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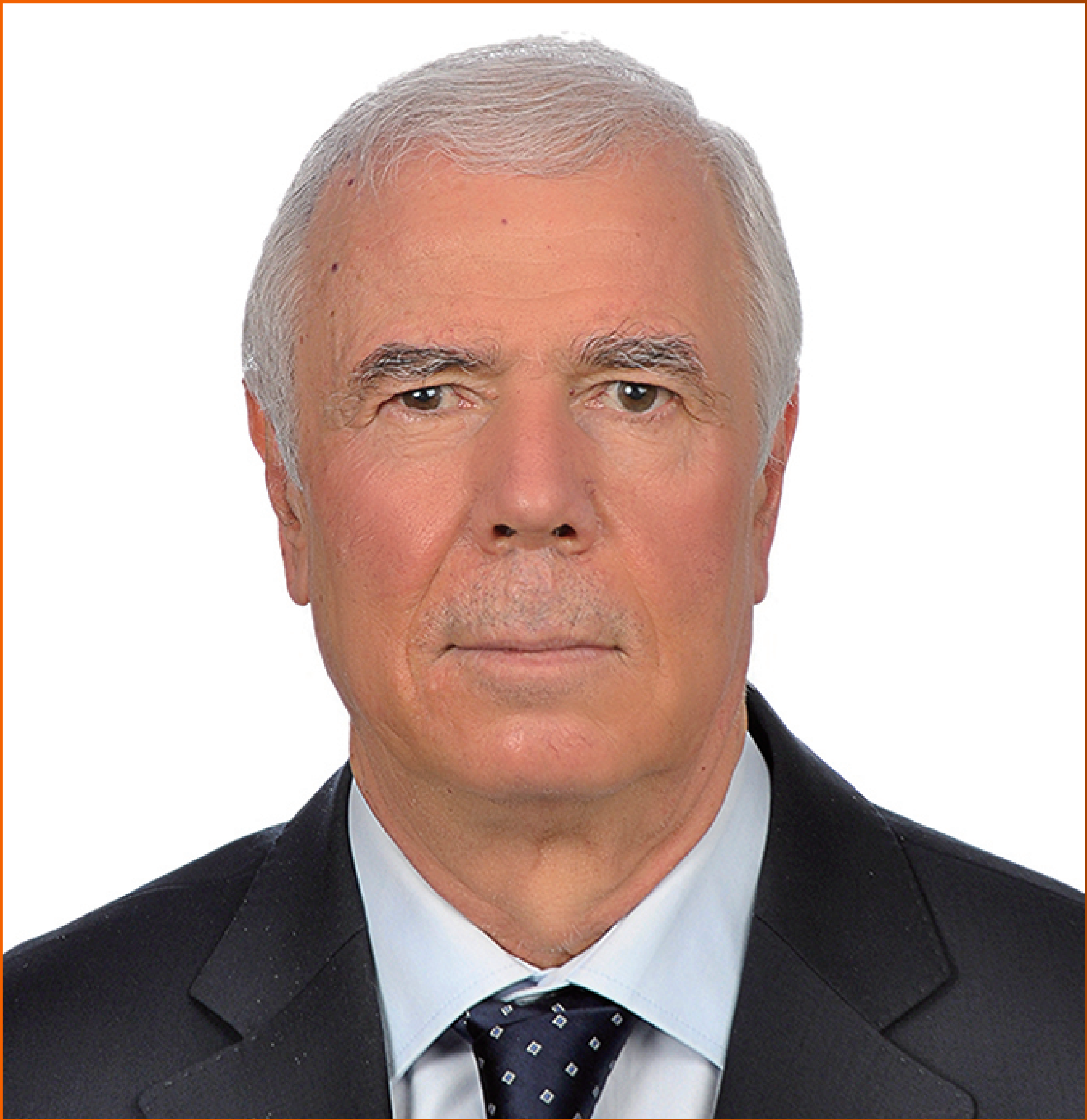

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The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research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

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https://www.wjgnet.com/bpg/GerInfo/287

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https://www.wjgnet.com/bpg/gerinfo/240

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https://www.wjgnet.com/bpg/gerinfo/208

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REVIEW

Acute appendicitis–advances and controversies

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Abstract

Being one of the most common causes of the acute abdomen, acute appendicitis (AA) forms the bread and butter of any general surgeon's practice. With the recent advancements in AA's management, much controversy in diagnostic algorithms, possible differential diagnoses, and weighing the management options has been generated, with no absolute consensus in the literature. Since Alvarado described his eponymous clinical scoring system in 1986 to stratify AA risk, there has been a burgeoning of additional scores for guiding downstream management and mortality assessment. Furthermore, advancing literature on the role of antibiotics, variations in appendicectomy, and its adjuncts have expanded the surgeon's repertoire of management options. Owing to the varied presentation, diagnostic tools, and management of AA have also been proposed in special groups such as pregnant patients, the elderly, and the immunocompromised. This article seeks to raise the critical debates about what is currently known about the above aspects of AA and explore the latest controversies in the field. Considering the ever-evolving coronavirus disease 2019 situation worldwide, we also discuss the pandemic's repercussions on patients and how surgeons' practices have evolved in the context of AA.

Key Words: Appendicitis; Diagnosis; Management; COVID-19; Controversy; Advances

Core Tip: Many controversies exist for the management of acute appendicitis (AA). Imaging modalities complement the clinical examination in AA diagnosis. Various imaging features of different imaging modalities should be considered to reduce diagnostic inaccuracies. Various diagnostic scoring systems augment clinical

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judgment, but uncertainty exists about the best score. Non-operative management of both uncomplicated and complicated AA is possible and reasonable, especially during the coronavirus disease 2019 pandemic. Intra-operative techniques of securing the base of the appendix stump *via* suture, clips, or stapling devices are all debated for superiority. Adjuncts and novel treatment ideas using endoscopic retrograde appendicitis therapy are emerging.

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INTRODUCTION

Acute appendicitis (AA) is a commonly encountered surgical emergency at all levels of seniority and across different specialties. First described by Fitz[1] in 1886, it is characterized by inflammation of the vermiform appendix. Treves[2] is credited as the first to treat AA in 1902. AA occurs when there is obstruction of the appendiceal orifice (such as lymphoid hyperplasia or fecaliths), resulting in inflammation. This causes progressive distension of the appendix, eventually leading to vascular compromise, allowing the growth of pathogenic microorganisms[3]. Left untreated, this culminates in the perforation of the appendix with a localized abscess or generalized peritonitis.

The diagnosis and management of AA have not changed radically over the years despite advances in imaging and technology and an improved understanding of sepsis. To consolidate these advancements, we set out to review current literature to reassess relevant issues in the diagnosis and management of AA, including the impact of the coronavirus disease 2019 (COVID-19) pandemic on previously accepted protocols.

LITERATURE SEARCH

A search of relevant articles on PubMed, OVID/MEDLINE, and Web of Science was conducted on 6 May 2021 for literature published in English by Teng TZJ, Thong XR, and Lau KY. Disagreements were resolved by mutual discussions and consensus with senior authors Balasubramaniam S and Shelat VG. The following terms were used, and relevant articles were considered: [“appendicitis” (MeSH Terms)/etiology, surgery, therapy, “appendectomy” (MeSH Terms), “diagnosis” or “differential”, “Guidelines”]. Results were screened by title, and relevant articles were obtained in full text for review. We present our findings as a narrative review covering current practices and advancements in appendicitis diagnosis, followed by management, differentials, histological variations, and finally, surgical variations in AA management

DIAGNOSIS AND CLASSIFICATION

The diagnosis of AA has historically been based on clinical judgment, though imaging is increasingly common where resources permit. The classic sequence of periumbilical pain radiating to the right iliac fossa (RIF), nausea or vomiting, and fever is Murphy's syndrome. Many clinical signs, such as Blumberg's sign (rebound tenderness), Rovsing's sign (RIF pain on left iliac fossa palpation), or the Psoas sign (pain upon right hip flexion suggesting retrocecal appendicitis) are described to augment diagnosis of AA. Clinical diagnosis is not absolute. Therefore, scoring systems combining clinical signs with serum markers of inflammation are widely advocated.

CLINICAL SCORING SYSTEMS

Scoring systems combine information from multiple sources to increase accuracy. Each score has its own merits and demerits discussed in Table 1[4-20]. The mere existence of so many systems endorses that none is perfect. The Alvarado score is widely cited and adopted in routine clinical care. However, the Alvarado score lacks specificity and is not widely validated in Asian populations. The Raja Isteri Pengiran Anak Saleha (RIPASA) scoring system was developed explicitly for the Asian population. Frountzas *et al*[17]'s meta-analysis comparing RIPASA and Alvarado reported higher accuracy for RIPASA score [area under the curve (AUC) 0.9431 *vs* 0.7944][17]. According to a retrospective study, including pregnant and non-pregnant female patients by Mantoglu *et al*[21], the RIPASA score was most helpful in pregnant patients (highest AUC at 0.806)[21]. In a trial involving 3878 patients, Andersson *et al* [5] noted the Appendicitis Inflammatory Response (AIR) score to have high sensitivity for complicated appendicitis[5]. As the AIR score more correctly identifies those with a high likelihood of appendicitis in whom supplemental imaging is unlikely to change management, AIR helps guide patient triaging for imaging. Sammalkorpi *et al*[6] compared the Adult Appendicitis Score (AAS) performance to the Alvarado and AIR scores in a prospective study of 829 patients. They reported that AAS had the highest AUC (0.882, 95%CI: 0.858-0.906)[6]. AAS is not widely validated. There are many other scoring systems, such as the Ohmann score, the Lintula score, the Tsanakis score, and the Fenyo-Lindburg score[22-27]. Validation studies for each scoring system are few. Ohmann's score differentiated innocent appendices from phlegmonous ones and phlegmonous from gangrenous appendices[22]. The Lintula score was developed for use in the pediatric population[28]. The Lintula score is advantageous in resource-limited settings, as no laboratory parameters are required. Tzanakis score includes the ultrasound scan (US), which can is validated in pregnant patients. Due to inter-observer variability for US scans, the scoring is not objective[29].

As most scoring systems are generated from retrospective data, a scoring system derived from prospective medical records may be more accurate, especially if it is derived from multiple hospitals. The World Society of Emergency Surgery (WSES) made such an attempt. Complicated intra-abdominal infections (cIAIs) are defined as abdominal infections that extend beyond organs, causing localized or diffused peritonitis. The WSES Sepsis Severity Score predicts mortality in patients with cIAIs, including AA. In a prospective multi-center validation study including 4533 patients from 132 hospitals, Sartelli *et al*[25] reported that the WSES sepsis severity score cut-off of 5.5 helps differentiate survivors from non-survivors (sensitivity 89.2%, specificity 83.5%)[25]. WSES sepsis severity score needs validation in AA patients. The systemic inflammatory response syndrome (SIRS) criteria are validated in the management of AA. In a single-center prospective study including 268 patients, Beltrán *et al*[26] reported that a longer interval between symptom onset and surgery was significantly correlated with a higher SIRS score and an increased rate of perforated appendicitis [26]. The perforation rate for patients rose from 7% for those operated on within 24 h to as high as 85% among those operated on after 73 h. This reinforces the fact that untreated AA worsens with time and supports the utility of SIRS in determining the urgency of surgical intervention. The SIRS score can be used as an adjunct in deciding between surgical and conservative antibiotic management. In a retrospective study including 125 patients, Nozoe *et al*[27] reported that the SIRS score was lower in patients who were recommended non-operative management (NOM)[27]. Similarly, diverticular disease of the appendix (DDA) is associated with a higher perforation rate, and Chia *et al*[30] have shown that a high SIRS score is useful in clinical decision making for surgery in DDA[30]. The total white blood cell count is a non-specific biochemical marker, and novel markers may improve the performance of scoring systems. The relationship between biochemical markers [C-reactive protein (CRP), leukocyte count, procalcitonin, bilirubin] and AA has been extensively studied, either as part of clinical scores mentioned above or as standalone diagnostic predictors. The appendistat™ scoring system uses biochemical parameters to differentiate uncomplicated from complicated AA. In a validation study, Birben *et al*[31] reported that CRP was adequate to differentiate uncomplicated from complicated AA[31]. In a prospective study involving 544 patients, Körner *et al*[32] noted that perforation was more likely when CRP concentration > 50 U/L (OR 4.6, 95%CI: 2.44-8.75)[32]. Birben *et al*[31] also reported that a high total bilirubin level at 0.75 mg/dL could diagnose AA even if leukocyte levels were normal[31]. In a meta-analysis of seven studies and 1011 patients by Yu *et al*[33], CRP had the best discriminative capability in diagnosing AA [33]. Although not helpful in diagnosing AA, procalcitonin has a high positive likelihood ratio in identifying complicated AA. Thus, different scoring systems serve

Table 1 Various scoring systems for acute appendicitis

Scoring system	Patient features	Clinical features	Laboratory/imaging features	Sensitivity	Specificity	Risk strata/recommended action
Alvarado	-	RIF tenderness (2); Elevated temperature (1); Rebound tenderness (1); Migration of pain to RIF (1); Anorexia (1); Nausea or vomiting (1)	Leucocytosis (2); Leukocyte left shift (1)	94.1%	90.4%	1-4: Discharge; 5-6: Admit and observe; 7-10: Surgery
AIR	-	Elevated temperature (1); Rebound tenderness: Light (1), medium (2), strong (3); RIF pain (1); Vomiting (1)	Leucocytosis, × 10^9/L: 10-14.9 (1); ≥ 15 (2); Polymorphonuclear leucocytosis, %: 70-84 (1); ≥ 85 (2); CRP level, mg/L: 10-49 (1); ≥ 50 (2)	97%		0-4: Outpatient follow-up; 5-8: Admit and observe; 9-12: Surgery
AAS	-	RIF tenderness: Women 16-49 yr (1); all other patients (3); Migration of pain (2); RIF pain (2); Guarding: Mild (2); moderate or severe (4)	Leucocytosis, × 10^9/L: ≥ 7.2 and < 10.9 (1); ≥ 10.9 and < 14.0 (2); ≥ 14.0 (3). Neutrophilia, %: ≥ 62 and < 75 (2); ≥ 75 and < 83 (3); ≥ 83 (4). CRP level, mg/L and symptoms < 24 h: ≥ 4 and < 11 (2); ≥ 11 and < 25 (3); ≥ 25 and < 83 (5); ≥ 83 (1). CRP level, mg/L and symptoms > 24 h: ≥ 12 and < 53 (2); ≥ 53 and < 152 (2); ≥ 152 (1)			1-10: Discharge without imaging; 11-15: Imaging; ≥ 16: Surgery
RIPASA	Age: < 40 (1); Age > 40 (0.5). Gender: Male (1); female (0.5). Foreign nationality registration identity card (1)	RIF tenderness (1); Elevated temperature (1); Rebound tenderness (1); Migration of pain to RIF (0.5); Anorexia (1); Nausea or vomiting (1); RIF pain (0.5); Duration of symptoms: < 48 h (1); > 48 h (0.5); Guarding (2); Rovsing sign (2)	Leucocytosis (1); Negative urine analysis (1)	91.67%	93.18%	-
Ohmann	Age < 50 (1.5)	RIF tenderness (4.5); Rebound tenderness (2.5); Migration of pain (1); No micturition difficulties (2.0); Steady pain (2); Rigidity (1)	Leucocytosis (1.5)	98.1% at cut-off score 9; 82.9% at cut-off score 13	94% at cut-off score 12	< 6: Low risk; 6-11.5: Monitoring; ≥ 12: Surgery
Lintula	Gender: Male (2); female (0)	Elevated temperature (3); Rebound tenderness (7); Migration of pain (4); Vomiting (2); RIF pain (4); Guarding (4); Pain intensity: severe (2); mild or moderate (0); Bowel sounds absent, tinkling or high-pitched (4)	-	79.0% at cut-off score 21	58.3% at cut-off score 21	≤ 15: Discharge; 16-20: Monitoring; ≥ 21: Surgery
Tzanakis	-	RIF tenderness (4); Rebound tenderness (3)	Leucocytosis (2); US imaging showing appendiceal inflammation (6)			0-4: Discharge; 5-7: Monitoring; 8-15: Surgery
Fenyo-Lindberg	Gender: Male (8); female (-8)	Rebound tenderness: Yes (5); no (-10); migration of pain to RIF: Yes (7); no (-9); Vomiting: Yes (7); no (-5); Duration of pain: < 24 h (3); > 48 h (-12); Progression of pain: Yes (3); no (-4); Aggravation with cough: Yes (4); no (-11); Rigidity: Yes (15); no (-4); Pain outside RIF: Yes (-6); no (4)	Leucocytosis, × 10^9/L: < 8.9 (-15); 9-13.9 (2); > 14 (10)	In a cross-sectional study including 100 patients with RIF pain, Sahu reported a sensitivity of 72% and specificity of 71%		≤ -17: Non-specific abdominal pain; ≥ -2: AA likely
Modified Alvarado Score	-	RIF tenderness (2); Elevated temperature (1); Rebound tenderness (1); Migration of pain to RIF (1); Anorexia (1); Nausea or vomiting (1)	Leucocytosis (2)			< 5: Surgery not required; 5-6: Monitor; 7-9: Surgery indicated
Christian	-	RIF tenderness (1); Elevated temperature (1); Vomiting (1); Abdominal pain (1)	Polymorphonuclear leucocytosis (1)			< 4: Monitoring; ≥ 4: Surgery

van den Broek *et al*[14]	Gender: Male (2)	Elevated temperature (1); Rebound tenderness (2); Duration of symptoms ≤ 48 h (1)	Leucocytosis (3)	0-3: Observe; 4-6: Diagnostic laparoscopy
Simplified Appendicitis Score	-	RIF tenderness (1); Elevated temperature (1); Rebound tenderness (1); Migration of pain to RIF (1)	Leucocytosis (1)	< 4: AA excluded with 90.1% sensitivity; ≥ 6: AA included with 91.7% specificity

RIF: Right iliac fossa; CRP: C-reactive protein; US: Ultrasound; AIR: Appendicitis inflammatory response; RIPASA: Raja Isteri Pengiran Anak Saleha.

to aid diagnostic accuracy, triage for imaging, differentiate complicated from uncomplicated AA, determine the timing of surgical intervention, and predict morbidity outcomes. No one-size-fits-all, so prudence is required if a scoring system is used to guide bed-side decisions.

INTERNATIONAL GUIDELINES

The European Association of Endoscopic Surgery (EAES) recommended a diagnostic algorithm in 2016. It risk stratifies patients into three main groups based on clinical scoring. Low-risk patients can be discharged following work-up for other possible causes. Moderate risk patients first undergo US, with computed tomography (CT) being recommended as a second-level diagnostic study only for those with inconclusive US results[34]. The EAES algorithm features only the Alvarado score as the initial risk stratification tool but differs from the original authors in that it follows Ebell and Shinholser[4]'s recommended cut-off of < 4 for differentiating low-risk AA.

In 2018, the American Academy of Family Physicians published their clinical recommendations on the efficient diagnosis and management of AA[35]. Some key recommendations for AA diagnosis include the use of Alvarado, Pediatric Appendicitis Score or AIR, and US as a front-line diagnostic sieve to reduce CT use. Unlike in EAES' guidelines, CT with IV or oral contrast or magnetic resonance imaging (MRI) is recommended for patients with negative (in addition to intermediate) US findings and high clinical suspicion to account for US' lower sensitivity.

The 2020 WSES algorithm recommends using either the Alvarado, AIR, or AAS systems to classify low, moderate, and high-risk AA patients. This algorithm differs from EAES by using the original < 5 cut-off for low-risk AA based on the Alvarado score. WSES applies a graded imaging strategy with US as the first-line imaging choice like the above two guidelines. Low-risk patients can be discharged as appropriate or worked up for other causes of abdominal pain[36]. Moderate-risk patients are recommended to undergo an US, proceeding to CT or MRI only if the US is equivocal or negative, but the patient fails to respond to treatment. Whether CT or US should be used as second-line imaging after the US for pediatric patients is mainly dependent on local resources[36]. High-risk patients may proceed for surgery without further imaging.

IMAGING STUDIES

Imaging is widely accessible and has become integral to AA's management–as an adjunct to confirm the diagnosis, rule out differential diagnoses, or assist surgical planning. Free air under the diaphragm on erect chest radiograph is rare in patients with perforated AA[37]. The plain abdominal radiograph showing an appendicolith, right lower quadrant soft tissue mass or extraluminal air, and psoas margin concealment is of historical interest[38]. As such, radiographs have a minimal role in AA diagnosis. Figure 1 illustrates the key imaging features of the US scan, CT scan, and MRI scan[39-44].

US scan and CT scan

Although CT scans having higher sensitivity in diagnosis[45], WSES and EAES guidelines recommend the US scan as the first line and reserve CT scan in patients with inconclusive US findings. Such a strategy increases cost-effectiveness and reduces radiation exposure. CT scan may be a more appropriate first-line investigation in overweight or elderly patients. In a prospective cohort study of 106 patients with suspected AA, Keller *et al*[46] reported that the US scan was five times more likely to be non-diagnostic in overweight patients[46]. Similarly, Sauvain *et al*[39] reported that the US scan was seven times more likely to be inconclusive in patients with a body mass index (BMI) > 25 kg/m^2[39]. In a retrospective study including 105 patients, Pelin *et al*[40] reported that CT scan was more accurate in patients with high BMI [26.7 ± 4.3 (mean ± SD) kg/m^2] and increased age [31 ± 14 (mean ± SD) years], possibly because of higher rates of complicated appendicitis[40]. This is consistent with the American College of Radiology Appropriateness Criteria's call for a lower threshold for CT imaging in elderly patients with RIF pain[41].

Intravenous contrasted CT scan enhances appendiceal wall thickening and aids AA diagnosis[38]. Per-rectal contrast does not increase diagnostic accuracy and is unnecessary[42]. Recently, there has been interest in low-dose CT scans that reduce radiation exposure without compromising diagnostic accuracy or impact on normal appendectomy rates (NARs). Randomized controlled studies and meta-analyses have shown that the low-dose protocol's diagnostic accuracy was non–inferior[43].

The role of CT scans in the evaluation of the complications of AA is well established. In particular, CT accurately detects periappendiceal abscess, peritonitis, and gangrenous changes[44]. CT scan findings of appendix mass, asymmetric wall abnormality, and diameter > 15 mm can also accurately detect concomitant appendiceal neoplasm[47]. Appendiceal mucocele, defined as a dilated mucin-filled appendix, can also be diagnosed *via* CT scan, with a luminal diameter > 1.3 cm having 88.2% accuracy in diagnosing a mucocele[48]. CT scan also aids in diagnosing complications such as portal vein thrombosis[49], pyogenic liver abscesss[50], and pylephlebitis[51]. Hence, imaging modalities in AA are not restricted to purely diagnostic purposes but serve prognostic utility.

MRI scan

MRI is a reasonable alternative to CT in diagnosing AA and confers the advantage of avoiding ionizing radiation and intravenous contrast in the investigation of pregnant and pediatric patients. Unfortunately, the cost and logistics involved in MRI mean it is usually not used as a first-line modality except in children[52] and pregnant women [53]. A meta-analysis of 11 studies has reported that an MRI scan improves diagnostic accuracy, reduces time to appendectomy, NAR, and aids in alternative diagnosis. Other considerations for children include an incomplete MRI due to fear from claustrophobia, staying still, and noise emitted from MRI. These concerns can be addressed with child and parental counseling or sedation[54].

Severity grading by imaging studies

In addition to diagnosis, imaging also assists in the severity grading of AA. With the increasing adoption of NOM of AA, it is essential to distinguish between complicated and uncomplicated AA. In a retrospective study of 223 patients, Rybkin and Thoeni [55] reported that retroperitoneal inflammatory changes predicted complicated AA (pars plana vitrectomy 0.64-0.92 for patients above 16-years)[55]. Imaging has also been shown to play a role in scoring systems, as previously mentioned, such as the

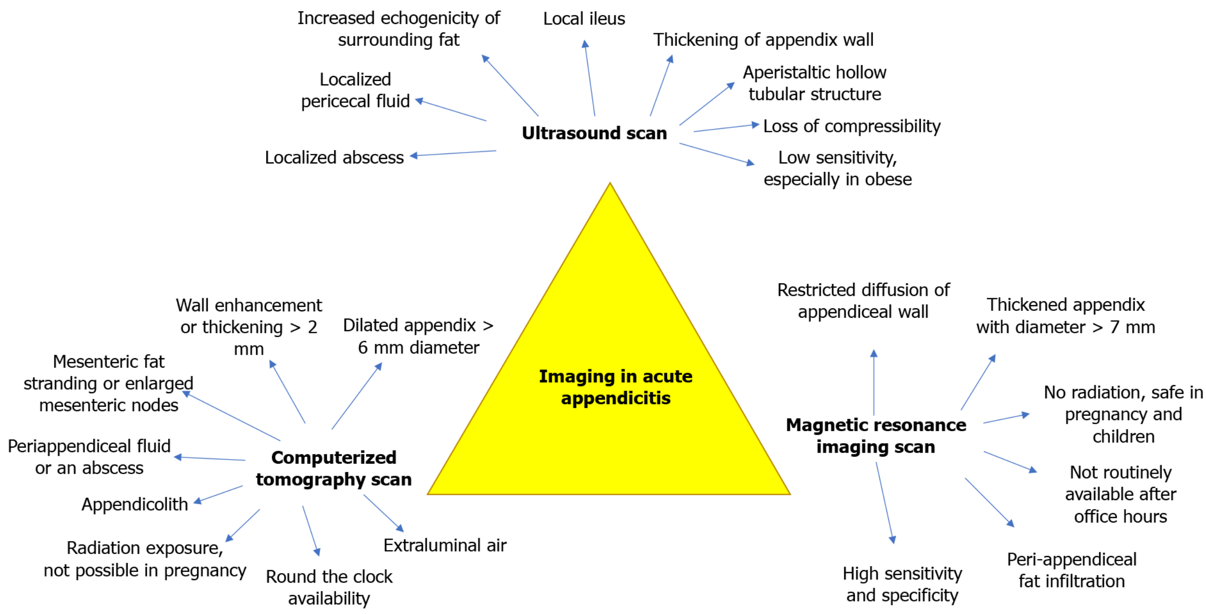

Figure 1 The key imaging features of the ultrasound scan, computed tomography scan, and magnetic resonance imaging scan.

Tzanakis scoring system[10]. A positive US finding of AA such as periappendiceal fluid, localized abscess, appendicolith, wall thickness, and other findings[56] yielded 6 out of the 15 points in the score, where a score of 8 and above is suggestive of AA.

Use of imaging across countries

Imaging improves diagnostic accuracy at a financial cost. Patients from lower-income countries may not have accessibility and affordability to CT scans and MRI scans. Management of AA in different countries revealed that CT scans were done more liberally in accordance with the countries' income level[36]. Within a country itself, there are discrepancies on which modality of imaging to consider first as well. This may be due to the proportion of special populations in the country (obese, children, pregnant women), the logistical constraints of the hospital (primary *vs* tertiary hospital) as well as the availability of radiologists' opinion (working hours, overnight shifts, public holidays)[57]. While prudence needs to be exercised to request imaging to aid AA diagnosis, a refusal or rejection of imaging request on the pretext of "appendicitis is a clinical diagnosis, and please do appendicectomy if clinically you feel so" or "do a serial examination and it will reveal itself over next few days" *etc.* from radiology colleagues is unacceptable. In our experience, liberal imaging policy is associated with low NAR. In a local audit of 2603 appendectomy patients, NAR was 3.34% (n = 87)[58]. The unmet need remains the lack of uniform standardized criteria that define imaging diagnosis of AA. In particular, the imaging features of the prominent or dilated appendix can be subjective and international collaboration is needed to define thresholds for AA imaging diagnosis.

DECISION TREE ANALYSIS

A decision tree (DT) analysis model is a tree-shaped graphical representation derived from empirical data to chart out a statistical probability outcome. In the setting of ambiguous CT scan findings, Kang *et al*[59] compared the diagnostic accuracy of various clinical scoring systems with DT analysis. DT analysis based on rebound tenderness severity, pain migration, urinalysis, symptom duration, leukocytosis, neutrophil levels, and CRP was more accurate (receiver operating characteristic and AUC 0.85) as compared to the Alvarado score (AUC 0.695), the Eskelinen score (AUC 0.715), and the AAS (AUC 0.749)[59]. In a study by Akmese *et al*[60] involving 595 clinical records, a boosted tree algorithm based on demographic data and serum biochemistry had predicted surgery necessity with 95.3% accuracy[60]. However, due to the retrospective nature, the subjective clinical judgment of the surgeon could influence the results. Evidence is emerging, and machine learning algorithms will have an increasing role in decision-making in AA management.

DIAGNOSTIC DILEMMA

No report on AA is complete without mentioning the common diagnostic pitfalls and possible differential diagnoses. Imaging is integral not only to establish a diagnosis but also to rule out another diagnosis. These include right colonic diverticulitis[30,61-63], *Yersinia* enterocolitis[64,65], right-sided renal disease[66], mesenteric lymphadenitis [67] and Meckel's Diverticulitis[68,69]. The meta-analysis investigating the role of MRI scan in pediatric AA reported that alternative diagnosis was present in about 20% of patients, most common being adnexal cyst and enteritis/colitis[61]. Various scoring systems, serum, and imaging biomarkers have improved diagnostic accuracy, and diagnostic dilemmas are uncommon. With the advent of minimal access surgery, the adage of "when in doubt, open and see" is replaced with "when in doubt, do a scan" or "when in doubt, look (diagnostic laparoscopy) and see."

MANAGEMENT OF APPENDICITIS

It is essential to distinguish between complicated and uncomplicated AA as it impacts management. Complicated AA typically includes perforation with peritonitis, phlegmon, or abscess formation, making up 2%-10% of all AA cases[70]. A phlegmon is described as an inflammatory mass including the inflamed adjacent viscera and greater omentum, while an abscess is described as a pus-containing appendiceal mass [71]. Appendicitis in the absence of these is defined as uncomplicated. Appendectomy (open or laparoscopic) is the standard of care for AA. However, recent evidence suggests that antibiotics alone may be adequate in selected patients–NOM. The classic description of NOM principles by Ochsner-Sherren relates to complicated AA-a patient with RIF mass. Currently, NOM is described both in uncomplicated and complicated AA[72].

NOM

In a meta-analysis including five studies and 1116 patients, Sallinen *et al*[73] reported lower rates of complications with NOM. However, the authors reported an increased incidence of recurrence of AA at one year and longer hospital stay[73]. Surgical intervention has higher treatment efficacy and a shorter length of stay than antibiotic treatment[74]. However, heterogeneity in antibiotic choice, dose and duration, inclusion and exclusion criteria, and other confounding variables could impact the results. In a retrospective cohort study of 81 uncomplicated AA patients, Loftus *et al* [75] reported NOM was more successful if patients had a longer duration of symptoms before admission, a lower temperature within 6 h of admission, lower modified Alvarado score, and a smaller appendiceal diameter[75]. Studies with long-term follow-up data are reported. In a 7-year prospective observational study involving 423 patients, Sippola *et al*[76] reported a 39.3% recurrence rate when uncomplicated AA patients were managed by NOM[76]. Patient satisfaction between the appendectomy and NOM group was similar (95%CI: 0.86-1.0; P = 0.96). Podda *et al*[77] reported that patients managed by NOM had a higher visual analog scale at 30-d follow-up (0.3 ± 0.6 *vs* 2.1 ± 1.7)[77]. O'Leary *et al*[78] reported that patients managed by surgery had a better quality of life (94.3 *vs* 91.0, P < 0.001)[78]. Thus, the decision for NOM *vs* surgery has multiple domains to consider, and each patient should be assessed and counseled on his own merits. Ideally, a patient-centric healthcare decision ought to be made, but a survey by Reinisch *et al*[79] involving 1300 surgeons revealed that decisions are made by surgeon preferences. Authors reported that only 14% of surgeons treat uncomplicated AA by NOM, 38.1% in selected cases, and 48.8% rejected NOM[79]. Thus, the inherent bias of the surgical community against NOM should be considered while critically appraising the evidence. More prospective multi-center collaborative studies, with long-term follow-up comparing NOM with appendectomy, including total cost of care, quality of life domains as outcome measures, are necessary before meaningful conclusions and valid recommendations can be made. In our opinion, NOM imposes a long-term recurrence risk and adds the burden of missing incidental tumours. In a systematic review of 455 patients, Peltrini *et al*[80] reported a 11% incidence of appendiceal neoplasms after interval appendectomies for complicated appendicitis[80]. It is possible that with such information, young patients may not participate in a randomized study due to fear of being allocated to the NOM group. Lastly, many authors have reported using carbapenems for NOM, which could contribute to antimicrobial resistance. Percutaneous drainage is integral to the NOM concept. Percutaneous drainage in perforated AA lowers the risk of hemorrhage, fistula formation, wound infection, prolonged ileus, and adhesions compared to immediate appendectomy[81].

Prophylactic antibiotics peri-operatively

Antibiotics are the bare minimum in AA management, regardless of NOM or appendectomy. A 2005 Cochrane review included 45 studies with 9576 patients and reported that antibiotics were superior to placebo in preventing wound infection and intra-abdominal abscess[72]. Beyond 24-h postoperative antibiotics are generally prescribed in patients with complicated AA[82]. Three days of antibiotics are as effective as a five-day course in reducing infectious complications[83,84]. The commonly affirmed practice is to stop postoperative antibiotics within 24 h in patients with uncomplicated AA[85,86], which is widely considered acceptable since source control is achieved. Abounozha *et al*[87] reported that postoperative antibiotics in patients with uncomplicated AA do not decrease surgical site infections but increase the length of stay and costs[87].

Choice and selection of antibiotics are equally crucial as duration. Local antibiotic stewardship initiatives and individual surgeons must ensure that antibiotics are rationally used to reduce the emergence of multi-drug resistance organisms. Our unit uses amoxicillin-clavulanate with a stat dose of gentamicin or ceftriaxone and metronidazole in AA patients. Studies reporting NOM tend to use more broad-spectrum antibiotics to increase treatment success. A meta-analysis by Wang *et al*[88] involving nine randomized controlled trials with 4551 patients reported that carbapenems were associated with fewer treatment-related complications than an appendectomy in uncomplicated AA[88]. Additionally, carbapenems were noted to be the only antibiotic with one-year treatment success rates greater than appendectomy. However, we caution to generalize these results, as each institution should remain guided to select antibiotics based on local antibiogram.

Timing of antibiotic administration is essential in managing patients with sepsis, as delay can increase mortality. An early administration of antibiotics is recommended [74]. In a systemic review involving 34 studies and 2944 uncomplicated AA patients, Talan *et al*[86] reported that most patients showed treatment response within 1-2 d [86]. On the other hand, complicated AA patients had a mean response time of approximately three days. This suggests that prolonged course antibiotics may be necessary for complicated AA patients[12]. An electronic clinical decision support tool allows for the rational use of antibiotics[89].

Surgical intervention

Appendectomy or NOM both remain valid options in selected patients with both uncomplicated and complicated AA. There is enough data that NOM is safe, feasible, cost-effective, and restores quality of life. In a retrospective study including 231,678 patients, McCutcheon *et al*[90] reported no differences in mortality and cost between appendectomy and NOM[90]. We remain cautious about recurrent AA risk, missing tumors, and antimicrobial resistance. In patients selected for appendectomy, timing (interval *vs* index appendectomy) and approach (laparoscopic *vs* open appendectomy) need discussion. In addition, with the laparoscopic approach, single incision *vs* conventional three-port incision and stump closure methods need discussion.

Index vs interval appendectomy

The timing of an appendectomy depends on the patient's clinical stability, available resources, and patient preference. Emergency appendectomy is warranted in patients who manifest signs of sepsis with hemodynamic instability[91]. If the patient is deemed to have high risk due to medical co-morbidity or organ failure, then percutaneous drainage of an abscess may be considered. If the patient with perforated AA is clinically stable, an appendectomy can be performed at the next available opportunity. Various studies have demonstrated both superior and inferior outcomes with early appendectomy when compared to NOM. Young *et al*[92] reported that early appendectomy resulted in reduced bowel resection incidence[92]. Others have reported higher morbidity, including the need for hemicolectomy in patients with complicated AA[93]. This is consistent with Gavriilidis *et al*[83]'s recent meta-analysis, where the overall complications, abdominal/pelvic abscess, wound infections and unplanned procedure performance were significantly lower in conservative treatment cohorts[83]. In our experience, surgeon experience and skill are essential to avoid a limited right hemicolectomy. In patients treated conservatively, Snyder *et al*[35] reported a 12% risk of recurrence[35]. Thus, a patient must be counseled adequately for possible increased morbidity from imminent surgery or interval appendectomy after a trial of conservative management.

Interval appendectomy can be done routinely following conservative management or selectively in patients with recurrent AA after NOM. We distinguish NOM from conservative management with relation to intent. NOM intends to avoid surgery, while conservative management intends to delay surgery later, accounting for safety. NOM can be repeated in patients with recurrent AA. In a systematic review by Darwazeh *et al*[84] involving 1943 patients and 21 studies, there was no morbidity difference between patients managed *via* interval appendectomy or repeat NOM (10.4% *vs* 13.3%)[84]. The study by Hall *et al*[94] involving 106 children who had a recurrence of AA recommended a conservative "wait-and-see" approach over interval appendectomy given the low incidence of complications[94]. A routine interval appendectomy may be beneficial in patients of advanced age to check for a possible malignancy. However, this could be circumvented by offering follow-up imaging and colonoscopy[95]. Due to the short follow-up duration of studies that recommend NOM, the authors practice recommending a routine interval appendectomy to all patients, especially in the presence of a fecolith at the appendix base.

Laparoscopic vs open appendectomy

Laparoscopic appendectomy is as safe as open appendectomy. Smaller wounds translate to less pain, a faster return to normal activities, and a shorter length of stay [23,96,97]. A surgical scar is a determinant of adhesive small bowel obstruction[98]. It is debatable if minimal access approach results in lower rates of postoperative adhesions and small bowel obstruction in patients with AA. In a retrospective analysis of 619 children managed with appendectomy, Håkanson *et al*[99] concluded that the risk for small bowel obstruction after appendectomy was significantly related to perforation or postoperative intra-abdominal abscess and not to the surgical approach [99]. Buia *et al*[96] revealed in a systematic review of 185 articles that laparoscopic appendectomy provides lower short-term bowel obstruction rates in pediatric and perforated AA populations while having lower long-term bowel obstruction rates in all patients[96]. There is a paucity of data regarding postoperative incisional hernia incidence. In a systematic review of 37 studies on appendectomy with sample size > 500 patients each and follow-up > 30 d, Rasmussen *et al*[100] reported a pooled estimate of 0.7% for incisional hernia at follow-up of 6.5 (range 1.9-10) years[100]. In our opinion, minimal access surgery probably reduces the rates of postoperative adhesions and incisional hernia.

Surgical site infection and intra-abdominal infection are crucial key performance indicators of appendectomy. Surgical site infection results in prolonged hospital stay, extended recovery time, increased total cost of care, and drain on healthcare resources [101]. In an umbrella review including ten meta-analyses, Poprom *et al*[102] concluded that surgical site infection rate was 48% to 70% lower in laparoscopic appendectomy than an open appendectomy, and intra-abdominal abscess rate was 1.34 to 2.20 higher in laparoscopic appendectomy than open appendectomy[102]. A higher rate of intra-abdominal abscess could be mitigated by judicious peritoneal lavage and a standard policy to aspirate peritoneal cavity dry before closure.

Laparoscopic appendectomy is associated with reduced 30-d readmission. In a meta-analysis including 45 studies and 836921 appendectomies, Bailey *et al*[103] has reported a 4.3% (range 0.0-14.4%) 30-d readmission rate. Diabetes mellitus, complicated appendicitis, and open appendectomy predicted 30-d readmission[103], and thus laparoscopic appendectomy may be superior if available and accessible. Laparoscopic appendectomy is also notably more cost-effective compared to not only open surgery but NOM as well. In an umbrella study by Sugiura *et al*[104], it is noted that three meta-analyses revealed NOM costs $235 more than operative management, making it less cost-effective than laparoscopic management[104].

Laparoscopic appendectomy can be performed by a single port or conventional three-port technique. A study involving 101 patients by Kim *et al*[105] reported that Single-incision laparoscopic appendectomy (SILA) reduced the length of hospitalization (1.2 ± 0.8 d *vs* 1.6 ± 0.8 d, $P = 0.037$) *vs* three-port appendectomy[105]. Systematic reviews and meta-analyses report that SILA is associated with a shorter length of hospital stay but longer operation duration and increased risk of open conversion[106,107]. SILA requires special training and may be associated with an increased risk of incisional hernia.

Laparoscopic appendectomy is safe and reduces postoperative morbidity in patients with morbid obesity[96]. In a systematic review and meta-analysis including 12 studies with 126237 elderly patients in the laparoscopy group and 213201 elderly patients in the open group, Wang *et al*[108] reported that laparoscopic appendectomy was associated with lower postoperative mortality, wound infection, and shorter length of hospital stay[108]. Thus, laparoscopic appendectomy is safe in obese and elderly patients. While there is the benefit of percutaneous drainage to manage a postoperative intra-abdominal abscess > 4 cm in size[109,110], routine abdominal drainage following an appendectomy for complicated appendicitis has no clinical benefit[111].

Stump closure

Appendiceal stump closure techniques, *e.g.*, surgical stapler or conventional sutures such as Endoloop, are debated. In a study of 333 patients, Rakić *et al*[112] reported that Endoloop was preferred over the stapler given the cost benefits and lack of difference in perioperative morbidity[112]. In a retrospective study of 708 patients, Escolino *et al* [113] reported that the use of Endoloop was associated with a higher incidence of an intra-abdominal abscess, postoperative ileus, and re-operations/readmissions compared to the use of a stapler[113]. Sohn *et al*[114] made a simplified recommendation for using Endoloops in low-grade AA and staplers in high-grade AA [114]. Other options for stump closure include intra-corporeal knotting and clips. In a prospective study of 61 patients by Ates *et al*[115], the use of titanium endoclips was associated with a shorter operation time than intracorporeal knot tying (41.27 ± 12.2 min *vs* 62.81 ± 15.4 min, P = 0.001)[115]. A similar comparison of Hem-o-lok and Endoloop was made in a study by Wilson *et al*[116]. Wilson *et al*[116] noted significantly reduced operative time when using polymer clips like Hem-o-lok compared to Endoloop (59 min *vs* 68 min, P = 0.008)[116]. We perform laparoscopic appendectomy using one 10 mm camera port and two 5 mm working ports. A surgeon requires two 10 mm ports for stapling devices, thus theoretically predisposing the patient to a higher risk of incisional port site hernia. Further, a stapler pin is associated with an increased risk of postoperative adhesions[117]. In our opinion, routine use of stapling devices for stump closure is not justified.

Incidental findings

Two categories of incidental findings need discussion. Firstly, situations where intra-operative AA is established, but a separate incidental pathology is detected[118]. In such instances, it is our opinion that a surgeon should proceed with an appendectomy and document the operative findings. The incidental pathology can be investigated and managed later. Secondly, situations where the appendix appears normal to visualization. Laparoscopy has an advantage in such situations; a surgeon can thoroughly explore the peritoneal cavity. If a definitive pathology is detected and the patient appropriately consented, the surgeon can proceed accordingly. It is debatable and controversial if a normal appendix must be removed, especially if another pathology is established. Our practice is to remove a "normal-appearing" appendix in the absence of other established diagnoses[119]. We do this for two reasons. Firstly, a "normal-appearing" appendix may be an early AA. Secondly, removal of the appendix eliminates future diagnostic dilemmas for RIF symptoms.

Endoscopic appendectomy

Other techniques such as endoscopic retrograde appendicitis therapy have also been proposed to treat uncomplicated AA[120]. In another retrospective study by Ding *et al* [121] involving 210 patients, there was a 100% success rate with a recurrence rate of 2.86% during the first 6 mo of postoperative follow-up[121]. Given the relatively low-powered studies currently, more evidence is necessary.

AA AND THE COVID-19 PANDEMIC

There are reports of AA associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. Many authors have also made suggestions for NOM and avoid surgery in selected AA patients. In patients managed by surgery, the use of personal protective equipment, strategies to reduce surgical aerosols, and the role of peritoneal fluid in viral isolation is proposed.

Associations of COVID-19 infection with AA

In a case series by Prichard *et al*[122], including 6047 patients, it was noted that AA was more likely in patients with COVID-19 positive results compared to those without (10.8% *vs* 1.3%, P < 0.001)[122]. Meyer *et al*[123] reported a higher prevalence of SARS-CoV-2 infection in children. Ahmad *et al*[124] reported a case where SARS-CoV-2 isolates were found in tissue samples of mesenteric lymph nodes despite having a

SARS-CoV-2 negative swab[124]. The converse was also reported, where a patient reported by Ngaserin *et al*[125] was COVID-19 positive but did not detect SARS-CoV-2 in the peritoneal fluid[125]. However, a small sample size limits the generalizability of such observations. We have not observed a similar trend in Singapore (unpublished data). More evidence is required, including histology analysis, before any meaningful conclusions can be drawn.

Management of AA during a pandemic

To reduce risk exposure to healthcare personnel and intra-operative airborne or droplet transmission of the virus, various societies have made recommendations including but not limited to: (1) Strict donning of personal protective equipment; (2) Goggles; (3) N-95 mask; (4) Gradual decompression of pneumoperitoneum; and (5) Reducing the operating personnel to bare necessary, *etc.* and so on. One of the primary considerations is the possibility of avoiding surgery to reduce COVID-19 risk, *i.e.*, NOM[126]. This is supported by the high risk of perioperative COVID-19-associated mortality[127]. In a large, randomized trial comparing outcomes of drugs and appendectomy involving 1552 patients, 29% of patients in the NOM group required surgical intervention[128]. Mai *et al*[127] did not detect perioperative COVID-19 infections and advocate that surgical treatment should be first-line unless COVID-19 infections have been proven or suspected[127]. However, the management should not only be dictated by the COVID-19 pandemic. Collard *et al*[126] propose using the Saint-Antoine scale, including BMI < 28 kg/m^2, leucocyte count < 15000/uL, CRP < 3 mg/dL, and no radiological signs of perforation and diameter of appendix ≤ 10 mm each for 1 point. A score of ≥ 4 is more likely to respond to antibiotic treatment only [126]. More evidence is required if such criteria could guide NOM during a pandemic.

Complications of appendicitis from COVID-19

The effect of COVID-19 on the severity of AA has to be considered in two ways–the fear of the virus delaying COVID-19 negative patients from seeking treatment and the effect of the virus itself in worsening AA.

The combination of government restrictions to leaving the house and fear of exposure in high-risk environments such as hospitals may cause a delay in seeking treatment. In a prospective study by Mowbray *et al*[129], only 64 patients presented with AA in April 2019 (before lockdown) compared to those previously (190 patients in April 2020 during lockdown)[129]. Patients were also noted to have increased their threshold for seeking treatment, presenting to the hospital one day later (2 d *vs* 3 d, P = 0.03). Consequently, some authors noted that the delay in seeking AA treatment might have resulted in more complex AA presentations. Mowbray *et al*[129] noted a higher American Society of Anesthesiology (ASA) score (P = 0.049)[129]. Finkelstein *et al*[130] 's retrospective analysis of 107 patients revealed a similar increase in AA perforations (33% *vs* 17% P = 0.04) than pre-COVID-19[130]. Interestingly, Finkelstein *et al*[130] did not notice a delay in presentation to the hospital (2 ± 3 d in both 2019 and 2020, P = 0.50) but noted that complicated AA seemed to present with a longer duration of symptoms (2 d *vs* 1 d, P = 0.03). The idea that more complicated AA presented in the COVID-19 era is also supported by Yang *et al*[131] in a study of 235 patients, where there was a significantly longer interval from onset of symptoms to seeking treatment (37.92 h *vs* 24.57 h comparing registration time of onset of symptoms to registration, P = 0.028) and higher incidence of complex AA (35.8% *vs* 19.4%, P = 0.005)[131]. However, the converse has also been reported where no differences in complications or severity in AA presentation were seen in other regions. In a retrospective study by Griffith *et al*[132] comparing 2020 and 2019 AA admissions, there was an increased admission rate (40.8% *vs* 34.1%, P = 0.036)[132]. Kohler *et al*[133] revealed in a population-based study in Germany that there was no difference in the number of perforated AA diagnosed during the pandemic or pre-pandemic[133]. Additionally, Bajomo *et al*[134] noted, in a study involving 78 patients, higher inflammatory markers (CRP 103 mg/L *vs* 53 mg/L, P = 0.03) and more severe disease on the histological examination pre-pandemic[134].

Adopting new practices post-COVID-19

Liberal use of imaging may improve diagnostic accuracy and reduce NAR. In a study by Somers *et al*[135] comparing AA management in 2020 and 2019, there was increased use of imaging (89.3% *vs* 69.3%, P = 0.007) and an accompanying decrease in NAR (0% *vs* 24.6%)[135]. Other additional measures enforced for surgeons' safety during the pandemic can also be considered in future circumstances where aerosol-driven pathogens are suspected. Examples include the presence of a negative-pressure operating room, enhanced personal protective equipment, and avoiding the use of electrocautery and other aerosol-generating instruments[136].

SPECIAL CONSIDERATIONS

Children, pregnant women, the elderly, and immunocompromised status pose unique diagnostic and management challenges for AA. We briefly discuss pertinent issues in Figure 2. The US scan is simple, cheap, readily available, and an accurate diagnostic modality. It also avoids radiation exposure. Mittal *et al*[137] conducted a 10-center prospective observational study on 2625 pediatric patients with suspected AA and reported that the US scan had an overall sensitivity of 72% and specificity of 97% in diagnosing AA[137]. The US is operator-dependent, and US sensitivity is higher at sites using it more frequently. US scan is also recommended in pregnant patients as it eliminates fetus radiation exposure[56]. However, Wi *et al*[138] reported very low appendix visualization rates and proposed using MRI scan as first-line imaging in pregnant patients with abdominal pain suspicious for AA[138]. We suggest that hospitals conduct regular audits and implement quality improvement practices to track US performance. Prompt management can reduce spontaneous abortion. In a study by Nakashima *et al*[139] involving 169 pregnant women, the incidence of fetal loss was low in NOM compared to appendectomy (4% *vs* 5%)[139]. Surgeons must be aware that gestational age leads to a significant change in the location of the appendiceal base relative to McBurney's point[140]. We routinely offer laparoscopic appendectomy in pregnant patients. Low-pressure pneumoperitoneum, left lateral tilt to reduce uterine compression of vena cava, and an anesthetic team with obstetric training are essential to good outcomes. In a systematic review and meta-analysis of 22 comparative cohort studies, including 4694 pregnant women (905 Laparoscopic appendectomies and 3789 open appendectomies), Lee *et al*[141] reported that fetal loss was significantly higher for laparoscopic appendectomy patients (pooled OR was 1.72, 95%CI: 1.22-2.42). However, the results were skewed due to one study. On excluding the outlying study, there was no significant difference between laparoscopic and open appendectomy concerning the risk of fetal loss (OR 1.163, 95%CI: 0.68-1.99; P = 0.581) [141]. As such, while caution should be taken, patients should not be unduly refused appendicectomy while pregnant. We recommend that appendectomy be done in a facility with resources available to deal with obstetric urgencies.

No age is immune to AA. AA in the elderly is uncommon and atypical. Late presentation, association with malignancy, association with DDA, and complicated AA are common. In a meta-analysis involving 12 studies and 126,237 patients, Wang *et al*[108] report that postoperative mortality was lower in elderly patients treated with laparoscopy *vs* open appendectomy (OR, 0.33; 95%CI: 0.28-0.39)[108]. Elderly and immunocompromised patients have limited inflammatory responses. In such patients, clinical scoring systems have a lesser role in diagnosis. Anshul *et al*[142] reported a patient with a silent abdomen but AA diagnosed on CT scan[142]. Perioperative care must be customized with a low threshold to suspect complications.

HISTOLOGY EVALUATION

Routine histopathological examination after appendectomy is the prevalent standard practice globally. In a meta-analysis of twenty-five studies and 57357 patients, Bastiaenen *et al*[143] reported 2.5% unexpected findings. They also observed that surgeons could rarely (3%) detect unexpected findings during surgery. Though granulomatous diseases such as Crohn's could be macroscopically detected almost half of the time (47.1%), endometriosis and parasitic infections could only be diagnosed following histopathology.

Neoplasms account for 1% of appendectomy histology specimens[144]. Patients above 50 years of age, with family history of colon cancer or inflammatory bowel disease, or with unexplained anemia are at risk of appendiceal neoplasm[47]. The most common appendiceal neoplasm is neuroendocrine tumours[145]. Appendiceal carcinoid tumors are seen in 1% of appendectomy specimens and same managed with the same caution as adenocarcinomas[139,140,146]. The presence of adenocarcinoma in the appendectomy specimen requires a right hemicolectomy. In a meta-analysis of six studies including 261 patients who had an appendiceal carcinoid tumor, Ricci *et al*[147] found a significant recurrence rate in tumors larger than 2 cm in size compared to those smaller than 2 cm, with a higher risk of lymph node metastases in the former

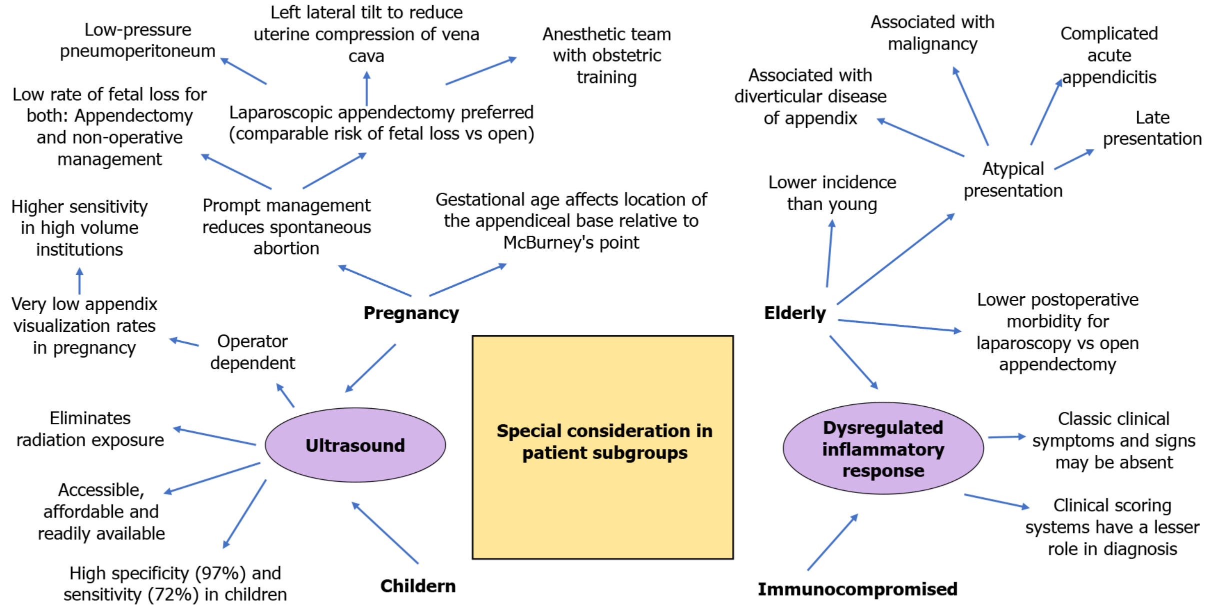

Figure 2 Special considerations in children, pregnancy, elderly and immunocompromised.

group[147]. A right hemicolectomy is warranted for carcinoid tumors > 2 cm size, located at the base of the appendix, or involved lymph nodes. Locally, the multidisciplinary oncology board makes management recommendations in such instances. In perforated AA, the goblet cell subtype of appendiceal carcinoid is associated with a greater risk of peritoneal metastasis than the classical subtype. In a systematic review involving 121 cases of appendiceal carcinoid tumors with perforation, Madani *et al* [148] noted that perforation accelerates the metastatic process[148]. A surgeon should avoid a spill of luminal contents. Metastasis to the appendix is a rare occurrence. The gastrointestinal tract is the most likely site of breast tumor metastases. Ng *et al*[149] reported 15 patients with breast cancer and appendix metastasis[149]. Each patient's treatment should be determined by multidisciplinary oncology teams considering disease stage, the extent of metastases, patient performance status, physician expertise, and patient choices. Appendiceal endometriosis (AE) may be associated with low-grade appendiceal mucinous neoplasms and small bowel obstruction secondary to an endometrial ileal stricture[150]. Prophylactic appendectomy in patients with AE may reduce intestinal obstruction risk, and further data is needed.

CONCLUSION

Multiple aspects of approach to management of AA remain well debated in the literature. The role of clinical scoring systems and imaging in the early and accurate diagnosis of AA can reduce NARs. NOM and appendectomy both remain valid options with their own merits and demerits. Laparoscopic appendectomy is widely accepted as safe with the benefits of early recovery and reduced wound infection compared to open appendectomy. Fear-related behavior is proven during the COVID-19 pandemic, as evidenced by a delay in presentation. Histologic evaluation of appendix specimens has value in detecting incidental malignancies. As the management of AA evolves with technological strides and a more refined understanding of the pathology, we foresee more flavorful discussions on such a staple condition.

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MINIREVIEWS

Application and progress of medical imaging in total mesopancreas excision for pancreatic head carcinoma

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Abstract

Pancreatic head carcinoma (PHC) is one of the common gastrointestinal malignancies with a high morbidity and poor prognosis. At present, radical surgery is still the curative treatment for PHC. However, in clinical practice, the actual R0 resection rate, the local recurrence rate, and the prognosis of PHC are unsatisfactory. Therefore, the concept of total mesopancreas excision (TMpE) is proposed to achieve R0 resection. Although there have various controversies and discussions on the definition, the range of excision, and clinical prognosis of TMpE, the concept of TMpE can effectively increase the R0 resection rate, reduce the local recurrence rate, and improve the prognosis of PHC. Imaging is of importance in preoperative examination for PHC; however, traditional imaging assessment of PHC does not focus on mesopancreas. This review discusses the application of medical imaging in TMpE for PHC, to provide more accurate preoperative evaluation, range of excision, and more valuable postoperative follow-up evaluation for TMpE through imaging. It is believed that with further extensive research and exploratory application of TMpE for PHC, large-sample and multicenter studies will be realized, thus providing reliable evidence for imaging evaluation.

Key Words: Pancreatic head carcinoma; Mesopancreas; Total mesopancreas excision; Imaging; Computed tomography; Magnetic resonance imaging reviewed.

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Core tip: As a new concept of radical treatment for pancreatic head carcinoma, total mesopancreas excision requires removal of all tissues (including nerves, capillaries and lymph nodes) in the mesopancreas and has potential for achievement of R0 resection. Correspondingly, imaging evaluation should include all of the anatomical structures within the mesopancreas to achieve precise preoperative evaluation for surgical resection and meet the needs of postoperative follow-up.

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INTRODUCTION

Pancreatic carcinoma (PC) is a highly malignant tumor of the digestive system with an increasing incidence and poor prognosis. Pancreatic head carcinoma (PHC) accounts for approximately 90% of all pancreatic malignancies, with a 5-year survival rate ranging from 6% to 20%[1,2]. Because of the posterior location, symptoms of PHC are usually insidious and it is difficult to diagnose in the early stage, thus losing the best opportunity for surgery or increasing its risk. It has been reported that approximately 20%–86% of PC patients do not reach curative surgical (R0) resection after surgical treatment (most common with a positive tumor margin), which adversely affects the prognosis of the patients[3-7].

PATHOGENESIS AND PATHOGENIC FACTORS OF PC

To date, the specific pathogenesis of PC has not been clear. At present, it is certain that the occurrence and development of PC are the result of a combined effect of lifestyle and the internal and external environments. A large number of clinical and epidemiological studies have confirmed that the risk factors for PC include smoking, chronic diabetes and obesity[8-10]. High alcohol consumption, diet and a family history are also associated with PC[11]. Japan's 2016 version of pancreatic ductal adenocarcinoma (PDAC) clinical guidelines[12] pointed out that risk factors for PDAC include a family history of PC, hereditary PC syndrome, pancreatic complications of diabetes/chronic pancreatitis/intraductal papillary mucinous neoplasm/pancreatic cysts/obesity, an unhealthy lifestyle (smoking, excessive alcohol intake) and occupational factors.

TREATMENT AND PROGNOSIS OF PHC

Surgical resection is still the most important and the only curative treatment for PHC. The prognosis of patients with surgically resected PHC is significantly better than that of unresectable PHC[13]. The National Comprehensive Cancer Network (NCCN) guidelines[14] recommend neoadjuvant therapy only for borderline resectable PC. Currently, pancreaticoduodenectomy (PD) is the standard surgical procedure for radical treatment of PHC, and the long-term recurrence rate and long-term survival rate of patients with PD are mainly dependent on radical R0 resection[15,16]. Even for patients unable to achieve an R0 resection, R1 resection can still improve the prognosis and achieve an improved quality of life. In the past 10 years, the perioperative mortality of pancreatic cancer has been reduced to 3%. Moreover, the expanded surgical indications for locally advanced tumors have also increased the 5-year overall survival (OS) rate close to 30%.

With the development of laparoscopic technology, the safety and feasibility of laparoscopic resection for pancreatic body and tail tumors has been confirmed, and laparoscopic resection has become the first choice for patients with resectable benign or low-grade malignant tumors in the pancreatic body and tail[17]. For pancreatic head cancer, due to the technical difficulty of the operation, the application of laparoscopic PD (LPD) is still hard to promote widely[18-20]. For LPD, R0 resection is the only way for patients with PHC to obtain long-term survival. Whether R0 resection can be achieved is the key factor for the prognosis of PHC[21]. Unfortunately, it has been reported that 20%–86% of patients with PHC undergoing surgical resection do not achieve R0 resection[22,23]; most of which are related to the insufficient removal of retroperitoneal tissue mainly concentrated in the retropancreatic tissue space, a well-known anatomical space recognized as the mesopancreas[16]. Recently, R1 resection in many PHCs has been believed to be caused by incomplete resection of the mesopancreas. Accordingly, the concept of total mesopancreas excision (TMpE) has been proposed, which is suggested to increase the R0 resection rate of pancreaticoduodenal surgery[24-26].

CONCEPT OF MESOPANCREAS AND SURGICAL PROGRESS OF TMpE

The pancreas has always been considered an extraperitoneal organ. In 2007, Gockel *et al*[27] proposed the concept of the mesopancreas and TMpE by analogizing total mesorectal excision based on the autopsy results of five corpses. According to this concept, TMpE requires resection of the entire pancreatic tumor and the peripancreatic lymph nodes and adipose tissue layer *en bloc* to achieve a negative retroperitoneal margin and to improve the R0 resection rate and the prognosis of the patients. Gockel *et al*[27] considered the mesopancreas to be the fibrous connective tissue between the pancreas neck and the mesenteric blood vessels. Although the exact anatomical boundary was not described, the mesopancreas was confirmed to be an anatomical region containing nerves, blood vessels, and lymphoid tissues, the most likely metastatic region of pancreatic cancer. In contrast, Agrawal *et al*[28] pointed out that although loose areolar tissue, adipose tissue, peripheral nerves, a nerve plexus, lymphatic ducts and capillaries could be found extending from the head, neck and uncinate process of the pancreas to the aortocaval groove in the retropancreatic tissue in 20 patients with autopsy, no fibrous sheath or fascia was detected around these structures. Therefore, the concept of the mesopancreas could not be confirmed anatomically. However, Popescu and Dumitrascu[29] insisted that even without a complete fascial structure, the mesopancreas could still be considered an anatomical structure. To date, there has been no consensus on the existence of a mesopancreas and whether it could be called a mesostructure. Adham and Singhirunnusorn[30] specifically described the superior, inferior, anterior and posterior resection margins of TMpE and characterized them as an inverted triangle, the mesopancreas triangle, whose anatomical boundaries are represented by a base lying on the posterior surface of the superior mesenteric vein (SMV) and portal vein (PV), a summit lying on the anterior surface of the aorta between the celiac trunk and superior mesenteric artery (SMA) origin, and limited on each side by the right semicircumferences of the celiac trunk and SMA plexus (Figure 1). Adham and Singhirunnusorn[30] emphasized thorough removal of all tissues in this area to achieve R0 resection (Figure 2). Kawabata *et al*[31] proposed the concept of the mesopancreatoduodenum, which consisted of a cluster of soft connective tissues along the inferior pancreaticoduodenal artery (IPDA) and the first jejuna artery (FJA). The mesoduodenum (fed by the IPDA) and the jejunal mesentery (dominated by the FJA) were demonstrated to form a common mesentery named the mesopancreatoduodenum in the resected specimens. Correspondingly, the concept of total mesopancreatoduodenum excision with an expanded range relative to the aforementioned mesopancreas was put forward to emphasize the circumferential resection of SMA. In view of the unclear mesopancreas boundary and various modes of local pancreatic invasion, Peparini *et al*[32] proposed that extending the resection as much as possible (including dissection of the para-aortic lymph nodes such as 16a2 and 16bl) should be implemented. In terms of pancreaticoduodenal resection, Wu *et al*[33] divided the mesopancreas at the head of the pancreas into the anterior and posterior parts, which mainly refers to the lymphatic connective tissues that attach to the anterior side of the abdominal aorta and surround the SMA and SMV and the celiac trunk. According to the Japan Pancreas Society General Rules for the Study of Pancreatic Cancer (7th edition)[34], the mesopancreas is defined as the pancreatic head plexus, which is more in compliance with anatomy. The existence and range of the mesopancreas is still controversial.

To date, the safety and effectiveness of TMpE have not been thoroughly discussed. Adham and Singhirunnusorn[30] found that TMpE showed no significance in terms of

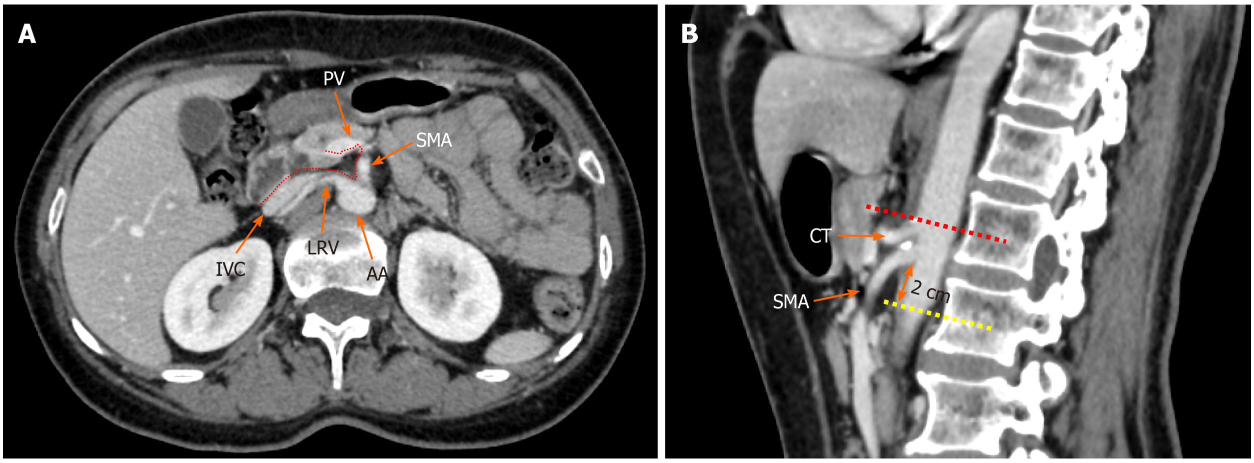

Figure 1 Radiological depiction of the mesopancreas in computed tomography. A: The dotted line outlines the boundary of the mesopancreas, a region identified as the retro pancreatic retro portal tissue; B: The inferior boundary of the mesopancreas is 2 cm below the origin of superior mesenteric artery. PV: Portal vein; SMA: Superior mesenteric artery; LRV: Left renal vein; IVC: Inferior vena cava; AA: Aorta artery; CT: Celiac trunk.

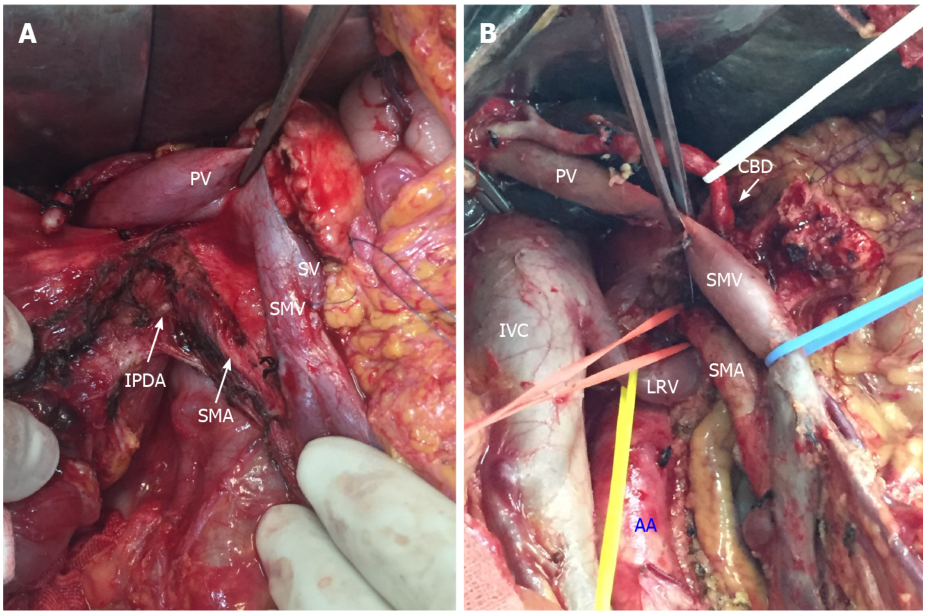

Figure 2 Key steps of total mesopancreas excision. A: Dissection of the right semi-circumference of the superior mesenteric artery and celiac trunk; B: Clearance of the retropancreatic retroportal space (mesopancreas triangular). PV: Portal vein; SV: Splenic vein; SMV: Superior mesenteric vein; SMA: Superior mesenteric artery; IPDA: Inferior pancreaticoduodenal arteries; IVC: Inferior vena cava; LRV: Left renal vein; AA: Aorta artery; CBD: Common bile duct.

operating time, intraoperative blood loss, incidence of postoperative complications, length of hospitalization or perioperative mortality compared with other surgical methods for PHC. Meanwhile, postoperative pathology confirmed a positive mesopancreas invasion by PHC rate of 23%, a median lymph node dissection of 24%, and an overall R0 resection rate of 80.7% for PHC after TMpE. Therefore, TMpE is believed to be an effective surgical method to reduce the positive rate of the posterior peritoneal resection margin and increase the R0 resection rate of PHC. Kawabata *et al* [31] compared the surgical methods of TMpE in 14 PHC patients with standard PD performed in 25 patients during the same period and achieved a higher number of lymph node dissections (26 *vs* 18, $P = 0.027$) and a higher R0 resection rate (93% *vs* 60%, $P = 0.019$) in the TMpE group. Some studies have also demonstrated that TMpE could significantly increase the R0 resection rate of pancreaticoduodenal surgery for PHC[29,30,35-38].

Known as the most common sites for invasion and metastasis of PHC, the region posterior to the head of the pancreas, the SMV, posterior PV, SMA, the right semicircumference of the celiac trunk, and the anterior and right sides of the abdominal aorta are the most likely sites of residual tumor and local recurrence after surgical resection, making it the key site of current radical resection of PHC. In fact, because the mesopancreas is included in the resection range of lymph node dissection for PHC, TMpE does not contradict traditional lymph node dissection and just differs in the emphasis of the importance of resection of the region near the posterior head of the pancreas. Currently, the absence of a definite anatomical boundary for the soft tissue posterior to the head of the pancreas brings challenges to precise resection of the mesopancreas in TMpE. This uncertainty may also increase the heterogeneity among studies and affect the evaluation of TMpE.

To our knowledge, until now, only a few studies have compared TMpE with traditional PD, and these studies mainly focused on OS and disease-free survival (DFS)[39-41]. Kurosaki *et al*[41] reported similar short-term survival but prolonged 3-year survival rates in patients with successful TMpE. Quero *et al*[43] also reported benefits in terms of DFS for TMpE. However, some studies found that TMpE did not influence short-term outcomes[35,39,42]. Quero *et al*[43] also reported a similar estimated 5-year OS between these two techniques, even though a slight advantage was observed in the TMpE group.

