ISSN 1948-9366 (online)

World Journal of

Gastrointestinal Surgery

World J Gastrointest Surg 2022 November 27; 14(11): 1179-1319

Published by Baishideng Publishing Group Inc

WJGS

World Journal of Gastrointestinal Surgery

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Monthly Volume 14 Number 11 November 27, 2022

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INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJGS* as 2.505; IF without journal self cites: 2.473; 5-year IF: 3.099; Journal Citation Indicator: 0.49; Ranking: 104 among 211 journals in surgery; Quartile category: Q2; Ranking: 81 among 93 journals in gastroenterology and hepatology; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

ISSN
ISSN 1948-9366 (online)

LAUNCH DATE
November 30, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Peter Schemmer

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-9366/editorialboard.htm

PUBLICATION DATE
November 27, 2022

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World J Gastrointest Surg 2022 November 27; 14(11): 1179-1197

DOI: 10.4240/wjgs.v14.i11.1179

ISSN 1948-9366 (online)

REVIEW

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

Kai Siang Chan, Vishal G Shelat

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Poddighe D, Kazakhstan; Yao J, China

Received: September 11, 2022
Peer-review started: September 11, 2022
First decision: September 26, 2022
Revised: October 8, 2022
Accepted: October 25, 2022
Article in press: October 25, 2022
Published online: November 27, 2022

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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.

Citation: Chan KS, Shelat VG. Diagnosis, severity stratification and management of adult acute pancreatitis–current evidence and controversies. *World J Gastrointest Surg* 2022; 14(11): 1179-1197
URL: https://www.wjgnet.com/1948-9366/full/v14/i11/1179.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i11.1179

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

Author contributions: Chan KS is involved in the conceptualization and drafting of the initial manuscript; Shelat VG is involved in the conceptualization, supervision and revision of the manuscript.

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

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S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2022 November 27; 14(11): 1198-1203

DOI: 10.4240/wjgs.v14.i11.1198

ISSN 1948-9366 (online)

MINIREVIEWS

Development and future perspectives of natural orifice specimen extraction surgery for gastric cancer

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D, D
Grade E (Poor): 0

P-Reviewer: Dumitraşcu T, Romania; Hori T, Japan

Received: July 18, 2022
Peer-review started: July 18, 2022
First decision: August 19, 2022
Revised: August 30, 2022
Accepted: October 18, 2022
Article in press: October 18, 2022
Published online: November 27, 2022

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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.

Citation: Zhang ZC, Luo QF, Wang WS, Chen JH, Wang CY, Ma D. Development and future perspectives of natural orifice specimen extraction surgery for gastric cancer. *World J Gastrointest Surg* 2022; 14(11): 1198-1203
URL: https://www.wjgnet.com/1948-9366/full/v14/i11/1198.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i11.1198

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.

Supported by Chongqing Medical Scientific Research Project (Joint Project of Chongqing Health Commission and Science and Technology Bureau), No. 2022ZDXM016.

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

Country/Territory of origin: China

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S-Editor: Wang JJ
L-Editor: Wang TQ
P-Editor: Wang JJ

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World J Gastrointest Surg 2022 November 27; 14(11): 1204-1218

DOI: 10.4240/wjgs.v14.i11.1204

ISSN 1948-9366 (online)

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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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D, D
Grade E (Poor): 0

P-Reviewer: Byeon H, South Korea; de Melo FF, Brazil; Tsujinaka S, Japan

Received: July 4, 2022
Peer-review started: July 4, 2022
First decision: July 31, 2022
Revised: August 27, 2022
Accepted: October 12, 2022
Article in press: October 12, 2022
Published online: November 27, 2022

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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.

Citation: Lyu SC, Wang HX, Liu ZP, Wang J, Huang JC, He Q, Lang R. Clinical value of extended lymphadenectomy in radical surgery for pancreatic head carcinoma at different T stages. *World J Gastrointest Surg* 2022; 14(11): 1204-1218
URL: https://www.wjgnet.com/1948-9366/full/v14/i11/1204.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i11.1204

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.

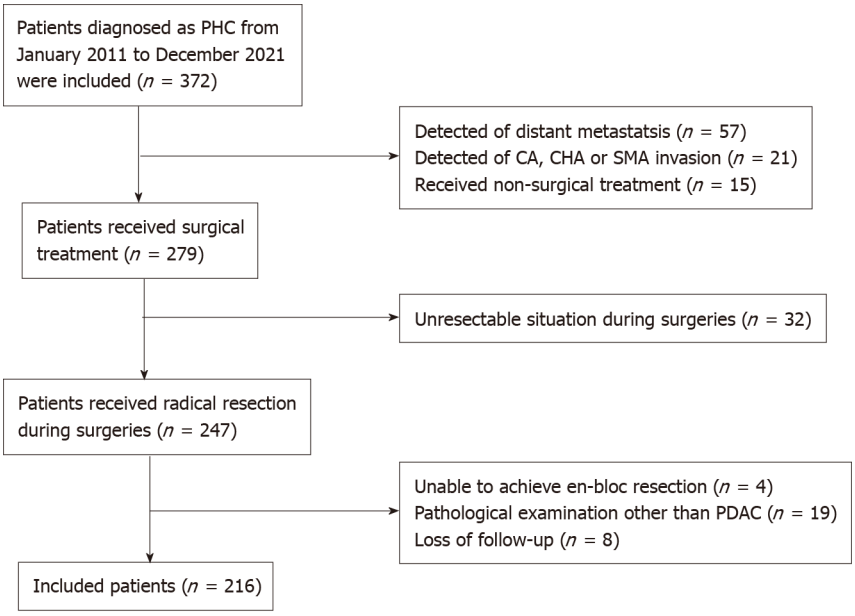
Lymph-node metastasis is an important PHC transfer pathway, and radical lymph-node dissection is mandatory following anti-tumor treatment[6]. Fortner[7] first proposed extended lymphadenectomy (ELD) in 1973, and this technique has been adopted increasingly widely with its improvement. However, randomized 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).



DOI: 10.4240/wjgs.v14.i11.1204

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.

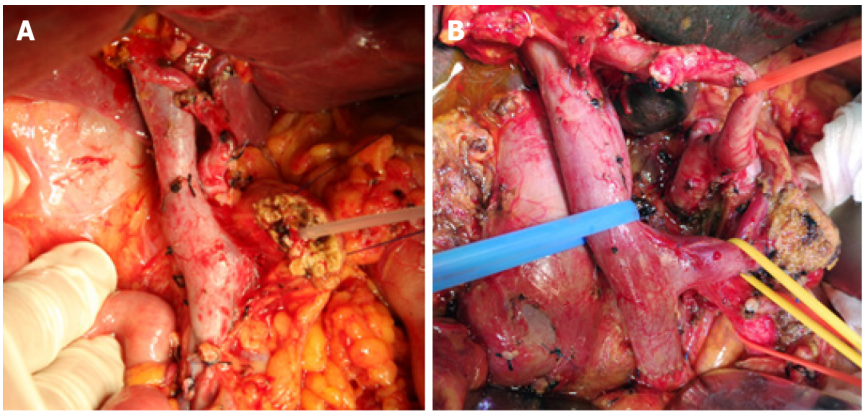
Index analysis and follow-up

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.



DOI: 10.4240/wjgs.v14.i11.1204

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.

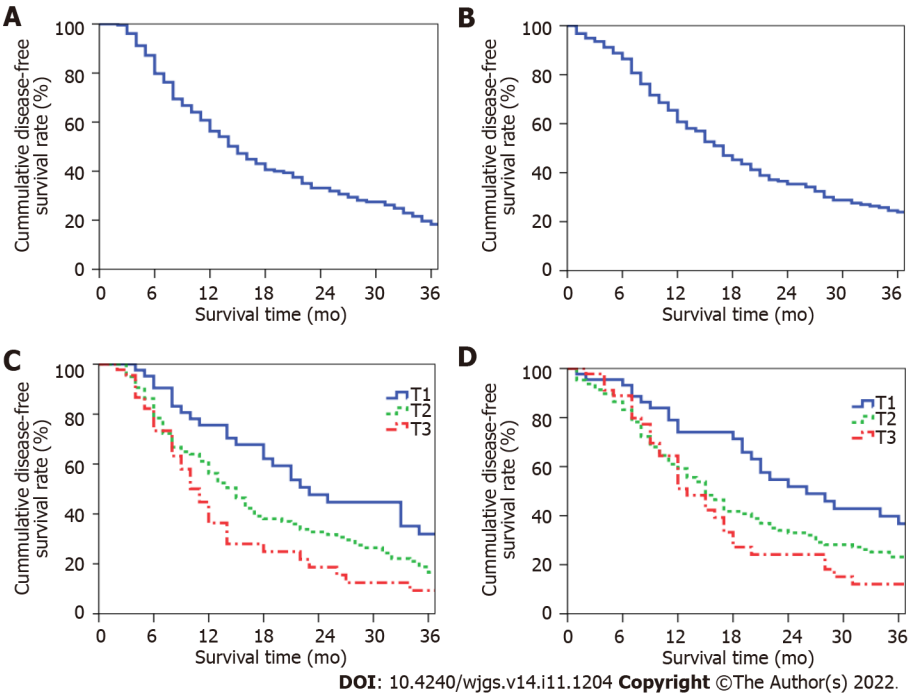


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Figure 3 Long-term prognosis of patients. A: The cumulative overall disease-free survival (DFS) curve of patients; B: The cumulative overall survival (OS) curve of patients; C: The cumulative DFS curves of patients at different T stages; D: The cumulative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

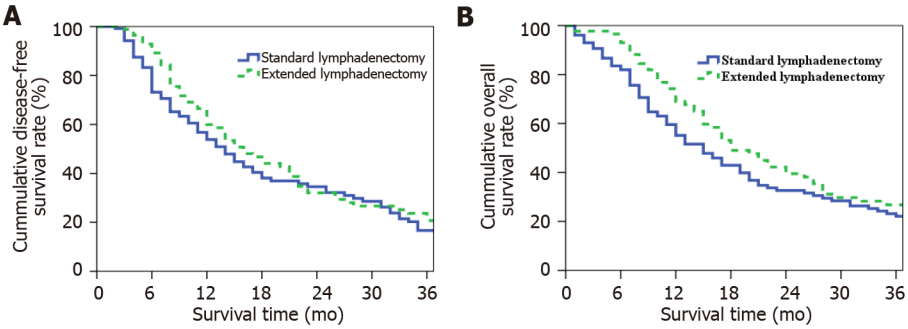

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Figure 4 Long-term prognosis of patients in extended lymphadenectomy group and standard lymphadenectomy group. A: The cumulative disease-free survival curve of patients in two groups; B: The cumulative overall survival curve of patients in two groups.

