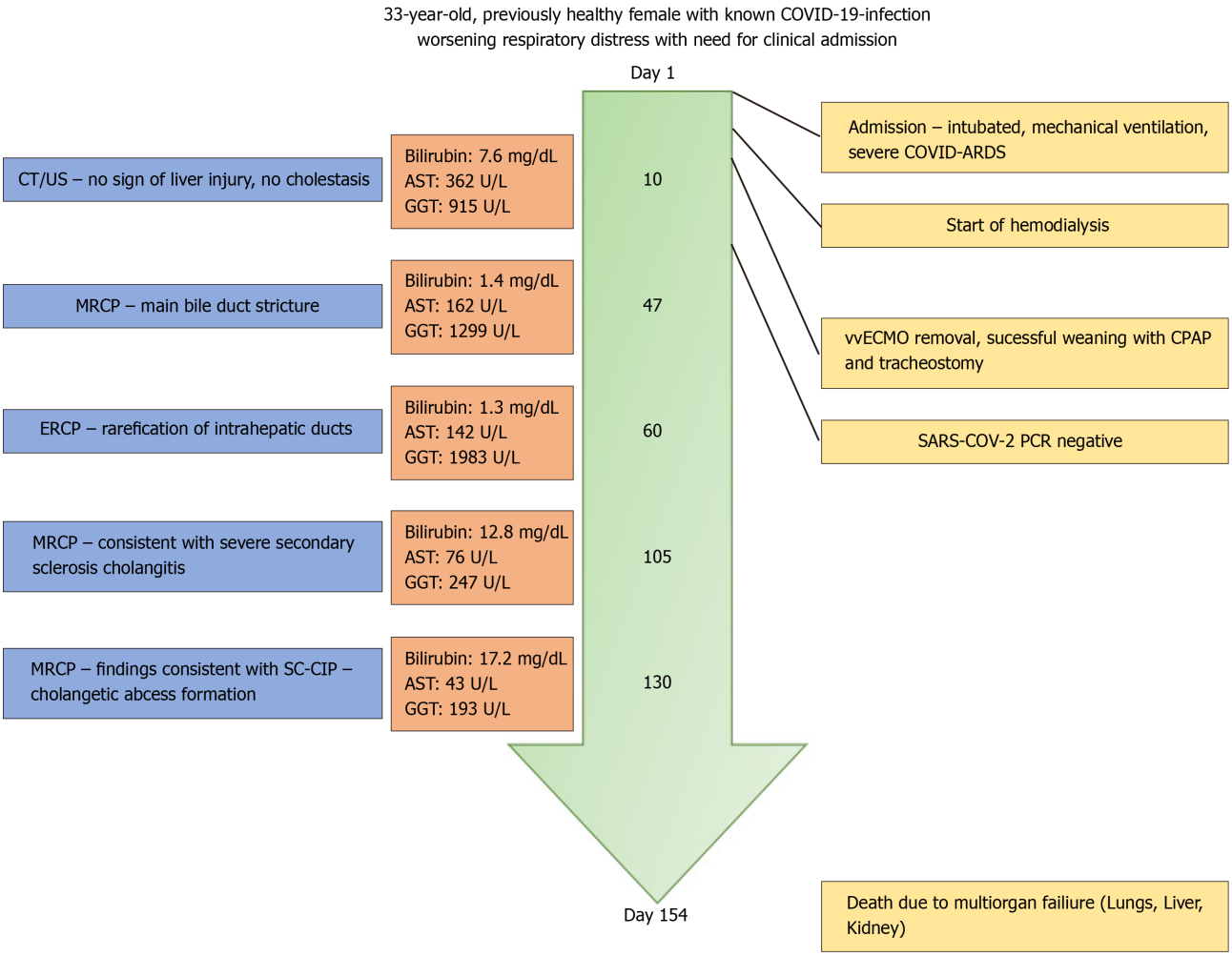

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Figure 1 The chart shows the chronological timeline of patient treatment with adjacent changes in laboratory parameters and imaging as well as intensive care unit interventions. MRCP: Magnetic resonance cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatography; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

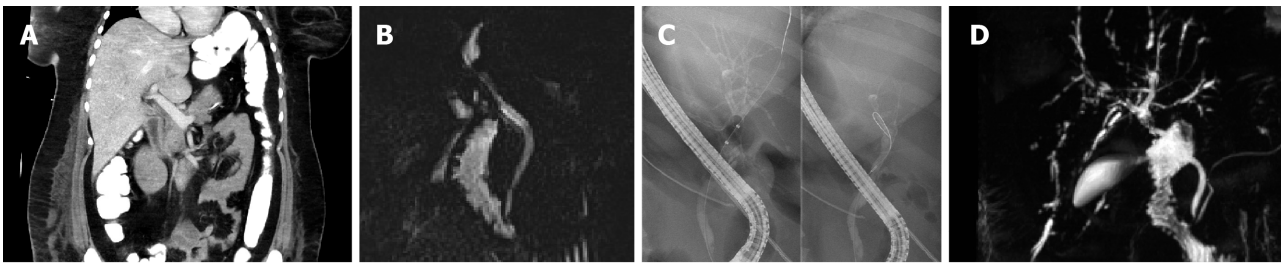

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Figure 2 Imaging throughout the hospital treatment. A: The image shows early contrast enhanced computed tomography of the upper abdomen on day 10 after admission without significant cholangetic stasis or narrowing of the common bile duct (CBD); B: A prepapillary narrowing of the CBD can be identified with at that point suspected CBD stricture (day 47); C: The image shows a rarefication of the peripheral bile ducts indicating early secondary sclerosing cholangitis on day 60; D: The image shows magnetic resonance cholangiopancreatography at day 105 after admission with classical appearance of secondary sclerosing cholangitis.

TREATMENT

Throughout the ICU period, she was treated according to guidelines, with additional remdesivir, a nucleotide analogue prodrug with broad-spectrum antiviral activity and Convalescent Plasma Transfusion as well as various treatments with additional antibiotics, including Noxafil®, Piperacillin/Tazobactam®, Tygacil® and Curam® due to superinfection.

OUTCOME AND FOLLOW-UP

On day 154, our patient passed away due to organ failure involving the respiratory system, kidneys and liver. No autopsy was performed.

DISCUSSION

SSC-CIP is a recently included form of cholestatic liver disease in a patient population undergoing prolonged intensive care for various reasons without known hepatic or biliary disease. It is usually the result of trauma, burn injuries, or major surgical procedures such as cardiothoracic surgery or transplantation procedures[6,7].

While up to 60% of SSC-CIP patients survive to ICU discharge, the need for later transplantation is high at up to 20%. One-year survival without transplantation has been reported to be 55%[8].

SSC-CIP is thought to be the result of direct damage to cholangiocytes, either by ischemia/hypoxia or by toxic bile with changes in bile composition or by infection. There is no single predisposing or causative factor for the development of SSC-CIP. Severe hypotension seems to directly cause ischemic bile duct damage and contribute to it by altering hepatobiliary transporters. Sepsis and microcirculatory disturbances have also been attributed to transporter alteration[9].

Liver damage resulting from SARS-CoV-2 infection has been described in the literature. Throughout the pandemic, many publications have described a close association between SARS-CoV-2 and elevated liver enzymes in the early stages of infection and liver parenchymal injury. Most authors theorize that increased angiotensin-converting enzyme 2 receptor expression in hepatocytes and even more in cholangiocytes leads to direct damage of cells by the virus, possibly causing cell destruction[2,10,11].

Additional changes in microvascular steatosis due to the thrombogenic characteristics of the novel coronavirus 19 appear to play a role in this parenchymal damage[10,11].

As described by Kaltschmidt *et al*[12], SARS-CoV-2 replicates in the liver parenchyma and is secreted into the bile ducts, which in combination with platelet activation and parenchymal injury appears to result in direct damage to the biliary system. The accompanying necrosis with the development of stenosis seem to directly promote the occurrence of sclerosing cholangitis[12].

SSC, as in our case, is usually diagnosed by imaging techniques such as ERCP and MRI. Distinguishing features include strictures and stenosis as well as newly developed dilations of intra- and extrahepatic bile ducts[13].

While ERCP offers the possibility of direct intervention such as stent placement, MRI, particularly MRCP, is a noninvasive modality for early diagnosis and follow-up, widely available in Western countries. With protocols starting at 15 min, it is also within a reasonable timeframe for monitoring intensive care patients.