IMAGING STUDIES ON PHC AND THE MESOPANCREAS

As a tumor with rapid progression, the early diagnosis of PHC has many difficulties. Approximately 80%–85% of patients are diagnosed with locally advanced tumors or distant metastasis, and only 15%–20% of patients are suitable for surgical resection [44]. Enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are currently the most commonly used examination methods for the diagnosis of PHC.

Typical imaging manifestations of PHC

Consistent with the microscopic pathological characteristics of PC, mixed tumor cells and a large amount of interstitial fibrosis with an irregular proportion, the direct signs of typical PHC include an isodense or slightly low-density mass in the pancreatic head area on noncontrast CT images and an avascular tumor with a lower density than normal pancreatic parenchyma in contrast imaging (Figure 3). On MRI, most tumors show a low signal on T1-weighted imaging (WI), an equal/low/slightly higher signal on T2WI, and a slightly higher signal on diffusion-weighted imaging (DWI). The signal intensity of most PHCs is lower than that of the pancreatic parenchyma in the early stage of enhancement and becomes iso-signal intensity in the later stage (Figure 4). Indirect signs of PHC include changes in the contour of the pancreas, parenchymal atrophy of the pancreatic body and tail, pancreatic and bile duct truncation sign, double duct sign[45] (Figure 4D), and secondary retention cyst.

It should be noted that 10%–14% of tumors on multidetector CT (MDCT) are isodense on both noncontrast and contrast scans[46], which is more common in histopathologically highly differentiated tumors. Early PHC is usually well differentiated and presents as an isodense tumor. Approximately 88% of isodense PCs with a diameter < 2 cm are accompanied by indirect signs, with an incidence of pancreatic duct truncation sign, double duct sign, and pancreatic atrophy of 59%, 63% and 21% [47]. Therefore, indirect signs are important for the early diagnosis of PHC, especially in cases without a definite tumor, and further examination should be performed to avoid a missed diagnosis. MRI using multiple sequences can significantly improve the sensitivity and specificity of the early diagnosis of pancreatic cancer[48,49].

Imaging evaluation of resectability of PHC

At present, surgical resection is the only possible radical curative treatment for PHC. However, only 15%–20% of patients with PHC are suitable for surgery due to local involvement or distant metastases. Therefore, accurate judgment of the resectability of PHC is of importance when selecting treatment options to avoid unnecessary surgery. Currently, the standard evaluation for the resectability of pancreatic cancer is the NCCN Clinical Practice Guidelines for Pancreatic Cancer (2017, 1st edition), including the evaluation of the peripancreatic artery, vein, pancreatic head, body and tail cancers and the contact surface between the tumor and blood vessels. Moreover, with a combination of tumor location, the type of involved blood vessels and the contact angle, tumors can be divided into resectable pancreatic cancer (RPC), borderline RPC (BRPC), locally advanced pancreatic cancer (LAPC) and metastatic PC[50]. Meanwhile, the importance of enhanced CT and MRI in the evaluation of PC has also been highlighted. High-quality images are especially significant for accurately assessing the relationship between pancreatic cancer and adjacent blood vessels, which is of guiding

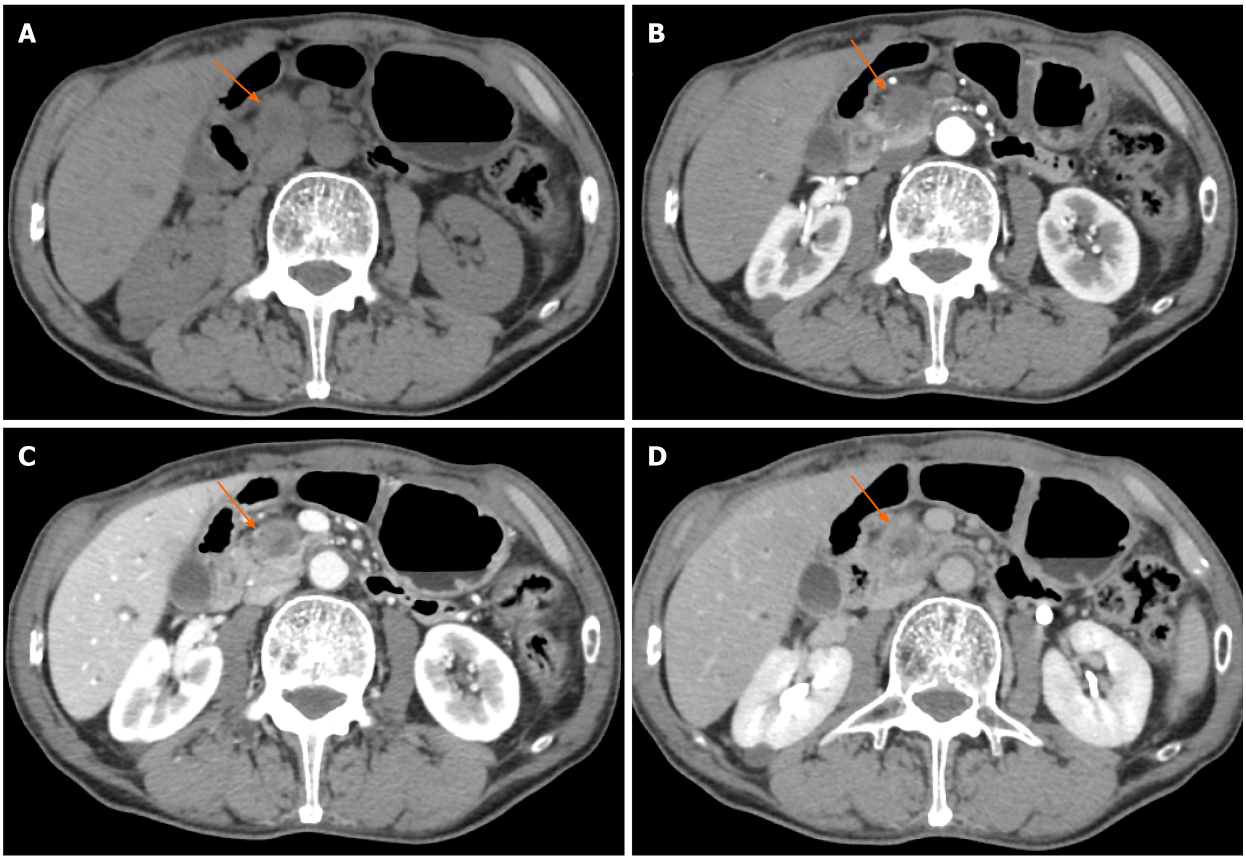

Figure 3 Typical CT features of pancreatic head carcinoma in a 73-year-old male patient. A: On noncontrast CT imaging a slightly low-density mass (arrow) in the pancreatic head area was identified; B–D: On contrast CT images, the tumor shows an avascular tumor with a lower density than normal pancreatic parenchyma on arterial phase (B), venous phase (C), and delay phase (D). CT: Computed tomography.

significance for the assessment of the resectability of PC and the selection of treatment options.

Unfortunately, there are still some problems with the NCCN guidelines. First, Hong *et al*[51] evaluated 371 PC patients with preoperative CT according to the NCCN guidelines and found that tumors with a diameter > 4 cm and tumor contact with PV were high risk factors for R1/2 resection margins. For those 104 patients diagnosed with BRPC by preoperative CT, 47 patients were pathologically confirmed as R1/2 margins after surgery. Therefore, the NCCN guidelines based on anatomical standards have significant limitations in the evaluation of resectability and cannot promise benefit from surgical treatment in some patients. Second, according to the 8th edition of the American Joint Cancer Committee in 2018, PC is distinguished as T1, T2 and T3 stages according to the largest tumor diameter and T4 stage (with involvement of celiac trunk, SMA, and/or the common hepatic artery, regardless of tumor size). This new T staging system undoubtedly promises more objectivity and reproducibility for MDCT, but it also brings challenges to radiologists. The sensitivity of MDCT in T staging differs in tumors of different sizes, with a sensitivity of 90%–98% for tumors with a diameter > 2 cm and 60%–77% for smaller tumors[52]. Therefore, difficulties still exist in the detection and further staging of T1 tumors for MDCT. MRI provides multisequence imaging, which is better than MDCT in the diagnosis of small PHCs. Third, the N staging system recommended in the NCCN guidelines is based on the number of metastatic lymph nodes: N0 (no regional lymph node metastasis); N1 (1–3 regional lymph node metastases); and N2 (> 4 lymph node metastases). Nevertheless, there are still some limitations in the imaging diagnosis of metastatic lymph nodes. As metastatic lymph nodes have no obvious correlation with tumor size or the tumor T stage, it is difficult to identify metastatic lymph nodes based only on morphological changes and distinguish them from inflammatory hyperplasia. As a functional imaging technology that can provide not only anatomical but also functional/metabolic features, MR-DWI may help detect metastatic lymph nodes combined with the apparent diffusion coefficient[53].

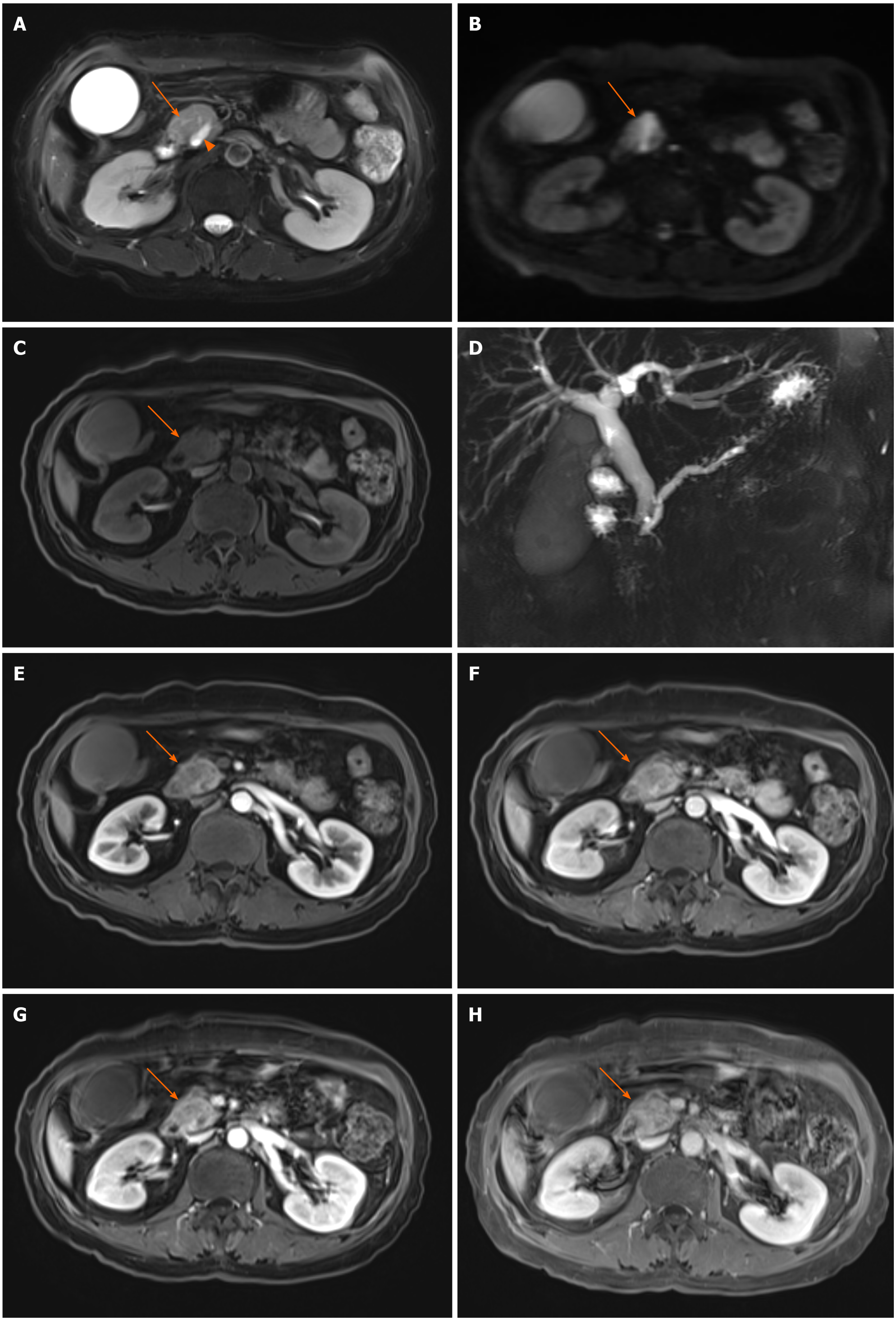

Figure 4 Typical magnetic resonance features of pancreatic head carcinoma in a 57-year-old female patient. A–C: Swollen pancreatic head

(arrow) with slightly higher signal on T2-weighted imaging (WI) (A) and diffusion-weighted imaging (B), and low signal on T1WI (C) was detected; D: Notes that the dilation of pancreatic duct (arow head) and double duct sign on magnetic resonance cholangiopancreatography; E–H: After administration of contrast agent, the tumor shows a progressive enhancement pattern similar to computed tomography on early arterial phase (E), late arterial phase (F), venous phase (G), and delay phase (H).

Positron emission tomography–CT has also been reported to be able to enable a qualitative diagnosis based on the uptake of ^{18}F-fluorodeoxyglucose in the lymph nodes with better sensitivity and specificity than MDCT[54]. In addition, the use of MR-targeted lymphatic imaging technology and radiomics may also help improve the accuracy of the diagnosis of metastatic lymph nodes in the future. Despite these developments in imaging modalities, the absence of pathological sampling standards for peripancreatic lymph nodes and the lack of a unified definition of regional lymph nodes make it difficult to establish a point-to-point correspondence between pathologically positive lymph nodes and positive lymph nodes on images, resulting in a disconnect among preoperative imaging evaluations, surgical lymph node dissections, and pathological assessments. In conclusion, although MDCT or MRI can show the tumor morphology, adjacent vascular invasion, lymph node and distant metastasis well, there are still some limitations in the current imaging assessment based on the TNM staging system, which may affect the treatment options and prognosis of patients to some extent.

Application status of imaging in TMpE

With the novel conception of the mesopancreas and advances in TMpE, all of the structures in the mesopancreas should be accurately preoperatively evaluated. However, the assessment of the resectability of PHC in previous studies has mainly focused on the size of the tumor, invasion of the peripheral blood vessels, and the presence of lymph node metastasis and distant metastasis. Current studies on TMpE are mostly focused on surgical methods, treatment effects, and patient prognosis.

In addition, with the proposal of a mesopancreas and developments in TMpE, peripancreatic vessel invasion is no longer an absolute contraindication for radical resection of PHC; therefore, the evaluation principles of preoperative imaging need to be changed correspondingly. Consistent with the anatomical concept of the mesopancreas, preoperative imaging evaluation of PHC should include all of the nerves, lymphatic vessels, and fatty tissues in the mesopancreas instead of only evaluating masses, vascular invasion, lymph nodes and distant metastasis. Wu[55] found an important anatomical level for TMpE, the posterior pancreatic space, containing a large number of nerves, lymphatic vessels, adipose tissue, and dense fibrous connective tissue surrounding the CA and the SMA within it. As a particularly important anatomical region for the occurrence of lymphatic and nerve metastasis, preoperative imaging evaluation should pay more attention to the posterior pancreatic space and the structures around the CA and SMA to achieve R0 resection. Liang *et al* [56] proposed 3D visualization technology in TMpE, which could help make more accurate preoperative assessments and select reasonable surgery approaches, thus, increasing the R0 resection rate of PHC.

However, there are many controversies regarding the scope and boundary of the mesopancreas because of the absence of a definite anatomical fascial structure. A definitely complete posterior capsule posterior to the head of the pancreas and the duodenum was found in a recent study[57], which has brought new challenges to clinical imaging. Similar to the mesorectum, which could be identified as low signal intensity on MRI, the mesopancreas should also be detectable. Unfortunately, whether the mesopancreas could be identified by imaging is questionable and requires extensive research with a comprehensive comparison of gross anatomy, surgery, pathology, and imaging. Furthermore, perineuronal invasion is characteristic of pancreatic cancer, generally first invading the intrapancreatic nerves and then to the nerve plexus outside the pancreas by spreading along the nerve bundles. It has been reported that a longer survival period could only be achieved in patients with peripancreatic nerve resection[58,59]; therefore, the evaluation of preoperative peripheral nerve invasion and postoperative resection margin is of great importance for the efficacy of TMpE. However, until now, neither CT nor MRI has been able to clearly visualize the nerve plexus of the pancreas. Further improvements in imaging technologies should be developed to achieve precise assessment of the perineuronal invasion of PHC.

CONCLUSION

Generally, as a new concept of radical treatment for PHC, TMpE requires removal of all tissues (including nerves, capillaries and lymph nodes) in the mesopancreas and has potential in the achievement of R0 resection. Correspondingly, imaging evaluation should include all of the anatomical structures within the mesopancreas to achieve precise preoperative evaluation for surgical resection and meet the needs of postoperative follow-up.

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MINIREVIEWS

Retrorectal tumors: A challenge for the surgeons

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Abstract

Retrorectal or presacral tumors are rare lesions located in the presacral area and considered as being derived from multiple embryological remnants. These tumors are classified as congenital, neurogenic, osseous, inflammatory, or miscellaneous. The most common among these are congenital benign lesions that present with non-specific symptoms, such as lower back pain and change in bowel habit. Although congenital and developmental tumors occur in younger patients, the median age of presentation is reported to be 45 years. Magnetic resonance imaging plays a crucial role in treatment management through accurate diagnosis of the lesion, the evaluation of invasion to adjacent structures, and the decision of appropriate surgical approach. The usefulness of preoperative biopsy is still debated; currently, it is only indicated for solid or heterogeneous tumors if it will alter the treatment management. Surgical resection with clear margins is considered the optimal treatment; described approaches are transabdominal, perineal, combined abdominoperineal, and minimally invasive. Benign retrorectal tumors have favorable long-term outcomes with a low incidence of recurrence, whereas malignant tumors have a potential for distant organ metastasis in addition to local recurrence.

Key Words: Retrorectal tumors; Congenital cystic lesions; Teratomas; Perineal approach; Transabdominal approach, Combined abdominoperineal approach

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Core Tip: With advances in imaging modalities and increased clinicians' awareness, the diagnosis of a retrorectal tumor has been improving over the years. This review article discusses the epidemiology, classification and suggested diagnostic methods, with current treatment options mostly focusing on surgical approaches and follow-up recommendations, for patients with retrorectal tumors.

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INTRODUCTION

Retrorectal or presacral tumors are extremely rare. Although their true incidence in the general population is unknown, it has been reported that the number of patients diagnosed yearly with retrorectal tumor is approximately 1-6 in tertiary referral centers and the estimated incidence is 1 in 40.000 hospital admissions[1]. Most of the retrorectal tumors are benign, but malignant cases account for 21%-50% of patients[1,2].

The retrorectal space is an anatomic area formed by the rectum's posterior wall anteriorly and the sacrum posteriorly. It extends to the peritoneal reflection superiorly and to Waldeyer's fascia inferiorly[3]. The histopathological varieties of retrorectal tumors result from the multiple embryological remnants located in this potential space [4]. Due to their unusual localization and mimicry of symptoms caused by other joint diseases, the diagnosis and treatment of retrorectal tumors are challenging for clinicians[5]. As well, different surgical approaches and procedures are described for these tumors, to provide optimal exposure to the lesional field and decrease postoperative morbidity[6-8].

Herein, we present a comprehensive review of surgical management and share our clinical experiences for retrorectal tumors.

CLINICAL PRESENTATION AND CLASSIFICATION

Retrorectal tumors are usually asymptomatic lesions (26%-50% of cases), being discovered incidentally on routine digital rectal examination. Symptoms such as sacral pain, constipation, incontinence, and pencil-thin stools usually indicate tumor invasion to adjacent structures[1]. Patients may present with lower back pain that worsens with sitting and is alleviated by walking and standing[4]. Patients who present with recurrent anal fistula and perirectal abscesses should be suspected of retrorectal tumor and subjected to additional imaging studies[9].

Retrorectal tumors are classified based on their origin, namely congenital, neurogenic, osseous, inflammatory, or miscellaneous. Moreover, these tumors can be divided according to the lesions' histopathology, as benign congenital, malignant congenital, benign acquired, and malignant acquired (Table 1)[10,11].

Congenital lesions

The most common type of retrorectal tumor is congenital, of which two-thirds are cystic lesions, such as tail-gut, epidermoid and dermoid cysts[1,4,10]. The incidence of those developmental cysts tends to be higher in females. Although many of them are benign lesions, malignant transformation of tail-gut cysts has also been reported by tertiary centers[12,13]. Epidermoid and dermoid cysts can communicate with skin and present as postanal dimple or sinus, which can be easily misdiagnosed as pilonidal sinus or perirectal abscess (Figures 1 and 2)[14,15].

The risk of malignancy is higher for solid retrorectal tumors, the most common of which are the chordomas[16]. These slow-growing tumors arise from the fetal notochord's vestiges, usually from within the vertebral bodies. Unlike developmental cysts, chordomas are more common in males. Patients with chordomas usually present with urinary or gas incontinence and intensive sacral or perineal pain due to invasion of the adjacent structures. Radical resection is usually required because of the

Table 1 The classification of retrorectal tumors[10,11]

	Benign	Malignant
Congenital	Developmental cysts (Tail-gut, epidermoid, dermoid, teratoma)	Chordoma
	Anterior sacral meningocele	Teratocarcinoma
	Adrenal rest tumor	
Neurogenic	Schwannoma	Neuroblastoma
	Neurofibroma	Malignant nerve sheath tumors
	Ganglioneuroma	Ganglioneuroblastoma Ependymoma
Osseous	Giant-cell tumor	Osteogenic sarcoma
	Osteoblastoma	Ewing sarcoma
	Aneurysmal bone cyst	Chondrosarcoma
		Myeloma
Inflammatory	Abscess/hematoma	
Miscellaneous	Lipoma	Liposarcoma
	Fibroma	Fibrosarcoma
	Hemangioma	Hemangiopericytoma
	Endothelioma	Leiomyosarcoma
	Leiomyoma	Metastatic carcinoma

Figure 1 A patient presented with complaints of recurrent fistula, which was ultimately diagnosed as epidermoid cyst.

relatively higher recurrence rates of this type of congential lesion[17,18].

Teratomas are true neoplasms, that include all three germ layers. They can be solid or cystic, and often contain both components. They are also more common in females and associated with a 40%-50% risk of malignant degeneration in the adult population [19]. In the absence of malignancy, they rarely adhere to the rectum or other adjacent viscera[4].

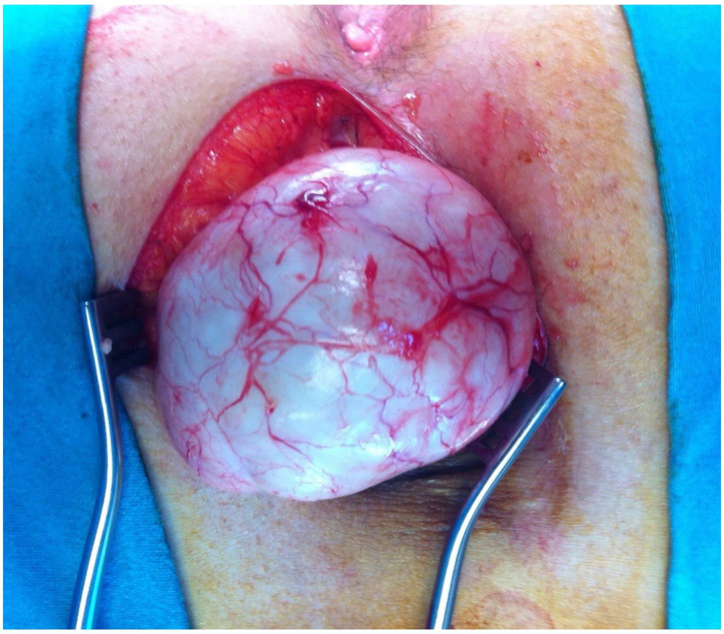

Figure 2 Intraoperative image of the epidermoid cyst.

Neurogenic lesions

Neurogenic tumors are the second most common retrorectal tumors, after congenital lesions. These are slow-growing tumors that typically arise from peripheral nerves, and 85% of them are benign, consisting of neurofibromas and schwannomas[20].

Osseous lesions

Osseous tumors account for 10% of retrorectal tumors and have a high risk of recurrence. These include benign tumors (*i.e.* osteoblastoma, giant-cell tumor) and malignant tumors (*i.e.* Ewing sarcoma, chondrosarcoma, osteogenic sarcoma), which arise from bone, cartilage, fibrous tissue, and marrow[4,21].

Inflammatory lesions

Inflammatory tumors are less common than congenital lesions and are considered secondary reactions to foreign substances left in the body from previous surgeries[22]. It has been reported that they can also result from an extension of infection from either the perirectal space or abdomen[2,6].

Miscellaneous lesions

Miscellaneous tumors account for 10%-25% of all retrorectal tumors, including lipoma, fibroma, hemangioma, leiomyoma, and liposarcoma[21]. These lesions can also be a metastasis from primary rectal cancer.

DIAGNOSIS

A careful rectal examination carries the utmost importance for making a diagnosis, accounting for diagnosis in 90% of cases. Unfortunately, unless the physician has a high index of suspicion, these soft and compressible lesions can easily be missed[4]. As such, magnetic resonance imaging (MRI) in conjunction with computed tomography (CT) has emerged as the diagnostic tool of choice (Figure 3)[5]. CT is useful for demonstrating the nature of the lesion (cystic-solid) and bone destruction, whereas MRI is more advanced in evaluating soft tissue and adjacent structures' involvement (Figures 4 and 5)[23]. On MRI, based on the lesion's internal signal characteristics, the lesion is diagnosed as a cystic tumor when it displays cystic elements comprising greater than 80% of the lesion and a solid tumor when the lesion shows solid elements in greater than 80%; the remainder are classified as heterogeneous[6]. Radiological features that indicate malignant lesions are heterogeneous signal intensity, irregular infiltrative margin, sacral destruction or remodeling, and enhancement[24]. MRI also enables the surgical care team to plan for extent of resection (local *vs en bloc*) and

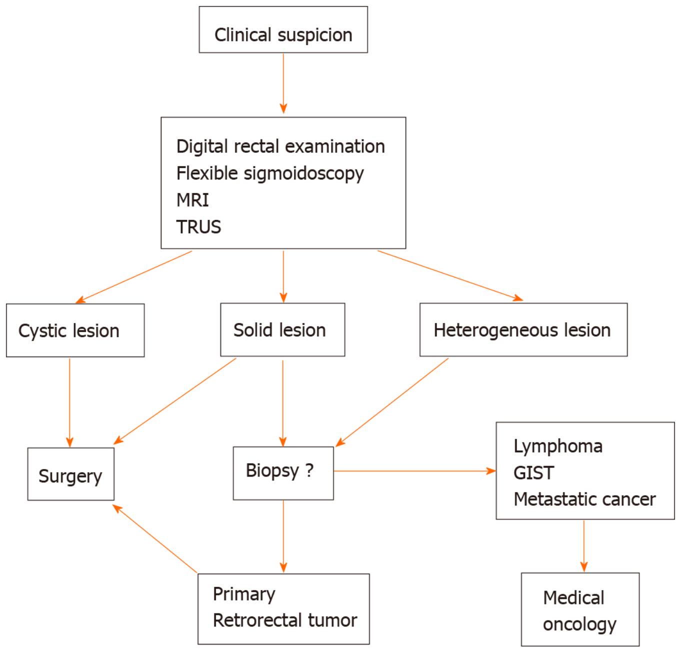

Figure 3 Flow diagram for the management of retrorectal tumors. MRI: Magnetic resonance imaging; GIST: Gastrointestinal stromal tumor; TRUS: Transrectal ultrasonography.

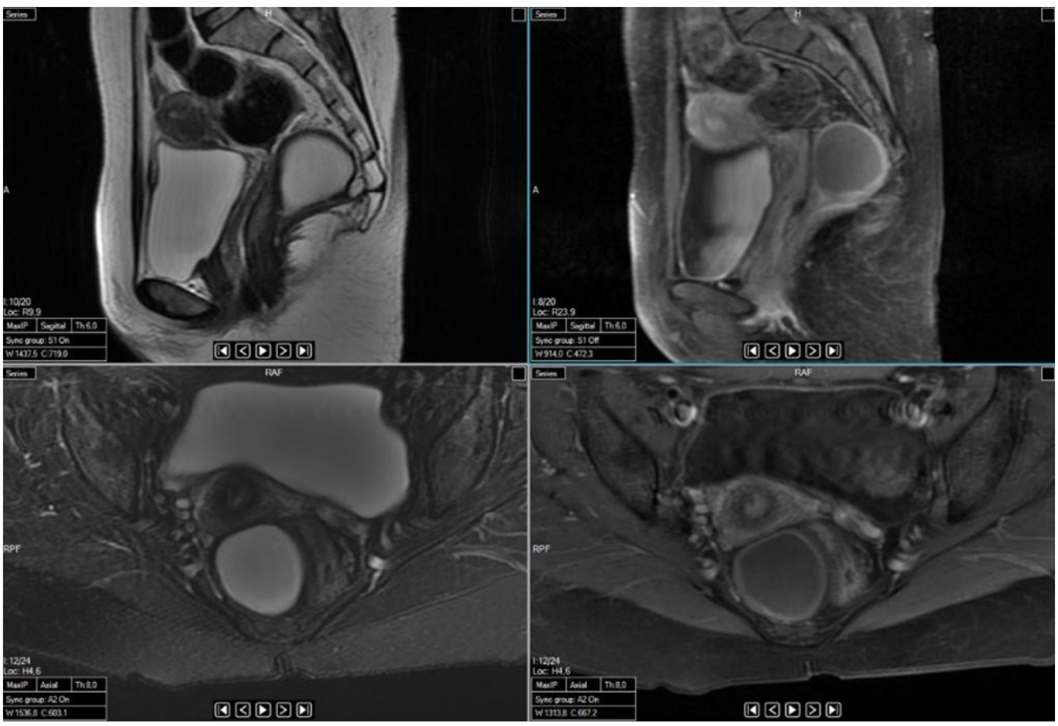

Figure 4 Sagittal and axial magnetic resonance images showing a cystic teratoma localized in the retrorectal area.

surgical approach (anterior *vs* posterior *vs* combined) in a preoperative setting[22].

Other applicable imaging modalities are flexible sigmoidoscopy, transrectal ultrasonography (TRUS), and fistulograms. The flexible sigmoidoscopy is a newly established option to demonstrate rectal mucosa involvement or exclude a primary rectal cancer, whereas TRUS provides detailed information on the size, consistency of the tumor, and evidence of local invasion[2,5]. Fistulograms can be preferred in patients with a chronically draining sinus, to evaluate underlying pathology such as developmental cyst[21].

Preoperative biopsy has been controversial for retrorectal tumors, according to the potential risk of secondary infection and seeding of the tumor[1,8,21]. With the

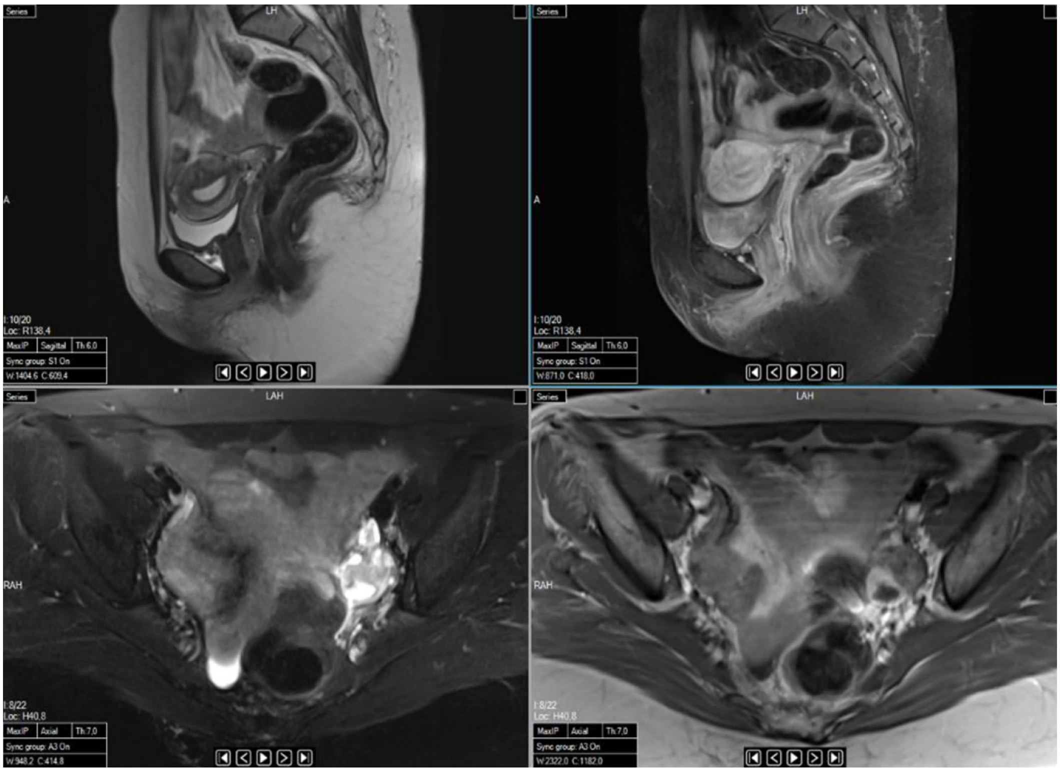

Figure 5 Sagittal and axial magnetic resonance images taken after resectioning the cystic teratoma shown in Figure 4.

advances in imaging modalities and improved neoadjuvant therapy options that have become available in recent years, it has become a feasible technique[25]. On the other hand, a preoperative biopsy may lead to misdiagnosis, with a reported rate of incorrect diagnosis as high as 44%[8]. Nevertheless, studies have demonstrated preoperative biopsy to have better diagnostic accuracy in solid or heterogeneous tumors and to affect treatment management[26,27]. Neoadjuvant chemotherapy is essential for some retrorectal tumors, such as Ewing sarcoma and osteogenic sarcoma, or metastatic chordoma, and tyrosine kinase inhibitors have been shown effective in progression-free survival[28-30].

In our clinical practice, if preoperative imaging modalities provide sufficient information regarding the nature of the lesion and if the treatment management will not change according to additional findings, we do not advocate performing a preoperative biopsy. It should be emphasized that if it is indicated, performing biopsies by an experienced radiologist and choosing the appropriate transperineal or parasacral approach have been recommended. However, transperitoneal, transretroperitoneal, transvaginal, and transrectal biopsies should be avoided, and the biopsy tract must be removed *en bloc*[21].

SURGICAL APPROACH

The optimal management of retrorectal tumors is surgical resection, including of benign tumors, given the potential for developing symptoms and malignancy[2,31,32]. The morphology of tumor determines the level of extension of surgery. Complete gross resection is recommended for benign tumors, whereas radical resection or *en bloc* resection of involved adjacent organs is required for malignant tumors[21]. Surgical approaches include those from the anterior (transabdominal), the combined abdominoperineal, and the posterior (perineal). A general consideration is that an anterior or combined approach is preferred for tumors above the level of S3 and a posterior approach for lesions below the level of S3.

Anterior (transabdominal) approach

The anterior approach is recommended for tumors located above S3 or which show sign(s) of pelvic wall involvement in the preoperative investigation. If the tumor cells have invaded into adjacent structures or an *en bloc* resection for malignant lesions

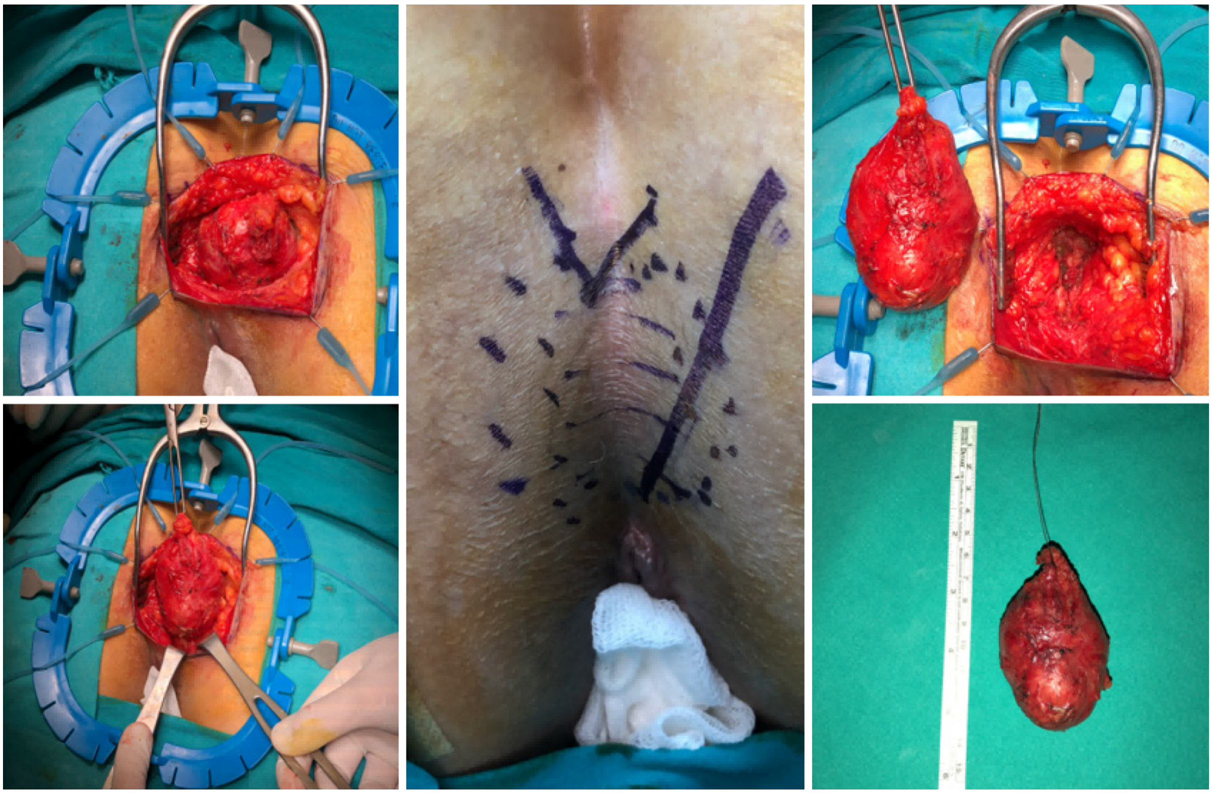

Figure 6 Perineal approach *via* parasagittal incision in a patient with a tail-gut cyst.

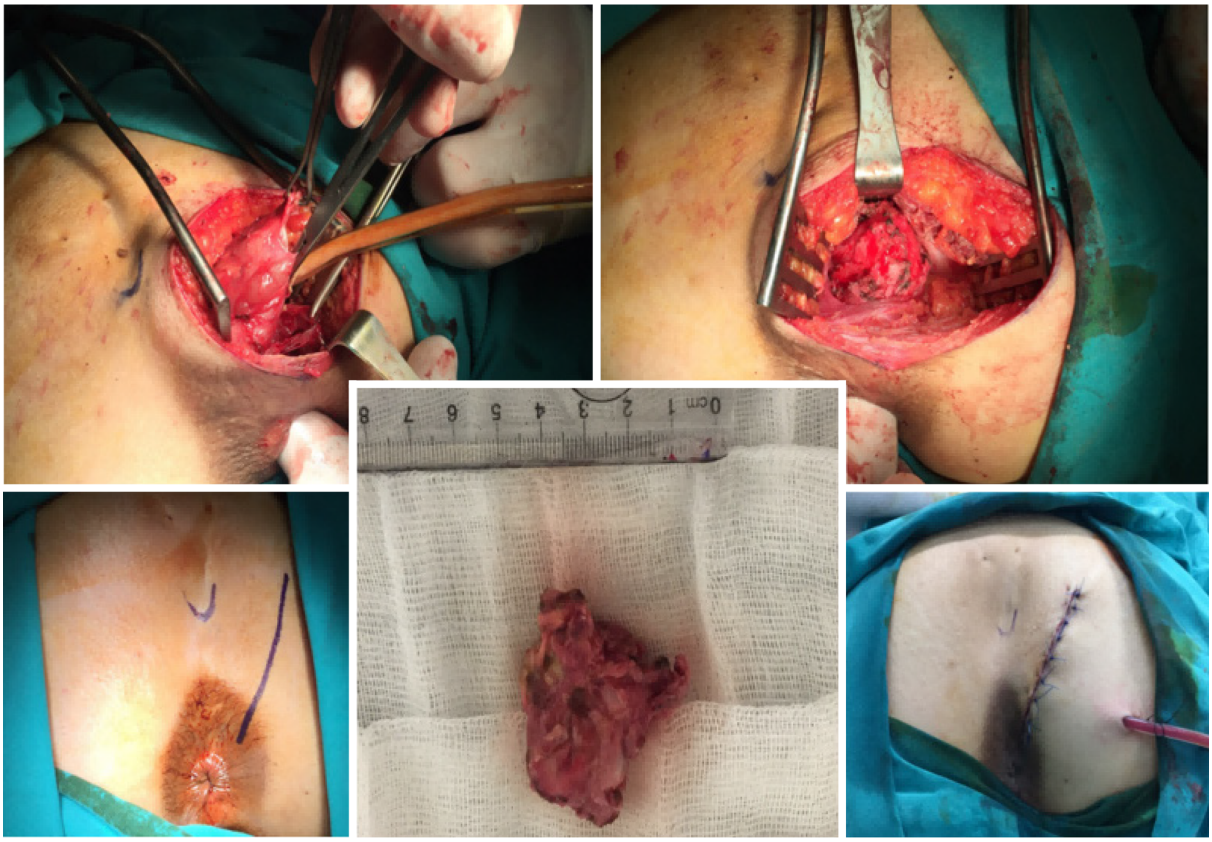

Figure 7 Perineal approach *via* parasagittal incision in a patient with an epidermoid cyst.

(such as sacrectomy) is required, this approach is more feasible[33,34]. For such, the patient is placed in the modified Lloyd-Davis position. The dissection starts with the opening of the pelvic peritoneum and continues to the posterior of the rectum. After the anterior margins of the tumor are dissected from the mesorectum, it is separated from the presacral fascia. Since the arterial supply of the tumor can originate from the middle sacral artery, it is crucial to identify and ligate the tumor's vascular structures first[25,35].

Posterior (perineal) approach

The posterior approach is indicated for tumors below S3 without any involvement of the sacrum and other pelvic organs (Figures 6-8). The patient is placed in the prone jack-knife position, and a midline or parasagittal incision is performed. Excision or elevation of the coccyx can be necessary for better exposure to the retrorectal space [23]. The division of the levator muscles follows, to enable access into the retrorectal space. Abdominoperineal resection may be required in patients with malignant tumors, as part of the *en bloc* resection. It has been reported that the posterior approach is preferred over the combined abdominoperineal approach, due to its lower morbidity rate than the latter, which has the highest recurrence and complication rate of all approaches[8,36-38].

Combined abdominoperineal approach

The combined abdominoperineal approach is recommended for malignant lesions, invading adjacent structures and obscuring normal surgical planes. The patient is placed in a modified Lloyd-Davies position, in order to access both areas[23]. If an extended soft tissue resection is required to achieve clear surgical margins, simultaneous or staged pedicle or free flap transfers can be used to prevent chronic sinus formation and fistulation[39,40]. Permacol mesh can also be applied for the reconstruction of the pelvic wall.

Minimally invasive surgery

Although it has not been reported whether laparotomy or laparoscopy has better long-term results, it is known that the laparoscopic approach provides an enhanced visualization of pelvic structures and facilitates precise dissection of the tumor from adjacent structures[8]. The laparoscopic approach has been demonstrated as a safe and feasible technique for treating retrorectal tumors[41,42]. There have also been case series reporting that the robotic approach can be chosen for large tumors, offering the benefits of shorter operation time and shorter length of hospitalization compared to laparotomy[43,44].

Transanal endoscopic microsurgery (TEMS) is also newly being applied to retrorectal tumors; however, with this approach, following oncological principles for malignant tumors is difficult[45,46]. Thus, it is recommended that malignancy should be excluded before TEMS is performed[23].

FOLLOW-UP AND SURVEILLANCE

Long-term results depend on the type of tumor and the successful surgical resection with clear margins achieved in the first operation. Although many authors have reported that benign retrorectal tumors have 100% overall survival rates with no recurrences[2,11], the patients should be followed-up for potential risk of local recurrence. Benign local recurrences' have been shown to have a good prognosis, even after repeated resection[47]. In contrast, malignant tumors can metastasize to the liver, lung, and brain, which are all associated with significantly worse prognosis[48-50].

CONCLUSION

Retrorectal tumors are uncommon lesions occurring in the retrorectal space. The most common retrorectal tumors are congenital benign tumors. The diagnostic algorithm starts with suspicion by a physician who carries out a thorough physical examination. MRI is the chosen imaging modality, with or without CT and TRUS. The preoperative biopsy is highly recommended for solid or heterogeneous tumors, although it is contraindicated for pure cystic lesions. The posterior approach is the preferred surgical method for most retrorectal tumors, producing lower morbidity rates. A multidiscip-

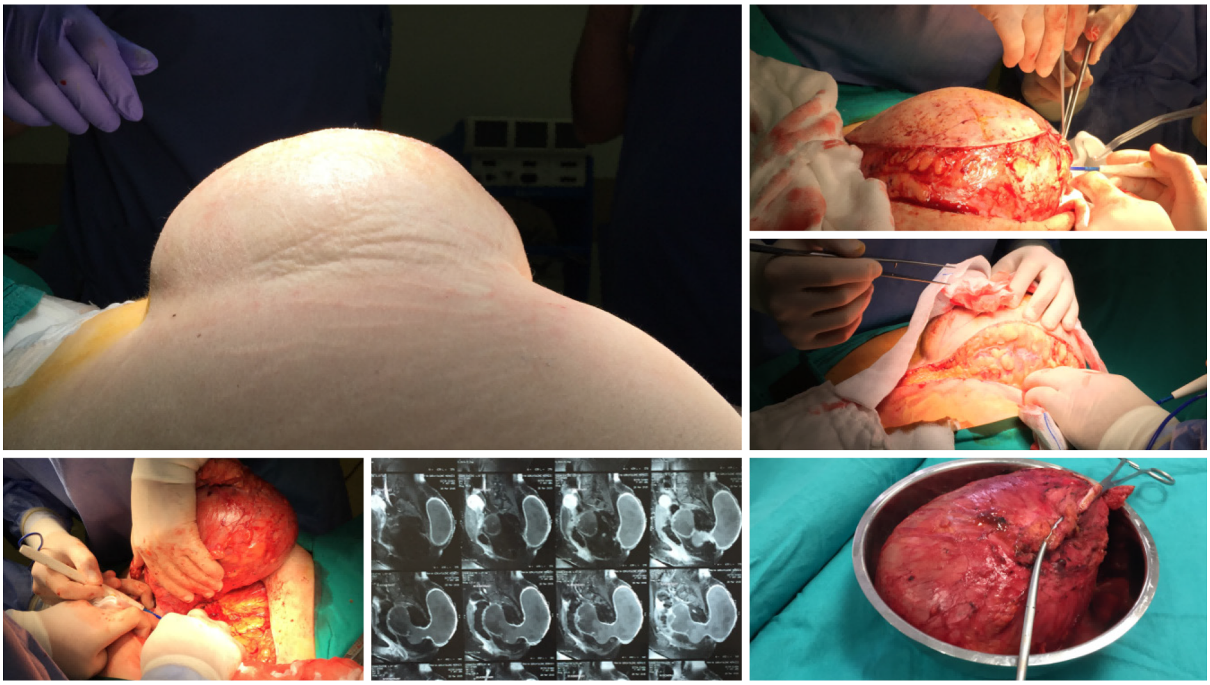

Figure 8 Perineal approach *via* parasagittal incision in a patient with a teratoma.

linary team is usually required, since these complex tumors have a potential risk of invading adjacent structures and necessitating an *en bloc* resection.

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MINIREVIEWS

Surgical ampullectomy: A comprehensive review

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Abstract

Tumours of the ampulla of Vater are relatively uncommon lesions of the digestive system. They are typically diagnosed at an earlier stage than other types of tumours in this region, due to their tendency to invoke symptoms by obstructing the bile duct or pancreatic duct. Consequently, many are potentially curable by excision. Surgical ampullectomy (SA) (or transduodenal ampullectomy) for an ampullary tumour was first described in 1899, but was soon surpassed by pancreatoduodenectomy (PD), which offered a more extensive resection resulting in a lower risk of recurrence. Ongoing innovation in endoscopic techniques over recent decades has led to the popularization of endoscopic papillectomy (EP), particularly for adenomas and even early cancers. The vast majority of resectable ampullary tumours are now treated using either PD or EP. However, SA continues to play a role in specific circumstances. Many authors have suggested specific indications for SA based on their own data, practices, or interpretations of the literature. However, certain issues have attracted controversy, such as its use for early ampullary cancers. Consequently, there has been a lack of clarity regarding indications for SA, and no evidence-based consensus guidelines have been produced. All studies reporting SA have employed observational designs, and have been heterogeneous in their methodologies. Accordingly, characteristics of patients and their tumours have differed substantially across treatment groups. Therefore, meaningful comparisons of clinical outcomes between SA, PD and EP have been elusive. Nevertheless, it appears that suitably selected cases of ampullary tumours subjected to SA may benefit from favourable peri-operative and long-term outcomes with very low mortality and significantly long survival, hence its role in this setting warrants further clarification, while it can also be useful in the management of specific benign entities. Whilst the commissioning of

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a randomised controlled trial seems unlikely, well-designed observational studies incorporating adjustments for confounding variables may become the best available comparative evidence for SA, potentially informing the eventual development of consensus guidelines. In this comprehensive review, we explore the role of SA in the modern management of ampullary lesions.

Key Words: Ampulla of Vater; Ampullary tumours; Surgical ampullectomy; Transduodenal ampullectomy; Endoscopic papillectomy; Pancreatoduodenectomy

Core Tip: The role of surgical or transduodenal ampullectomy in the management of ampullary lesions has not been well-defined and the available evidence has been entirely observational. However, it appears that suitably selected cases of ampullary tumours may benefit from favourable peri-operative and long-term outcomes with very low mortality and significantly long survival, hence the role of surgical ampullectomy in this setting warrants further clarification, while it can also be useful in the management of specific benign entities. In this comprehensive review, we explore the role of surgical ampullectomy in the modern management of ampullary lesions.

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INTRODUCTION

Ampullary adenocarcinoma (AAC) is the most common cancer of the ampulla of Vater, but represents only 7% of peri-ampullary cancers, and fewer than 1% of all cancers of the digestive system[1,2]. Its prognosis is relatively favourable compared to other cancers near the ampulla: 5-year survival is 41.5%-53% following surgical resection[1,3,4]. AACs are widely believed to develop within adenomas following an adenoma-carcinoma sequence[5]. Histological examinations have detected AACs within 40.9% of surgically resected lesions which were pre-operatively considered to be adenomas[6]. Therefore, ampullary adenomas are typically considered to be pre-cancerous rather than benign lesions, and some authors have suggested that all ampullary lesions should be regarded as potentially malignant[6].

Ampullary tumours may cause symptoms by obstructing the flow of bile or pancreatic juice, even when relatively small, and many asymptomatic tumours are easily detected during endoscopic investigations for unrelated issues[6].Consequently, ampullary tumours are often detected at an earlier stage than other tumours in this region[6,7]. Accordingly, many patients will be potentially curable by surgical excision. Surgical ampullectomy (SA) (or transduodenal ampullectomy) for ampullary cancer was first described by Halsted in 1899[8]. Recurrences were common, therefore SA was largely abandoned in favour of the more extensive pancreatoduodenectomy (PD), first described in 1898 by Codivilla and subsequently refined throughout the first half of the 20th century[9]. A study at the John Hopkins Hospital, Maryland, United States, found that PD was performed for 96.7% of ampullary tumours resected between 1970 and 2007[6]. The major criticism of PD has been its historically high morbidity and mortality, often associated with pancreatic fistulae. However, it has become evident in recent years that specialist high-volume tertiary centres can achieve comparatively better clinical outcomes and a mortality less than 5%[2].

Recent innovation in endoscopic techniques has led to increasing interest in endoscopic papillectomy (EP), which is considerably less invasive than SA and PD. It is worth noting that the endoscopic procedure is often referred to as an *ampullectomy*. However, only excision of the duodenal mucosa and submucosa at the papilla is involved; it is therefore more accurately referred to as a *papillectomy*[10]. Accordingly, whilst EP and SA are both local excision techniques, EP is less extensive than SA, which involves excision of the entire ampulla together with small parts of the duodenal wall, bile duct, pancreatic duct, and occasionally pancreatic parenchyma. A recent study of EP for non-invasive ampullary tumours demonstrated eventual endoscopic tumour clearance in 91.1% of patients, including repeat procedures for recurrences, which occurred in 32.7%[11]. Adverse events occurred in 18.9%, most commonly haemorrhage (11.3%); other complications included papillary stenosis, acute pancreatitis, and duodenal perforation. The mortality of EP has been reported as 0.3% or lower[10]. Many authors have advocated EP as the preferred treatment for small non-invasive ampullary tumours, including adenomas containing high-grade dysplasia (HGD) or carcinoma *in-situ* (Cis), although historically objections against EP were expressed from authors of studies which reported procedure-related deaths[10-16]. EP has also been suggested as a suitable treatment for carefully selected early ampullary cancers, although this has been controversial and some authors have advocated PD for all ampullary cancers in patients who are adequately fit due to the risk of lymphatic involvement[6,10,17,18].

Despite the dominance of EP and PD, SA is still performed in certain circumstances. Determining which patients will benefit from SA requires an understanding of specific factors which may make EP or PD unfeasible or unacceptable. We aim to review the role of SA in the modern management of resectable ampullary tumours.

PRE-OPERATIVE EVALUATION

The purpose of pre-operative evaluation of ampullary tumours is to determine their malignant potential, assess resectability, and establish stage in the case of possible cancers. There has been particular emphasis on the role of endoscopic biopsies and endoscopic ultrasound (EUS)[12]. However, supporting information from other investigations has usually been required, including endoscopy, computed tomography (CT), magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP), and intraductal ultrasonography (IDUS)[10].

It has been well demonstrated that pre-operative endoscopic biopsies cannot reliably exclude the presence of small foci of cancer, as small superficial tissue samples are not representative of the whole tumour[19,20]. The reported sensitivity of endoscopic biopsies for detecting cancer, relative to post-operative histology of excised tumours, ranges from 42%-89%, and specificity from 79%-100%[12,18,20-22]. Positive predictive value ranges from 50%-100%, and negative predictive value from 73%-94%[12,20,22]. Diagnostic accuracy has been reported from 45%-100%[12,14,21-28]. The type of endoscope used has been found to affect the diagnostic accuracy of biopsies: those obtained using side-viewing duodenoscopes have outperformed samples taken using forward-viewing endoscopes (85.7% *vs* 45%, P = 0.004)[29]. Perhaps the most clinically significant performance metric for endoscopic biopsy is the false negative rate, ranging from 10%-60%[7,18,22-24,27,30].

EUS has been described as a critical investigation for ampullary tumours, due to its ability to determine the extent of local invasion and identify lymph node metastases [12]. It has therefore assumed an important role in evaluating likelihood of malignancy, resectability, and pre-operative staging. Its sensitivity for detecting ampullary tumours is 97.6%[31]. EUS findings suggestive of malignancy include intraductal extension, invasion of the sphincter of Oddi, duodenum or portal vein, and lymphadenopathy[12]. In addition, fine needle aspiration of lymph nodes can be performed during EUS to obtain samples for cytological examination, further enhancing its utility in detecting cancer and staging. Its accuracy in determining N-stage has been reported as 66.7%[31]. EUS has been found to have an accuracy of 78%-87.8% in assessing the extent of local invasion, and has a tendency towards overestimation rather than underestimation[22,31,32]. Differentiation of T3 and T4 cancers from non-invasive tumours and early cancers has been described as easy, however some authors have found EUS unhelpful, particularly for discriminating non-invasive tumours from T1 cancers[19,22,33]. Its sensitivity for intraductal extension relative to post-operative histology is 80%, and specificity 93%[34]. Accuracy in determining resectability of ampullary and pancreatic cancers has been reported as 72%[35]. Rejeski *et al*[36] reported a set of EUS findings which detected ampullary tumours requiring surgery rather than EP with a sensitivity of 97.1%, although this was not prospectively validated on an independent data sample.

CT has been found to have a relatively low sensitivity for detecting ampullary tumours, sometimes as low as 20%[30,31]. It has a similarly poor performance in evaluating local invasion, with a T-stage accuracy of 26.1%[31]. However, its N-stage accuracy has been measured at 43.5% with no statistically significant difference from

EUS or MRI, and it can detect distant metastases[12,31]. MRI has been demonstrated to be comparable to EUS: Its sensitivity for detecting ampullary tumours was 81.3%, T-staging accuracy 53.8%, and N-staging accuracy 76.9%, with no statistically significant differences from EUS[31].

Endoscopy using either a forward-viewing endoscope or side-viewing duodenoscope allows visualization of the ampullary lesion, to evaluate malignant potential and endoscopic resectability[37]. In general, tumours which are firm, immobile, friable, ulcerated, or have an indistinct margin are likely to be malignant[10,12]. A small study in 2015 found a sensitivity of 94.7% and a specificity of 89.5% for AAC diagnosed using the following endoscopic criteria: "enlarged papilla with uneven granular or nodular appearance of overlying mucosa, associated with spontaneous bleeding, ulceration, and friable or indurated surface"[29]. However, there has not been a robust evaluation of specific criteria for distinguishing ampullary adenomas from early AAC based on endoscopic appearances[10]. There has been controversy regarding whether tumour size correlates with the likelihood of cancer: whilst some authors have supported this assertion, several studies, including a recent meta-analysis, have found no correlation[6,12,37,38]. ERCP is useful for evaluating intraductal extension: it has been found to have a sensitivity of 83% and a specificity of 93% for detecting intraductal extension relative to post-operative histology, which was comparable to EUS[34].

INDICATIONS

Studies of SA have all been observational and heterogenous in their methodologies and findings, resulting in a deficient evidence base[38]. Furthermore, SA has been an uncommon treatment for a rare tumour, and has therefore attracted relatively little attention. Consequently, no evidence-based consensus guidelines have been produced regarding suitable indications for SA. Recognizing this, many authors have described specific indications or decision-making algorithms based on their own data, practices, or interpretations of the literature[6,10,12-14,17,19-24,27,28,32,39-50]. A summary of generally accepted indications, contra-indications, and controversies is presented in Table 1.

The least controversial indication has been ampullary adenoma. Historically, PD was considered preferable due to diagnostic uncertainty, however the trend over time has been towards less invasive options. For smaller adenomas, EP has become the preferred option, with SA reserved for cases which are too large for endoscopic resection[46]. Suggested minimum sizes to consider SA range from 2 to 3 cm, or what the endoscopist considers too large for EP[10,13,26,39,49]. A few authors have proposed maximum sizes for SA of 2.5-4 cm, on the justification that larger adenomas may be more likely to contain cancer[20,22,51]. However, most authors have not reported an upper size threshold; this position is supported by the significant amount of data finding no such correlation between size and malignant potential[6,12,37,38]. Accordingly, SA has been successfully performed for carefully selected large adenomas (Figure 1). Many authors have suggested SA is suitable for adenomas containing HGD, whilst EP is adequate for low-grade dysplasia[13,42,49,51,52]. Similarly, adenoma with Cis has been widely reported as an indication for SA[12,21,23,24,40,44]. SA has also been recommended for adenomas which recur after EP, and when EP has failed to achieve clear margins[42,52].

Ampullary tumours may occur in patients with familial adenomatous polyposis (FAP), an inherited syndrome characterized by hundreds or thousands of polyps in the colon and rectum, and commonly also in the duodenum[53]. The risk of ampullary cancer in FAP patients has been reported to be 124-fold that of the general population [54]. A classification of duodenal polyposis was developed by Spigelman *et al*[55], based on the number, size and histology of polyps, as shown in Table 2. A consensus guideline produced by the Mallorca Group in 2008 considered PD or pancreas-sparing duodenectomy necessary for older patients with Spigelman stage IV polyposis, due to the high risk of developing duodenal cancer[53]. It was suggested that local surgery may be appropriate for patients under 40 years with stage III or IV disease. The most important advantage of local surgery was considered to be the postponement of more extensive resections in younger FAP patients. The role of SA, relative to EP and PD, in FAP patients has not been well-defined.

Intraductal extension of tumours has been found to be suggestive of malignancy, and therefore has been regarded as a contra-indication by those who oppose SA for early cancers in fit patients[12,26]. However, up to 1 cm of intraductal extension has

Table 1 Indications for surgical ampullectomy

Lesion type	Generally accepted indications	Uncertainties	Generally accepted contra-indications	Ref.
Adenoma	Lesion too large for EP, including those with HGD or Cis	Tumour size thresholds		[6,10,12,13,20-24,26,37-40,42,44,46,49,51,52]
	Failed EP, including recurrence or positive margins			[42,52]
		FAP patients		[53-55]
AAC	T1 or T2, unfit for PD	T1 or T2, fit for PD	T3 or T4, fit for PD	[6,21-24,30,39,41,43-46,49,51,58]
	Well-differentiated	Moderately-differentiated	Poorly-differentiated	[21,23,30,39,43,49,56,57,60]
			Nodal or distant metastases	[21,23,24,30,39,41,49]
		Requirement for lymphadenectomy		[39,57]
		Intraductal extension		[10,12,19,21,26,56]
Others	Sphincterotomy-associated biliary stricture			[70]
		Neuroendocrine tumours		[66,67]

AAC: Ampullary adenocarcinoma; FAP: Familial adenomatous polyposis; EP: Endoscopic papillectomy; HGD: High-grade dysplasia; PD: Pancreatoduodenectomy.

Table 2 Spigelman's classification of duodenal polyposis

Characteristics		Points
Number of polyps	1 to 4	1
	5 to 20	2
	> 20	3
Size of polyps	1 to 4 mm	1
	5 to 10 mm	2
	> 10 mm	3
Histological type	Tubular polyp, hyperplasia, inflammation	1
	Tubulovillous	2
	Villous	3
Dysplasia	Mild	1
	Moderate	2
	Severe	3

A total of 0 points = stage 0; 1 to 4 points = stage I; 5 to 6 points = stage II; 7 to 8 points = stage III; and 9 to 12 points = stage IV[55].

been considered permissible when undertaking EP for tumours measuring less than 2 cm which are not thought to be malignant[10]. Among proponents of SA for early cancers in fit patients, there has been some disagreement regarding the extent to which intraductal extension is permissible before conversion to PD. Lai *et al*[21] reported that SA was indicated for up to 1 cm of extension into the bile duct or pancreatic duct. However, Aiura *et al*[19,56] precluded from consideration any cases with tumour extension into the pancreatic duct, while considering any degree of ingress into the bile duct, as this could be addressed by resection of the extrahepatic bile duct.

The role of SA as a treatment for AAC has been extensively debated. Particular attention has been paid to predictors of lymph node metastasis, as this may be the major factor responsible for recurrence following SA, and is also associated with poor

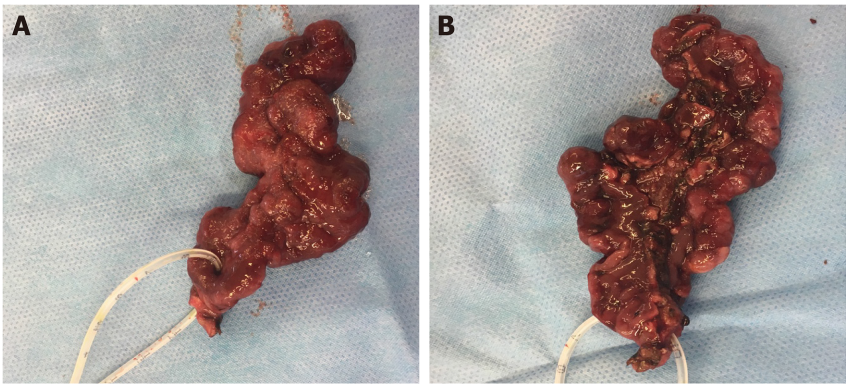

Figure 1 A 7-cm polypoid tubulovillous adenoma extending from the ampulla of Vater down to D3, removed by means of open surgical ampullectomy-excision of adenoma en block, following cholecystectomy and catheterization of the ampulla for identification. Preoperative biopsies showed low-grade dysplasia (LGD) and this 74-year old patient with severe comorbidities was initially counselled for pancreatoduodenectomy. Meticulous preoperative endoscopic evaluation revealed its polypoid configuration, possibly emanating from a mucosal stalk, which was confirmed intraoperatively. A: The ampulla is encircled by a fine catheter. Final histology confirmed the presence of a tubulovillous adenoma with extensive LGD and focal high-grade dysplasia. All margins were clear of tumour or dysplasia. (V. Mavroeidis' archive). B: Inferior aspect of the specimen, depicting the duodenal margin along the tumour, and the insertion point of the catheter into the ampulla. (V. Mavroeidis' archive).

prognosis[2,4,32,56]. It has been widely recognized that PD is the most effective treatment for ampullary cancer[6]. Proponents of SA have argued that it may be adequately effective for certain early cancers, whilst avoiding unnecessary morbidity associated with PD[41]. Although there has been unanimous agreement that the absence of lymph node and distant metastases (N0 M0) is an absolute prerequisite for SA, there has been variability in criteria for size, T-stage, intraductal extension, and grade[21,23,24,30,39,41,49]. Several authors have recommended a maximum tumour size of 2 or 3 cm, as size has been found to correlate to risk of lymph node metastases; however, the majority has not specified a maximum size limit[6,21,24,30,41,45,49]. The use of SA as an alternative to PD for T1 Lesions has been widely supported[21-24,30, 39,41,43,45,46,49]. Lymphadenectomy has been considered essential by some authors when SA was performed for T1 lesions[39,57]. Some authors have objected to SA for T1 cancers in patients who are adequately fit for PD, as the risk of lymph node metastasis from T1 tumours is 22%-30%[6,39,44,51,58]. The majority of studies have not supported the use of SA for T2 cancers in fit patients, although some have suggested it is appropriate provided the tumour measures less than 2 or 3 cm[41,45]. SA has not been advised for T3 or T4 cancers in fit patients. The interpretation of recommendations regarding T-stage is further complicated by differences in definitions proposed by various editions of the Union for International Cancer Control TNM classification, and some authors have not specified which edition their recommendations have been based on. Further changes to T-stage definitions for ampullary cancer have been proposed, as the correlation of the 8th edition definitions with prognosis has been questioned by some authors[59].

The histological grade has been found to predict the risk of lymph node metastases. A study by Amini *et al*[57] found lymph node metastases in 10% of well-differentiated, 12% of moderately-differentiated, and 27% of poorly-differentiated ampullary cancers (P = 0.007). Well-differentiated lesions have therefore been considered the most suitable cancerous candidates for SA[21,23,30,39,43,49,56]. Some authors have also supported its use for moderately-differentiated tumours[21,39,43,49]. However, Aiura *et al*[56] regarded SA as inappropriate for moderately- and poorly-differentiated lesions as their study reported lymph node metastases in 62.1% of cancers of these grades. Beger *et al*[39] also considered SA unsuitable for poorly-differentiated cancers. Furthermore, over recent years, the clinical relevance of the histological heterogeneity of AAC has become better understood, with accumulating evidence regarding differences in responses to treatment between the intestinal, pancreatobiliary and mixed types[60].

There has been general agreement that SA may be particularly appealing for early ampullary cancers in patients who are unfit for PD and in whom EP is not feasible, although there has been some controversy regarding the appropriateness of SA in elderly, frail patients[3,7,13,17,28,32,50,52,61-63]. Some studies have suggested SA may have value as a palliative treatment; however, it has not been made apparent how SA would be advantageous compared to common palliative options such as stenting and bypass procedures[12,50,62,64,65].

Although SA has most commonly been used for adenomas and AACs, treatment of other lesions has been described. Milanetto *et al*[66] considered SA appropriate for well-differentiated ampullary neuroendocrine tumours (NETs) less than 2 cm in size, and for larger well-differentiated NETs in patients unfit for PD; however, some authors have expressed concern regarding its potential to underestimate the stage and under-treat NETs[67]. SA for a patient with an intraductal papillary neoplasm of the bile duct, considered unsuitable for EP due to intraductal extension of more than 10 mm, has also been reported[68]. SA has also been employed for the treatment of inflammatory and fibrotic stenoses of the ampulla[69]. Endoscopic biliary sphincterotomy has been proposed as an effective first-line treatment for post-sphincterotomy stenosis, as the lesion is limited to the intra-duodenal portion of the orifice and the sphincterotomy can be extended[70]. In cases of sphincterotomy-associated biliary stricture, in which the stenosis extends along the bile duct, either endoscopic balloon dilatation or SA has been considered necessary[70].

SURGICAL TECHNIQUE

The technique of SA has been extensively described, including reports of minimal access approaches[20,30,39,46,62,68,71-73]. Pre-operative endoscopic stenting of the bile duct may be employed to relieve jaundice, and is helpful in locating the bile duct during surgery. The abdomen is accessed, either by laparotomy using a right subcostal or upper midline incision, or by minimal access methods. The abdomen is then explored for evidence of metastases. If the bile duct was not stented pre-operatively and a cholecystectomy is to be performed, a stent may be inserted *via* the cystic duct through the ampulla to assist in its identification (Figure 1). The hepatic flexure of the colon is mobilized, followed by the second part of the duodenum using the Kocher manoeuvre. The position of the ampulla is determined by palpation of the tumour or stent. A 4-5 cm longitudinal duodenotomy is then performed opposite the ampulla. Stay sutures are placed in the duodenal wall using 2-0 silk to maintain adequate exposure. The bile duct and pancreatic duct can be cannulated *via* the ampulla to assist with their identification, if a stent was not already in place. Once the ampullary tumour has been identified, some authors have recommended placing a 2-0 silk suture through it to facilitate retraction. Submucosal injection of adrenaline solution has been reported, to elevate the lesion and reduce bleeding[73].

Several variations of excision and reconstruction have been described. The duodenal tissue may be dissected circumferentially, leaving the bile duct and pancreatic duct initially intact; the ducts are marked with sutures before transecting them. The ducts are then approximated to the duodenal wall using interrupted 4-0 or 5-0 absorbable sutures, and to each other at their closest margins to form a common wall. Alternatively, Mathiel *et al*[71] recommended a “suturing as you go” method, to prevent duct retraction. Dissection begins at the 11 o’clock position, proceeding towards the bile duct. When the bile duct is entered, a 4-0 or 5-0 absorbable suture is placed to approximate the bile duct to the wall of the duodenum. As the bile duct is gradually opened, further sutures are placed. Dissection proceeds clockwise, until the pancreatic duct is encountered at the 2 o’clock position. The pancreatic duct is progressively sutured in a similar manner. After the mass is completely excised, the common wall of the bile and pancreatic ducts is formed using 5-0 absorbable sutures. There has not been a comparative evaluation of excision and reconstruction techniques.

Histological examination of the excised lesion by intra-operative frozen section to confirm clear margins has been strongly advocated for, particularly when cancer is suspected[7,62,63]. SA with frozen section has been conceptualized as a “macro biopsy”, having both diagnostic and therapeutic functions[50,58]. Schoenberg *et al*[18] described performing frozen section allowing a 1 cm margin of macroscopically normal tissue around the lesion. The operation can be converted to PD if clear margins cannot be obtained, or if the histological characteristics are worse than anticipated. Frozen section has generally been found to be accurate relative to post-operative histology of the resected specimen: reported accuracy ranges from 75%-100%[14,20,21,23,25-27,30,43,63]. The lowest reported diagnostic sensitivity has been 57%, in a cohort of 7 patients[63]. Other measurements of sensitivity range from 85.6% to 97%[18,21,24]. The combination of pre-operative endoscopic biopsies and intra-operative frozen section has been found to improve diagnostic accuracy to 100%[30,62].

Having confirmed complete excision has been achieved, the patency of the bile and pancreatic ducts is then assessed. Visualization of the expulsion of bile and pancreatic juice has been suggested to adequately confirm duct patency[71]. However, probing of the ducts using biliary dilators has also been reported, to ensure the diameter of the ducts is sufficient to tolerate an expected contraction of 50% due to scarring; 6-8 mm for the bile duct, and 4-5 mm for the pancreatic duct has been considered adequate[30,62]. Some surgeons have advocated temporary stenting to maintain patency during healing, for example by inserting a 14-gauge silicone catheter into each duct and securing it in place with an absorbable suture[46,73]. The duodenum can then be closed transversely to avoid stricturing, using an absorbable suture in either a single or double layer, or a stapling device. In minimal access cases, a single-layer 3-0 continuous barbed absorbable suture may be preferable[73]. A drain may be placed near the duodenotomy at the discretion of the surgeon.