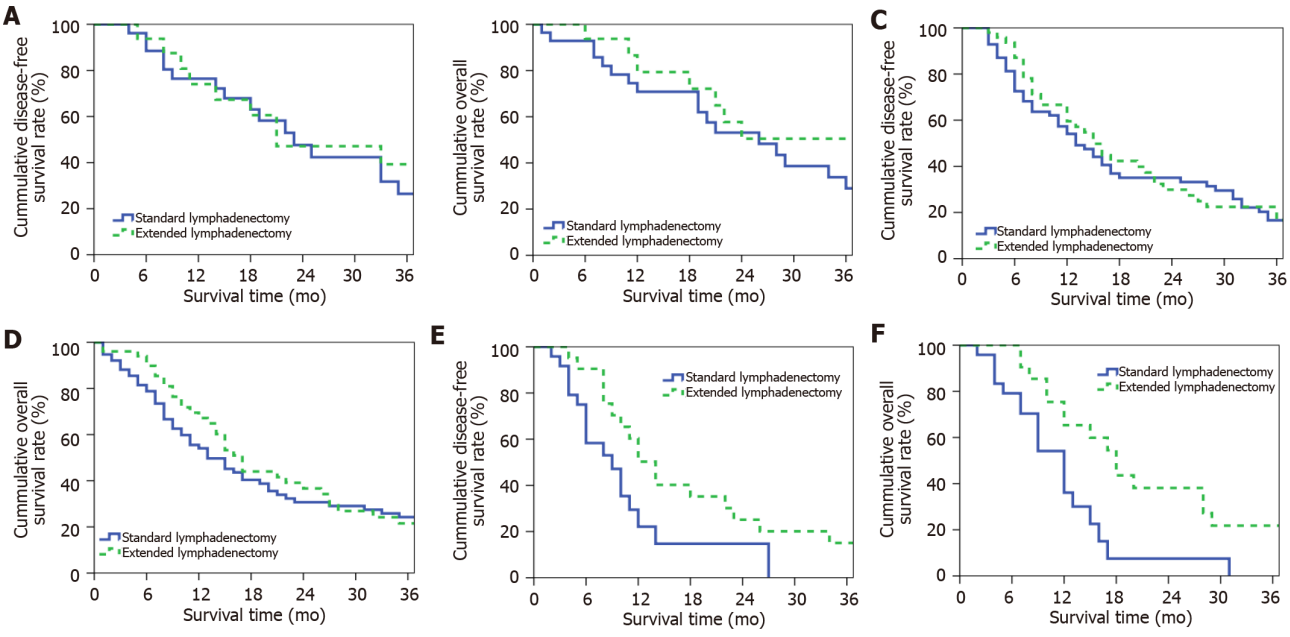

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Figure 5 Long-term prognosis of patients at different T stages in extended lymphadenectomy group and standard lymphadenectomy group. A: The cumulative disease-free survival (DFS) curve of patients at T1 stage in two groups; B: The cumulative overall 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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S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

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World J Gastrointest Surg 2022 November 27; 14(11): 1219-1229

DOI: 10.4240/wjgs.v14.i11.1219

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

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

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Nah YW, South Korea; Sripongpun P, Thailand

Received: July 22, 2022
Peer-review started: July 22, 2022
First decision: September 26, 2022
Revised: October 10, 2022
Accepted: October 19, 2022
Article in press: October 19, 2022
Published online: November 27, 2022

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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.

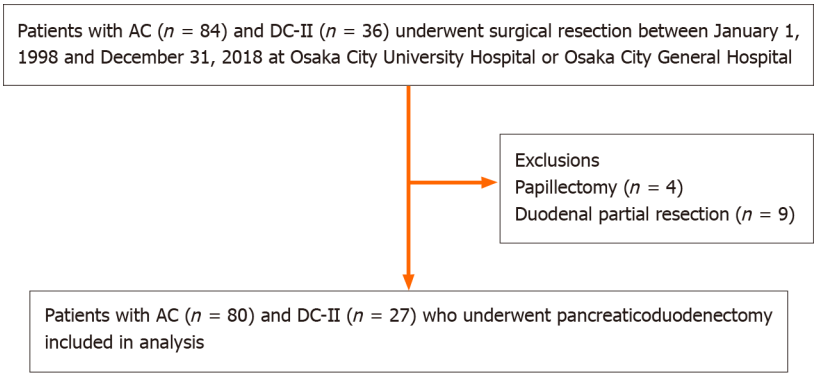
Citation: Nishio K, Kimura K, Murata A, Ohira G, Shinkawa H, Kodai S, Amano R, Tanaka S, Shimizu S, Takemura S, Kanazawa A, Kubo S, Ishizawa T. Comparison of clinicopathological characteristics between resected ampullary carcinoma and carcinoma of the second portion of the duodenum. *World J Gastrointest Surg* 2022; 14(11): 1219-1229
URL: https://www.wjgnet.com/1948-9366/full/v14/i11/1219.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i11.1219

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



DOI: 10.4240/wjgs.v14.i11.1219

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

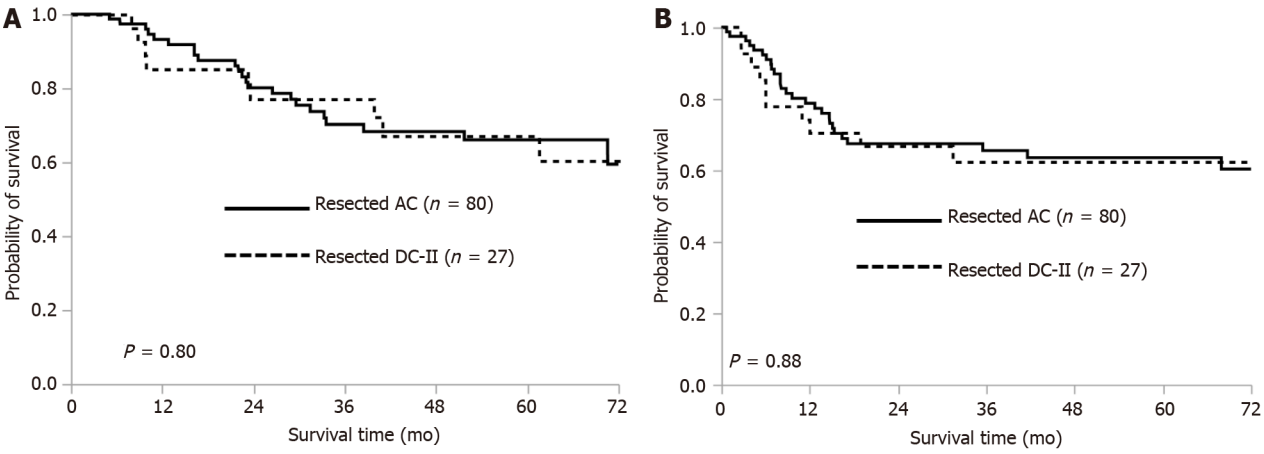
Table 2 shows the results of the comparative analysis of the affected sites and the frequency of LNM to specific sites between the patients with DC-II and AC. In summary, the rates of LNM to the N-He and

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.



DOI: 10.4240/wjgs.v14.i11.1219

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%).

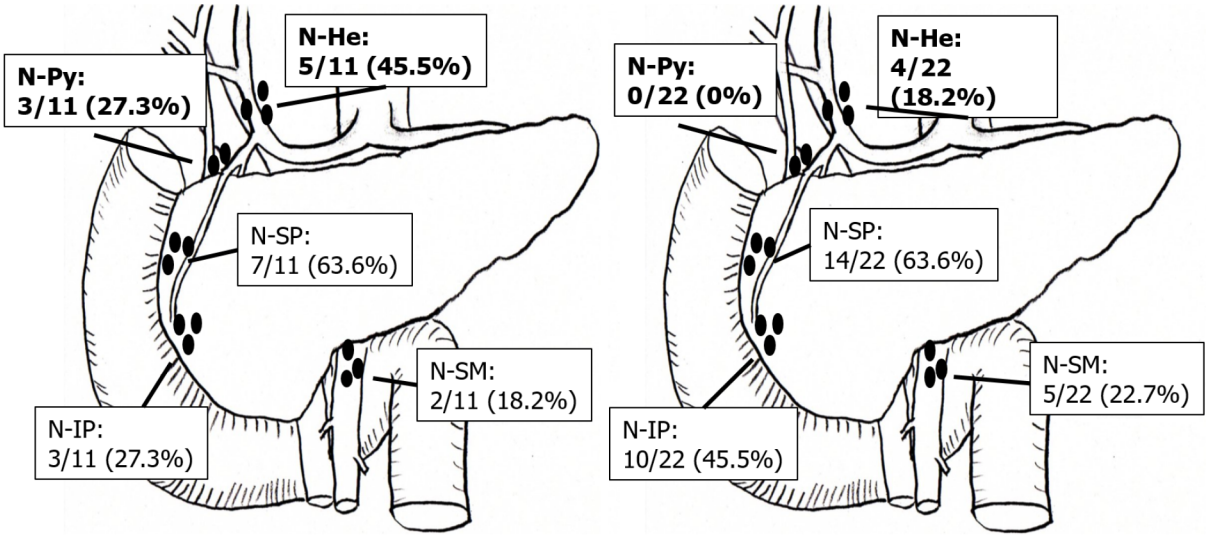
Analysis of the initial recurrent sites in patients with DC-II and AC

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.



DOI: 10.4240/wjgs.v14.i11.1219

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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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2022 November 27; 14(11): 1230-1249

DOI: 10.4240/wjgs.v14.i11.1230

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

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

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Kawabata H, Japan; Lieto E, Italy

Received: July 20, 2022
Peer-review started: July 20, 2022
First decision: September 12, 2022
Revised: September 17, 2022
Accepted: October 19, 2022
Article in press: October 19, 2022
Published online: November 27, 2022

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, Department of Gastroenterological Surgery, Harbin Medical University Cancer Hospital, Harbin Medical University Cancer Hospital, Harbin 150081, Heilongjiang Province, China

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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.

Citation: 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, Zhang Y, Xue YW. Metastatic lymph nodes and prognosis assessed by the number of retrieved lymph nodes in gastric cancer. *World J Gastrointest Surg* 2022; 14(11): 1230-1249
URL: https://www.wjgnet.com/1948-9366/full/v14/i11/1230.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i11.1230

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

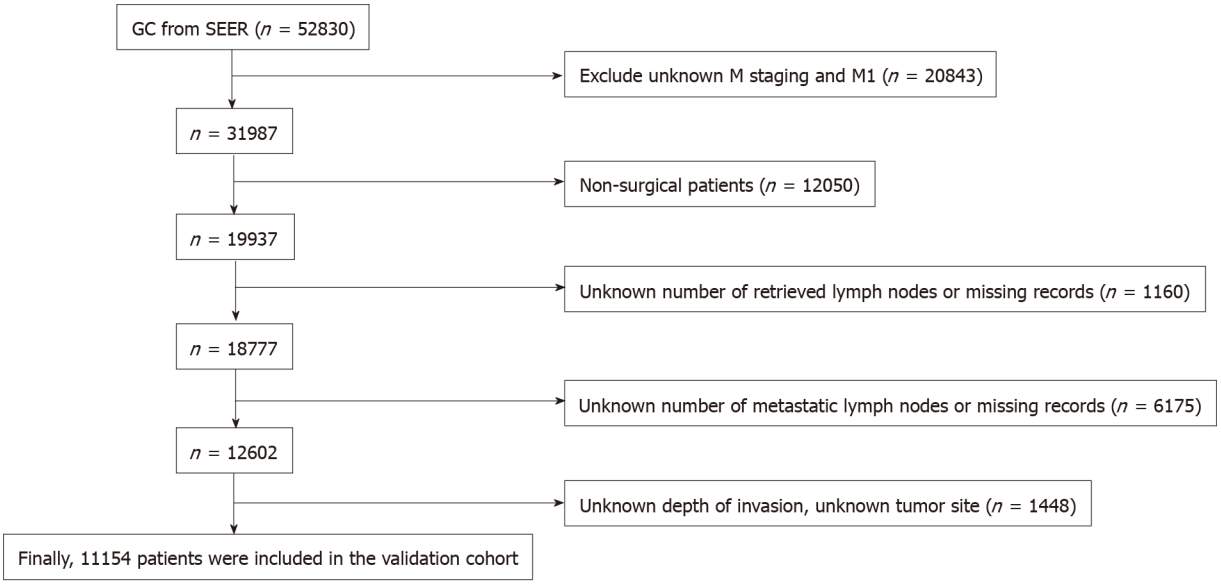
Ultimately, at our institution, a total of 4968 patients were included in the study as a training cohort (Table 1). Among them, there were 1106 patients in the pT1 stage, 745 patients in the pT2 stage, 1583 patients in the pT3 stage, and 1534 patients in the pT4 stage. In the entire cohort, the median 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