Although our patient was ultimately not a candidate for transplantation, there are a growing number of case reports showing promising results with orthotopic liver transplantation for SSC-CIP following COVID-19[14,15].

As mentioned above SSC-CIP can occur due to various underlying conditions including pharmacological toxicity, prolonged intensive care treatment and interventions. In our case, the rapid onset of liver parameter changes with early elevated GGT/AST compared with relatively low bilirubin, followed by subsequent increasing bilirubin levels and textbook appearance on MRCP strongly suggest a close correlation between SSC-CIP and SARS-CoV-2 infection. In our case, this was most likely due to recently described post-COVID-19 cholangiopathy, in which early cholangiocytic injury leads to late stenosis and sclerosis, ultimately resulting in death. Differential diagnoses of the cause could include the mentioned prolonged intensive treatment, which seemed in our experience less likely.

Due to the lack of autopsy or biopsy, the major limitation in our case is the lack of confirmation of histopathological findings suggestive of SSC-CIP with liver parenchymal changes associated with viral damage, such as the presence of cytokeratin 7 metaplasia of periportal hepatocytes, compared with SCC with a possible other cause, most likely caused by drugs - due to prolonged mechanical ventilation and sedation.

CONCLUSION

Despite its limitations, our case fits other cases and case series in the current literature and demonstrates the importance of early and regular evaluation of cholestatic parameters. SSC-CIP seems to be a rare but serious complication in patients with SARS-CoV-2 infection, of which treating physicians should be aware.

Imaging with MRCP and/or ERCP seems to be indicated and a valid method for early diagnosis. Although our case resulted in death as the patient was unfit for transplantation, liver transplantation seems to be a promising treatment in severe cases.

Given the still unknown long time span after complications in a post-pandemic medical world, the awareness of secondary liver injury and cholestatic damage should be monitored and further studies on the effects of early and late SSC in (post-) COVID-19 patients need to be performed.

FOOTNOTES

Author contributions: Talakić E and Steiner J were responsible for the conceptualization, data acquisition and original manuscript drafting; Kaufmann-Bühler AK and Fuchsjäger M reviewed and edited the manuscript, and provided helpful discussions; Schemmer P was responsible for data acquisition and both reviewed and edited the manuscript; all authors have read and approved the final version of the manuscript.

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CASE REPORT

Rectal tubular adenoma with submucosal pseudoinvasion misdiagnosed as adenocarcinoma: A case report

Dan Chen, Ding-Fu Zhong, Hong-Ying Zhang, Ying Nie, Dong Liu

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Abstract

BACKGROUND

Differential diagnosis of colorectal intramucosal tumors from invasive adenocarcinoma is important in clinical practice due to the different risks of lymph node metastasis and different treatment options. The phenomenon of a colorectal adenoma with part of the gland entering the submucosa is known as pseudoinvasion of the adenoma, which is a major challenge for pathological diagnosis. It is essential to raise awareness of colorectal adenoma with submucosal pseudoinvasion clinically to avoid overtreatment.

CASE SUMMARY

We describe a case of rectal adenoma with submucosal pseudoinvasion in a 48-year-old man. The patient was admitted to Jinhua People's Hospital due to a change in stool habit for 5 d. We performed colonoscopy, and the results suggested a submucosal bulge approximately 1.0 cm × 1.0 cm in size in the rectum 8 cm from the anal verge, with red surface erosion. Ultrasound colonoscopy was also performed and a homogeneous hypoechoic mass about 0.52 cm × 0.72 cm in size was seen at the lesion, protruding into the lumen with clear borders and invading the submucosa. Endoscopic surgery was then performed and the pathological specimen showed a tubular adenoma with high-grade intraepithelial neoplasia (intramucosal carcinoma) involving the adenolymphatic complex. In addition, we performed a literature review of rectal tubular adenoma with submucosal pseudoinvasion to obtain a deeper understanding of this disease.

CONCLUSION

The aim of this study was to improve awareness of this lesion for clinicians and

pathologists to reduce misdiagnosis.

Key Words: Colorectal adenoma; Submucosal pseudoinvasion; Ultrasound endoscopy; Pathological diagnosis; Treatment; Case report

Core Tip: Colorectal adenoma with submucosal pseudoinvasion has only been studied in a small number of small cases in the current national and international literature. At present, endoscopists diagnose our patient's lesion by electronic staining endoscopy (NBI), magnification endoscopy and ultrasound enteroscopy. A more accurate diagnosis of the depth of infiltration was obtained by pathological support. And if the pathologist misjudges, it will lead to overtreatment in clinical practice.

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INTRODUCTION

Both neoplastic and non-neoplastic epithelium of the mucosa may enter the submucosa for some reason, a phenomenon known as pseudoinvasion or misplaced epithelium of the submucosa. When part of the gland of a colorectal adenoma mistakenly enters the submucosa, it is called pseudoinvasion of the adenoma[1]. The incidence of colorectal adenoma with submucosal pseudoinvasion is low, and those occurring in the rectal region are extremely rare, with few reports in the national and international literature. The definitive diagnosis relies mainly on pathological support[2]. If the pathologist misjudges, this will lead to overtreatment in clinical practice. Here we present a case of rectal adenoma with submucosa pseudoinvasionin order to benefit both patients andpractitioners.

CASE PRESENTATION

Chief complaints

A 48-year-old man was admitted to Jinhua People's Hospital on June 29, 2021 due to change in stool habit for 5 d.

History of present illness

His symptoms started 5 d previously and were accompanied by a change in stool habit (yellow, thin, pasty stools 3-5 times a day, without mucus and blood). No significant change in body weight was noted.

History of past illness

The patient had a history of surgery for hypofractionated adenocarcinoma of the stomach 6 mo ago. According to the World Health Organization (WHO) Classification of Digestive System Tumor, hypofractionated adenocarcinoma is defined as the cancer cells are short columnar or indefinite, arranged in small nests or strands, and basically without glandular tube structure.

Personal and family history

The patient had no relevant personal and family history.

Physical examination

On examination, his abdomen was soft, old surgical scars were visible in the upper abdomen, and no pressure pain, rebound pain, or masses were found.

Laboratory examinations

Laboratory examinationsshowed that routine blood, urine, stool, liver and kidney function, carcinoembryonic antigen, alpha-fetoprotein and carbohydrate antigen 199 were all within the normal range.

Imaging examinations

The patient was advised to undergo abdominal enhanced computed tomography (CT) and colonoscopy, and the results of colonoscopy on July 1, 2021 suggested a submucosal bulge approximately 1.0 cm × 1.0 cm in the rectum 8 cm from the anal verge, with red surface erosion (Figure 1A). Narrow band imaging (NBI) and magnification colonoscopy showed uneven caliber and distribution of blood vessels. Type2B was considered according to JNET staging (Figure 1B).

MULTIDISCIPLINARY EXPERT CONSULTATION

Ultrasound colonoscopy was performed on July 1, 2021 and a homogeneous hypoechoic mass about 0.52 cm × 0.72 cm in size was seen at the lesion, protruding into the lumen with clear borders and invading the submucosa (Figure 1C). CT on June 30, 2021 (enhancement of two sites) showed a nodule in the posterior rectal wall (Figure 1D and E).

FINAL DIAGNOSIS

Postoperative pathological results in our hospital [rectal endoscopic submucosal dissection (ESD) specimen] showed moderately differentiated adenocarcinoma with significant hyperplasia of lymphoid tissue, about 1.0 cm × 0.8 cm in size, infiltrated to the submucosa. No cancer thrombus was seen in the vasculature, and the surrounding cut edge was not involved approximately 200 μm from the basal cut edge. Immunohistochemical results were as follows: CD10 (-), CD56 (-), CDX2 (+), CgA (-), CK20 (+), CK7 (-), EGFR (1+), Ki67 (30%+), P53 (missense expression), and Syn (-).

In order to quickly improve the pathological understanding of early GI tumors in our hospital and better carry out our ESD surgery, the pathological specimen was sent to the Department of Pathology of the Second Affiliated Hospital of Zhejiang University School of Medicine and the results suggested (rectal ESD specimen) tubular adenoma with high-grade intraepithelial neoplasia (intramucosal carcinoma) involving the adenolymphatic complex. No clear vascular invasion was seen. The horizontal and vertical margins were negative (Figure 1F-I). Based on the above pathological findings, the patient was advised to undergo repeat colonoscopy. A follow-up colonoscopy on January 12, 2022 showed post-rectal scar formation and no local recurrence. A repeat pelvic MRI on April 12, 2022 suggested post-rectal changes and no lymphatic metastases were found.