Some authors have incorporated additional components within SA procedures. Excision of supraduodenal lymph nodes and nodes anterior and posterior to the pancreatic head has been described during SA for T1 AACs, on the justification that such lesions are often associated with local lymph node metastases[39,49,57]. SA combined with excision of the extrahepatic bile duct has also been reported, to deal with intraductal extension along the bile duct, provided none occurred along the pancreatic duct[19,56].

CLINICAL OUTCOMES

No randomized controlled trial (RCT) has been conducted to compare SA to EP or PD for any indication[38]. The evidence has been entirely observational; most studies have been retrospective single-centre case series or cohort studies. Comparing clinical outcomes of SA to those of EP or PD is therefore problematic, because characteristics of patients assigned to each treatment have differed substantially[58]. Similarly, there has been a lack of comparative evaluations of minimal access *vs* open surgical techniques for SA. A summary of clinical outcomes of SA is presented in Table 3.

A recent systematic review and meta-analysis by Heise *et al*[38] reported a pooled complete excision (R0) rate for SA of 96.4%, from 10 studies including adenomas and AACs. However, some small studies which were not included have reported less favourable results. Lindell *et al*[74] reported an R0 rate of 50% in a series of 10 SAs for AACs in patients unfit for PD. Similarly, Kobayashi *et al*[17] achieved R0 in only 50% of 6 SAs performed for adenomas and T1 cancers in unfit patients. In a series of 17 cases described by Zhong *et al*[50], R0 was achieved in 52.9%; this series included patients with T2 and T3 cancers, and 76% were of moderate or poor histological grade.

Local recurrence has been considered the major weakness of SA compared to PD [12]. The main recurrence pattern after R0 excision appears to be lymph node metastasis[75]. The meta-analysis by Heise *et al*[38] calculated a pooled recurrence rate of 9.4% over 12 studies of SA. Recurrence rates reported by individual studies within the meta-analysis ranged from 0-31.8%[24,26,49]. However, some studies not included within the analysis have observed significantly higher rates, up to 80% for AACs[41,62,74]. Recurrence rates as high as 100% have been reported in patients with FAP[16]. The wide range of recurrence rates may be explained by methodological heterogeneity between studies: there have been considerable differences in indications, patient characteristics, and follow-up duration[7]. Lifelong surveillance endoscopy has been considered necessary owing to the risk of tumour recurrence following SA[23,25,47,62].

There has been considerable interest in complications following SA, as comparatively low surgical morbidity has been the primary justification for its use in preference to PD. The pooled complication rate in the meta-analysis by Heise *et al*[38] was 28.3% among 13 studies; individual studies reported rates ranging from 7.7%-68%. Acute pancreatitis has been described in 10%-50% of patients following SA[12,76]. Post-operative haemorrhage has occurred in 3.8%-25% of cases, sometimes necessitating emergency re-operation[3,52]. Reported wound infection rates range from 5%-20.7%[25,30]. Other less frequent complications have included biliary or pancreatic fistulae, duodenotomy leakage, cholangitis, delayed gastric emptying, biliary strictures, adhesional intestinal obstruction, and other general post-operative complications[12,13,25,30,51,52,58,62,63,76]. Surgical mortality risk associated with SA has proven to be very favourable: across 30 studies reporting mortality statistics, only 5 deaths have occurred in 532 patients (0.9%)[6,12,14,20,22,24,25,28,30,32,39,41,43,45,47-52,58,62,64,67,72,74,76-79].

Long-term survival in patients undergoing SA for cancers has been inconsistently reported, as follow-up durations have varied within studies and among different studies. Reported overall 5-year survival rates range from 10%-77.3%[24,30,41,43,50,74]. A more useful insight may be gained by considering studies which have reported

Table 3 Clinical outcomes of surgical ampullectomy

Indication	Outcome		Estimate	Ref.
Adenoma or AAC	Complete excision (R0)		96.4%	[38]
Adenoma or AAC	Recurrence		9.4%	[38]
Adenoma or AAC	Complications		28.3%	[38]
Adenoma or AAC	Mortality[1]		0.9%	[6,12,14,20,22,24,25,28,30,32,39,41,43,45,47-52,58,62,64,67,72,74,76-79]
AAC	Survival at 5 yr	T1	40%	[50]
		T1 + T2	64.3%	[41]
		T2	16%	[50]
		T3	0%	[50]
		T3 + T4	18.2%	[41]

[1]Pooled mortality of cited studies (5 deaths in 532 surgical ampullectomies across 30 studies).
AAC: Ampullary adenocarcinoma.

subset analyses by cancer stage. Feng *et al*[41], in a cohort of 25 patients, reported 5-year survival rates of 64.3% for T1/T2, and 18.2% for T3/T4 cancers. Zhong *et al*[50] observed 40% survival at 5 years for T1 disease, 16% for T2, and 0% for T3, in a study of 17 patients. The interpretation of long-term survival metrics is further complicated by the tendency for SA to be used in co-morbid patients.

FUTURE RESEARCH

The likelihood of an RCT being conducted to evaluate SA seems low, as it has been an uncommon treatment for a rare tumour and therefore attracts relatively little attention from researchers and funders. Furthermore, the available evidence strongly suggests that randomization would be unethical. However, the ESAP study is a planned international multicentre retrospective cohort study which aims to compare EP, SA and PD for ampullary neoplasms[80]. Its methodology includes propensity score matching to account for differences in baseline characteristics of the cohorts. The ESAP study may have the potential to become the best available evidence for SA in lieu of an RCT. Its findings could stimulate the development of consensus guidelines to clarify the role of SA in the management of ampullary tumours.

CONCLUSION

SA may be the best available treatment option for a specific subset of patients with ampullary tumours. It can be conceptualized as an intermediate type of excision in terms of extensiveness and morbidity, between EP and PD. Therefore, it may be appropriate in situations where EP is inadequate or impossible, or where PD is unnecessary or prohibitively risky. Whilst many authors have proposed specific indications for SA, there has been significant controversy, particularly regarding the management of early ampullary cancers. The least controversial indication appears to be ampullary adenoma, with SA being reserved for cases which are too large for endoscopic excision. Its role in the treatment of AAC has been debated. The absence of lymph node and distant metastases is an absolute prerequisite for consideration of the procedure. Its use as an alternative to PD has been supported for T1 tumours and less frequently for selected T2 tumours, whilst it has largely been discouraged for T3 and T4 tumours. Equally, it may be unsuitable for poorly-differentiated AACs. There seems to have been general agreement that SA may be particularly appealing for early ampullary cancers in patients who are unfit for PD, and in whom EP is not feasible. Importantly, high rates of long-term survival have been achieved, particularly in suitable cases of T1 tumours, whereas prognosis has been unfavourable following excision of T3 and T4 tumours. Additionally, SA may have a role in carefully selected cases of NETs, as well as in cases of inflammatory and fibrotic strictures of the ampulla. When undertaken for ampullary tumours, frozen sections of the margins have been strongly advised, particularly when cancer is suspected. Importantly, while SA may be associated with considerable morbidity, the reported mortality is less than 1%.

The available evidence has been entirely observational, and an RCT seems impractical. However, further cohort studies incorporating adjustments for confounding variables may provide more meaningful data, facilitating the definition of specific criteria and potentially informing the development of consensus guidelines. Subsequently, the use of SA in the management of ampullary lesions may increase in a more standardized fashion.

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MINIREVIEWS

Is surgery the best treatment for elderly gastric cancer patients?

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Abstract

As the elderly population increases, the number of patients with gastric cancer has also been increasing. Elderly people have various preoperative problems such as malnutrition, high frequency of comorbidities, decreased performance status, and dementia. Furthermore, when surgery is performed, high postoperative complication rates and death from other diseases are also concerns. The goal of surgery in the elderly is that short-term outcomes are comparable to those in nonelderly, and long-term outcomes reach life expectancy. Perioperative problems in the elderly include: (1) Poor perioperative nutritional status; (2) Postoperative pneumonia; and (3) Psychological problems (dementia and postoperative delirium). Malnutrition in the elderly has been reported to be associated with increased postoperative complications and dementia, pointing out the importance of nutritional management. In addition, multidisciplinary team efforts, including perioperative respiratory rehabilitation, preoperative oral care, and early postoperative mobilization programs, are effective in preventing postoperative pneumonia. Furthermore, there are many reports on the usefulness of laparoscopic surgery for the elderly, and we considered that minimally invasive surgery would be the optimal treatment after assessing preoperative risk.

Key Words: Elderly; Gastric cancer; Surgery; Laparoscopy; Gastrectomy; Dementia

Core Tip: The definition of elderly varies from 75 to 85 years of age and over. Therefore, we classified individuals into ages 75, 80, and 85 years and over. In addition, long-term functional performance in the elderly should consider not only prognosis but also life expectancy. Perioperative problems were discussed separately for preoperative, intraoperative, and postoperative procedures. Regarding surgery,

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based on the latest findings, we discussed surgical indications compared with best supportive care, laparoscopic surgery, total gastrectomy, and the extent of lymph node dissection.

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INTRODUCTION

Although gastric cancer (GC) has declined over the past decades[1], it is still one of the most common cancers worldwide. It is the fifth leading cancer and the third leading cause of cancer-related death globally[2]. Surgery is the main treatment for GC, and chemotherapy and radiation therapy are adjuvants. Gastric carcinogenesis is a multifactor and multistep process characterized by a complex interplay between the host and environmental factors[3]. Although there are many reports of an association between *Helicobacter pylori* (*H. pylori*) infection and GC, recent reports show that *H. pylori* might be more a commensal and an opportunistic pathogen than a confirmed pathogen[4]. In addition, gut microbiota dysbiosis and chronic inflammation play a greater role in the initiation and progress of GC than in the presence of *H. pylori*[5]. GC due to *H. pylori* infection is recognized as noncardia GC, and a decrease in *H. pylori* infection contributes to a decrease in noncardia GC[6]. On the other hand, cardia GC caused by obesity and gastroesophageal reflux disease has increased[7].

Life expectancy has increased globally. According to the 2020 World Health Statistics released by the World Health Organization, Japan has the highest life expectancy, 84.2 years, followed by Switzerland, with a life expectancy of 83.3 years. Twenty-eight countries have an average life expectancy of over 80 years. Many European countries are ranked high, and Asia, Singapore, and South Korea, in addition to Japan, are also ranked high[8]. As a result, the prevalence of elderly patients with GC increases significantly as the population ages[9].

However, GC treatment in the elderly faces several challenges, such as increased underlying comorbidities[10], low organ function, low immune function, and decreased willingness for treatment. Other problems that arise when surgery is performed are high postoperative complication rates and death from other diseases [11]. In addition, weight loss after gastrectomy significantly worsens quality of life and adversely affects the long-term prognosis of elderly patients with GC[12]. Herein, we consider the problems encountered in GC treatment in the elderly.

OVERVIEW OF SURGICAL TREATMENTS IN ELDERLY PATIENTS WITH GC

Regarding the evaluation of surgical outcomes, short-term outcomes include postoperative complications and hospital mortality, whereas long-term outcomes include prognosis. The goal of surgical treatment in the elderly is short-term outcomes comparable to the nonelderly and long-term outcomes that reach life expectancy.

Many studies of surgery for elderly patients with GC have been reported. Preoperative characteristics of the elderly include decreased nutritional status, high frequency of comorbidities[13], and high frequency of dementia[14]. In general, the incidence of complications increases with age[10,13]. However, the definition of elderly varies from 75 to 85 years and over.

In studies divided by 75 and 80 years, some reports stated no difference in the postoperative complication rate even though the elderly had many comorbidities and a high American Society of Anesthesiologists (ASA) physical status[15-17]. However, several reports suggest that mortality due to surgical[13,18,19] and severe complications[10] was higher in the elderly (Table 1).

On the other hand, in a report defining the elderly as individuals aged 85 years and over, there was no difference in the complication rate related to surgery. Still, the incidence of pneumonia[20] and delirium[21] was high. However, there are limits to the interpretation of these results, such as the same ASA physical status and performance status in the control group and the elderly[20] and a low rate of total gastrectomy[22] (Table 1).

Several reports[10,13] have shown that the 5-year overall survival as a long-term outcome is lower with older age; however, cancer-related survival was not significantly different. This finding means that elderly individuals often die from other illnesses[23,24]. Some reports revealed that a low preoperative prognostic nutritional index (PNI) or sarcopenia[25] and multiple comorbidities[24] were significant risk factors for death from other diseases. Hashimoto *et al*[11]. revealed that the causes of death from other diseases in the elderly group were other malignancies (22%), pneumonia (18%), cardiovascular disease (10%), cerebrovascular disease (10%), and malnutrition (8%).

Two studies compared life expectancy and long-term outcomes. Life expectancy varies from country to country and should be considered individually for each country.

The first study is from Japan, in which postoperative life expectancy of late-elderly patients (≥ 80 years) was assessed by analyzing patient survival, except for cancer recurrence-related death. As a result, the median estimated life expectancy was equivalent to the life expectancy in the demographic data presented by the Japanese Ministry of Health, Labor, and Welfare[18].

The second study was from South Korea. The postoperative life expectancy of late-elderly patients (≥ 80 years) after eliminating death from recurrence was comparable to the corresponding aged general population after eliminating death from GC[10].

Treatment goals in these studies were achieved because survival from surgery was equivalent to life expectancy.

CRITICAL PROBLEMS IN THE PERIOPERATIVE CARE FOR ELDERLY PATIENTS

Nutritional status during the perioperative period

Elderly patients with GC are often poorly nourished. Therefore, the nutritional status before surgery in elderly patients is important for surgical risk assessment. Body mass index (BMI), the PNI, controlling nutritional status (CONUT), serum albumin, skeletal muscle mass, and the geriatric nutritional risk index (GNRI) have been reported as nutritional parameters. Among these, GNRI is reported as useful for predicting postoperative complications[26]. The CONUT score is reported as useful for predicting postoperative procedure-unrelated infectious morbidity and prognosis in elderly patients with GC[27].

Furthermore, malnutrition in the elderly is associated with weakness, sarcopenia, and frailty. Preoperative sarcopenia has been reported as a risk factor for severe postoperative complications in elderly patients undergoing gastrectomy[28]. Preoperative exercise and nutritional support programs have recently been actively attempted[29]. Nutritional support[30] and social and financial support are also needed in patients with muscle loss after gastrectomy[31].

Postoperative pneumonia

Postoperative pneumonia is one of the most frequent complications in the elderly and can be fatal[32]. The causes reported are swallowing dysfunction due to age-related anatomical and physiological changes, lower respiratory function, and poor immunocompetence[33].

Age and preoperative albumin levels, hypertension, male gender, D2 dissection[34,35], impaired postoperative respiratory function, diabetes mellitus, and blood transfusion[36] have been reported as risk factors for pneumonia. Postoperative pneumonia is associated with reduced long-term survival[37,38]. Recent multidisciplinary team efforts, including perioperative respiratory rehabilitation, preoperative oral care, and early postoperative mobilization programs, have generally been reported effective in preventing postoperative pneumonia[33,39,40].

Psychological problems

Dementia is increasing due to the aging population. Malnutrition in the elderly has been reported to be associated with dementia[41]. The degree of dementia varies from mild to severe, and it is necessary to consider the surgical indication. In addition, patients with GC after gastrectomy, especially after total gastrectomy, show an increased risk of Alzheimer's disease[42]. Therefore, those who received continual vitamin B12 supplementation after a total gastrectomy were less likely than controls to develop Alzheimer's.

Likewise, postoperative delirium is common in the elderly[38]. Shim *et al*[43] reported a significant decrease in delirium symptom severity (DSS) over three postoperative days. Age and anesthesia time were positively associated with the initial DSS level, and medication history for memory complaints was related to a slower recovery from delirium symptoms. While propofol as an anesthetic agent was associated with a lower initial DSS, it predicted slower recovery from DSS.

Risk factors for subsyndromal delirium have also been reported in the elderly and poorly educated[44]. Multivariate analysis revealed that male gender, age ≥ 75 years, a history of cerebrovascular disease, and frequent use of sleeping pills were independent predictive factors for postoperative delirium[45]. Therefore, artificial control of the sleep–wake cycle by drug therapy is effective for postoperative delirium[46].

TREATMENT-RELATED ASPECTS

Laparoscopic surgery

The use of laparoscopic gastrectomy (LG) has become widespread. It is a surgical option for GC that is minimally invasive. Some multicenter randomized clinical trials have demonstrated that LG can provide similar short- and long-term results to open surgery patients with GC[47,48]. However, the age criteria of these clinical trials were 80 years or younger; therefore, the safety and feasibility of laparoscopic procedures were not fully evaluated in elderly patients.

Several studies of laparoscopic surgery for the elderly over 80 years of age have reported no difference in postoperative complications in the elderly despite a high prevalence of cardiovascular disease, decreased respiratory function[49], and a higher ASA physical score and PS[50,51].

Yoshida *et al*[52] compared the elderly to the nonelderly, and there were significant differences between the two groups in preoperative respiratory and renal function, hemoglobin, and nutritional indicators. However, the only significant differences in postoperative complications were pneumonia and delirium. There were no significant differences in surgery-related complications. On the other hand, some reports have demonstrated the advantages of LG rather than open gastrectomy (OG).

Using propensity score matching analysis, the incidence of postoperative complications grade ≥ 2 in the OG subgroup was significantly higher than in the LG subgroup [53]. Another large-scale propensity score analysis also demonstrated that LG might reduce in-hospital mortality and reduce the incidence of postoperative complications in patients with an ASA ≥ 3[54].

In a nationwide Japanese prospective cohort study, postoperative complications and mortality were significantly higher in OG than in LG. In addition, LG shortened the length of postoperative hospital stay[55].

Adjuvant chemotherapy

The usefulness of adjuvant chemotherapy for Stage II and III GC has been reported in Japan[56-58] and South Korea[59], and it has become a standard treatment. However, since most of the clinical trials in Japan are conducted in patients aged 80 years or younger, the usefulness of adjuvant chemotherapy cannot be directly applied to elderly adults aged 80 years or older. Therefore, in Japan, a phase III study is currently underway to define the prognosis of adjuvant chemotherapy for stage II/III patients aged 80 years or older who have undergone gastrectomy[60]. On the other hand, in South Korea, surgery alone and adjuvant chemotherapy were examined in elderly patients with GC aged 75 years or older. There was no significant difference in the overall 5-year survival rate between the two groups[61].

Elderly adults have reduced physical fitness and organ function, especially renal function; therefore, it is necessary to consider the individual patient's condition before adding adjuvant chemotherapy[62].

Table 1 Short- and long-term outcomes of surgical treatments in elderly patients with gastric cancer

Variables	Gretschel *et al*[13]	Park *et al*[15]	Otowa *et al*[16]	Sakurai *et al*[17]	Takeshita *et al*[18]	Katai *et al*[19]	Yang *et al*[10]	Yamada *et al*[20]	Hikage *et al*[21]	Isobe *et al*[22]
Definition of elderly (yr)	> 75	≥ 80	≥ 80	≥ 80	≥ 80	≥ 80	≥ 80	≥ 85	≥ 85	≥ 85
No. of elderly people	48	291	39	95	104	112	68	24	55	56
BMI	ND	E < N-E	E = N-E	ND	ND	ND	ND	E = N-E	E = N-E	ND
Comorbidities	E > N-E[a]	E > N-E[a]	E > N-E	E > N-E[a]	ND	E > N-E[a]	ND	E = N-E	E = N-E	E = N-E
PS	ND	ND	ND	ND	ND	ND	ND	E = N-E	E > N-E[a]	ND
ASA physical status	E > N-E[a]	E > N-E[a]	E > N-E[a]	E > N-E[a]	ND	ND	E > N-E[a]	E = N-E	E > N-E[a]	ND
cStage	ND	E > N-E[a]	ND	ND	E > N-E[a]	E = N-E	E > N-E[a]	E = N-E	E = N-E	E = N-E
Rate of TG in surgery	E < N-E[a]	ND	E = N-E	E = N-E	E = N-E	E = N-E	E = N-E	E = N-E	E = N-E	E < N-E[a]
Percentage of TG in surgery	46	ND	35.9	29.5	24	32	20.6	37.5	23.6	8.9
Complication rate	E = N-E	ND	E = N-E	E = N-E	E = N-E	E = N-E	E > N-E[a]	E = N-E	E = N-E	E < N-E[a]
Respiratory complication	E = N-E	ND	E = N-E	E = N-E	E = N-E	E > N-E[a]	E = N-E	E > N-E[a]	E = N-E	E = N-E
Delirium rate	ND	ND	ND	ND	ND	ND	ND	ND	E > N-E[a]	E = N-E
Mortality rate	E > N-E[a]	ND	ND	E = N-E	E > N-E	E > N-E	E > N-E[a]	ND	E = N-E	E = N-E
Adjuvant chemotherapy	ND	ND	E < N-E[a]	E < N-E[a]	ND	ND	E < N-E[a]	ND	E < N-E[a]	ND
Overall survival rate	E < N-E[a]	E < N-E[a][1]	E < N-E(stage II)[a]	E < N-E(stage II, III)[a]	E < N-E[a]	E < N-E[a]	E < N-E[a]	ND	E < N-E[a]	E = N-E
Disease-specific mortality	E = N-E	E < N-E[a][1]	E < N-E(stage II)	E < N-E(stage II, III)[a]	E = N-E	E = N-E	E = N-E	ND	E = N-E	E = N-E

[1]Curative treated patient.

[a]$P < 0.05$. BMI: Body mass index; E: Elderly; N-E: Nonelderly; ND: Not described; PS: Performance status; ASA: American Society of Anesthesiologists; TG: Total gastrectomy.

OPTIMAL SURGICAL TREATMENT FOR ELDERLY GC

Male gender, low BMI, poor PS, low serum albumin levels, and advanced tumor stage were reported as predictors of overall survival[20]. In a report comparing supportive care and surgery in patients aged 85 and older, distal gastrectomy resulted in significantly better long-term survival in women, but not in men[63]. In addition, it has been reported that surgery contributes to a better prognosis than supportive care for patients with early or low-risk GC[64]. In clinical practice, in elderly patients with GC, it is very important to correctly evaluate the patients' organ reserve functions and mental status to select and provide appropriate treatment options to each patient according to these assessments. Also, the indications for surgery of elderly patients over 85 years of age should be carefully considered based on the prognosis.

Extent of gastrectomy

We have reported that total gastrectomy is a risk factor for postoperative pneumonia [37]. However, in this study, the rate of laparotomy was relatively high. Abdominal breathing could be impaired due to incision pain and impairment of the abdominal rectus muscle in laparotomy cases, which might increase pulmonary complications.

On the other hand, in recent years, several studies[53,65,66] of laparoscopic total gastrectomy (LTG) in patients with GC have reported favorable short- and long-term outcomes compared with open surgery. However, LTG is more difficult due to technology than laparoscopic distal gastrectomy, reconstruction is complicated, and it has been reported that the complication rate is high in the real world[67]. It has been reported that LTG does not increase complications even in the elderly[68]; however, LTG has been reported to have anastomotic leakage[69] and complications[70]. Only well-trained laparoscopic teams should perform LTG. Recent reports have shown that laparoscopic subtotal gastrectomy[71], which leaves a very small residual stomach, has better short-term outcomes and nutritional status than LTG and laparoscopic proximal gastrectomy, suggesting that it may be possible in elderly adults[72].

The extent of lymph node dissection

Standard treatment strategies for Japanese patients with GC, especially the extent of lymph node dissection, have been established in the Japanese Gastric Cancer Treatment Guidelines[73]. However, these guidelines are not standardized for elderly patients with GC, and standard treatments can be highly invasive.

Several studies have reported the extent of reduced dissection in the elderly, and no difference was found between the incidence of complications and prognosis[17] or disease-specific mortality[18] after 80 years of age.

In studies on elderly patients who are over 85 years of age, there was no association between limited lymph node dissection and comorbidities, except for cerebrovascular events. Gastrectomy with radical lymph node dissection appears to be an effective treatment for patients with Stage II GC[74]. On the other hand, D2 dissection has been reported as a risk factor for postoperative pneumonia[34,35]. Studies using the Charson complications score reported a high incidence of postoperative complications and no significant improvement in overall survival[75]. From these studies, the extent of dissection is still controversial.

Preoperative prediction of various complications

Preoperative risk predictions for developing complications have been reported, with male gender, combined resection[76], preoperative albumin, PNI, and Hiroshima POSSUM[77] being risk factors.

Japan has a nationwide database called the National Clinical Database, which can calculate risks, such as postoperative 30-d mortality, surgery-related mortality, suture failure rate, and the pneumonia rate[78,79]. Reliable predictive models must be useful in treatment strategy decision-making in elderly patients with GC.

CONCLUSION

There are specific problems in the elderly, such as preoperative malnutrition, dementia, postoperative pneumonia, and delirium. However, in recent years, it has been shown that the minimal invasiveness of laparoscopic surgery is as useful or better than open surgery. Pre- and postoperative nutritional support are also important. It is necessary to use these and some risk predictions regarding surgical indications.

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ORIGINAL ARTICLE

Case Control Study

Nomogram for predicting chylous ascites after right colectomy

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Abstract

BACKGROUND

Chylous ascites following right colectomy has a high incidence which is a critical challenge. At present, there are few studies on the factors affecting chylous ascites after right colectomy and especially after D3 Lymphadenectomy. A predictive model for chylous ascites has not yet been established. Therefore, we created the first nomogram to predict the incidence of chylous ascites after right hemicolectomy.

AIM

To analyze the risk factors for chylous ascites after right colectomy and establish a nomogram to predict the incidence of chylous ascites.

METHODS

We retrospectively collected patients who underwent right hemicolectomy between January 2012 and May 2021 and were pathologically diagnosed with cancer. Multivariate logistic regression was used to analyze the influencing factors of chylous ascites and a nomogram was established. The predictive ability was assessed by the area under the receiver operating characteristic (ROC) curve.

RESULTS

Operative time, the type of operation (standard or extended), the number of lymph nodes retrieved, and somatostatin administration were considered important risk factors. Multivariate logistic regression and nomograms can be used to accurately predict whether chylous ascites occurs. The area under the ROC curve of the model is 0.770. The C-statistic of this model is 0.770 which indicates that it has a relatively moderate ability to predict the risk of chylous ascites.

CONCLUSION

We found a novel set of risk factors, created a nomogram, and validated it. The

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nomogram had a relatively accurate forecasting ability for chylous ascites after right hemicolectomy and can be used as a reference for risk assessment of chylous ascites and whether to prevent it after surgery.

Key Words: Nomogram; Right colectomy; Chylous ascites; Risk factors

Core Tip: The article retrospectively analyzed the incidence of chylous ascites after right colectomy, and through multivariate analysis, the operative time, the type of operation (standard or extended), and the number of lymph nodes retrieved were identified as risk factors, while the administration of somatostatin or synthetic analogs after surgery was a protective factor. Based on these factors, we created a nomogram with moderate ability to predict the risk of chylous ascites.

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INTRODUCTION

Colorectal cancer is the second most common cause of cancer-related death worldwide [1]. At present, although there are many treatment methods, surgical treatment is still the most important approach. Recent studies have shown that the incidence of colon cancer or rectal cancer on the left has remained stable or decreased and the survival rate of right-sided colon cancer is significantly lower than that of left colon cancer[2]. Moreover, there are differences in the incidence of complications, especially the incidence of chylous ascites.

Chylous ascites (CA) is defined as milky or milky peritoneal fluid that is rich in triglycerides[3]. It is generally believed that the main reason for the occurrence of CA is direct damage to the chylous duct, chylous branches or lymph nodes caused by surgery[4]. Complete mesocolic excision with D3 Lymph node dissection is regarded as a priority choice for right colectomy as more lymph nodes can be removed[5]. In clinical work and literature review, we were surprised to discover that the incidence of CA after right colectomy was significantly higher than that after other colorectal surgeries. Baek Se-Jin conducted a retrospective analysis of 779 patients after colorectal surgery and found that the incidence of CA after right colectomy was as high as 10.5%, which was significantly higher than the incidences of 5.75% after left colectomy and 4.6% of chyle leakage after rectal surgery[6]. Professor Chipan analyzed CA after colorectal surgery and the results showed that the incidence of CA following right hemicolectomy could be as high as 13.3%[7]. Therefore, according to the existing research, CA has become a complication that cannot be ignored after right colectomy. Because chyle drainage fluid contains many nutrients, CA may cause malnutrition, dehydration, electrolyte disorders, and delayed healing of incisions. In addition, CA contains lymph fluid that is enriched in lymphocytes and immunoglobulins; therefore, severe and long-term CA may lead to weakened immunity, which can cause severe infection and even death due to sepsis[8].

Thus, it is very important to establish a predictive model of CA after right hemicolectomy and to determine the risk reduction factors in a controllable strategy. At present, there are few studies evaluating the risk factors for CA after colorectal cancer surgery. The few existing studies suggested that the possible risk factors for CA were age, tumor location, preoperative albumin level, number of lymph nodes retrieved, operative time, intraoperative blood loss, D3 Lymphadenectomy, and surgeon[6,7,9,10]. However, no one has established a predictive model for CA that made sense in terms of preventive decision-making and risk assessment. This study aims to construct a nomogram to predict the incidence of CA after right hemicolectomy. Clinicians can eventually personalize the management of patients and take effective preventive measures through the nomogram and improve the prognosis and quality of life while reducing the length of hospitalization and costs.

MATERIALS AND METHODS

Patients

This retrospective study was approved by the Ethics Committee. We collected 516 consecutive patients who underwent right hemicolectomy in the Second Affiliated Hospital of Fujian Medical University from January 2012 to May 2021. The inclusion criteria were pathologically confirmed right colon adenocarcinoma and right colectomy. The exclusion criterion was that the operation was an emergency operation. Ultimately, we collected a total of 516 patients. We divided patients into two groups: CA and without CA.

All operations were performed by clinical colorectal surgeons with extensive experience. D3 Lymphadenectomy is defined as the removal of the main lymph nodes at the roots of the blood vessels (ileocolonic vessels and the middle colon artery or the right branch of the middle colon artery) and then ligation of the blood vessels at the origin site. Tumor staging was reidentified according to the eighth edition of the American Joint Committee on Cancer staging system (AJCC).

All patients completed the necessary preoperative examinations, including colonoscopy with biopsy, to confirm the diagnosis. The perioperative treatments were essentially the same. Some patients were administered somatostatin or its synthetic analogs for 3 d after surgery in the collected data. In the following, the term somatostatin includes its synthetic analogs, such as octreotide.

Definition of CA and Follow-Up

CA is defined as milky or milky white ascites without infectious exudation in the drainage tube, with a volume of ≥ 200 mL/d and a triglyceride (TG) level of ≥ 110 mg/dL. When CA occurs, there should be no signs of fever, peritonitis, or other signs of infection to rule out the possibility of anastomotic leakage or other abdominal infections[6,7,9,10]. All patients with CA were cured after conservative treatment, avoiding a second operation.

Variables

Variables analyzed as risk factors for CA included age, sex, body mass index, history of abdominal surgery, neoadjuvant therapy, ASA score, combined organ resection, type of surgery, surgical approach, blood loss, operative time, number of positive lymph nodes (LNs), number of lymph nodes retrieved, tumor diameter (cm), preoperative albumin, preoperative CEA, pathological T stage, pathological N stage, metastasis, differentiation, vascular invasion, perineural invasion, and somatostatin administration.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 22.0. Continuous variables are presented as the mean ± SD and were compared using the Mann-Whitney *U* test (2-tailed). Categorical variables were represented by numbers (percentage), which were compared by using the χ^2 test or Fisher's exact test. Potential univariate and multivariate factors were analyzed by logistic regressions. Variables with a P value < 0.1 were included in the multivariate model.

We used R (version 4.0.5) to build a nomogram, and bootstraps with 1000 resamples were used to validate the internal nomogram. The coordination statistic (C-statistic) was used to measure the performance of the nomogram. A calibration curve was used to express the relationship between the observed frequency and the predicted probability, which was assessed by the area under the receiver operating characteristic (ROC) curve (AUC). The differences were considered statistically significant when the P value < 0.05.

RESULTS

Patients

After reviewing all included data, 29 patients were diagnosed with CA. Table 1 summarizes the characteristics of patients. A long operative time (P = 0.032), number of LNs retrieved (P = 0.005), standard or extended surgery (P = 0.012), and

Table 1 Patient characteristics

Variables	No CA (n = 487)	CA (n = 29)	P value
Age (yr)	64.3 ± 11.5	66.0 ± 10.3	0.436
Sex			0.384
Male	245 (93.5%)	17 (6.5%)	
Female	242 (95.3%)	12 (4.7%)	
BMI (kg/m^2)			0.122
≤ 25	337 (93.4%)	24 (6.6%)	
> 25	150 (96.8%)	5 (3.2%)	
History of abdominal surgery			0.406
Yes	70 (97.2%)	2 (2.8%)	
No	417 (93.9%)	27 (6.1%)	
Neoadjuvant therapy			0.142
Yes	10 (83.3%)	2 (16.7%)	
No	477 (94.6%)	27 (5.4%)	
ASA score			0.565
1 or 2	363 (94.0%)	23 (6.0%)	
≥ 3	124 (95.4%)	6 (4.6%)	
Combined organ resection			0.495
Yes	38 (92.7%)	3 (7.3%)	
No	449 (94.5%)	26 (5.5%)	
Type of surgery			0.012
Standard	357 (96.0%)	15 (4.0%)	
Extended	130 (90.3%)	14 (9.7%)	
Surgical approach			0.094
Open	94 (97.9%)	2 (2.1%)	
Laparoscopy	391 (93.5%)	27 (6.5%)	
Blood loss (mL)	83.8 ± 81.5	94.5 ± 64.2	0.252
Operative time (min)	155.0 ± 21.5	164.1 ± 19.3	0.032
Number of positive LNs	2.79 ± 5.3	2.3 ± 7.0	0.668
Number of LNs retrieved	25.69 ± 8.7	29.79 ± 6.6	0.005
Tumor diameter (cm)	5.4 ± 2.4	5.6 ± 1.9	0.377
Preoperative albumin	38.5 ± 5.5	39.7 ± 4.1	0.163
Preoperative CEA	22.3 ± 81.7	5.0 ± 4.0	0.110
Pathological T stage			0.220
T0-T2	50 (90.9%)	5 (9.1%)	
T3-T4	437 (94.8%)	24 (5.2%)	
Pathological N stage			0.101
N0	226 (92.6%)	18 (7.4%)	
N1-N2	261 (96.0%)	11 (4%)	
Metastasis			0.749
Yes	46 (93.9%)	3 (6.1%)	
No	441 (94.4%)	26 (5.6%)	

Differentiation			0.299
w/d, m/d	302 (93.5%)	21 (6.5%)	
p/d	30 (100.0%)	0 (0.0%)	
Lymphovascular Invasion			0.098
Negative	259 (92.8%)	20 (7.2%)	
Positive	228 (96.2%)	9 (3.8%)	
Perineural invasion			0.665
Negative	369 (94.1%)	23 (5.9%)	
Positive	118 (95.2%)	6 (4.8%)	
Somatostatin administration			0.039
Yes	156 (97.5%)	4 (2.5%)	
No	331 (93.0%)	25 (7.0%)	

CA: Chylous ascites; BMI: Body mass index; ASA: American Society of Anesthesiologists; LNs: Lymph nodes; CEA: Carcinoembryonic antigen.

somatostatin administration (*P* = 0.039) were related to CA. However, intraoperative blood loss and open or laparoscopic surgery seemed not to be significantly related to the occurrence of CA.

Univariate and multivariate analyses

As shown in Table 2, after univariate logistic regression analysis, a long operative time, number of LNs retrieved, type of surgery (standard or extended surgery), somatostatin administration and preoperative CEA were associated with CA. Multivariate analysis showed that a long operative time (OR = 1.019, 95%CI: 1.001-1.037; *P* = 0.041), number of LNs retrieved (OR = 1.058, 95%CI: 1.015-1.103; *P* = 0.008), type of surgery (OR = 2.493, 95%CI: 1.097-5.669; *P* = 0.029), and somatostatin administration (OR = 0.240, 95%CI: 0.078-0.744; *P* = 0.013) were independent influencing factors of CA. According to these results, a forest plot was established (Figure 1).

Nomogram for CA

According to the multivariate logistic regression analysis, we established a nomogram to predict the risk of CA after right hemicolectomy and showed that operative time, number of LNs retrieved, type of surgery, and somatostatin had greater impacts on CA (Figure 2). The higher the total points assigned based on each factor in the nomogram, the higher the risk of CA. For example, a patient with a long operative time (160 min), a D3 type of operation, extended lymphadenectomy, with 30 LNs retrieved and without somatostatin administration postoperatively would have a total of 157.5 points (37.5 points for operative time, 30 points for type of operation, 45 points for number of LNs retrieved, and 45 points for without somatostatin administration postoperatively), for a predicted risk of CA of 15%. According to ROC analysis, the AUC of the model was 0.770. Because it was a binary variable model, the C-statistic of the model was 0.770, indicating that the model had considerable predictive potential (Figure 3A). The calibration curve showed that there was optimal agreement between the results predicted by the nomogram and actual observations, indicating good calibration (Figure 3B).

DISCUSSION

To the best of our knowledge, few articles have specifically studied the occurrence of CA after right colectomy and no one has established a nomogram to predict the occurrence of CA. At present, no auxiliary examination that can accurately predict CA has been proposed. This study analyzed the possible risk factors for CA after right colectomy in 516 cases and created a nomogram to predict the incidence of CA. We observed that the probability of CA after right colectomy was 5.6%. A long operative time, number of lymph nodes retrieved, and type of surgery (standard or extended surgery) were independent risk factors for CA after right colectomy, and somatostatin

Table 2 Univariate and multivariate logistic regression models for risk factors of chylous ascites

		Univariate	Multivariate	
		P value	OR (95% CI)	*P* value
Age (yr)		0.449		
Sex	Male or female	0.386		
BMI (kg/m^2)	> 25 *vs* ≤ 25	0.130		
History of abdominal surgery	Absent *vs* present	0.272		
Neoadjuvant therapy	Absent *vs* present	0.114		
ASA score	1 or 2 *vs* ≥ 3	0.566		
Combined organ resection	Absent *vs* present	0.624		
Type of surgery	Standard *vs* extended	0.015	2.493 (1.097-5.669)	0.029
Surgical approach	Open *vs* laparoscopy	0.112		
Blood loss (mL)		0.492		
Operative time (min)		0.028	1.019 (1.001-1.037)	0.041
Number of positive LNs		0.668		
Number of LNs retrieved		0.014	1.058 (1.015-1.103)	0.008
Tumor diameter (cm)		0.199		
Preoperative albumin		0.228		
Preoperative CEA		0.087	0.952 (0.900-1.008)	0.090
Pathological T stage	T0-T2 *vs* T3-T4	0.243		
Pathological N stage	N0 *vs* N1-N2	0.106		
Metastasis	Absent *vs* present	0.873		
Differentiation	w/d, m/d *vs* p/d	0.784		
Lymphovascular Invasion	Absent *vs* present	0.103		
Perineural invasion	Absent *vs* present	0.665		
Administration of somatostatin	Absent *vs* present	0.048	0.240 (0.078-0.744)	0.013

CA: Chylous ascites; BMI: Body mass index; ASA: American Society of Anesthesiologists; LNs: Lymph nodes; CEA: Carcinoembryonic antigen.

administration was a protective factor. All patients with CA were cured by conservative treatment and the short- and long-term survival results of patients were not affected by CA[9].

Looking back at previous research reports, the incidence of CA after major abdominal surgery ranges from 0.2% to 11.0%[11]. In our data, the incidence of CA fell in that range. However, because of the protective effect of somatostatin after surgery, the incidence was low compared to other studies. After we removed patients who were administered somatostatin after surgery, the incidence of CA was 7.0%. Why the incidence of CA after right colectomy with D3 Lymphadenectomy was so high, even as high as 13.3%, is closely associated with the anatomy of the region[6]. It is generally believed that the chyle cistern is located on the right side of the aorta, the anterior side of the first or second lumbar vertebrae has abundant lymphatic branches nearby, and it is closely related to the surgical area of D3 dissection[12]. In the process of D3 Lymph node dissection, the retroperitoneal lymph vessels and fat were removed, which resulted in the cutting and interruption of lymphatic drainage[13,14]. As the area for lymph node dissection expands, the number of lymph nodes retrieved increases, and the incidence of CA increases, which is consistent with previous reports on the risk factors for CA[6,7,9-11].

A previous study stated that CA occurrence was affected by various factors. For patients who have undergone right colectomy, there are few large-scale studies to provide risk factors for CA. We found that a long operative time, number of LNs retrieved, type of surgery (standard or extended surgery), and somatostatin adminis-

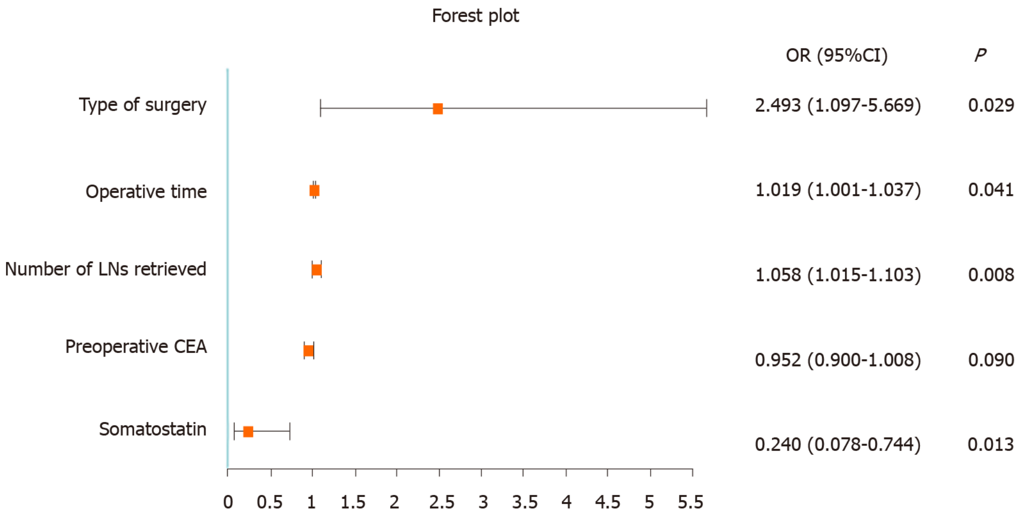

Figure 1 Forest plot. LNs: Lymph nodes; CEA: Carcinoembryonic antigen.

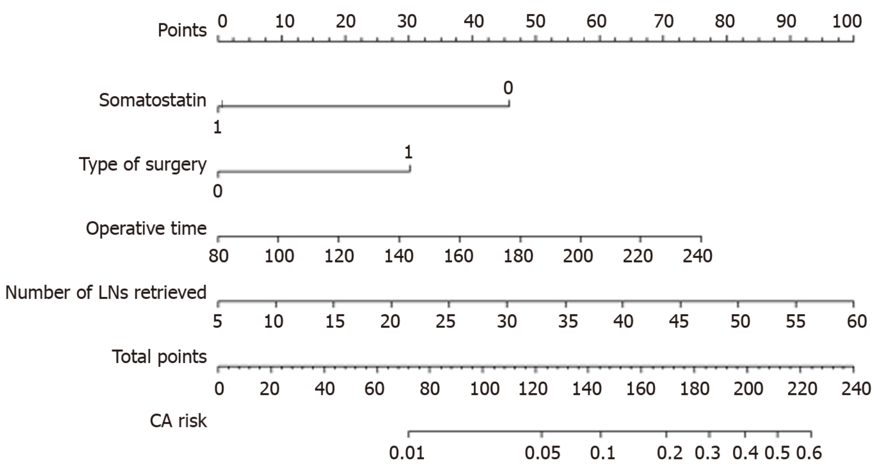

Figure 2 Nomogram for predicting chylous ascites after right colectomy. The nomogram to predict the incidence of chylous ascites (CA) was created based on four independent risk factors, including somatostatin administration, type of surgery, operative time and number of lymph nodes retrieved. The “Nomogram for CA” section of the article provides a detailed description of the nomogram. LNs: Lymph nodes; CA: Chylous ascites.

tration were independent influencing factors. The operative time was related to many factors including the surgeon, the operation method, and whether the abdominal cavity had adhesions. The differences in the skills of the surgeon would cause differences in the operative time. If surgeons had not mastered a comprehensive understanding of vascular anatomy or advanced laparoscopic techniques[15] or if the abdominal cavity was severely adhered[16], the surgeon may enter the wrong anatomy level, leading to the destruction of a larger area of the lymphatic network and lymphatic vessels, prolonging the operative time, and increasing the incidence of CA, which was inconsistent with previous reports that considered short operative times; additionally, the occurrence of CA may be caused by incomplete sealing of lymphatic vessels and energy devices due to insufficient sealing time during laparoscopic surgery[6,9]. However, laparoscopy was not a risk factor in our study ($P > 0.05$). The increase in the incidence of postoperative CA may be directly related to more extensive and more detailed lymph node dissection; thus, the number of LNs retrieved can be explained as an independent risk factor. As the principle of D3 Lymphadenectomy is to remove more LNs in the mesenteric root, the number of LNs retrieved was quite large, but it was still less than in the study by Liang *et al*[17] (25.9 ± 8.7 *vs* 34.4 ± 8.4, $P < 0.05$). Due to the larger area of lymph node removal in D3 extended mesenterectomy, CA was more likely to occur, which was confirmed in Agustsdottir EES’s study that the incidence of CA after D3 extended mesenterectomy was 41.0% [18], which was higher than our data (41.0% *vs* 9.7%). Somatostatin, or its synthetic analog octreotide, which can reduce the absorption of triglycerides and inhibits

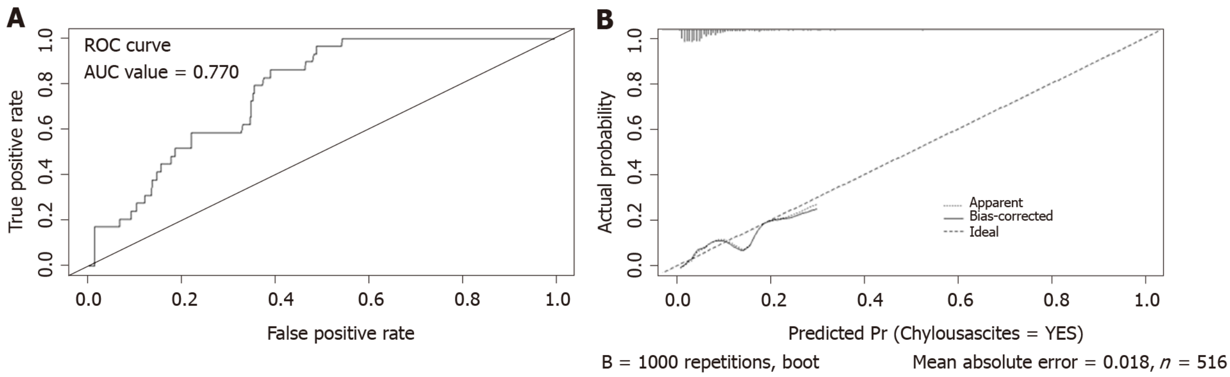

Figure 3 Validation of the nomogram. A: receiver operating characteristic (ROC) curve for the nomogram. C statistic/ area under the receiver operating characteristic curve (AUC) = 0.770 (95%CI: 0.706-0.834); B: Nomogram calibration curve. The y-axis represents the actual probability of chylous ascites. The x-axis represents estimated probability. The ideal line represents a perfect prediction model. The apparent line represents the performance of the nomogram, and a close fit to the ideal line represents a good prediction.

visceral circulation and gastrointestinal motility, thereby reducing the concentration of triglycerides in the thoracic duct and reducing the lymphatic flow of the main lymphatic vessels[19]. It can provide valuable time for the healing of damaged lymphatic vessels and can thus play a preventive role.

There are few articles in the literature addressing the prevention of CA. At present, the main methods of prevention are that the injured lymphatics must be controlled and ligated intraoperatively during the operation[20], and the diet must be controlled. The surgical habit of our center was to use a slow range and double cauterization of the ultrasonic scalpel when performing laparoscopic lymphadenectomy, especially in the root of the main artery, and follow the integrity principle of lymphadenectomy to avoid partial lymphadenectomy. In open surgery, the use of an electrosurgical scalpel should be minimized for thicker lymphatic ducts or lymph nodes near the lymphatic trunk, and silk suture or ligation should be used. This may be part of the reason why our incidence of CA was lower than that in other studies. The study by Agustsdottir *et al*[18] considered that a routine fat-reduced diet (FRD) had a prophylactic effect and prevented the lymphatic vessels from collapsing, thereby reducing the occurrence of CA. According to our study, somatostatin played a protective role, indicating that somatostatin administration can reduce the occurrence of CA, but there is currently no relevant research to confirm this hypothesis. In our study, the average time for CA to occur was 3.9 d, and it often appeared after eating. However, Lizaola *et al*[21] believed that CA may occur in the early period (approximately 1 wk) after abdominal surgery because of the rupture of lymphatic vessels. In our study, the reason for the earlier appearance of CA was the accelerated rehabilitation surgery (ERAS) we implemented, which led to the patient eating earlier. Therefore, early intervention in the occurrence of CA is significant.

There are two modalities for the conservative treatment of CA: nutritional support and the use of somatostatin. Pan *et al*[22] revealed that in treating CA, enteral nutrition (EN) + medium-chain triglyceride (MCT) instead of total parenteral nutrition (TPN) was the best nutritional support and somatostatin should be used immediately. Aalami *et al*[23] published a large review of 156 cases and concluded that the resolution rate of conservative treatment was 67% while the remaining 33% of patients required surgical intervention such as lymphangiography and embolization[24]. The patients with CA that we included in this study were all cured by conservative treatment, such as diet control and the administration of somatostatin or its synthetic derivatives but the hospital stay was significantly prolonged with an average length of stay of 15.7 d, leading to a significant increase in hospital costs and was not conducive to the turnover rate of hospital beds.

We focused on patients after right colectomy who were reported to have a high risk of CA. According to the data of multiple logistic regression analysis, we established a nomogram that included operative time, type of surgery, number of LNs retrieved, and somatostatin administration. The nomogram can provide clinicians with an accurate approximation of CA risk after right colectomy because it is composed of data throughout the perioperative period which will make it convenient and feasible for doctors to better control the occurrence of CA and surgeons will be able to judge whether a patient is at high risk through our model so that the patient can take preventive measures. Considering that the cost of an extra day of hospitalization far exceeds the cost of somatostatin or octreotide administration, and there are potential economic effects of low risk, high benefit, and shortening the length of hospitalization [11]. For patients who are assessed as high-risk for CA by nomogram, it is recommended to start administering somatostatin or octreotide for 3 d immediately after the operation and to implement a 3-d fat-reduced diet at the same time[18].

The advantage of our study was that it focused on the high incidence of CA after right hemicolectomy, which has rarely been reported. We analyzed multiple factors that may be related to CA and created a nomogram that can provide a valuable prediction of the risk of CA after surgery. However, the study has several limitations. First, this is a retrospective, single-center study with a small sample size. Second, the mechanisms of most of the risk factors for CA we discussed were hypothetical and have not been confirmed on a scientific basis. For example, whether somatostatin can truly prevent CA has not been reported in the previous literature; carefully designed prospective clinical trials will be needed to confirm our results. Finally, it is currently uncertain whether the nomogram we created can be used by all surgeons because its effectiveness has not been evaluated in another study cohort. We expect to conduct forward-looking, large-sample, multicenter research to improve the reliability and value of the prediction model in future research.

CONCLUSION

In our study, the risk factors for CA after right hemicolectomy were screened by multivariate analysis and a nomogram was constructed to predict the possibility of CA. The nomogram had a good predictive ability for CA which can provide a reference for whether preventive measures need to be taken after the operation.

ARTICLE HIGHLIGHTS

Research background

Chylous ascites is a relatively rare postoperative complication but its incidence in patients after right hemicolectomy is relatively high.

Research motivation

If it is possible to assess which postoperative patients are at high risk for chylous ascites, appropriate preventive measures can be taken which will greatly speed up the recovery of patients and reduce hospitalization costs.

Research objectives

To identify the risk factors for chylous ascites and to establish a novel nomogram for predicting chylous ascites after right colectomy.

Research methods

A hospital-based retrospective study was conducted. Multivariate logistic regression was used to analyze the risk factors for chylous ascites and a novel nomogram was created. We used the receiver operating characteristic curve to assess the predictive ability of the model.

Research results

Operative time, the type of operation (standard or extended), and the number of lymph nodes retrieved were risk factors and somatostatin administration was considered a protective factor. Multivariate logistic regression and nomogram had relatively moderate abilities to predict the risk of chylous ascites.

Research conclusions

The nomogram had a relatively accurate predictive ability for chylous ascites. Thus, we can use this model to assess the risk of patients for developing chylous ascites.

Research perspectives

A multicenter prospective study should be performed to improve the practicality of the model.

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ORIGINAL ARTICLE

Case Control Study

Comparison of safety, efficacy, and long-term follow-up between "one-step" and "step-up" approaches for infected pancreatic necrosis

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Author contributions: Zheng Z, Lu JD and Ding YX carried out the studies, participated in collecting data; Zheng Z drafted the manuscript; Guo YL, Mei WT and Qu YX performed the statistical analysis and participated in its design; Cao F and Li F participated in acquisition, analysis, or interpretation of data and revised the manuscript; all authors read and approved the final manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of Xuan Wu Hospital, Capital Medical University, No. 2020-158.

Informed consent statement: Since this was a retrospective study and only analyzed the clinical data of the patients, the need for informed consent was waived. All patient data were analyzed after anonymization.

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Abstract

BACKGROUND

Although the "Step-up" strategy is the primary surgical treatment for infected pancreatic necrosis, it is not suitable for all such patients. The "One-step" strategy represents a novel treatment, but the safety, efficacy, and long-term follow-up have not yet been compared between these two approaches.

AIM

To compare the safety, efficacy, and long-term follow-up of two surgical approaches to provide a reference for infected pancreatic necrosis treatment.

METHODS

This was a retrospective analysis of infectious pancreatic necrosis patients who underwent "One-step" or "Step-up" necrosectomy at Xuan Wu Hospital, Capital Medical University, from May 2014 to December 2020. The primary outcome was the composite endpoint of severe complications or death. Patients were followed up every 6 mo after discharge until death or June 30, 2021. Statistical analysis was performed using SPSS 21.0 and GraphPad Prism 8.0, and statistical significance was set at $P < 0.05$.

RESULTS

One-hundred-and-fifty-eight patients were enrolled, of whom 61 patients underwent "One-step" necrosectomy and 97 patients underwent "Step-up" necrosectomy. During the long-term follow-up period, 40 patients in the "One-step" group and 63 patients in the "Step-up" group survived. The time from disease onset to hospital admission (53.69 ± 38.14 *vs* 32.20 ± 20.75, $P < 0.001$) and to initial surgical treatment was longer in the "Step-up" than in the "One-step" group (54.38 ± 10.46 *vs* 76.58 ± 17.03, $P < 0.001$). Patients who underwent "Step-

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up" necrosectomy had a longer hospitalization duration (65.41 ± 28.14 *vs* 52.76 ± 24.71, $P = 0.02$), and more interventions (4.26 ± 1.71 *vs* 3.18 ± 1.39, $P < 0.001$). Postoperative inflammatory indicator levels were significantly lower than preoperative levels in each group. Although the incisional hernia incidence was higher in the "One-step" group, no significant difference was found in the composite outcomes of severe complications or death, new-onset organ failure, postoperative complications, inflammatory indicators, long-term complications, quality of life, and medical costs between the groups ($P > 0.05$).

CONCLUSION

Compared with the "Step-up" approach, the "One-step" approach is a safe and effective treatment method with better long-term quality of life and prognosis. It also provides an alternative surgical treatment strategy for patients with infected pancreatic necrosis.

Key Words: Acute pancreatitis; Follow-up; Infectious pancreatic necrosis; Safety and efficacy; Surgical approach

Core Tip: This was a retrospective study comparing the safety, efficacy, and long-term follow-up between the "One-step" approach and "Step-up" approach for patients with infected pancreatic necrosis. The results indicated that the "One-step" approach is a safe and effective treatment method, with better long-term quality of life and prognosis, which provides a novel surgical treatment strategy for infected pancreatic necrosis patients.

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INTRODUCTION

Acute pancreatitis (AP) is a common disease of the digestive system[1]. The associated mortality rate of severe AP is 15%–20%, while that of infectious necrotizing pancreatitis (IPN) is as high as 30%[2]. Generally, surgical intervention for IPN is often delayed[3]. In terms of surgical intervention, pancreatic debridement has changed from a large incision and a wide range of anatomical debridement to minimally invasive treatment over time. The "Step-up" surgical treatment strategy has become the mainstream IPN surgical treatment. In this strategy, at the early stage of the disease, percutaneous drainage (PCD) is first performed under imaging guidance, and surgical debridement is then performed when necessary using incremental and progressive treatment[4,5]. Compared with traditional open necrosectomy, the "Step-up" strategy can effectively reduce the incidence of complications and mortality in patients and has good long-term efficacy[6]. However, in clinical practice, the pancreatic necrotic tissue cannot be removed completely even after repeated puncture and drainage treatment in some IPN patients due to the lack of a safe and effective puncture and drainage paths; this prolongs the treatment cycle and may even make it impossible to complete the PCD treatment[7]. In addition, due to individual differences among IPN patients, the degree of necrosis and liquefaction of pancreatic tissue vary. Therefore, when some IPN patients with "dry" necrosis undergo "Step-up" treatment, the poor drainage effect of PCD often leads to insignificant relief of infection and poisoning symptoms, and there remains a need to remove necrotic tissue [8,9]. This not only increases the surgical trauma and medical burden on the patient but may also delay the patient's optimal treatment time, which is not conducive to recovery[3]. Therefore, it remains unclear whether the "Step-up" strategy is suitable for all patients with IPN.

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Based on this, we have developed and applied the "One-step" surgical approach to treat IPN. This approach involves direct minimally invasive debridement instead of PCD. A preliminary retrospective study from our center confirmed that the "One-step" approach has better surgical efficacy and safety, but there is a lack of clinical data comparing it with the "Step-up" approach[7].

Consequently, the present study compared the safety, efficacy, and long-term follow-up survival data in IPN patients treated with the "One-step" approach and those treated with the "Step-up" approach, aiming to present a new surgical approach to guide clinical treatment. We present the following article in accordance with the STROBE reporting checklist.

MATERIALS AND METHODS

Study design and setting

This study was a retrospective analysis of the clinical data of IPN patients who underwent "One-step" necrosectomy or "Step-up" necrosectomy at Xuan Wu Hospital, Capital Medical University, from May 2014 to December 2020. The study was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University, No. 2020-158 and was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013). The registration number was ChiCTR2100044348. Because this was a retrospective study that only analyzed existing clinical and follow-up data, the need to obtain informed patient consent was waived. All patient data were analyzed anonymously using an electronic data capture system. A detailed flowchart is illustrated in Figure 1.

Patient's enrollment criteria

The following patients were included: (1) Patients suspected of having or diagnosed with IPN based on abdominal computed tomography (CT) and laboratory examinations, such as the "bubble" sign on CT or bacteria or fungi detected by culture of fine-needle aspiration samples; (2) Patients with IPN, mainly those with acute necrotic collection with infection and walled-off necrosis with infection; (3) Patients of either sex who were aged 18-80 years; (4) Patients who had undergone "One-step" or "Step-up" necrosectomy; (5) Patients who underwent video-assisted minimally invasive debridement; (6) Patients who had not previously undergone necrosectomy or surgery for pancreatic-related complications; and (7) Patients with complete clinical and follow-up data.

The exclusion criteria were as follows: (1) A previous history of pancreatic necrotic tissue drainage or debridement; (2) Previous exploratory laparotomy for acute abdominal disease or pancreatitis. (3) Acute exacerbation of chronic pancreatitis or recurrent AP (RAP); (4) Inability to tolerate video-assisted minimally invasive debridement and anesthesia due to physical conditions; (5) AP with abdominal compartment syndrome or abdominal organ perforation; and (6) Incomplete clinical data or data that could not be statistically analyzed.

Surgical procedure

"One-step" minimally invasive necrosectomy: "One-step" minimally invasive necrosectomy can be performed *via* the omentum sac, retroperitoneal, or combined approach. The surgical procedure was described in detail previously[7] and included incision *via* the omental sac and/or retroperitoneal approach, after which video-assisted pancreatic necrotic tissue debridement was performed.

"Step-up" minimally invasive necrosectomy: "Step-up" minimally invasive pancreatic necrosectomy used PCD as the initial treatment option for IPN. The surgical approach was the same as for "One-step" treatment. If there was residual infection in the abdominal cavity after minimally invasive surgery, PCD treatment was preferred. The detailed surgical procedures have been described previously[4].

Observation indicators and data collection

Primary outcomes: The primary outcome of this study was the composite endpoint of severe complications or death. Severe complications were defined as Clavien-Dindo grade IIIa or higher[10].

Secondary outcomes: The secondary outcomes included the time from disease onset to hospital admission; time from disease onset to initial surgical treatment; new-onset

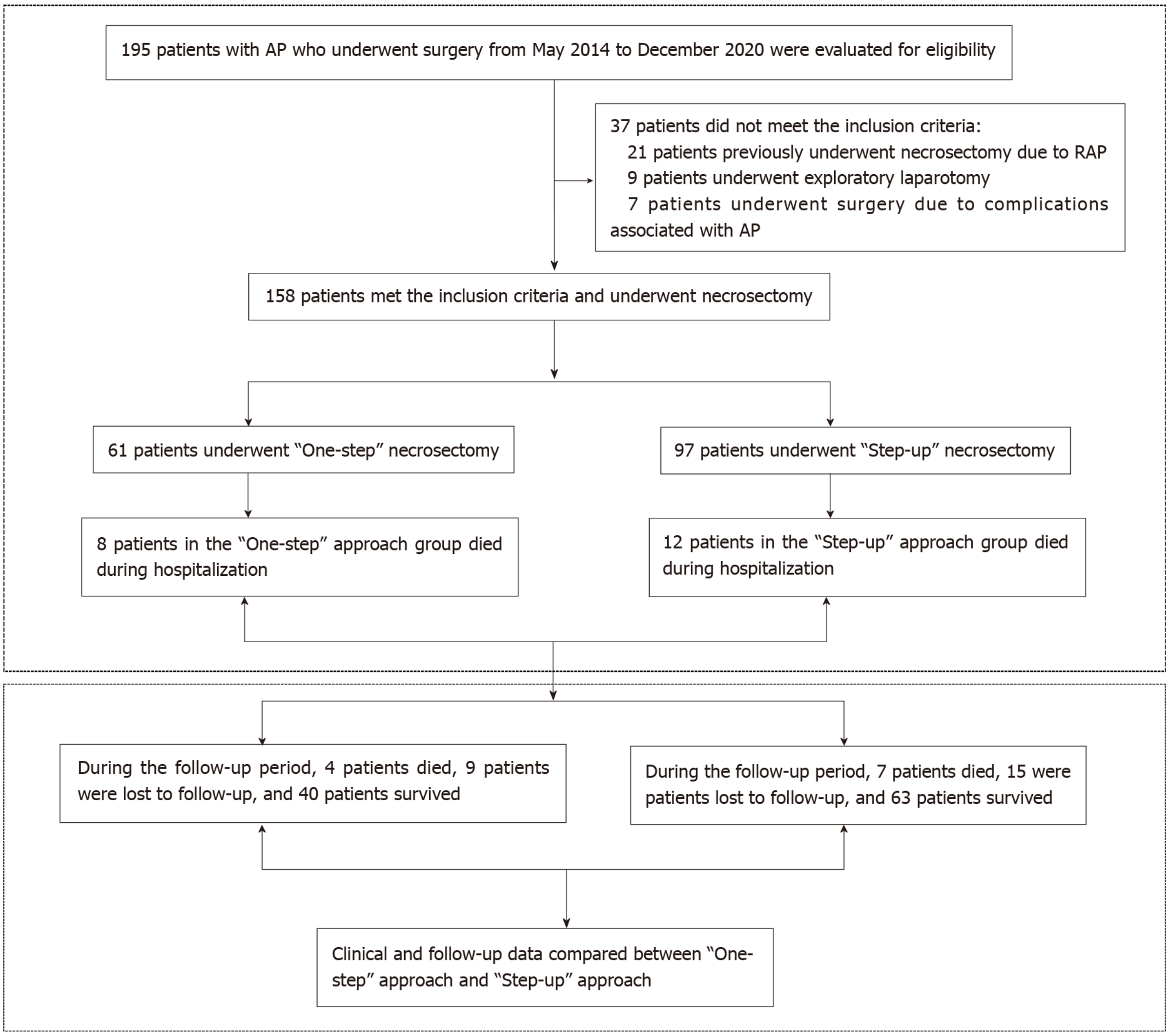


Figure 1 The research of patient's recruitment and follow-up and flow chart. AP: Acute pancreatitis; RAP: Recurrence acute pancreatitis.

organ failure; number of organs in failure; postoperative short-term complications (such as pancreatic fistula, intra-abdominal bleeding, enterocutaneous fistula, or viscera perforation); length of stay in the intensive care unit (ICU); total length of hospital stay; number of operations; operation time; number of interventions; number of drainage tubes used; overall survival rate; changes in perioperative inflammatory indicators, including white blood cell (WBC), interleukin-6 (IL-6), C-reactive protein (CRP), and procalcitonin (PCT); long-term complications (such as endocrine insufficiency, exocrine insufficiency, chronic pancreatitis, incisional hernia, recurrence pancreatitis, pancreatic pseudocyst, pancreatic portal hypertension, and pancreatic cancer); scores on the SF-36 and EQ-5D rating scales; Izbicki pain score; and perioperative medical costs. The specific definitions of the primary and secondary outcomes are described in Table 1. Clinical data were extracted from internet-based case records of Xuanwu Hospital, Capital Medical University, by three local doctors (DYX, GYL, and MWT). Follow-up was performed by three other local doctors (ZZ, LJD, and QYX).

Follow-up

The patients were followed up every 6 mo after surgery. After discharge, the patients were followed up by means of outpatient visits, inpatient visits, telephone contact, or mail. During the follow-up period, patients were required to undergo physical examinations, abdominal CT scans, and laboratory tests. In addition, researchers monitored related clinical symptoms, such as abdominal pain, bloating, weight loss, and diarrhea. Physical examinations were conducted mainly to check for postoperative incisional hernia. Abdominal CT scans primarily focused on morphological changes of the pancreas and blood vessels in the abdominal cavity. Laboratory

Table 1 The definitions of primary endpoints and secondary endpoints

Endpoints	Definition
Primary endpoints	
Composite endpoint consisting of mortality and severe complications (Clavien-Dindo ≥ IIIa)	There are five grades of Clavien-Dindo Classification: Grade I, any complication that deviates from the natural course after surgery; Grade II, medications other than those permitted for Grade I complications are required; Grade III, surgical, endoscopic, and radiotherapy are required, including Grade IIIa (no general anesthesia is required) and IIIb (need for general anesthesia); Grade IV, life-threatening complication, including Grade IVa (single organ dysfunction) and IVb (multi-organ dysfunction) that require intermittent monitoring or ICU treatment; Grade V, death
Secondary endpoints	
New-onset organ failure	New-onset failure of one or more organs in the 24 h prior to the first intervention
Pulmonary failure	Partial pressure of oxygen (PO_2) < 60 mmHg with or without partial pressure of carbon dioxide (PCO_2) > 50 mmHg, or need for mechanical ventilation
Circulatory failure	Blood pressure < 90/60 mmHg, or need for inotropic catecholamine to maintain blood pressure
Renal failure	The level of creatinine (Cr) > 177 μmoL/L, or need for hemofiltration or hemodialysis
Postoperative intra-abdominal bleeding	Need for operation, radiological, or endoscopic intervention
Pancreatic fistula	Drainage fluid amylase level more than 3 times that of serum amylase
Enterocutaneous fistula	Intestinal contents, including intestinal fluids, food residues, and feces, break through the intestinal wall (small bowel or large bowel) and leak into the abdominal cavity or outside the body. It can also be confirmed by radiology or surgery
Viscera perforation	Need for operation, radiological, or endoscopic intervention
Endocrine insufficiency	Oral hypoglycemic drugs or insulin therapy for at least 6 mo, with no need to take these drugs before the onset of AP
Pancreatic enzyme	Clinical symptoms were improved by oral pancreatic enzyme use for more than 6 mo, with no need to take this drug before the onset of AP
Recurrent pancreatitis	A history of two or more episodes with and interval of at least 3 mo
Chronic pancreatitis	Patients experience abdominal pain, weight loss, diabetes, and fatty diarrhea. The condition is also confirmed by radiological and laboratory examinations. The symptoms did not occur before the onset of AP
Incisional hernia	Six months after discharge, the full-thickness abdominal wall is discontinuous and abdominal contents bulge, with or without obstruction
Pancreatic portal hypertension	AP causes splenic vein thrombosis, which causes obstruction of splenic venous return

AP: Acute pancreatitis; ICU: Intensive care unit.

tests included routine blood tests, blood biochemistry tests, and fecal elastase-1 examination to clarify whether patients had long-term complications. In addition, enrolled patients also needed to receive the SF-36, EQ-5D, and Izbicki pain scores to further evaluate the quality of life of patients after surgery. The survival time was estimated from the date of operation to the date of death or until June 30, 2021. The follow-up period ended on June 30, 2021.

Statistical analysis

Statistical analysis was performed using SPSS (version 21.0; IBM Corp., Armonk, NY, United States) and GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA, United States). Continuous variables with normal distributions were described as mean ± standard deviation, and an independent sample *t*-test was used for comparisons. Continuous variables with non-normal distributions were presented as medians (interquartile ranges), and the Mann-Whitney U test was used for comparisons. The chi-square test or Fisher's exact test was used to compare categorical variables and assess adverse events. The Kaplan-Meier method was used for survival analysis. The log-rank test was used to compare the complication rates between the two surgical approaches. P values < 0.05, were considered statistically significant.

RESULTS

Baseline characteristics of enrolled patients

Overall, 195 patients with AP who underwent surgery between May 2014 and

December 2020 were retrospectively analyzed. Of these, 37 patients did not meet the inclusion criteria and were excluded. Among them, 21 patients had previously undergone pancreatic necrosectomy due to RAP, 9 patients had undergone exploratory laparotomy, and 7 patients had undergone surgery because of AP-related complications. Finally, 158 patients met the inclusion criteria, of which 61 underwent "One-step" necrosectomy and 97 underwent "Step-up" necrosectomy. Eight and 12 patients died during hospitalization in the "One-step" necrosectomy and "Step-up" necrosectomy groups, respectively. After discharge, all patients underwent regular follow-ups. The research flow chart is shown in Figure 1.

The baseline characteristics were similar between the two groups. Gallstones were the most common etiology in our study. However, since the majority of IPN patients were referred to our center and most of the patients who underwent the "Step-up" approach had already undergone PCD treatment at other hospitals, the time from onset of disease to admission was significantly longer in the "Step-up" than in the "One-step" group (53.69 ± 38.14 *vs* 32.20 ± 20.75, $P < 0.001$). In the "One-step" group, the time from onset of disease to receiving initial surgical treatment was shorter than in the "Step-up" group (54.38 ± 10.46 *vs* 76.58 ± 17.03, $P < 0.001$). There were no significant differences in the ASA score, APACHE II score, CT severity index, pancreatic necrosis extent, and AP severity (Table 2).

Perioperative clinical outcomes

All patients underwent minimally invasive surgical treatment. In the "Step-up" group, 32 patients (32.9%) were cured after PCD treatment alone, without pancreatic necrosectomy. The remainder of the patients in the "Step-up" group (65 patients, 67.1%) underwent necrosectomy after PCD due to continuous progression of the disease. Among them, trans-lesser sac pancreatic necrosectomy was the most common surgical approach used in both groups at our center. In addition, severe complications or death composite outcomes (18% *vs* 20.6%, $P = 0.69$) were comparable between the two groups. Although new-onset organ failure involving pulmonary and cardiovascular diseases was common, there were no statistically significant differences between the groups ($P = 0.73$). No significant difference was found in postoperative complications, blood loss, number of operations, and operation time between the groups. Compared with the "One-step" group, patients who underwent "Step-up" necrosectomy had longer total length of hospitalization and underwent more interventions (total length of hospitalization: 65.41 ± 28.14 *vs* 52.76 ± 24.71, $P = 0.02$; number of interventions: 4.26 ± 1.71 *vs* 3.18 ± 1.39, $P < 0.001$). However, the postoperative ICU stay and total length of ICU stay were not significantly different between the groups. Additionally, there were fewer drainage tubes used in the "One-step" group than in the "Step-up" group (3.9 ± 1.0 *vs* 4.43 ± 1.77, $P = 0.04$) (Table 3).