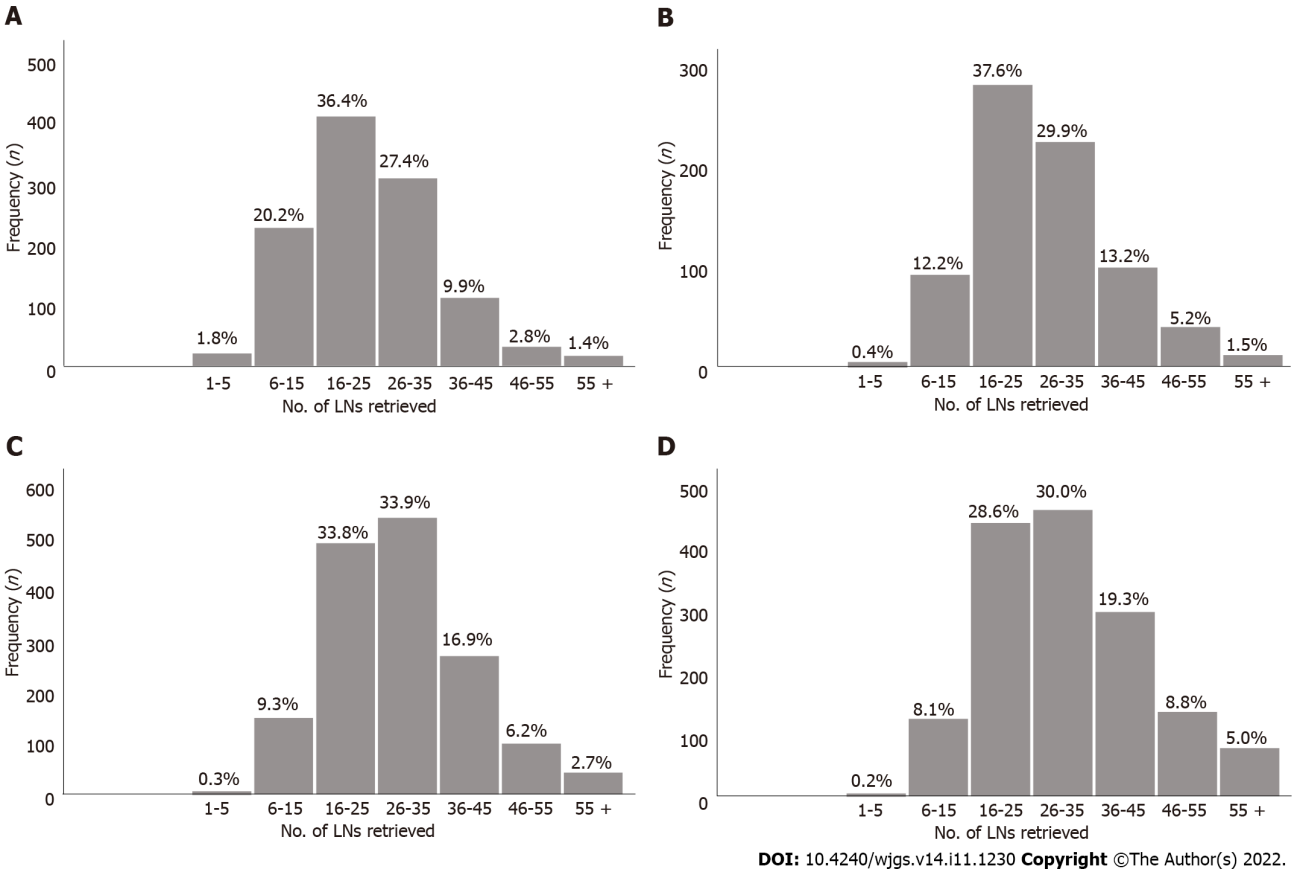
Characteristics	Training cohort	Validation cohort	*P* value
	n = 4968	*n* = 11154	
Sex			< 0.001
Male	3634 (73.1)	7214 (64.7)	
Female	1334 (26.9)	3940 (35.3)	
Age (yr)			< 0.001
≤ 60	2845 (57.3)	3418 (30.6)	
> 60	2123 (42.7)	7736 (69.4)	
Tumor location			< 0.001
Upper third	552 (11.1)	3954 (35.4)	
Middle 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.



DOI: 10.4240/wjgs.v14.i11.1230

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.



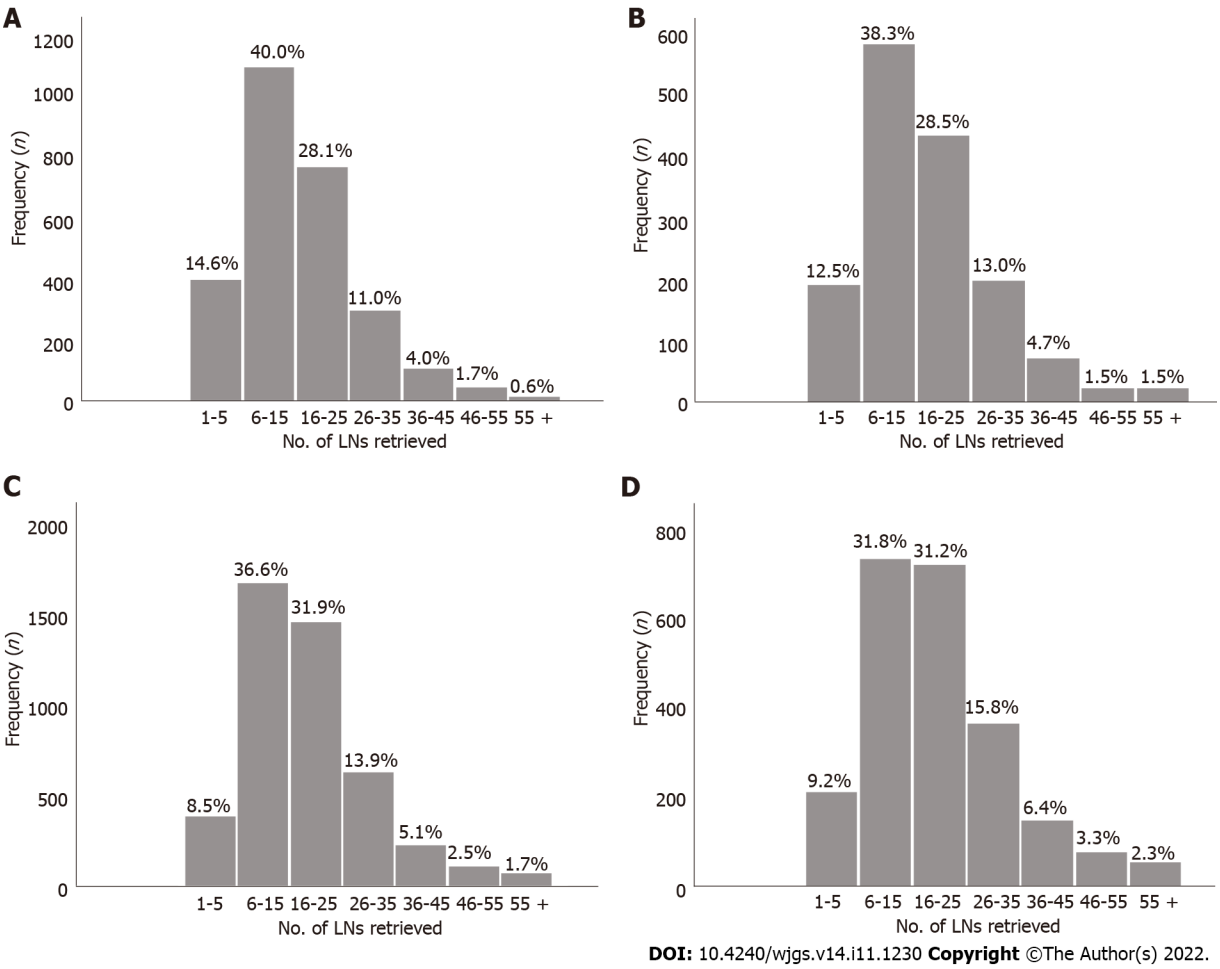
DOI: 10.4240/wjgs.v14.i11.1230

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



DOI: 10.4240/wjgs.v14.i11.1230

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 %.

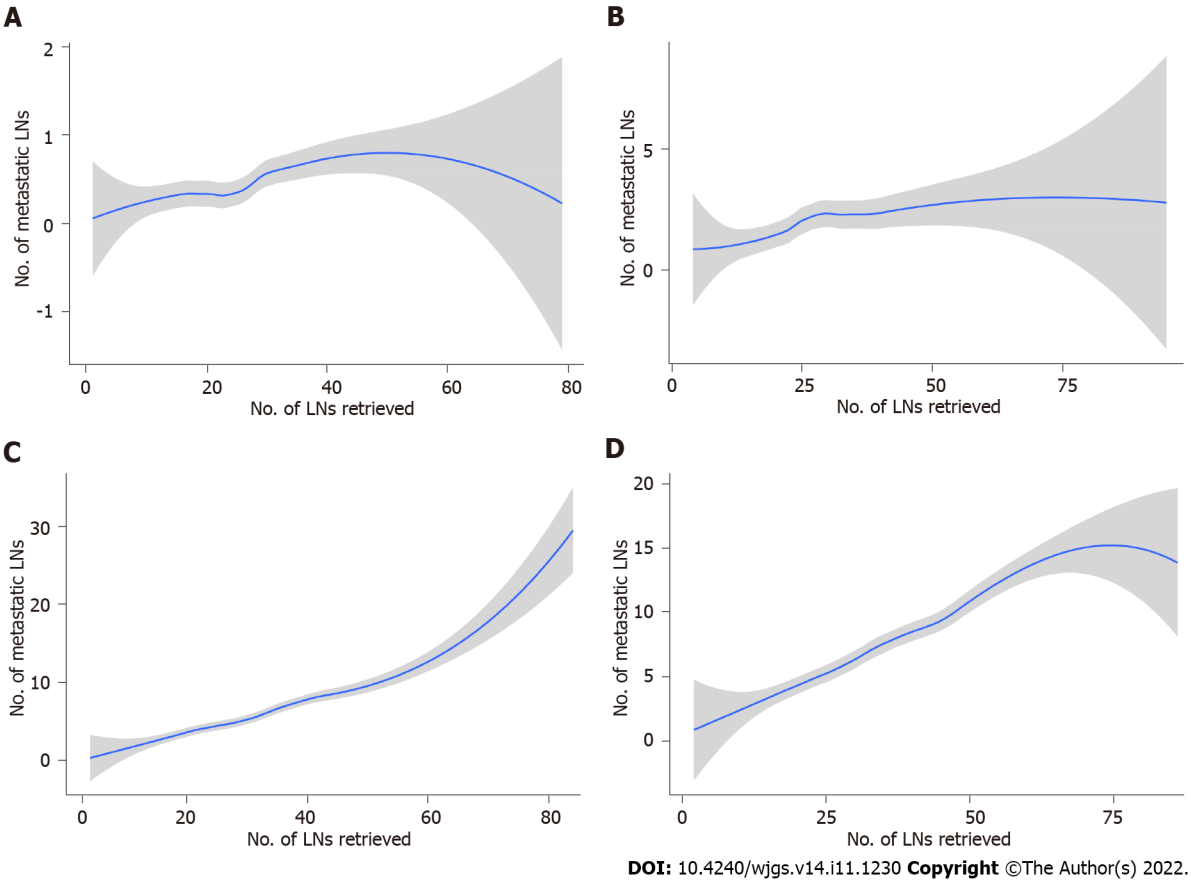


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Figure 4 The association between the number of examined lymph nodes and the number of metastatic lymph nodes locally weighted smoothing in the Chinese training cohort. A: pT1; B: pT2; C: pT3; D: pT4. The shaded area is the 95% confidence interval.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