TREATMENT

After full communication with the patient and obtaining his consent, ESD was performed on July 5, 2021.

OUTCOME AND FOLLOW-UP

One year after ESD, colonoscopy showed a postoperative scar in the rectum without local recurrence (Figure 1J).

DISCUSSION

Pseudoinvasion or misplaced epithelium of the submucosa was first described by Muto *et al*[3] in 1972 and its characteristic histological manifestation was defined as the mislocation of non-neoplastic or adenomatous epithelium into the submucosa for some reasons. Its predilection is in the sigmoid colon, accounting for about 85% of cases, followed by the descending colon, accounting for about 10%, and the rectum is relatively uncommon[2]. The average age of patients is 60 years for men and 56 years for women, similar to the average age of patients with common adenomatous polyps, with a male to female ratio of 3:1. Single lesion resection or local excision was effective, with no recurrence or metastasis at follow-up[3]. In 2006, a national colorectal cancer screening program was launched in the United Kingdom, and as the program progressed, an increasing number of difficult cases emerged, among which the differential diagnosis of epithelial malposition of colonic adenoma and adenocarcinoma was the most difficult. Therefore, an Expert Board was established to analyze and discuss the pathologies with diagnostic doubts. The percentage of misplaced epithelium diagnosed by the original pathologists increased from 30.6% to 80.3%, indicating that pathologists lack sufficient knowledge of this pathology and a number of misdiagnoses occurred[4]. This is undoubtedly a major challenge in clinical and

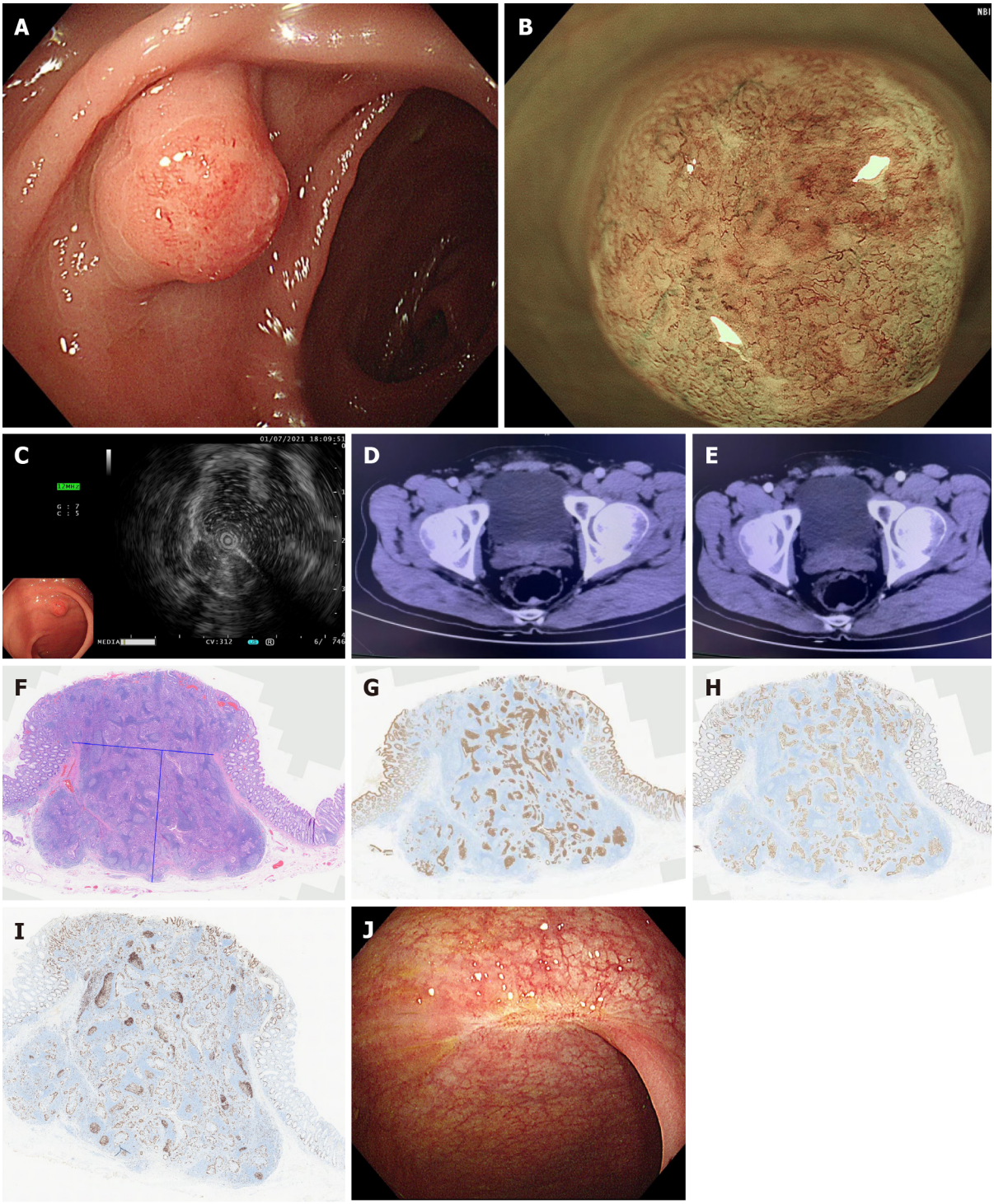

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Figure 1 Clinical data of the patient with rectal tubular adenoma and submucosal pseudoinvasion. A: Normal colonoscopy showing Is-type lesion; B: Narrow band imaging magnification colonoscopy; C: Ultrasound colonoscopy image; D: Posterior rectal wall in the venous phase showing the lesion; E: Posterior rectal wall in the arterial phase showing the lesion; F: The epithelial tumors seen microscopically are glandular ductal and sieve shaped with a high-grade heterogeneous morphology. The tumors are located in the lymphatic interstitium rich in lymphoid follicles. The lymphoid interstitium is located in the deep mucosal and submucosal layers with smooth and well-defined borders, H&E × 200 magnification; G: Immunohistochemistry CK20 (+), magnification × 200; H: Immunohistochemistry CDX2 (+), magnification × 200; I: Immunohistochemistry Ki67 (30%+), magnification × 200; J: Colonoscopy results after the operation.

pathological diagnosis.

Colorectal adenoma with submucosal pseudoinvasion has only been studied in a small number of cases in the current national and international literature. The morphological patterns were sorted and categorized in a limited number of cases, and two patterns of pseudoinvasion were summarized[5,6]. One type is lobulated, defined as a submucosal neoplastic gland forming a lobulated or nested mass. This type is more prevalent in the sigmoid colon with leptomeningeal lesions. The mechanism of onset may be increased luminal pressure due to intestinal contractility and repeated physical injury due to

traction, or tip torsion due to intestinal peristalsis, impaired blood flow, and subsequent entry of the gland into the submucosa through a relaxed mucosal muscle gap or weak area. Therefore, this type of pseudoinvasion may occur with ruptured glandular necrosis and hemorrhage, causing an inflammatory reaction and fibrosis[1,2,5,7]. The other type is lymphoglandular complex-like, in which the adenoma participates in the formation of a lymphoglandular complex into the submucosa, which can mimic invasive adenocarcinoma with lymphatic metastasis, with broad-based elevated lesions being the most common[5]. The available case studies show that almost all adenomas with pseudoinvasion have a maximum diameter greater than 10 mm, which means that there is a correlation between the size of the adenoma and the presence of submucosal pseudoinvasion. It can be inferred that even in the absence of excessive pressure or mechanical force, adenomas can easily enter the submucosa through the mucosal weak zone when they exceed a certain size[1,4,5,8]. When diagnosing colorectal adenoma with submucosal pseudoinvasion, it is important to be alert to the possibility that both patterns of pseudoinvasion components may have direct true infiltration in the submucosa, which should be treated as invasive adenocarcinoma, and therefore the pathology report needs to reflect the presence or absence of true infiltration[9]. In addition to the pathomorphological features of interest, in a small number of case studies of submucosal pseudoinvasion[6], immunohistochemical testing was performed and a Ki-67 positivity index of 25%-80% was found. P53 showed a wild-type pattern in positive cells within adenoma tissue and a missense mutation pattern in tumor tissue within a pooled lymph node that continued with a region of high-grade heterogeneous hyperplasia in one case.