Changes in inflammatory indicators

Interestingly, there were no significant differences in perioperative inflammatory indicators and vital signs between the two groups (Table 4). However, within each group, compared with before the operation, the inflammatory indicators were significantly decreased on the 3rd day after the operation. The vital signs and inflammatory indicators were significantly improved on the 7th day after surgery. In the "One-step" group, the postoperative level of WBC (11.04 ± 6.31 *vs* 7.51 ± 3.0, $P = 0.003$), NE (80.86 ± 8.3 *vs* 69.30 ± 6.1, $P = 0.019$), CRP (115.3 ± 81.8 *vs* 62.63 ± 25.6, $P = 0.0002$), PCT (1.18 ± 1.0 *vs* 0.37 ± 0.3, $P < 0.001$), and IL-6 (113 ± 91.8 *vs* 46.3 ± 22.6, $P = 0.00097$) were significantly lower than the preoperative levels. Postoperative vital signs were also better than preoperative values (Figure 2). In the "Step-up" group, the postoperative level of WBC (11.33 ± 6.03 *vs* 7.48 ± 2.4, $P = 0.0012$), NE (79.57 ± 8.9 *vs* 65.14 ± 7.8, $P = 0.0367$), CRP (118.5 ± 85.7 *vs* 68.05 ± 38.1, $P = 0.0089$), PCT (1.08 ± 2.2 *vs* 0.31 ± 0.2, $P = 0.0004$), IL-6 (116 ± 95.1 *vs* 49.7 ± 27.4, $P = 0.00073$) and vital signs were also better than the preoperative levels (Figure 3).

Long-term complications in surviving patients

In the follow-up period, 103 patients survived and received regular follow-ups after discharge. Of these, 40 patients were in the "One-step" group and 63 were in the "Step-up" group. As shown in Table 5, the incidence of incisional hernia was higher in the "One-step" group (20.5% *vs* 6.3%, $P = 0.03$). New-onset endocrine insufficiency was present in 12 patients (30%) in the "One-step" group and in 28 patients (45%) in the "Step-up" group, which was not statistically significantly different ($P = 0.143$). Fecal elastase-1 (FE-1) levels were used for detecting exocrine insufficiency, with mean values of 254.1 ± 107.8% and 257.9 ± 93.3% in the two groups, respectively ($P = 0.85$).

Table 2 Baseline characteristics of infectious necrotizing pancreatitis patients who underwent necrosectomy

Groups	"One-step" approach (n = 61)	"Step-up" approach (n = 97)	P value
Baseline characteristics			
Sex			0.61
Female	19	34	
Male	42	63	
Age (yr)	52.16 ± 11.51	50.57 ± 13.71	0.45
BMI (kg/m^2)	26.20 ± 3.78	25.91 ± 3.91	0.73
Cause of AP			0.36
Gallstone	31	48	
Alcohol	3	2	
Hyperlipidaemia	15	34	
Others	12	13	
Concomitant disease			0.15
Cardiovascular disease	29	37	
Pulmonary disease	8	13	
Chronic renal insufficiency	4	21	
Diabetes	13	16	
Others	7	10	
ASA score			0.42
I: Healthy status	30	58	
II: Mild systemic status	30	38	
III: Severe systemic status	1	1	
APACHE-II score	13.9 ± 5.1	14.2 ± 5.4	0.71
CT severity index	6.65 ± 2.55	7.19 ± 2.18	0.18
Severity of AP			0.79
Moderately AP	27	45	
Severely AP	34	52	
Extent of pancreatic necrosis			0.07
< 30%	35	41	
30%-50%	11	33	
> 50%	15	23	
Preoperative inflammatory indicators			
White blood cells (10^9/L)	11.04 ± 6.31	11.33 ± 6.03	0.77
Neutrophil percentage (%)	80.86 ± 8.3	79.57 ± 8.9	0.36
C-reactive protein (mg/L)	115.3 ± 81.8	118.5 ± 85.7	0.81
Procalcitonin (ng/mL)	1.18 ± 1.0	1.08 ± 2.2	0.73
Interleukin 6 (pg/mL)	113 ± 91.8	116 ± 95.1	0.93
Organ failure			0.49
Single	10	14	
Multiple	5	14	
None	46	69	
Time from onset of disease to admission (days)	32.20 ± 20.75	53.69 ± 38.14	< 0.001

Time from onset of disease to initial surgical treatment (days)	54.38 ± 10.46	76.58 ± 17.03	< 0.001
Tertiary referral (%)	56 (91.8%)	96 (98.9%)	0.06

CT: Computed tomography; AP: Acute pancreatitis; BMI: Body mass index.

Table 3 Comparison of perioperative clinical outcomes between the "One-step" approach and the "Step-up" approach

Group	"One-step" approach (*n* = 61)	"Step-up" approach (*n* = 97)	*P* value
Outcomes			
Primary composite outcomes			
Severe complications or death, *n* (%)[1]	11 (18)	20 (20.6)	0.69
Secondary outcomes			
New-onset organ failure	10	18	0.73
Pulmonary	6	12	
Cardiovascular	8	10	
Renal	1	3	
Single-organ failure	5	12	0.41
Multiple-organ failure	5	6	0.63
Death	8	12	0.89
Postoperative intraabdominal bleeding	2	5	0.58
Pancreatic fistula	16	28	0.72
Enterocutaneous fistula or Viscera perforation	3	5	0.95
Surgical approach			0.77
Trans-lesser sac	40	39	
Retroperitoneal	17	20	
Combined	4	6	
Length of stay in ICU after operation (days)	10.9 ± 22.7	14.4 ± 26.1	0.18
Total length of ICU stay (days)	22.5 ± 30.1	25.7 ± 28.7	0.43
Total length of hospital stay (days)	52.76 ± 24.71	65.41 ± 28.14	0.02
Number of operations	2.89 ± 1.23	3.42 ± 1.69	0.65
Operation time (min)	82.19 ± 29.34	87.01 ± 30.12	0.92
Number of interventions	3.18 ± 1.39	4.26 ± 1.71	0.000
Blood loss during the operation (mL)	49.5 ± 58.3	55.5 ± 72.1	0.51
Number of drainage tubes	3.9 ± 1.0	4.43 ± 1.77	0.04

[1]Severe complications defined as postoperative complications classified as higher than Grade IIIa according to the Clavien-Dindo Classification.
ICU: Intensive care unit.

Levels of FE-1 < 200 μg/g were present in 14 patients (35%) in the "One-step" group, and 21 patients (33.3%) in "Step-up" group (*P* = 0.86). There was no significant difference in exocrine insufficiency between the two groups. In addition, there was no difference in other long-term complications between the two groups, which further confirmed that the "One-step" approach could obtain therapeutic effects similar to those of the "Step-up" approach.

Quality of life in surviving patients

Patients underwent quality of life evaluation every 6 mo after discharge during the follow-up period. There was no statistically significant difference in the SF-36 physical

Table 4 The changes of inflammatory indicators and vital signs between two surgical approaches during the perioperative period

Groups	"One-step" approach (*n* = 61)	"Step-up" approach (*n* = 97)	*P* value
Indicators			
Preoperative inflammatory indicators			
White blood cells (10^9/L)	11.04 ± 6.31	11.33 ± 6.03	0.77
Neutrophil percentage (%)	80.86 ± 8.3	79.57 ± 8.9	0.36
C-reactive protein (mg/L)	115.3 ± 81.8	118.5 ± 85.7	0.81
Procalcitonin (ng/mL)	1.18 ± 1.0	1.08 ± 2.2	0.73
Interleukin-6 (pg/mL)	113 ± 91.8	116 ± 95.1	0.93
Preoperative vital signs			
Body temperature (°C)	38.5 ± 0.6	38.0 ± 0.8	0.94
Respiratory frequency (times/min)	25.8 ± 4.8	23.1 ± 4.9	0.67
Heart rate (times/min)	116.1 ± 14.2	107 ± 15.1	0.33
Inflammatory indicators on the 3rd postoperative day			
White blood cells (10^9/L)	9.91 ± 4.5	10.1 ± 4.4	0.54
Neutrophil percentage (%)	78.9 ± 6.8	78.1 ± 7.2	0.97
C-reactive protein (mg/L)	91.6 ± 40.6	91.1 ± 53.3	0.92
Procalcitonin (ng/mL)	0.84 ± 0.6	0.79 ± 0.5	0.71
Interleukin-6 (pg/mL)	91.2 ± 60.2	94.7 ± 68.4	0.31
Vital signs on the 3rd postoperative day			
Body temperature (°C)	38.1 ± 0.4	37.8 ± 0.7	0.49
Respiratory frequency (times/min)	23.8 ± 6.1	22.7 ± 4.3	0.86
Heart rate (times/min)	105.1 ± 21.9	100 ± 24.9	0.68
Inflammatory indicators on the 7th postoperative day			
White blood cells (10^9/L)	7.51 ± 3.0	7.48 ± 2.4	0.96
Neutrophil percentage (%)	69.30 ± 6.1	65.14 ± 7.8	0.43
C-reactive protein (mg/L)	62.63 ± 25.6	68.05 ± 38.1	0.54
Procalcitonin (ng/mL)	0.37 ± 0.3	0.31 ± 0.2	0.94
Interleukin-6 (pg/mL)	46.3 ± 22.6	49.7 ± 27.4	0.48
Vital signs on the 7th postoperative day			
Body temperature (°C)	37.0 ± 0.6	37.3 ± 0.4	0.95
Respiratory frequency (times/min)	19.4 ± 2.3	19.1 ± 2.8	0.83
Heart rate (times/min)	90.1 ± 13.7	85.2 ± 14.1	0.61

or mental health score, EQ-5D health status score, or Izbicki pain score between the groups (Table 6).

Medical costs

As shown in Table 7, the surgical costs of the "One-step" approach were lower than those of the "Step-up" approach, as the former approach did not require PCD (18582.37 ± 5918.45 *vs* 29641.63 ± 6795.11, P < 0.001). However, due to the similar baseline characteristics of AP severity and extent of pancreatic necrosis, the ICU costs (*P* = 0.87) and perioperative total medical costs (*P* = 0.34) were not different between the two groups. The follow-up costs *per* year, which included outpatient costs (*P* = 0.71), auxiliary examination costs (*P* = 0.58), and drug costs (*P* = 0.82), were also similar for the two surgical approaches.

Table 5 The long-term complication between the two surgical approaches during the follow-up period

Groups	"One-step" approach (*n* = 40)	"Step-up" approach (*n* = 63)	*P* value
Long-term complications			
New-onset endocrine insufficiency, *n* (%)			
Number of patients	12 (30)	28 (45)	0.143
Oral medication	9 (75)	20 (71.4)	
Insulin	5 (41.7)	13 (46.4)	
Exocrine insufficiency, *n* (%)			
Fecal elastase-1, mean value	254.1 ± 107.8	257.9 ± 93.3	0.85
Fecal elastase-1 < 200 μg/g, *n* (%)	14 (35)	21 (33.3)	0.86
Pancreatic enzyme, *n* (%)	8 (20)	11 (20.8)	0.93
Recurrent pancreatitis, *n* (%)	7(17.5)	13(20.6)	0.69
Chronic pancreatitis, *n* (%)	4 (10)	7 (11.1)	0.86
Incisional hernia, *n* (%)	9 (20.5)	4 (6.3)	0.03
Clinical symptoms, *n* (%)			
Diarrhea	16 (40)	23 (36.5)	0.72
Bloating	21(52.5)	28(44.4)	0.43
Abdominal pain	10 (25)	13 (20.6)	0.60
Weight loss	31 (77.5)	47 (74.6)	0.74
Pancreatic pseudocyst, *n* (%)	2 (5)	5 (7.9)	0.56
Pancreatic portal hypertension, *n* (%)	2 (5)	3 (4.8)	0.96
Pancreatic cancer, *n* (%)	0	0	-

Table 6 Quality of life rating scale during the follow-up period every 6 mo after treatment of surviving acute pancreatitis patients with the "One-step" approach or "Step-up" approach

Groups	"One-step" approach (*n* = 40)	"Step-up" approach (*n* = 63)	*P* value
Rating scale			
SF-36 physical health score[1]	40 ± 9	41 ± 7	0.61
SF-36 mental health score[1]	47 ± 13	49 ± 13	0.58
EQ-5D health status score[2]	75 ± 20	76 ± 18	0.76
Izbicki pain score[3]	23 ± 26	21 ± 24	0.87

[1]SF-36, Short Form-36. The SF-36 physical and mental health scores range from 0 to 100. The higher the score, the better the quality of life.
[2]EQ-5D, EuroQol 5 dimensions. The scores also range from 0 to 100, and the higher the score, the better the health.
[3]The higher the Izbicki pain score, the more severe the discomfort. The Izbicki pain score scale includes four parts (ranging from 0 to 100 *per* part), the sum of the values of the four parts are divided by 4.

Survival analysis

During the follow-up period, 11 patients died, 24 were lost to follow-up, and 103 patients survived. Of these, 4 patients who died, 9 patients who were lost to follow-up, and 40 patients who survived were in the "One-step" group, while 7 patients who died, 15 patients who were lost to follow-up, and 63 patients who survived were in the "Step-up" group. As illustrated in Figure 4, the mean follow-up time was 69.17 ± 2.53 mo (95%CI: 64.02-74.16). The total loss to follow-up rate was 15.2%. The overall survival (OS) in the "One-step" and "Step-up" groups was 10% (4/40) and 11.1% (7/63), respectively, with no significant difference ($P = 0.875$).

Table 7 The comparison of perioperative medical costs between two surgical approaches

Groups	"One-step" approach (*n* = 61)	"Step-up" approach (*n* = 97)	*P* value
Medical costs			
Surgical costs[1] (RMB)	18582.37 ± 5918.45	29641.63 ± 6795.11	< 0.001
ICU costs (RMB)	276812.39 ± 183417.12	281133.73 ± 193252.47	0.87
Perioperative medical total costs (RMB)[2]	529958.23 ± 171128.74	569768.07 ± 193184.68	0.34
Follow-up costs *per* year			
Outpatient costs (RMB)	2040.79 ± 519.48	2169.08 ± 463.71	0.71
Auxiliary examination costs[3] (RMB)	9751.96 ± 1012.37	9003.65 ± 1102.29	0.58
Drug costs[4] (RMB)	2855.36 ± 318.12	2994.21 ± 372.95	0.82

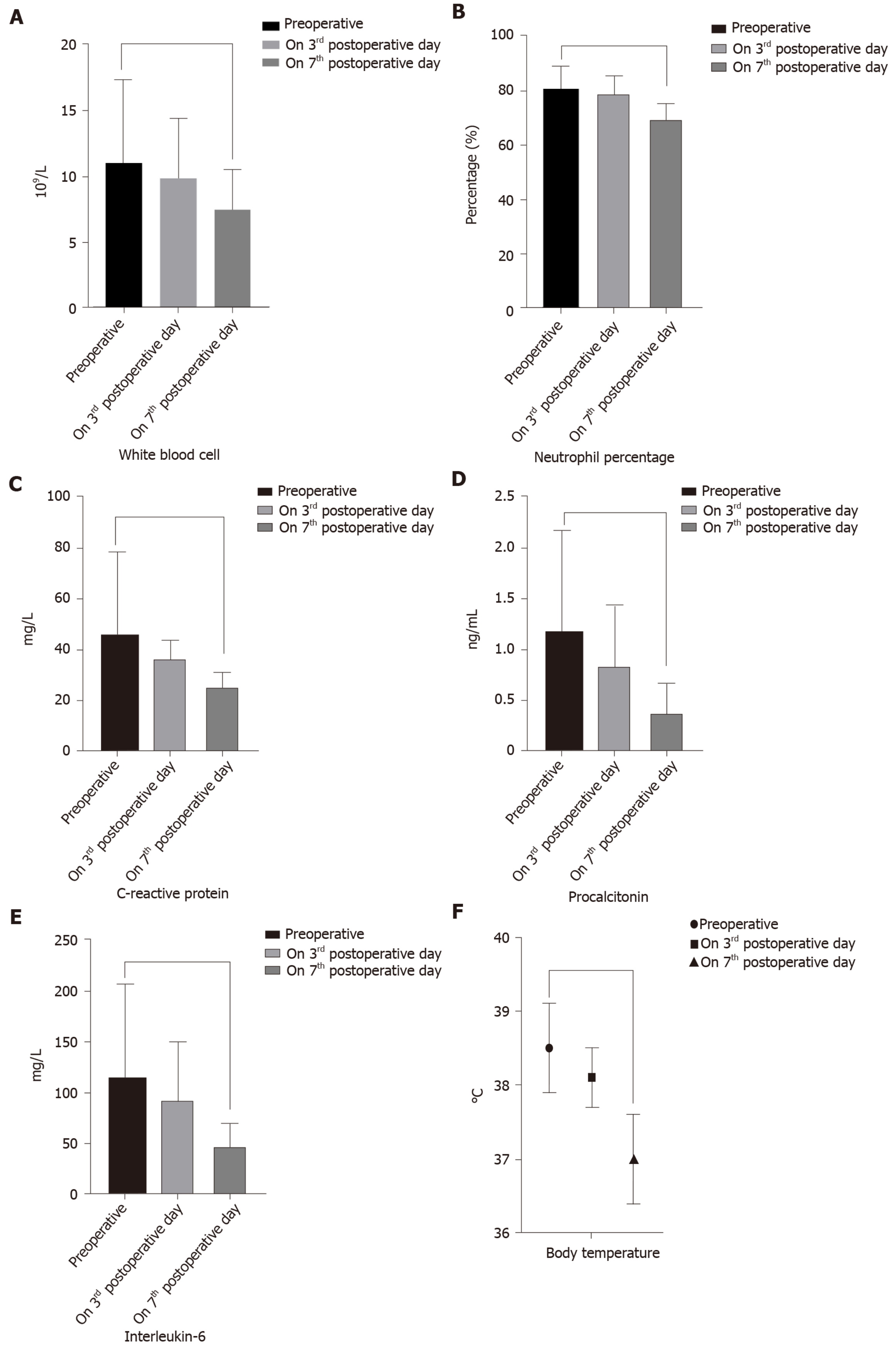
[1]Surgical costs include percutaneous drainage, necrosectomy, or disease-related drainage tube replacement.
[2]Perioperative medical total costs include surgical costs, intensive care unit costs, general ward costs, and auxiliary examination costs.
[3]Auxiliary examination costs include laboratory examination, microbiological examination, radiological examination, and endoscopic examination (except drainage).
[4]Drug costs include oral medicine or insulin for treating.
ICU: Intensive care unit.

DISCUSSION

The PANTER study, conducted by the Dutch Pancreatitis Working Group in 2010, was regarded as a milestone event in IPN treatment and has attracted extensive attention, making the minimally invasive "Step-up" strategy become an important method for the current treatment of IPN[4,11]. However, as this strategy does not apply to all IPN patients, we here compared it to our "One-step" approach. We showed that, compared with the "Step-up" approach, the "One-step" approach has the advantages of effectively reducing the total length of hospital stay, number of interventions, number of drainage tubes used, and surgical costs. While it does not increase the incidence of severe complications, organ failure, or mortality, it significantly improves the perioperative inflammatory indicators and stabilizes the vital signs of patients, achieving a short-term efficacy and safety similar to the "Step-up" approach. In addition, our long-term follow-up showed that pancreatic endocrine or exocrine insufficiency incidence, quality of life, and long-term prognosis were not significantly different in patients who underwent the "One-step" approach and those who underwent the "Step-up" approach. Moreover, the medical costs to patients were not increased. The results of this study demonstrated that there was a similar effect between the two approaches in the long-term follow-up. However, the disadvantage of the "One-step" approach is that the long-term probability of incisional hernia is higher than that of the "Step-up" approach. The main reason for this is that the "One-step" approach usually involves a small incision to assist in pancreatic necrosectomy. The long-term indwelling drainage tube in the local abdominal wall and repeated inflammatory stimulation lead to a decrease in abdominal wall tension, which may cause incisional hernia.

In addition, since the vast majority of patients enrolled in our center were referred from other hospitals, the referral rate was over 90%. Among them, some patients who underwent "Step-up" treatment were transferred to our center for further treatment after receiving PCD, which failed, at another hospital. Consequently, the time from disease onset to hospital admission of the patients and then to the initial surgical treatment was significantly longer for these patients than for those treated with the "One-step" approach. This also partly delayed the optimal timing of treatment, increased the number of interventions, and increased the total length of hospital stay for patients in the "Step-up" group.

The present study found that compared to preoperatively, the inflammatory indicators and vital signs in the "One-step" group were significantly improved on the 7th day after the operation. Among them, the level of WBC decreased from 11.04 ± 6.31 to 7.51 ± 3.0, the level of NE decreased from 80.86 ± 8.3 to 69.30 ± 6.1, the level of CRP decreased from 115.3 ± 81.8 to 62.63 ± 25.6, the level of PCT decreased from 1.18 ± 1.0 to 0.37 ± 0.3 and the level of IL-6 decreased from 113 ± 91.8 to 46.3 ± 22.6; these differences were statistically significant (P < 0.05). However, there were no significant differences in perioperative inflammatory indicators and vital signs between the "One-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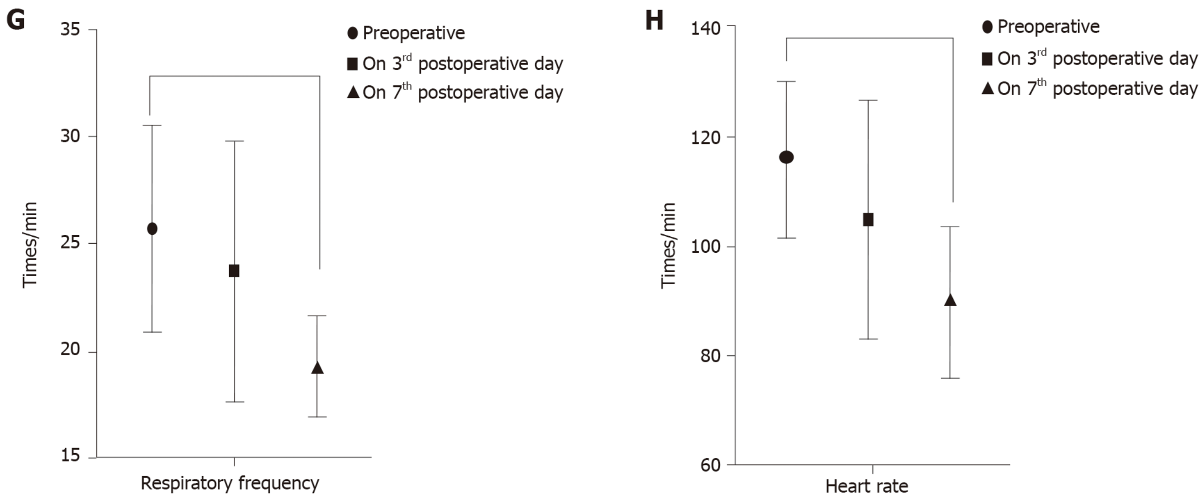


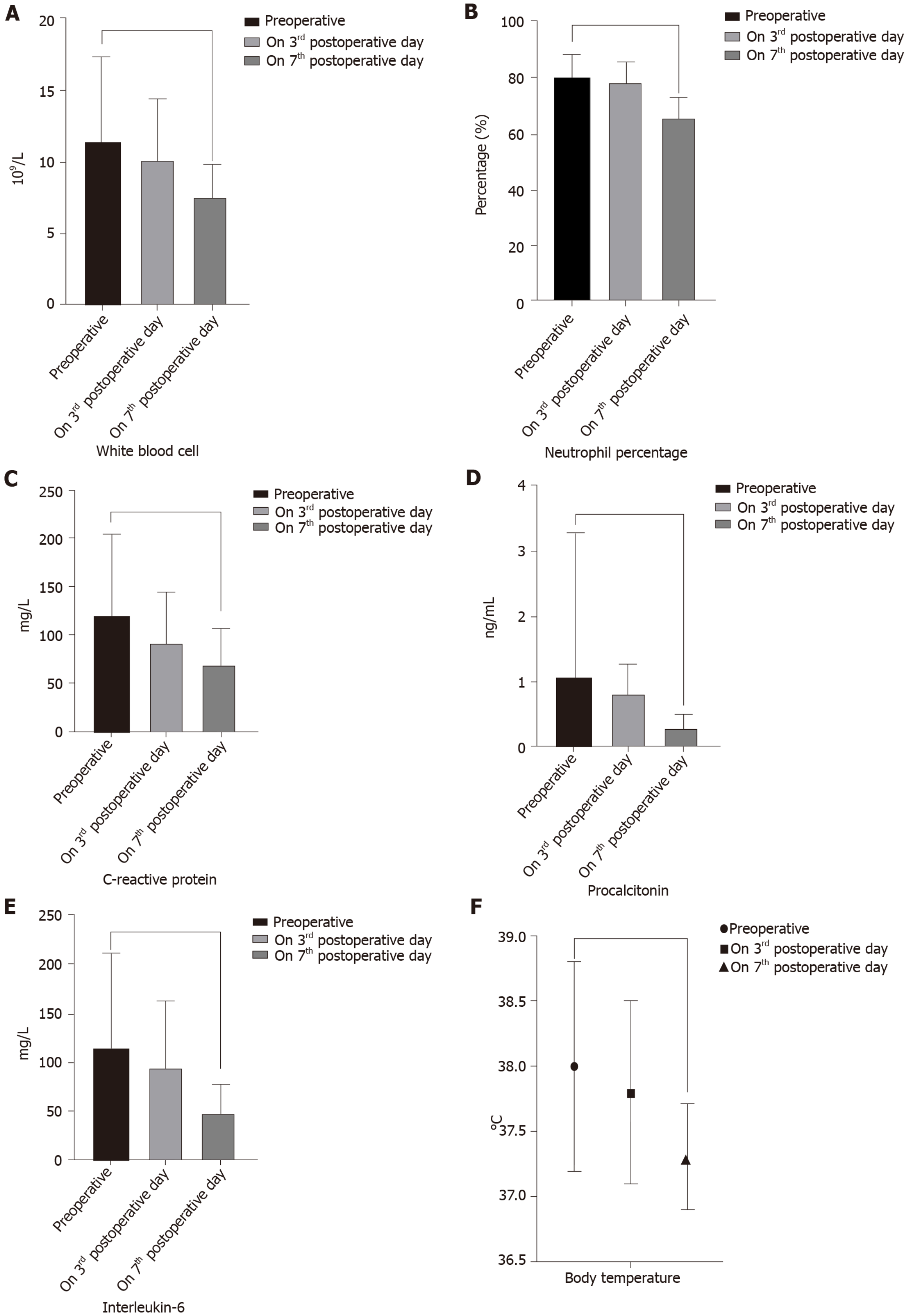
Figure 2 The changes of inflammatory indicators and vital signs in "One-step" approach during the perioperative period. A-E: The postoperative level of white blood cell (A, P = 0.003), neutrophil percentage (B, P = 0.019), C-reactive protein (C, P = 0.0002), procalcitonin (D, P < 0.001) and interleukin-6 (E, P = 0.00097) were significantly lower than preoperative; F-H: Meanwhile, the vital signs were also better than preoperative.

step" approach and the "Step-up" approach. This demonstrates that the "One-step" approach has similar surgical efficacy as the "Step-up" approach.

In terms of surgical safety, the 61 patients who underwent "One-step" treatment in this study were all treated successfully. The mortality rate of the patients was 13.1% (8/61). The incidence of new-onset organ failure was 16.4% (10/61), of which 5 patients had multiple organ failure (mainly respiratory and circulatory failure). The incidence of postoperative complications, such as intrabdominal bleeding (3.3%, 2/61), pancreatic fistula (26.2%, 16/61), and enterocutaneous fistula or viscera perforation (4.9%, 3/61), with the "One-step" approach were similar to those with the "Step-up" approach. Some studies have reported that the "One-step" approach was first used by endoscopists for the treatment of pancreatic pseudocysts, and its therapeutic effect and surgical safety were better than that of the "Step-up" approach[12,13]. Currently, only a few centers have reported using the "One-step" approach, including the trans-lesser sac approach, retroperitoneal approach, or combined approach for treating IPN[7,14]. Among these approaches, the trans-lesser sac is the most commonly used surgical approach in our center[7]. The advantage of "One-step" necrosectomy through the trans-lesser sac is that it can reduce interference with the patient's abdominal cavity and reduce the incidence of operation-related complications. It can help avoid PCD treatment, shorten the overall hospitalization time to some extent, and promote the patient's recovery. In addition, under laparoscopy, the surgical view is wide, and the surgeon can better perform accurate anatomical positioning, which facilitates thorough removal of pancreatic necrotic tissue, reduces iatrogenic injury, and reduces surgical risks, while ensuring the patient's safety to the greatest extent and facilitating the therapeutic effect.

During the follow-up period, we analyzed the clinical data of 103 surviving IPN patients to explore long-term complications, quality of life, medical costs, and OS rate. The OS rate in the "One-step" group was 10%, similar to that of the "Step-up" group. Except for incisional hernia, other long-term complications, including pancreatic endocrine or exocrine insufficiency, chronic pancreatitis, recurrent pancreatitis, pancreatic pseudocyst, and pancreatic portal hypertension, were not significantly different between the two surgical groups. However, although the "One-step" approach can achieve a similar long-term effect with the "Step-up" approach, postoperative pancreatic endocrine/exocrine insufficiency and patient's quality of life still require attention from clinicians[15].

According to the research results, approximately 1/3rd of patients had pancreatic endocrine insufficiency, and about 40% of patients had diabetes or pre-diabetes after AP, which was mainly caused by irreversible pancreatic damage[16,17]. Winter Gasparoto *et al*[18] followed-up AP patients for an average of 2.9 years and found that 43.7% of the patients developed pre-diabetes and 31.3% developed diabetes after AP [18]. A large study in Taiwan that followed 2966 patients with AP and 11864 healthy controls over a long period found that the incidence of diabetes in the first 3 mo after the onset of AP was 60.8/1000 *per* year compared to 8.0/1000 *per* year in the control group[19]. The risk of developing diabetes in the first 3 mo after AP onset was 5.9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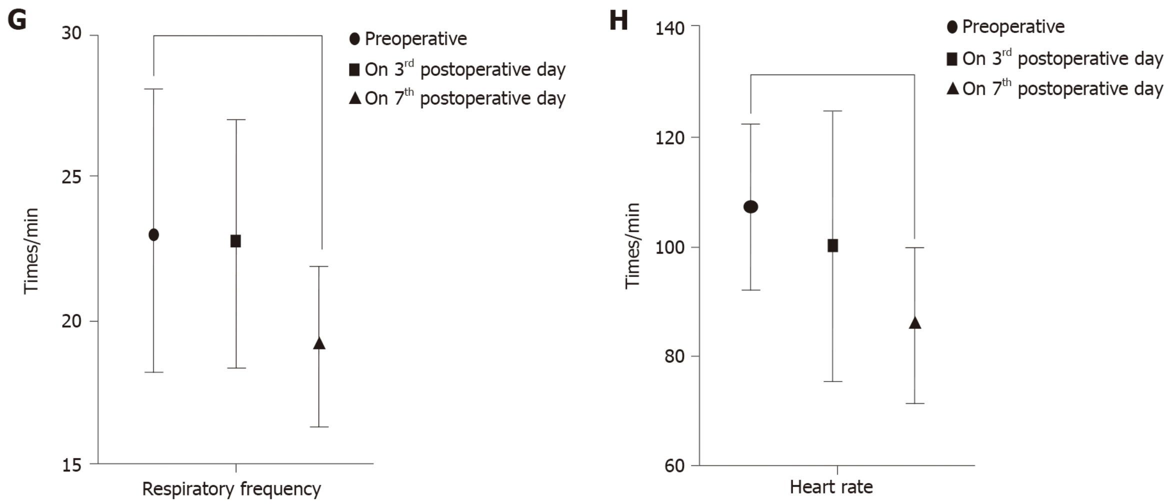

Figure 3 The changes of inflammatory indicators and vital signs in "Step-up" approach during the perioperative period. The postoperative level of white blood cell (A, $P = 0.0012$), neutrophil percentage (B, $P = 0.0367$), C-reactive protein (C, $P = 0.0089$), procalcitonin (D, $P = 0.0004$) and interleukin-6 (E, $P = 0.00073$) were significantly lower than preoperative; F-H: Meanwhile, the vital signs were also better than preoperative.

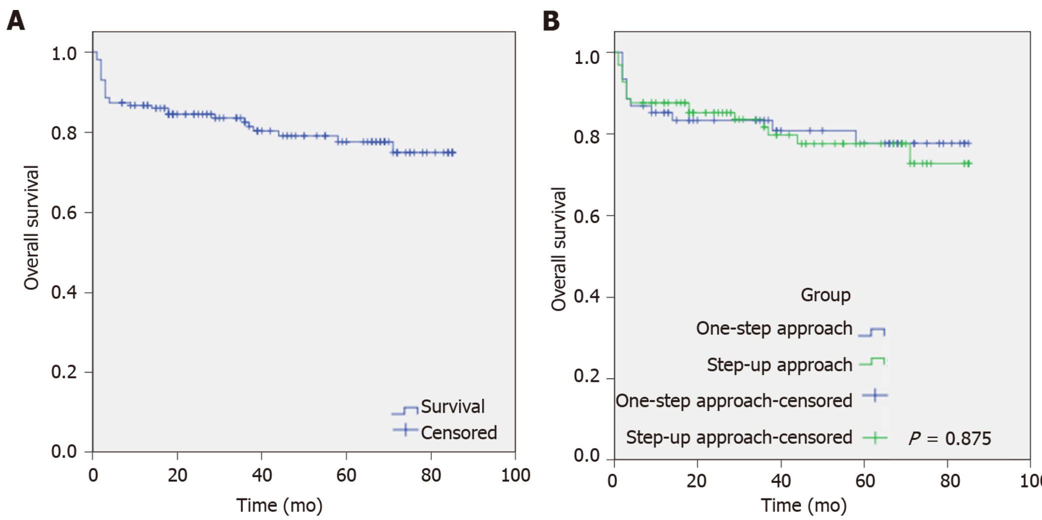

Figure 4 The comparison of overall survival between "One-step" approach and "Step-up" approach. A: The mean follow-up time was 69.17 ± 2.53 mo (95%CI: 64.02-74.16). There are 31 patients died, 24 patients lost to follow-up and 103 patients survived, respectively; B: There are 12 patients died in "One-step" approach. Among them, 8 patients died during the hospitalization and 4 patients died in follow-up period, respectively. In addition, there are 19 patients died in "Step-up" approach, among them, 12 patients died during the hospitalization and 7 patients died in follow-up period, respectively. The rate of overall survival between "One-step" and "Step-up" was 10% and 11.1%, respectively ($P = 0.875$).

times higher than that in the control group. The incidence of diabetes 3 mo after the onset of AP was 22.5/1000 *per* year compared to 6.7/1000 *per* year in the control group. The risk of diabetes 3 mo after the onset of AP was 2.54 times higher than that in the control group[20]. Additionally, Gupta *et al*[20] found that 40% of AP patients developed diabetes after an average of 31.3 mo of follow-up[20]. The above results are consistent with the results of the present study, indicating that the proportion of AP patients with long-term pancreatic endocrine insufficiency gradually increases with prolonged follow-up time and patient age. This suggests that clinicians should pay attention to postoperative glucose monitoring and regulation, as well as long-term follow-up of patients' pancreatic secretion function.

In addition, another study reported that the probability of pancreatic exocrine insufficiency (PEI) within 1 year in patients with AP is 61%-85% and that PEI will last for 6-18 mo in some patients[16,21]. However, pancreatic function improves with the passage of postoperative time in some patients, and the incidence of PEI also decreases [22]. However, some patients still require long-term oral trypsin to improve their clinical symptoms, which is consistent with the present study results. As a common complication after pancreatic surgery, PEI can lead to decreased quality of life and malnutrition in patients, which can be life-threatening in severe cases. Pancreatic surgeons should pay appropriate attention to this issue. Additionally, because some patients with pancreatic endocrine or exocrine insufficiency require long-term oral medications or need to undergo necessary imaging and laboratory examinations regularly, the medical expenses of these patients are significantly increased, and their long-term quality of life is affected to varying degrees. However, there was no significant difference between the two surgical approaches in terms of long-term complications and medical costs. Consequently, the present study confirms that the "One-step" surgical approach has similar long-term efficacy and prognosis as the "Step-up" approach.

In summary, we believe that the "One-step" approach is indicated when the lesion area is mainly involved in the peripancreatic or peripancreatic involving the posterior colonic space. The patients are usually generally stable and can tolerate minimally invasive surgery. The advantages of this procedure are: (1) The lesions on the pancreatic head and pancreatic body and tail can be treated simultaneously; (2) Laparoscopy has a broad field of vision, strong ability to remove necrotic tissue, and can be used to control intraoperative bleeding by a variety of means; (3) This procedure has little interference with laparoscopy and is helpful to the rapid recovery of digestive tract function; (4) The anatomical position is clear, and the localization is more accurate; and (5) This procedure avoids PCD treatment and helps to shorten the length of hospital stay. The disadvantage is that there is the possibility of stomach and colon injury. For non-low drainage, negative pressure suction should be carried out in the early postoperative period to maintain the drainage effect. Meanwhile, there is a risk of long-term incisional hernia. In addition to the condition mentioned above, the "Step-up" approach can be applicable for IPN patients in other conditions.

However, the present study also has some limitations. First, this was a retrospective, single-center study involving a small sample size; as such, there may be a certain bias in the analysis of clinical data. Secondly, the research and exploration of the "One-step" approach mainly focused on patients without organ failure or who had passed the delayed operative waiting period through conservative treatment. Thus, this surgical approach has not been applied in the treatment of patients with IPN complicated with organ failure. Hence, we need to confirm the current findings further using large-sample, randomized controlled studies.

CONCLUSION

Compared with the "Step-up" approach, the "One-step" approach is a safe and effective treatment method, with better long-term quality of life and prognoses. These findings provide a new concept that allows diversification of surgical treatment strategies for IPN patients and also indicates that an individualized treatment strategy for each patient is more appropriate than a single set treatment strategy for a complex and variable disease such as IPN. Thus, this approach can be used as a new surgical treatment option for IPN in the future.

ARTICLE HIGHLIGHTS

Research background

Although the "Step-up" strategy is the primary surgical treatment for infected pancreatic necrosis, it is not suitable for all infected pancreatic necrosis patients.

Research motivation

The "One-step" strategy represents a novel treatment; however, there is a lack of safety, efficacy, and long-term follow-up clinical data compared with the "Step-up" approach.

Research objectives

This study aimed to compare the safety, efficacy, and long-term follow-up of two surgical approaches.

Research methods

Patients were retrospectively assessed, with a composite endpoint of severe complications or death as the primary outcome. *t*-test, chi-square test or Fisher's exact test, and Kaplan-Meier curves were used for further analysis.

Research results

The time from disease onset to hospital admission (53.69 ± 38.14 *vs* 32.20 ± 20.75, P < 0.001) and to initial surgical treatment was longer in the "Step-up" than in the "One-step" group (54.38 ± 10.46 *vs* 76.58 ± 17.03, P < 0.001). Patients who underwent "Step-up" necrosectomy had a longer hospitalization duration (65.41 ± 28.14 *vs* 52.76 ± 24.71, P = 0.02), and more interventions (4.26 ± 1.71 *vs* 3.18 ± 1.39, P < 0.001). Postoperative inflammatory indicator levels were significantly lower than preoperative levels in each group. Although the incisional hernia incidence was higher in the "One-step" group, there were no significant differences in other observation indicators.

Research conclusions

The "One-step" approach is a safe and effective treatment method with better long-term quality of life and prognosis.

Research perspectives

The "One-step" approach provides an alternative surgical treatment strategy for patients with infected pancreatic necrosis.

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ORIGINAL ARTICLE

Retrospective Study

Risk of station 12a lymph node metastasis in patients with lower-third gastric cancer

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Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Tianjin Medical University Cancer Institute and Hospital.

Informed consent statement: All

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Abstract

BACKGROUND

Controversy over the issue that No. 12a lymph node involvement is distant or regional metastasis remains, and the possible inclusion of 12a lymph nodes in D2 lymphadenectomy is unclear. As reported, gastric cancer (GC) located in the lower third is highly related to the metastasis of station 12a lymph nodes.

AIM

To investigate whether the clinicopathological factors and metastasis status of other perigastric nodes can predict station 12a lymph node metastasis and evaluate the prognostic significance of station 12a lymph node dissection in patients with lower-third GC.

METHODS

A total of 147 patients with lower-third GC who underwent D2 or D2+ lymphadenectomy, including station 12a lymph node dissection, were included in this retrospective study from June 2003 to March 2011. Survival prognoses were compared between patients with or without station 12a lymph node metastasis. Logistic regression analyses were used to clarify the association between station 12a lymph node metastasis and clinicopathological factors or metastasis status of

other perigastric nodes. The metastasis status of each regional lymph node was evaluated to identify the possible predictors of station 12a lymph node metastasis.

RESULTS

Metastasis to station 12a lymph nodes was observed in 18 patients with lower-third GC, but not in 129 patients. The incidence of station 12a lymph node involvement was reported as 12.2% in patients with lower-third GC. The overall survival of patients without station 12a lymph node metastasis was significantly better than that of patients with station 12a metastasis (P < 0.001), which could also be seen in patients with or without extranodal soft tissue invasion. Station 12a lymph node metastasis and extranodal soft tissue invasion were identified as independent predictors of poor prognosis in patients with lower-third GC. Advanced pN stage was defined as independent risk factor significantly correlated with station 12a lymph node positivity. Station 3 lymph node staus was also proven to be significantly correlated with station 12a lymph node involvement.

CONCLUSION

Metastasis of station 12a lymph nodes could be considered an independent prognosis factor for patients with lower-third GC. The dissection of station 12a lymph nodes may not be ignored in D2 or D2+ lymphadenectomy due to difficulties in predicting station 12a lymph node metastasis.

Key Words: Gastric cancer; Lymph node; Metastasis; No. 12a; Proper hepatic artery

Core Tip: The possible inclusion of 12a lymph nodes in D2 lymphadenectomy remains unclear. As reported, gastric cancer (GC) located in the lower third was highly related to the metastasis of station 12a lymph nodes. The clinicopathological factors related to station 12a lymph node metastasis in patients with lower-third GC were investigated. The results showed that station 3 lymph node status was highly related to station 12a lymph node metastasis. The poor prognosis of patients with station 12a lymph node metastasis compared with those without 12a indicated that station 12a lymph node dissection must be considered.

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eligible patients delivered written informed consent.

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INTRODUCTION

Gastric cancer (GC) prevails as the fourth most common malignancy worldwide, and its mortality ranks second among all cancer-related deaths in China[1]. Surgery, including radical gastrectomy and lymphadenectomy, still plays a dominant role in patients with operable GC[2]. However, controversy has persisted for decades over the issue of performing D2 lymphadenectomy because of the high perioperative morbidity and mortality rate of D2 dissection[3-5]. Nevertheless, considerably extensive lymph node excision (D2 or D2+) helped reduce the cancer burden and identify the N status of patients[6]. Thus, D2 Lymphadenectomy combined with radical gastrectomy has become the standard treatment for advanced GC in Japan[7-9].

Station 12a lymph nodes are defined as the hepatoduodenal ligament lymph nodes along the proper hepatic artery. However, whether station 12a lymph node metastasis should be regarded as regional or distant and whether resection of this station should be included in D2 lymphadenectomy remain controversial. Station 12a lymph node metastasis, which was categorized as distant metastasis by the 7th American Joint Committee on Cancer (AJCC) classification[10,11], was reclassified as regional lymph node metastasis by the 8th AJCC classification[12]. However, the concept of station 12a lymph node involvement as regional metastasis once occurred in the 6th AJCC[13] and the 3rd Japanese classifications of gastric carcinoma[14]. Station 12a lymph nodes, as well as stations 1, 3, 4sb, 4d, 5, 6, 7, 8a, 9, and 11p lymph nodes, are all indispensable for D2 lymphadenectomy during distal or total gastrectomy despite the aforementioned classifications. Additionally, D2 lymphadenectomy plus dissection of any of stations 8p, 10, 11d, 12b, 12p, 13, 14v, 16a2, and 16b1, so-called D2+ lymphadenectomy, as a more extended dissection, was an option for selected patients. D2 lymphadenectomy is essential to lower-third GC according to the 5th Japanese treatment guidelines[15]. Nevertheless, other studies indicated that station 12a lymph node dissection during D2 lymphadenectomy is unnecessary due to the absence of survival benefits with the additional 12a lymph node dissection[16,17].

As reported, with an incidence ranging from 1.7% to 18.2%[18-23], station 12a lymph node metastasis was highly related to the lower third tumor[23]. Therefore, in the present study some patients with lower-third GC were retrospectively reviewed to investigate the risk factors for station 12a lymph node metastasis and evaluate the survival outcomes of station 12a lymph node dissection.

MATERIALS AND METHODS

Patients

A total of 705 patients with lower-third GC at the Department of Gastroenterology of the Tianjin Medical University Cancer Hospital (TJMUCH) were recruited in this retrospective study between June 2003 and March 2011. All eligible patients delivered written informed consent, and the study was approved by the institutional review board of the TJMUCH. The eligibility criteria were as follows: (1) Histological confirmation of primary gastric adenocarcinoma located in the lower third; (2) D2 or D2+ lymphadenectomy with station 12a lymph node dissection; (3) Radical gastrectomy with pathologically negative margin (R0 resection); and (4) Negative peritoneal lavage cytology without peritoneal metastasis or other distant metastasis. The exclusion criteria were as follows: (1) History of gastric surgery; (2) Prior chemotherapy, radiotherapy, or endocrine therapy for any malignancy; (3) Psychologically diagnosed disorders or other life-threatening diseases; or (4) Part of the stomach tumor pathologically diagnosed as stromal tumor or lymphoma.

The following 16 clinicopathologic factors were reviewed from the medical and pathological record: Sex, age at surgery, Lauren classification, Borrmann type, maximum diameter, examined lymph node count, station 12a lymph node metastasis, pT stage, pN stage, extranodal soft tissue invasion [defined as the presence of tumor cells in an isolated tumor nodule between extranodal adipose tissues that was discontinuous with either the primary lesion and beyond the capsule of the lymph node (Figure 1)], perineuronal invasion, vessel invasion, adjuvant chemotherapy, histopathological subtype, surgical procedure, and blood transfusion. The postoperative pathological stages of all included cases were determined following the 8th AJCC gastric cancer guidelines.

Surgical management

Curative gastrectomy and lymphadenectomy were delivered to all included patients by experienced surgeons according to the guidelines of the Japanese Gastric Cancer Association. Almost all the patients underwent open surgery. Primary tumors were resected *en bloc* by gastrectomy plus D2 or D2+ lymphadenectomy with the dissection of station 12a lymph nodes because the surgical procedures were mainly based on the Japanese Gastric Cancer Treatment Guidelines[15].

Follow-up

After surgery, the patients were followed at 3-mo to 6-mo intervals up to the first 2 years, every 6 mo for the next 3 years, and annually thereafter until the end of the study (November 2015) or death. The median follow-up duration for the entire cohort was 42 (range, 2-145) mo. The main endpoint of the study was overall survival (OS), which was recorded from the date of surgery to the death of subjects or the latest follow-up. A total of 109 patients (74.1%) died during the follow-up period.

Statistical analysis

SPSS software (version 19.0, SPSS Inc, Chicago, IL, United States) was employed for all

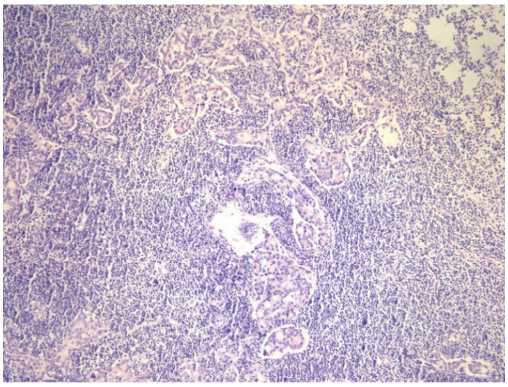

Figure 1 Tumor cells in adipose tissue discontinuous with the primary lesion and beyond the capsule of the lymph node. Hematoxylin-eosin staining, original magnification × 40.

statistical analyses. Kaplan-Meier methods were performed to generate the survival curves, and log-rank tests were applied to compare the OS by corresponding clinicopathological factors. These factors, which might be associated with station 12a lymph node metastasis, were evaluated by univariate and multivariate logistic regression analyses. Factors with significance (P value < 0.05) in the univariate analysis were included in the subsequent multivariate analysis. Cox proportional hazards model was used for multivariate survival analysis to identify independent risk factors for prognosis in patients with lower-third GC. Moreover, χ^2 test, McNemar paired-sample test, or Fisher's test was applied to compare the sensitivity, specificity, and false-negative and false-positive rates between other regional lymph node metastasis and station 12a lymph node metastasis to identify the possible predictors of station 12a lymph node involvement. $P < 0.05$ was considered statistically significant.

RESULTS

Clinicopathological characteristics of patients

Overall, 147 patients with lower-third GC underwent R0 gastrectomy with D2 or D2+ lymphadenectomy, including station 12a lymph node dissection, were eligible for this study inclusion. Moreover, of all eligible patients, 129 were histopathologically diagnosed without station 12a lymph node involvement and 18 had station 12a lymph node metastasis. The mean age for all patients was 52.9 (range, 26-79) years. Among these included patients, 18 patients (12.2%) had station 12a lymph node metastasis. The mean number of station 12a lymph node metastases was 1.33 ± 0.59 (range: 1-3). The characteristics of the patients and clinicopathological variables are shown in Table 1.

Univariate and multivariate analyses of OS

Univariate analysis showed that station 12a lymph node metastasis, extranodal soft tissue invasion, large tumor diameter (maximum diameter > 4 cm), advanced pT and pN category, and no adjuvant chemotherapy were significantly associated with a poor prognosis in patients with lower-third GC (Table 1). Multivariate analysis revealed that pN stage and extranodal soft tissue were regarded as independent risk factors for the OS of GC patients. However, station 12a lymph node metastasis was defined as a part of pN stage, and pN stage exhibited a significant correlation with station 12a lymph node metastasis (Table 2). Therefore, pN stage were excluded in multivariate analysis to avoid multicollinearity. The results excluding the pN stage revealed that station 12a lymph node metastasis and extranodal soft tissue invasion were both independent prognostic factors for the OS of patients with lower-third GC (Table 3).

Survival significance of station 12a lymph nodes

By the end of follow-up, all 18 patients with station 12a lymph node metastasis died, and the mean OS for patients with and without station 12a lymph node metastasis was 22.4 and 74.8 mo, respectively. The 5-year survival rate (5-YSR) for patients with or without station 12a lymph node metastasis was 5.6% and 39.5%, respectively. The patients with station 12a lymph node involvement showed a poorer prognosis

Table 1 Clinicopathological characteristics of patients with station 12a lymph node dissection

Characteristic	*n*	Station 12a lymph nodes		χ^2	*P* value
		Negative (*n* = 129)	Positive (*n* = 18)		
Gender				0.061	0.806
Male	91	82	9		
Female	56	47	9		
Age at surgery, yr				0.242	0.622
< 60	84	74	10		
≥ 60	63	55	8		
Lauren classification				5.911	0.052
Intestinal	78	69	9		
Diffuse	68	60	8		
Mixed	1	0	1		
Borrmann type				1.165	0.761
I	7	6	1		
II	52	47	5		
III	81	71	10		
IV	7	5	2		
Maximum diameter				4.491	**0.034**
4 cm or less	77	73	4		
More than 4 cm	70	56	14		
Examined lymph node count				1.241	0.538
< 16	47	42	5		
16-30	69	61	8		
> 30	31	26	5		
pT stage				10.112	**0.039**
T1	2	2	0		
T2	28	28	0		
T3	10	9	1		
T4a	102	86	16		
T4b	5	4	1		
pN stage				61.092	**< 0.001**
N0	56	56	0		
N1	22	22	0		
N2	36	32	4		
N3a	19	10	9		
N3b	14	9	5		
Soft tissue invasion				19.249	**< 0.001**
Yes	31	23	8		
No	115	105	10		
Perineuronal invasion				0.719	0.397
Yes	1	1	0		
No	146	128	18		

Vessel invasion				0.279	0.597
Yes	2	2	0		
No	145	127	18		
Adjuvant chemotherapy				5.997	**0.014**
Yes	97	82	15		
No	50	47	3		
Blood transfusion				1.394	0.238
Yes	19	17	2		
No	128	112	16		

Table 2 Univariate and multivariate analyses of predictive factors for station 12a lymph nodes metastasis

Variables	Univariate analysis			Multivariate analysis[1]			Multivariate analysis[2]		
	OR	95%CI	*P* value	OR	95%CI	*P* value	OR	95%CI	*P* value
Gender	1.745	0.648-4.700	0.271						
Age at surgery	1.076	0.399-2.906	0.885						
Lauren classification	1.427	0.549-3.709	0.465						
Borrmann type	1.404	0.643-3.066	0.396						
Maximum diameter	4.562	1.424-14.619	**0.011**	2.838	0.743-10.840	0.127	4.012	1.231-13.078	**0.021**
Examined lymph node count	1.268	0.641-2.510	0.495						
pT stage	2.935	1.807-7.924	**0.034**	1.456	0.389-5.449	0.577	2.055	0.749-5.642	0.162
pN stage	3.336	1.971-5.648	**< 0.001**	3.322	1.962-5.625	**< 0.001**			
Soft tissue invasion	3.500	1.249-9.804	**0.017**	1.201	0.350-4.121	0.771	2.912	1.007-8.420	**0.048**
Perineuronal invasion	0.000	0.000	1.000						
Vessel invasion	0.000	0.000	0.999						
Surgical options	0.568	0.240-1.343	0.197						
BMI	1.400	0.519-3.779	0.507						
Adjuvant chemotherapy	2.866	0.789-10.415	0.11						
Blood transfusion	0.824	0.174-3.903	0.807						

[1]Four factors with significance ($P < 0.05$) in the univariate analysis were included in the multivariate analysis.
[2]Factors with significance in univariate analysis excluding pN stage were included in the multivariate analysis.
CI: Confidence interval; OR: Odds ratio; BMI: Body mass index.

compared with those without ($P < 0.001$; Figure 2). Moreover, all factors related to station 12a lymph node metastasis were included in the survival analysis for patients with positive or negative 12a lymph nodes (Table 4). OS rates were all significantly associated with soft tissue invasion despite the presence or absence of station 12a lymph node metastasis, which were both defined as independent predictors of OS (Figures 3 and 4). However, station 12a lymph node metastasis was unavailable for patients with pN0 and pN1 stages (Figure 5). By contrast, no statistically significant difference was found between patients with and without station 12a lymph node metastasis for patients with pN2 stage. Moreover, similar results could be obtained for patients with pN3 stage (Figure 6).

Clinicopathological risk factors for station 12a lymph node metastasis

Station 12a lymph node metastasis was significantly related to the maximum diameter of tumor (more than 4 cm), pT stage, advanced pN stage, and extranodal soft tissue invasion by univariate analyses. However, the results of multiple logistic regression analysis, including the four above-mentioned factors, only indicated that pN stage was significantly correlated with station 12a lymph node metastasis ($P < 0.001$; Table 3).

Table 3 Multivariate analysis of risk factors for survival of patients with lower-third gastric cancer

Variable	Cox regression analysis[1]		Cox regression analysis[2]	
	95%CI	*P* value	95%CI	*P* value
Station 12a lymph node metastasis	0.775-2.576	0.260	1.659-5.043	**< 0.001**
Maximum diameter	0.690-1.559	0.859	0.722-1.644	0.682
pT stage	0.852-1.439	0.446	0.926-1.524	0.175
pN stage	1.291-1.809	**< 0.001**		
Soft tissue invasion	1.189-3.063	**0.007**	1.334-3.386	**0.002**
Adjuvant chemotherapy	0.841-2.028	0.234	0.823-1.969	0.279

[1]Five factors with significance ($P < 0.05$) in the univariate analysis of survival were included in the multivariate analysis.
[2]Four factors with significance excluding pN stage.
CI: Confidence interval.

The maximum diameter of tumor (more than 4 cm) and extranodal soft tissue invasion were both significantly correlated with 12a lymph node metastasis (P = 0.021 and P = 0.048, respectively) during multivariate analysis with the exclusion of pN to avoid multicollinearity (Table 2).

Association between status of regional lymph nodes and station 12a lymph node metastasis

The univariate analyses indicated that the status of stations 1, 2, 3, 4sb, 6, 7, and 8a lymph node was significantly associated with station 12a lymph node metastasis (P < 0.05; Table 5). Station 3 lymph node status was found to be significantly related to station 12a lymph node metastasis by multivariate analysis. However, the correlation between the status of each regional lymph node and station 12a lymph node metastasis displayed high false-negative ratios ranging from 1%-10%. Therefore, significant predictors with relatively high kappa values were absent based on the consistency analysis. Such finding may be due to the small sample size of patients with other regional lymph node metastases (Table 6).

DISCUSSION

Lymph node metastasis was considered a significant prognostic factor for GC patients. The incidence of station 12a lymph node metastasis varied from 1.7% to 18.2% among studies[18-23]. However, many studies found that tumor located in the lower third was significantly associated with metastasis to station 12a lymph nodes. Moreover, patients with lower-third GC even showed a high incidence of station 12a lymph node metastasis[23,24]. The present study reported that the incidence of station 12a lymph node involvement was as high as 12.2% in patients with lower-third GC. Station 12a lymph node metastasis and extranodal soft tissue were defined in this study as independent prognosis factors for patients with lower-third GC. By contrast, station 12a lymphadenectomy was suggested as an independent prognostic factor for stage III patients by other investigations[24].

In addition to the tumor located in the lower third, many other clinicopathological factors were also significantly associated with station 12a lymph node metastasis. For example, lesser curvature or circumferential involvement and tumor diameter of more than 81.5 mm were identified as independent risk factors for station 12a lymph node metastasis[23]. Moreover, N and M stages were reported to be significantly correlated with the metastasis of station 12a lymph nodes[24], while T and N stages were proven to have significant associations with station 12a lymph node metastasis. However, while excluding the pN stage to avoid multicollinearity, the maximum diameter of tumor (more than 4 cm) and extranodal soft tissue invasion were verified in this study to have a significant correlation with the metastasis of station 12a lymph nodes. Nonetheless, only pN stage was significantly associated with 12a lymph node metastasis while including pN stage in the multivariate analysis. These differences may come from the included cohorts of the current study, which focused on patients with lower-third GC. This study showed that patients with early-stage GC did not

Table 4 Survival analysis of clinicopathological characteristics based on status of station 12a lymph nodes

Variable	No. 12a (+)		No. 12a (-)	
	5-YSR (%)	*P* value	5-YSR (%)	*P* value
Maximum diameter		0.408		0.142
4 cm or less	0		45.2	
More than 4 cm	7.1		32.1	
pT stage		0.152		0.158
T1	-		100.0	
T2	-		60.7	
T3	0		55.6	
T4a	6.3		31.4	
T4b	0		0	
pN stage		0.619		**< 0.001**
N0	-		60.7	
N1	-		31.8	
N2	0		31.3	
N3a	11.1		20.0	
N3b	0		0	
Soft tissue invasion		**0.003**		**0.002**
+	0		12.5	
-	10		45.7	
No. 1 LNs		0.873		0.292
+	0		28.6	
-	7.7		40.2	
No. 2 LNs		0.171		0.407
+	33.3		20.0	
-	0		40.3	
No. 3 LNs		0.950		**< 0.001**
+	7.7		12.5	
-	0		48.5	
No. 4sb LNs		0.408		**0.042**
+	14.3		0	
-	0		42.1	
No. 6 LNs		0.290		**< 0.001**
+	0		10.8	
-	14.3		51.1	
No. 7 LNs		0.143		**0.028**
+	0		23.1	
-	10		43.7	
No. 8a LNs		0.173		**< 0.001**
+	0		6.3	
-	8.3		44.2	

5-YSR: Five-year survival rate; LN: Lymph node.

present with station 12a lymph node metastasis, including pT1-2, pN0-1, and Ia-IIb stages, which may cause a significant relation to station 12a lymph node metastasis.

Controversy over performing D2 lymphadenectomy with or without station 12a lymph node dissection has persisted for decades possibly due to the uncertainty that station 12a lymph node positivity should be regarded as distant or regional metastasis. As mentioned above, station 12a lymph node positivity was considered to be a distant metastasis by the 7th AJCC classification[10,11]. Meanwhile, such positivity was not assigned to D2 lymphadenectomy according to the 7th AJCC staging and guidelines of the National Cancer Comprehensive Network of GC (Version 3, 2015)[25]. Nevertheless, station 12a lymph node positivity was regarded as a regional metastasis by the 8th AJCC staging[12], and the dissection of station 12a lymph nodes should be included in D2 lymphadenectomy with distal or total gastrectomy according to the 5th Japanese treatment guidelines[15], which were also supported by the studies of Shirong *et al*[22] and Lee *et al*[26] studies. Several studies argued about this issue for long periods. Moreover, some studies suggested that excluding the dissection of station 12a lymph nodes would not affect survival compared with standard D2 lymphadenectomy[16,17]. All patients underwent station 12a lymph node dissection in the current study, but the 5-YSR of patients with station 12a lymph node metastasis was substantially lower than that of patient without station 12a lymph node metastasis. This finding may be due to the advanced pN stage for patients with station 12a lymph node metastasis. However, the poor prognosis of station 12a lymph node metastasis and the survival benefits of station 12a lymph node dissection for patients with station 12a lymph node metastasis from previous studies[23] revealed the possible consideration of the dissection of station 12a lymph nodes in D2 lymphadenectomy for GC patients. As well, considering that none of enrolled patients with station 12a lymph node metastasis underwent any neoadjuvant therapy, preoperative enhanced computed tomography (CT) and endoscopic ultrasonography must be performed to evaluate preoperative CT stage, and preoperative chemotherapy should be given to patients with station No. 12a lymph node metastases to improve their survival rate.

Station 12a lymph nodes are located around the common hepatic artery, and the portal vein must be exposed during the dissection, thus posing a risk for major vessel damage during the operation. Therefore, confirming whether the metastasis-free status of other regional lymph nodes could be identified as a predictor to avoid station 12a dissection is necessary. Kumagai *et al*[23] reported that station 11p lymph node status demonstrated a significant correlation to 12a metastasis. By contrast, station 5 lymph node status was significantly associated with the metastasis of 12a lymph nodes in the study of Yang *et al*[24]. Shirong *et al*[22] also demonstrated a significant relation of stations 3, 5, and 6 lymph node involvement to 12a metastasis. However, in our study, station 3 lymph node involvement was certified as an independent predictor of station 12a lymph node metastasis in patients with GC in the lower third. However, these differences may come from the small sample size and different inclusion criteria. Now, the lymphatic drainage to station 12a lymph nodes remains unclear. Therefore, large-scale studies should be conducted to further investigate relevant regional lymph nodes as predictors of station 12a lymph node metastasis.

Nevertheless, this study has some limitations. The small sample size constrained the number of patients with other positive regional lymph nodes. Moreover, the number of patients with station 12a lymph node metastasis was remarkably small. Thus, obtaining additional significant outcomes, including survival benefit and safety of station 12a lymph node dissection for GC patients, is difficult.

CONCLUSION

Overall, the obtained results reveal that station 12a lymph node metastasis is an independent risk factor for patients with lower third GC. Extranodal soft tissue invasion and the maximum diameter of tumor (more than 4 cm) are independent risk factors significantly correlated with the metastasis of station 12a lymph nodes. Station 3 lymph node status is significantly correlated with station 12a lymph node involvement. However, no regional lymph node was defined as an effective predictor of station 12a lymph node metastasis, indicating the necessity of large multicenter

Table 5 Association between status of other regional lymph nodes and station 12a lymph node metastasis

Variables	No. 12a metastasis	Univariate analysis			Multivariate analysis		
		OR	95%CI	*P* value	OR	95%CI	*P* value
No. 1 LNs							
+	5	6.703	1.860-24.163	**0.004**			
-	13						
No. 2 LNs							
+	3	4.960	1.076-22.868	**0.040**			
-	15						
No. 3 LNs							
+	13	7.881	2.608-23.821	**< 0.001**	7.881	2.608-23.821	**< 0.001**
-	5						
No. 4sa LNs							
+	3	3.025	0.723-12.657	0.130			
-	15						
No. 4sb LNs							
+	7	4.836	1.626-14.383	**0.005**			
-	11						
No. 4d LNs							
+	0	0.000	0.000	0.999			
-	18						
No .5 LNs							
+	4	3.065	0.860-10.929	0.084			
-	14						
No. 6 LNs							
+	11	3.907	1.407-10.853	**0.009**			
-	7						
No. 7 LNs							
+	8	3.169	1.138-8.828	**0.027**			
-	10						
No. 8a LNs							
+	6	3.531	1.163-10.726	**0.026**			
-	12						
No. 8p LNs							
+	0	0.000	0.000	0.999			
-	18						
No. 9 LNs							
+	2	1.115	0.230-5.403	0.892			
-	16						
No. 10 LNs							
+	0	0.000	0.000	0.999			
-	18						
No. 11p LNs							

+	1	3.735	0.321-43.427	0.292
-	17			
No. 11d LNs				
+	0	0.000	0.000	1.000
-	18			

CI: Confidence interval; OR: Odds ratio; LN: Lymph node.

Table 6 Possibility of regional lymph node predictors of station 12a lymph node invasion

Possible predictor	Sensitivity	Specificity	False negative	False positive	*P* value	Kappa value
No. 1	27.8	94.6	72.2	5.4	0.263	0.261
No. 2	16.7	96.1	83.3	3.9	0.041	0.168
No. 3	72.2	75.2	27.8	24.8	0.000	0.288
No. 4d	0.0	97.7	100.0	2.3	1.000	-0.036
No. 4sa	16.7	93.8	83.3	6.2	0.210[1]	0.126
No. 4sb	38.9	88.4	61.1	11.6	0.557	0.249
No. 5	22.2	91.5	77.8	8.5	0.148	0.690
No. 6	61.1	72.1	38.9	27.9	0.000	0.196
No. 7	44.4	79.8	55.6	20.2	0.011	0.176
No. 8a	33.3	87.6	66.7	12.4	0.191	0.572
No. 8p	0.0	97.7	100.0	2.3	1.000[1]	-0.036
No. 9	11.1	89.9	88.9	10.1	0.011	0.711
No. 10	0.0	98.4	100.0	1.6	1.000[1]	-0.025
No. 11d	0.0	99.2	100.0	0.8	1.000[1]	-0.013
No. 11p	5.6	98.4	94.4	1.6	0.001	0.062

[1]Fisher test.

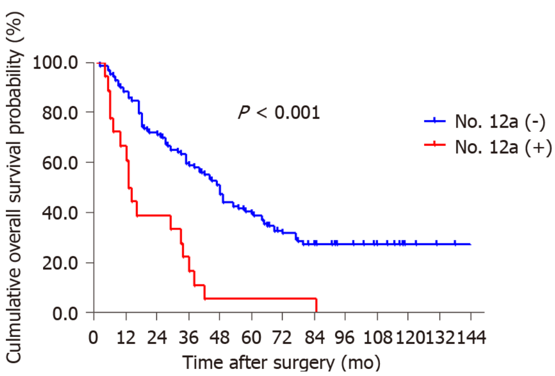

Figure 2 Overall survival of gastric cancer patients with station 12a lymph node involvement *vs* those without.

prospective randomized controlled studies in the future. However, station 12a lymph nodes should be resected in D2 gastrectomy due to increased difficulties in predicting station 12a lymph node metastasis.

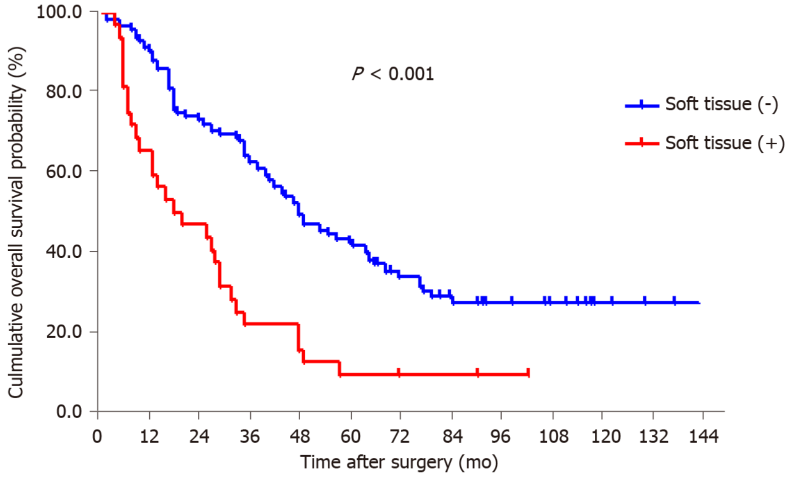

Figure 3 Overall survival of gastric cancer patients with soft tissue invasion *vs* those without.

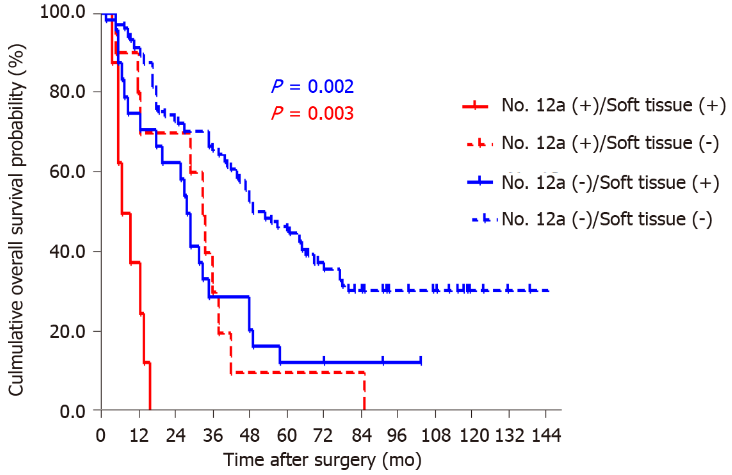

Figure 4 Survival analysis of gastric cancer patients with or without soft tissue invasion stratified by metastatic status of station 12a lymph nodes.

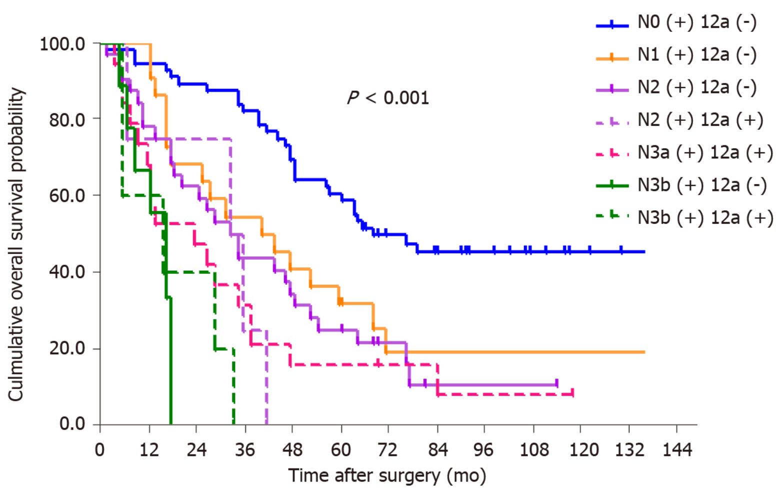

Figure 5 Survival analysis of gastric cancer patients with different pN stages stratified by metastatic status of station 12a lymph nodes.