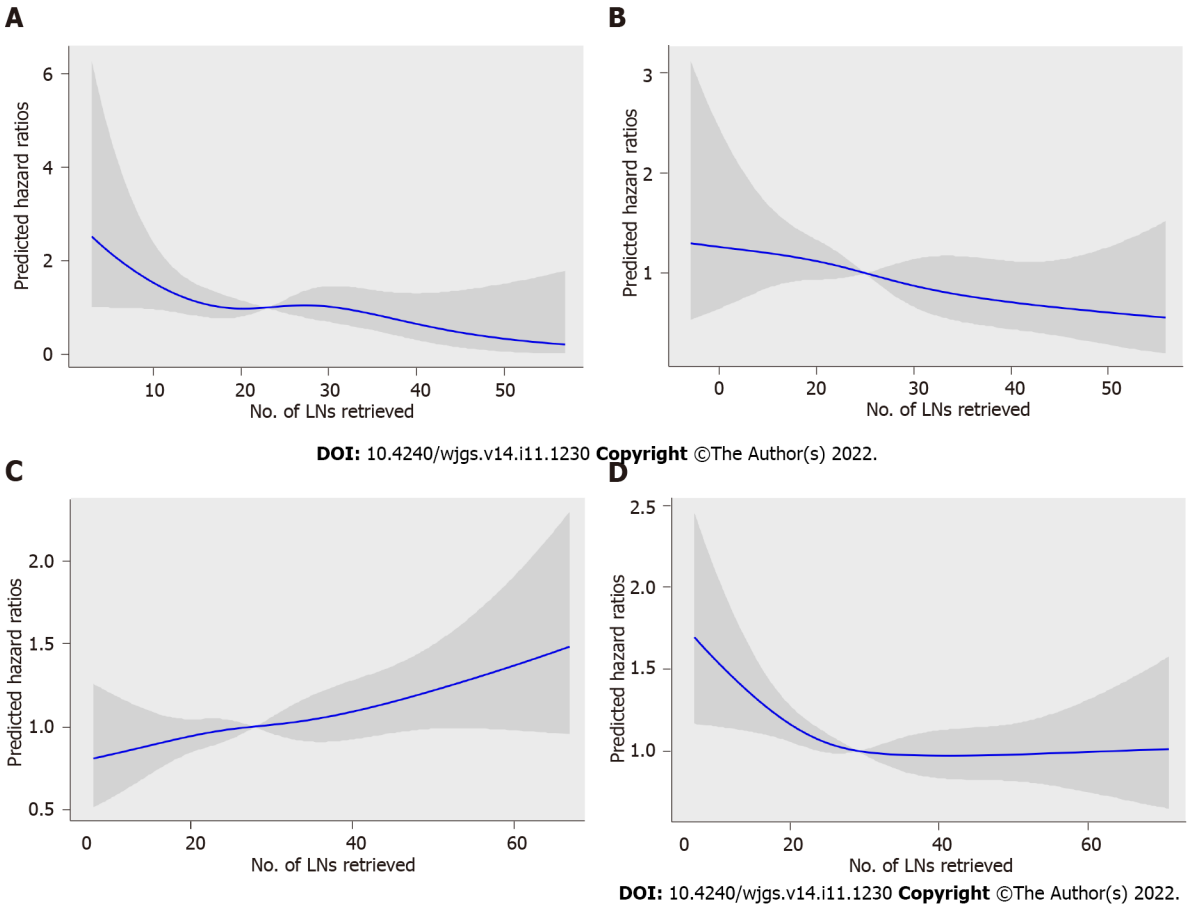
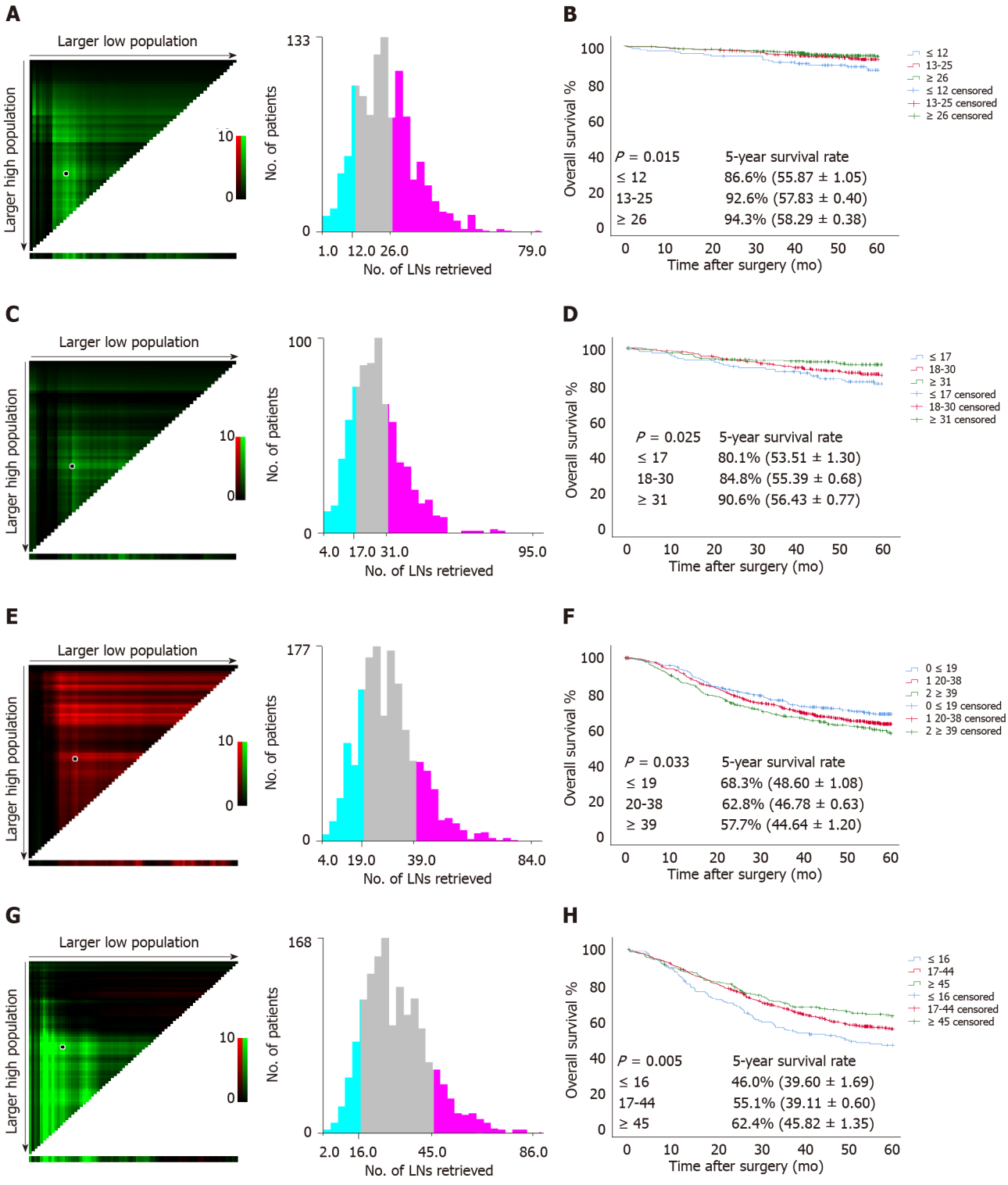


Figure 5 Association between the number of examined lymph nodes and the hazard ratios in the Chinese training cohort. A: pT1; B: pT2; C: pT3; D: pT4. The blue line represents the estimated hazard ratios, and the shaded area is the 95% confidence interval. LNs: Lymph nodes; HRs: Hazard ratios.

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



DOI: 10.4240/wjgs.v14.i11.1230

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.

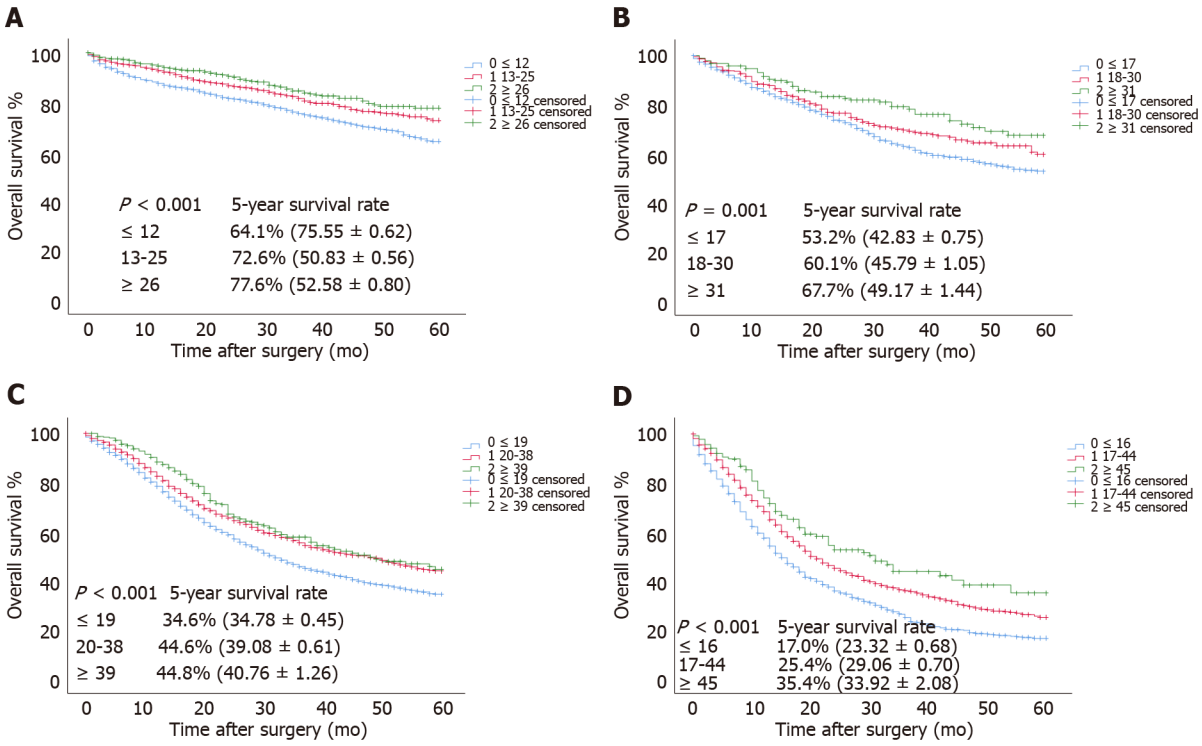


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Figure 7 The overall survival curves of pT1-pT4 patients in the validation cohort stratified according to the estimated cutoff value. A: pT1; B: pT2; C: pT3; D: pT4.

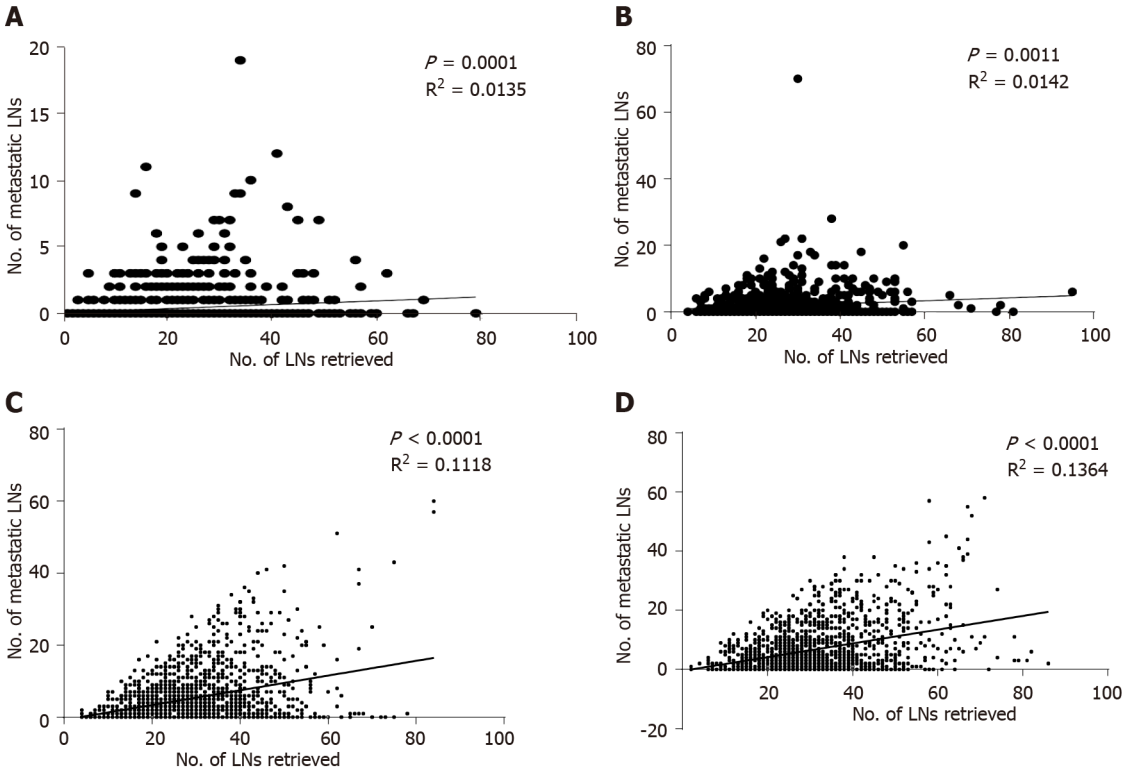

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Figure 8 Scatter plot and linear regression analysis of the number of metastatic lymph nodes and the number of positive lymph nodes in the overall patient population. A: pT1; B: pT2; C: pT3; D: pT4. LNs: Lymph nodes.