The principles of the treatment options for colorectal adenoma with submucosal pseudoinvasion are consistent with those for colorectal intramucosal tumors, with endoscopic mucosal resection or ESD being the mainstay. Colorectal intramucosal tumors are defined as tumor infiltration confined to the mucosal layer (M-stage carcinoma). Those infiltrating into the submucosal layer without invading the intrinsic muscular layer are called submucosal carcinoma (SM-stage carcinoma)[10]. Those infiltrating into the upper 1/3, middle 1/3, and lower 1/3 of the submucosal layer are defined as SM1-stage carcinoma, SM2-stage carcinoma, and SM3-stage carcinoma, respectively[11]. The WHO classification of gastrointestinal tumors describes colorectal carcinoma as "epithelial malignant tumors originating from the colorectum which are diagnosed as cancer when they penetrate the mucosal muscle and infiltrate into the submucosa"[9]. Colorectal intramucosal tumors and invasive adenocarcinoma both have significantly different risks in terms of local recurrence and lymph node metastasis[12,13]. The absence of lymph node as well as vascular metastasis in intramucosal carcinoma is an absolute indication for endoscopic treatment. The percentage of lymph node metastasis from tumor infiltration to the superficial submucosa (SM1) is only 3.3%. Therefore, it can be a relative indication for endoscopic treatment. However, a rigorous pathological evaluation is required to determine whether lymphatic and vascular infiltration is present, and the need for additional surgical procedures will be determined on a situational basis. A previous report[14] showed no significant difference in the efficacy of endoscopic and surgical treatment for intramucosal and superficial submucosal carcinoma. For highly infiltrative submucosal lesions, additional surgery is required for submucosal infiltrations of 1000 μm or more[15].

Our patient's rectal lesion was diagnosed based on the morphology, vascular configuration, and surface structure in terms of pathological type by plain endoscopy, electronic staining endoscopy (NBI), and magnification endoscopy. A more direct diagnosis of the depth of infiltration was obtained vertically by ultrasound enteroscopy. Ultrasound can clearly display the structure of each layer of the colorectal wall and accurately determine the depth of lesion invasion and infiltration of surrounding organs[16-18]. Although crystal violet staining is suitable for the precise diagnosis of glandular duct openings in the pit pattern, it is currently not recommended *in vivo* due to its toxicity; therefore, it was not performed in this patient. After comprehensive evaluation, the preoperative lesion was considered to be superficial submucosal invasive carcinoma, and endoscopic ESD surgery is still indicated. Endoscopic surgery was performed after fully informing the patient of his condition and obtaining his consent. The postoperative pathological findings showed specific changes that led us to misdiagnose it as an invasive moderately differentiated adenocarcinoma. Fortunately, the pathological staging, basal cut margins, depth of submucosal invasion, and vascular invasion of this lesion did not suggest the need for additional surgery and did not result in overtreatment. The lesion was found to be a rare high-grade tubular adenoma of the rectum with pseudoinvasion of the submucosa only after late review of the pathology. To date, no effective clinical adjuvant examination has been availableto confirm whether the lesion is pseudoinvasion or not[2,4,14,19], and the definitive diagnosis still relies to a great extent on the pathologists' knowledge of its pathology.

CONCLUSION

The aim of this study was to improve the awareness of clinicians and pathologists regarding this type of lesion, in order to reduce the probability of misdiagnosis as invasive adenocarcinoma and avoid overtreatment.

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FOOTNOTES

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CASE REPORT

Malignant transformation of perianal tailgut cyst: A case report

Yuan Fang, Yong Zhu, Wei-Zhen Liu, Xia-Qing Zhang, Yu Zhang, Kang Wang

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Abstract

BACKGROUND

Tailgut cyst is a congenital enterogenous cyst that rarely undergoes malignant transformation. Its clinical manifestations mainly correlate to the mass effect caused by the development of cysts and the infections that originate from these. Furthermore, the complete resection of this cyst is curative. We report our diagnostic and treatment experience with one case of malignant transformation of a perianal tailgut cyst, which was initially misdiagnosed as perianal abscess.

CASE SUMMARY

A 72-year-old woman visited our institution with complaints of a refractory nonhealing lesion on the right hip, which repeatedly broke and suppurated for more than 70 years, and aggravated in 4 mo. The patient was given a diagnosis of refractory perianal abscess with repeated incision and drainage procedures. Computed tomography of the pelvic cavity revealed a giant perianal cyst. Subsequent biopsy revealed a tumor with moderate-to-severe glandular epithelial dysplasia, and suggested that this was derived from the developmental cysts in the posterior rectal space. After further clarifying the nature and extent of the tumor by magnetic resonance imaging, total cystic resection was performed. Postoperative histopathological examination confirmed the malignancy, dictating the investigators to add postoperative chemotherapy to the treatment regimen.

CONCLUSION

The malignant transformation of perianal tailgut cysts is very uncommon, and this should be differentiated from perianal abscess. Complete surgical removal is curative, and postoperative pathology may determine the necessity of additional postoperative chemotherapy or radiotherapy, which may be beneficial for preventing local recurrence and metastasis.

Key Words: Tailgut cyst; Perianal cyst; Perianal abscess; Adenocarcinoma; Chemotherapy; Case report

Core Tip: We report our diagnostic and treatment experience with a unique case of malignant transformation of perianal tailgut cyst. Since perianal tailgut cysts are difficult to differentiate from other perianal diseases, the reported case was initially misdiagnosed as perianal abscess with repeated incision and drainage procedures. The patient underwent complete resection and received salvage chemotherapy for 3 mo after the surgery.

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INTRODUCTION

Tailgut cysts are developmental congenital enterogenous cysts that mostly occur in the retrorectal or presacral space[1]. The clinical features include the mass effect caused by the development of cysts, and the infection that originates from these[2]. Magnetic resonance imaging (MRI) can display the typical cyst appearance, which is crucial for distinguishing the cyst from perianal abscess. Complete resection of the cyst is curative and clinically preferred[3]. Postoperative histopathological analysis is routinely performed to pathologically confirm the diagnosis and mainly rule out the chance of malignancy. Clinically, this entity is not complicated in its diagnosis and treatment. We report a case of malignant transformation after the perianal tailgut cyst was misdiagnosed as perianal abscess, in which total resection was performed and postoperative chemotherapy was added.

CASE PRESENTATION

Chief complaints

A 72-year-old woman was transferred to our hospital with complaints of a tumor on the right hip, which repeatedly broke and suppurated for more than 70 years, and aggravated in 4 mo.

History of present illness

The patient was born with a 5 mm × 5 mm mass under the right hip, which covered the skin. Perianal distending pain and discomfort were experienced by the patient with the gradual increase of the tumor. At a local hospital, the patient was diagnosed with perianal abscess due to its fluctuating feature. During the incision and drainage procedures, copious brownish pus was repeatedly drained out from the mass. In particular, during the recent 4 mo, the mass progressively become larger, with multiple ulcers on its surface, cauliflower-like objects at its base, and jelly-like liquid inside.

History of past illness

The patient had a history of hypertension, and her daily blood pressure was maintained at approximately 120/60 mmHg with regular oral medication.

Personal and family history

The patient denied any family history of malignancy.

Physical examination

The physical examination did not unveil any significant finding, except for the 5 cm ulcerative mass under the right hip.

Laboratory examinations

The patient had a slightly elevated carbohydrate antigen 7-24 of 23.04 U/mL, but no abnormalities were detected in other blood and urine analyses.

Imaging examinations

Computed tomography (CT) revealed a multilocular cystic soft tissue mass in the right hip, which extended into the sacrococcygeal region, with an enhanced edge and a size of 6.0 cm × 5.8 cm × 9.5 cm (Figure 1A and B). In order to establish a diagnosis, biopsy was performed on the cystic mass. The results revealed a tumor with moderate-to-severe glandular epithelial dysplasia, and suggested the origin of developmental cysts in the posterior rectal space (Figure 2A). After the patient was transferred to our hospital, intestinal lesions were further excluded by proctoscopy. Endorectal ultrasonography further revealed multiple hypoechoic areas (diameter: 1.0-2.5 cm), with clear boundaries in the sacrococcygeal region, and uneven echo areas in the right hip with unclear boundaries (Figure 1C and D). MRI revealed an abnormal hypointense T1 and hyperintense T2 signal shadow in irregular quasi-circular lesion, and diffusion-weighted imaging (DWI) revealed a size of 107 mm in the sagittal position with wall enhancement (Figure 1E-H).