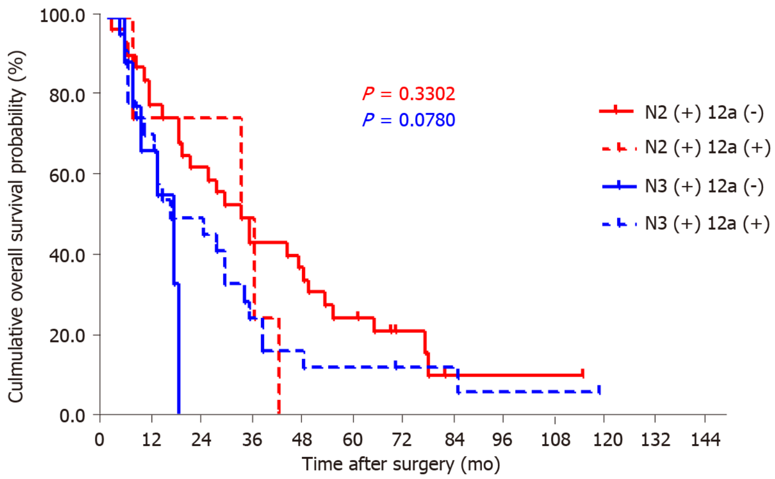

Figure 6 Survival analysis of gastric cancer patients with pN2 or pN3 stage stratified by metastatic status of station 12a lymph nodes.

ARTICLE HIGHLIGHTS

Research background

Controversy over the issue that station 12a lymph node involvement is distant or regional metastasis remains, and whether station 12a lymph nodes should be included in D2 lymphadenectomy or not is unclear.

Research motivation

To investigate the risk factors for station 12a lymph node metastasis and evaluate the survival outcomes of station 12a lymph node dissection in patients with lower-third gastric cancer (GC).

Research objectives

To investigate whether the clinicopathological factors and metastasis status of other perigastric lymph nodes can predict station 12a lymph node metastasis and evaluate the prognostic significance of station 12a lymph node dissection in patients with lower-third GC.

Research methods

Survival prognoses were compared between patients with or without station 12a lymph node metastasis. Logistic regression analyses were used to clarify the association between station 12a lymph node metastasis and clinicopathological factors or metastasis status of other perigastric lymph nodes.

Research results

The incidence of station 12a lymph node involvement was reported as 12.2% in patients with lower-third GC. The overall survival of patients without station 12a lymph node metastasis was significantly better than that of patients with station 12a lymph node metastasis (P < 0.001), which could also be seen in patients with or without extranodal soft tissue invasion. Advanced pN stage was defined as an independent risk factor significantly correlated with station 12a lymph node positivity. Station 3 lymph node status was also proven to be significantly correlated with station 12a lymph node involvement.

Research conclusions

The dissection of station 12a lymph nodes may not be ignored in D2 or D2+ lymphadenectomy due to difficulties in predicting station 12a lymph node metastasis.

Research perspectives

Controversy over the issue that station 12a lymph node involvement is distant or regional metastasis remains, and the possible inclusion of station 12a lymph nodes in the D2 lymphadenectomy is unclear. As reported, GC located in the lower third was highly related to the metastasis of station 12a lymph nodes. The clinicopathological factors related to station 12a lymph node metastasis in patients with lower-third GC were investigated in this study. The results showed that station 3 lymph node status was highly related to station 12a lymph node metastasis. The poor prognosis of patients with station 12a lymph node metastasis compared with those without indicated that station 12a lymph node dissection must be considered. This study further validated the significance of the study of station 12a lymph node metastasis in patients with lower third GC.

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ORIGINAL ARTICLE

Retrospective Study

Choice of operative method for pancreaticojejunostomy and a multivariable study of pancreatic leakage in pancreaticoduodenectomy

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Abstract

BACKGROUND

As one of the major abdominal operations, pancreaticoduodenectomy (PD) involves many organs. The operation is complex, and the scope of the operation is large, which can cause significant trauma in patients. The operation has a high rate of complications. Pancreatic leakage is the main complication after PD. When pancreatic leakage occurs after PD, it can often lead to abdominal bleeding and infection, threatening the lives of patients. One study found that pancreatic leakage was affected by many factors including the choice of pancreaticojejunostomy method which can be well controlled.

AIM

To investigate the choice of operative methods for pancreaticojejunostomy and to conduct a multivariate study of pancreatic leakage in PD.

METHODS

A total of 420 patients undergoing PD in our hospital from January 2014 to March 2019 were enrolled and divided into group A (n = 198) and group B (n = 222) according to the pancreatointestinal anastomosis method adopted during the operation. Duct-to-mucosa pancreatojejunostomy was performed in group A and bundled pancreaticojejunostomy was performed in group B. The operation time, intraoperative blood loss, and pancreatic leakage of the two groups were assessed. The occurrence of pancreatic leakage after the operation in different patients was analyzed.

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RESULTS

The differences in operative time and intraoperative bleeding between groups A and B were not significant (P > 0.05). In group A, the time of pancreatojejunostomy was 26.03 ± 4.40 min and pancreatic duct diameter was 3.90 ± 1.10 mm. These measurements were significantly higher than those in group B (P < 0.05). The differences in the occurrence of pancreatic leakage, abdominal infection, abdominal hemorrhage and gastric retention between group A and group B were not significant (P > 0.05). The rates of pancreatic leakage in patients with preoperative albumin < 30 g/L, preoperative jaundice time ≥ 8 wk, and pancreatic duct diameter < 3 mm, were 23.33%, 33.96%, and 19.01%, respectively. These were significantly higher than those in patients with preoperative albumin ≥ 30 g/L, preoperative jaundice time < 8 wk, and pancreatic duct diameter ≥ 3 cm (P < 0.05). Logistic regression analysis showed that preoperative albumin < 30 g/L, preoperative jaundice time ≥ 8 wk, and pancreatic duct diameter < 3 mm were risk factors for pancreatic leakage after PD (odds ratio = 2.038, 2.416 and 2.670, P < 0.05).

CONCLUSION

The pancreatointestinal anastomosis method during PD has no significant effect on the occurrence of pancreatic leakage. The main risk factors for pancreatic leakage include preoperative albumin, preoperative jaundice time, and pancreatic duct diameter.

Key Words: Pancreatoduodenectomy; Pancreatojejunostomy; Choice of operative methods; Pancreatic leakage; Multivariate analysis

Core Tip: From retrospective studies, it was confirmed that the type of pancreaticojejunostomy during pancreaticoduodenectomy had no significant effect on the occurrence of postoperative pancreatic leakage. The main risk factors for pancreatic leakage include preoperative albumin, preoperative jaundice time and pancreatic duct diameter.

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INTRODUCTION

As one of the major abdominal operations, pancreaticoduodenectomy (PD) involves many organs. The operation is complex, and the scope of the operation is large, which can cause significant trauma in patients. The operation has a high rate of complications. Pancreatic leakage is the main complication after PD[1-5]. When pancreatic leakage occurs after PD, it can often lead to abdominal bleeding and infection, threatening the lives of patients. One study found that pancreatic leakage was affected by many factors including the choice of pancreaticojejunostomy method, which can be well controlled. Due to the differences in the specific surgical mechanism of the two commonly used anastomosis methods after PD, duct-to-mucosa pancreatojejunostomy and bundled pancreaticojejunostomy, and the individual differences among patients, not all patients can undergo pancreaticojejunostomy. However, each method has advantages and disadvantages. There are still some differences regarding the type of pancreaticojejunostomy that is more favorable for patients[6]. Therefore, in this study, the curative effect of duct-to-mucosa pancreaticojejunostomy and binding pancreaticojejunostomy in PD was reviewed. Multiple factors of postoperative pancreatic leakage were analyzed.

MATERIALS AND METHODS

Patients

A total of 420 patients undergoing PD in our hospital between January 2014 and March 2019 were selected. The inclusion criteria were as follows: (1) American Association of Anesthesiologists classification I–II; (2) Age > 18 years; and (3) Complete preservation of clinical variables. The exclusion criteria were abnormal coagulation function, blood system diseases, immune system diseases, and other basic diseases. These patients were divided into group A (n = 198) and group B (n = 222) according to the pancreatointestinal anastomosis method adopted during the operation. There was no significant difference in the general parameters between groups A and B (P > 0.05, Table 1).

Surgical method

In PD, reconstruction of the digestive tract was in the order of pancreaticojejunostomy, choledochojejunostomy, and gastrojejunostomy to conduct Roux-Y anastomosis. Duct-to-mucosa pancreatojejunostomy was performed in group A. First, we sutured the jejunal seromuscular layer intermittently with the pancreatic tissue at the posterior edge of the pancreatic section. We cut a small hole in the jejunal wall corresponding to the pancreatic duct, then the posterior wall of the jejunum was sutured intermittently with the entire jejunum using three needles, and a silicone tube was inserted into the jejunum and beyond the bilioenterostomy. Next, the anterior wall of the pancreatic duct and the whole jejunum were sutured intermittently using three needles so that the pancreatic duct was placed into the jejunal mucosa as far as possible. We then sutured the anterior tissue of the pancreatic section and the jejunal seromuscular layer intermittently. If necessary, the jejunal seromuscular layer and pancreatic capsule were intermittently embedded and sutured.

Bundled pancreaticojejunostomy was performed in group B. A multifunctional surgical dissector was used to cut the pancreas at the neck, and scrape suction was used to bluntly separate the pancreas. The jejunum was cut near the terminal jejunal artery. The jejunum was turned over to 3 o'clock, so that the mucosal surface of the jejunum was outward. After that, we closed the pancreas and intestinal stump and sutured the two sides with silk thread as a single layer. The posterior lip was sutured first, and then the anterior lip was sutured. The two loose temporary ligation knots were cut off and the mucosal surface was destroyed. The jejunum was returned to its original position. A number 0 absorbable suture was passed through the mesenteric puncture hole between the two groups of blood vessels near the broken end of the jejunum to ligate the jejunum so that the jejunum and pancreas were closely attached. The tightness of ligation was such that the ligation coil could just extend into the small vascular clamp end.

Data collection

The operative time, anastomotic time, intraoperative bleeding loss, and pancreatic duct diameter were compared between the two groups. The rates of pancreatic leakage, abdominal infection, abdominal hemorrhage, and gastric retention were recorded. The preoperative albumin, preoperative jaundice time, pancreatic duct diameter, and other important clinical variables were analyzed and compared.

Statistical analysis

SPSS 22.0 software was used for parameter statistics. The measurement data are expressed as mean ± SD. The differences between these two groups were compared by independent sample t-tests. Categorical variables are expressed as frequency or percentage, and the comparison between the two groups was performed using the χ^2 test. Multivariate analysis adopted the logistic regression analysis, where α = 0.05 was the test level.

RESULTS

Comparison of operation time and anastomosis time between group A and group B

The differences in operative time and intraoperative bleeding between groups A and B were not significant (P > 0.05). The time of pancreatojejunostomy and pancreatic duct diameter in group A were significantly higher than those in group B (P < 0.05, Table 2 and Figure 1).

Table 1 Comparison of general parameters between group A and group B

Group	Cases	Male/female	Age (yr)	Albumin(g/L)	Hemoglobin (g/L)	Disease types			
						Carcinoma of the head of the pancreas	Carcinoma of the ampulla	Carcinoma of the lower common bile duct	Duodenal carcinoma
A group	198	110/88	60.33 ± 9.82	36.70 ± 4.40	110.02 ± 10.43	93 (46.97)	52 (26.26)	31 (15.66)	22 (11.11)
B group	222	132/90	59.81 ± 10.11	36.12 ± 5.53	109.82 ± 12.21	108 (48.65)	72 (32.43)	29 (13.06)	13 (5.86)
t/χ^2		0.653	0.533	1.180	0.179	5.372			
P value		0.419	0.594	0.239	0.858	0.146			

Table 2 Comparison of operation time and anastomosis time between group A and group B

Group	Cases	Operation time (h)	Intraoperative blood loss (mL)	Pancreaticojejunostomy time (min)	Diameter of pancreatic duct (mm)
A group	198	5.02 ± 0.82	430.40 ± 50.03	26.03 ± 4.40	3.90 ± 1.10
B group	222	4.97 ± 0.90	429.28 ± 47.74	21.19 ± 3.77	2.50 ± 0.88
t		0.593	0.235	12.139	14.470
P value		0.554	0.815	0.000	0.000

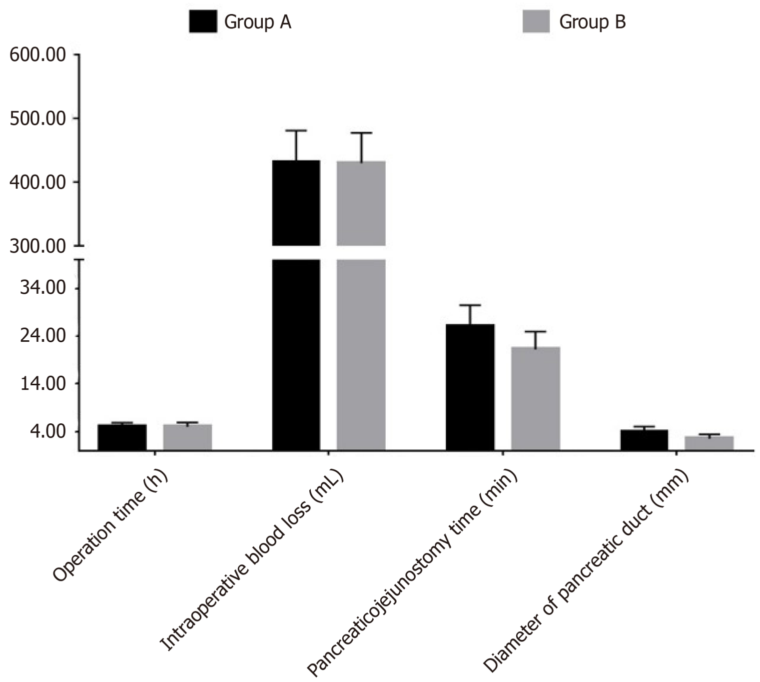

Figure 1 Comparison of operation time and anastomosis time between group A and group B.

Comparison of pancreatic leakage and other complications between group A and group B

The differences in the occurrence of pancreatic leakage, abdominal infection, abdominal hemorrhage, and gastric retention between groups A and B were not significant ($P > 0.05$, Table 3).

Table 3 Comparison of pancreatic leakage and other complications between group A and group B, *n* (%)

Group	Cases	Pancreatic leakage	Abdominal infection	Abdominal hemorrhage	Gastric retention
A group	198	14 (7.07)	8 (4.04)	7 (3.54)	7 (3.54)
B group	222	21 (9.46)	10 (4.50)	9 (4.05)	8 (3.60)
χ^2		0.782	0.055	0.077	0.001
P value		0.377	0.815	0.782	0.970

Relationship between postoperative pancreatic leakage and clinical indicators

The rates of pancreatic leakage in patients with preoperative albumin < 30 g/L, preoperative jaundice time ≥ 8 wk, and pancreatic duct diameter < 3 mm were significantly higher than those in patients with preoperative albumin ≥ 30 g/L, preoperative jaundice time < 8 wk, and pancreatic duct diameter ≥ 3 cm ($P < 0.05$, Table 4).

Multivariate analysis

Logistic regression analysis showed that preoperative albumin < 30 g/L, preoperative jaundice time ≥ 8 wk, and pancreatic duct diameter < 3 mm were risk factors for pancreatic leakage after PD (odds ratio = 2.038, 2.416, and 2.670, $P < 0.05$, Table 5).

DISCUSSION

The anatomical structures adjacent to the pancreas are relatively important; therefore, PD is a highly complex operation that involves many organs. The procedure can cause significant damage to the body, and the morbidity and mortality associated with postoperative complications are high[7]. Pancreatic leakage is the most dangerous complication of PD[8]. Preventing pancreatic leakage is key to the success of the operation, specifically with regard to selection of the procedure used for pancreaticojejunal anastomosis[9]. A previous study[10] found that different anastomosis methods have different effects in different patients. Therefore, clinical recommendations should be made according to the patient's condition, the surgical characteristics, and the selection of the appropriate pancreaticointestinal anastomosis method to improve the surgical effect.

Duct-to-mucosa pancreaticojejunostomy and bundled pancreaticojejunostomy are the most common procedures performed in PD. The results showed that there was no significant difference in operation time and intraoperative blood loss between groups A and B, but the pancreaticojejunostomy duration and pancreatic duct diameter in group A were significantly larger than those in group B. These results indicate that pancreaticojejunal mucosal anastomosis is slow and is mostly used for patients with larger pancreatic duct diameters. Pancreaticojejunostomy can ensure the continuity and patency of the jejunal mucosa and pancreatic duct, thus better maintaining the exocrine function of the pancreas and the patency of the anastomosis. Burying the pancreatic stump under the jejunal serosa can effectively protect the anastomosis and reduce bleeding caused by pancreatic juice eroding the pancreatic stump. However, the operation is relatively difficult, the technical requirements of the anastomosis are high, and they are mostly suitable for patients with large-diameter pancreatic ducts[11,12]. Bundled pancreaticojejunostomy can be used to avoid pinhole indwelling by ensuring the sealing of anastomosis *via* binding instead of suturing, thus reducing the incidence of pancreatic leakage. However, previous studies[13,14] have indicated that this method is not suitable for patients in whom the pancreatic stump is too thick, which must be addressed with certain surgical requirements.

Through further study, no significant differences in the occurrence of pancreatic leakage, abdominal infection, intraperitoneal hemorrhage, and gastric retention between groups A and B were found. These results indicate that the rates of pancreatic leakage and other complications after duct-to-mucosa pancreaticojejunostomy and bundled pancreaticojejunostomy were similar. At present, there is no consensus on which specific operation is best for digestive tract reconstruction in PD. Therefore, surgeons need to understand the specific indications for different anastomosis methods. With the development of clinical technology, more ideal pancreatic stump management methods are expected to be explored through large sample and prospective studies to reduce the rate of postoperative pancreatic leakage and improve

Table 4 Relationship between postoperative pancreatic leakage and clinical indicators, *n* (%)

Index	Cases	Postoperative pancreatic leakage	χ^2	*P* value
Age (yr)			0.072	0.789
≤ 60	243	21 (8.64)		
> 60	177	14 (7.91)		
Sex			0.004	0.953
Male	242	20 (8.26)		
Female	178	15 (8.43)		
Diabetes			0.153	0.696
Yes	120	11 (9.17)		
No	300	24 (8.00)		
Hypertension			0.089	0.766
Yes	178	14 (7.87)		
No	242	21 (8.68)		
Preoperative albumin			33.739	0.000
< 30 g/L	90	21 (23.33)		
≥ 30 g/L	330	14 (4.24)		
Preoperative jaundice time			52.154	0.000
< 8 wk	367	17 (4.63)		
≥ 8 wk	53	18 (33.96)		
Operation time			0.022	0.883
< 4 h	209	17 (8.13)		
≥ 4 h	211	18 (8.53)		
Intraoperative blood loss			0.087	0.768
< 430 mL	230	20 (8.70)		
≥ 430 mL	190	15 (7.89)		
Vascular resection and reconstruction			0.000	1.000
Yes	60	5 (8.33)		
No	360	30 (8.33)		
Pancreatic texture			0.022	0.883
Soft	221	18 (8.14)		
Hard	199	17 (8.54)		
Diameter of pancreatic duct			25.355	0.000
< 3 mm	121	23 (19.01)		
≥ 3 mm	299	12 (4.01)		
Pancreaticojejunostomy time			0.305	0.580
< 30 min	320	28 (8.75)		
≥ 30 min	100	7 (7.00)		
Pancreatic duct indwelling support tube			0.162	0.687
Yes	335	27 (8.06)		
No	85	8 (9.41)		
Disease types			0.018	0.999
Carcinoma of the head of the pancreas	201	17 (8.46)		

Carcinoma of the ampulla	124	10 (8.06)
Carcinoma of the lower common bile duct	60	5 (8.33)
Duodenal carcinoma	35	3 (8.57)

Table 5 Multivariate analysis

Factor	β	SE	Walds	*P* value	Odds ratio (95%CI)
Preoperative albumin < 30 g/L	0.712	0.202	12.424	0.000	2.038 (1.372-3.028)
Preoperative jaundice time ≥ 8 wk	0.882	0.329	7.187	0.000	2.416 (1.268-4.604)
Diameter of pancreatic duct < 3 mm	0.982	0.311	9.970	0.000	2.670 (1.451-4.911)

the safety of the operation.

Analysis of the relationship between postoperative pancreatic leakage and clinical indicators showed that the rate of postoperative pancreatic leakage in patients with preoperative albumin < 30 g/L, preoperative jaundice duration ≥ 8 wk, and pancreatic duct diameter < 3 cm were significantly higher than those before the operation. Logistic regression showed that preoperative albumin < 30 g/L, preoperative jaundice duration ≥ 8 wk, and pancreatic duct diameter < 3 cm were risk factors for pancreatic leakage in patients with PD. These results indicate that preoperative albumin level, preoperative jaundice duration, and pancreatic duct diameter are the main risk factors for pancreatic leakage after PD. Therefore, patients with abnormal preoperative bilirubin and albumin levels and a long duration of jaundice need to be given special attention before the operation and should receive good perioperative supportive treatment to reduce the rate of postoperative pancreatic leakage. Pancreatic leakage is not only related to surgical and pancreatic factors but is also closely related to the basic state of the patient during the perioperative period. As the duration of jaundice increases, the decreased liver function in patients is gradually aggravated. Related studies[15-17] indicated that vitamin K1 could be used to improve coagulation function and jaundice symptoms, but the absorption of toxins in the body could lead to damage to multiple organs and the liver, inducing pancreatic leakage. Perioperative hypoproteinemia is another main cause of abdominal infection, wound infection, and pancreatic leakage. Patients with relatively poor nutritional status require timely supplementation with albumin and nutrients. A good visual field and pancreatic duct exposure are important factors for ensuring a successful pancreaticoenteric anastomosis; therefore, a large diameter is needed to suture the pancreaticoenteric anastomosis, which should then be left in place. The pinhole is an important cause of pancreatic leakage and requires special attention[18-20].

CONCLUSION

In summary, intraoperative pancreaticojejunostomy in PD had no significant effect on postoperative pancreatic leakage. The main risk factors for pancreatic leakage included preoperative albumin, preoperative jaundice time and pancreatic duct diameter.

ARTICLE HIGHLIGHTS

Research background

Pancreaticoduodenectomy (PD) involves many organs, and the operation is complex and the scope of operation is large. The operation can cause significant trauma in patients and has a high rate of complications. Pancreatic leakage is the main complication after PD.

Research motivation

This study discussed the selection of surgical methods for pancreaticojejunostomy and pancreatic leakage during PD.

Research objectives

This study aimed to investigate the choice of operative methods for pancreaticojejunostomy and conduct a multivariate analysis of pancreatic leakage in PD.

Research methods

A total of 420 patients undergoing PD were selected and divided into group A and group B according to the pancreatointestinal anastomosis method adopted during the operation. Duct-to-mucosa pancreatojejunostomy was performed in group A and bundled pancreaticojejunostomy was performed in group B. The operation time, intraoperative blood loss, and pancreatic leakage in the two groups were observed, and the occurrence of pancreatic leakage after the operation in different patients was analyzed.

Research results

The differences in operative time and intraoperative bleeding between groups A and B were not significant. In group A, the duration of pancreatojejunostomy was 26.03 ± 4.40 min and the pancreatic duct diameter was 3.90 ± 1.10 mm. These measurements were significantly higher than those in group B. The differences in the occurrence of pancreatic leakage, abdominal infection, abdominal hemorrhage, and gastric retention between group A and group B were not significant. The rates of pancreatic leakage in patients with preoperative albumin < 30 g/L, preoperative jaundice time ≥ 8 wk, and pancreatic duct diameter < 3 mm were 23.33%, 33.96%, and 19.01%, respectively.

Research conclusions

The pancreatointestinal anastomosis method during PD has no significant effect on the occurrence of pancreatic leakage. The main risk factors for pancreatic leakage include preoperative albumin, preoperative jaundice time, and pancreatic duct diameter.

Research perspectives

A more advantageous surgical method for pancreaticojejunostomy should be selected.

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ORIGINAL ARTICLE

Retrospective Study

Laparoscopic *vs* open surgery in ileostomy reversal in Crohn's disease: A retrospective study

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Abstract

BACKGROUND

Although minimally invasive surgery is becoming more commonly applied for ileostomy reversal (IR), there have been relatively few studies of IR for patients with Crohn's disease (CD). It is therefore important to evaluate the potential benefits and risks of laparoscopy for patients with CD.

AIM

To compare the safety, feasibility, and short-term and long-term outcomes of laparoscopic IR (LIR) *vs* open IR (OIR) for the treatment of CD.

METHODS

The baseline characteristics, operative data, and short-term (30-d) and long-term outcomes of patients with CD who underwent LIR and OIR at our institution between January 2017 and January 2020 were retrieved from an electronic database and retrospectively reviewed.

RESULTS

Of the 60 patients enrolled in this study, LIR was performed for 48 and OIR for 12. There were no statistically significant differences in baseline characteristics, operation time, intraoperative blood loss, days to flatus and soft diet, postoperative complications, hospitalization time, readmission rate within 30 d, length of hospitalization, hospitalization costs, or reoperation rate after IR between the two groups. However, patients in the LIR group more frequently required lysis of adhesions as compared to those in the OIR group (87.5% *vs* 41.7%, respectively, $P < 0.05$). Notably, following exclusion of patients who underwent enterectomy plus IR, OIR was more advantageous in terms of postoperative recovery of gastrointestinal function and hospitalization costs.

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CONCLUSION

The safety and feasibility of LIR for the treatment of CD are comparable to those of OIR with no increase in intraoperative or postoperative complications.

Key Words: Crohn's disease; Laparoscopy; Ileostomy reversal; Intestinal adhesion; Enterolysis; Faster recovery

Core Tip: Laparoscopic surgery has been shown to promote faster recovery, decrease postoperative pain and morbidity, and improve postoperative quality of life. For Crohn's disease (CD) patients who require IR, laparoscopy greatly improves the rate of enterolysis and reduces the incidence of ileus. Meanwhile, laparoscopy can effectively explore the entire gastrointestinal tract to identify strictures within short segments of the small bowel, while avoiding large incisions. The aim of the present study was to compare the operative data and short-term and long-term outcomes of laparoscopic ileostomy reversal *vs* open ileostomy reversal to explore the safety and feasibility of laparoscopic ileostomy reversal for CD.

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INTRODUCTION

A temporary ileostomy is frequently created during low colorectal anastomosis to prevent fistula formation. After intestinal anastomosis, patients with active Crohn's disease (CD) are at a greater risk for anastomotic fistula formation, which often requires ileostomy[1,2] to alleviate symptoms. Given the proclivity for recurrence, ileostomy reversal (IR) is limited to relatively few CD patients[3]. However, as compared with colostoma, ileostoma requires more complex care and is associated with a greater risk for complications[4]. Therefore, in the remission stage of CD, many patients consider IR. Normally, open IR (OIR) is not overly complicated. But, the varying degrees of intestinal adhesions in CD require intraoperative enterolysis[5]. In addition, with the progression of CD, the whole digestive system will inevitably become fibrotic, eventually leading to stricture[6]. Therefore, it is essential to check the whole gastrointestinal tract during IR for patients with CD.

Previous studies have shown that laparoscopic surgery promotes faster recovery, decreases postoperative pain and morbidity, and improves postoperative quality of life[5,7,8]. During open surgery for CD, surgeons often have to explore the entire gastrointestinal tract to avoid missing occult diseased segments and critical proximal strictures. Laparoscopy can effectively explore the entire gastrointestinal tract to identify strictures within short segments of the small bowel, while avoiding large incisions. Although laparoscopy has become more commonly applied in IR[9], relatively few studies have compared OIR with laparoscopic IR (LIR) for CD. It is therefore important to evaluate the potential benefits and risks of LIR in patients with CD. The aim of the present study was to compare the operative data and short-term and long-term outcomes of LIR *vs* OIR to explore the safety and feasibility of LIR for CD.

MATERIALS AND METHODS

Patients

The study protocol was approved by the Ethics Committee of the Shanghai Tenth People's Hospital Affiliated to the Tongji University School of Medicine (approval No.

21K53) and conducted in accordance with the tenets of the Declaration of Helsinki. The cohort of this retrospective study consisted of 60 patients who underwent IR at our institution from January 2017 to January 2020. Of these 60 patients, LIR was performed for 48 and OIR for 12. The inclusion criteria were age 18-75 years and pathological confirmation of CD. All procedures were performed by two experienced laparoscopic colorectal surgeons. Standardized treatment regimens were used during the perioperative period. The following data were retrieved from the electronic database of Shanghai Tenth People's Hospital: Age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status classification, duration of ileostomy, duration of CD, history of abdominal surgery, hematologic parameters (WBC, CRP, ESR, ALB, HB, PLT, PT, and APTT), operation time, intraoperative blood loss, enterolysis rate, days to flatus and soft diet, postoperative complications, hospitalization time, readmission rate within 30 days, length of stay, and hospitalization cost. As a long-term outcome, the reoperation rate after IR was determined by telephone interviews.

Preoperative preparation

Preoperative preparation included physical examination, computed tomography, magnetic resonance imaging, ultrasonography, and colonoscopy. Patients in the remission stage of CD were considered for IR.

Surgical procedure

Laparoscopy was performed using the four-port method. Briefly, two transverse sites below the umbilicus were punctured with 12-mm trocars for observation, the right abdomen was punctured with a 5-mm trocar, and the left abdomen was punctured with 5- and 12-mm trocars. The entire gastrointestinal tract was explored laparoscopically to separate the intraperitoneal adhesions at the stoma and the distal intestinal stump (Figure 1A-C). Following incision of the annulus of the skin around the stoma, the stoma and distal intestinal stump were pulled out. If the bowel segment was obviously fibrotic with a stricture, strictureplasty or resection of the strictured segment was performed. The proximal and distal intestines were anastomosed side to side with auto sutures (GIA 80 mm; Medtronic plc, Dublin, Ireland). Then, the openings were closed and the anastomosis was reinforced with 3-0 absorbable sutures. For open surgery, an incision was made directly along the skin around the stoma. Then, the stoma and distal intestinal stump were separated under direct visualization. The anastomosis method was the same as that in the laparoscopic group.

Statistical analysis

All data analyses were conducted using IBM SPSS Statistics for Windows, version 24.0. (IBM Corporation, Armonk, NY, United States) and GraphPad Prism version 8.0 (GraphPad Software Inc., San Diego, CA, United States). Quantitative data are expressed as the mean ± SD (range). Data were compared using the Student's *t*-test and chi-squared test. A probability (P) value of < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

There were no statistically significant differences in age, gender, BMI, ASA class, duration of ileostomy, CD duration, history of abdominal operation, or hematologic examination between the LIR and OIR groups ($P > 0.05$) (Table 1).

Characteristics of intraoperative and postoperative observation indexes

Postoperative recovery, operation time, intraoperative blood loss, and days to flatus and soft diet were similar between the two groups. Enterolysis was required for 42/48 (87.5%) patients in the LIR group and 5/12 (41.7%) in the OIR group ($P < 0.05$). However, when cases of enterectomy combined with IR were excluded, OIR was still advantageous for patients with CD. In those cases, OIR was superior to LIR in terms of days to flatus (1.7 ± 0.7 d *vs* 2.3 ± 0.6 d, respectively, $P < 0.05$), days to soft diet (2.7 ± 0.7 d *vs* 4.5 ± 1.7 d, respectively, $P < 0.05$), and hospitalization costs (37301 RMB *vs* 57967 RMB, respectively, $P < 0.05$) (Table 2). There was no significant difference in postoperative complications between the LIR and OIR groups (10.4% *vs* 16.7%, respectively). One patient in the LIR group developed an anastomotic fistula after

Table 1 Baseline characteristics

Variable	Laparoscopic (*n* = 48)	Open (*n* = 12)	*P* value
Age, yr, mean (range)	36.5 (18-70)	39.8 (20-73)	NS
Gender, male	36	8	NS
BMI, kg/m^2, mean ± SD	20.2 ± 4.9	20.3 ± 2.9	NS
ASA class			NS
I-II	45	11	
III-IV	3	1	
Duration of ileostomy, mo, mean ± SD (range)	7.6 ± 6.8 (3-48)	13.0 ± 18.5 (3-72)	NS
Disease duration, mo, mean ± SD (range)	46.1 ± 48.7 (3-168)	39.3 ± 33.5 (4-96)	NS
History of abdominal operation	1.4 ± 0.7	1.4 ± 0.9	NS
Hematologic examination			
WBC (/L)	5.2 ± 1.3	5.2 ± 1.0	NS
CRP (mg/L)	5.9 ± 8.9	8.9 ± 17.6	NS
ESR (mm)	15.4 ± 11.5	15.8 ± 6.9	NS
ALB (g/L)	45.4 ± 4.8	43.6 ± 4.0	NS
Hb (g/L)	134.0± 18.2	131.0 ± 16.0	NS
PLT (/L)	240.8 ± 105.6	206.3 ± 49.3	NS
PT (s)	11.5 ± 0.9	11.2 ± 0.8	NS
APTT (s)	29.3 ± 3.4	28.2 ± 4.0	NS

BMI: Body mass index; ASA: American Society of Anesthesiologists; WBC: White blood cell count; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; ALB: Albumin; Hb: Hemoglobin; PLT: Platelets; PT: Prothrombin time; APTT: Activated partial thromboplastin time; NS: Not significant.

surgery and recovered after continuous double-cannula irrigation, which explains why one patient in the LIR group was hospitalized for 32 d. Another patient developed anastomotic bleeding, which was resolved after hemostasis treatment. One patient with ileus recovered after conservative treatment. Two patients developed incisional infections in both the LIR and OIR groups and recovered after periodic dressing change. As a long-term outcome, the reoperation rate after IR was similar between the LIR and OIR groups. One patient in the LIR group and one in the OIR group underwent enterectomy again at 22 and 24 mo, respectively (Figure 2).

DISCUSSION

The aim of this retrospective study was to compare the feasibility, safety, and short-term and long-term outcomes of LIR *vs* OIR for CD. The results showed that LIR is a safe and feasible technique with acceptable outcomes and, thus, is worthy of further promotion and clinical study.

For high-risk intestinal anastomosis, the use of prophylactic ileostomy can significantly reduce the incidence of anastomotic leakage[10,11]. However, enterostomy is often associated with many complications due to improper management. According to multiple studies, the overall stoma complication rate ranges from 12% to 72%, with the most common complications being retraction, hernia, prolapse, peristomal skin problems, and necrosis, which severely affect the psychosocial status of the patient and the ability to return to normal daily activities[12-14]. Restoration of intestinal continuity by IR is an ideal strategy to improve quality of life. In recent decades, laparoscopic techniques have become increasingly widely applied in gastrointestinal surgery[15,16]. LIR has also attracted the attention of surgeons because this procedure is associated with earlier gastrointestinal recovery, shorter postoperative hospital stay, and lower complication rates[17,18]. However, CD is characterized by extensive intestinal inflammation and thickening of the mesentery and blood vessels, which pose

Table 2 Operative data and short-term (30-d) outcomes

	Ileostomy reversal (without enterectomy)			Ileostomy reversal		
Variable	**Laparoscopic (*n* = 30)**	**Open (*n* = 7)**	***P* value**	**Laparoscopic (*n* = 48)**	**Open (*n* = 12)**	***P* value**
Operative time, min	116.5 ± 38.4	117.1 ± 28.6	NS	128.2 ± 41.7	142.5 ± 41.7	NS
Estimated blood loss, mL	69.7 ± 93.1	71.4 ± 94.8	NS	73.1 ± 91.3	94.2 ± 88.1	NS
Days to flatus, d, mean ± SD	2.3 ± 0.6	1.7 ± 0.7	$P < 0.05$	2.3 ± 0.8	2.0 ± 0.7	NS
Days to soft diet, d, mean ± SD	4.5 ± 1.7	2.7 ± 0.7	$P < 0.05$	5.1 ± 3.9	3.8 ± 1.4	NS
Total postoperative complication, *n* (%)	3 (10)	1 (14.3)	NS	5 (10.4)	2 (16.7)	NS
Anastomotic hemorrhage	1	0		1	0	
Anastomotic leakage	0	0		1	0	
Ileus	0	0		1	0	
Wound infection	1	1		2	2	
Reoperation	0	0		0	0	
Readmission after discharge	0	0	-	0	0	-
Length of stay, d, mean ± SD (range)	9.6 ± 2.7 (5-15)	8.6 ± 2.8 (6-15)	NS	10.3 ± 4.0 (5-32)	10.8 ± 3.7(6-18)	NS
Cost (RMB)	57967	37301	$P < 0.05$	62916	52274	NS

NS: Not significant.

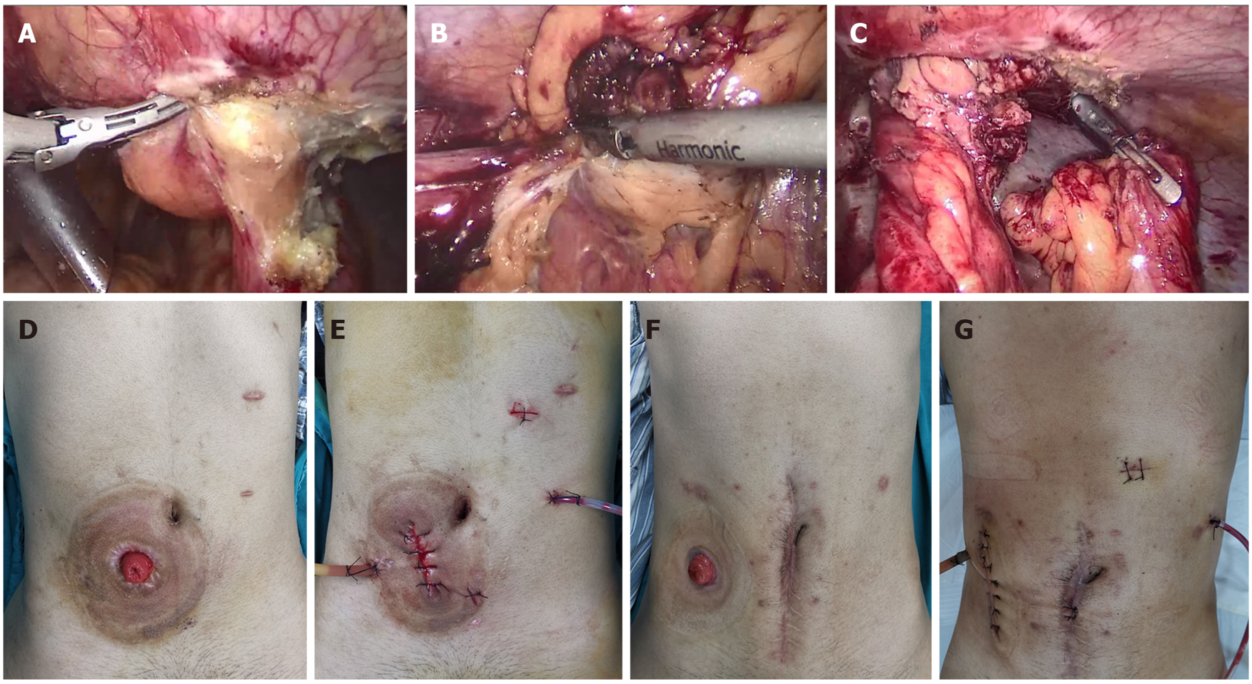

Figure 1 Laparoscopic ileostomy reversal and open ileostomy reversal. A: The intraperitoneal adhesions at the stoma were separated; B: The distal intestinal stump was separated; C: Separation was completed under laparoscopy; D and E: Abdominal incision of laparoscopic ileostomy reversal; F and G: Abdominal incision of open ileostomy reversal.

significant risks and difficulties in laparoscopic surgery[19]. Moreover, widespread inflammation can invade peripheral organs, such as the ureters, which can limit the application of minimally invasive surgery. Previous clinical studies have confirmed that laparoscopic resection in patients with ileocecal CD following failure of conventional therapy should be considered as a reasonable alternative[20]. The advantages of minimally invasive surgery for CD include reduced immune and inflammatory responses, fewer postoperative intestinal adhesions, less incision pain, and faster recovery[21,22]. Although laparoscopic techniques remain challenging in patients with

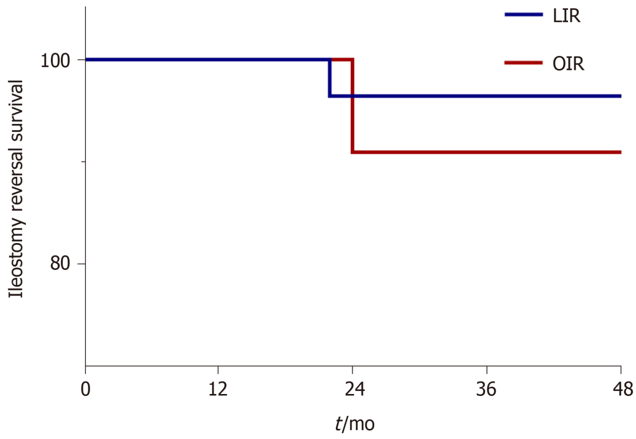

Figure 2 Long-term outcomes after ileostomy reversal. The reoperation rate after ileostomy reversal was similar between laparoscopic ileostomy reversal and open ileostomy reversal. LIR: Laparoscopic ileostomy reversal; OIR: Open ileostomy reversal.

CD, Bitner *et al*[3] reported that LIR was a safe and feasible option in 44 patients with CD after subtotal colectomy. However, larger studies are needed to confirm this claim. To date, LIR has been mainly applied for treatment of non-inflammatory diseases, such as colorectal cancer[23,24]. A study conducted by Russek *et al*[25] of 24 patients who underwent LIR found that the complication rate and surgical time were comparable to those of open surgery. In addition, extending the time to IR improved the patients' nutritional status and allowed time for the adhesions to become less dense. A retrospective review of 133 patients demonstrated similar estimated blood loss, mean length of stay, and 30-d morbidity rates between LIR and OIR. Although the duration of LIR was longer, the additional procedures may provide long-term benefits[26].

To the best of our knowledge, this study is the first to evaluate the surgical approach and postoperative recovery of LIR for CD. In this study, cases of enterectomy during IR were excluded in order to compare OIR *vs* LIR alone. The results showed that postoperative recovery of patients with CD was better in the OIR group than the LIR group. This result is not difficult to explain. CD is a progressive disease resulting in fibrosis of the entire digestive tract. So, the entirety of the small intestine and colon can be explored during laparoscopic surgery, while only relatively small portions can be explored by open surgery. Also, in both LIR and OIR, incisions of the same length were made around the original ileostomy. Moreover, less minimally invasive instruments were used in OIR, so hospitalization costs were lower. In addition, laparoscopy is more convenient for the surgeon to dissociate the ileostoma from the abdominal cavity because of the good field of vision. Meanwhile, laparoscopy provides a clear field of vision of the entire gastrointestinal tract, which facilitates assessment of the remaining length of the healthy intestine, as well as the diseased portions. Therefore, laparoscopy greatly improves the rate of enterolysis and reduces the incidence of ileus. In this study, there was a significant difference in the rate of enterolysis between the IR and OIR groups (87.5% *vs* 41.7%, respectively, $P < 0.05$). In this regard, laparoscopy is undoubtedly beneficial to patients with CD. Hence, we continue to combine IR with enterectomy. The results of the present study showed that LIR did not increase the operative time, intraoperative blood loss, postoperative recovery time, length of hospitalization stay, hospitalization costs, or reoperation rate. Therefore, LIR is not a contraindication for patients with CD. In this study, 18 patients underwent enterectomy simultaneously with IR. In general, there are two main reasons for resection of the diseased intestinal segment at the same time of IR. First, ileostomy is often performed as an emergency surgery, as the diseased intestine can be removed at a later stage in the remission stage of CD. Second, during surgery for CD, excision of the intestine should be limited to avoid the occurrence of short bowel syndrome, as disease of the bowel can be alleviated with the use of biological agents. However, if drug treatment fails, simultaneous resection of the diseased bowel can be considered during IR.

Studies have shown that LIR with intracorporeal anastomosis was associated with shorter length of hospitalization without increasing overall costs[17]. A double-blind randomized controlled trial showed that intracorporeal anastomosis can reduce bowel manipulation and mesentery traction, which promotes quicker recovery of bowel function[27]. However, in the case of CD, extracorporeal anastomosis is preferred in our center because CD is often accompanied by thickening of the mesentery and vasculature, thus hemostasis and reinforcing sutures are often required after anastomosis. These procedures will be safer and more reliable *in vitro*. In order to avoid anastomotic stoma-associated strictures in patients with CD, in addition to side-to-side anastomosis in digestive tract reconstruction, extracorporeal anastomosis can ensure the maximum size of the anastomotic stoma. For extracorporeal anastomosis, the length of the incision was not increased, which alleviated postoperative pain and improved satisfaction with the cosmetic result (Figure 1D-G).

CONCLUSION

LIR for CD is both safe and feasible. The short-term and long-term outcomes of LIR are comparable to those of OIR and do not prolong postoperative recovery. In view of the fact that this is a retrospective study with a small sample size, larger prospective trials are required to further confirm these findings.

ARTICLE HIGHLIGHTS

Research background

The advantages of minimally invasive surgery for ileostomy reversal (IR) have attracted increasing attention, although relatively few studies have investigated the benefits of IR for patients with Crohn's disease (CD).

Research motivation

It is worthwhile to evaluate the potential benefits and risks of laparoscopy for patients with CD.

Research objectives

To compare the safety, feasibility, and short-term and long-term outcomes of laparoscopic IR (LIR) *vs* open IR (OIR) for treatment of CD.

Research methods

The baseline characteristics, operative data, and short-term (30-d) and long-term outcomes of patients with CD who underwent LIR and OIR between January 2017 and January 2020 were retrieved from an electronic database and retrospectively reviewed.

Research results

A total of 60 eligible patients were enrolled into the study, including 48 in the LIR group and 12 in the OIR group. There were no statistically significant differences in baseline characteristics, operative data, or short-term and long-term outcomes between the two groups. However, patients in the LIR group more frequently required lysis of adhesions as compared to those in the OIR group. Notably, following exclusion of patients who underwent enterectomy plus IR, OIR was more advantageous in terms of postoperative recovery of gastrointestinal function and hospitalization costs.

Research conclusions

The safety and feasibility of LIR for the treatment of CD are comparable to those of OIR with no increase in intraoperative or postoperative complications.

Research perspectives

LIR is feasible and safe for the treatment of CD patients with IR, and the short-term and long-term results are similar to those of OIR, thus further studies are warranted. In view of the fact that this is a retrospective study with a small sample size, larger prospective trials are required to further confirm these findings.

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ORIGINAL ARTICLE

Retrospective Study

Preoperative serum carbohydrate antigen 19-9 levels predict early recurrence after the resection of early-stage pancreatic ductal adenocarcinoma

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Abstract

BACKGROUND

Pancreatic ductal adenocarcinoma (PDAC) is a serious disease with a poor prognosis. Only a minority of patients undergo surgery due to the advanced stage of the disease, and patients with early-stage disease, who are expected to have a better prognosis, often experience recurrence. Thus, it is important to identify the risk factors for early recurrence and to develop an adequate treatment plan.

AIM

To evaluate the predictive factors associated with the early recurrence of early-stage PDAC.

METHODS

This study enrolled 407 patients with stage I PDAC undergoing upfront surgical resection between January 2000 and April 2016. Early recurrence was defined as a diagnosis of recurrence within 6 mo of surgery. The optimal cutoff values were determined by receiver operating characteristic (ROC) analyses. Univariate and multivariate analyses were performed to identify the risk factors for early recurrence.

RESULTS

Of the 407 patients, 98 patients (24.1%) experienced early disease recurrence: 26 (26.5%) local and 72 (73.5%) distant sites. In total, 253 (62.2%) patients received adjuvant chemotherapy. On ROC curve analysis, the optimal cutoff values for early recurrence were 70 U/mL and 2.85 cm for carbohydrate antigen 19-9 (CA 19-9) levels and tumor size, respectively. Of the 181 patients with CA 19-9 level > 70 U/mL, 59 (32.6%) had early recurrence, compared to 39 (17.4%) of 226 patients with CA 19-9 level ≤ 70 U/mL (P < 0.001). Multivariate analysis revealed that CA 19-9 level > 70 U/mL (P = 0.006), tumor size > 2.85 cm (P = 0.004), poor differentiation (P = 0.008), and non-adjuvant chemotherapy (P = 0.025) were significant risk factors for early recurrence in early-stage PDAC.

CONCLUSION

Elevated CA 19-9 level (cutoff value > 70 U/mL) can be a reliable predictive factor for early recurrence in early-stage PDAC. As adjuvant chemotherapy can prevent early recurrence, it should be recommended for patients susceptible to early recurrence.

Key Words: Pancreatic ductal adenocarcinoma; Early recurrence; Upfront surgery; Carbohydrate antigen 19-9; Adjuvant chemotherapy

Core Tip: Pancreatic ductal adenocarcinoma (PDAC) is a serious disease with a poor prognosis. Only a minority of patients undergo surgery due to the advanced stage of the disease, and recurrence, an important prognostic factor, often occurs even after surgical resection. We identified the factors associated with the early recurrence of early-stage PDAC evaluating 407 patients with stage I PDAC undergoing upfront surgical resection. Early recurrence was defined as disease recurrence within 6 mo of surgery. Preoperative carbohydrate antigen 19-9 level > 70 U/mL determined by receiver operating characteristic analyses was a significant risk factor for early recurrence in early-stage PDAC.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a serious disease with a poor prognosis, with a 5-year survival rate of only 6%-10%[1,2]. While surgical resection offers the only possibility of cure[3], only a minority of patients are diagnosed with resectable disease because of local advancement or metastases at initial presentation[4]. Furthermore, even if patients undergo surgical treatment, about 70% experience disease recurrence [5-7]. Thus, efforts have been made to improve prognosis by early detection of the disease. However, even if patients are diagnosed and undergo surgery in the early stages, recurrence often occurs, and early recurrence is an important factor associated with a poor prognosis[8-10]. Therefore, it is necessary to identify the factors associated with the early recurrence of early-stage PDAC.

Various factors associated with PDAC prognosis have been reported including tumor size, preoperative carbohydrate antigen 19-9 (CA 19-9) concentration, histological grade, resection margin status, lymph node metastasis, and vascular

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invasion[11,12]. Among them, CA 19-9 levels, histological grade, and microvascular invasion are also associated with early recurrence[9,13-15]. Especially, serum CA 19-9 level, the only parameter that can be evaluated before surgery, has been regarded as a means of diagnosing malignant pancreatic neoplasms with high sensitivity and specificity[16,17]. Previous studies have also shown that CA 19-9 levels are a predictive factor for poor prognosis[18-22]. Elevated serum CA 19-9 levels are suggestive of pancreatic cancer recurrence, and serum CA 19-9 measurement is usually performed during surveillance, along with imaging tests, to detect cancer progression. Although imaging tests are performed to confirm cancer recurrence, CA 19-9 measurement is easier and more reproducible in terms of surveillance.

To improve the prognosis of pancreatic cancer, the risk factors for early recurrence should be evaluated, and active treatment, such as surgical treatment followed by chemotherapy, should be performed. Furthermore, as patients with early-stage disease, who are expected to have a better prognosis, often experience early recurrence, it is important to identify the risk factors for early recurrence and develop an adequate treatment plan. Pre- and post-operative CA 19-9 levels have been used to predict disease progression; however, few studies have demonstrated the effectiveness of CA 19-9 as a marker for early recurrence. This study evaluated the risk factors for early recurrence in patients with American Joint Committee on Cancer (AJCC) 8th edition stage I PDAC after upfront surgery. We set the optimal cutoff CA 19-9 level and evaluated the power of CA 19-9 as a detector of early recurrence of early-stage PDAC. We also evaluated the importance of adjuvant chemotherapy as a therapeutic modality for early-stage patients to reduce the chance of early recurrence.

MATERIALS AND METHODS

Between January 2000 and April 2016, 2029 consecutive patients underwent surgical resection for PDAC at Asan Medical Center (Seoul, South Korea). PDAC was histologically confirmed in all patients, and patients with other pancreatic tumors such as intraductal papillary mucinous adenocarcinoma, adenosquamous carcinoma, mucinous carcinoma, acinar cell carcinoma, and malignant endocrine carcinoma were excluded. Of these, 648 patients had tumor-node-metastasis (TNM) stage IA and IB disease based on permanent pathologic reports. Forty-eight patients who received neoadjuvant chemotherapy, forty-four who were lost to follow-up, and five with incomplete data on preoperative serum CA 19-9 levels were excluded. Patients whose CA 19-9 levels were measured when they had jaundice (preoperative total bilirubin levels ≥ 2 mg/dL) were excluded to avoid the effect of obstructive jaundice on CA 19-9 values. Patients with preoperative CA 19-9 level < 2 U/mL were considered as Lewis antibody-negative patients; thus, they were considered to be unable to express CA 19-9 and were excluded from this study. Finally, 407 patients who underwent upfront surgical resection for stage I PDAC were enrolled in this study (Figure 1). Data regarding age, sex, body mass index, type of operation, pathology, recurrence, and preoperative serum CA 19-9 levels were obtained retrospectively from medical records. All patients underwent either abdominal computed tomography (CT), magnetic resonance imaging, or both preoperatively for the evaluation of tumor lesion and resectability. The pathologic stage was determined according to the TNM Classification of Malignant Tumors, 8th edition, from the AJCC.

All serum CA 19-9 values were measured using an electrochemiluminescence immunoassay kit in the institution's laboratory. The recommended upper normal limit for CA 19-9 is 37 U/mL. CA 19-9 levels were examined within 1 mo before the surgery. When patients developed jaundice due to tumor invasion of the biliary tract, interventions were performed, including endoscopic nasobiliary drainage, endoscopic retrograde biliary drainage, or percutaneous transhepatic biliary drainage.

Distal pancreatectomy was the standard procedure for tumors of the pancreatic neck, body, or tail. Pancreaticoduodenectomy (pylorus-preserving or pylorus-resecting) was performed for tumors located in the pancreas head or uncinate. Total pancreatectomy was performed in patients in whom intra-operative frozen biopsy showed positive resection margin, remnant pancreas was atrophied, pancreatitis was very severe involving the whole pancreas, and pancreatic duct was dilated throughout the pancreas. The surgeries were performed using either an open approach or laparoscopically. The pathologic characteristics included tumor size, resection margin status, lymph node metastasis, differentiation, lymphovascular invasion, and perineural invasion status. The resection margins were evaluated by a pathologist as either R0 (no cancer cells observed microscopically at the resection margin) or R1 (cancer cells

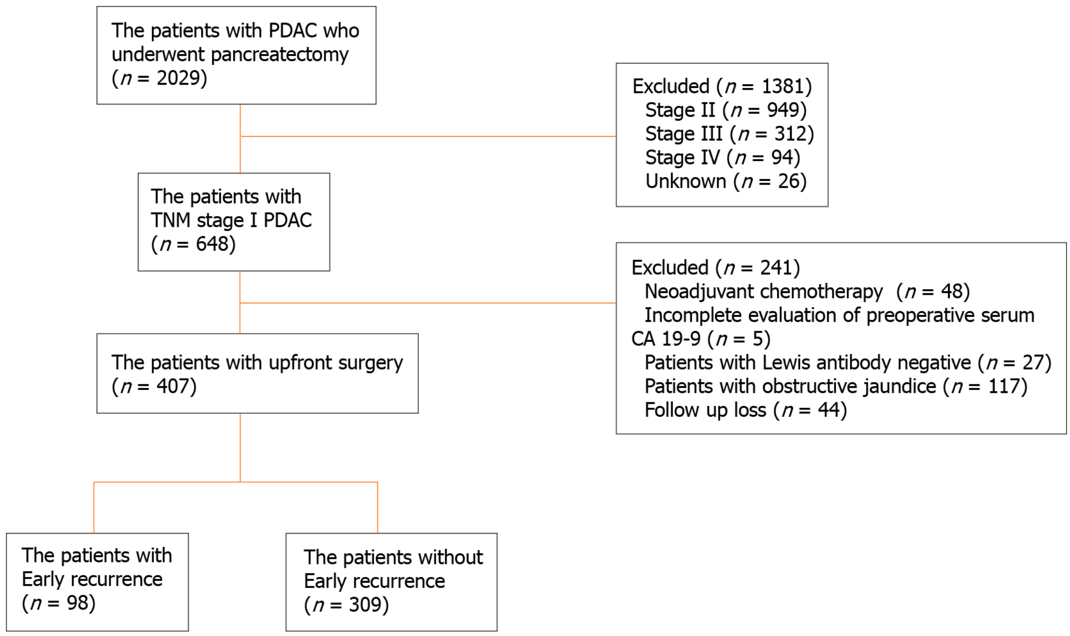

Figure 1 Flowchart of patient selection. CA 19-9: Carbohydrate antigen 19-9; PDAC: Pancreatic ductal adenocarcinoma; TNM: Tumor-node-metastasis.

observed microscopically at the resection margin or a free margin of < 1 mm).

The patients were followed up with abdominal CT and blood tests, including tests for tumor markers, CA 19-9, and carcinoembryonic antigen levels, every 3 mo for the first 2 years after surgery and every 3-6 mo thereafter. When the CA 19-9 level was elevated or abdominal CT suggested tumor recurrence, additional positron emission tomography (PET) was performed. Tumor recurrence was defined based on radiological or biopsy-proven evidence. Radiological recurrence was determined by radiologists and defined as progressive soft-tissue growth or hypermetabolic lesions at specific sites, as determined by CT or PET. Biopsy was not routinely required for the diagnosis of tumor recurrence.

Overall survival (OS) was defined as the time from surgery to the date of death from any cause or the last follow-up visit. Disease-free survival (DFS) was defined as the time from surgery to the first documented detection of recurrence on CT or PET during regular follow-up or death, whichever occurred first. Early recurrence was defined as disease relapse within 6 mo of surgery.

Statistical analyses

Continuous variables are expressed as medians and interquartile ranges. OS and DFS were estimated using the Kaplan–Meier method, and the values were compared using log-rank tests. Receiver operating characteristic (ROC) curves were constructed to estimate the optimal cutoff values for preoperative CA 19-9 levels and tumor size as predictors of postoperative early recurrence, with the Youden index used as a summary measure of the ROC curve. The χ^2 or Fisher's exact test was performed for categorical variables. Univariate and multivariate analyses were performed using a logistic regression model to determine the predictive variables associated with early recurrence. P < 0.05 was considered statistically significant. The statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, United States).

RESULTS

Patient's characteristics

This study included 407 patients. Of them, 225 (55.3%) were male and 182 (44.7%) were female, with a median age of 62 years (30-88). The median follow-up time was 31 mo (1-227). A total of 254 patients (62.4%) underwent pancreatectomy for tumors located at the head or uncinate, and 151 (37.1%) underwent pancreatectomy for tumors located at the pancreatic neck, body, or tail. Permanent biopsy result revealed that the tumor involved both head and body in two cases (0.5%). The median tumor size was

2.5 cm (0.3-4), and the median number of harvested lymph nodes was 14. A total of 253 patients (62.2%) received adjuvant chemotherapy. The median OS durations in the early and non-early recurrence groups were 11 and 42 mo, respectively (P < 0.001). The demographic and pathologic findings are summarized in Table 1.

The median follow-up duration was 31 mo. A total of 304 patients (75.4%) showed disease recurrence, with a median time to recurrence of 10 mo. In this study, 99 (32.6%) and 205 (67.4%) patients had local and distant recurrences, respectively. Among the patients with distant recurrence, the most common recurrence site was the liver, followed by peritoneal seeding and the lungs. A total of 98 patients (24.1%) had early recurrence, and 309 (75.9%) had either non-early or no recurrence. Among patients with early recurrence, 26 (26.5%) had local recurrence and 72 (73.5%) had distant recurrence. The most common recurrence site was the liver (37.8%).

Preoperative serum CA 19-9 and early recurrence

ROC curve analysis revealed 70 U/mL as the optimal cutoff preoperative CA 19-9 level for predicting early recurrence (area under the curve [AUC] 0.605; sensitivity 60.2%, specificity 60.5%; Figure 2A). In this study, 181 patients had preoperative serum CA 19-9 level ≥ 70 U/mL; among them, 59 patients (32.6%) had early recurrence. In contrast, 39 of the 226 patients (17.4%) with CA 19-9 level < 70 U/mL had early recurrence (P < 0.001). We had postoperative serum CA 19-9 values checked within 1 mo after the operation. Among the 181 patients with preoperative serum CA 19-9 values ≥ 70 U/mL, 171 patients (94%) had decreased serum CA 19-9 values after the operation, and of these, 49 patients (28.7%) experienced early disease recurrence. Nine patients had rather increased serum CA 19-9 value, and all of these patients experienced early recurrence. In one patient, we did not check the postoperative CA 19-9 value. ROC curve analysis also revealed 2.85 cm as the optimal cutoff tumor size for predicting early recurrence (AUC 0.619; sensitivity 56.1%, specificity 65.0%; Figure 2B).

Multivariate analysis on risk factors for early recurrence

Table 2 shows the risk factors associated with early recurrence after curative surgical resection for TNM stage I PDAC. In the univariate analysis, preoperative serum CA 19-9 level (P < 0.001), tumor size (P < 0.001), and differentiation (P = 0.005) were significant. In the multivariate analysis, a CA 19-9 level ≥ 70 U/mL (odds ratio [OR] 1.987; P = 0.006), tumor size ≥ 2.85 cm (OR 2.039; P = 0.004), poor differentiation (OR 3.493 for poorly differentiated *vs* well differentiated; P = 0.008), and non-adjuvant chemotherapy (OR 1.745; P = 0.025) were significantly associated with early recurrence after surgical resection.

Early recurrence vs non-early recurrence

Table 3 shows the comparisons between the early and non-early recurrence groups. Of the 407 patients, 98 (24.1%) had early disease recurrence and 309 (75.9%) had non-early or no recurrence. The preoperative CA 19-9 level significantly differed between the groups (P = 0.004), with higher CA 19-9 levels prevalent among patients in the early recurrence group. Tumors in the early recurrence group were larger (P = 0.001) and showed a more poorly differentiated histology (P = 0.002) than those in the non-early recurrence group. Although the difference was not significant (P = 0.058), more patients in the non-early recurrence group received adjuvant chemotherapy. The recurrence pattern did not differ between the two groups.

DISCUSSION

PDAC is one of the most lethal malignancies and is a leading cause of cancer-related deaths worldwide. Despite substantial improvements in the survival rates of patients with other major malignancies, the survival rates of patients with PDAC have remained relatively unchanged. PDAC is usually detected in the advanced stage, and restricted treatment options contribute to its poor overall prognosis. Approximately 70%-80% of patients with PDAC experience locoregional and/or distant recurrence after surgery[5-7]. Recent efforts have sought to improve the early diagnosis of PDAC [23-27]. Early detection and treatment of PDAC can help improve the dismal prognosis of this aggressive cancer. We evaluated the OS of 407 early-stage (stage I) PDAC patients who underwent upfront pancreatic surgery between January 2000 and April 2016. The median OS of those with early-stage disease was 34.5 mo, significantly longer than that of those with advanced-stage disease (18.5 mo; P < 0.001). However,

Table 1 Patient demographics

Characteristics	Patients, *n* = 407 (%)
Age in yr, median (range)	62 (30-88)
Sex, *n* (%)	
Male	225 (55.3)
Female	182 (44.7)
BMI in kg/m^2, median (range)	23.2 (15.3-31.6)
Pre-op CA 19-9 in U/mL, *n* (%)	
Normal	167 (41)
Abnormal	240 (59)
Tumor location, *n* (%)	
Head/uncinate	254 (62.4)
Neck/body/tail	151 (37.1)
Head/body	2 (0.5)
Tumor size, median, cm (range)	2.5 (0.3-4.0)
Total number of harvested lymph nodes, median (range)	14 (1-74)
Differentiation, *n* (%)	
Well	60 (14.9)
Poor	288 (71.6)
Unknown	54 (13.4)
Moderate	5 (1.2)
Stage, *n* (%)	
IA	109 (26.8)
IB	298 (73.2)
Adjuvant chemotherapy, *n* (%)	
No	154 (37.8)
Yes	253 (62.2)
Recurrence within 6 mo, *n* (%)	
No	309 (75.9)
Yes	98 (24.1)

BMI: Body mass index; CA 19-9: Carbohydrate antigen 19-9.

patients with early-stage PDAC often experience early recurrence after curative resection, leading to a poor prognosis. The results of the present study suggested the presence of a heterogeneous microenvironment in terms of pre-existing occult metastasis in early-stage PDAC as 24.1% (*n* = 98) of patients with early recurrence showed a relatively poor prognosis compared to that in the non-early recurrence group (75.9%, *n* = 309) (median OS: 11 *vs* 42 mo; $P < 0.001$). Therefore, it is important to identify the clinicopathological factors and therapeutic modalities that are significantly associated with early recurrence in early-stage PDAC to improve the prognosis of this dismal disease.

Several studies have reported risk factors associated with OS and recurrence after surgical resection for PDAC, including tumor size, histological grade, resection margin status, lymph node metastasis, perineural invasion, venous invasion, and preoperative CA 19-9 levels[6,28-31]. The results of our study suggested that high preoperative serum CA 19-9 levels, large tumor size, poor differentiation, and non-adjuvant chemotherapy were independent predictors of early recurrence in early-stage PDAC.

Table 2 Univariate and multivariate analyses of the factors associated with early recurrence

Factors	Number of patients, n (%)	Univariate, P value	Odds ratio (95%CI)	Multivariate, P value
Age in yr		0.211	`	
< 65	234 (57.5)			
≥ 65	173 (42.5)			
Sex		0.261		
Male	225 (55.3)			
Female	182 (44.7)			
Tumor size in cm		< 0.001		0.004
< 2.85	244 (60.0)			
≥ 2.85	163 (40.0)		2.039 (1.251-3.323)	
RM		0.555		0.638
Negative	348 (85.5)			
Positive	59 (14.5)		1.177 (0.583-2.287)	
Tumor location		0.394		
Head/uncinate	254 (62.4)			
Neck/body/tail	151 (37.1)			
Differentiation		0.005		0.019
Well	60 (14.9)			
Moderate	288 (71.6)	0.196	1.430 (0.652–3.133)	0.372
Poor	54 (13.4)	0.005	3.493 (1.377–8.858)	0.008
CA 19-9 in U/mL		< 0.001		0.006
< 70	226 (55.5)			
≥ 70	181 (44.5)		1.987 (1.217–3.243)	
LVi		0.126		0.372
No	263 (64.6)			
Yes	144 (35.4)		1.270 (0.749–2.144)	
PNi		0.517		0.911
No	110 (27.0)			
Yes	297 (73.0)		0.966 (0.535–1.780)	
NLR		0.768		
< 2	244 (60.0)			
≥ 2	163 (40.0)			
Adj. CTx.		0.059		0.025
No	154 (37.8)			
Yes	253 (62.2)		0.573 (0.352–0.933)	

Adj. CTx.: Adjuvant chemotherapy; CA 19-9: Carbohydrate antigen 19-9; CI: Confidence interval; LVi: Lymphovascular invasion; NLR; Neutrophil-lymphocyte ratio; PNi; Perineural invasion; RM: Resection margin.

Tumor size is an independent predictor of poor prognosis in patients with PDAC [32-34]. Based on previous studies, we further evaluated the effect of tumor size on recurrence and survival in patients with early-stage PDAC treated with curative resection. The median DFS and OS were 10 mo and 23 mo, respectively, in the larger tumor group (≥ 2.85 cm) and 21 mo and 38 mo in the smaller tumor group (< 2.85 cm), demonstrating that tumor size was an independent clinical predictor for early

Table 3 Comparisons between the early and non-early recurrence group

Factors	Early recurrence, *n* (%)	Non-early recurrence, *n* (%)	*P* value
	N = 98 (24.1%)	*N* = 309 (75.9%)	
Age in yr			0.21
<65	51 (52.0)	183 (59.2)	
≥ 65	47 (48.0)	126 (40.8)	
Sex			0.261
Male	59 (60.2)	166 (53.7)	
Female	39 (39.8)	143 (46.3)	
Tumor size, median in cm			0.001
< 2.5	23 (23.5)	129 (41.7)	
≥ 2.5	75 (76.5)	180 (58.3)	
RM			0.555
Negative	82 (83.7)	266 (86.1)	
Positive	16 (16.3)	43 (13.9)	
Tumor location			0.712
Head/uncinate	63 (64.3)	191 (62.2)	
Neck/body/tail	35 (35.7)	116 (37.8)	
Differentiation			0.002
Well	9 (9.2)	51 (16.5)	
Moderate	65 (66.3)	223 (72.2)	
Poor	22 (22.4)	32 (10.4)	
Preoperative CA 19-9 in U/mL			0.004
Normal	28 (28.6)	139 (45.0)	
Abnormal	70 (71.4)	170 (55.0)	
LVi			0.125
No	57 (58.2)	206 (66.7)	
Yes	41 (41.8)	103 (33.3)	
PNi			0.516
No	24 (24.5)	86 (27.8)	
Yes	74 (75.5)	223 (72.2)	
NLR			0.768
< 2	60 (61.2)	184 (59.5)	
≥ 2	38 (38.8)	125 (40.5)	
Adj. CTx.			0.058
No	45 (45.9)	109 (35.3)	
Yes	53 (54.1)	200 (64.7)	
Recurrence pattern			0.121
Local	26 (26.5)	73 (35.4)	
Systemic	72 (73.5)	133 (64.6)	

Adj. CTx.: Adjuvant chemotherapy; CA 19-9: Carbohydrate antigen 19-9; LVi: Lymphovascular invasion; *N*: Total number of patients; NLR: Neutrophil-lymphocyte ratio; PNi: Perineural invasion; RM: Resection margin.

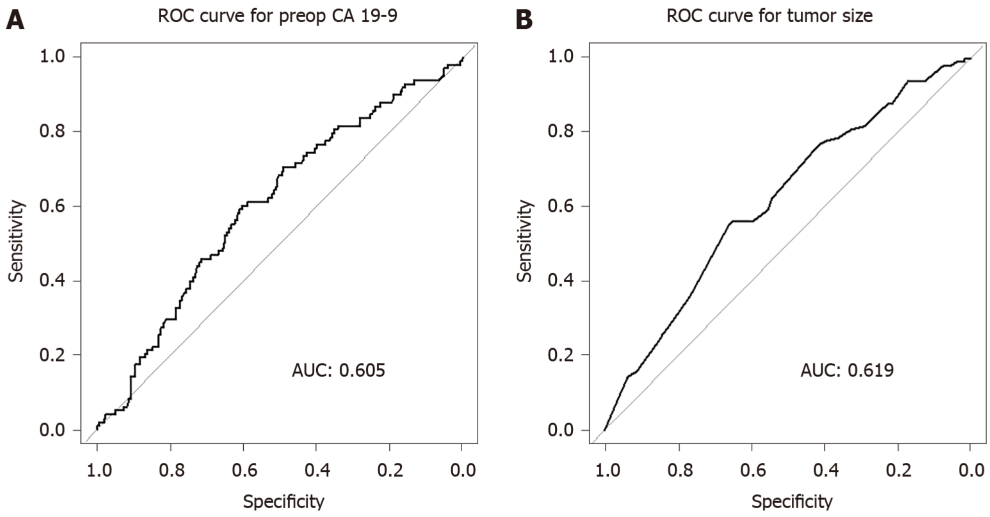

Figure 2 Receiver operating characteristic curve of serum carbohydrate antigen 19-9. A: Receiver operating characteristic (ROC) curve for carbohydrate antigen 19-9 (CA 19-9) values and early recurrence in tumor-node-metastasis (TNM) stage I patients who underwent pancreatic resection; B: ROC curve for tumor size and early recurrence in TNM stage I patients who underwent pancreatic resection. AUC: Area under the curve.

recurrence in early-stage PDAC. Since tumor size, as expected, affected disease prognosis and early recurrence even in early-stage disease, scheduled surveillance for detecting early recurrence is necessary in early-stage patients with large tumors.

Tumor histological grade is an important independent prognostic factor for PDAC. In general, poorly differentiation reflects aggressive malignant behavior accompanying a larger tumor size, a high rate of nodal metastases, microvascular invasion, and perineural invasion, causing poor OS[35-38]. The results of this study demonstrated that poor tumor differentiation was a significant factor for early recurrence in early PDAC compared to well differentiation (P = 0.008). Tumor grade is associated with not only survival but also recurrence. Although tumor grade is not used to evaluate tumor stage in PDAC according to the AJCC 8th edition guidelines, it should be considered critical for predicting disease prognosis and recurrence, especially in patients with early-stage PDAC.