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.

Supported by the Nn 10 Program of Harbin Medical University Cancer Hospital, No. Nn 10 PY 2017-03.

Institutional review board statement: The study was approved by the Ethics Committee of the Affiliated Tumor Hospital of Harbin Medical University.

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

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

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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S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

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World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Surg 2022 November 27; 14(11): 1250-1259

DOI: 10.4240/wjgs.v14.i11.1250

ISSN 1948-9366 (online)

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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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Rama N, Portugal; Urlin VM, Romania

Received: August 2, 2022
Peer-review started: August 2, 2022
First decision: September 4, 2022
Revised: September 27, 2022
Accepted: November 4, 2022
Article in press: November 4, 2022
Published online: November 27, 2022

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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.

Citation: Shao SL, Li YK, Qin JC, Liu L. Comprehensive abdominal composition evaluation of rectal cancer patients with anastomotic leakage compared with body mass index-matched controls. *World J Gastrointest Surg* 2022; 14(11): 1250-1259

URL: https://www.wjgnet.com/1948-9366/full/v14/i11/1250.htm

DOI: https://dx.doi.org/10.4240/wjgs.v14.i11.1250

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

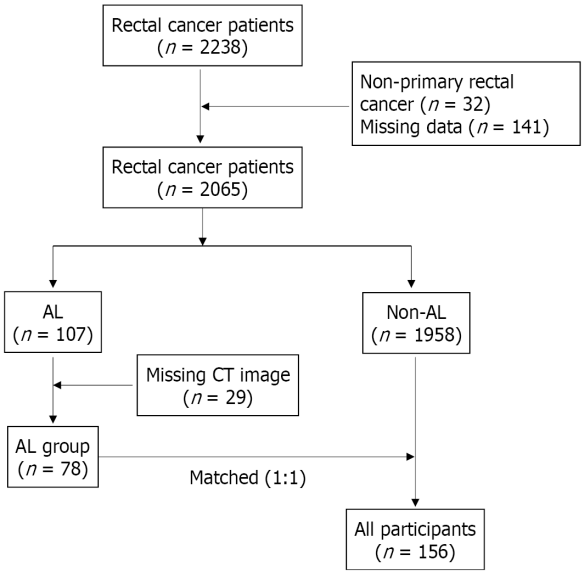
A total of 156 patients were included in the final analysis. Table 1 shows the comparison of the clinical characteristics between the AL group and the control group. Compared to the controls, the patients in

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.



DOI: 10.4240/wjgs.v14.i11.1250

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

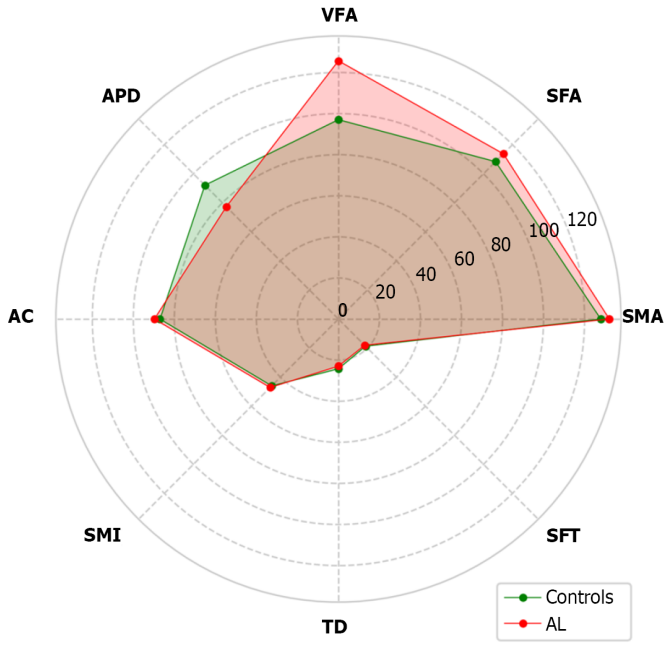
The mechanism underlying AL occurrence involves several factors. The present work compared the clinical characteristics and abdominal composition in rectal cancer patients who received anterior resection and developed AL to controls who were matched for sex and BMI. This study was conducted in a large 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.

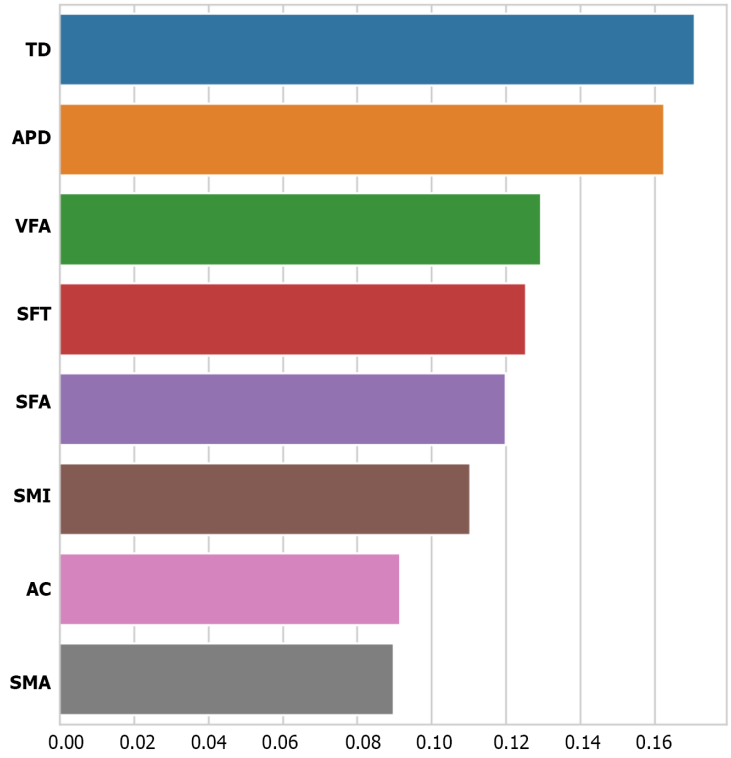


DOI: 10.4240/wjgs.v14.i11.1250

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,



DOI: 10.4240/wjgs.v14.i11.1250

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.

Data sharing statement: Data used in this study is available from the corresponding author on reasonable request.

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S-Editor: Chen YL
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P-Editor: Chen YL

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World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Surg 2022 November 27; 14(11): 1260-1271

DOI: 10.4240/wjgs.v14.i11.1260

ISSN 1948-9366 (online)

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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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Nio M, Japan; Wagner-Skacel J, Austria

Received: September 19, 2022
Peer-review started: September 19, 2022
First decision: October 21, 2022
Revised: October 30, 2022
Accepted: November 16, 2022
Article in press: November 16, 2022
Published online: November 27, 2022

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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.

Citation: Ding JN, Feng TT, Sun W, Cai XY, Zhang Y, Zhao WF. Recombinant human thrombopoietin treatment in patients with chronic liver disease-related thrombocytopenia undergoing invasive procedures: A retrospective study. *World J Gastrointest Surg* 2022; 14(11): 1260-1271
URL: https://www.wjgnet.com/1948-9366/full/v14/i11/1260.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i11.1260

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,

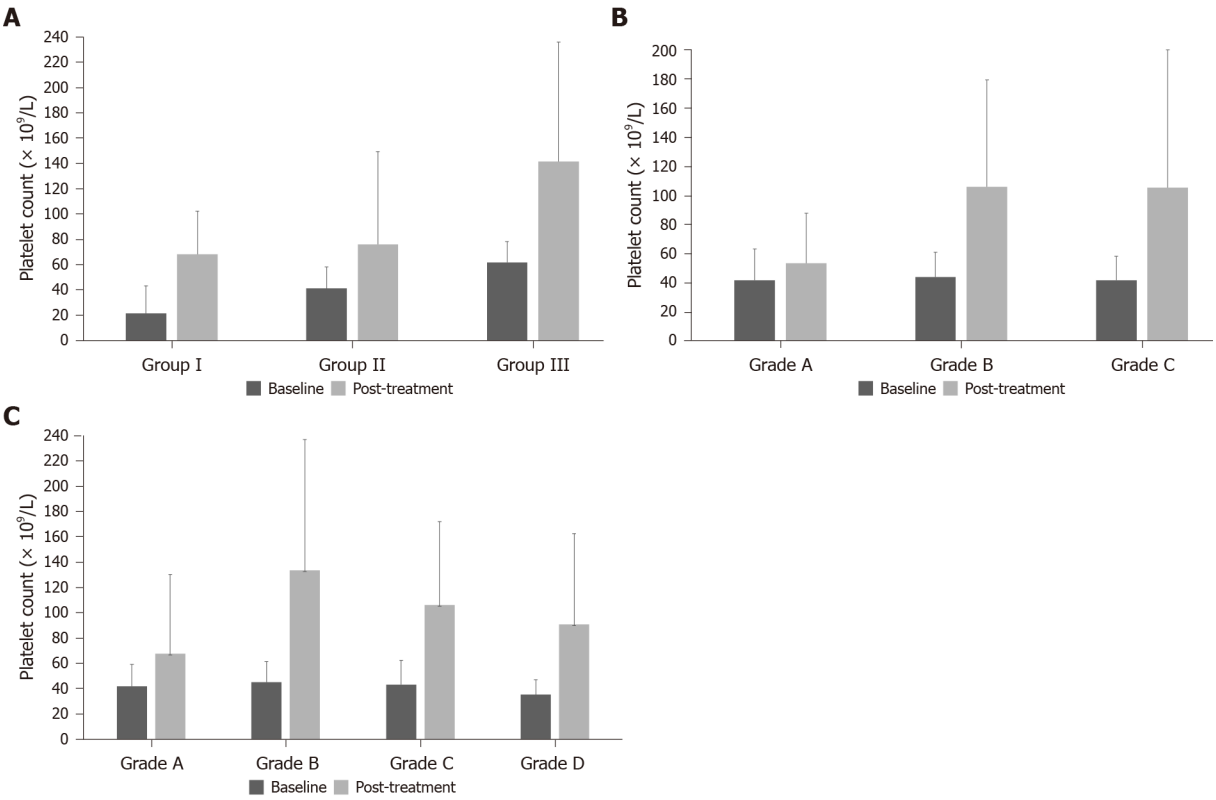

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Figure 1 Platelet count for chronic liver disease-patients treated with recombinant human thrombopoietin. A: Platelet count in different baseline platelet count groups; B: Platelet count in different Child-Pugh grades groups; C: Platelet count in different medication durations groups.

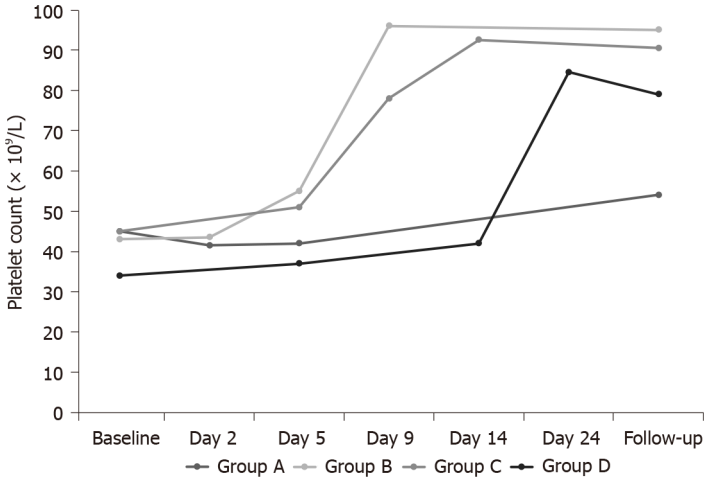

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Figure 2 Variation trend of platelet count with different medication durations.