MULTIDISCIPLINARY EXPERT CONSULTATION

Through the discussion of the multidisciplinary team, enterogenous cyst with malignant transformation was suggested as the preliminary diagnosis. The patient underwent a transperineal operation, during which the tailgut cyst was identified to extend into the posterior rectal space, and reach the sacral vertebrae at the 4th-5th levels above the tip of the coccyx. Since the sacrococcyx fascia was considered to be the origin of the cyst and attached to the coccyx, a part of this was resected to expose the surgical field. After radically resecting the cystic lesion with the surrounding tissues without injuring the posterior rectal wall, endorectal ultrasonography was performed to confirm that no cystic remnants were present, and a free-flap procedure to reconstruct the extensive resection site was performed by co-operating with the plastic surgery team (Figure 3). The operation lasted for approximately 270 min, with an unexpected intraoperative blood loss of more than 600 mL. The patient was hospitalized for 36 d for postoperative recovery.

Postoperatively, pathological examination revealed a diagnosis of malignant transformation of the perianal tailgut cyst, and this was identified as mucinous adenocarcinoma, with a size of 6.5 cm × 4.0 cm × 6.0 cm, without local infiltration (Figure 2B). Histologically, tumorous cells were found 0.2 cm away from the resection margin, confirming a pathological R0 resection. Further immune-histological examinations were paneled, as follows: MLH1 (+), MSH2 (+), MSH6 (+), PMS2 (+), P53S100 (-), CD34 (-), D2-40 (-), Ki-67 (70%), CDH-17 (+), CDX-2 (+), CK7 (+), CK20 (+), and SATB-2 (+).

FINAL DIAGNOSIS

Pathologically, the patient was given a final diagnosis of malignant transformation of the perianal tailgut cyst.

TREATMENT

Three months after the surgery, MRI revealed a small cyst under the right levator ani (Figure 1I), and the carbohydrate antigen 7-24 decreased to normal. According to the postoperative pathology, oral salvage chemotherapy with capecitabine 1000 mg, twice per day, for eight cycles, was added, and an MRI examination was recommend every 3 mo to monitor the change in size of the cyst.

OUTCOME AND FOLLOW-UP

After the 3rd cycle of chemotherapy with capecitabin, the patient did not have any special complaints or discomfort.

DISCUSSION

As a rare congenital disease, tailgut cyst originates from the tailgut and neurenteric canal[4], and most likely occurs in the retrorectal or presacral space[1]. Clinically, this disease is more commonly observed in middle-aged females with the presentation of a mass lesion, with or without infection[2]. Malignancy infrequently occurs in presacral tailgut cysts, at a rate of less than 8%, and when this occurs, it may most likely be adenocarcinoma or carcinoid[3]. For the present case, the patient presented with an infected and inflammatory mass, with the dissemination of cells from the cyst wall as the result of repeated

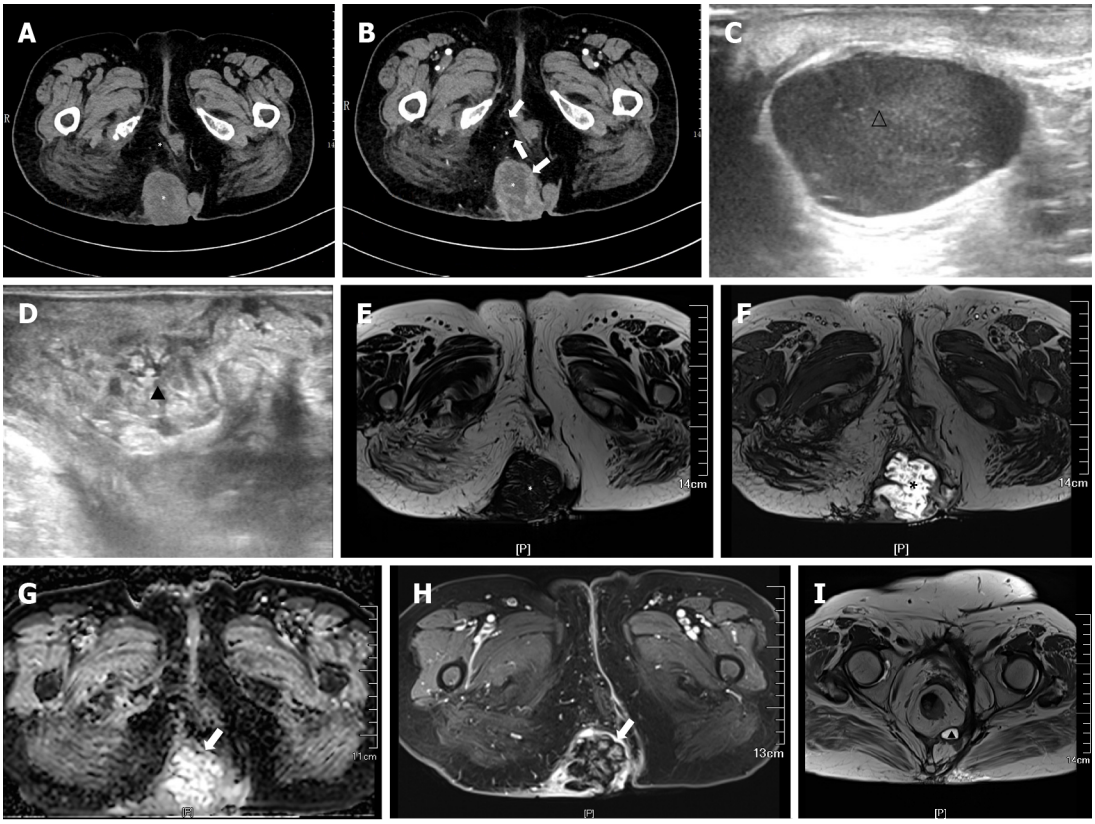

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Figure 1 Computed tomography and magnetic resonance imaging. A: A soft tissue mass and cystic density shadow were observed in the right hip and sacrococcygeal region (*), and the largest range was approximately 6.0 cm × 5.8 cm × 9.5 cm; B: The cyst was uneven, and the edge and septal of the focus were enhanced (↑); C and D: Multiple hypoechoic areas with a clear boundary (1.0–2.5 cm) were observed in the sacral region (Δ) (C), and uneven echo areas in the right hip (▲) (D); E and F: The lesion had low-attenuation on T1 (*) (E) and high-attenuation on T2 (*) (F); G: Diffusion weighted image (↑). The longest diameter of the sagittal position was approximately 107 mm; H: The edge of the lesion was obviously enhanced (↑); I: Magnetic resonance imaging (T2) revealed a small cyst (▲) under the right levator ani.

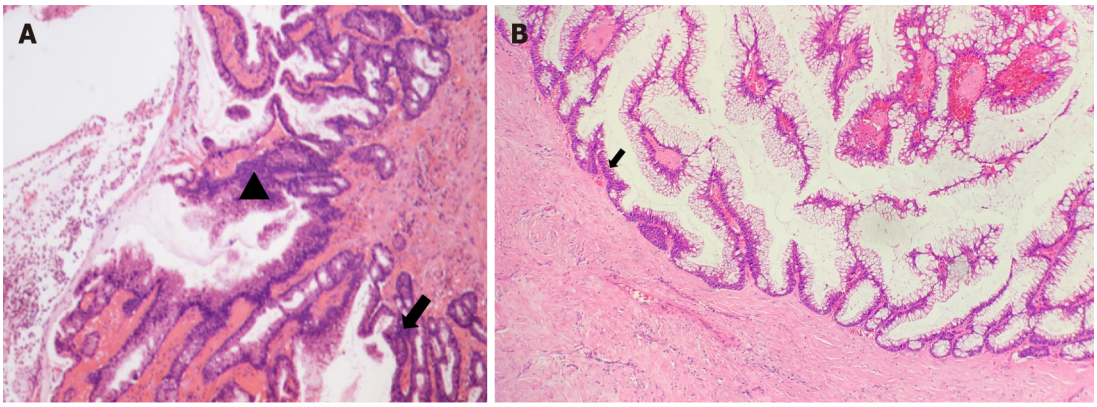

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Figure 2 Histopathological analysis. A: Moderate (▲)-to-severe (↑) dysplasia of the glandular epithelium; B: The columnar epithelial lining of the cyst wall had a large amount of mucus secretion, some of the epithelium had moderate dysplasia, and deranged smooth muscle bundles could be observed in the cyst wall (↑).

incision, and this might have been the main cause of the local recurrence that contributed to the malignant transformation[5].