CA 19-9, also referred to as Sialyl Lewis-A, is regularly expressed on cancer cells and can be detected by the monoclonal antibody 19-9[8]. Although it was originally isolated from a human colorectal cancer cell line[39], CA 19-9 is a good marker for the diagnosis of PDAC and the detection of recurrence during routine surveillance. It can be easily evaluated by a simple blood test, and numerous reports have suggested CA 19-9 as a meaningful tumor marker not only for diagnosis but also for prognosis prediction[18]. However, the specific role of CA 19-9 and the optimal serum CA 19-9 cutoff values for predicting early PDAC recurrence have remained controversial. We focused on early-stage PDAC patients who underwent primary pancreatectomy to evaluate the clinical impact of preoperative serum CA 19-9 levels on early recurrence. To the best of our knowledge, this is the first study to identify the independent relationship between serum CA 19-9 levels and early recurrence of early-stage PDAC in a large number of patients. In this study, we demonstrated that an elevated CA 19-9 level (cutoff value: > 70 U/mL) can be a reliable predictive marker for early recurrence in early-stage PDAC. This finding supports the notion that preoperative serum CA 19-9 levels could reflect biological aggressiveness and the presence of tumor micrometastases in early-stage PDAC.

Adjuvant chemotherapy was introduced following the assessment of its benefits, in which 5-fluorouracil (5-FU) and gemcitabine (GEM)-based regimens showed a survival effect[40,41]. The CONKO-005 trial also demonstrated that adjuvant chemotherapy with GEM and capecitabine doubled the 5-year OS rate to approximately 30%-50% compared to mono-regimen chemotherapy[42]. Adjuvant chemotherapy improved not only OS but also DFS[43,44]. In our institution, adjuvant chemotherapy is recommended to basically all patients regardless of the disease stage. However, the final decision is made based on the oncologists' decision and patients' postoperative general condition. In our study, patients who were in poor general condition, with postoperative complication, old, or reluctant to chemotherapy did not undergo adjuvant chemotherapy. Otherwise, 5-FU or GEM-based regimens were generally administered. We found that the number of patients who received adjuvant chemotherapy was higher in the late- and non-recurrence groups than in the early recurrence group (n = 200 *vs* 53), with adjuvant chemotherapy being an independent predictor of early recurrence (OR 0.573 [0.352–0.933]; P = 0.025) in early-stage PDAC. As few studies have assessed the effect of chemotherapy in early-stage disease, this result is meaningful in that we focused on early-stage patients. Adjuvant chemotherapy could be an effective treatment modality for reducing recurrence rates even in early-stage patients.

CONCLUSION

In conclusion, early recurrence often occurs even in stage I PDAC patients after upfront surgery, suggesting the need for the evaluation of predictive factors for early recurrence. In particular, CA 19-9 levels can be easily checked preoperatively and elevated CA 19-9 level (cutoff value > 70 U/mL) can be a reliable predictive factor. Furthermore, adjuvant chemotherapy should be considered for patients who are susceptible to early recurrence to achieve a better prognosis, even in patients with early-stage PDAC.

ARTICLE HIGHLIGHTS

Research background

One of the reasons that pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis is that the disease is diagnosed at advanced stage. Various factors associated with PDAC prognosis have been evaluated and effort have been made to improve prognosis by early detection of the disease.

Research motivation

Serum carbohydrate antigen 19-9 (CA 19-9) has been used as a means of diagnosing malignant pancreatic neoplasm and detection of disease recurrence. However, the effectiveness of CA 19-9 as a marker for early recurrence of disease has not been well studied yet.

Research objectives

This study aimed to set the optimal cutoff preoperative CA 19-9 level and evaluate the effectiveness of CA 19-9 as a detector of early recurrence of early-stage PDAC.

Research methods

A total of 407 patients with stage I PDAC undergoing upfront surgical resection between January 2000 and April 2016 were evaluated. The optimal cutoff values were determined by receiver operating characteristic and the risk factors for early recurrence were identified using a logistic regression model.

Research results

Ninety-eight patients (24.1%) experienced early disease recurrence. The optimal cutoff value of preoperative CA 19-9 for early recurrence was determined as 70 U/mL. Patients with high CA 19-9 level showed the tendency to have early recurrence more frequently. Tumor size > 2.85 cm, poor differentiation, and non-adjuvant chemotherapy were also demonstrated to be significant risk factors for early recurrence in early-stage PDAC.

Research conclusions

Elevated CA 19-9 level can be regarded as a reliable parameter predicting early disease recurrence. Adjuvant chemotherapy should be recommended for patients susceptible to early recurrence.

Research perspectives

Preoperative CA 19-9 can be a guidance for patients to undergo effective treatment modality to reduce early recurrence, thus leading to a better prognosis.

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ORIGINAL ARTICLE

Retrospective Study

Patients with *Clostridium difficile* infection and prior appendectomy may be prone to worse outcomes

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Abstract

BACKGROUND

Clostridium difficile infection (CDI) occurs due to a dysbiosis in the colon. The appendix is considered a 'safe house' for gut microbiota and may help repopulate gut flora of patients with CDI.

AIM

To study the impact of prior appendectomy on the severity and outcomes of CDI.

METHODS

We retrospectively reviewed data of 1580 patients with CDI, admitted to our hospital between 2008 to 2018. Patients were grouped based on the presence or absence of the appendix. The primary aim was to (1) assess all-cause mortality and (2) the severity of CDI. Severity was defined as per the Infectious Diseases Society of America criteria. Logistic regression, and propensity score analysis using inverse probability of treatment weights (IPTW) was performed.

RESULTS

Of the 1580 patients, 12.5% had a history of appendectomy. There was no statistical difference in mortality between patients with a prior appendectomy or without (13.7% *vs* 14%, $P = 0.877$). However, a history of appendectomy affected the severity of CDI [odds ratio (OR) = 1.32, 95% confidence interval: 1.01-1.75]. On IPTW, this association remained significant (OR = 1.59, $P < 0.05$). On multivariable

authors are involved in the final review and approval of the manuscript for submission.

Institutional review board statement: The study protocol was approved by the Institution Review Board at BronxCare Health System and was performed as per the Declaration of Helsinki (IRB No. 12131804).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous data, that was obtained after each patient had agreed to the hospital evaluation and treatment *via* written consent.

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Grade D (Fair): 0
Grade E (Poor): 0

analysis of secondary outcomes, prior appendectomy was also associated with toxic megacolon (OR = 5.37, $P < 0.05$) and colectomy (OR = 2.77, $P < 0.05$).

CONCLUSION

Prior appendectomy may affect the severity of CDI, development of toxic megacolon and the eventual need for colectomy. Since treatment of CDI is governed by its severity, stronger antibiotic regimens or earlier use of fecal microbiota transplant may be a viable option for patients with prior appendectomy.

Key Words: Appendectomy; *Clostridium difficile*; Toxic megacolon; Colectomy; Gut microbiome

Core Tip: *Clostridium difficile (C. difficile)* infection occurs due to a dysbiosis of the gut. The appendix is known to host immune tissue and favorable gut microbiota, which may indirectly influence the disease course and outcomes in *C. difficile* infection. We found that prior appendectomy may affect the severity of *C. difficile* infection, and it may also increase the risk of developing toxic megacolon or requiring colectomy in these patients. Thus, earlier implementation of advanced therapeutic options may be necessary in patients without an appendix who develop *C. difficile* infection.

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INTRODUCTION

Clostridium difficile (*C. difficile*) is a gram positive, spore forming bacterium that spreads *via* the fecal-oral route, and causes an opportunistic Infection when a disruption in the normal intestinal flora occurs. *C. difficile* infection (CDI) is typically acquired in the healthcare setting, such as during hospitalizations, however community spread is also established. Recent prevalence studies demonstrate a decline in health care-associated CDI (by 24% from 2011 through 2017) as a result of better prevention practices and antibiotic stewardship programs, whereas the national burden of community-associated CDI has remained unchanged[1,2]. The clinical spectrum of CDI ranges from a mild diarrheal illness to a fulminant colitis, leading to shock and possible death. It is diagnosed *via* stool studies (presence of *C. difficile* toxins or toxigenic strain of *C. difficile* in stool), or the presence of typical colonoscopy findings of pseudomembranous colitis.

Treatment of CDI is governed by its severity on presentation, and in order to define the severity, several scoring systems are available. The components of the majority of these scales include patient comorbidities, clinical manifestations, laboratory tests, and imaging studies[3]. The most widely used of these scores was published in the 2010 Society for Healthcare Epidemiology of America and Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines (Table 1). It categorizes CDI into mild, severe, and severe, complicated[4]. The term "fulminant" is sometimes used to describe severe, complicated CDI[5]. This classification was derived from expert opinion and includes factors that predict unfavorable outcomes in CDI, such as serum creatinine > 1.5 mg/dL, leukocyte count > 15 × 10^9/L, ileus, toxic megacolon and shock.

In recent times, reports have emerged that recognize a history of appendectomy as an influence on the severity of CDI[6-8]. The vermiform appendix has long been considered a vestigial organ, however recent studies have elicited an abundance of favorable gut microbiota within the appendix, with the highest concentration in the

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Table 1 Classification of *Clostridium difficile* infection severity based on the Infectious Diseases Society of America criteria

Severity	IDSA criteria
Mild	WBC < 15 × 10^9/L and serum creatinine < 1.5 times premorbid level
Severe	WBC ≥ 15 × 10^9/L, or serum creatinine ≥ 1.5 times premorbid level
Fulminant (severe, complicated)	Hypotension, shock, ileus, or megacolon

IDSA: Infectious Diseases Society of America; WBC: White blood cell.

innermost region, safely sheltered from colonic fecal stream[9,10]. The appendix is also said to harbor gut associated lymphoid tissue comprising of plasma B cells that produce high levels of secretory immunoglobulin A[11]. These antibodies may play a protective role in CDI, as reported by several small studies[12,13]. Larger epidemiological studies have also reinforced the appendix's role as an immunomodulatory organ. A history of appendectomy is believed to prevent the development of ulcerative colitis (UC)[14,15], and reduce the risk of colectomy in these patients[16].

We postulate that the appendix may be able to repopulate the large intestine with commensal organisms, or provide passive immunity should the colon fall prey to *C. difficile*. Accordingly, its absence may be detrimental to recovery from CDI. Previous reports have corroborated a similar claim. Im *et al*[8], demonstrated the protective role of the appendix in CDI recurrences in 254 patients. Clanton *et al*[17] reported a higher rate of appendectomy in patients with fulminant CDI that resulted in a colectomy.

Based on the appendix's 'safe house' theory, we set out to determine if there exists an association between prior appendectomy and outcomes (severity, recurrence, mortality) of CDI.

MATERIALS AND METHODS

Study design

This was a single-center, retrospective cohort study, spanning a period of 10 years from April 2008 to November 2018. The study protocol was approved by the Institution Review Board at BronxCare Health System and was performed as per the Declaration of Helsinki (IRB # 12131804). Data for hospitalized patients with positive *C. difficile* stool test was retrieved using the electronic medical record (EMR). A positive stool test was defined as (1) positive results of stool *C. difficile* toxin (Toxin A or Toxin B) and glutamate dehydrogenase (GDH) antigen, or (2) positive *C. difficile* nucleic acid amplification test in cases of discrepancy between *C. difficile* toxin and GDH antigen. Medical records for patients with CDI were reviewed, and all asymptomatic carriers were excluded.

Baseline socio-demographic characteristics included age, gender, body mass index (BMI) and ethnicity. Data was extracted from admission records except for ethnicity, which was self-reported. EMR was used to obtain patients' comorbidities. The blood chemistry and cell counts were obtained from the first set of the laboratory parameters acquired after the diagnosis of CDI. Past surgical history was scanned for information on prior appendectomy. Available abdominal imaging [ultrasound or computed tomography (CT) scan] prior to the onset of CDI was also reviewed to assess for the presence or absence of the appendix. When information was not available on history or imaging, the patient was considered to have an intact appendix. Records were also reviewed to assess prior use (within the preceding three months of CDI onset) of antibiotics, proton pump inhibitors (PPI), steroids and chemotherapy.

Study outcomes

The primary outcomes for the current study were: (1) All-cause mortality; and (2) Severity of CDI. The charts of all patients, including their hospital course, were reviewed to document these findings including the recurrence rate, development of toxic megacolon, and the subsequent need for colectomy attributable to CDI. Mortality was defined as death within the same hospital admission as the CDI. Ileus was obtained from reported abdominal imaging (X-ray or CT scan) during the same hospital admission as the CDI. Additionally, data regarding the incidence of toxic megacolon was obtained from abdominal imaging (X-ray or CT scan) or the surgical operative note in cases where patients underwent colectomy during the same hospital admission as the CDI diagnosis. The severity of CDI was defined as per the IDSA guidelines (Table 1).

Recurrence was defined as a new episode of symptom onset, and positive assay result following a successfully treated prior episode of CDI in the previous 2-8 wk. Length of stay (LOS) was calculated from the EMR from the day of admission to discharge or death.

Statistical analysis

Patients were divided into two groups based on the history of appendectomy. The demographic information, comorbid medical conditions, and laboratory parameters were collected and stratified across both groups. Frequencies and percentages were reported for categorical variables. The mean and standard deviation were used to summarize continuous normal variables, while the median and interquartile range were used for continuous non-normal variables such as the LOS.

Univariate analysis was performed using Chi-square test independence for categorical variables. Continuous variables were compared using unpaired t-test and one-way ANOVA for two and more than two groups, respectively. For non-normal variables, Mann-Whitney and Kruskal-Wallis tests were used alternatively.

Multivariate analysis was performed using two methods in order to control and reduce the selection bias and other potential confounders in retrospective studies: (1) Multivariate logistic regression; and (2) Inverse probability of treatment weights (IPTW). Logistic regression was used to assess the association of prior appendectomy with primary and secondary outcomes after correcting for age, gender, BMI, comorbidities, and the prior use of antibiotics, steroids, and PPI. The binominal logistic regression was used for mortality and recurrence. Ordinal logistic regression and Poisson regression were used for CDI severity and LOS, respectively.

For IPTW, propensity scores were created by matching groups based on gender, age, prior PPI use, prior steroid use, and use of chemotherapy. Weights were calculated as the inverse of the propensity scores for patients with appendectomy. The control group weights were calculated by subtracting the propensity scores from unity and inverting the resulting score. Boosted logistic regression (using 20000 trees) was used to calculate propensity score. Average treatment effect (ATE) was used as an estimate during calculations. The balance was measured and assessed using the standardized effect size or standardized mean difference (SMD).

SPSS version 25 and R version 3.6.3 was used to perform the analysis.

RESULTS

CDI was diagnosed in 1580 hospitalized patients during the study period. The mean age of the patients was 57.1 ± 15.7 years at diagnosis. Females represented 51.2% of all patients. Data regarding race was missing for 40% of the patients. Of the remaining, African Americans constituted the majority (39%). Less than half of the patients presented with a mild CDI presentation (45%, n = 710), 36% (n = 566) were categorized into the severe CDI presentation and 19% (n = 304) presented with fulminant (severe, complicated) CDI. The all-cause mortality in the study population was 14% (n = 220). The recurrence rate was 14.4% (n = 228), with a mean and a median of 1.48 and 1.0 recurrences, respectively. The average LOS was 17.8 ± 31.89 d.

There was evidence of prior appendectomy in 12.5% (n = 198) of the patients. The appendectomy status in most of these patients (61%, n = 122) was documented on the CT scan of the abdomen. Comparing baseline characteristics between both groups (Table 2) revealed some differences. The percentage of females who had a prior appendectomy was significantly higher than the percentage who did not (59% *vs* 50%, P = 0.022). Information regarding BMI was available in less than half of the study population (n = 691), and there was no significant difference observed between the two groups. The age of the patients in both groups was also comparable, with no statistical significance. The prior use of antibiotics and PPI was more prevalent in individuals with prior appendectomy than individuals with no history of appendectomy, however only prior PPI use was statistically significant (P = 0.001). Prevalence of major comorbid conditions such as hypertension, diabetes, asthma/chronic obstructive pulmonary disease, coronary artery disease, and chronic kidney disease was comparable between the two groups. The prevalence of UC in patients with CDI was slightly higher amongst patients with a history of

Table 2 Baseline information of patients with *Clostridium difficile* infection compared between patients with appendectomy and no history of appendectomy

Variable	All patients (%)	No prior appendectomy (%)	Prior appendectomy (%)	*P* value	*n*
	1580	1382 (87.5)	198 (12.5)		
Age	57.1 ± 15.7	57.1 ± 15.6	56.8 ± 17.0	0.812	1580
Gender				**0.022**	1580
Female	809 (51.2)	692 (50.1)	117 (59.1)		
Male	771 (48.8)	690 (49.9)	81 (40.9)		
Ethnicity				0.439	1580
African American	611 (38.67)	540 (39.1)	71 (35.9)		
Hispanic	262 (16.6)	228 (16.5)	34 (17.2)		
Caucasian	58 (3.73)	52 (3.8)	6 (3.03)		
Others	10 (0.63)	7 (0.51)	3 (1.52)		
Not available	639 (40.4)	555 (40.2)	84 (42.4)		
Comorbidities					1580
Hypertension	1210 (76.58)	1022 (73.95)	153 (77.27)	0.815	
Diabetes mellitus	741 (46.89)	618 (44.71)	102 (51.51)	0.384	
Obstructive lung disease	752 (47.56)	633 (45.80)	95 (47.97)	0.933	
Coronary artery disease	480 (30.37)	407 (29.45)	57 (28.78)	0.802	
Chronic kidney disease	477 (30.18)	406 (29.37)	56 (28.28)	0.819	
Inflammatory bowel diseases					1580
Ulcerative colitis	117 (7.40)	103 (7.45)	9 (4.54)	0.203	
Crohn's disease	42 (2.66)	37 (2.67)	4 (2.02)	0.803	
Risk Factor of CDI					
Prior use of antibiotics	768 (52.2)	656 (51.3)	112 (58.3)	0.086	1470
Prior use of PPI	429 (29.0)	353 (27.4)	76 (39.4)	**0.001**	1480
Prior use of steroids	128 (8.73)	110 (8.63)	18 (9.1)	0.838	1467
Prior chemotherapy	50 (3.35)	45 (3.46)	5 (2.59)	0.678	1492
Known malignancy	175 (11.4)	147 (11.0)	28 (14.1)	0.232	1539
Liver cirrhosis	117 (8.42)	98 (8.19)	19 (9.84)	0.531	1389
HIV infection	406 (34.5)	362 (35.2)	44 (29.3)	0.186	1389
C. difficile related complication					
Ileus on imaging	52 (3.90)	41 (3.59)	11 (5.67)	0.237	1335
Admission to ICU	615 (40.6)	526 (39.8)	89 (46.1)	0.113	1514
Intubation	298 (19.9)	258 (19.8)	40 (20.7)	0.846	1494
Clinical variable					
Body mass index (kg/m^2)	27.69 ± 7.7	27.78 ± 7.79	26.70 ± 6.75	0.1890	690
Mean arterial pressure (mmHg)	92.4 ± 18.2	92.6 ± 18.3	90.5 ± 17.5	0.115	1467
Pulse beats per minute	91.7 ± 20.8	91.6 ± 21.0	92.3 ± 20.0	0.700	1464
Laboratory parameters					
Hemoglobin g/dL	11.2 ± 2.93	11.2 ± 2.98	11.2 ± 2.58	0.819	1533
White blood cell (cells/mm^3)	11.6 ± 8.04	11.4 ± 8.06	13.1 ± 7.71	**0.005**	1533
Albumin (mg/dL)	3.37 ± 0.82	3.38 ± 0.81	3.31 ± 0.87	0.309	1502

Blood urea nitrogen (mg/dL)	26.9 ± 26.0	26.9 ± 25.8	26.7 ± 27.3	0.925	1531
Serum creatinine (mg/dL)	1.85 ± 2.26	1.85 ± 2.24	1.88 ± 2.43	0.830	1531
Lactic acid (mg/dL)	2.13 ± 2.27	2.16 ± 2.33	1.92 ± 1.82	0.127	1372

C. difficile: *Clostridium difficile*; CDI: *Clostridium difficile* infection; PPI: Proton pump inhibitors; HIV: Human immunodeficiency virus; ICU: Intensive care unit.

appendectomy (7.45%), compared to those with an intact appendix (4.54%), though this was not clinically significant (P = 0.203). We found no difference in the prevalence of Crohn's disease in our study population between patients with and without an appendix (2.02% *vs* 2.67%, P = 0.803). There were no differences in the laboratory parameters except for leukocytosis. Individuals with prior appendectomy demonstrated higher leukocyte counts (13.1 × 10^4 cells/dL) as compared to those without prior appendectomy (11.4 × 10^4 cells/dL) (P = 0.005). Both groups revealed no significant difference in the requirement of critical care monitoring for CDI, the need for endotracheal intubation, or ileus on imaging studies.

Prior appendectomy was associated with the severity of presentation, toxic megacolon attributable to *C. difficile* colitis, and colectomy (Table 3). The association with the latter two parameters was statistically significant at the 0.1 level, whereas, association of prior appendectomy with the severity of presentation was significant at P < 0.05 level. Patients with prior appendectomy were more likely to present with a higher grade of severity [odds ratio (OR) = 1.32, P < 0.05]. The rates of severe and fulminant CDI were higher in patients with prior appendectomy (39% and 23%, respectively) than patients with no prior appendectomy (35% and 19%, respectively). Mild presentation was more common in patients with no prior appendectomy. There was no significant difference in the recurrence rates of CDI.

After the use of IPTW, the association between prior appendectomy and the IDSA severity did not change (OR = 1.59, P < 0.05), which indicates that a history of appendectomy in CDI is associated with 59% higher odds of presenting with a higher IDSA severity. The association between appendectomy and toxic megacolon did not change either. Prior appendectomy did not show a statistically significant association with recurrence, LOS, the need for colectomy, or mortality after the use of IPTW.

The severity of *C. difficile* (Table 4) was associated with mortality. Mortality was highest in patients with a fulminant presentation (46%, n = 146 of 314), as compared to the severe or mild manifestation of CDI (P < 0.001). The severity of CDI was as per the IDSA criteria, and patients with toxic megacolon and colectomy were considered in the fulminant *C. difficile* colitis category. The median LOS increased with increasing IDSA severity. Patients with mild CDI had a median LOS of 8 d, while patients with severe and fulminant CDI had median LOS of 10 and 19 d, respectively (P < 0.001). The mean BMI was similar between mild and severe presentations of CDI, whereas, patients with fulminant CDI were noted to have a slight increase in mean BMI, though not statistically significant (Table 5).

Multivariate logistic regression analysis (Table 6) showed that older age was associated with higher mortality in CDI patients (OR = 1.02, P < 0.001). Age did not show a statistically significant association with recurrence, toxic megacolon, or the need for colectomy. None of the included factors showed a statistically significant association with recurrence of CDI. Interestingly, prior appendectomy status was associated with higher odds of toxic megacolon (OR = 5.37, P < 0.05) and higher odds of requiring a colectomy (OR = 2.77, P < 0.05).

DISCUSSION

Appendectomy remains the standard of care for the treatment of acute uncomplicated appendicitis. More than 300000 appendectomies are performed annually in the United States, making it one of the most commonly performed procedures by general surgeons. Our study demonstrated a 12.5% prevalence of prior appendectomy in our patient population, which is similar to the general population (12%-23%), based on epidemiological studies. More females had prior appendectomy compared to males (59% *vs* 50%, P = 0.019), a claim which is also consistent with population studies that demonstrate a higher lifetime risk of appendectomy in females compared to males[18].

Table 3 Comparison of the *Clostridium difficile* infection outcomes based on the prior appendectomy status and the inverse probability of treatment weights analysis

Outcome	Total	No prior appendectomy	Prior appendectomy	OR (95%CI)	*P* value
n	1580	1382	198		
n IP-weighted		1572	1354		
Mortality					
n (%)	220 (13.9)	193 (14.2)	27 (13.7)	0.97 (0.61-1.47)	0.877
n IP-weighted (%)		218 (14)	207 (15.5)	1.12 (0.65-1.92)	0.685
Recurrence					
n (%)	228 (14.4)	199 (14.4)	29 (14.6)	1.02 (0.66-1.54)	0.915
n IP-weighted (%)		228 (14.5)	204 (15.1)	1.05 (0.66-1.67)	0.847
Toxic megacolon					
n (%)	7 (0.4)	4 (0.34)	3 (1.57)	4.75 (0.87-22.9)	**0.069**
n IP-weighted (%)		5 (0.3)	19 (1.5)	4.32 (0.91-20.57)	**0.066**
Colectomy					
n (%)	22 (1.4)	16 (1.19)	6 (3.06)	2.65 (0.93-6.59)	**0.067**
n IP-weighted (%)		18 (1.2)	24 (1.8)	1.53 (0.55-4.27)	0.413
Severity (IDSA)					
Before IPTW				1.32 (1.01-1.75)	**0.043**
Mild, *n* (%)	710 (44.9)	634 (45.9)	76 (38.4)		
Severe, *n* (%)	566 (35.8)	489 (35.4)	77 (38.9)		
Fulminant, *n* (%)	304 (19.2)	259 (18.7)	45 (22.7)		
After IPTW				1.59 (1.15-2.18)	**0.005**
Mild, *n* (%)		724 (46.1)	472 (34.8)		
Severe, *n* (%)		557 (35.4)	526 (38.8)		
Fulminant, *n* (%)		291 (18.5)	356 (26.3)		
LOS among survivors					
Median (IQR)		9 (5.00; 18.0)	10 (6.50; 20.0)	1.1 (0.94-1.28)	0.233
Median (IQR)-IPTW		10 (5.00; 20.0)	12 (7.00; 23.00)	0.9 (0.74-1.1)	0.318

Data were summarized using counts and percentages before inverse probability of treatment weights (IPTW) and weighed counts and percentages after IPTW. Statistical analysis was performed using logistic regression for categorical variables and Poisson regression for length of stay (LOS). Analysis for LOS included only patients who were discharged. Ordinal logistic regression was used to assess the association between history of appendectomy and Infectious Diseases Society of America severity. CI: Confidence interval; OR: Odds ratio; IQR: Interquartile range; IPTW: Inverse probability of treatment weights; LOS: Length of stay; IDSA: Infectious Diseases Society of America.

CDI is the leading cause of hospital-acquired diarrhea in the United States and accounts for significant morbidity and mortality, burdening the healthcare system an additional 1 to 3 billion dollars in costs annually[7]. The all-cause mortality, attributable to CDI in our study population was 14%, whereas epidemiological studies estimate a mortality rate directly related to CDI at 5%, and a mortality associated with CDI complications between 15%-25%[19].

Our results show that patients with a prior appendectomy had a more severe course of CDI (Figure 1), and outcomes of toxic megacolon and colectomy were also higher (Figure 2). Even though patients with appendectomy did have more severe and fulminant course of CDI, our research did not demonstrate a higher rate of mortality in these patients. Of the two markers of severity, namely serum creatinine and white cell count, there was no significant difference seen in the serum creatinine level between the two groups. Thus the higher severity was mostly attributable to a higher leukocyte count in CDI patients with a prior appendectomy. Furthermore, a history of

Table 4 Association between *Clostridium difficile* infection outcomes and severity of the presentation

	Severity (IDSA)			
Outcomes	**Mild (*n* = 710)**	**Severe (*n* = 566)**	**Fulminant (*n* = 304)**	***P* value**
Mortality (%)	29 (4.1)	44 (7.7)	147 (48.3)	< 0.001
Recurrence (%)	98 (13.8)	81 (14.3)	49 (16.1)	0.063
Toxic megacolon (%)	0	0	7 (2.3)	< 0.001
Colectomy (%)	0	0	22 (7.2%)	< 0.001
Length of stay (median)	8 (4.00; 14.00)	10.0 (6.00; 18.0)	19 (10.0; 30.0)	< 0.001

Counts and percentages were used to summarize categorical variables. The median (interquartile range) was used to summarize length of stay (LOS). Statistical analysis was performed using the Chi-square test of independence. LOS was compared using the Kruskal-Wallis test. Analysis for LOS included only patients who were discharged. IDSA: Infectious Diseases Society of America.

Table 5 Association between body mass index and severity of *Clostridium difficile* infection presentation

Severity (IDSA)	Body mass index (kg/m^2)	*P* = 0.412
Mild	27.66 ± 7.39	
Severe	27.34 ± 7.63	
Fulminant	28.4 ± 8.59	

IDSA: Infectious Diseases Society of America.

appendectomy was positively associated with the development of toxic megacolon and the need for colectomy at the $P < 0.1$ level on bivariate analysis. We postulate that significance was not met at the $P < 0.05$ level due to a small overall number of patients with toxic megacolon (n = 7) and those that underwent colectomy (n = 22), in our study population. However, the trajectory of data suggests a possible association that could have yielded significance at the $P < 0.05$ level, if the study power was increased. Our conjecture was confirmed on multivariate regression analysis, where prior appendectomy in CDI patients was identified as an independent predictor of both toxic megacolon (P = 0.031) and colectomy (P = 0.044).

Prior antibiotic use, defined as use of antibiotics within 3 months prior to the onset of CDI, was more likely in patients with appendectomy than those without, however this was not statistically significant. Similarly, PPI use was also more likely in patients with a history of appendectomy, and this was met with statistical significance. Antibiotic use has a known association with the development of CDI[20], and several meta-analysis have also reported PPI use as a risk factor for CDI, even in the absence of antibiotics[21,22]. However, to date, both antibiotics and PPI have not been shown to affect the severity of CDI at presentation.

Our study did not demonstrate an increased risk of CDI recurrence in patients with prior appendectomy compared to those without, contrary to previous reports[8]. Although PPI use has also been associated with an increased risk of recurrent CDI[23], this was not observed in our study cohort.

Other risk factors for acquiring CDI, such as a history of steroid use, chemotherapy, cirrhosis and HIV infection were evenly distributed between the appendectomy and non-appendectomy group.

In 2015, an estimated 1.3% of US adults (3 million) reported being diagnosed with inflammatory bowel diseases (IBD), namely Crohn's disease or UC[24]. The appendix may also serve a role in IBD. Several large epidemiological cohort studies have demonstrated the preventive effect of appendectomy on the development of UC, a finding that has been confirmed in murine colitis models[14], though this has not been replicated in CDI populations. A recent systematic review showed a significant inverse association between an appendectomy and the development of UC with an overall OR of 0.39 (95% confidence interval: 0.29-0.52)[15]. While it is known that CDI can complicate underlying IBD, given the immunosuppressive nature of the disease[25], a higher prevalence of UC was seen in our patients with CDI and appendectomy keeping in line with prior studies.

Table 6 Multivariate analysis for primary and secondary outcomes

	Mortality		Recurrence		Toxic megacolon		Need for colectomy	
Variable	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI	*P* value
Age	1.02 (1.01-1.03)	**< 0.001**	1.00 (0.99-1.01)	0.626			0.99 (0.96-1.02)	0.547
Female gender	Ref		Ref		Ref		Ref	
Male gender	1.32 (0.97-1.81)	0.079	0.91 (0.67-1.22)	0.518	0.86 (0.17-4.00)	0.846	1.36 (0.55-3.46)	0.501
Prior appendectomy = no	Ref		Ref		Ref		Ref	
Prior appendectomy = yes	1.03 (0.64-1.59)	0.905	0.92 (0.58-1.42)	0.727	5.37 (1.03-25.09)	**0.031**	2.77 (0.95-7.17)	**0.044**
Prior antibiotics (no)	Ref		Ref		Ref		Ref	
Prior antibiotics (yes)	1.04 (0.76-1.43)	0.788	1.07 (0.79-1.44)	0.668	0.13 (0.01-0.81)	0.065	1.58 (0.62-4.31)	0.348
Prior steroids (no)	Ref		Ref		Ref		Ref	
Prior steroids (yes)	0.72 (0.37-1.30)	0.309	1.08 (0.63-1.77)	0.774	1.99 (0.10-12.38)	0.533	0.41 (0.02-2.07)	0.391
Prior PPI (no)	Ref		Ref		Ref		Ref	
Prior PPI (yes)	0.89 (0.62-1.27)	0.530	1.05 (0.74-1.46)	0.790	1.08 (0.15-5.38)	0.933	1.83 (0.71-4.60)	0.196
Prior chemotherapy (no)	Ref		Ref		Ref		Ref	
Prior chemotherapy (yes)	0.92 (0.34-2.07)	0.851	0.76 (0.26-1.79)	0.570	-		4.26 (0.65-16.24)	0.063

Multivariate analysis for mortality and recurrence was performed using binomial logistic regression. Chemotherapy was not included in the analysis of toxic megacolon due to convergence issues. OR: Odds ratio; CI: Confidence interval; PPI: Proton pump inhibitors.

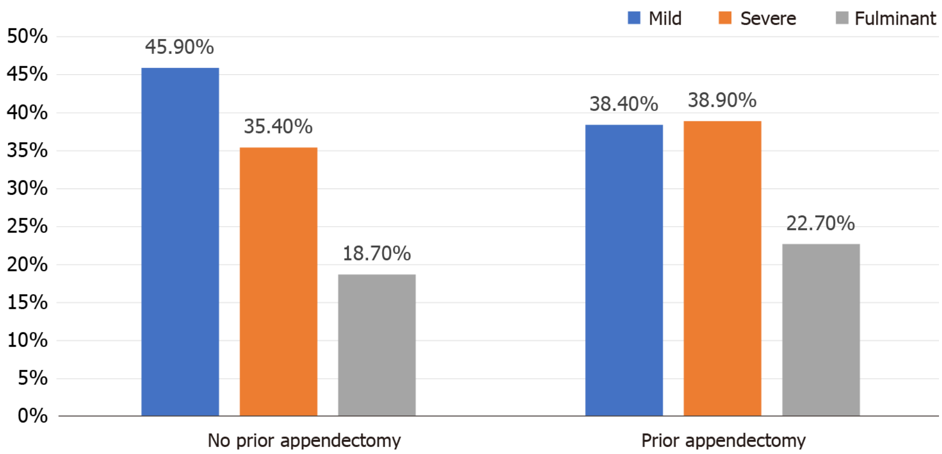

Figure 1 Infectious Diseases Society of America severity amongst *Clostridium difficile* infection patients with and without a history of prior appendectomy.

The study data was further validated as it rightfully portrayed the highest mortality and increased LOS in those with the most fulminant presentation of CDI. Our data also demonstrated that older age had a higher risk of mortality. Age is a well-known risk factor for CDI, especially greater than 65 years, and it also correlates with increasing severity of infection[26].

Based on our results and analysis, we postulate that a history of appendectomy may lead to worse outcomes in CDI, likely secondary to an attenuated response to the dysbiosis of the gut, leading to an increased inflammatory reaction. Since disease severity is used to guide therapy, perhaps it's prudent to screen patients with new onset CDI for factors associated with impaired immune response, such as an absent appendix. It would be worthwhile to investigate stronger antibiotic regimens or earlier institution of fecal microbiota transplantation in such patients.

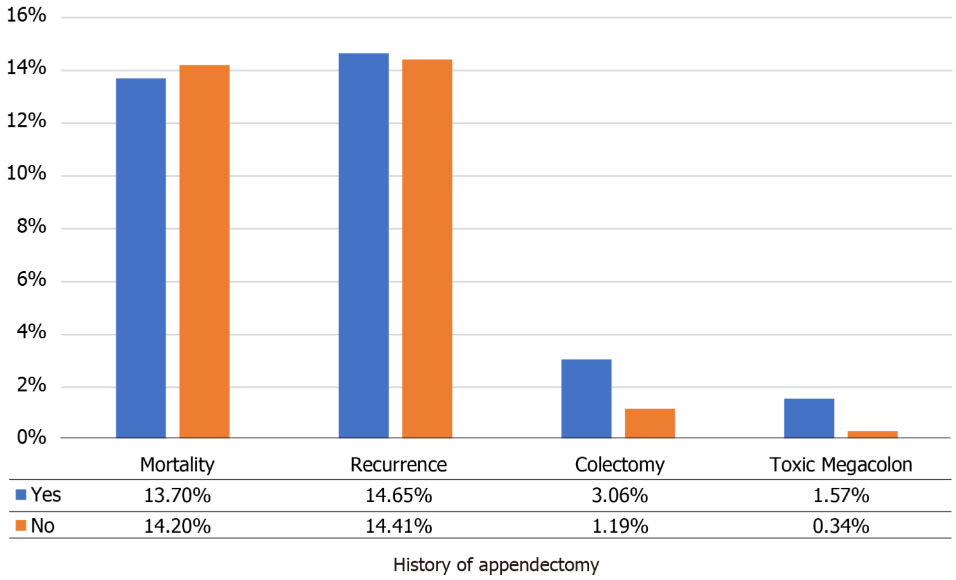

Figure 2 Outcomes of *Clostridium difficile* infection stratified according to the prior appendectomy status.

Contrary to our hypothesis, deterministic ecological models of the colon microbiome have not demonstrated a protective role of the appendix in CDI. These models studied the effect of the appendicular migration rate of commensal microbiota, and the boost to antibody production exerted by the appendix[27]. Further, a handful of small retrospective studies did not show a positive correlation between a history of appendectomy and CDI. Khanna *et al*[28], reported no difference in outcomes such as severity, treatment failure or recurrence in patients who had undergone an appendectomy before the development of CDI as compared to patients without an appendectomy. Ward *et al*[29], studied the presence and severity of CDI in relation to the presence or absence of an appendix, which did not demonstrate a statistically significant association. More recently, two further analyses demonstrated that *C. difficile* recurrence rate is not affected by a prior appendectomy[30], nor is there any statistical difference in the severity or complications of CDI in the presence or absence of the appendix[31]. It is worth noting that all of the above mentioned negative studies had a smaller patient population compared to ours, with most under 500 patients. Yet interestingly, the prevalence of patients with appendectomy in these studies was similar to ours and the general population at large.

The limitations of our study include its inherent retrospective design. Our case-control methodology does not allow for us to determine causality between appendectomy and CDI. It is also subject to selection bias, as the history of appendectomy was obtained *via* CT findings and on chart review. Our study, in keeping with the common narrative, did not show a statistical increase in mortality in patients with CDI and a history of appendectomy. Nevertheless, larger prospective studies are needed to establish significant causation and validate our findings. To date, no prospective studies have elicited the relationship between appendectomy and CDI.

CONCLUSION

Prior appendectomy may affect the severity of CDI, development of toxic megacolon and the eventual need for colectomy. Since treatment of CDI is governed by its severity, stronger antibiotic regimens or earlier use of fecal microbiota transplant may be a viable option for patients with prior appendectomy.

ARTICLE HIGHLIGHTS

Research background

Clostridium difficile (*C. difficile*) is the leading cause of hospital-acquired diarrhea in the United States and accounts for significant morbidity, mortality and healthcare costs.

Research motivation

The vermiform appendix hosts immune tissue and favorable gut microbiota, which may indirectly influence the disease course and outcomes in *C. difficile* infection (CDI).

Research objectives

We aimed to study the association between prior appendectomy and outcomes (severity, recurrence, mortality) of CDI.

Research methods

Retrospective review of 1580 patients with CDI, assessing mortality and severity based on the presence or absence of the appendix, using logistic regression and propensity score analysis.

Research results

There was no statistical difference in mortality between *C. difficile* patients with a prior appendectomy or without (13.7% *vs* 14%, P = 0.877). However, a history of appendectomy affected the severity of CDI [odds ratio (OR) = 1.32, 95% confidence interval: 1.01-1.75] and was also associated with the development of toxic megacolon (OR = 5.37, $P < 0.05$), and colectomy (OR = 2.77, $P < 0.05$).

Research conclusions

A history of appendectomy may lead to worse outcomes in CDI, likely secondary to an attenuated response to the dysbiosis of the gut, leading to an increased inflammatory reaction.

Research perspectives

Clinicians should be aware of the association between CDI and a history of appendectomy, and may consider screening all patients with *C. difficile* for a history of appendectomy. Further investigation into stronger antibiotic regimens or earlier institution of fecal microbiota transplantation for patients with prior appendectomy should be conducted if larger prospective studies can confirm and validate our results.

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ORIGINAL ARTICLE

Observational Study

Novel roles of lipopolysaccharide and TLR4/NF-κB signaling pathway in inflammatory response to liver injury in Budd-Chiari syndrome

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Author contributions: Cheng DL and Lv WF designed the study; Li J, Cheng DL, Zhou CZ, Chen ZM and Fang WW performed the experiments, collected and analyzed the data; Lv WF, Zhou CZ, Chen XM and Fang WW contributed to sample collection and experimental data input into computer; Li J and Cheng DL drafted and wrote the manuscript; Li J and Cheng DL gave advice on the experimental design, interpreted the results and critically revised the manuscript; Lv WF, Zhou CZ and Chen XM provided pathological assistance; all authors read and approved the final version of the manuscript.

Institutional review board statement: All procedures were performed in accordance with the ethical standards of the committee of human experimentation (institutional and national) and with the guidelines of the Helsinki Declaration of 1975 that have been

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Abstract

BACKGROUND

Budd-Chiari syndrome (BCS) is an uncommon disorder characterized by obstruction of hepatic venous outflow. To date, the exact mechanism underlying hepatic injury derived from the hepatic venous outflow obstruction in BCS remains largely unknown.

AIM

To assess the role of NF-κB-mediated inflammation in BCS-induced liver injury in humans and rats.

METHODS

A total of 180 rats were randomly assigned into nine groups, including four BCS model groups (1, 3, 6 and 12 wk), four sham-operated groups (1, 3, 6 and 12 wk), and a control group. Lipopolysaccharide (LPS) levels in each group were detected by the Tachypleus Amebocyte Lysate assay. The mRNA and protein levels of TLR4, NF-κB, tumor necrosis factor (TNF)-α, interleukin (IL)-2 and interferon (IFN)-γ were quantified. In addition, 60 patients with BCS and 30 healthy controls were enrolled, and their blood samples were analyzed.

revised in 2008 (5).

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

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

Data sharing statement: Data are available on reasonable request from the corresponding author.

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

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RESULTS

Hepatic and plasma LPS levels were significantly increased in rats. The mRNA and protein expression levels of TLR4, NF-κB and inflammatory cytokines (TNF-α, IL-2 and IFN-γ) in liver tissues were significantly higher in the BCS model groups compared with the other two groups. In addition, the model groups (1, 3, 6 and 12 wk after BCS induction) showed significant differences in the levels of LPS, TLR4, NF-κB, TNF-α, IL-2 and IFN-γ. Notably, there was a significant correlation between the LPS concentrations and mRNA and protein levels of TLR4, NF-κB and inflammatory cytokines. Importantly, it was revealed that the levels of LPS, TLR4, NF-κB and inflammatory cytokines were significantly greater in chronic BCS patients than healthy controls and acute BCS patients.

CONCLUSION

LPS level is markedly elevated in BCS, in turn activating the TLR4/NF-κB signaling pathway, leading to induction of inflammatory cytokines (TNF-α, IL-2 and IFN-γ) in response to BCS-induced liver injury.

Key Words: Budd-Chiari syndrome; Liver injury; Lipopolysaccharide; Nuclear factor-kappa B; Toll-like receptor 4

Core Tip: Budd-Chiari syndrome (BCS) is an uncommon disorder characterized by obstruction of hepatic venous outflow. When the liver becomes congested and damaged, liver fibrosis and cirrhosis can occur. We explored the mechanism involving NF-κB in BCS-induced liver injury in humans and animal models. Results suggest that LPS level is markedly elevated in BCS, and in turn it activates the TLR4/NF-κB signaling pathway, leading to induction of inflammatory cytokines (tumor necrosis factor-α, interleukin-2 and interferon-γ) in response to BCS-induced liver injury. Importantly, our novel findings indicated that the TLR4/NF-κB signaling pathway could be a potential therapeutic target.

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INTRODUCTION

Budd-Chiari syndrome (BCS) is a clinical condition caused by the outflow tract obstruction of the hepatic vein (HV)[1-5]. The primary cause of BCS includes portal vein thrombosis or HV obstruction, while secondary BCS may occur with parasite infection, abscess, cyst, or benign or malignant tumors[1-6]. It has been demonstrated that liver injury is induced by HV outflow tract occlusion in BCS regardless of the etiological factors. However, to date, the exact mechanism underlying BCS-induced hepatic injury remains elusive[6,7].

Previous studies have shown that NF-κB, consisting of two subunits (p50 and p65 heterodimers), plays a pivotal role in the inflammatory response to external stimuli [*e.g.*, lipopolysaccharide (LPS), reactive oxygen species (ROS), tumor necrosis factor (TNF)-α, and interleukin (IL)-2][8-13]. In the NF-κB signaling pathway, the NF-κB heterodimers are phosphorylated by NF-κB (IκB) inhibitor mediated by the IκB kinase (IKK)[8-13]. This activation can result in transportation of activated NF-κB (p50 and p65 heterodimers) from the cytoplasm to the nucleus, and triggers the expression of target genes, generating and releasing inflammatory cytokines, such as TNF-α, IL-2 and interferon (IFN)-γ. Additionally, these inflammatory cytokines can promote the activation of NF-κB, which in turn can mediate a cascade of inflammatory reactions to inflammatory injury.

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NF-κB-dependent inflammatory responses are involved in the regulation of liver injury due to a variety of factors, including hepatitis virus, poisoning, alcohol and cholestasis[14,15]. Importantly, portal hypertension and imbalance of intestinal flora in BCS can lead to intestinal congestion and edema, as well as increased levels of LPS in the liver. In addition, the congested liver leads to a decrease in blood flow, and thus, LPS is further accumulated. We hypothesized that accumulation of LPS can activate the TLR4/NF-κB signaling pathway through combination of TLR4 in hepatic cells, thereby regulating NF-κB-dependent liver acute and chronic inflammatory damage. To date, however, no relevant research has been carried out[16-18].

In this study, we investigated whether LPS and the LPS-activated TLR4/NF-κB signaling pathway could be involved in the inflammatory response to BCS-induced liver injury in a rat model of BCS and human patients with BCS. The results may assist researchers to better understand the mechanism of the hepatic injury caused by BCS.

MATERIALS AND METHODS

Reagents

Chloroform was purchased from Shanghai Suyi Chemical Reagent Co. Ltd. (Shanghai, China) and Limulus reagent was obtained from Xiamen Limulus Reagent Experimental Factory Co. Ltd. (Xiamen, China). Goat anti-mouse and goat anti-rabbit IgG, as well as phosphate-buffered saline were purchased from Beijing Zhongshan Golden Bridge Biotechnology Co. Ltd. (ZSbio) (Beijing, China). Tween-20 was obtained from Beijing Solarbio Science & Technology Co. Ltd. (Beijing, China).

Induction of BCS in the experimental animals

Male Sprague-Dawley rats (n = 180; body weight, 205-260 g) were used. All animals were housed in individual cages and maintained at room temperature (15-25 °C), with a humidity of 50%-60%. Food and water were given *ad libitum*. The rats were fasted for 12 h before operation and were anesthetized by intraperitoneal injection of 10% chloral hydrate (3 mL/kg). The rats were randomly divided into nine groups of 20 rats each, including four model-based groups (1, 3, 6 and 12 wk after surgical induction of BCS), four sham-operated groups (1, 3, 6 and 12 wk following sham operation), and one control group. Rats in the model groups underwent the following surgical procedures to induce BCS: The retro hepatic inferior vena cava (IVC) was exposed, the tissues surrounding the IVC were dissociated, the 4F catheter was paralleled to the IVC, and the IVC and the catheter were tightly fastened using No. 0 suture, followed by pulling the catheter out and closing the abdomen (Supplementary Figure 1). Penicillin (20 U/rat) was injected intramuscularly after 5 d. In the sham-operated groups, the tissues surrounding the IVC were separated, while they were not ligated. Rats in the control group were fed for 6 wk without any other interventions.

The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of University of Science and Technology of China (Hefei, China; approval No. 2020-N(H)-094).

Digital subtraction angiography of rats

Digital subtraction angiography (DSA) was performed in all rats. On the day before rats were killed, they were anesthetized intraperitoneally with 10% chloral hydrate (3 mL/kg). The skin was incised on either side of the groin to expose the femoral vein. The skin was punctured with a 24G intravenous needle and iodixanol (Jiangsu Hengrui Pharmaceutical Co. Ltd., Nanjing, China) was injected through an intravenous indwelling needle at a flow rate of 1 mL/s with a total volume of 2.5 mL. DSA was performed to visualize the blood flow of the HV and IVC, as well as the formation of IVC occlusion and collateral circulation.

Collection of liver tissues from the experimental rats

According to the random number table method, 12 rats were killed at various time points after treatment. The left lobe of the liver tissue was fixed with 10% formalin and Bouin's solution for histopathological examination.

Measurements of hepatic and plasma LPS levels in rats

Hepatic or plasma LPS levels were determined in the experimental rats. The standard curve was plotted *via* increasing LPS levels: 0.1, 0.25, 0.5 and 1.0 EU/mL solutions. For measurement of LPS levels, 100 μL LPS standards or samples (or rat liver homogenate solution, or plasma) were added to the non-pyrogen tube, and 100 μL Limulus amebocyte lysate solution was added, gently and evenly shaken, and incubated in a 37 °C incubator for 10 min. After that, they were mixed well with 100 μL chromogenic substrate solution and incubated for 6 min in a 37 °C incubator. At the end of incubation, we added 500 μL azo reagent 1, 2 and 3 solutions in sequence, shaking gently each time until fully mixed, waited for 5 min, and recorded the optical density at 545 nm. The absorbance of the rat liver homogenate sample was substituted into the standard curve, and the sample concentration was calculated, and was multiplied by the dilution multiple to obtain LPS level.

Real-time polymerase chain reaction measurement of β-actin, TLR4, NF-κBp65, IL-2, TNF-α and IFN-γ

The liver tissue (50-100 mg) was cut into pieces, ground in liquid nitrogen, and total RNA was isolated using TRIzol reagent (Life Technologies, Carlsbad, CA, United States). The cDNA was obtained by the RevertAid First Strand cDNA Synthesis Kit (Thermo Fisher Scientific, Waltham, MA, United States). Real-time polymerase chain reaction system (Thermo Fisher Scientific) was used, with the following amplification conditions: 95 °C for 2 min, 95 °C for 5 s, and 60 °C for 10 s for 40 cycles. β-Actin was taken as a reference gene, and the relative expression levels were calculated using the $2^{-\Delta\Delta CT}$ method. The primers used were synthesized by Shanghai Shenggong Bioengineering Co. Ltd. (Shanghai, China), and are summarized in Table 1. All experiments were carried out on three rats.

Western blotting for detection of protein levels of β-actin, TLR4, NF-κBp65, IL-2, TNF-α and IFN-γ

Western blotting was performed to detect the protein levels. In brief, 100 mg liver tissue was extracted and lysed with 1 mL radio-immunoprecipitation assay lysis buffer (Beyotime Institute of Biotechnology, Shanghai, China). The supernatant containing total protein of rat liver tissue was collected after centrifugation at 12000 rpm for 15 min at 4 °C. Protein concentrations were measured using the BCA method. Proteins (30 μg) were separated *via* 10% SDS-PAGE and electrophoretically transferred to equilibrated polyvinylidene difluoride membranes (Millipore, Burlington, MA, United States). After being blocked, the membranes were incubated overnight at 4 °C with the following primary antibodies: TLR4 (1:300; ZSbio), NF-κB (1:300; ZSbio), TNF-α (1:300; ZSbio), IL-2 (1:300; ZSbio), IFN-γ (1:300; ZSbio), and β-actin (Santa Cruz Biotechnology, Dallas, TX, United States). Bound primary antibody was detected by incubation with horseradish-peroxidase-conjugated secondary antibody for 2 h. The protein was detected by an enhanced chemiluminescent kit (Thermo Fisher Scientific), and the ImageJ software (National Institutes of Health, Bethesda, MD, United States) was used for image processing.

Histopathological examination

The liver tissues of rats were fixed in formaldehyde and Bouin's solution, embedded in paraffin and sectioned. According to the standard procedure, liver sections were subjected to hematoxylin-eosin (HE) staining and Masson's trichrome staining, dehydrated, sealed, and images of sections were visualized using a microscope.

Human subjects and detection of LPS levels and key molecules in the TLR4/NF-κB signaling pathway

A total of 60 patients with acute or chronic BCS were enrolled from the First Affiliated Hospital of the University of Science and Technology of China (Hefei, China) from January 2018 to December 2019. The inclusion criteria for acute BCS were as follows: (1) BCS patients with the disease course < 3 mo; (2) Diagnosed with BCS for the first time; (3) No history of alcohol abuse and toxic exposure; and (4) No history of pulmonary heart disease, viral hepatitis, immune hepatitis, or other related diseases. The chronic BCS group included patients with disease course > 3 mo, and with other inclusion criteria similar to the acute BCS group. We also enrolled 30 healthy volunteers as controls.

Blood samples (8 mL) were collected from the cubital veins of the human subjects for subsequent analysis. Then, 3-mL blood samples were anticoagulated with 2% EDTA and were used for measurement of TLR4, in which the positive expression rate of TLR4 in monocytes of each subject was detected by flow cytometry. Next, 3 mL heparin was used for preparation of plasma to detect LPS level in BSC patients. Afterwards, 2 mL non-anticoagulated blood samples was used for preparation of

Table 1 Primers used in this study

	Forward	Reverse
β-actin (150 bp)	5′-CCCATCTATGAGGGTTACGC-3′	5′-TTTAATGTCACGCACGATTTC-3′
TLR4 (186 bp)	5′-GCCGGAAAGTTATTGTGGTGGT-3′	5′-ATGGGTTTTAGGCGCAGAGTTT-3′
NF-κB p65 (108 bp)	5′-AAGATCTGCCGAGTAAACCG-3	5′-TCCCGTGAAATACACCTCAA-3′
IL-2 (113 bp)	5′-CAAGCAGGCCACAGAATTGA-3′	5′-TTCCAGCGTCTTCCAAGTGA-3′
TNF-α (89 bp)	5′-AGGAGGGAGAACAGCAACTC-3′	5′-TGTATGAGAGGGACGGAACC-3′
IFN-γ (130 bp)	5′-CAGGCCATCAGCAACAACAT-3′	5′-GCTGGATCTGTGGGTTGTTC-3′

TLR4: Toll-like receptor 4; NF-κB: Nuclear factor-κB; TNF-α: Tumor necrosis factor-α; IL-2: Interleukin-2; IFN-γ: Interferon-γ.

serum after centrifugation at 1000 rpm for 10 min to detect the levels of NF-κB, IL-2, TNF-α and IFN-γ in BSC patients by commercial ELISA kits (Shanghai Baiwo Technology Co. Ltd., Shanghai, China).

Statistical analysis

Statistical analysis was performed with SPSS 22.0 software (IBM, Armonk, NY, United States). All data were normally distributed and they were expressed as mean ± SD. Comparisons among three groups were performed by one-way analysis of variance (ANOVA). Comparisons between two groups (model and sham-operated groups) was carried out by two-way ANOVA, while the follow-up analysis was conducted by the least significant difference test. Pearson's correlation analysis was used to analyze the correlation among different factors. $P < 0.05$ was considered statistically significant.

RESULTS

Induction of BCS by surgical procedure for HV outflow obstruction in rats

To investigate the mechanism for inflammatory response to liver injury derived from HV outflow obstruction in BCS patients, we initially established a rat model of BCS. The induction of BCS was confirmed by DSA. In the control and sham-operated groups, all rats presented no signs of vascular occlusive disease (*e.g.*, stenosis and occlusion) and collateral angiogenesis of IVC (Figure 1A1 and A2). In the model groups, all rats had HV outflow obstruction caused by IVC obstruction, in which ligation of the IVC above the HV opening was found in 35 rats (72.9%, 35/48), with a coronary lumen stenosis rate of > 85%. In the other 13 rats (17.1%, 13/48), the IVC above the HV opening was fully occluded. In each model group, the formation of collateral circulation in the rat model gradually increased and thickened, with the order of effects as follows: 12 wk > 6 wk > 3 wk > 1 wk after BCS induction (Figure 1A3-A6).

Histopathological analysis revealed that there was no formation of ascites in the model group after 1 wk of BCS induction, and degrees of abdominal effusion were elevated in other model groups at 3, 6 and 12 wk after BCS induction. It was noted that there were no significant changes in the liver tissues in the model group at 1 wk, while different degrees of congestion and enlargement were observed in other model groups at 3, 6 and 12 wk. The HE and Masson's trichrome staining methods confirmed that the liver injury and liver fibrosis showed a gradually aggravating trend, with the most significant effects in the model group at 12 wk. Histopathological findings exhibited no significant difference in liver sections of rats in the sham-operated and the control groups (Figure 1B and Supplementary Figure 2).

Hepatic and plasma levels of LPS in rats with BSC

LPS levels in the liver and plasma samples were calculated by using the standard curve of LPS. The LPS levels in the model group at 1, 3, 6 and 12 wk were 1.16 ± 0.08, 1.80 ± 0.10, 1.31 ± 0.09, and 1.23 ± 0.10 ng/mL, respectively, which were significantly higher than those in the sham-operated groups (0.87 ± 0.07, 0.86 ± 0.06, 0.85 ± 0.07 and 0.85 ± 0.09 ng/mL), and the control group (0.86 ± 0.08 ng/mL). However, there were no significant differences in LPS levels between the control and sham-operated groups. There were significant differences between each pair of model groups. The LPS levels

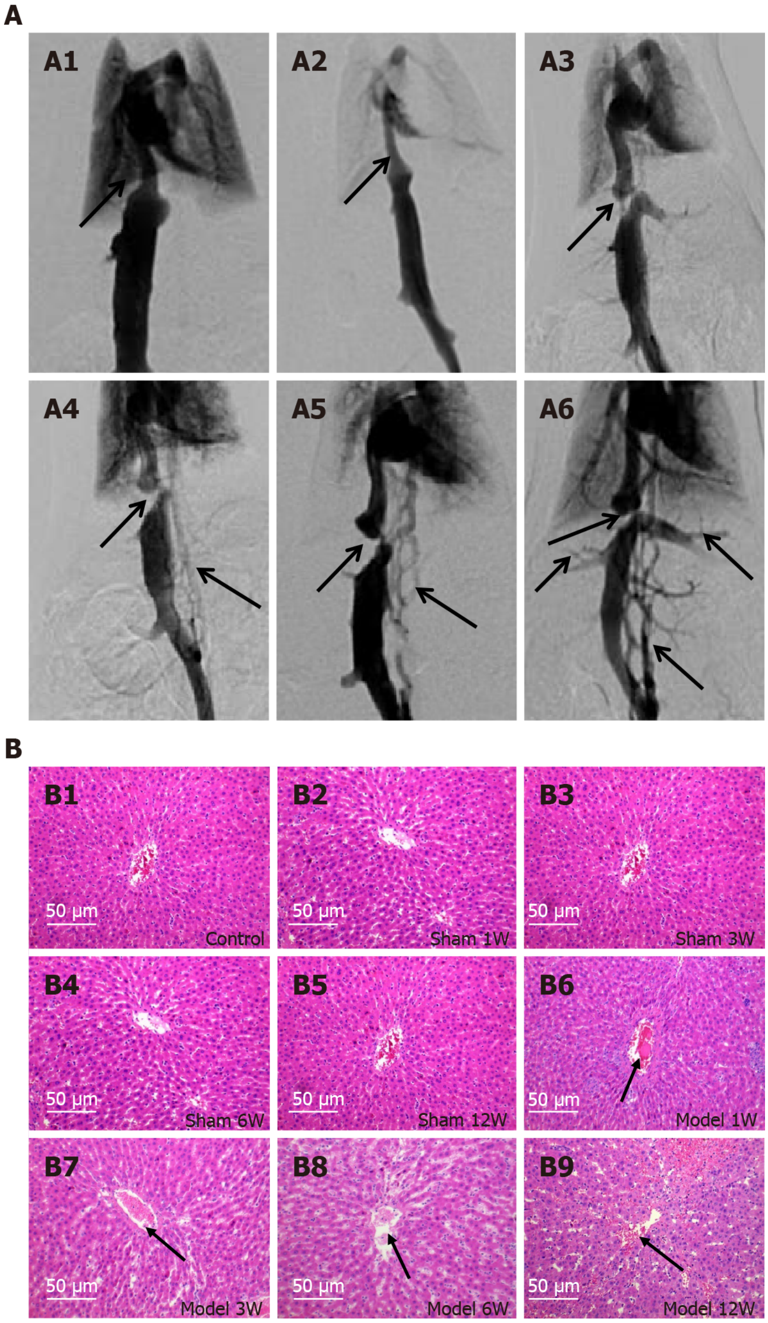
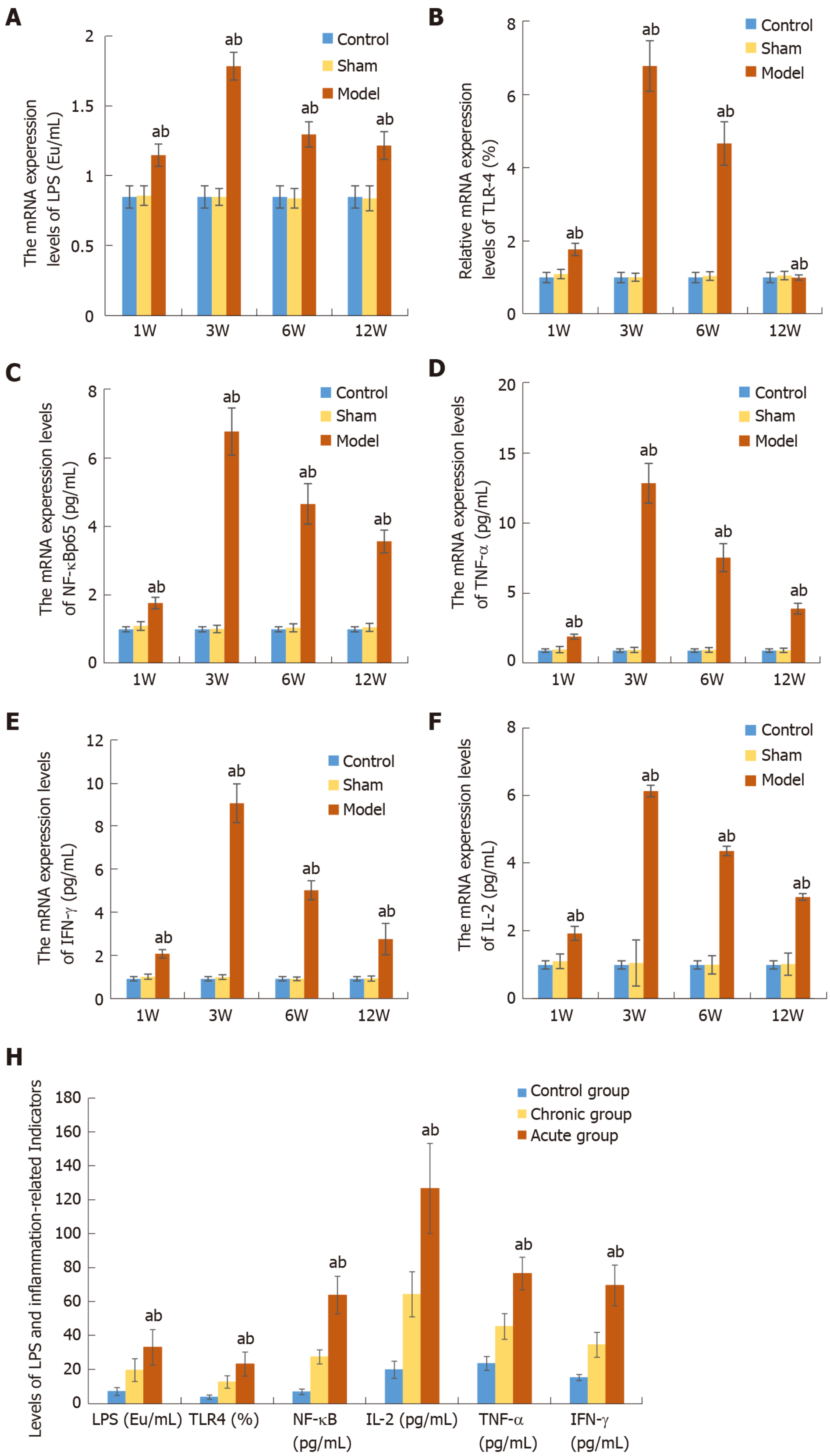


Figure 1 Digital subtraction angiography images and hematoxylin-eosin staining images in the rat model of Budd-Chiari syndrome. A: A1: Control group; A2: The sham operation group. Two groups showed that the inferior vena cava (IVC) blood flow was smooth, but no stenosis or occlusion of the IVC and hepatic vein (HV) (black arrow); A3: In the 1 model group 1W, IVC stenosis above the opening of the HV could be seen, and the contrast agent passed through in a line, without obvious collateral vessel formation (black arrow); A4: In the model group 3W, a small amount of collateral vessel formation around the IVC (black arrow); A5: In the model group 6W, a large number of collateral vessels around the IVC (black arrow); A6: In the model group 12W, the collateral vessels around the IVC were further increased and thickened (black arrow); B: B1: Control group; B2-B5: Four groups of sham operation group, 1W (B2), 3W (B3), 6W (B4) and 12W (B5). Hepatocytes were arranged in a single row radially centered on the central vein, with no change in hepatocytes and hepatic sinusoids (B1–B5); B6: Model group 1W. Hyaline degeneration of rat hepatocytes and no obvious dilation and stagnation of red blood cells in hepatic sinusoids (black arrow); B7: Model group 3W. The hyaline degeneration of rat hepatocytes was aggravated, the hepatocytes around the central vein were necrotic, and the hepatic sinusoids were dilated with a small amount of stasis red blood cells (black arrow); B8: Model group 6W. Large sheet necrosis of liver cells around the central vein, further expansion of liver sinusoids, more stasis of red blood cells in the expanded liver sinusoids (black arrow); B9: Model group 12W. The arrangement of liver cells was disordered, the normal hepatocyte cord disappeared, the hepatic sinusoids were significantly expanded and there was a large number of erythrocytes (black arrow). Original magnification × 200. Bar = 50 μm.

reached the peak in the model group at 3 wk after BCS induction, and then decreased progressively, while it remained higher than that in the control and sham-operated groups until 12 wk, and the difference was significant (Figure 2A).


A
The mRNA experession levels of LPS (Eu/mL)
Control
Sham
Model
ab
1W
3W
6W
12W
B
Relative mRNA experession levels of TLR-4 (%)
C
The mRNA experession levels of NF-κBp65 (pg/mL)
D
The mRNA experession levels of TNF-α (pg/mL)
E
The mRNA experession levels of IFN-γ (pg/mL)
F
The mRNA experession levels of IL-2 (pg/mL)
H
Levels of LPS and inflammation-related Indicators
Control group
Chronic group
Acute group
LPS (Eu/mL)
TLR4 (%)
NF-κB (pg/mL)
IL-2 (pg/mL)
TNF-α (pg/mL)
IFN-γ (pg/mL)

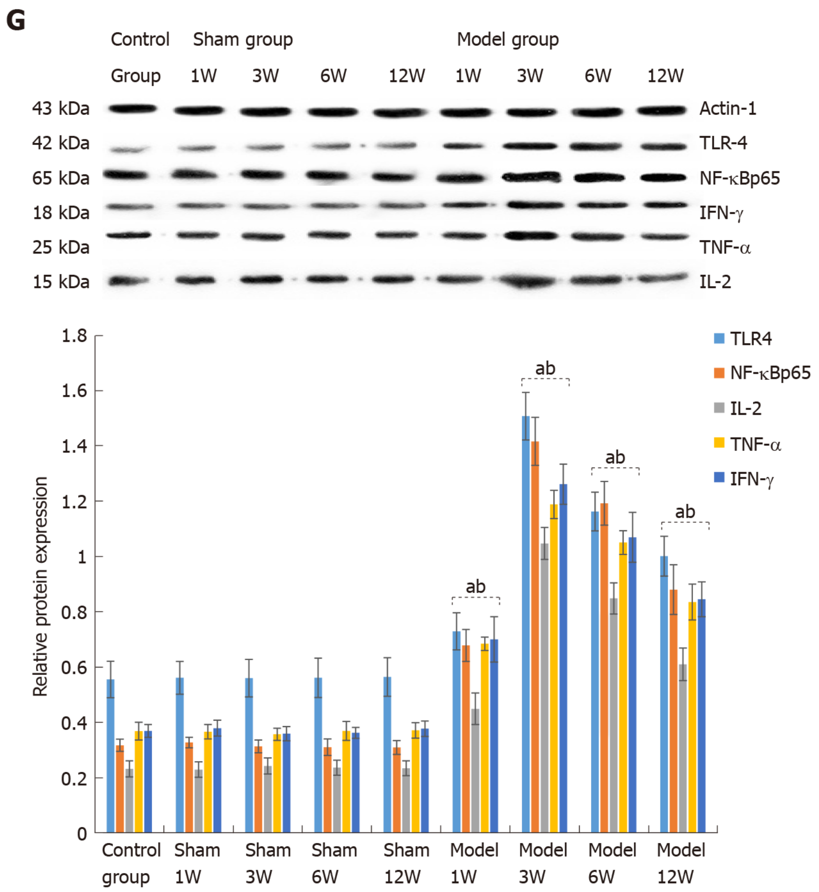


Figure 2 Hepatic mRNA and protein expression levels of lipopolysaccharide and various factors in rats and humans. A: The expression levels of lipopolysaccharide (LPS) in each group; B: TLR4 expression in each group; C: Nuclear factor-kappa B p65 expression in each group; D: Tumor necrosis factor-α expression in each group; E: Interferon-γ expression in each group; F: Interleukin-2 expression in each group; G: Western blot analysis of protein express levels of various factors in the rat liver tissues; H: Levels of LPS and TLR4/NF-κB mediated inflammation-related indicators in the blood samples from human subjects. LPS: Lipopolysaccharide; TLR4: Toll-like receptor 4; NF-κB: Nuclear factor-kappa B; TNF-α: Tumor necrosis factor-α; IL-2: Interleukin-2; IFN-γ: Interferon-γ. $^aP < 0.05$ comparisons between subgroups. $^bP < 0.05$ comparisons between model subgroups.

Expression levels of TLR4, NF-κB and inflammatory cytokines in rats with BSC

In comparison with the control and sham-operated groups, the mRNA levels of TLR4, NF-κB, TNF-α, IL-2 and IFN-γ were markedly higher in the model groups. However, there were no significant differences in the expression levels between the control and sham-operated groups, while the expression levels were significantly different between each of the model groups and control and sham-operated groups. In the model groups, the expression levels of TLR4, NF-κB, TNF-α, IL-2 and IFN-γ were gradually elevated in the early stage, which reached a peak at 3 wk, and decreased in the later stages, while it was significantly higher than that in the control and sham-operated groups at 12 wk (Figure 2B-F and Table 2).

Similarly, the protein levels of TLR4, NF-κB, TNF-α, IL-2 and IFN-γ were significantly greater in the model groups than those in the sham-operated and control groups, and there were significant differences among the three groups. The levels of these proteins were significantly higher than the normal ranges and reached a peak at 3 wk after BCS induction (Figure 2G and Table 3).

Correlation between LPS concentrations and levels of TLR4, NF-κB, TNF-α, IL-2 and IFN-γ in rats with BSC

mRNA levels of TLR4, NF-κB, TNF-α, IL-2 and IFN-γ were positively correlated with the corresponding protein synthesis (r = 0.959, 0.947, 0.956, 0.964 and 0.971; P < 0.001). The LPS and mRNA levels of TLR4, NF-κB, TNF-α, IL-2 and IFN-γ in the model group were highly positively correlated (r > 0.90, P < 0.001) (Tables 4 and 5 and Figure 3).

Expression levels of TLR4, NF-κB and inflammatory cytokines in patients with BSC

The main findings of the animal experiments were tested in human subjects. Similarly, we found that the levels of LPS, TLR4, NF-κB, IL-2, TNF-α and IFN-γ were

Table 2 mRNA expression levels of TLR4/NF-κB-mediated inflammation-related indicators

	TLR4	NF-κBp65	IL-2	TNF-α	IFN-γ
Control group	1.004 ± 0.139	1.003 ± 0.074	1.001 ± 0.121	1.001 ± 0.126	1.005 ± 0.101
Sham-operated group					
1W	1.101 ± 0.127	1.101 ± 0.127	1.108 ± 0.206	1.068 ± 0.222	1.102 ± 0.121
3W	1.013 ± 0.109	1.013 ± 0.109	1.061 ± 0.168	1.042 ± 0.181	1.082 ± 0.111
6W	1.045 ± 0.118	1.045 ± 0.118	1.006 ± 0.141	1.047 ± 0.164	1.004 ± 0.084
12W	1.059 ± 0.115	1.059 ± 0.115	1.025 ± 0.097	1.017 ± 0.157	1.019 ± 0.118
Model group					
1W	1.773 ± 0.165[a,b]	1.773 ± 0.165[a,b]	1.935 ± 0.217[a,b]	1.991 ± 0.181[a,b]	2.170 ± 0.195[a,b]
3W	6.789 ± 0.692[a,b]	6.789 ± 0.692[a,b]	6.144 ± 0.681[a,b]	12.931 ± 1.424[a,b]	9.172 ± 0.902[a,b]
6W	4.671 ± 0.593[a,b]	4.671 ± 0.593[a,b]	4.372 ± 0.268[a,b]	7.629 ± 0.999[a,b]	5.131 ± 0.441[a,b]
12W	1.003 ± 0.074[a,b]	3.575 ± 0.334[a,b]	3.011 ± 0.326[a,b]	3.991 ± 0.391[a,b]	2.855 ± 0.732[a,b]
Statistics	333.288	464.025	426.396	555.318	509.268
P value	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

[a]$P < 0.05$, comparisons between subgroups, the differences are statistically significant.
[b]$P < 0.05$, comparisons between model subgroups, the differences are statistically significant.
TLR4: Toll-like receptor 4; NF-κB: Nuclear factor-κB; TNF-α: Tumor necrosis factor-α; IL-2: Interleukin-2; IFN-γ: Interferon-γ.