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.

Supported by the Science and Technology Development Plan of Suzhou, Jiangsu Province, China, No. SYS2020009.

Institutional review board statement: 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).

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

Data sharing statement: Dataset available from the corresponding author at zhaoweifeng@suda.edu.cn. Participants gave informed consent for data sharing.

Country/Territory of origin: China

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S-Editor: Zhang H
L-Editor: A
P-Editor: Zhang H

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World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Surg 2022 November 27; 14(11): 1272-1284

DOI: 10.4240/wjgs.v14.i11.1272

ISSN 1948-9366 (online)

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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Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Peng XC, China; Zhou Z, China

Received: July 13, 2022
Peer-review started: July 13, 2022
First decision: July 31, 2022
Revised: August 20, 2022
Accepted: October 12, 2022
Article in press: October 12, 2022
Published online: November 27, 2022

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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

URL: https://www.wjgnet.com/1948-9366/full/v14/i11/1272.htm

DOI: https://dx.doi.org/10.4240/wjgs.v14.i11.1272

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

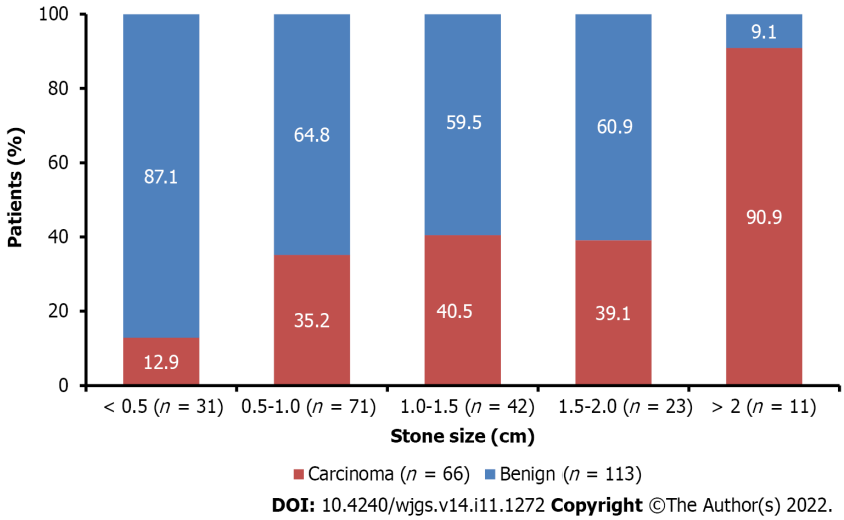
Group	*n*	1 marker	2 markers	3 markers	4 markers
Benign GB disease	120	29 (24.2)	6 (5.0)	1 (0.8)	0
GBC	80	14 (17.5)	27 (33.7)	25 (31.3)	3 (3.8)
Positive likelihood rate		0.5%	4.5%	25%	100%

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.



DOI: 10.4240/wjgs.v14.i11.1272

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

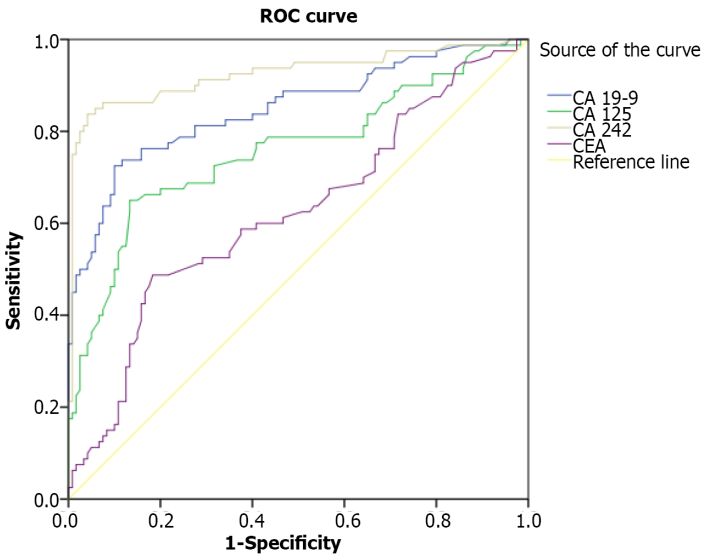


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Figure 2 Receiver operating characteristic curve analysis showing diagnostic performance of carbohydrate antigen 19-9 (U/mL), carbohydrate antigen 125 (U/mL), carcinoembryonic antigen (μg/L), and carbohydrate antigen 242 (U/mL) in predicting gallbladder cancer *vs* benign gallbladder disease. ROC: Receiver operating characteristic curve.

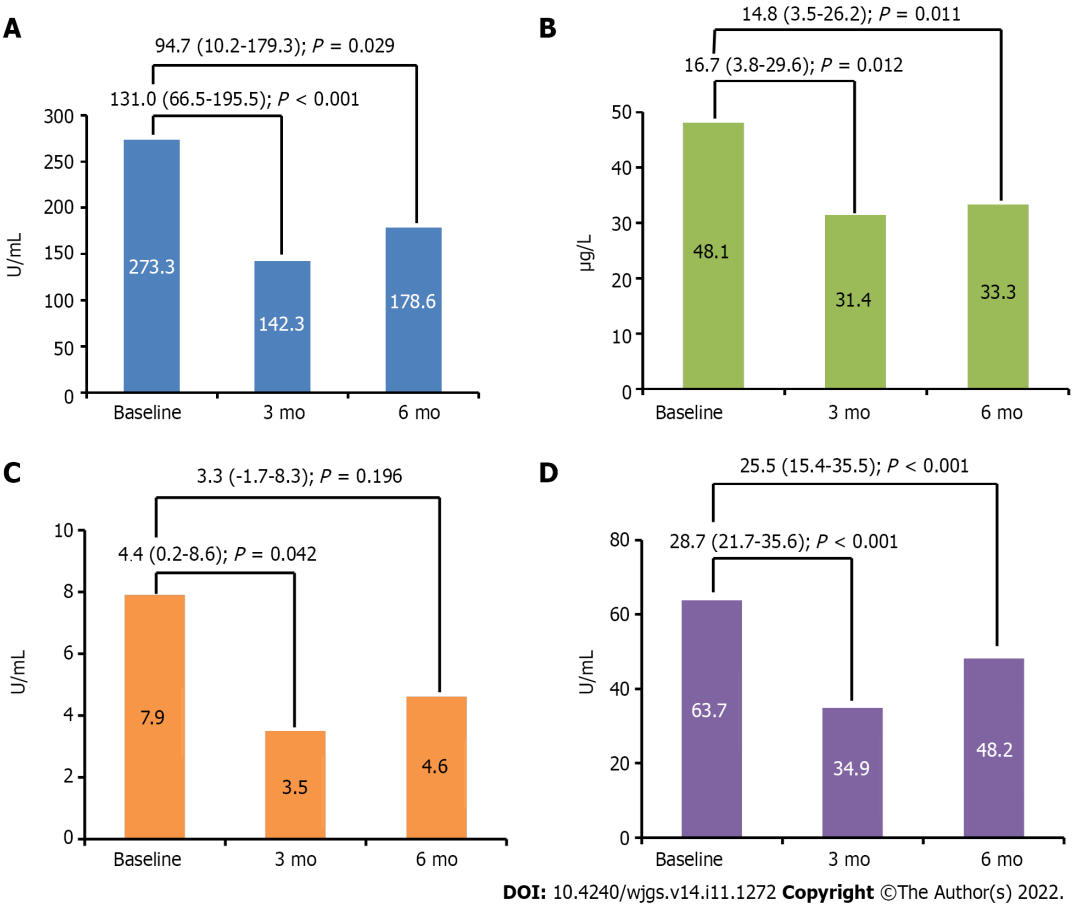

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Figure 3 Comparison of tumor marker levels of carbohydrate antigen 19-9, carbohydrate antigen 125, carcinoembryonic antigen, and carbohydrate antigen 242 before and after surgical management of gallbladder cancer. A: Carbohydrate antigen 19-9; B: Carbohydrate 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.

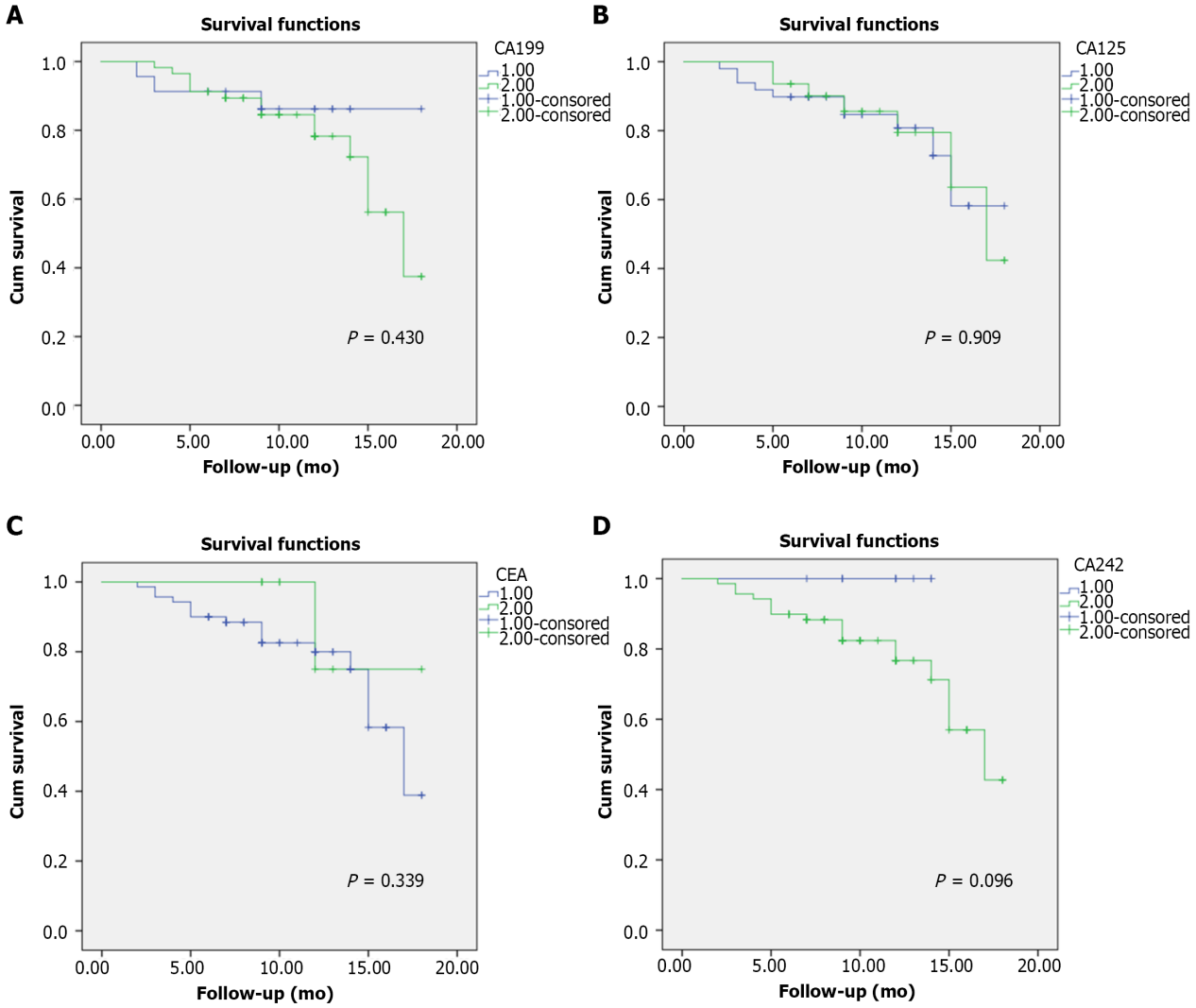

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Figure 4 Survival of patients with gallbladder cancer according to elevated *vs* normal marker levels of serum carbohydrate antigen 19-9 (U/mL), serum carbohydrate antigen 125 (U/mL), serum carcinoembryonic antigen (μg/L), and serum carbohydrate antigen 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).