The present report emphasizes the differentiation of a perianal tailgut cyst from a perianal abscess. For perianal abscess in the retrorectal space, when it exhibits the reluctance to complete healing due to the discharge of residual pus, when no anal fistula is found, or when this recurs multiple times after repeated surgical treatment, tailgut cyst should be suspected and completely resected for further pathological diagnosis. Since the specimens obtained from the biopsy often contain merely the inflamed fibrous tissue without the epithelia, or merely one type of epithelium, which may not consequently

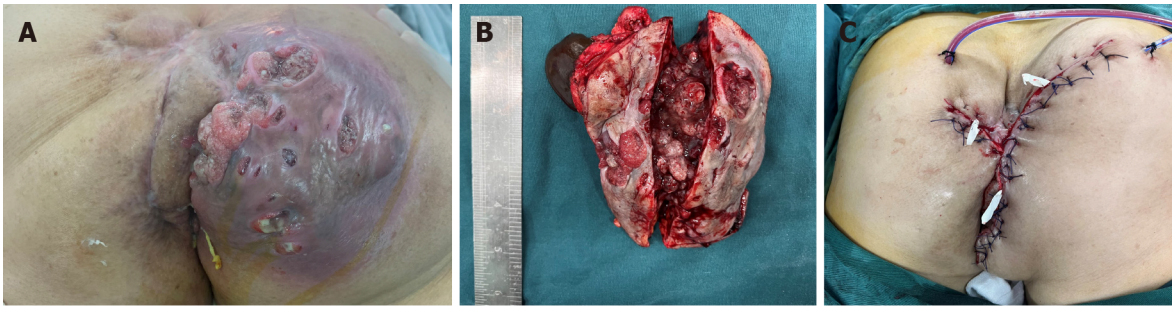

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Figure 3 Macroscopic examination. A: A 13 cm × 12 cm lesion was found on the right hip, with obvious fluctuation, reddish skin on the surface, multiple ruptures, jelly-like fluid outflow, and cauliflower-like objects attached to the base; B: Gross examination of the specimen revealed brown and jelly-like fluid in the cyst; C: The orthopedists assisted with the free skin flap, and closed the incision.

support any diagnosis[6], the biopsy of the cystic lesion is not recommended.

Pathohistologically, the cyst would be filled with brown and jelly-like fluid from the wall of the tailgut cyst[6], which would be partially or completely covered with intestinal epithelium, and this may contain columnar cells, squamous cells, and transitional cells with mucus secretion function[2], while the smooth muscle fibers in the cyst wall would be disorganized without the nerve plexus[7]. The canceration of caudal cysts is mostly focal, allowing for a thorough postoperative histopathological analysis of the resected specimen to be mandated, in order to confirm the diagnosis and rule out malignant tumors. Unlike perianal abscesses, tailgut cysts possess a multilocular nature, which demands preoperative endorectal ultrasonography, or pelvic MRI or CT imaging studies[8]. MRI can reveal the typical cyst appearance as low attenuation on T1 and high-attenuation on T2, and DWI can allow for the tailgut cyst to be distinguished from a perianal abscess[9]. Furthermore, although the importance of MRI in the diagnosis of tailgut cysts has been emphasized, endorectal ultrasonography is more convenient and accessible than MRI, especially in operations for complete cyst resection[10].

For the risk of malignant transformation of a cyst, surgical resection is the first choice for the treatment of tailgut cysts[3], and the surgical approach should be selected according to the location of the cyst shown in the imaging studies. Since the incidence of canceration of the tailgut cyst remains low, there is still a risk of local recurrence and distant metastasis. At present, three cases of local recurrence and two cases of distant metastasis have been reported[11-14]. Among these cases (Table 1), a patient with pseudomyxoma peritonei benefited from chemotherapy. After 3 mo, MRI revealed a small cyst under the right levator ani, which might putatively be correlated to the local implantation of cyst wall cells caused by the partial rupture of the cyst wall during the operation. Since the preoperative carbohydrate antigen 724 was also slightly elevated, with a Ki-67 index of 70%, oral capecitabine chemotherapy was given to the patient, who refused to undergo a reoperation for the relatively tiny lesion, as a salvage chemotherapy. In addition, close follow-up with MRI study was recommended. Indeed, a study suggested that postoperative adjuvant radiotherapy be recommended for patients with canceration of the tailgut cyst and remnant lesions for incomplete lesion resection, in order to achieve good outcomes, with or without chemotherapy[15].

CONCLUSION

In summary, perianal caudal cysts are difficult to differentiate from other perianal diseases, especially perianal abscesses. Due to the risk of cancerization of the cyst, multi-disciplinary treatment should be emphasized clinically.

Table 1 Characteristics of patients with perianal tailgut cyst who accepted chemotherapy therapy

Ref.	Gender	Age (yr)	Pathology	Cause of chemotherapy	Scheme	Follow-up	PMID
Akira *et al* [14], 1998	Female	66	Moderately differentiated adenocarcinoma	Elevated carcinoembryonic antigen level	Oral tegafur, 200 mg daily	3.2 yr	9872560
Luis *et al* [13], 2009	Female	37	Mucinous adenocarcinoma	Resection was complete, but not *en bloc*	Intraperitoneal mitomycin C and doxorubicin plus systemic 5-fluorouracil and leucovorin	3.0 yr	19856666
Zhao *et al* [5], 2015	Female	44	Moderately differentiated adenocarcinoma	Elevated carcinoembryonic antigen level	Intracapsular tumor necrosis factor and raltitrexed plus systemic oxaliplatin 3-cycles (130 mg/m^2)	9.0 wk	26656372

FOOTNOTES

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CASE REPORT

Acute appendicitis in the short term following radical total gastrectomy misdiagnosed as duodenal stump leakage: A case report

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Abstract

BACKGROUND

Common diseases after radical gastrectomy include cholecystitis and pancreatitis, but the sudden onset of acute appendicitis in a short period following radical gastrectomy is very rare, and its clinical symptoms are easily misdiagnosed as duodenal stump leakage.

CASE SUMMARY

This is a case report of a 77-year-old woman with lower right abdominal pain 14 d after radical resection of gastric cancer. Her pain was not relieved by conservative treatment, and her inflammatory markers were elevated. Computed tomography showed effusion in the perihepatic and hepatorenal spaces, right paracolic sulcus and pelvis, as well as exudative changes in the right iliac fossa. Ultrasound-guided puncture revealed a slightly turbid yellow-green fluid. Laparoscopic exploration showed a swollen appendix with surrounding pus moss and no abnormalities of the digestive anastomosis or stump; thus, laparoscopic appendectomy was performed. The patient recovered well after the operation. Postoperative pathology showed acute purulent appendicitis. The patient continued adjuvant chemotherapy after surgery, completing three cycles of oxaliplatin plus S-1 (SOX regimen).

CONCLUSION

Acute appendicitis in the short term after radical gastrectomy needs to be differentiated from duodenal stump leakage, and early diagnosis and surgery are the

most important means of treatment.

Key Words: Gastric cancer; Acute appendicitis; Surgery; Complications; Case report

Core Tip: Common forms of abdominal inflammation occurring after radical gastrectomy are cholecystitis and pancreatitis, of which cholecystitis has the highest incidence. In contrast, the incidence of appendicitis in the short term after radical gastrectomy is rare and has not been reported before. Herein, we present a case of acute appendicitis in the short term following radical total gastrectomy. We suggest that acute appendicitis in the short term after gastric cancer surgery needs to be differentiated from duodenal stump leakage and that early diagnosis and surgery are the most important means of treatment.