Table 3 Relative protein expression levels of TLR4/NF-κB-mediated inflammation-related indicators

	TLR4	NF-κBp65	IL-2	TNF-α	IFN-γ
Control group	0.555 ± 0.066	0.317 ± 0.022	0.232 ± 0.029	0.368 ± 0.032	0.369 ± 0.023
Sham-operated group					
1W	0.561 ± 0.059	0.327 ± 0.019	0.229 ± 0.028	0.366 ± 0.026	0.379 ± 0.029
3W	0.560 ± 0.068	0.313 ± 0.023	0.242 ± 0.029	0.357 ± 0.022	0.359 ± 0.026
6W	0.561 ± 0.071	0.310 ± 0.030	0.236 ± 0.027	0.369 ± 0.034	0.362 ± 0.020
12W	0.564 ± 0.070	0.309 ± 0.025	0.234 ± 0.027	0.371 ± 0.028	0.377 ± 0.028
Model group					
1W	0.729 ± 0.067[a,b]	0.678 ± 0.058[a,b]	0.449 ± 0.057[a,b]	0.684 ± 0.024[a,b]	0.700 ± 0.082[a,b]
3W	1.507 ± 0.086[a,b]	1.416 ± 0.087[a,b]	1.047 ± 0.058[a,b]	1.188± 0.051[a,b]	1.261 ± 0.073[a,b]
6W	1.162 ± 0.070[a,b]	1.192 ± 0.079[a,b]	0.848 ± 0.056[a,b]	1.050 ± 0.043[a,b]	1.069 ± 0.090[a,b]
12W	1.001 ± 0.072[a,b]	0.880 ± 0.090[a,b]	0.610 ± 0.059[a,b]	0.835 ± 0.065[a,b]	0.845 ± 0.063[a,b]
Statistics	291.836	711.802	608.214	897.062	488.525
P value	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

[a]$P < 0.05$, comparisons between subgroups, the differences are statistically significant.
[b]$P < 0.05$, comparisons between model subgroups, the differences are statistically significant.
TLR4: Toll-like receptor 4; NF-κB: Nuclear factor-κB; TNF-α: Tumor necrosis factor-α; IL-2: Interleukin-2; IFN-γ: Interferon-γ.

significantly higher in BCS patients compared with those in healthy controls. Comparably, the protein levels of LPS, TLR4, NF-κB, IL-2, TNF-α and IFN-γ in patients with acute BCS were significantly higher than those in patients with chronic BCS (Figure 2H and Table 6).

Table 4 Correlation between lipopolysaccharide and mRNA levels of various inflammation-related indicators

	LPS	TLR4	NF-κBp65	IFN-γ	TNF-α	IL-2
LPS	1	0.959[a]	0.945[a]	0.939[a]	0.942[a]	0.944[a]
NF-κBp65	0.945[a]	0.930[a]	1	0.941[a]	0.954[a]	0.966[a]
IL-2	0.939[a]	0.952[a]	0.941[a]	1	0.982[a]	0.946[a]
TNF-α	0.942[a]	0.953[a]	0.954[a]	0.982[a]	1	0.954[a]
IFN-γ	0.944[a]	0.932[a]	0.966[a]	0.946[a]	0.954[a]	1

[a]$P < 0.01$.
LPS: Lipopolysaccharide; TLR4: Toll-like receptor 4; NF-κB: Nuclear factor-κB; TNF-α: Tumor necrosis factor-α; IL-2: Interleukin-2; IFN-γ: Interferon-γ.

Table 5 Correlation between lipopolysaccharide and protein expression of inflammation-related indicators

	LPS	TLR4	NF-κBp65	IFN-γ	TNF-α	IL-2
LPS	1	0.954[a]	0.929[a]	0.931[a]	0.930[a]	0.936[a]
TLR4	0.954[a]	1	0.915[a]	0.900[a]	0.930[a]	0.910[a]
NF-κBp65	0.929[a]	0.915[a]	1	0.954[a]	0.949[a]	0.961[a]
IFN-γ	0.931[a]	0.900[a]	0.954[a]	1	0.938[a]	0.957[a]
TNF-α	0.930[a]	0.930[a]	0.949[a]	0.938[a]	1	0.954[a]
IL-2	0.936[a]	0.910[a]	0.961[a]	0.957[a]	0.954[a]	1

[a]$P < 0.01$.
LPS: Lipopolysaccharide; TLR4: Toll-like receptor 4; NF-κB: Nuclear factor-κB; TNF-α: Tumor necrosis factor-α; IL-2: Interleukin-2; IFN-γ: Interferon-γ.

Table 6 Levels of lipopolysaccharide and TLR4/NF-κB-mediated inflammation-related indicators in the blood samples from human subjects

	LPS (Eu/mL)	TLR4 (%)	NF-κB (pg/mL)	IL-2 (pg/mL)	TNF-α (pg/mL)	IFN-γ (pg/mL)
Control group	8.42 ± 2.33	5.05 ± 1.29	8.15 ± 1.65	21.19 ± 5.01	24.88 ± 4.07	16.60 ± 1.80
Chronic group	20.96 ± 6.70	14.00 ± 3.67	28.75 ± 4.17	65.62 ± 13.26	46.68 ± 7.55	35.87 ± 7.36
Acute group	34.44 ± 10.45[a,b]	24.55 ± 7.0[a,b]	65.17 ± 11.09[a,b]	127.90 ± 26.57[a,b]	77.88 ± 9.61[a,b]	70.90 ± 11.95[a,b]
F	95.541	132.171	524.000	285.085	384.673	340.340

[a]$P < 0.05$, Acute group *vs* Chronic group, the differences are statistically significant.
[b]$P < 0.05$, Acute group *vs* Control group, the differences are statistically significant.
LPS: Lipopolysaccharide; TLR4: Toll-like receptor 4; NF-κB: Nuclear factor-κB; TNF-α: Tumor necrosis factor-α; IL-2: Interleukin-2; IFN-γ: Interferon-γ.

DISCUSSION

The following novel outcomes can be drawn from the results of the present study: (1) LPS levels were significantly elevated in rats with BCS in and human subjects; (2) The TLR4/NF-κB signaling pathway was activated by LPS as demonstrated by a positive correlation between LPS concentrations and expression levels of TLR4 and NF-κB in rats with BSC and human subjects; and (3) Expression of key inflammatory cytokines, including IL-2, TNF-α and IFN-γ, was positively correlated with LPS concentrations. These findings suggest that the LPS-activated TLR4/NF-κB signaling pathway may play a role, at least in part, in the inflammatory response to BCS-induced liver damage.

A large number of previous studies have confirmed that the inflammatory response mediated by NF-κB is involved in the regulation of liver injury caused by hepatitis viruses, alcohol and poisoning[19-24]. NF-κB has also been shown to play a vital role in regulating the inflammation and liver damage, as well as directly regulating the liver fibrosis[25]. In line with findings of previous studies, the results of the present

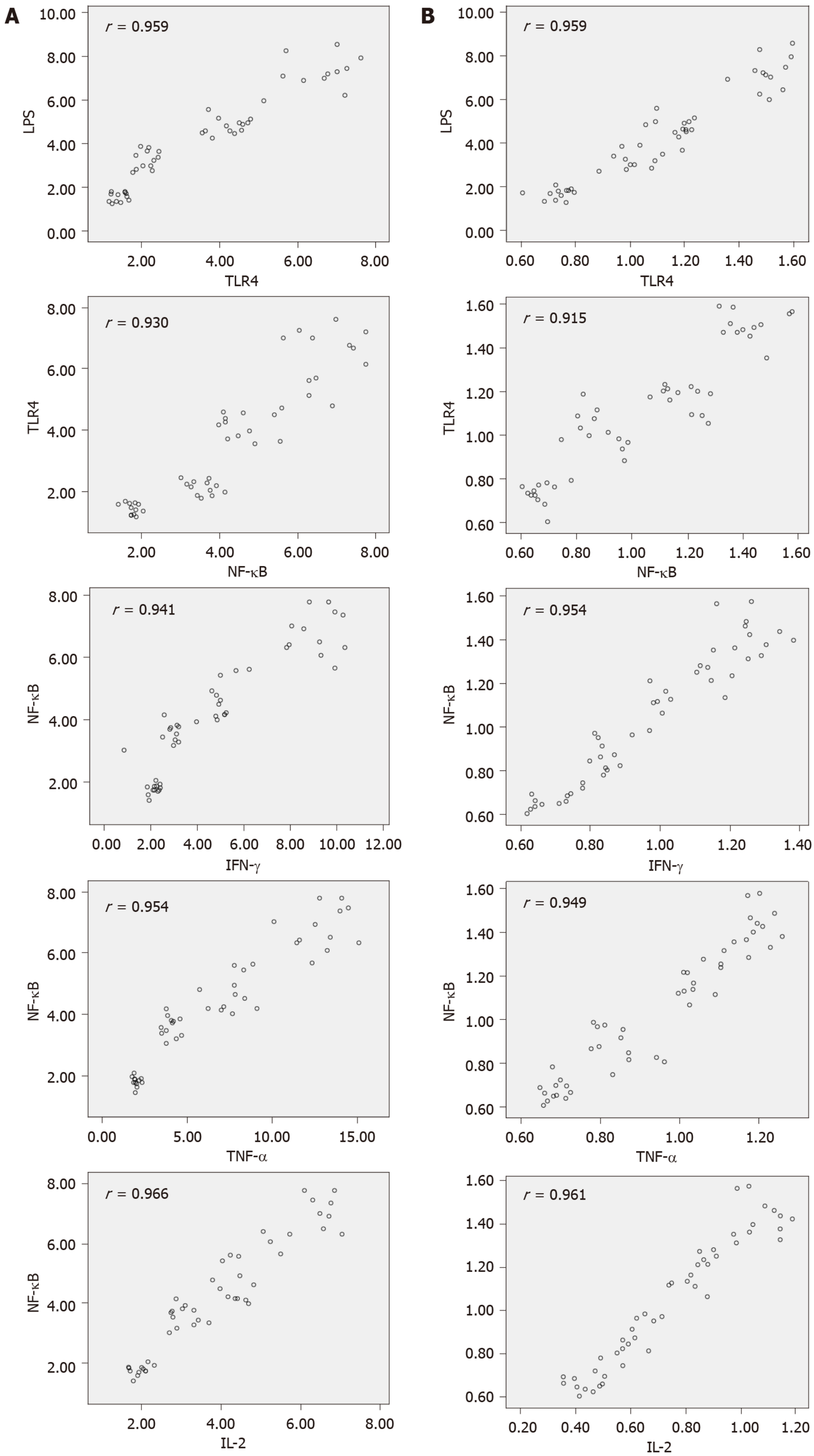


Figure 3 Scatter diagram of lipopolysaccharide and nuclear factor-κB-mediated inflammation-related factors. A: mRNA level; B: Protein level.

LPS: Lipopolysaccharide; TLR4: Toll-like receptor 4; NF-κB: Nuclear factor-κB; TNF-α: Tumor necrosis factor-α; IL-2: Interleukin-2; IFN-γ: Interferon-γ.

study showed that NF-κB mediated inflammation and participated in the BCS-induced liver damage. In an animal model of viral hepatitis and cholestatic liver injury, the level of LPS in the intestine was changed (increased or decreased), and NF-κB was activated through the TLR4 signal transduction pathway to regulate the increase of downstream target gene expression, thereby mediating hepatitis damage or causing delay in the process of liver fibrosis[26,27]. In the current study, expression of LPS, TLR4, NF-κB, TNF-α, IL-2 and IFN-γ in three groups of patients' blood samples and in liver tissues of rats with BCS were significantly higher than those in other groups. The differences in the expression of corresponding indicators between the two groups were significant. In addition, expression levels of hepatic LPS, TLR4, NF-κB, TNF-α, IL-2 and IFN-γ were highly positively correlated at each stage in the BCS animal model (correlation coefficient $r > 0.90$). The results confirmed that the inflammatory response mediated by NF-κB is also involved in the regulation of BCS-induced liver damage. There is a possibility that the increase in NF-κB-mediated inflammation indicators in the liver of BCS rats is associated with IVC obstruction. Under the condition of blocked HV outflow, liver congestion and hypoxia may directly induce NF-κB-mediated inflammation, resulting in liver inflammatory damage. In addition, the obstruction of HV outflow leads to portal hypertension, thereby increasing LPS levels. The accumulated LPS entered the portal venous system, bound to the TLR4 receptor in the liver, activated the TLR4/NF-κB signaling pathway, and induced inflammatory response to BCS-induced liver injury.

The results of this study showed that in the liver tissue of rats with BCS, NF-κB and other inflammatory-related indicators showed an increasing trend in the early stage, reaching a peak at 3 wk, and decreased at a later stage, while it remained significantly higher than other two groups at 12 wk, which showed that the inflammatory reaction mediated by NF-κB not only penetrated the entire course of BCS-associated liver damage, but also caused a different degree of reaction at different periods. The results of DSA also confirmed that the collateral vessels of BCS rats in the 6- and 12-wk groups were significantly more than those in the 1- and 3-wk groups. This finding is also consistent with the indicators of liver damage such as liver transaminase and ascites in patients with acute BCS that are higher than those of chronic BCS patients [7]. However, the liver inflammation-related indicators of BCS rats were still higher than those in the control group at 12 wk, indicating that the autologous collateral formation only relieved the intrahepatic portal hypertension and liver damage to a certain extent, but could not completely resolve the liver congestion and hypoxia, such as the liver inflammatory damage persisted in the HV and IVC, without recanalization by percutaneous transluminal angioplasty.

Our study had some limitations: First, the survival time of experimental rats was limited; therefore, we failed to gain further understanding of the mechanism of liver cirrhosis. Second, the sample size in the rat model groups was small. Percutaneous transluminal angioplasty and intrahepatic portosystemic shunts were not performed, and the NF-κB-mediated inflammatory injury changes in the liver of rats with BCS could not be further studied.

CONCLUSION

This study demonstrated that LPS level becomes markedly elevated in BCS and in turn activates the TLR4/NF-κB signaling pathway. Furthermore, the LPS-activated TLR4/NF-κB signaling pathway may mediate inflammatory response to BCS-induced liver injury. Notably, in the early stage of BCS-induced liver injury, NF-κB-mediated inflammatory response was progressively aggravated, while in the later stage, the inflammatory response was decreased, although it remained abnormally high. These results may assist researchers to better understand the mechanism underlying the BCS-induced hepatic injury. Our novel findings indicated that the LPS-activated TLR4/NF-κB signaling pathway could be a potential target for the development of new treatments for BCS.

ARTICLE HIGHLIGHTS

Research background

Budd-Chiari syndrome (BCS) is an uncommon but potentially life-threatening clinical syndrome of portal and/or inferior vena cava hypertension caused by obstruction of the hepatic and/or inferior vena cava. Liver injury in BCS is considered to be a specific form of liver injury with a mechanism different from that caused by common factors (*e.g.*, viruses, poisoning, alcohol or biliary stasis). Until now, the exact mechanism underlying BCS-induced liver injury is not yet known. It has been shown that lipopolysaccharide (LPS) inactivation is diminished in all causes of liver injury, leading to intrahepatic LPS accumulation, as is the case in acute hepatic injury. LPS accumulation can bind to TLR4 in intrahepatic tissue cells to activate the TLR4/NF-κB pathway and thereby regulate NF-κB-dependent acute and chronic inflammatory liver injury. To date, it remains to be elucidated whether LPS and the TLR4/NF-κB signaling pathway could play a role in the inflammatory response to liver injury in BCS.

Research motivation

We anticipated that investigating the mechanism with involvement of NF-κB may advance our understanding of the pathogenesis of liver injury in BCS, and help to develop new therapeutic strategies for treatment of patients with BCS.

Research objectives

We performed this study, aiming to investigate the potential role of NF-κB-mediated inflammation in BCS-induced liver injury in humans and rats.

Research methods

In this study, 180 rats were randomly assigned into nine groups: four BCS model groups (1, 3, 6 and 12 wk), four sham-operated groups (1, 3, 6 and 12 wk), and one control group. LPS levels in each group were detected by the Tachypleus amebocyte lysate test. The mRNA and protein levels of TLR4, NF-κB, tumor necrosis factor (TNF)-α, interleukin (IL)-2 and interferon (IFN)-γ were quantified. In addition, 60 patients with BCS and 30 healthy controls were enrolled, and their blood samples were analyzed.

Research results

Hepatic and plasma LPS levels were significantly increased in rats. The mRNA and protein expression levels of TLR4, NF-κB and inflammatory cytokines (TNF-α, IL-2 and IFN-γ) in liver tissues were significantly higher in the BCS model groups compared with those in the other two groups. In addition, the model groups (1, 3, 6 and 12 wk after BCS induction) showed significant differences in the levels of LPS, TLR4, NF-κB, TNF-α, IL-2 and IFN-γ. Notably, there was a significant correlation between the LPS concentrations and mRNA and protein levels of TLR4, NF-κB and inflammatory cytokines. Importantly, it was revealed that the levels of LPS, TLR4, NF-κB and inflammatory cytokines were significantly greater in chronic BCS patients than healthy controls and acute BCS patients.

Research conclusions

This study has demonstrated that LPS level is markedly elevated in BCS, in turn activating the TLR4/NF-κB signaling pathway, leading to induction of inflammatory cytokines (TNF-α, IL-2 and IFN-γ) in response to BCS-induced liver injury.

Research perspectives

The findings of the present study implicated that the TLR4/NF-κB signaling pathway could serve as a potential target in the developing of new therapeutic strategies for BCS-induced liver injury, which may ultimately improve the care for patients with BCS.

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ORIGINAL ARTICLE

Observational Study

Long-term survival of patients with stage II and III gastric cancer who underwent gastrectomy with inadequate nodal assessment

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Author contributions: Desiderio J, Sagnotta A and Terrenato I designed the study, conducted the research, collected the data, analyzed the results and drafted the manuscript; Terrenato I performed the statistics; Parisi A, D'Andrea V, Bracarda S, Woo Y and Fong Y supervised the study, and revised the manuscript; Trastulli S, Garofoli E, Mosillo C, Tozzi F confirmed the statistics, interpreted the data, and revised the manuscript; All authors read and approved the final manuscript.

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Abstract

BACKGROUND

Gastric cancer is an aggressive disease with frequent lymph node (LN) involvement. The NCCN recommends a D2 lymphadenectomy and the harvesting of at least 16 LNs. This threshold has been the subject of great debate, not only for the extent of surgery but also for more appropriate staging. The reclassification of stage IIB through IIIC based on N3b nodal staging in the eighth edition of the American Joint Committee on Cancer (AJCC) staging system highlights the efforts to more accurately discriminate survival expectancy based on nodal number. Furthermore, studies have suggested that pathologic assessment of 30 or more LNs improve prognostic accuracy and is required for proper staging of gastric

applicable.

Informed consent statement: This is a study using a population-based registry, so informed consent was not applicable.

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cancer.

AIM

To evaluate the long-term survival of advanced gastric cancer patients who deviated from expected survival curves because of inadequate nodal evaluation.

METHODS

Eligible patients were identified from the Surveillance, Epidemiology, and End Results database. Those with stage II–III gastric cancer were considered for inclusion. Three groups were compared based on the number of analyzed LNs. They were inadequate LN assessment (ILA, < 16 LNs), adequate LN assessment (ALA, 16-29 LNs), and optimal LN assessment (OLA, ≥ 30 LNs). The main outcomes were overall survival (OS) and cancer-specific survival. Data were analyzed by the Kaplan-Meier product-limit method, log-rank test, hazard risk, and Cox proportional univariate and multivariate models. Propensity score matching (PSM) was used to compare the ALA and OLA groups.

RESULTS

The analysis included 11607 patients. Most had advanced T stages (T3 = 48%; T4 = 42%). The pathological AJCC stage distribution was IIA = 22%, IIB = 18%, IIIA = 26%, IIIB = 22%, and IIIC = 12%. The overall sample divided by the study objective included ILA (50%), ALA (35%), and OLA (15%). Median OS was 24 mo for the ILA group, 29 mo for the ALA group, and 34 mo for the OLA group (P < 0.001). Univariate analysis showed that the ALA and OLA groups had better OS than the ILA group [ALA hazard ratio (HR) = 0.84, 95% confidence interval (CI): 0.79–0.88, P < 0.001 and OLA HR = 0.73, 95%CI: 0.68–0.79, P < 0.001]. The OS outcome was confirmed by multivariate analysis (ALA HR = 0.68, 95%CI: 0.64–0.71, P < 0.001 and OLA: HR = 0.48, 95%CI: 0.44–0.52, P < 0.001). A 1:1 PSM analysis in 3428 patients found that the OLA group had better survival than the ALA group (OS: OLA median = 34 mo *vs* ALA median = 26 mo, P < 0.001, which was confirmed by univariate analysis (HR = 0.81, 95%CI: 0.75–0.89, P < 0.001) and multivariate analysis: (HR = 0.71, 95%CI: 0.65–0.78, P < 0.001).

CONCLUSION

Proper nodal staging is a critical issue in gastric cancer. Assessment of an inadequate number of LNs places patients at high risk of adverse long-term survival outcomes.

Key Words: Gastric Cancer; Lymphadenectomy; Gastrectomy; Staging; N stage; Surveillance, Epidemiology, and End Results

Core Tip: A large database was analyzed to investigate survival outcomes related to lymph node assessment in locally advanced gastric cancer patients with radical gastrectomy. Independent of TNM-stage, the group with assessment of < 16 lymph nodes (LNs) had significantly worse survival than two other groups, 16-29 LNs and ≥ 30 LNs. Stage migration because of inadequate specimen analysis and improper lymphadenectomy was the main root cause.

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INTRODUCTION

Lymph node (LN) involvement in gastric cancer is one of the most significant prognostic factors for survival. Starting with the fifth edition of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) cancer staging manual, the N category has been evaluated based on the total number of metastatic LNs detected in a surgical specimen, independent of their retrieved locations[1]. Until recently, the N3 category required the identification of at least 15 positive LNs. However, the seventh edition revisions of nodal classification introduced the N3a (7–15 positive LNs) and N3b (≥ 16 positive LNs) substages[2], with the updates having a significant impact on the eighth edition updates to stages IIB through IIIA-C[3]. Consequently, the current guidelines recommend the analysis of at least 16 LNs[4].

Despite the national guidelines, many studies particularly those from Western countries continue to show high rates of inadequate nodal assessment[5-7]. To mitigate the effects of stage migration and survival inaccuracies in patients with locally advanced gastric cancer, use of the ratio of positive to total LN has been proposed[8]. However, the utility of existing prognostic methods remains limited in patients with an insufficient total number of assessed LNs. This study aimed to evaluate the survival impact of inadequate LN assessment (ILA) in patients with advanced gastric cancer disease (stages II and III) compared with that of patients receiving adequate and optimal nodal evaluation (≥ 30 LNs), as defined in the latest AJCC cancer staging manual[9].

MATERIALS AND METHODS

Patient source and definitions

Eligible patients were identified in the Surveillance, Epidemiology, and End Results (SEER) database[10] and detailed data were retrieved with SEER*Stat 8.3.5 software (https://seer.cancer.gov/seerstat/). Patients 18 years of age or older with a diagnosis of stage II–III gastric cancer, according to the eighth edition of the AJCC cancer staging manual[9], were included in the study. Patients with cardiac tumors, without resective surgery, without available LN assessment information, and patients without follow-up duration data were excluded from the study. Tumor location was identified using the “primary site labeled” variable (C16.1: fundus of stomach; C16.2: body of stomach; C16.3: gastric antrum; C16.4: pylorus; C16.5: lesser curvature of stomach, NOS; C16.6: greater curvature of stomach, NOS; C16.8: overlapping lesion of stomach; and C16.9: stomach, NOS). Histology was evaluated by the International Classification of Disease for Oncology (ICD-O-3; M-8010/3-M-8015/3, M-8020/3-M-8022/3, M-8030/3-M-8035/3, M-8041/3, M-8043/3, M-8050/3-M-8052/3, M-8070/3-M-8078/3, M-8140/3-M-8145/3, M-8147/3, M-8210/3-M-8211/3, M-8214/3, M-8220/3, M-8221/3, M-8230/3, M-8231/3, M-8255/3, M-8260/3-M-8263/3, M-8310/3, M-8323/3, M-8480/3, M-8481/3, M-8490/3, M-8510/3, M-8560/3, M-8562/3, M-8570/3-M-8576/3, and M-8980/3-M-8982/3).

Decoding of treatment

The study population was divided into three groups based on the number of retrieved and analyzed LNs, which were inadequate LN assessment (ILA), < 16 LNs, adequate LN assessment (ALA), 16-29 LNs, and optimal LN assessment (OLA), ≥ 30 LNs. The type of gastrectomy was identified using cancer-specific codes (40–42, 50, 52, and 62 indicated total or near-total gastrectomy and 30–33, 51, 60, 61, and 63 indicated partial gastrectomy). “CHT recode” and “radiation recode” were used to determine whether single or combined treatments were administered. The “CS Tumor Size/Ext Eval (2004 +)” and “CS Reg Node Eval (2004 +)” codes were used to identify patients who received neoadjuvant treatment.

Statistical analysis

Patient characteristics were summarized by descriptive statistics. The study groups were compared using Pearson’s chi square test or Student’s *t*-test, as appropriate. Overall survival (OS) was defined as the duration from the date of diagnosis to death or last follow-up, with no restriction on the cause of death. Cancer-specific survival (CSS) was defined as the duration from the date of diagnosis to death from gastric cancer other than other causes. Patients with a follow-up of less than 1 mo and patients without data on their alive or dead status were excluded from the survival analysis.

OS and CSS were calculated using the Kaplan-Meier product-limit method.

The log-rank test was used to assess potential differences between subgroups. The hazard ratio (HR) and its relative 95% confidence interval (CI) were estimated for each parameter of interest using the Cox proportional univariate model while adopting the most suitable prognostic category as the referent group. In addition, a multivariate Cox proportional hazard model was developed by stepwise regression (forward selection). The enter and remove limits were $P = 0.05$ and $P = 0.10$, respectively. Significance was defined at the $P < 0.05$ level.

To control for potential confounders that could affect the outcomes of interest, propensity score matching (PSM)[11,12] was employed to generate two treatment groups with a balanced distribution of baseline features. Propensity scores were obtained from logistic regression, and the dependent variable was the choice to undergo surgery. The retrieval of 16–29 LNs was the control. The selected covariates were diagnosis period, age at diagnosis, sex, race, primary site, eighth edition N, and T stage, histology, and grading. To ensure good matches, patients were matched 1:1 using the nearest neighbor method and a caliper distance of 0.25 of the standard deviation of the logit of the estimated propensity score. Balance between the two groups was assessed using the relative multivariate imbalance measure, L1, as proposed by Iacus *et al*[13,14]. All analyses were carried out with SPSS v. 21.0. The statistical methods were reviewed by one of the authors of this manuscript (Terrenato I).

RESULTS

Baseline patient characteristics of the total sample population

Based on the inclusion criteria, we studied 11,607 patients with stage II–III gastric carcinoma diagnosed between 2004 and 2015 (Table 1). There were 6697 men (58%) in the sample population, and the mean age at diagnosis was 69 years of age. In 4626 patients (40%), the tumor was located at the antrum/pylorus, and a poorly/undifferentiated adenocarcinoma was reported in 8524 patients (73%). Neoadjuvant chemotherapy was administered in 11% of cases, and a partial gastrectomy was performed in 72%. Most patients had advanced T stages (T3 = 5,569, 48%; T4a = 3,551, 31%; T4b = 1,254, 11%), while T1–T2 stages accounted for only 10% of the total sample. The patient distribution based on the N stages reported in the SEER registry was N0 = 2,863, 25%; N1 = 2,422, 21%; N2 = 2,757, 24%; N3a = 2,498, 21%; and N3b = 1,067, 9%. The patient distribution based on gastric cancer stage was IIA = 2,585, 22%; IIB = 2,129, 18%; IIIA = 3,049, 26%; IIIB = 2,511, 22%; and IIIC = 1,333, 12%.

Treatment groups

Based on the overall number of retrieved LNs, patients were divided into three groups, ILA (< 16 LNs = 5806, 50%), ALA (16–29 LNs = 4085, 35%), and OLA, 30 + LNs = 1716, 15%). Clinicopathologic characteristics are reported in Table 2. In the last study period, a distribution trend for the total sample population was identified and determined to be in favor of the OLA group (30% *vs* 19% in the ILA and ALA groups, respectively). The median age was higher in the ILA group (71 years) than in the other two groups, 68 years in the ALA group and 65 years in the OLA group. No differences were found in the T1, T2, and T4b stage rates, and only slight differences were found in the T3 (50% *vs* 47% *vs* 46%) and T4a (29% *vs* 32% *vs* 33%) stage rates ($P < 0.001$).

As expected, significant differences were identified for the N stage variable. In particular, most patients in the ILA group were classified in the N0 and N1 stages (31% and 26%, respectively). However, that was not the case in the ALA (19% and 16%, respectively) and OLA (15% and 13%, respectively) groups. Regarding staging, no patients in the ILA group were staged as N3b, and 16% were staged as N3a. The findings affected the attribution of the condensed stage. Most patients in the ILA group were in stage II or IIIA, while only 18% and 3% were in stages IIIB and IIIC, respectively. In contrast, 27% and 16% of the patients in the ALA group were in these stages, respectively, and 21% and 31% of the patients in the OLA group were in these stages, respectively ($P < 0.001$). Differences were also seen in the treatments administered; most patients in the ILA group received a partial gastrectomy, and few received neoadjuvant therapy (7%).

Survival outcomes in the total sample population

Figure 1 shows the survival curves of the overall sample. The median OS was 27 mo (95%CI: 26.1–27.9), and the median CSS was 33 mo (95%CI: 31.5–34.5). OS in each

Table 1 Sample characteristics, *n* (%)

Characteristic	*n* (%)
Year of diagnosis	
2004-2006	3142 (27)
2007-2009	3028 (26)
2010-2012	2850 (25)
2013-2015	2587 (22)
Age at diagnosis (yr)	
Median (range)	69 (12-99)
Sex	
Male	6697 (58)
Female	4910 (42)
Race	
White	7045 (61)
Black	2076 (18)
Asian/Pacific	2486 (21)
Marital status	
Single/divorced	2539 (22)
Married	6805 (58)
Widowed	1837 (16)
NA	426 (4)
Insurance status	
Insured	8033 (69)
Uninsured	432 (4)
NA	3142 (27)
Site of tumor	
Fundus/body	1866 (16)
Antrum/pylorus	4626 (40)
Overlapping lesion	1299 (11)
Stomach, NOS	3816 (33)
Tumor size (cm)	
≤ 5	5431 (47)
5.1-10	4203 (36)
≥ 10.1	1135 (10)
NA	838 (7)
Histology	
ADC, NOS	4481 (39)
Signet ring cell carcinoma	2726 (23)
ADC, instestinal type	1943 (17)
Carcinoma, diffuse type	958 (8)
ADC with mixed subtypes	424 (4)
Other	1075 (9)
Grade	

Well/moderately differentiated	2674 (23)
Poorly/undifferentiated	8524 (73)
NA	409 (4)
T stage, 8th ed.	
T1	290 (2)
T2	943 (8)
T3	5569 (48)
T4a	3551 (31)
T4b	1254 (11)
N stage, 8th ed.	
N0	2863 (25)
N1	2422 (21)
N2	2757 (24)
N3a	2498 (21)
N3b	1067 (9)
Stage, 8th ed.	
IIA	2585 (22)
IIB	2129 (18)
IIIA	3049 (26)
IIIB	2511 (22)
IIIC	1333 (12)
Chemotherapy	
Yes	6473 (56)
No	5134 (44)
Neoadjuvant chemotherapy	
Yes	1255 (11)
No	10352 (89)
Radiotherapy	
Yes	4285 (37)
No	7322 (63)
Type of surgery	
Partial gastrectomy	8320 (72)
Total gastrectomy	3287 (28)
Number of retrieved lymphnodes	
< 16 LNs (ILA)	5806 (50)
16-29 LNs (ALA)	4085 (35)
≥ 30 LNs (OLA)	1716 (15)

ADC: Adenocarcinoma; ALA: Adequate lymph node assessment; ILA: Inadequate lymph node assessment; LN: Lymph node; NA: Not available, NOS: Not otherwise specified; OLA: Optimal lymph node assessment.

disease stage (Figure 1) was stage IIA = 69 mo (95%CI: 63.1–74.9), stage IIB = 42 mo (95%CI: 38.6–45.4), stage IIIA = 24 mo (95%CI: 22.5–25.5), stage IIIB = 17 mo (95%CI: 16.1–17.9), and stage IIIC = 13 mo (95%CI: 12.2–13.8). OS in each N stage was N0 = 51 mo (95%CI: 46.2–55.8), N1 = 36 mo (95%CI: 33.0–39.0), N2 = 27 mo (95%CI: 25.2–28.8), N3a = 17 mo (95%CI: 16.0–18.0), and N3b = 14 mo (95%CI: 13.1–14.9).

Table 2 Sample characteristics by the number of retrieved lymph nodes, *n* (%)

Characteristic	ILA *n* = 5806	ALA *n* = 4085	OLA *n* = 1716	*P* value
Year of diagnosis				< 0.001
2004-2006	1861 (32)	947 (23)	334 (20)	
2007-2009	1563 (27)	1071 (26)	394 (23)	
2010-2012	1299 (22)	1080 (27)	471 (27)	
2013-2015	1083 (19)	987 (19)	517 (30)	
Age at diagnosis (yr)				< 0.001
Median (range)	71 (12-99)	68 (14-98)	65 (18-93)	
Sex				0.218
Male	3365 (58)	2318 857)	1014 (59)	
Female	2441 (42)	1767 (43)	702 (41)	
Race				< 0.001
White	3695 (64)	2377 (58)	973 (57)	
Black	1061 (18)	747 (18)	268 (15)	
Asian/Pacific	1050 (18)	961 (24)	475 (28)	
Marital status				< 0.001
Single/divorced	1261 (22)	900 (22)	378 (22)	
Married	3282 (57)	2439 (60)	1084 (63)	
Widowed	1059 (18)	595 (15)	183 (11)	
NA	204 (3)	151 (4)	71 (4)	
Insurance status				< 0.001
Insured	3721 (64)	2998 (73)	68 (4)	
Uninsured	224 (4)	140 (4)	1314 (77)	
NA	1861 (32)	924 (23)	334 (20)	
Primary site				< 0.001
Fundus/body	835 (14)	696 (17)	335 (19)	
Antrum/pylorus	2562 (44)	1511 (37)	553 (32)	
Overlapping lesion	549 (10)	515 (13)	235 (14)	
Stomach, NOS	1860 (32)	1363 (33)	593 (35)	
Tumor size (cm)				< 0.001
≤ 5	2977 (51)	1808 (44)	646 (38)	
5.1-10	1906 (33)	1573 (39)	724 (42)	
≥ 10.1	438 (8)	448 (11)	249 (15)	
NA	485 (8)	256 (6)	97 (6)	
Hystology				< 0.001
ADC, NOS	2426 (42)	1517 (37)	538 (31)	
Signet ring cell carcinoma	1248 (22)	997 (24)	481 (28)	
ADC, instestinal type	928 (16)	702 (17)	313 (18)	
Carcinoma, diffuse type	422 (7)	360 (9)	176 (10)	
ADC with mixed subtypes	170 (3)	166 (4)	88 (5)	
Other	612 (10)	343 (9)	120 (7)	

Grade				< 0.001
Well/moderately differentiated	1493 (26)	862 (21)	319 (19)	
Poorly/undifferentiated	4072 (70)	3106 (76)	1346 (78)	
NA	241 (4)	117 (3)	51 (3)	
T stage, 8th ed.				< 0.001
T1	111 (2)	131 (3)	48 (3)	
T2	490 (8)	321 (8)	132 (8)	
T3	2877 (50)	1897 (47)	795 (46)	
T4a	1658 (29)	1321 (32)	572 (33)	
T4b	670 (11)	415 (10)	169 (10)	
N stage, 8th ed.				< 0.001
N0	1810 (31)	794 (19)	259 (15)	
N1	1528 (26)	671 (16)	223 (13)	
N2	1517 (26)	900 (22)	340 (20)	
N3a	951 (16)	1167 (29)	380 (22)	
N3b	0	553 (14)	514 (30)	
Stage, 8th ed.				< 0.001
IIA	1557 (27)	775 (19)	253 (15)	
IIB	1293 (22)	621 (15)	215 (13)	
IIIA	1754 (30)	942 (23)	353 (20)	
IIIB	1055 (18)	1091 (27)	365 (21)	
IIIC	147 (3)	656 (16)	530 (31)	
Chemotherapy				< 0.001
Yes	2814 (48)	2490 (61)	1169 (68)	
No	2992 (52)	1595 (39)	547 (32)	
Neoadjuvant chemotherapy				< 0.001
Yes	408 (7)	536 (13)	311 (18)	
No	5398 (93)	3549 (87)	1405 (82)	
Radiotherapy				< 0.001
Yes	1993 (34)	1630 (40)	662 (39)	
No	3813 (66)	2455 (60)	1054 (61)	
Type of surgery				< 0.001
Partial gastrectomy	4623 (80)	2742 (67)	955 (56)	
Total gastrectomy	1183 (20)	1343 (33)	761 (44)	

ADC: Adenocarcinoma; NA: Not available; NOS: Not otherwise specified.

Survival by group

As shown in Figure 2, the ILA group had the worst median OS (24, 95%CI: 22.9–25.1 mo) and median CSS (30, 95%CI: 28.4–31.6 mo) compared with the ALA group (median OS = 29, 95%CI: 27.2–30.8 mo and median CSS = 36, 95%CI: 32.9–39.1 mo, P < 0.001) and the OLA group (median OS = 34, 95%CI: 30.0–38.0 mo and median CSS = 42, 95%CI: 35.9–48.1 mo, P < 0.001). Of note, when comparing the ALA and OLA groups, the difference was significant for OS (P < 0.001) but not for CSS (P < 0.078). Figures 3-5 show OS and CSS by the stage of disease and are arranged by study group. The actual survival curves for ILA group within stage IIA revealed significantly worse outcomes for ILA and ALA compared with OLA. The three substages of stage III in the

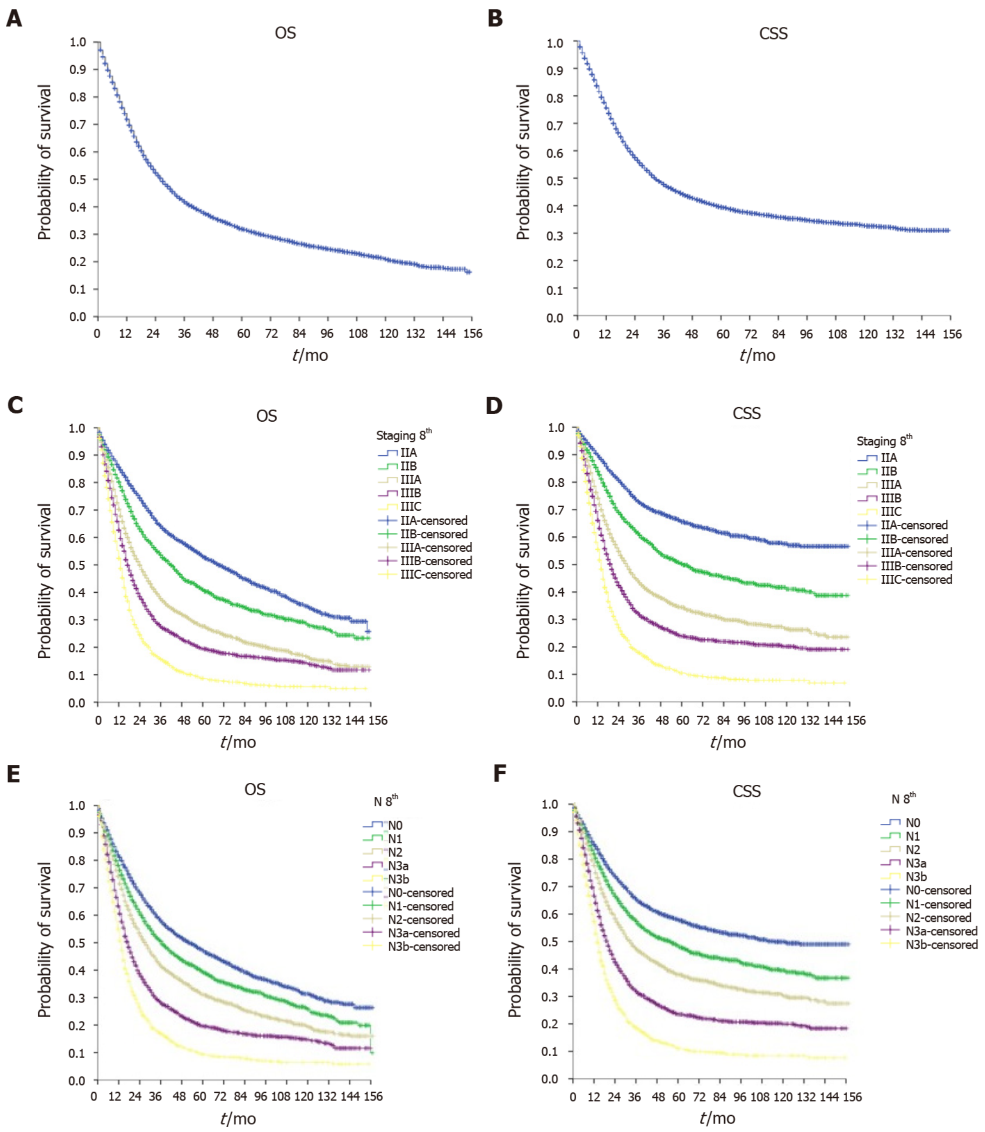

Figure 1 Survival analysis of the entire sample. A and B: Kaplan-Meier curves of overall survival (OS) (A) and cancer-specific survival (CSS) (B); C and D: Kaplan-Meier curves of OS (C) and CSS (D) of different stages; E and F: Kaplan-Meier curves of OS (E) and CSS (F) based of different N categories.

ILA group did not have the expected distribution, as found in the ALA and OLA groups.

The findings were confirmed after evaluating OS and CSS by the N stage (Figures 3-5). The OLA group had the best discrimination profile among the survival curves (Figure 5). In contrast, the ILA group did not have a survival curve for the N3b substage, and the difference between the N0 and N+ patients in that group was not as consistent as in the other two groups (Figure 3). Of note, the ALA group had an adequate patient distribution (Figure 4). However, the mean difference between the N3a and N3b substages was only 7 mo in the ALA group compared with 23 mo in the OLA group.

Univariate and multivariate analyses of the total population

As shown in Table 3, the Cox regression model univariate analysis clearly showed that the ALA and OLA groups had better OS (ALA HR = 0.84, 95%CI: 0.79–0.88, P < 0.001 and OLA HR = 0.73, 95%CI: 0.68–0.79, P < 0.001) and CSS (ALA HR = 0.85, 95%CI: 0.81–0.90, P < 0.001 and OLA HR = 0.80, 95%CI: 0.74–0.86, P < 0.001) than the ILA group. Other prognostic factors related to OS and CSS included age, race, site of tumor, histology, grade, T stage, N stage, stage of disease, type of gastrectomy, chemotherapy, neoadjuvant therapy, and radiotherapy. After adjusting for other variables in the multivariate Cox analysis (Table 3), the ALA and OLA groups still had significantly better OS (ALA HR = 0.68, 95%CI: 0.64–0.71, P < 0.001 and OLA HR = 0.48, 95%CI: 0.44–0.52, P < 0.001) and CSS (ALA HR = 0.64, 95%CI: 0.60–0.68, P < 0.001

Table 3 Cox regression analysis of overall survival and cancer-specific survival

Variable	Overall survival				Cancer-specific survival			
	Univariable		Multivariable[1]		Univariable		Multivariable[1]	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Sex								
Male	Reference				Reference			
Female	1.03 (0.99-1.08)	0.171			1.07 (1.02-1.13)	0.006		
Age, yr								
< 70	Reference		Reference		Reference		Reference	
≥ 70	1.57 (1.50-1.64)	< 0.001	1.51 (1.43-1.59)	< 0.001	1.32 (1.26-1.39)	< 0.001	1.33 (1.26-1.41)	< 0.001
Race								
White	Reference				Reference		Reference	
Black	0.97 (0.91-1.03)	0.283	1.11 (1.05-1.18)	0.001	0.97 (0.90-1.03)	0.317	1.10 (1.03-1.18)	0.005
Asian/Pacific	0.80 (0.75-0.85)	< 0.001	0.82 (0.77-0.87)	< 0.001	0.82 (0.77-0.87)	< 0.001	0.83 (0.78-0.89)	< 0.001
Insurance status								
NA	Reference				Reference			
Insured	0.92 (0.88-0.97)	0.001			1.05 (0.91-1.21)	0.550		
Uninsured	0.96 (0.84-1.09)	0.501			0.95 (0.83-1.09)	0.459		
Site of tumor								
Fundus-body	Reference				Reference			
Antrum-pylorus	1.08 (1.01-1.15)	0.030			1.08 (0.99-1.16)	0.055		
Overlapping lesion of the stomach	1.30 (1.19-1.42)	< 0.001			1.35 (1.23-1.49)	< 0.001		
Stomach, NOS	1.05 (0.98-1.13)	0.167			1.04 (0.96-1.12)	0.373		
Histology								
ADC, NOS	Reference		Reference		Reference		Reference	
Signet ring cell carcinoma	1.16 (1.09-1.23)	< 0.001	1.14 (1.07-1.21)	< 0.001	1.28 (1.20-1.37)	< 0.001	1.16 (1.09-1.25)	< 0.001
ADC, instestinal type	0.87 (0.81-0.93)	< 0.001	0.98 (0.91-1.05)	0.547	0.79 (0.73-0.86)	< 0.001	0.93 (0.86-1.01)	0.086
Carcinoma, diffuse type	1.15 (1.06-1.26)	0.001	1.12 (1.03-1.23)	0.011	1.22 (1.11-1.34)	< 0.001	1.11 (1.00-1.22)	0.045
ADC with mixed subtypes	1.06 (0.94-1.20)	0.349	1.09 (0.96-1.24)	0.169	1.12 (0.98-1.28)	0.103	1.08 (0.94-1.24)	0.281
Other	0.92 (0.85-1.00)	0.062	0.97 (0.89-1.06)	0.543	0.95 (0.86-1.04)	< 0.001	1.01 (0.92-1.11)	0.862
T stage, 8th ed.								
T1	Reference		Reference		Reference		Reference	
T2	1.13 (0.93-1.36)	0.217	1.08 (0.88-1.32)	0.455	1.12 (0.89-1.41)	0.322	1.01 (0.79-1.28)	0.963
T3	1.52 (1.28-1.80)	< 0.001	1.37 (1.09-1.73)	0.008	1.69 (1.37-2.07)	< 0.001	1.34 (1.02-1.76)	0.033
T4a	2.34 (1.98-2.78)	< 0.001	1.72 (1.33-2.22)	< 0.001	2.89 (2.35-3.55)	< 0.001	1.70 (1.27-2.28)	< 0.001
T4b	2.83 (2.37-3.38)	< 0.001	2.08 (1.48-2.93)	< 0.001	3.54 (2.86-4.39)	< 0.001	2.06 (1.40-3.01)	< 0.001
N stage, 8th ed.								
N0	Reference		Reference		Reference		Reference	
N1	1.22 (1.14-1.31)	< 0.001	1.30 (1.16-1.46)	< 0.001	1.31 (1.21-1.43)	< 0.001	1.26 (1.10-1.43)	0.001
N2	1.49 (1.39-1.59)	< 0.001	1.49 (1.28-1.73)	< 0.001	1.70 (1.57-1.84)	< 0.001	1.44 (1.22-1.70)	< 0.001
N3a	2.05 (1.92-2.19)	< 0.001	2.10 (1.61-2.74)	< 0.001	2.51 (2.32-2.71)	< 0.001	2.06 (1.55-2.76)	< 0.001
N3b	2.90 (2.66-3.15)	< 0.001	3.22 (2.17-4.80)	< 0.001	3.68 (3.36-4.03)	< 0.001	3.29 (2.14-5.05)	< 0.001

Stage, 8th ed.								
IIA	Reference		Reference		Reference		Reference	
IIB	1.34 (1.24-1.45)	< 0.001	1.17 (1.05-1.31)	0.005	1.62 (1.47-1.78)	< 0.001	1.38 (1.22-1.57)	< 0.001
IIIA	1.96 (1.83-2.10)	< 0.001	1.43 (1.21-1.70)	< 0.001	2.53 (2.33-2.75)	< 0.001	1.78 (1.48-2.15)	< 0.001
IIIB	2.47 (2.30-2.66)	< 0.001	1.44 (1.08-1.92)	0.012	3.38 (3.11-3.68)	< 0.001	1.87 (1.37-2.55)	< 0.001
IIIC	3.68 (3.39-3.99)	< 0.001	1.59 (1.04-2.44)	0.034	5.19 (4.73-5.70)	< 0.001	2.05 (1.29-3.26)	0.003
Grade								
Well/moderately differentiated	Reference		Reference		Reference			
Poorly/undifferentiated	1.35 (1.28-1.43)	< 0.001	1.19 (1.12-1.26)	< 0.001	1.59 (1.49-1.70)	< 0.001		
Type of surgery								
Partial gastrectomy	Reference		Reference		Reference		Reference	
Total gastrectomy	1.25 (1.19-1.32)	< 0.001	1.23 (1.17-1.30)	< 0.001	1.32 (1.25-1.40)	< 0.001	1.22 (1.15-1.29)	< 0.001
Chemotherapy								
No	Reference		Reference		Reference		Reference	
Yes	0.62 (0.59-0.64)	< 0.001	0.68 (0.64-0.72)	< 0.001	0.71 (0.67-0.74)	< 0.001	0.73 (0.68-0.78)	< 0.001
Neoadjuvant chemotherapy								
No	Reference				Reference			
Yes	0.76 (0.71-0.83)	< 0.001			0.82 (0.75-0.89)	< 0.001		
Radiotherapy								
No	Reference		Reference		Reference		Reference	
Yes	0.65 (0.62-0.68)	< 0.001	0.77 (0.73-0.82)	< 0.001	0.70 (0.66-0.73)	< 0.001	0.75 (0.71-0.80)	< 0.001
Number of retrieved lymph nodes								
ILA	Reference		Reference		Reference		Reference	
ALA	0.84 (0.79-0.88)	< 0.001	0.68 (0.64-0.71)	< 0.001	0.85 (0.81-0.90)	< 0.001	0.64 (0.60-0.68)	< 0.001
OLA	0.73 (0.68-0.79)	< 0.001	0.48 (0.44-0.52)	< 0.001	0.80 (0.74-0.86)	< 0.001	0.47 (0.43-0.51)	< 0.001

[1]Forward selection model. ADC: Adenocarcinoma; ALA: Adequate lymph node assessment; CI: Confidence interval; HR: Hazard ratio; ILA: Inadequate lymph node assessment; OLA: Optimal lymph node assessment; NA: Not available, NOS: Not otherwise specified.

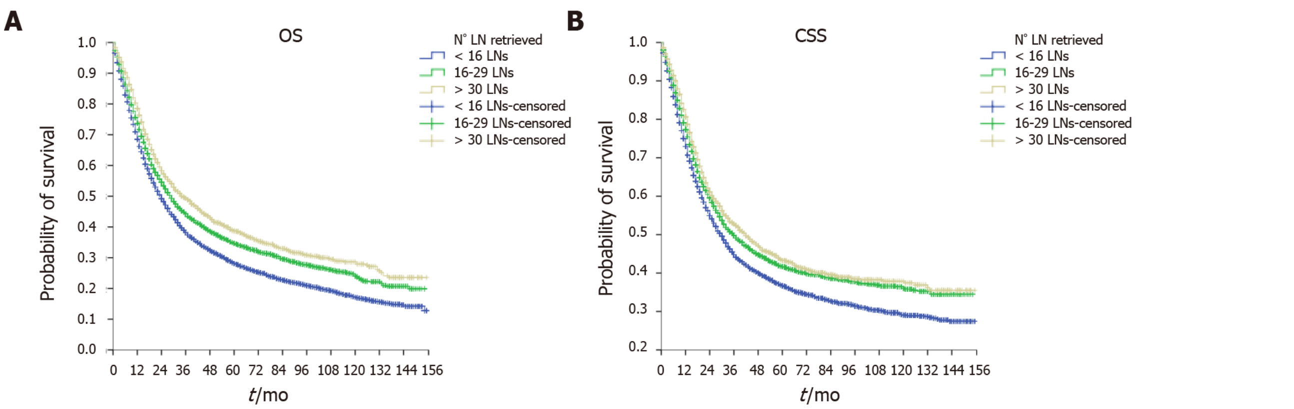

Figure 2 Comparison of the survival of patients with inadequate (< 16), adequate (16-29), and optimal (> 30) lymph node assessment. Kaplan-Meier curves of A: Overall survival; B: Cancer-specific survival.

and OLA HR = 0.47, 95%CI: 0.43–0.51, P < 0.001) than the ILA group. Age, race, histology, T stage, N stage, stage of disease, type of gastrectomy, chemotherapy, and radiotherapy were confirmed as significant prognostic factors in the multivariate

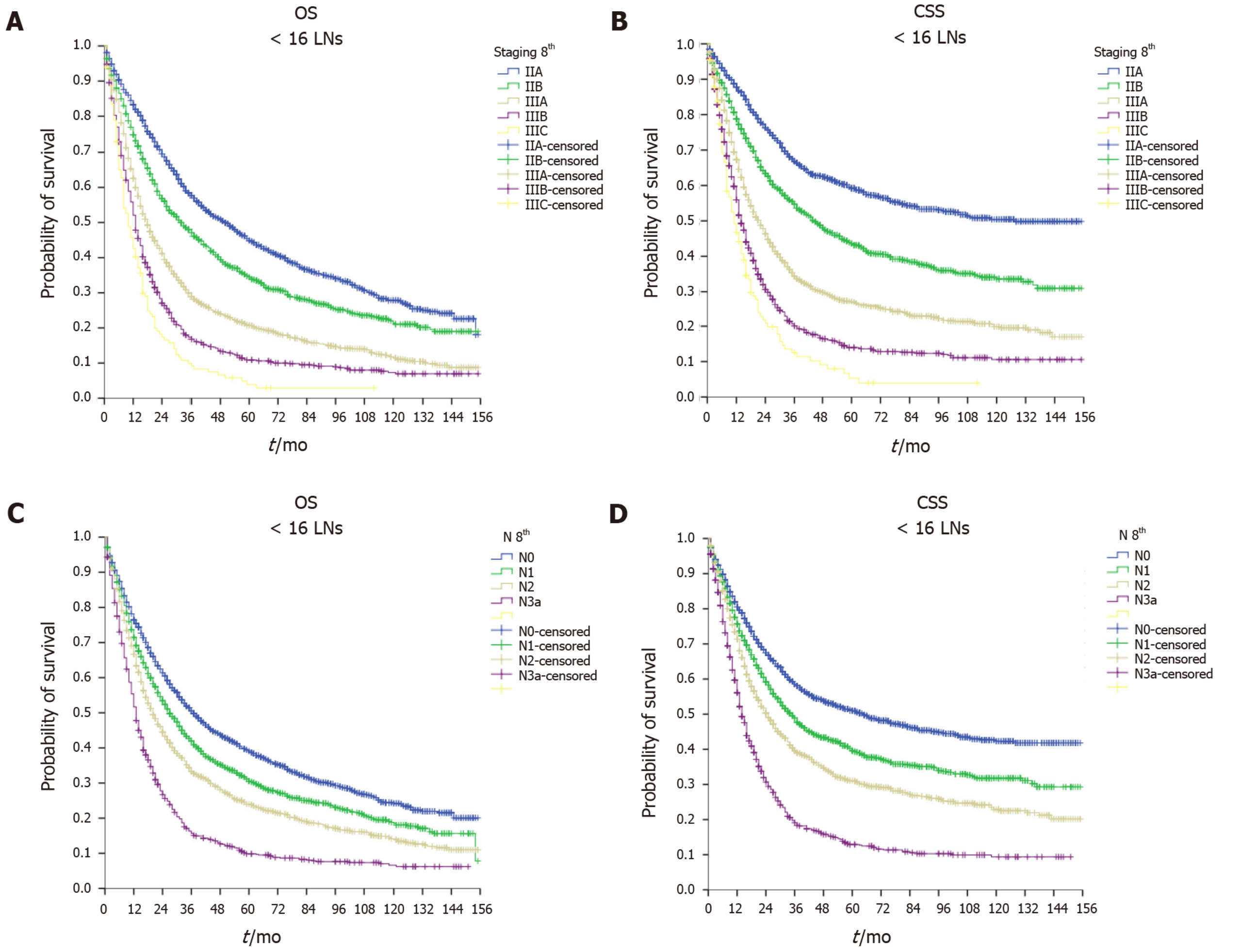

Figure 3 Analysis of survival of patients with inadequate lymph node assessment. Kaplan-Meier curves of A: Overall survival (OS); B: Cancer-specific survival (CSS) based on stage; C and D: OS (C) and CSS (D) based on the N classification.

model for both OS and CSS.

PSM

ALA and OLA were compared in in 3428 PSM 1:1 patient pairs (*n* = 1,714 per group) out of a total of 5801 patients. The L1 test measure was larger in the unmatched sample (0.989) than in the matched sample (0.964), indicating that the two groups were well-balanced across all considered variables. Successful matching (Table 4) was confirmed during the analysis because there were no differences between the two groups in the year of diagnosis, patient characteristics (age, sex, race, marital status, and insurance status), and tumor characteristics (site, grade, T stage, and N stage). As shown in Table 5, the OLA group had better OS and CSS than the ALA group (OLA median OS = 34 mo *vs* ALA median = 26 mo, $P < 0.001$, respectively; CSS: OLA median = 42 mo *vs* ALA median = 31 mo, $P < 0.001$, respectively). The Cox analysis conducted after PSM (Table 6) confirmed that OLA was associated with significantly improved OS (univariable HR = 0.81, 95%CI: 0.75–0.89, $P < 0.001$ and multivariable HR = 0.71, 95%CI: 0.65–0.78, $P < 0.001$) and CSS (univariable HR = 0.84, 95%CI: 0.76–0.92, $P < 0.001$ and multivariable HR = 0.74, 95%CI: 0.67–0.82, $P < 0.001$).

DISCUSSION

In this study evaluating the impact of nodal assessment in patients who underwent resection for locally advanced gastric cancer in the United States between 2004 and 2015, we found significant discrepancies between expected and actual survival differences in stage II and III gastric cancer patients who had a minimum of 30 LNs assessed compared with those who had <16 or 16-29 LNs. The adverse impact of insufficient nodal analysis was found to be significant in both II and III stage disease.

Table 4 Propensity score matching subgroups

Characteristic	ALA, *n* = 1714	OLA, *n* = 1714	*P* value
Year of diagnosis			0.978
2004-2006	339 (20)	334 (19)	
2007-2009	385 (23)	394 (23)	
2010-2012	468 (27)	471 (28)	
2013-2015	522 (30)	515 (30)	
Age at diagnosis (yr)			0.861
Median (range)	66 (14-98)	66 (18-93)	
Sex			0.945
Male	1011 (59)	1013 (59)	
Female	703 (41)	701 (41)	
Race			0.181
White	972 (57)	973 (57)	
Black	303 (18)	268 (16)	
Asian/Pacific	439 (25)	473 (28)	
Marital status			0.234
Single/divorced	389 (23)	378 (22)	
Married	1035 (60)	1082 (63)	
Widowed	218 (13)	183 (71)	
NA	72 (4)	71 (4)	
Insurance status			0.958
Insured	1305 (76)	1312 (77)	
Uninsured	339 (20)	334 (19)	
NA	70 (4)	68 (4)	
Primary site			0.926
Fundus/body	327 (19)	333 (19)	
Antrum/pylorus	571 (33)	553 (32)	
Overlapping lesion	235 (14)	235 (14)	
Stomach, NOS	581 (34)	593 (35)	
Tumor size (cm)			0.016
≤ 5	737 (43)	645 (38)	
5.1-10	663 (39)	724 (42)	
≥ 10.1	222 (13)	248 (15)	
NA	92 (5)	97 (6)	
Hystology			0.046
ADC, NOS	557 (32)	538 (31)	
Signet ring cell carcinoma	492 (29)	480 (28)	
ADC, Instestinal type	289 (17)	313 (18)	
Carcinoma, diffuse type	177 (10)	175 (10)	
ADC with mixed subtypes	69 (4)	88 (5)	
Other	130 (8)	110 (7)	
Grade			0.892

Well/moderately differentiated	310 (18)	319 (19)	
Poorly/undifferentiated	1351 (79)	1345 (79)	
NA	53 (3)	50 (3)	
T stage, 8th ed.			0.553
T1	59 (3)	48 (3)	
T2	137 (8)	132 (8)	
T3	769 (45)	793 (46)	
T4a	597 (35)	572 (33)	
T4b	152 (9)	169 (10)	
N stage, 8th ed.			0.659
N0	250 (15)	259 (15)	
N1	252 (15)	223 (13)	
N2	342 (20)	340 (20)	
N3a	380 (22)	380 (22)	
N3b	490 (29)	512 (30)	
Stage, 8th ed.			0.808
IIA	263 (15)	253 (15)	
IIB	226 (13)	215 (13)	
IIIA	351 (21)	353 (21)	
IIIB	377 (22)	365 (21)	
IIIC	497 (29)	528 (30)	
Chemotherapy			0.025
Yes	1105 (65)	1167 (32)	
No	609 (35)	1167 (68)	
Neoadjuvant chemotherapy			< 0.001
Yes	225 (13)	310 (18)	
No	1499 (87)	1404 (82)	
Radiotherapy			0.051
Yes	718 (42)	662 (39)	
No	996 (58)	1052 (61)	
Type of surgery			< 0.001
Partial gastrectomy	1099 (64)	955 (56)	
Total gastrectomy	615 (36)	759 (44)	

ADC: Adenocarcinoma; ALA: Adequate lymph node assessment; NOS: Not otherwise specified; OLA: Optimal lymph node assessment.

The results suggest that proper assessment of nodal status requires at least 16 LNs, and optimally 30 LNs. Optimization of gastric cancer care across Eastern and Western countries continues to make substantial progress. The updated eighth edition of the TNM-staging system incorporated survival data from additional Eastern nations to provide a more accurate prognosis of all patients diagnosed with gastric cancer worldwide. One of the most important unresolved issues is understanding the true impact of surgical resection and extent of nodal assessment[15,16].

Gastrectomy, including LN dissection, has a major role in optimizing the treatment strategy for locally advanced gastric cancer. Improper LN dissection not only increases the risk of residual tumor and disease recurrence, but also compromises the patient's stage attribution[17] and more important may affect the choice of adjuvant therapies. The AJCC cancer staging system has been developed over the years to improve

Table 5 Kaplan-Meier estimates in propensity score matching subgroups

	Median OS, mo(95%CI)	*P* value	Median CSS, mo(95%CI)	*P* value
ALA	26 (23.5-28.4)	< 0.001	31 (27.3-34.7)	< 0.001
OLA	34 (30.0-38.0)		42 (35.9-48.1)	

ALA: Adequate lymph node assessment; CI: confidence interval; CSS: Cancer-specific survival; OLA: Optimal lymph node assessment; OS: Overall survival.

pathology assessment, facilitate comparisons, and increase compliance among centers. Nodal status is a relevant prognostic factor, and assessing an adequate number of LNs enables proper staging and, consequently leads to optimal treatment management[18, 19].

Significant variation has been seen in different series across the East and West[7]. Asian countries generally have a median number of harvested LNs that is three or four times higher than those in other regions. The variation affects staging accuracy and long-term patient survival. Meanwhile, insufficient LN assessment is often apparent in the current literature[20]. For example, in his review of 15 studies, which included 27,942 patients, Khanjani *et al*[5] showed that only 52.2% of the patients received an adequate nodal evaluation, given the AJCC's current recommendation to assess at least 16 LNs[9].

In this study, we focused on patients whose staging was expected to have the greatest impact on their treatment pathway, namely patients with potentially curable advanced disease that was formally classified as stage II or III. This issue is particularly relevant in Western countries, where most patients are belatedly diagnosed with gastric cancer because of a lack of screening programs and where gastric cancer treatments vary greatly by center. As the SEER database is one of the largest cancer databases in the West, it is particularly representative of the current management of patients with gastric cancer. We selected 11,607 patients who had undergone radical gastrectomy. In total, 50% of the patients did not reach the AJCC criteria for correct staging (< 16 LNs). Moreover, only 15% had an analysis of ≥ 30 LNs, which is considered the optimal assessment of N status. However, if we only considered the last study period, awareness of the complexity of disease treatment, and the development of referral centers seemed to result in more attention and more patients with correct management. For example, in the last study period, 30% of the overall sample population was in the OLA group.

For pathological staging, two factors are interrelated the depth of tumor invasion of the gastric wall (T stage) and the number of positive nodes among all retrieved nodes (N stage). T stage evaluation is not subject to significant surgical or pathological issues, but N stage evaluation is strongly influenced by surgical skill and pathologist interpretation. Regarding the latter, a difference in the analysis can be easily detected if the specimen is sent to the pathologist in a single piece or already divided by LN stations by the surgeon. Therefore, an inadequate assessment reflects a process bug that is generated at some point between the surgical procedure and the final specimen analysis. There is a need for a dedicated multidisciplinary team to manage gastric cancer patients. Interestingly, in our analysis, no significant differences between the three study groups were seen in the T stage distribution, meaning that the number of retrieved LNs was not influenced by the primary site extension.

As expected, we found a large disparity in patients classified as N0 and N1 in the ILA and OLA groups, with 30% *vs* 15% N0 and 26% *vs* 13% N1, respectively. If an inadequate number of nodes is assessed, a patient may be inappropriately considered node negative or assigned to a lower N stage. Consequently, the patient is assigned to a lower overall stage. Moreover, while the current recommendation to analyze at least 16 LN allows for N3b substage classification, which requires ≥ 16 positive LNs, the likelihood that a patient would be classified as N3b with only 16 analyzed nodes is extremely low. Therefore, a larger number of nodes is needed for this evaluation[21]. Based on this classification requirement, the N3b substage could not be assessed in the ILA group. However, 30% of patients in the OLA group were in that substage. The N3a and N2 categories can also be influenced by the overall number of analyzed nodes, and patients can therefore be subject to a stage migration effect. As a consequence, patients in the ILA group were formally assigned to the earlier II and IIIA stages, and very few patients fell within the more advanced stages. There was a 10-fold difference in the percentage of patients in the IIIC category in the ILA and OLA

Table 6 Overall survival Cox regression results for overall survival and cancer-specific survival after propensity score matching

Variable	Overall survival				Cancer-specific survival			
	Univariable		Multivariable[1]		Univariable		Multivariable[1]	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Sex								
Male	Reference				Reference			
Female	0.98 (0.90-1.07)	0.662			1.03 (0.94-1.14)	0.517		
Age								
< 70	Reference				Reference			
≥ 70	1.56 (1.43-1.71)	< 0.001			1.35 (1.23-1.49)	< 0.001		
Race								
White	Reference				Reference		Reference	
Black	0.96 (0.85-1.08)	0.528	1.10 (0.97-1.24)	0.147	0.94 (0.83-1.08)	0.383	1.08 (0.94-1.23)	0.274
Asian/pacific	0.80 (0.72-0.89)	< 0.001	0.84 (0.75-0.93)	0.001	0.81 (0.72-0.90)	< 0.001	0.87 (0.77-0.97)	0.014
Insurance status								
NA	Reference				Reference			
Insured	0.87 (0.79-0.97)	0.009			0.87 (0.78-0.97)	0.013		
Uninsured	0.99 (0.78-1.27)	0.972			0.96 (0.74-1.25)	0.754		
Site of tumor								
Fundus-body	Reference				Reference			
Antrum-pylorus	1.07 (0.95-1.22)	0.275			1.11 (0.97-1.27)	0.140		
Overlapping lesion of the stomach	1.33 (1.15-1.55)	< 0.001			1.39 (1.18-1.64)	< 0.001		
Stomach, NOS	1.04 (0.92-1.18)	0.516			1.03 (0.90-1.19)	0.631		
Histology								
ADC, NOS	Reference				Reference		Reference	
Signet ring cell carcinoma	1.26 (1.13-1.41)	< 0.001			1.37 (1.22-1.54)	< 0.001	1.22 (1.08-1.38)	0.001
ADC, instestinal type	0.89 (0.79-1.03)	0.114			0.81 (0.70-0.95)	0.008	0.91 (0.78-1.06)	0.238
Carcinoma, diffuse type	1.23(1.06-1.44)	0.008			1.29 (1.09-1.52)	0.003	1.18 (0.99-1.40)	0.054
ADC with mixed subtypes	1.15 (0.93-1.43)	0.193			1.28 (1.02-1.60)	0.032	1.13 (0.89-1.42)	0.318
Other	0.93 (0.77-1.13)	0.472			0.99 (0.81-1.21)	0.913	1.15 (0.93-1.41)	0.199
T stage, 8^{th} ed								
T1	Reference				Reference			
T2	1.18 (0.83-1.67)	0.356			1.43 (0.91-2.24)	0.121		
T3	1.85 (1.37-2.51)	< 0.001			2.60 (1.74-3.87)	< 0.001		
T4a	2.84 (2.10-3.86)	< 0.001			4.28 (2.87-6.39)	< 0.001		
T4b	3.44 (2.49-4.75)	< 0.001			5.13 (3.39-7.77)	< 0.001		
N stage, 8^{th} ed								
N0	Reference				Reference			
N1	1.09 (0.89-1.34)	0.380			1.08 (0.86-1.36)	0.518		
N2	1.56 (1.31-1.87)	< 0.001			1.63 (1.33-1.99)	< 0.001		
N3a	2.28 (1.93-2.69)	< 0.001			2.61 (2.16-3.16)	< 0.001		
N3b	4.58 (3.91-5.37)	< 0.001			5.50 (4.59-6.58)	< 0.001		

Stage, 8th ed								
IIA	Reference		Reference		Reference		Reference	
IIB	1.38 (1.12-1.70)	0.003	1.47 (1.18-1.81)	< 0.001	1.70 (1.33-2.18)	< 0.001	1.77 (1.38-2.29)	< 0.001
IIIA	1.96 (1.63-2.35)	< 0.001	2.21 (1.83-2.66)	< 0.001	2.39 (1.92-2.98)	< 0.001	2.66 (2.12-3.32)	< 0.001
IIIB	2.85 (2.39-3.40)	< 0.001	3.31 (2.76-3.96)	< 0.001	3.75 (3.04-6.64)	< 0.001	4.22 (3.40-5.23)	< 0.001
IIIC	5.73 (4.85-6.77)	< 0.001	6.32 (5.31-7.52)	< 0.001	8.06 (6.58-9.88)	< 0.001	8.58 (6.97-10.57)	< 0.001
Grade								
Well/moderately differentiated	Reference		Reference		Reference			
Poorly/undifferentiated	1.52 (1.35-1.72)	< 0.001	1.19 (1.05-1.35)	0.007	1.70 (1.49-1.96)	< 0.001		
Type of surgery								
Partial gastrectomy	Reference		Reference		Reference		Reference	
Total gastrectomy	1.40 (1.29-1.53)	< 0.001	1.28 (1.17-1.40)	< 0.001	1.43 (1.31-1.58)	< 0.001	1.24 (1.13-1.37)	< 0.001
Chemotherapy								
No	Reference		Reference		Reference		Reference	
Yes	0.56 (0.51-0.61)	< 0.001	0.63 (0.56-0.70)	< 0.001	0.61 (0.55-0.67)	< 0.001	0.66 (0.89-0.74)	< 0.001
Neoadjuvant chemotherapy								
No	Reference		Reference		Reference		Reference	
Yes	0.71 (0.62-0.81)	< 0.001	1.48 (1.35-1.63)	< 0.001	0.76 (0.66-0.87)	< 0.001	1.33 (1.20-1.48)	< 0.001
Radiotherapy								
No	Reference		Reference		Reference		Reference	
Yes	0.64 (0.59-0.70)	< 0.001	0.77 (0.69-0.86)	< 0.001	0.67 (0.61-0.73)	< 0.001	0.76 (0.68-0.85)	< 0.001
Number of retrieved lymph nodes								
ALA	Reference		Reference		Reference		Reference	
OLA	0.81 (0.75-0.89)	< 0.001	0.71 (0.65-0.78)	< 0.001	0.84 (0.76-0.92)	< 0.001	0.74 (0.67-0.82)	< 0.001

[1]Forward selection model. ADC: Adenocarcinoma; ALA: Adequate lymph node assessment; ILA: Inadequate lymph node assessment; NA: Not available, NOS: Not otherwise specified; OLA: Optimal lymph node assessment.

groups (3% *vs* 31%, respectively).