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

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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S-Editor: Chen YL
L-Editor: Webster JR
P-Editor: Chen YL

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World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Surg 2022 November 27; 14(11): 1285-1296

DOI: 10.4240/wjgs.v14.i11.1285

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Observational Study

Disturbed passage of jejunal limb near esophageal hiatus after overlapped esophagojejunostomy following laparoscopic total gastrectomy

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Hosogi H, Japan; Jiang X, China

Received: July 25, 2022
Peer-review started: July 25, 2022
First decision: September 4, 2022
Revised: September 16, 2022
Accepted: October 31, 2022
Article in press: October 31, 2022
Published online: November 27, 2022

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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.

Citation: Noshiro H, Okuyama K, Yoda Y. Disturbed passage of jejunal limb near esophageal hiatus after overlapped esophagojejunostomy following laparoscopic total gastrectomy. *World J Gastrointest Surg* 2022; 14(11): 1285-1296
URL: https://www.wjgnet.com/1948-9366/full/v14/i11/1285.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i11.1285

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.

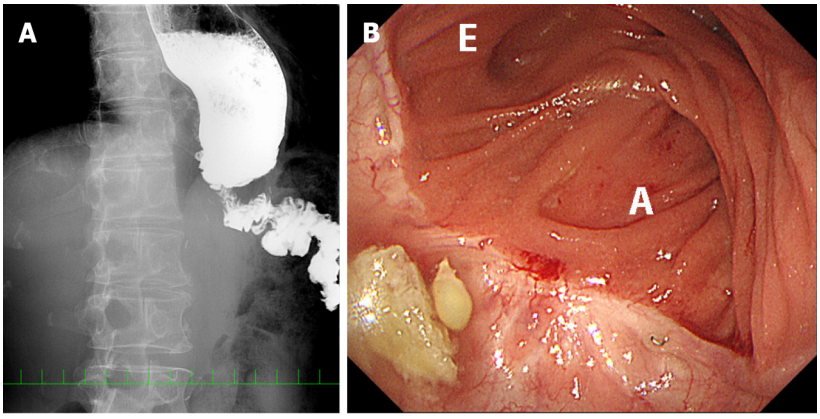
Anastomotic stenosis is a well-known postoperative complication after esophagojejunostomy following total gastrectomy. In early reports, Tsujimoto *et al*[8] summarized that the complication occurred in 0% to 3.8% of patients undergoing LTG following by OEJ; this rate was lower than that after circular-stapled 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.



DOI: 10.4240/wjgs.v14.i11.1285

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

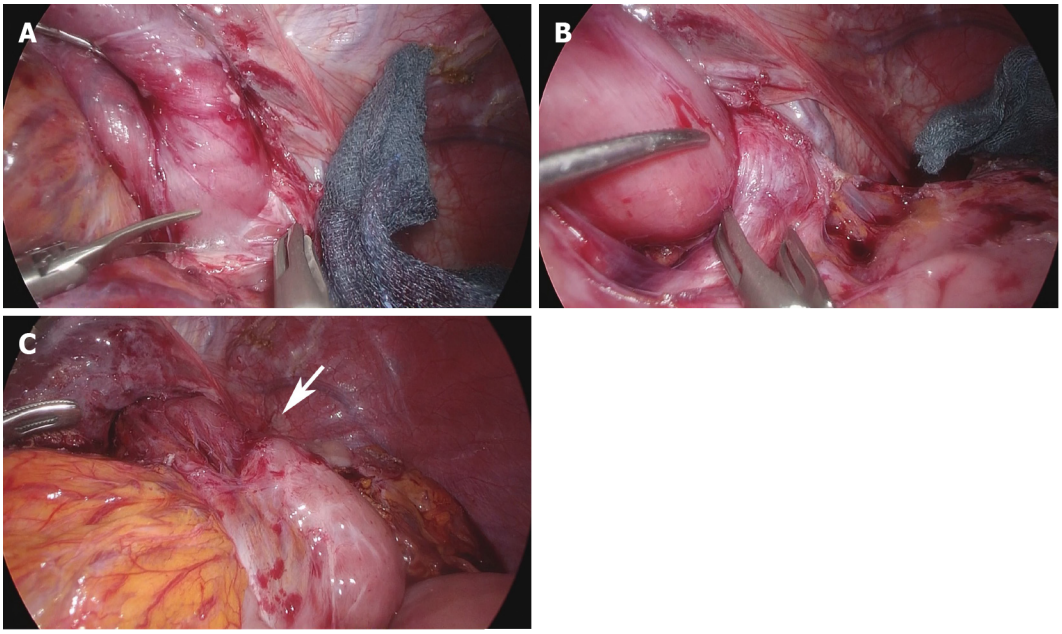


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Figure 2 Stricture of the jejunal limb during reoperation in case 5. A: Fibrous adhesions are observed around the hiatus; B: Loose adhesions are present on the left crus; C: A pressure mark (white arrow) is identified on the jejunal limb after completion of adhesiolysis up to the anastomosis.

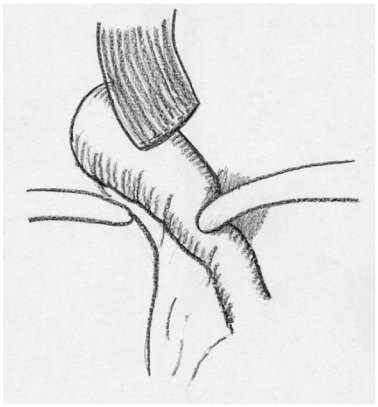

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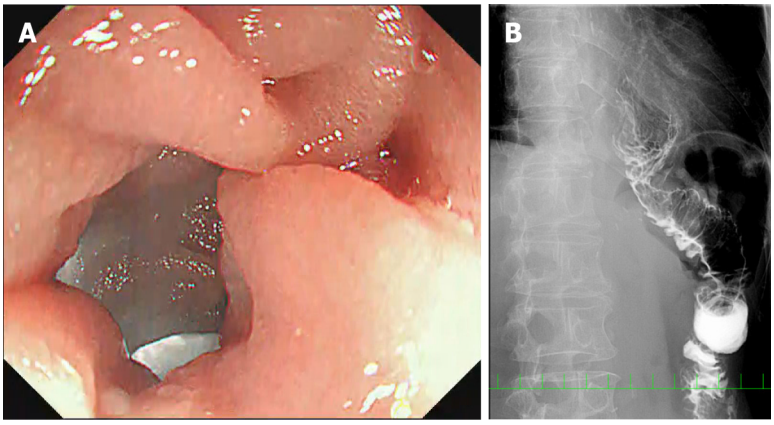
Figure 3 Schema of the complicated disorder after overlapped esophagojejunostomy following laparoscopic total gastrectomy. The jejunal limb stricture was resulted from the shortened remnant esophagus and jejunal bending resulting from loose and fibrous adhesions on the left crus at the esophageal hiatus.

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



DOI: 10.4240/wjgs.v14.i11.1285

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.

Institutional review board statement: This study was approved by the Institutional Review Board of Saga University Hospital (Approval No. 2020-05-R-02).

Informed consent statement: Informed written consent was obtained from the patient and her family for publication of this report and any accompanying images.

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

Data sharing statement: No additional data are available.

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

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S-Editor: Liu GL
L-Editor: A
P-Editor: Liu GL

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2022 November 27; 14(11): 1297-1309

DOI: 10.4240/wjgs.v14.i11.1297

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Observational Study

Development of a warning score for early detection of colorectal anastomotic leakage: Hype or hope?

Nuno J G Rama, Óscar Lourenço, Patrícia C Motta Lima, Maria Pedro S Guarino, Diana Parente, Ricardo Castro, Ana Bento, Anabela Rocha, Fernando Castro-Poças, João Pimentel

Specialty type: Surgery

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Brisinda G, Italy; Gao W, China

Received: September 12, 2022
Peer-review started: September 12, 2022
First decision: October 3, 2022
Revised: September 22, 2022
Accepted: October 27, 2022
Article in press: October 27, 2022
Published online: November 27, 2022

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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.

Citation: Rama NJG, Lourenço Ó, Motta Lima PC, Guarino MPS, Parente D, Castro R, Bento A, Rocha A, Castro-Poças F, Pimentel J. Development of a warning score for early detection of colorectal anastomotic leakage: Hype or hope? *World J Gastrointest Surg* 2022; 14(11): 1297-1309
URL: https://www.wjgnet.com/1948-9366/full/v14/i11/1297.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i11.1297

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).

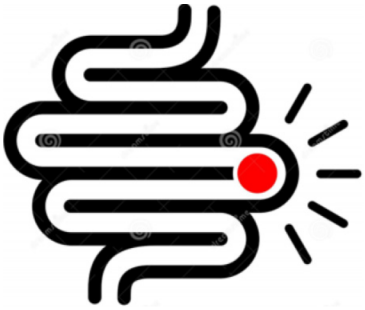

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Figure 1 Early ColoRectAL Leakage score logotype.

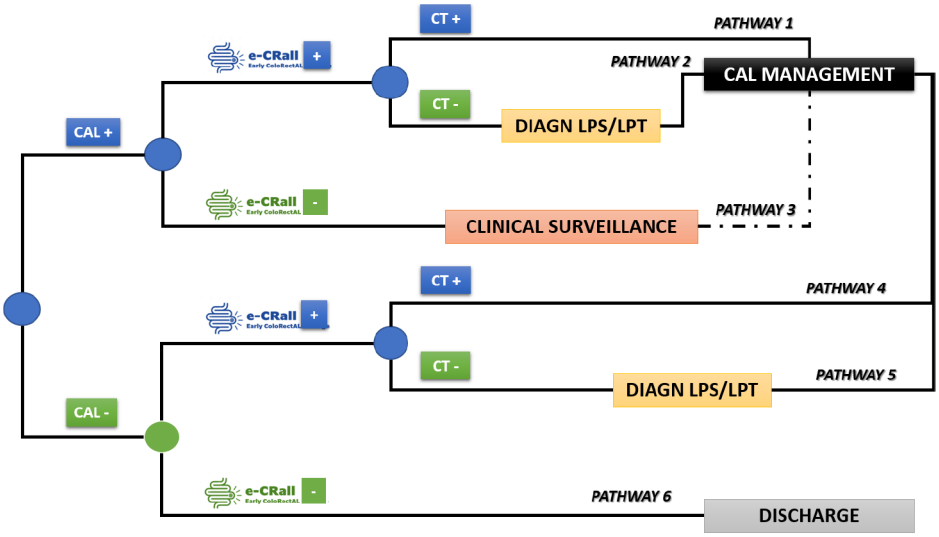

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Figure 2 The decision tree model scenario with adoption of the Early ColoRectAL Leakage score, considering postoperative days 3, 4, or 5 independently). CAL: Colorectal anastomotic leakage; CT: Computed tomography; Diagn: Diagnosis; E-CRALL: Early 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

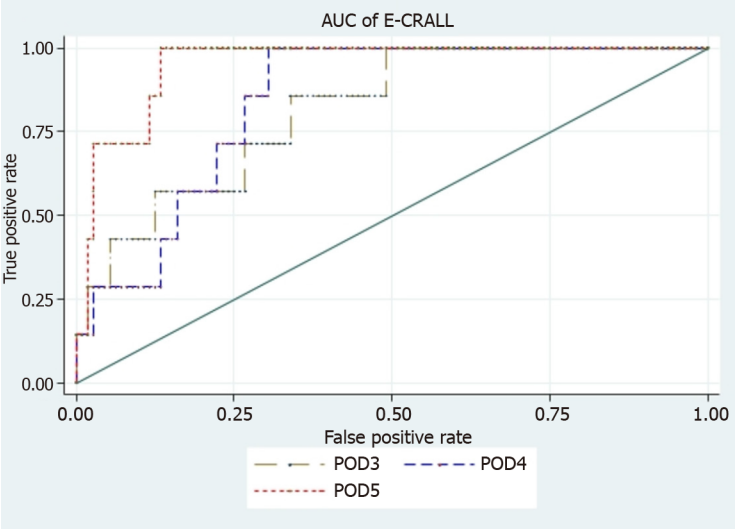
Cost	Non-CAL patients	CAL patients	All patients
E-CRALL score costs, € (%)	722277.79 (77.9)	204422.00 (22.1)	926699.79
Standard practice costs, € (%)	1143720.00 (82.9)	236496.00 (17.1)	1380216.00
Cost savings, € (%)	421442.20 (92.9)	32074.00 (7.1)	453516.20

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,



DOI: 10.4240/wjgs.v14.i11.1297

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.