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INTRODUCTION

Acute appendicitis is mainly caused by bacteria, fecal stones, and malformations, and the pathogenic condition must be mucosal damage and bacterial invasion[1]. Common forms of abdominal inflammation occurring after radical gastrectomy are cholecystitis and pancreatitis, of which cholecystitis has the highest incidence[2]. In contrast, the incidence of appendicitis in the short term after radical resection of gastric cancer is rare and has not been reported. The lack of typical symptoms of metastatic lower right abdominal pain is attributed to resection of the stomach and greater omentum. The symptoms mainly manifest as persistently aggravated right-sided abdominal pain and a high perforation rate; therefore, the inflammation is not easily confined, and the clinical symptoms are easily misdiagnosed as duodenal stump leakage.

CASE PRESENTATION

Chief complaints

Durative pain in the lower right abdomen 14 d after radical total gastrectomy.

History of present illness

A 77-year-old woman was diagnosed with gastric cancer, and preoperative pathology showed adenocarcinoma, moderately differentiated, HP (-). On May 23, 2022, computed tomography (CT) showed that the cardia was thickened and reinforced (Figure 1A), and the appendix was normal (Figure 1B). Preoperative clinical staging showed cT4Nx; preoperative neoadjuvant therapy was recommended, but the patient refused due to advanced age, and "radical total gastrectomy (D2 lymph node dissection)" was performed under general anesthesia on May 26, 2022. Intraoperative exploration: The gallbladder had been removed; the omentum was adhered to the gallbladder bed, no ascites was seen, and no metastatic nodules were seen in the liver or peritoneum. Postoperative pathology indicated stage IIIB, moderately differentiated, intestinal-type adenocarcinoma with lymph node involvement (7/30) (Figure 2A). The resection margin was negative. The immunohistochemical marker results were as follows: CK (+), Her-2 (3+), MSH2 (+), MSH6 (+), PMS2 (+), MLH1 (+), and Ki-67 (approximately 70%).

The patient recovered well after the operation; all inflammatory indexes gradually decreased, and her blood sugar was well controlled. On June 3, 2022, her D-dimer level was significantly elevated, and ultrasound showed intermuscular thrombosis located in the lower right extremity, which was treated with low-molecular-weight heparin. On June 4, 2022, CT showed no abnormalities around the anastomosis or stump, no leakage of oral pantothenic glucosamine into the abdominal cavity, no abnormalities in the ileocecal region or appendix, and no significant fluid accumulation in the abdominopelvic cavity (Figure 3). On June 8, 2022, her blood count, calcitonin and C-reactive protein (CRP) levels were normal, and she was ready to be discharged. However, during the night of June 9, 2022, the patient complained of persistent pain on the right side of the abdomen, and the abdominal pain became

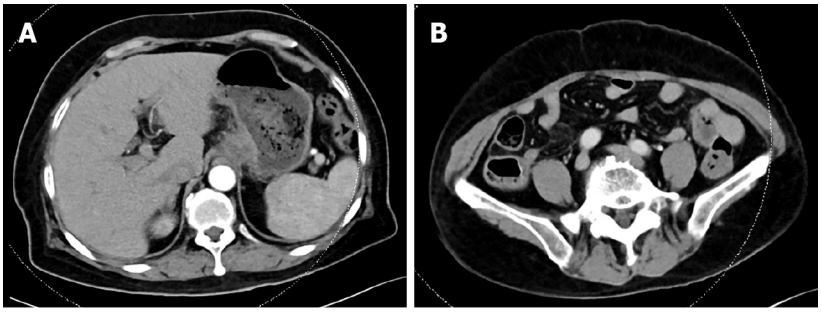

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Figure 1 Imaging data of May 23, 2022. A: Computed tomography (CT) showed that the cardia was thickened and reinforced; B: CT showed that the appendix was normal.

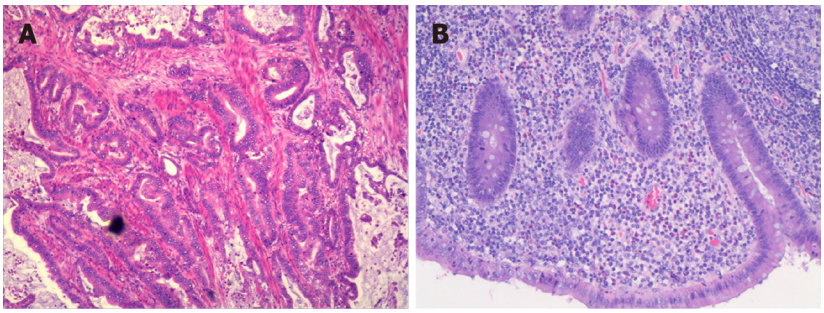

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Figure 2 Photomicrographs (hematoxylin and eosin, × 200 magnification). A: Moderately differentiated tubular adenocarcinoma; B: Acute purulent appendicitis and periapical inflammation.

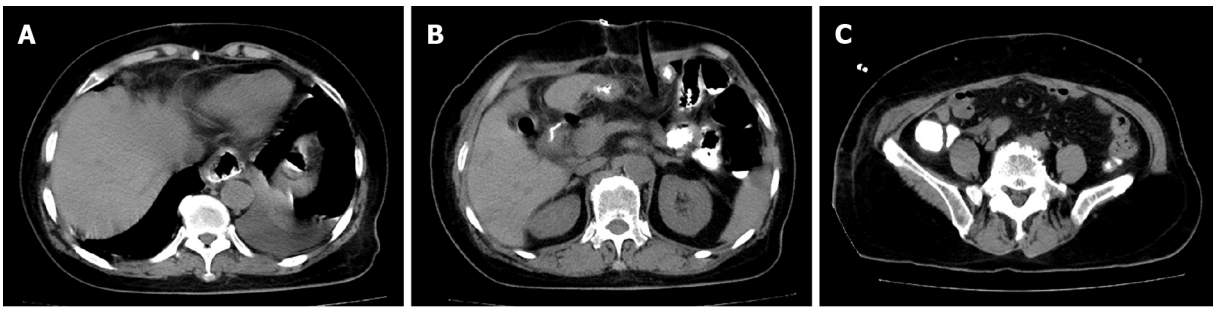

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Figure 3 Imaging data of June 4, 2022. A: Computed tomography showed no abnormalities around the anastomosis or stump, no leakage into the abdominal cavity from oral pantothenic glucosamine, no abnormalities in the ileocecal region or appendix, and no significant fluid accumulation in the abdominopelvic cavity; B: No abnormalities were found in the ileocecal region or duodenal stump; C: No abnormalities were found in the appendix.

significantly worse on the morning of June 10, 2022.

History of past illness

The patient had a previous history of diabetes, hypertension, cholecystectomy and no history of chronic appendicitis.

Personal and family history

There was no family history of tumors.

Physical examination

On June 6, the abdominal incision was healing well, and the patient reported tenderness in the lower right abdomen, muscle tension and rebound pain.

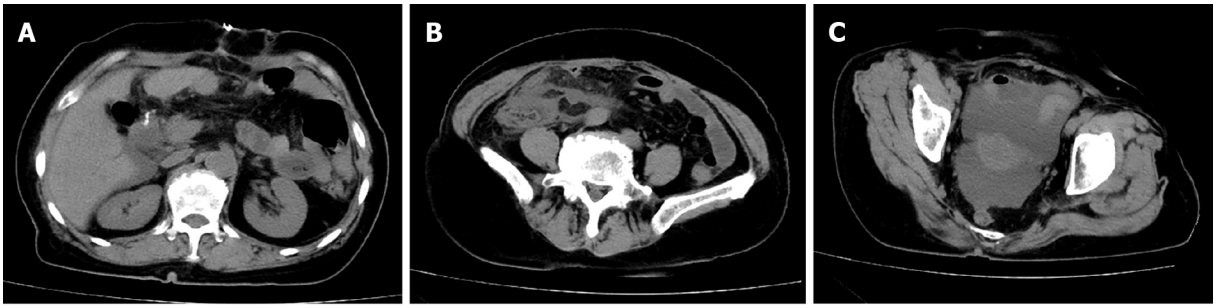

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Figure 4 Imaging data of June 10, 2022. A: Computed tomography showed that there was effusion in the perihepatic and hepatorenal interstitial areas; B: There was effusion in the right paracolic sulcus and exudative changes in the right iliac fossa; C: Effusion was seen in the pelvis.

Laboratory examinations

The patient's leukocyte level was 17.18 × 10^9/L; neutrophil ratio, 88.4%; calcitonin level, 0.19 ng/mL; and CRP level, 65.20 mg/L.