Supported by the Ministry of Health – Incentive Program for the Integration of Care and Valuation of Patients' Pathways in the National Health Service of Portugal.

Institutional review board statement: This study was conducted in accordance with the Declaration of Helsinki and was approved by the Local Ethical Committee of the Colorectal Referral Centre, after authorization obtained from the Portuguese Data Protection Authority.

Informed consent statement: Informed consent was obtained from all participants included in the study.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Data sharing statement: For additional data, Dr. Nuno Rama can be contacted by e-mail at ramanuno@gmail.com.

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.

Country/Territory of origin: Portugal

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2022 November 27; 14(11): 1310-1319

DOI: 10.4240/wjgs.v14.i11.1310

ISSN 1948-9366 (online)

CASE REPORT

Preoperative blood circulation modification prior to pancreaticoduodenectomy in patients with celiac trunk occlusion: Two case reports

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Specialty type: Surgery

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Chiu CC, Taiwan; Zhao K, China

Received: July 15, 2022
Peer-review started: July 15, 2022
First decision: September 12, 2022
Revised: September 24, 2022
Accepted: October 19, 2022
Article in press: October 19, 2022
Published online: November 27, 2022

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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.

Citation: Colella M, Mishima K, Wakabayashi T, Fujiyama Y, Al-Omari MA, Wakabayashi G. Preoperative blood circulation modification prior to pancreaticoduodenectomy in patients with celiac trunk occlusion: Two case reports. *World J Gastrointest Surg* 2022; 14(11): 1310-1319
URL: https://www.wjgnet.com/1948-9366/full/v14/i11/1310.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i11.1310

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.

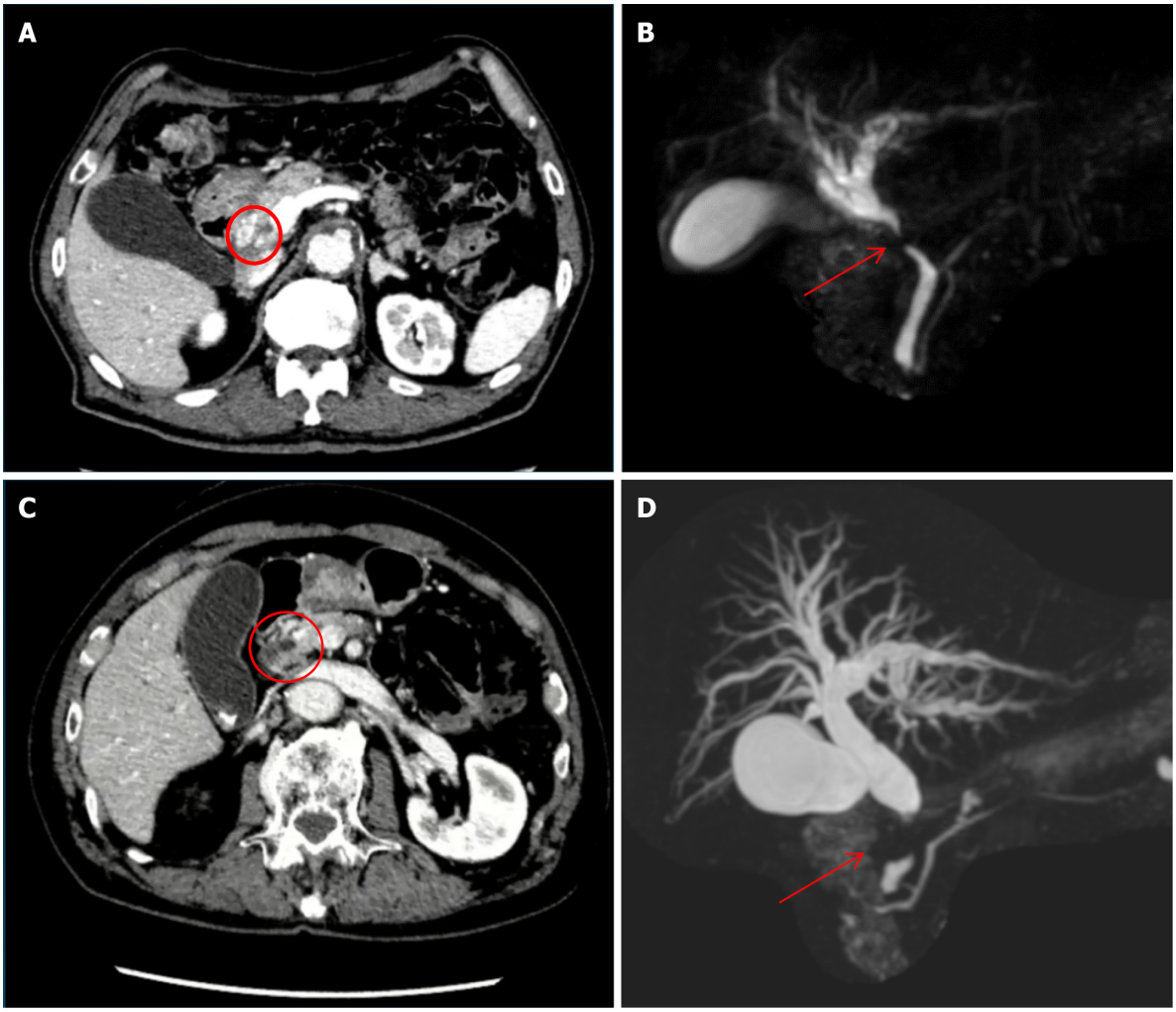
Distal cholangiocarcinoma was suspected following magnetic resonance cholangiopancreatography (MRCP), which revealed a stricture of the extrahepatic bile duct and mild dilatation of the intrahepatic bile duct (Figure 1A and B). An ERCP with brushing cytology was performed to confirm the diagnosis, and 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.



DOI: 10.4240/wjgs.v14.i11.1310

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.

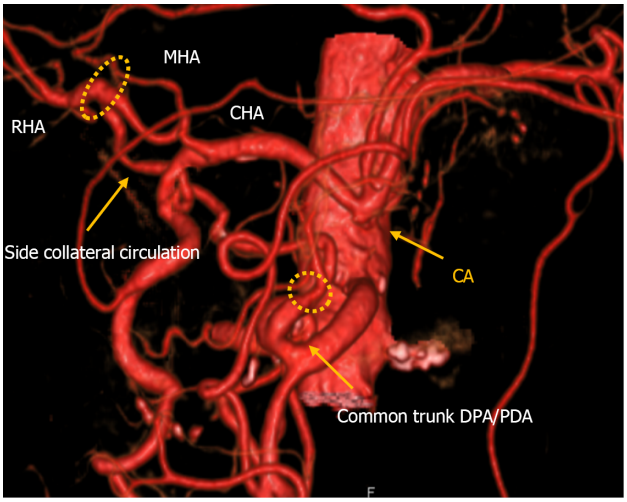


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Figure 2 Computed tomography with 3D reconstruction of the vascular anatomy in case 1. Computed tomography showed a right hepatic artery (RHA) and middle hepatic artery originating from the common hepatic artery, the usual pancreaticoduodenal arcade 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.

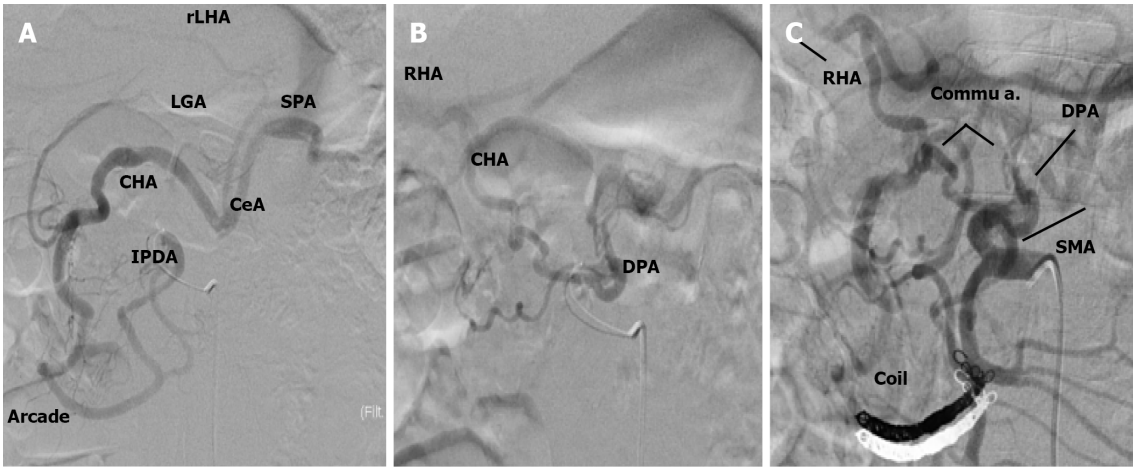

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Figure 3 Angiographic study. A: The inferior pancreaticoduodenal artery was responsible for the main back flow to the celiac artery; B: The dorsal pancreatic artery (DPA) was responsible for the blood flow of the right hepatic artery; C: Blood re-flow 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

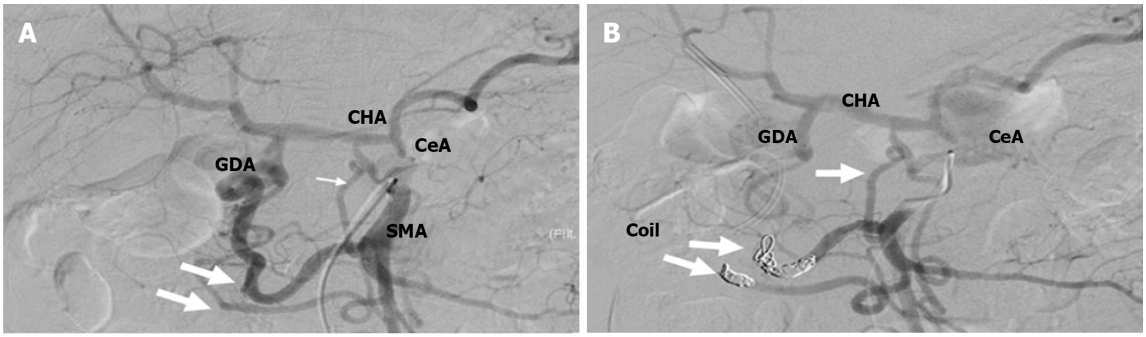
Case 1

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.



DOI: 10.4240/wjgs.v14.i11.1310

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

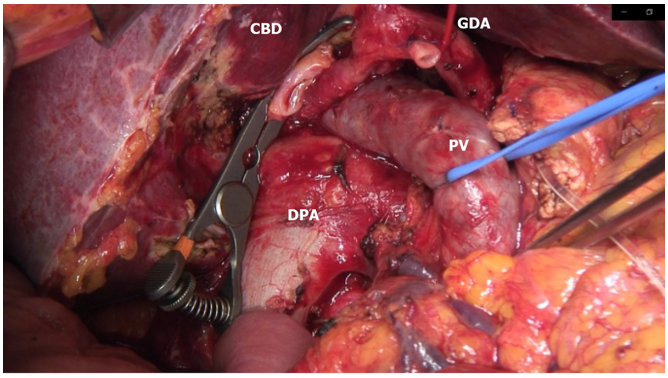
Postoperatively, the patient developed pneumonia, pulmonary embolism, and delayed gastric emptying but did not show any major surgical complications and was discharged on POD 41. No evidence of recurrence was observed at the 3-year follow-up.

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



DOI: 10.4240/wjgs.v14.i11.1310

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

Author contributions: Colella M and Mishima K wrote the manuscript; Mishima K treated the patients; Wakabayashi G, Wakabayashi T, Fujiyama Y, and Alomari M critically reviewed the manuscript; all authors read and approved the final manuscript.

Informed consent statement: Informed written consent was obtained from the patients for the publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: Japan

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S-Editor: Chen YL
L-Editor: Wang TQ
P-Editor: Chen YL

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