Imaging examinations

On June 10, 2022, CT showed effusion in the perihepatic and hepatorenal spaces, right paracolic sulcus and pelvis and exudative changes in the right iliac fossa (Figure 4). Subsequent ultrasound-guided puncture revealed a slightly turbid yellow-green fluid.

FINAL DIAGNOSIS

Acute suppurative appendicitis after radical gastrectomy.

TREATMENT

On June 10, 2022, laparoscopic exploration revealed yellow-green fluid in the perihepatic and pelvic cavities (Figure 5A and B); the duodenal stump was wrapped in tissue and did not show leakage (Figure 5C), and there were no abnormalities in the esophageal-jejunal anastomosis or jejunal-jejunal anastomosis. A large amount of pus moss was seen in the ileocecal region, and the terminal ileum wrapped around the appendix (Figure 6A). A septic and swollen appendix was seen after careful laparoscopic separation of the adhesions (Figure 6B). The appendiceal mesentery was treated with harmonic scissors and absorbable clips, the root of the appendix was ligated with thread, and the appendiceal stump was cauterized (Figure 6C). A pelvic drainage tube was placed after aspiration of intra-abdominal fluid.

OUTCOME AND FOLLOW-UP

Postoperative pathology showed acute purulent appendicitis and periapical inflammation (Figure 2B). The patient recovered well after surgery and was successfully discharged two weeks later. Follow-up CT showed no significant abnormalities in the abdominal cavity (Figure 7). The patient continued adjuvant chemotherapy after surgery, completing three cycles of oxaliplatin and S-1 (SOX regimen).

DISCUSSION

Cholecystitis and pancreatitis are common diseases after radical resection of gastric cancer. Appendicitis occurs rarely, as early as several months later, and perioperative combined episodes of appendicitis are even rarer.

There were several reasons for misdiagnosis in this case. First, we usually used one etiology to explain all the symptoms of the patient; we would focus on postoperative complications but might ignore the possibility of common diseases. Second, the most common abdominal complication after radical gastrectomy is duodenal stump leakage[3]. The patient had a history of diabetes and presented with postoperative right abdominal pain. CT showed hepatorenal and pelvic effusion, and the puncture

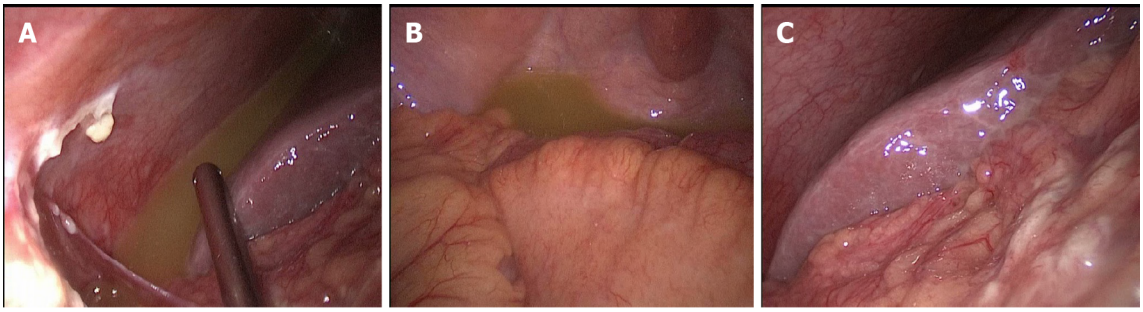

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Figure 5 laparoscopic exploration. A and B: Yellow-green fluid could be found in the perihepatic and pelvic cavities; C: The duodenal stump was wrapped in tissue and did not show leakage.

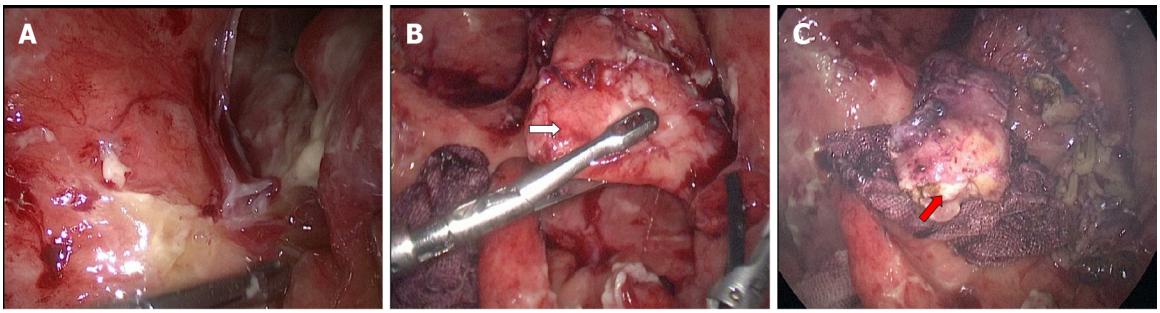

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Figure 6 Surgical procedure. A: A large amount of pus moss was seen around the ileocecal region, and the terminal ileum wrapped around the appendix; B: A septic and swollen appendix was seen after careful laparoscopic separation of the adhesions (white arrow); C: Resected appendix (red arrow) and treated appendiceal stump and mesentery.

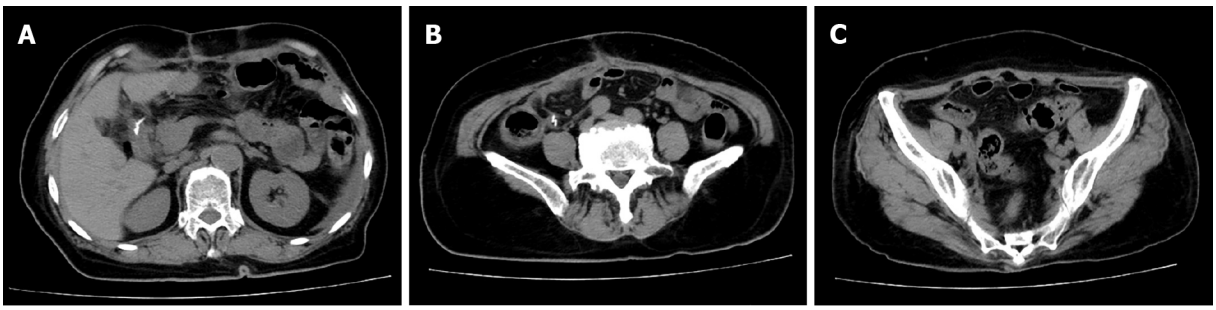

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Figure 7 Imaging data of July 12, 2022. Computed tomography showed no significant abnormalities of the duodenal stump, appendiceal stump or pelvic. A: Duodenal stump; B: Appendiceal stump; C: Pelvic.

revealed yellow-green turbid fluid, which could not exclude the occurrence of duodenal stump leakage.

This is a successful case in which laparoscopic exploration was promptly performed to clarify the diagnosis. This case is enlightening for the following reasons: (1) For patients with a history of diabetes and postoperative lower right abdominal pain, the possibility of appendicitis must be considered, as diabetes is a high-risk factor for appendicitis[4]; (2) Patients with appendicitis following gastrectomy have atypical abdominal pain due to surgical removal of all or a large part of the stomach, and reconstruction of the digestive tract alters the original physiological structure; (3) The large omentum was removed and could no longer easily confine the acute inflammation of the appendix; thus, as the disease worsened, diffuse peritonitis developed; (4) The occurrence of appendicitis has been reported in conjunction with several other diseases, such as colon cancer, tuberculosis, herniation and gynecological diseases[5-8]; and (5) Gastric cancer combined with appendiceal metastasis would cause symptoms of acute appendicitis, but in this case, there was no peritoneal or appendiceal metastasis[9]. In conclusion, acute appendicitis occurring within a short period after radical gastrectomy has its own characteristics and is easily confused with postoperative complications of gastric cancer; thus, a clear diagnosis and

early surgical treatment are needed.

CONCLUSION

Acute appendicitis in the short term after gastric cancer is rare and easily ignored clinically and needs to be differentiated from duodenal stump leakage.

FOOTNOTES

Author contributions: Ma J wrote and edited the original draft; Duan SQ and Miao X contributed to data collection and analysis; Zhou CP and Zha ZP reviewed the literature; Zhang YM reviewed and approved the final manuscript; All authors have read and approve the final manuscript.

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