Three main questions can be answered by the present study: (1) Does this have an overall impact on long-term survival? (2) How beneficial is the correct staging of patients? and (3) Given the same stage conditions and patient characteristics, is there a survival difference between ALA and OLA? The answer to the first question is yes. The ILA group had the worst OS (median = 24 mo) and CSS (median = 30 mo) compared with the ALA (median OS = 29 mo, median CSS = 36 mo, P < 0.001) and OLA (median OS = 34 mo, median CSS = 42 mo, P < 0.001) groups. Our findings clearly show that the stage-specific survival curves of the ILA group do not follow the expected trend. In particular, there were 49-month and 81-month mean differences between patients in stage IIA in the ILA group and in the ALA and OLA groups, respectively. Regarding the second question, correct staging requires the efforts of surgeons and pathologists. Of course, several other factors may influence survival in this context. Therefore, we included patient and tumor characteristics and treatment variables in the Cox regression analysis. The multivariate model confirmed that the ALA and OLA groups significantly improved OS (ALA HR = 0.68 and OLA HR = 0.48, P < 0.001) and CSS (ALA HR = 0.64 and OLA HR = 0.47, P < 0.001). Regarding the third question, PSM in the ALA and OLA groups (3428 matched patients) demonstrated that optimal assessment was key for better survival (univariable OS HR = 0.81, P < 0.001; multivariable HR = 0.71, P < 0.001).

Limitations and strengths

This study evaluated patients included in a population registry who were selected by both direct and indirect variables related to a code system. One major study limitation

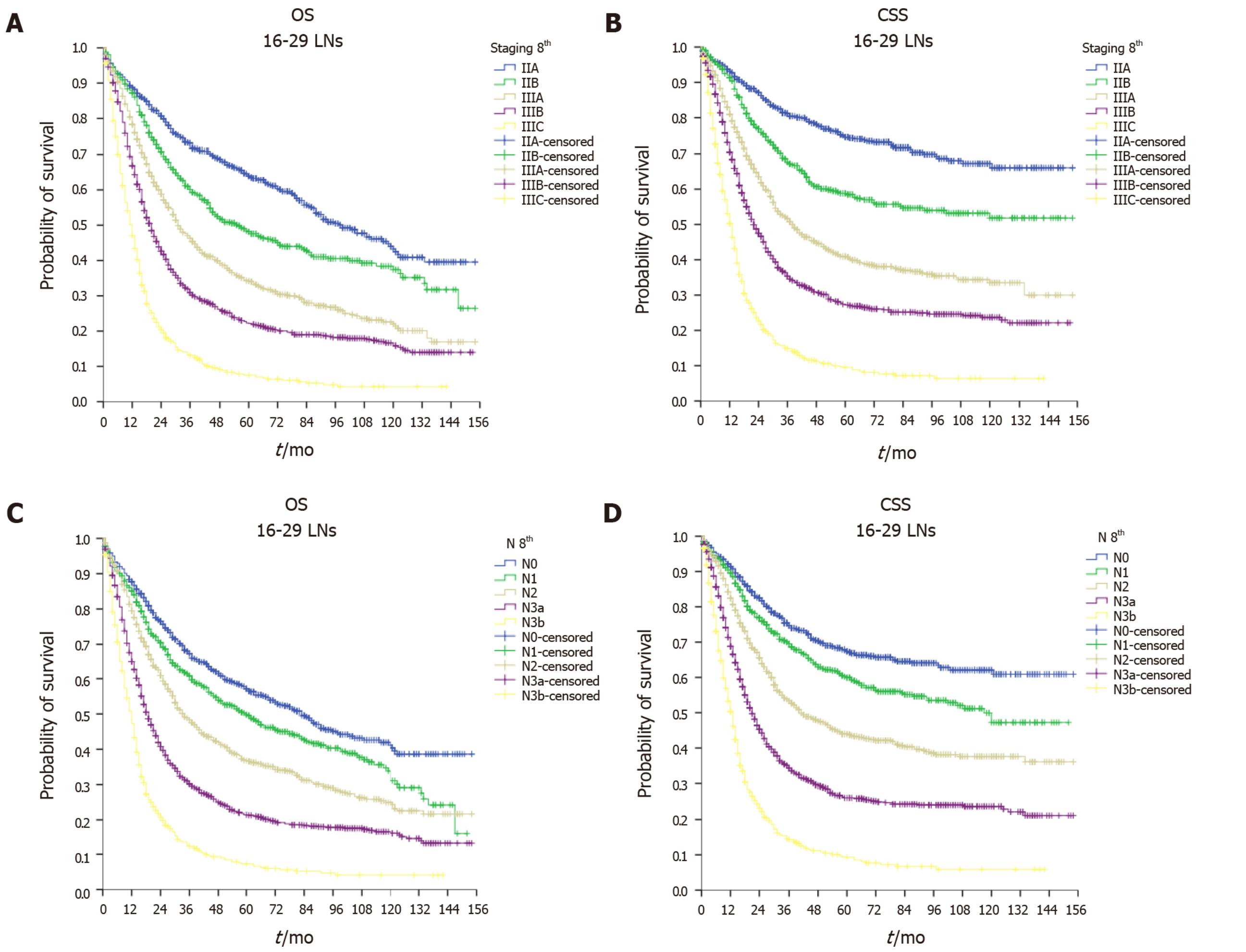

Figure 4 Analysis of survival of patients with lymph node assessment group. Kaplan-Meier curves of A: Overall survival (OS); B: Cancer-specific survival (CSS) based on stages; C and D: OS (C) and CSS (D) based on the N classification.

was the use of a population registry based on a coding system of direct and indirect variables, which reduced the availability of more detailed information of the patient characteristics and treatment details. For example, the extent of lymphadenectomy performed or the type of neoadjuvant and adjuvant chemotherapy regimens were not known. In particular, standard D2 LN dissection may not have been performed in the elderly or in high-risk patients who were included in the analysis. As a result, it is presumed that the prognosis in these categories was poor independent of the inadequate staging effect. Despite the limitations, the strength of the study is the large sample of patients analyzed, which allowed statistical rigor. Moreover, the SEER database contains rigorous, standardized information and the guarantee of a high-quality data collection process.

CONCLUSION

Inadequate staging is an important issue in gastric cancer management that adversely impacts the survival of a large proportion of patients undergoing radical resection. Our study findings demonstrate that analyzing < 16 LNs is insufficient for accurate staging and prognostically misleading. In contrast, analyzing 16–29 LNs improves the accuracy of staging, and evaluation of ≥ 30 LNs offers the most consistent chance of correctly classifying patients into the appropriate N3 substages. Therefore, surgeons and pathologists should make concerted efforts to analyze as many LNs as possible beyond the current NCCN recommendations. That may require a D2 lymphadenectomy as recommended by experienced surgeons in patients without restrictive surgical risk. Moreover a more thorough reassessment of the surgical specimen may be required if an inadequate number of LNs is initially found after a radical gastrectomy. Most important, all patients with inadequate LNA should be considered at high risk

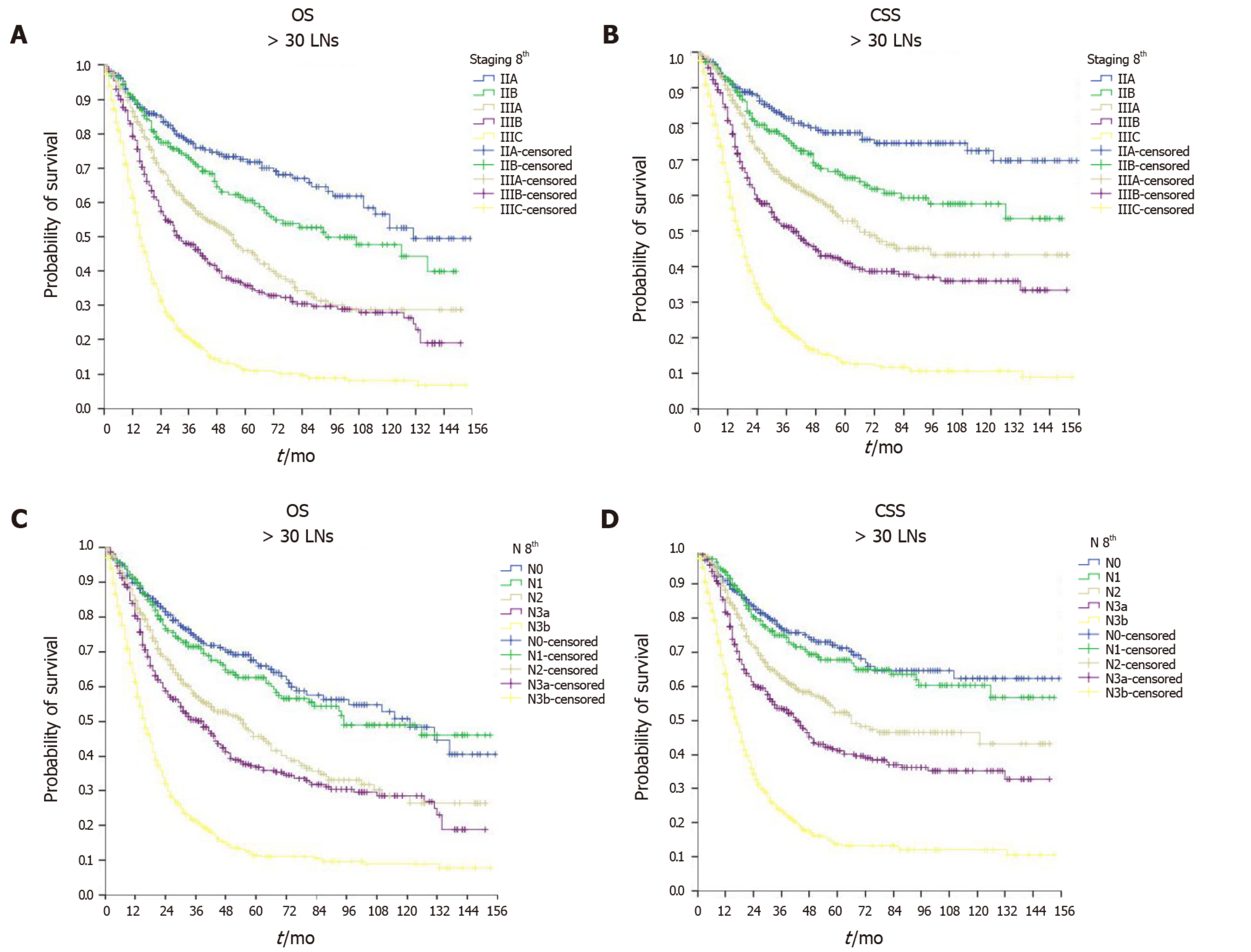

Figure 5 Analysis of survival of patients with optimal lymph node assessment. Kaplan-Meier curves of A: Overall survival (OS); B: Cancer-specific survival (CSS) based on stage; C: OS; D: CSS based on the N category.

for stage migration and can expect a survival rate significantly worse than their formally assigned TNM-stage.

ARTICLE HIGHLIGHTS

Research background

Lymphadenectomy in gastric cancer remains a relevant issue because of its impact on survival. The SEER database is one of the largest Western cancer databases. Patients were assigned to three groups depending on the number of analyzed lymph nodes (LNs) to evaluate survival differences and the stage migration effect.

Research motivation

Gastric cancer should be treated in dedicated centers to offer the patient both optimal surgery and a correct pathological assessment and to avoid improper staging.

Research objectives

We aimed to analyze the survival of patients with inadequate numbers of assessed LNs and to quantify the effect *vs* correctly staged patients, based on the stage definitions in the AJCC staging manual.

Research methods

Eligible gastric cancer patients were identified in the SEER database and assigned of three groups, inadequate LN assessment (< 16 LNs), adequate LN assessment (16-29 LNs), and optimal LN assessment (≥ 30 LNs).

Research results

The ILA group had the worst survival. The finding was confirmed in by univariate and multivariate analysis. OLA gave the best chance of both correct staging and proper surgery performed as demonstrated after propensity score matching.

Research conclusions

Inadequate staging led to a significant reduction in the expected survival associated with the formally attributed stage. An analysis of at least > 16 LNs should be offered to all patients treated with curative intent.

Research perspectives

The role of referral centers for gastric cancer should be strengthened to obtain optimal treatment and accurate patient staging.

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ORIGINAL ARTICLE

Observational Study

Defecation disorders are crucial sequelae that impairs the quality of life of patients after conventional gastrectomy

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Author contributions: Nakada K, Ikeda M, Takahashi M, Kodera Y designed the study, and collected and managed the data; Kinami S, Yoshida M, Uenosono Y, Terashima M collected and managed the data; Oshio A contributed to statistical analysis; Nakada K wrote the paper; All authors have read and approved the final version to be published.

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Informed consent statement: Written informed consent was obtained from all enrolled patients.

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Abstract

BACKGROUND

Defecation disorders are obscure sequelae that occurs after gastrectomy, and its implication on daily lives of patients have not been sufficiently investigated.

AIM

To examine the features of defecation disorders after gastrectomy and to explore its implication on daily lives of patients in a large cohort using the Postgastrectomy Syndrome Assessment Scale (PGSAS)-45.

METHODS

We conducted a nationwide multi-institutional study using PGSAS-45 to examine the prevalence of postgastrectomy syndrome and its impact on daily lives of patients after various types of gastrectomy. Data were obtained from 2368 eligible patients at 52 institutions in Japan. Of these, 1777 patients who underwent total gastrectomy (TG; *n* = 393) or distal gastrectomy (DG; *n* = 1384) were examined. The severity of defecation disorder symptoms, such as diarrhea and constipation, and their correlation with other postgastrectomy symptoms were examined. The importance of defecation disorder symptoms on the living states and quality of life (QOL) of postgastrectomy patients, and those clinical factors that affect the severity of defecation disorder symptoms were evaluated using multiple regression analysis.

RESULTS

Among seven symptom subscales of PGSAS-45, the ranking of diarrhea was 4th in TG and 2nd in DG. The ranking of constipation was 5th in TG and 1st in DG. The symptoms that correlated well with diarrhea were dumping and indigestion in both TG and DG; while those with constipation were abdominal pain and meal-related distress in TG, and were meal-related distress and indigestion in DG. Among five main outcome measures (MOMs) of living status domain, constipation significantly impaired four MOMs, while diarrhea had no effect in TG. Both diarrhea and constipation impaired most of five MOMs in DG. Among six MOMs of QOL domain, diarrhea impaired one MOM, whereas constipation impaired all six MOMs in TG. Both diarrhea and constipation equally impaired all MOMs in DG. Male sex, younger age, division of the celiac branch of vagus nerve, and TG, independently worsened diarrhea, while female sex worsened constipation.

CONCLUSION

Defecation disorder symptoms, particularly constipation, impair the living status and QOL of patients after gastrectomy; therefore, we should pay attention and adequately treat these relatively modest symptoms to improve postoperative QOL.

Key Words: Postgastrectomy syndrome; Defecation disorders; Quality of life; Patient-reported outcome measures; Gastrectomy

Core Tip: Symptoms of defecation disorders, such as diarrhea and constipation, are relatively modest and have not received sufficient attention among various postgastrectomy symptoms; therefore, their implication on the daily lives of patients have not been adequately investigated. We evaluated these symptoms using a nationwide multi-institutional collaborative study called the Postgastrectomy Syndrome Assessment Study. The severity of symptoms of defecation disorders were unexpectedly high and both symptoms, particularly constipation, impaired the living status and quality of life (QOL) of patients after gastrectomy; therefore, we should also pay attention and adequately treat these symptoms to improve postoperative QOL.

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INTRODUCTION

Various symptoms have been known to appear after gastrectomy and these symptoms affect the daily lives of patients[1-4]. Among these symptoms, dumping[5-8], small stomach syndrome[9-11], and esophageal reflux[12-14] have been noted as characteristic postgastrectomy symptoms and have frequently become clinical problems. However, symptoms of defecation disorders, such as diarrhea and constipation, and especially constipation, are often less conspicuous compared to other characteristic postgastrectomy symptoms, and their features have not yet been adequately assessed. Therefore, in this study, we used data from a large number of patients that were collected in the Postgastrectomy Syndrome Assessment Study (PGSAS), in order to identify the actual distribution and features of defecation disorders, their effects on living status and quality of life (QOL), and clinical factors that strengthen the symptoms of defecation disorders in patients who underwent conventional gastrectomy [total gastrectomy (TG) and distal gastrectomy (DG)].

MATERIALS AND METHODS

Patients

Fifty-two institutions participated in this study. The patient eligibility criteria were: (1) Diagnosis of pathologically-confirmed stage IA or IB gastric cancer; (2) First-time gastrectomy status; (3) Age ≥ 20 and ≤ 75 years; (4) No history of chemotherapy; (5) No indication of recurrence or distant metastasis; (6) Underwent gastrectomy one or more years prior to the date of enrollment; (7) Performance status ≤ 1 on the Eastern Cooperative Oncology Group scale; (8) Full capacity to understand and respond to the questionnaire; (9) No history of other diseases or surgeries that might influence the patient’s responses to the questionnaire; (10) Absence of organ failure or mental illness; and (11) Written informed consent. Patients with dual malignancy and those that underwent concomitant resection of other organs (with a co-resection equivalent to a cholecystectomy being the exception) were excluded (Figure 1).

QOL assessment

The postgastrectomy Syndrome Assessment Scale (PGSAS)-45[15] is a newly developed, multidimensional QOL questionnaire that is based on the 8-item short form health survey (SF-8)[16] and the Gastrointestinal Symptom Rating Scale (GSRS) [17]. The PGSAS-45 questionnaire consists of a total of 45 questions, with eight items from the SF-8, 15 items from the GSRS, and 22 important clinical items selected by the Japan Postgastrectomy Syndrome Working Party. The PGSAS-45 questionnaire includes 23 items that pertain to postoperative symptoms (items 9–33), including 15 items from the GSRS and eight newly selected items. In addition, 12 questionnaire items that pertain to dietary intake (eight items), work (one item), and level of satisfaction with daily life (three items) were selected. Twenty-three symptom items were consolidated into seven symptom subscales using factor analysis. Afterwards, 19 main outcome measures (MOMs) were refined through the process of consolidation and selection, and were classified into three domains, namely, symptoms, living status, and QOL (Table 1). Details of the PGSAS-45 have been reported previously[15].

Study methods

Continuous sampling from a central registration system was used to enroll participants into this study. The questionnaires were distributed to all eligible patients during their visits to the participating clinics. After completing the questionnaire, patients were instructed to return the forms to the data center. All QOL data from the questionnaires were matched with the data of individual patients that were collected *via* the case report forms.

This study was registered with the University Hospital Medical Information Network’s Clinical Trials Registry (UMIN-CTR; registration number 000002116), and was approved by the local ethics committees at each institution. This study also conformed to the principles of the Declaration of Helsinki, and written informed consent was obtained from all enrolled patients. Of the 2922 patients who were given questionnaires between July 2009 and December 2010, 2520 (86%) responded and 2368 were confirmed to be eligible for the study. Of these, data from 1777 patients who underwent either TG or DG were analyzed in this study.

Table 1 Relationship of the domains and main outcome measures of the Postgastrectomy Syndrome Assessment Scale-45

Domain	Main outcome measures
Symptoms	*Esophageal reflux SS*
	Abdominal pain SS
	Meal-related distress SS
	Indigestion SS
	Diarrhea SS
	Constipation SS
	Dumping SS
	Total symptom score
Living status	Change in BW
	Ingestion amount of food per meal
	Necessity for additional meals
	Quality of ingestion SS
	Ability for working
QOL	Dissatisfaction with symptoms
	Dissatisfaction at the meal
	Dissatisfaction at working
	Dissatisfaction for daily life SS
	PCS of SF-8
	MCS of SF-8

Integrated subscales are italicized in the table. SS: Subscale; BW: Body weight; PCS: Physical component summary; MCS: Mental component summary.

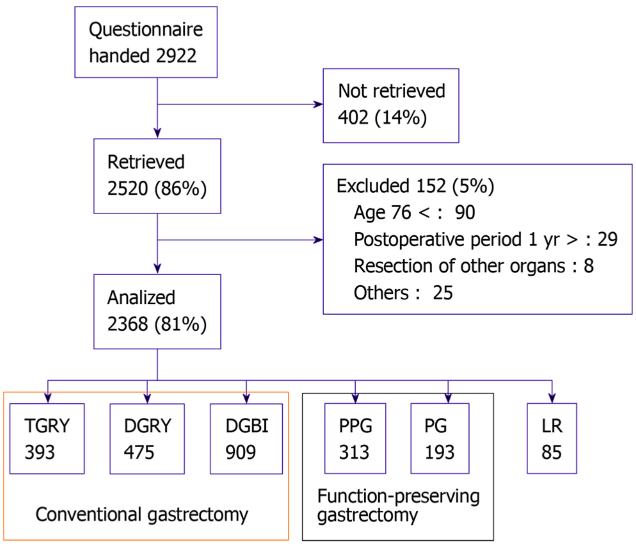

Figure 1 CONSORT flowchart of the Postgastrectomy Syndrome Assessment Study. TGRY: Total gastrectomy with Roux- en-Y reconstruction; DGRY: Distal gastrectomy with Roux-en-Y reconstruction; DGBI: Distal gastrectomy with Billroth-I reconstruction; PPG: Pylorus-preserving gastrectomy; PG: Proximal gastrectomy; LR: Local resection.

Statistical analysis

The statistical methods used to compare patients' characteristics and severity of symptoms of defecation disorders (*i.e.*, diarrhea and constipation) after TG and DG, included the *t*-test and chi-square test. Correlations between each symptom of defecation disorders and other postgastrectomy symptoms were calculated in terms of

Pearson's product–moment correlation coefficient (r). The impact of each symptom of defecation disorders on the living status and QOL of patients after gastrectomy were examined using multiple regression analysis. Furthermore, multiple regression analysis was used to explore the effects of independent clinical factors on symptoms of defecation disorders. P value of < 0.05 were considered statistically significant.

To evaluate effect sizes, Cohen's d, Pearson correlation coefficient (r), standardization coefficient of regression (β), and coefficient of determination (R^2) were used. Interpretation of effect sizes were as follows: using Cohen's d: ≥ 0.2, small; ≥ 0.5, medium; and ≥ 0.8, large; using Pearson correlation coefficient (r) and standardization coefficient of regression (β): ≥ 0.1, small; ≥ 0.3, medium; and ≥ 0.5, large; while using coefficient of determination (R^2): ≥ 0.02, small; ≥ 0.13, medium; and ≥ 0.26, large. Statistical analyses were performed using the JMP version 12.0.1 software (SAS Institute Inc., Cary, NC, United States).

RESULTS

Patient background

Of the 2368 patients whose data were collected in the PGSAS, data from a total of 1777 patients were analyzed, comprising 393 TG cases and 1384 DG cases (Billroth-I method: 909 cases; Roux-en-Y method: 475 cases). Comparisons of patients' characteristics between those that underwent TG and those that underwent DG showed that those that underwent TG were significantly older, likely to be males, had a shorter postoperative period, and were less likely to undergo laparoscopic approaches as well as preservation of the celiac branch of the vagus nerve (Table 2).

Ranking of severity of defecation disorders

Among the seven symptom subscales, the most prominent among patients that underwent TG were meal-related distress (including small stomach syndrome) (1st) and dumping (2nd). The ranking of the severity of symptoms of defecation disorders after TG revealed that diarrhea was the 4th and constipation was the 5th most severe. Meanwhile, the most severe symptoms after DG were constipation (1st) and diarrhea (2nd) (Table 3). Comparisons of the symptoms of defecation disorders between patients that underwent TG and those that had DG showed that diarrhea was significantly more severe after TG; however, no differences were observed between the severity of constipation after TG and after DG (Table 3).

Correlation with other postgastrectomy symptoms

Both diarrhea and constipation had significant positive correlations with all other postgastrectomy symptoms (P < 0.001). However, diarrhea had particularly strong correlations with dumping (1st) and indigestion (2nd) after both TG and DG (Table 4). On the other hand, constipation had particularly strong correlation with abdominal pain (1st) and meal-related distress (2nd) after TG; and meal-related distress (1st) and indigestion (2nd) after DG (Table 4).

Effects of defecation disorders symptoms on postgastrectomy living status

Multiple regression analysis was used to investigate the effects of diarrhea and constipation on five MOMs that belong to the living status domain covered in PGSAS-45. No significant effects due to diarrhea were seen after TG; however, constipation had significant adverse effects on the amount of food ingested per meal, necessity for additional meals, quality of ingestion, and ability to work (Table 5).

In patients that underwent DG, both diarrhea and constipation were found to be independent factors that had significant adverse effects on the amount of food ingested per meal, necessity for additional meals, quality of ingestion, and ability to work. However, the effect of constipation was larger in terms of the magnitude of effect size β. Diarrhea had significant adverse effects on weight loss, while constipation had no effect on weight loss (Table 5).

Effects of defecation disorders symptoms on postgastrectomy QOL

Multiple regression analysis was used to investigate the effect of diarrhea and constipation on six MOMs that belong to the QOL domain covered in PGSAS-45. For TG, diarrhea was found to have significant adverse effects on the mental component summary of SF-8 and had a significant tendency to worsen dissatisfaction with symptoms. Meanwhile, constipation had a significant adverse effect on all six MOMs

Table 2 Patients' characteristics, *n* (%)

	TG (*n* = 393)	DG (*n* = 1384)	*P* value
Age (yr)[1]	63.4 ± 9.2	61.8 ± 9.1	0.002[2]
Gender:			0.080[3]
Male	276 (71.0)	912 (66.2)	
Female	113 (29.0)	46 5(33.8)	
Postoperative period (mo)[1]	35.0 ± 24.6	37.6 ± 27.4	0.092[2]
Preoperative BMI (kg/m^2)[1]	23.0 ± 3.3	22.8 ± 3.0	0.176[2]
Surgical approach:			< 0.001[3]
Laparoscopic	97 (24.9)	567 (41.2)	
Open	293 (75.1)	809 (58.8)	
Celiac branch of vagus:			< 0.001[3]
Preserved	12 (3.1)	161 (11.9)	
Divided	371 (96.9)	1196 (88.1)	

[1]Data are presented as mean ± SD.
[2]*t*-test.
[3]Chi-square test.
BMI: Body mass index.

Table 3 Comparison of the severity and ranking of postgastrectomy symptoms between total and distal gastrectomy

	TG (*n* = 393)		DG (*n* = 1384)			
	Mean ± SD	Ranking	Mean ± SD	Ranking	*P* value	Cohen's *d*
Esophageal reflux SS	2.00 ± 1.03	6	1.64 ± 0.78	7	< 0.001	0.43
Abdominal pain SS	1.77 ± 0.79	7	1.68 ± 0.77	6	0.055	0.11
Meal-related distress SS	2.65 ± 1.11	1	2.07 ± 0.88	3	< 0.001	0.62
Indigestion SS	2.30 ± 0.91	3	2.01 ± 0.84	4	< 0.001	0.34
Diarrhea SS	2.28 ± 1.19	4	2.10 ± 1.11	2	0.007	0.16
Constipation SS	2.09 ± 0.93	5	2.19 ± 1.03	1	0.107	0.09
Dumping SS	2.30 ± 1.10	2	1.96 ± 1.01	5	< 0.001	0.32

Integrated subscales are italicized in the table. The interpretation of effect size, Cohen's *d*: Small, ≥ 0.2; medium, ≥ 0.5; large, ≥ 0.8. SS: Subscale.

(Table 5).

In patients that underwent DG, both diarrhea and constipation were factors that worsened all the MOMs in the QOL domain. The effects of diarrhea and constipation were similar in terms of the effect size β; however, the effect of constipation on the physical component summary (PCS) of SF-8 was larger (Table 5).

Background factors that worsen defecation disorders symptoms

Multiple regression analysis was used to investigate the background factors that strengthen diarrhea and constipation. Significant factors that worsened diarrhea were young age, division of the celiac branch of vagus, being a male, and undergoing total gastrectomy. Meanwhile, the significant factor that worsened constipation was being a female (Table 6).

DISCUSSION

The various symptoms that appear after gastrectomy and the resultant lower QOL are

Table 4 Correlation between each defecation disorder symptom and other postgastrectomy symptoms after total and distal gastrectomy

		TG (n = 393)			DG (n = 1384)		
		r	P value	Ranking	r	P value	Ranking
Diarrhea SS	*Esophageal reflux SS*	0.273	< 0.001	6	0.260	< 0.001	5
	Abdominal pain SS	0.340	< 0.001	4	0.377	< 0.001	3
	Meal-related distress SS	0.305	< 0.001	5	0.358	< 0.001	4
	Indigestion SS	0.443	< 0.001	2	0.420	< 0.001	2
	Constipation SS	0.341	< 0.001	3	0.232	< 0.001	6
	Dumping SS	0.447	< 0.001	1	0.467	< 0.001	1
Constipation SS	*Esophageal reflux SS*	0.392	< 0.001	3	0.396	< 0.001	5
	Abdominal pain SS	0.436	< 0.001	1	0.444	< 0.001	3
	Meal-related distress SS	0.402	< 0.001	2	0.479	< 0.001	1
	Indigestion SS	0.365	< 0.001	4	0.469	< 0.001	2
	Diarrhea SS	0.341	< 0.001	6	0.232	< 0.001	6
	Dumping SS	0.350	< 0.001	5	0.415	< 0.001	4

Integrated subscales are italicized in the table. The interpretation of effect size, Pearson correlation coefficient (r): Small, ≥ 0.1; medium, ≥ 0.3; large, ≥ 0.5. SS: Subscale.

known clinical problems[1-4]. Among these symptoms, dumping[5-8], small stomach syndrome[9-11], and esophageal reflux[12-14] are well known postgastrectomy symptoms, and have been reported to worsen living status and the QOL[11]. Symptoms of defecation disorders, such as diarrhea and constipation, also occur after gastrectomy[3,18]; however, these symptoms are relatively inconspicuous, particularly constipation. Therefore, their actual distribution, features, and effects on daily life have not been clarified.

Therefore, we used multiple data from the PGSAS to investigate defecation disorders among patients after conventional gastrectomy. Arranging symptoms of defecation disorders in order of severity among the seven symptom subscales that occur after gastrectomy showed that constipation and diarrhea were the most severe in patients that underwent DG. In those that had TG, diarrhea and constipation were ranked relatively low in terms of the severity of symptoms; however, the severity of constipation was almost the same as in those that underwent DG, and diarrhea, was significantly more severe than in those that underwent DG. The correlation results between each symptom of defecation disorders and other symptoms showed that diarrhea had a strong and significant correlation with dumping and indigestion after both TG and DG. Furthermore, constipation showed a strong positive correlation with abdominal pain and meal-related distress after TG; and meal-related distress and indigestion after DG. A multivariate analysis was performed to investigate the impact of defecation disorders on living status and QOL, and this showed that diarrhea had a small effect after TG, whereas constipation had an adverse effect on almost all MOMs. Both diarrhea and constipation had adverse effects on almost all MOMs of living status and QOL after DG, with the effects of constipation being slightly greater. A multivariate analysis that was performed to investigate those clinical factors that strengthened these defecation disorders showed that significant factors that worsened symptoms were being a male, being young, division of the celiac branch of the vagus nerve, and TG for diarrhea; and being a female for constipation. This is the first study to report the actual features, and effects of defecation disorders on daily life, as well as the background factors that enhance defecation disorders.

Various symptoms appear after gastrectomy and are known to interfere with the daily lives of the patients and cause clinical problems[1-4]. Our previous study on which postgastrectomy symptoms had a significant effect on the daily life of patients, showed that among the various postgastrectomy symptoms the daily life of patients after gastrectomy was impaired the most by meal-related distress (including small stomach syndrome) and dumping[11]. Furthermore, esophageal reflux and abdominal pain also had a clear effect on the daily life of patients after gastrectomy[11]. These

Table 5 The effects of defecation disorder symptoms on the living status and quality of life after total and distal gastrectomy (multiple regression analysis)

		TG (*n* = 393)						DG (*n* = 1384)					
		Diarrhea SS		*Constipation SS*				*Diarrhea SS*		*Constipation SS*			
		β	*P* value	β	*P* value	R^2	*P* value	β	*P* value	β	*P* value	R^2	*P* value
Living status	Change in BW	-0.003	0.960	-0.052	0.359	0.003	0.613	-0.061	0.034	-0.039	0.170	0.006	0.017
	Ingested amount of food per meal	0.087	0.113	-0.182	0.001	0.030	0.004	-0.150	< 0.001	-0.183	< 0.001	0.069	< 0.001
	Necessity for additional meals	-0.060	0.270	0.147	0.008	0.019	0.027	0.111	< 0.001	0.182	< 0.001	0.055	< 0.001
	Quality of ingestion SS	0.058	0.292	-0.177	0.001	0.028	0.006	-0.080	0.004	-0.138	< 0.001	0.030	< 0.001
	Ability for working	-0.071	0.189	0.275	< 0.001	0.068	< 0.001	0.122	< 0.001	0.260	< 0.001	0.097	< 0.001
QOL	Dissatisfaction with symptoms	0.100	0.055	0.276	< 0.001	0.105	< 0.001	0.257	< 0.001	0.244	< 0.001	0.155	< 0.001
	Dissatisfaction at the meal	0.012	0.813	0.275	< 0.001	0.078	< 0.001	0.266	< 0.001	0.269	< 0.001	0.176	< 0.001
	Dissatisfaction at working	0.066	0.205	0.292	< 0.001	0.102	< 0.001	0.234	< 0.001	0.237	< 0.001	0.137	< 0.001
	Dissatisfaction for daily life SS	0.067	0.189	0.338	< 0.001	0.134	< 0.001	0.297	< 0.001	0.294	< 0.001	0.216	< 0.001
	PCS of SF-8	-0.058	0.258	-0.323	< 0.001	0.120	< 0.001	-0.140	< 0.001	-0.242	< 0.001	0.094	< 0.001
	MCS of SF-8	-0.147	0.005	-0.227	< 0.001	0.096	< 0.001	-0.214	< 0.001	-0.244	< 0.001	0.130	< 0.001

Integrated subscales are italicized in the table. The interpretation of effect size, standardization coefficient of regression (*β*): Small, ≥ 0.1; medium, ≥ 0.3; large, ≥ 0.5. The interpretation of effect size, coefficient of determination (R^2): Small, ≥ 0.02; medium, ≥ 0.13; large, ≥ 0.26. QOL: Quality of life. SS: Subscale; BW: Body weight; PCS: Physical component summary; MCS: Mental component summary.

relatively prominent postgastrectomy symptoms have often been reported and are widely recognized[5-14]. However, symptoms of defecation disorders, such as diarrhea and constipation are also often seen after gastrectomy. Diarrhea has been reported to become worse after vagotomy[9,19] and gastrectomy[3,19], and it is a relatively well recognized symptom. Meanwhile, constipation has not received adequate attention and has not been sufficiently investigated.

The relationship between the type of surgical procedure and the ranking of the severity of defecation disorder symptoms showed that defecation disorders were most severe after DG, and constipation ranked first, and diarrhea ranked second. The most severe symptoms after TG were meal-related distress and dumping, which were the first and second, respectively. Symptoms of defecation disorders were ranked relatively low after TG, as diarrhea and constipation ranked fourth and fifth, respectively, among the seven symptoms. However, comparison of the symptom severity in patients that underwent DG showed that constipation was almost identical

Table 6 The effects of various clinical factors on defecation disorder symptoms after gastrectomy (multiple regression analysis)

	Objective variables			
	Diarrhea SS		*Constipation SS*	
Explanatory variables	β	*P* value	β	*P* value
Type of gastrectomy	0.061	0.013	-0.032	0.198
Postoperative period (mo)	-0.038	0.123	-0.010	0.697
Age (yr)	-0.102	< 0.0001	0.031	0.213
Gender (Male)	0.062	0.010	-0.073	0.003
Approach (laparoscopic)	-0.027	0.288	-0.002	0.947
Celiac branch of vagus (preserved)	-0.070	0.004	0.007	0.790
R^2	0.023	< 0.0001	0.007	0.068

Integrated subscales are italicized in the table. SS: Subscale

after either DG or TG, and diarrhea was significantly more severe after TG than after DG. In other words, the results showed that the symptoms of defecation disorders after TG were not necessarily mild compared to those that occur after DG, and that they were only less prominent due to the presence of other more severe symptoms. Therefore, paying attention to the occurrence of symptoms of defecation disorders and taking appropriate measures are also important after TG.

Correlation analyses between each symptom of defecation disorders and other postgastrectomy symptoms showed that diarrhea had a strong correlation with dumping (1st) and indigestion (2nd) for both TG and DG. Accelerated gastric emptying has been observed after gastrectomy[20,21], and the increased dumping and diarrhea that occurs is considered consistent with the pathogenesis of these symptoms[8,22,23]. Previous studies has revealed that there was a significant relationship between accelerated gastric emptying and diarrhea as well as dumping after gastrectomy[24,25]. The results of their study may, in part, explain the results of the present study.

Furthermore, constipation was strongly correlated with abdominal pain (1st) and meal-related distress (2nd) after TG; and meal-related distress (1st) and indigestion (2nd) after DG. Postprandial distress syndrome of functional dyspepsia, abdominal pain, abdominal distension and indigestion are known to be often accompanied with constipation[26,27]. Similarly, these symptoms were shown to be commonly accompanied with postgastrectomy constipation.

Symptoms of defecation disorders, such as diarrhea and constipation have been reported to decrease the QOL of patients with irritable bowel syndrome (IBS)[28,29]. Our results showed that symptoms of defecation disorders were factors that also had significantly adverse effects on living status and QOL in postgastrectomy patients. The magnitude of the effects of symptoms of defecation disorders on QOL after gastrectomy was significantly greater with regards to constipation than diarrhea after TG. Meanwhile, both constipation and diarrhea had significant effects on living status and QOL after DG, but constipation had slightly larger effects than diarrhea. Symptoms of defecation disorders, particularly constipation, are not prominent when compared to other characteristic postgastrectomy symptoms and are not often noticed. However, as our results showed that their effects on daily life were more significant than expected; hence, it is thought that taking appropriate measures to relieve these symptoms without overlooking their appearance would lead to the improved daily lives of patients.

Results of the multivariate analysis of factors that strengthen the symptoms of postgastrectomy defecation disorders showed that those significant independent factors in descending order of their effect on diarrhea were young age, division of the celiac branch of the vagus nerve, being male, and undergoing TG; and being female was a significant independent factor for constipation. The relationship between sex, age, and defecation disorders has been reported and diarrhea was found to be more significant in males and younger patients, while constipation was found to be more significant in females and older patients[30-32]. Regarding IBS, which is a functional gastrointestinal disease, it has also been reported that the diarrhea-type is more common among men, and the constipation-type is more common among women[33]. Reports on the relationship between surgical procedures and defecation disorders have shown that vagotomy worsens diarrhea[9,19], and diarrhea became more severe after TG compared to other surgical procedures[34,35]. The results of our study were consistent with those of previous reports, therefore, these clinical factors should be recognized as valid factors that worsen postgastrectomy defecation disorders.

Factors that cause diarrhea after gastrectomy were thought to include rapid influx of food into the small intestine due to accelerated gastric emptying[23], accelerated intestinal peristalsis due to increased load on the small intestine[36], changes in intestinal flora due to low or no acidity[18,37], decreased pancreatic exocrine function [38], and discrepancies in the timing of the mixing of food and duodenal fluid such as pancreatic juice and bile (postcibal pancreatico-biliary asynchrony)[39]. Meanwhile, factors that cause constipation after gastrectomy are thought to include reduced gastro-colic reflex due to vagotomy[40], decreased food intake (especially fiber, water, fat)[4,41], decreased abdominal pressure due to decreased skeletal muscle mass (especially abdominal muscles)[42], lack of exercise[43], and changes in the intestinal flora and intestinal environment[18,44].

Gastrectomy induces the above-mentioned changes that can induce defecation disorders; hence, attention must also be paid to the occurrence of defecation disorders after gastrectomy.

This study has several limitations. First, this is a retrospective study; there is a possibility that unknown clinical factors other than gastrectomy may have affected the results. Second, this is a cross-sectional study at a single-time point, and there are variations in the postoperative period. However, this effect is considered minimal even if present because it has been reported that postgastrectomy QOL decreased the most in the first month postoperatively and stabilized after approximately 6 mo to a year[45], and this study used stable patients over one year postoperatively as subjects. Despite these limitations, we were able to obtain clinically useful information on postgastrectomy defecation disorders by investigating a rather large number of cases from various perspectives using the PGSAS-45 questionnaire, which is specialized for the evaluation of postgastrectomy.

CONCLUSION

In this study, we were able to clarify the features of postgastrectomy defecation disorders and its effects on daily life, although they have not been regarded as significant problems to date. Attention has often been given to characteristic postgastrectomy symptoms, such as dumping and small stomach syndrome. However, since inconspicuous symptoms of defecation disorders (especially constipation) also affect the daily lives of post-operative patients to some extent, paying attention to the occurrence of these symptoms as well and implementing the appropriate guidance and treatment were considered necessary in order to improve the QOL of postgastrectomy patients.

ARTICLE HIGHLIGHTS

Research background

Various symptoms that can interfere with the postoperative quality of life (QOL) of patients occur after gastrectomy. The symptoms of defecation disorders, particularly constipation, are relatively modest compared to other postgastrectomy symptoms; therefore, their features and implications on the daily lives of patients have not been adequately investigated.

Research motivation

Several studies have investigated the effect of characteristic postgastrectomy symptoms, such as dumping, small stomach syndrome, and esophageal reflux on the daily lives of patients. However, the implications of symptoms of defecation disorders on patient’s QOL postgastrectomy are poorly understood.

Research objectives

The central goal of this research was to reveal the features of symptoms of defecation disorders and their effects on the daily lives of patients in a large population of gastrectomized patients using the Postgastrectomy Syndrome Assessment Scale (PGSAS)-45, and analyze the data derived using multivariate analysis.

Research methods

The 1777 patients who underwent total gastrectomy (TG; *n* = 393) or distal gastrectomy (DG; *n* = 1384) were enrolled in this study. The severity of defecation disorder symptoms, such as diarrhea and constipation, and their correlation with other postgastrectomy symptoms were examined. The importance of defecation disorder symptoms on the living states and QOL of postgastrectomy patients, and those clinical factors that affect the severity of defecation disorder symptoms were evaluated using multiple regression analysis.

Research results

The ranking of defecation disorder symptoms were unexpectedly high in DG among seven symptom subscales of PGSAS-45. There were significant correlation between defecation disorder symptoms and other postgastrectomy symptoms. The defecation disorder symptom, constipation in particular, impaired postgastrectomy living status and QOL. Male sex, younger age, division of the celiac branch of vagus nerve, and TG, independently worsened diarrhea, while female sex worsened constipation.

Research conclusions

The severity of symptoms of defecation disorders were unexpectedly high and both symptoms, particularly constipation, impaired the living status and QOL of patients after gastrectomy.

Research perspectives

Paying attention to the symptoms of defecation disorders as well as characteristic postgastrectomy symptoms and treating these symptoms adequately may improve the QOL of patients after gastrectomy.

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SYSTEMATIC REVIEWS

Is omentectomy necessary in the treatment of benign or malignant abdominal pathologies? A systematic review

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Abstract

BACKGROUND

The omentum is an organ that is easily sacrificed during abdominal surgery. The scope of omentectomy and whether a routine omentectomy should be performed are still unknown.

AIM

To review the literature in order to determine the physiological functions of the omentum and the roles it plays in pathological events in order to reveal the necessity for removal and preservation of the omentum.

METHODS

A clinical review of the English language literature based on the MEDLINE (PubMed) database was conducted using the keywords: "abdomen", "gastrointestinal", "tumor", "inflammation", "omental flap", "metastasis", "omentum", and "omentectomy". In addition, reports were also identified by systematically reviewing all references in retrieved papers.

RESULTS

The omentum functions as a natural barrier in areas where pathological processes occur in the abdominal cavity. The omentum limits and controls inflammatory and infectious pathologies that occur in the abdomen. It also aids in treatment due to its cellular functions including lymphatic drainage and phagocytosis. It shows similar behavior in tumors, but it cannot cope with increasing tumor burden. The stage of the disease changes due to the tumor mass it tries to control. Therefore, it is considered an indicator of poor prognosis. Due to this feature, the omentum is one of the first organs to be sacrificed during surgical procedures. However, there are many unknowns regarding the role and efficacy of the omentum in cancer.

CONCLUSION

The omentum is a unique organ that limits and controls inflammatory processes, foreign masses, and lesions that develop in the abdominal cavity. Omental flaps

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can be used in all anatomical areas, including the thorax, abdomen, pelvis, and extremities. The omentum is an organ that deserves the title of the abdominal policeman. It is generally accepted that the omentum should be removed in cases where there is tumor invasion. However, the positive or negative contribution of omental resection in the treatment of abdominal pathologies should be questioned.

Key Words: Abdomen; Inflammation; Stomach; Omentectomy; Omentum; Tumor

Core Tip: The omentum is a unique organ that monitors and controls inflammatory processes, foreign masses, and lesions that develop in the abdominal cavity. Omental flaps can be used in all anatomical areas, including the thorax, abdomen, pelvis, and extremities. The omentum is an organ that deserves the title of the abdominal policeman. It is generally accepted that the omentum should be removed in cases where there is tumor invasion. However, the positive or negative contribution of omental resection in the treatment of abdominal pathologies should be questioned.

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INTRODUCTION

The omentum is the first organ to be removed in cases scheduled for cytoreductive surgery (CRS). It is an organ that is easily sacrificed during various abdominal surgeries. The omentum is very effective in defending the body against pathogens as well as injuries. It is also considered to be an immunological organ[1,2].

The omentum can reach all parts of the abdomen[1-3]. It has an extensive lymphatic-functioning cellular network of mesenchymal cells, also called milky spots. Milky spots are primitive lymphatic tissue rich in macrophages and lymphocytes clustered around capillaries. These cells function as lymphoid tissue[4]. For example, this mechanism is found in many cases such as plastron appendicitis, diverticulitis, cholecystitis and so on. Milky spots capture antigens, and pathogenic organisms that are released into the peritoneum. Lymphatic ducts then remove them from the environment[2,5,6]. Nevertheless, when the tumor load increases, this system does not function well and becomes insufficient. An increase in tumor volume results in seeding to the omentum. This, in turn, causes tumor growth and nodular forms emerge due to the "polypeptide growth hormone" secreted by macrophages. Attachment and growth of tumor cells is also facilitated by another factor: The "angiogenesis factor" which is secreted from the omentum[2,6]. It not only allows formation of adhesives and neovascularization, but also protects the body and the organ against damage due to radiation. According to Morrison, the omentum is the "abdominal policeman"[1]. It tries to control the process by turning it into a local inflammation site. In cases with progression towards infection, the omentum attempts to control the progress by forming an abscess. This is a mechanism that is seen in diverticulitis, cholecystitis, and plastron appendicitis.

MATERIALS AND METHODS

The omentum is a unique organ due to its extraordinary functional properties in the abdomen, but the reasons for its frequent removal rather than preservation by surgeons have been questioned, according to literature data. With this aim, clinical retrospective and prospective studies have been carried out as well as experimental studies. A review of the English language literature based on a MEDLINE (PubMed) database was conducted using the keywords: "Abdomen", "gastrointestinal", "tumor", "inflammation", "omental flap", "metastasis", "omentum", and "omentectomy". In addition, reports were also found by systematically reviewing all references in retrieved papers.

RESULTS

Our literature search of MEDLINE found 1305 articles with the keyword "omentectomy". Articles related to the gastrointestinal system were separated with the help of other keywords. It was found that most of the articles were on gynecological (n = 519), stomach (n = 121), colorectal (n = 104), and appendix (n = 52) pathologies and were mostly related to tumors. Articles related to the gastrointestinal system were evaluated. A brief review of its use in the treatment or reconstruction of all other clinical pathologies was also included in this article. Interestingly, 1623 articles were identified with the keyword "omental flap". That is an interesting finding as it shows that the properties of the omentum are being used more.

DISCUSSION

Experimental studies

Experimental studies in rats indicated that the omentum displays angiogenic activity. Myofibroblasts in the wound area multiply due to increased blood supply. This, in return, promotes the healing process[7]. Nevertheless, another study showed just the opposite: In gastric ulcer-generated and omentectomy rats, the healing of ulcers was accelerated[8]. This contradiction indicates the need for further clinical studies on this subject.

Studies show that excess fat in the internal organs causes metabolic syndrome. In an experimental study, overweight rats subjected to omentectomy showed that nonalcoholic fatty liver, and metabolic syndrome were prevented[9]. C-reactive protein and interleukin-6 are believed to mediate the omentum, which results in leptin resistance and induces obesity.

Tumor behavior with or without the omentum has been a topic of several studies. In an experimental study by Lawrance *et al*[6] in rats, tumors were detected in the colon and omentum of 38% and 43% of rats, respectively, that underwent colon resection and anastomosis, and intraluminal injection of tumor cells. When the same procedure was repeated in the omentectomy group, tumors developed in 14% and 9% of rats in the anastomosis and abdominal cavity, respectively. While 53% and 79% of rats developed tumors in the anastomosis and abdominal cavity (omentum), respectively, in the groups intraperitoneally injected with tumor cells, and these rates were found to be 16% and 29%, respectively, in the omentectomy group. The omentum is believed to have a capturing function to collect and cover tumor cells, especially colon tumors. On the other hand, studies have reported that omentectomy rats developed fewer tumors (26%), as in an experimental colon cancer model performed by Weese *et al*[10]. Yokoyama *et al*[11] proposed that removal of the omentum with metastases would cause not only relapse but also tumor spread.

It was determined that dogs who underwent pancreatic resection and whose pancreatic duct were left open, and who underwent omentectomy had reduced survival, but those who did not undergo omentectomy lived much longer[12].

An experimental study on the role of omentectomy in the formation of adhesions suggested that rats subjected to omentectomy had a lower level of plasminogen activator and higher adhesions[13].

Gastrointestinal procedures

Gastrointestinal tumors: The first areas of attachment of tumors beyond the serosa, especially gastric tumors, are the peritoneal surfaces and the omentum. The omentum captures and surrounds (capturing function) any antigenic lesion in the abdominal cavity[3,6] (Figure 1). There are several studies that disagree on the necessity of omentectomy in gastric tumors. D2/modified D2 dissection is performed as a standard procedure in patients with stomach cancer. Barchi *et al*[14] in their series of 284 patients who underwent omentectomy, D2 dissection, and gastrectomy due to stomach cancer, found omental metastasis in only five patients (1.8%). They determined that omental metastasis prevalence was higher in patients who had T3-T4

Figure 1 The situation in which tumor cells from peritoneal seeding are captured and surrounded in a patient with gastric cancer.

lesions. They recommended avoiding omentectomy in patients with T1--2M0 tumors (diameter < 5.2 cm). They also stated that tumors in the greater omentum lymph nodes were more common in advanced stages of the disease. Hasegawa *et al*[15] studied 330 patients who had advanced-stage gastric tumors. They did not detect a statistical difference between the groups with omentum-sparing gastrectomy and gastric tumor and those who underwent omentectomy. In their study of 100 patients with gastric tumor, Jongerius *et al*[16] reported that 5% of the patients had omental metastases, and these were patients with T3 and T4 lymph node involvement. Moreover, they reported that the probability of omental metastasis in patients who were considered operable as a result of preoperative evaluations was very low and that omentectomy was not required during radical gastrectomy. Kim *et al*[17] reported that there was no significant difference between the groups after 38 mo of follow-up in their gastric tumor series of 37 cases who underwent partial (n = 17) or total omentectomy (n = 20).

Kurokawa *et al*[18] conducted a multicentric study involving 1204 patients with gastric tumor recruited from 57 hospitals. They divided the patients with gastric resection and D2 dissection into two groups: Omentectomy or bursectomy. They observed no significant difference between the groups concerning their 5-year survival rates. They also concluded and recommended D2 dissection and omentectomy as the routine approach for the surgical treatment of gastric cancer. Bursectomy is not routinely performed as it causes more complications such as fistula and bleeding and does not provide an advantage in terms of survival. For this reason, it is only performed in patients who suffer from posterior gastric wall tumors. On the other hand, there are also studies in the literature suggesting preservation of the omentum in patients with T1-T2 gastric cancer (M0). In advanced cases, however, there is a need for prospective clinical trials; because surgeons tend to perform radical surgery and omentectomy in advanced cases. In tumors with peritoneal involvement, such as pseudomyxoma peritonei, complete CRS can significantly contribute to survival. It can be an aggressive operation that involves organ resection and omentectomy[19].

Colon and rectum: There is a belief among surgeons that the remaining omentum after colectomy will cause adhesions in the small intestine. However, studies refute this. Ambroze *et al*[20] demonstrated that this belief was incorrect in their large series of colectomy, ileoanal anastomosis, and omentectomy. They observed no significant difference in ileus.

CRS is also performed to eliminate the macroscopic and microscopic spread of colorectal cancers. In a large data analysis performed by Bonnefoy *et al*[21], they found that 71% of patients in the colorectal cancer series of 337 cases who underwent total omentectomy had macroscopic omental metastasis. They also found that 17% of patients without macroscopic omental metastases had microscopic metastases in the omentum. They recommend routine omentectomy in colorectal cancer cases with peritoneal metastasis. Complete supracolic omentectomy is recommended as part of CRS, especially in mucinous type colorectal cancer[22].

Hepato-pancreato-biliary: The omentum may be involved in many benign and malignant pathologies of the liver. In inflammatory liver lesions, the omentum adheres to the lesion and tries to limit it. In peripheral tumors and after liver surgery, the omentum may adhere to the liver and form new collaterals. The omentum is one of the two organs that most commonly form a collateral circulation with the liver. Because the omentum is free and mobile, it can reach every segment of the liver. It may contribute to the blood supply and venous drainage with collaterals that develop in cirrhotic or tumor patients[23]. Chu *et al*[24] reported that new collaterals developed in patients with portal hypertension who underwent partial splenectomy and retrosternal omental flap fixation to prevent complications due to esophageal varices and may be effective against hemostasis and hypersplenism. Studies suggest repetitive aggressive surgeries and adding omentectomy to the procedure in patients with ruptured hepatocellular carcinoma[25]. The omentum can also be used to fill cavities (omentoplasty) that occur during the treatment of liver hydatid cysts (Figure 2)[26].

In acute cholecystitis, the omentum surrounding the inflamed gallbladder is commonly seen (Figure 3). As in acute appendicitis, the omentum surrounding the gallbladder during cholecystitis attacks may form permanent adhesions even with regression of inflammation. In the case of progression of the inflammatory process and perforation of the gallbladder, it can contribute to pericholecystic abscess formation, keep the infection local, and prevent the spread of infection. Cases in which bile duct injury developed and the resulting defect was closed with an omentum flap have also been reported in the literature[27].

Omentectomy has no place in the surgery of pancreatic tumors. However, it is often added to the procedure, especially in locally advanced distal pancreatic tumors[28]. Although different results have been found when the anastomosis is wrapped with an omental flap in patients who underwent pancreaticoduodenectomy, a recent meta-analysis reported that an omental wrap might be beneficial in reducing complications [29].

Appendix: Appendectomy is the only treatment option in acute or perforated appendicitis. However, the management of plastron appendicitis bordered and surrounded by the omentum is different. Plastron appendicitis occurs in 6% of appendicitis cases. The omentum is the organ that makes the most significant contribution to plastron formation. In plastron appendicitis, which manifests as a mass in the right lower quadrant, the omentum limits the inflammatory process and tries to keep it under control. A conservative approach is the first option in patients with plastron appendicitis. However, the presence of tumors and inflammatory bowel diseases that can mimic appendicitis should be investigated with colonoscopy and computed tomography (CT) imaging in healed patients[30].

Complete omental resection is performed as a routine procedure in patients who have decided to undergo CRS. In addition to appendectomy, cecectomy, right hemicolectomy, and lymph node dissections are also performed in epithelial tumors of the appendix[31,32]. On the other hand, pseudomyxoma peritonei (PMP) is one of the most lethal complications of appendix tumors. PMP is seen in 9% of low-grade tumors, and it is reported that PMP develops in 67.9% of perforated mucinous neoplasms. CRS and hyperthermic intraperitoneal chemotherapy are also recommended for appendiceal neoplasms[33,34].

Bariatric surgery: Bariatric surgery for obesity is one of the most performed procedures in the last two decades. Gastrointestinal resections and bypass procedures are the most preferred methods. Meta-analyses have reported that adding omentectomy to the procedure during bariatric surgery has no positive contribution other than a minimal reduction in body mass index[35]. Another study indicated that omentectomy included in Roux-en-Y gastric bypass (RYGB) surgery was not successful in reducing insulin resistance. There is literature concerning metabolically positive feedbacks in similar cases in which omentectomy was included in the RYGB. Still there is a need for extensive and prospective studies[36].

Reconstruction tool: The omentum promotes healing in the areas where it is placed and in surrounding organs and facilitates the recovery of function. Omental free flaps can be used in all anatomical areas, including the thorax, abdomen, and pelvis[37]. Fistulas are a well-known entity that can cause very complex problems and have a high risk of morbidity and mortality.

The omentum can be used to seal, shield, wrap, to fill any defects, especially peptic ulcer perforations. Placing and fixing the omental flap in the perforation area (Graham's repair) in peptic ulcer perforations is a method that has been known since 1937 and is still in use[38,39]. It has been reported that a falciform ligament was used to close the perforation in a patient who underwent total omentectomy for intraabdominal tumors and developed peptic ulcer perforation over time[40]. Several clinical

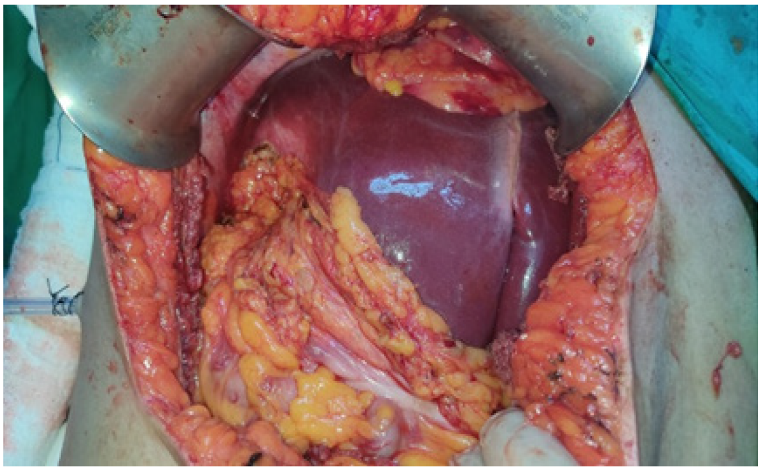

Figure 2 This image shows a patient in whom an omental flap was used to fill the cavity of the liver hydatid cyst.

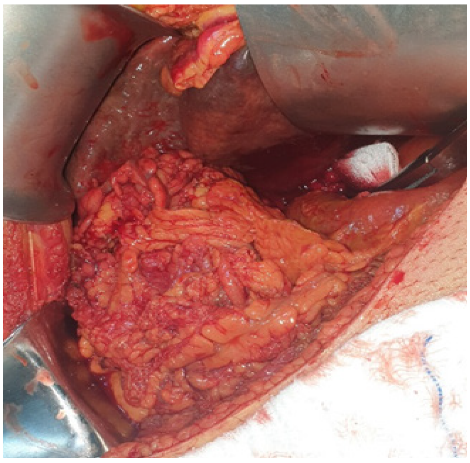

Figure 3 In a patient with acute cholecystitis, the omentum appears to surround the gallbladder and adhere to it.

studies have investigated the contribution of the omentum to healing following it being wrapped around the anastomosis. Studies have reported that wrapping intrathoracic esophagogastric anastomoses with the omentum decreases complications such as anastomosis opening and stricture development. In an esophagectomy series of 255 cases by Dai *et al*[38], fewer complications were reported in the group in which the omentum was wrapped around the anastomosis. In their study of 171 cases of colon resection in which anastomoses were protected by omental wrapping, Agnifili *et al*[41] observed a positive impact of omental wraps. They concluded that omentectomy should not be performed in colorectal surgery.

Abdominal procedures

Gynecological tumor surgery: Gynecological tumor surgery is one of the most common abdominal operations with omentectomy. Surgeons tend to prefer aggressive resection during laparotomy due to peritonitis carcinomatosis-like appearance. Specifically, omentectomy has a significant role in staging of endometrium- and ovarian-origin tumors[42-44]. In gynecological tumors, omental involvement is observed in 9%-37.5% of cases[45-47]. Involvement of the omentum indicates a poor prognosis. In order to reduce the tumor burden, omentectomy is added to the procedures during CRS. Nevertheless, the contribution of omentectomy to survival is still debated. As omental involvement is minimal in early-stage tumors, omentectomy does not affect survival. Therefore, unless there is macroscopic involvement, omentectomy should be avoided[48]. In the early stages, random omental biopsies can help in reliable staging.

Adhesions: Adhesions are the most common complications after abdominal surgery. The omentum has a tendency to gravitate towards areas of surgery. In their study, Ariake *et al*[49] focused on 113 patients who underwent surgery due to intestine obstruction caused by adhesions. In the 5-year follow-up, they observed that in 18 patients (20.8%) the ileus recurred. They also found that 54.5% of the patients with omentectomy and 21.3% without omentectomy developed ileus. This indicates that omentectomy may be considered a risk factor for ileus formation.

(1) Capturing function: The omentum also has a capturing function. The omentum tries to limit foreign bodies that remain or emerge in the abdominal cavity after surgery by surrounding them. It wraps the stones that are spilled from the gallbladder during cholecystectomies. It can also turn them into an inflammatory mass[50]. The tracing of stones without clinical symptoms is possible. However, due to rarely spilled stones, abscesses originating from the omentum may become a fistula. In such cases, without omentectomy, drainage may suffice.

(2) Shielding system: A shielding system (omental spacer) using the omentum may help prevent complications such as radiation enteritis, which is a severe pelvic irradiation complication. Yamada *et al*[51] reported that the created omental spacer was very useful in preventing radiation to the intestines.

(3) Hernia incarceration: The most important prognostic factor of hernia incarceration is hernia content. With penetration of the omentum into the hernia sac, the possibility of strangulation of the intestines decreases (Figure 4). In a study of 2184 pediatric patients, the rate of incarcerated hernia was 1.6%. Intestine (62%) and omentum (12%) were the most common organs in the hernia sac. Partial bowel resection was reported in four cases, and partial omentectomy in only 2 cases[52].

Miscellaneous/other conditions

Omental torsion and necrosis: Omental torsion and necrosis are infrequent entities which can mimic many clinical pathologies. Abdominal CT is helpful in the diagnosis. In patients who do not recover following medical treatment (Figure 5), surgery can resolve the problem. Therefore, in cases who undergo exploration, the laparoscopic approach should be the first option. Some surgeons also want to perform an appendectomy while laparoscopically resecting the omental necrosis[53].

The omentum also limits and controls infections. If the infection has caused too much damage to the omentum, omentectomy may be necessary. In the literature, there are cases where laparotomy was performed for abscesses due to melioidosis (*Burkholderia pseudomallei*). As the mass detected during laparotomy and lesions in the omentum resemble a tumor implant, the tendency to perform omentectomy increases. Omental involvement in patients with abdominal tuberculosis may mimic ovarian tumor[54,55]. In order to prevent unnecessary radical surgical resection, it is more appropriate to perform laparoscopic exploration and biopsy first.

Some clinical studies have shown that omentectomy affects inflammation-related genes. A clinical study by Tamboli *et al*[56] observed that inflammation in skeletal muscles decreased after RYGB surgery, which was greater in those who also underwent omentectomy. Adding omentectomy to a partial jejunal resection in patients with metabolic syndrome resulted in better-controlled type 2 diabetes mellitus [57].

Peritoneal dialysis catheter (Tenckhoff catheter) dysfunction is a common problem in nephrology clinics (23%-36%). Among its most commonly reported causes are malposition and omental wrap. There are reports indicating that partial omentectomy in some patients with catheter dysfunction contributes to the dialysis catheter being more functional. On the contrary, in another clinical study involving 154 patients with peritoneal dialysis catheters, it was concluded that omentectomy had no contribution to catheter occlusion[58].

The use of omental flaps and lymph nodes in the treatment of lymphedema can significantly contribute to patients' quality of life and wound healing[59].

As in peptic ulcer perforation and selected cases with bile duct trauma, many case reports have undergone reconstruction with an omental flap for the treatment of bronchopleural fistula[60].

CONCLUSION

The omentum is a unique organ with unlimited mobility and protective physiological properties in the abdomen. However, this does not prevent the omentum from being one of the first organs to be sacrificed in radical abdominal surgery. Omental flaps can be used in all anatomical areas, including the thorax, abdomen, pelvis, and extremities. It is an organ that is first affected by inflammatory and pathological events that occur

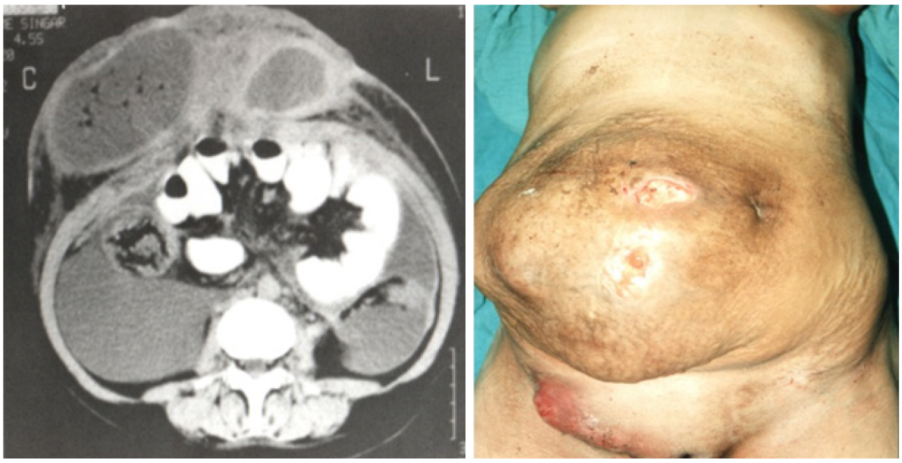

Figure 4 Computed tomography view of omental strangulation and necrosis findings in our patient who underwent laparotomy due to strangulated incisional hernia and right femoral hernia.

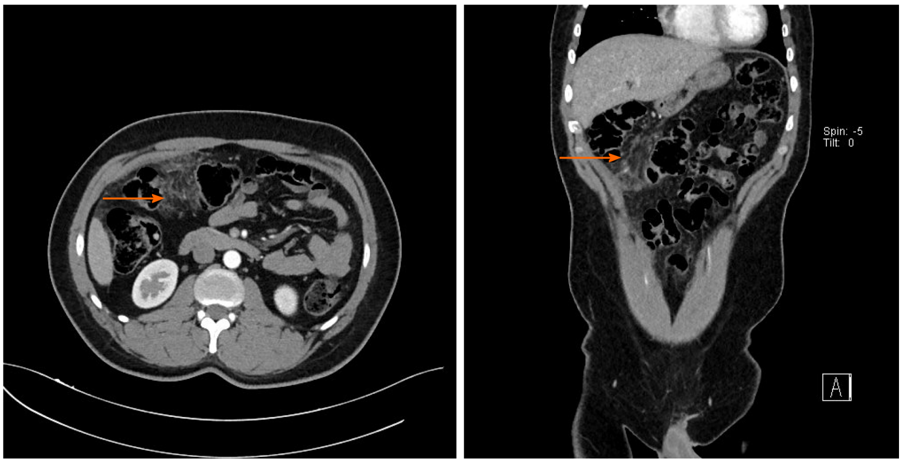

Figure 5 Computed tomography image of a patient with omental necrosis (arrow) detected in the postoperative period.

in the abdominal cavity, limits developing pathological processes, and tries to control them, saving treatment time.

The omentum is called the “abdominal policeman”. It limits and controls inflammatory and infectious pathologies, and thus contributes to patient survival. It shows similar behavior in tumors, but it cannot cope with increasing tumor burden and the stage of the disease changes due to the tumor mass it tries to control, and therefore it is considered an indicator of poor prognosis. Experimental and clinical studies are needed to determine the behavior of the omentum in different pathological conditions. During this process, the effect of omental resection on morbidity, mortality and survival in the treatment of abdominal pathologies should be carefully calculated in each case.

ARTICLE HIGHLIGHTS

Research background

The omentum is an organ that is easily sacrificed during various abdominal surgeries. It is one of the first organs to be removed in cases scheduled for cytoreductive surgery.

Research motivation

As it plays an effective role in defense against pathogens and injuries, the omentum is classified as an immunological organ. It can also reach almost anywhere in the abdomen.

Research objectives

The omentum is a unique organ due to its extraordinary functional properties in the abdomen, but the reasons for its frequent removal rather than preservation by surgeons have been questioned in the light of literature data.

Research methods

A review of the English language literature based on the MEDLINE (PubMed) database was conducted using the keywords "abdomen", "gastrointestinal", "tumor", "inflammation", "omental flap", "metastasis", "omentum", and "omentectomy".

Research results

Our literature search found 1305 articles with the keyword "omentectomy". It was found that most of the articles were on gynecological (n = 519), stomach (n = 121), colorectal (n = 104), and appendix (n = 52) pathologies and were mostly related to tumors. A brief review of its use in the treatment or reconstruction of other clinical pathologies was also included in this article.

Research conclusions

The omentum tries to limit and control inflammatory and pathological events that occur in the abdomen. As it limits and controls inflammatory and infectious pathologies, it contributes to the survival of the patient.

Research perspectives

The omentum is not an organ that can be easily sacrificed at random. Experimental and prospective clinical studies on the control of tumor spread, control of infection, adhesion formation and the protective role of the omentum in patients undergoing omentectomy are needed.

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SCIENTOMETRICS

Global trends in research related to sleeve gastrectomy: A bibliometric and visualized study

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Abstract

BACKGROUND

One of the most popular bariatric procedures is sleeve gastrectomy, and it has become significantly more common in recent years.

AIM

To evaluate the research activity in sleeve gastrectomy over the last two decades, and to visualize the hot spots and emerging trends in this type of bariatric surgery

to declare.

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using bibliometric methods.

METHODS

The Scopus database was used to search for publications related to sleeve gastrectomy. The retrieved publications were reviewed in terms of year of publication, type of study, country of origin, institutions, journals, and citation patterns by using descriptive analysis. Collaboration network and term co-occurrence analysis were visualized by using VOSviewer software.

RESULTS

The search strategy yielded a total of 6508 publications on sleeve gastrectomy from 2001 to 2020. As regards the document type, the majority were articles (n = 5230; 80.36%), followed by reviews (n = 544; 8.36%). The top three countries are the United States, with 1983 publications (30.47%), followed by France (600; 9.22%) and Italy (417; 6.71%). The most cited publication was published in 2012 by Schauer *et al* in the *New England Journal of Medicine* (n = 1435 citations). This publication found that weight loss was greater in the sleeve gastrectomy group than in the medical therapy group. Furthermore, this study demonstrated that 12 mo of medical therapy plus bariatric surgery greatly improved glycemic regulation in obese patients with uncontrolled type 2 diabetes compared with medical therapy alone. The focus of the current literature on sleeve gastrectomy was directed toward several themes such as morbidity and potential complications, the complexity of the procedure and different surgical approaches, and diabetes and body mass index in correlation to sleeve gastrectomy.

CONCLUSION

The number of sleeve gastrectomy publications has gradually grown over the last 20 years. This bibliometric analysis could help researchers better understand the knowledge base and research frontiers surrounding sleeve gastrectomy. In addition, future studies may focus on emerging research hotspots.

Key Words: Sleeve gastrectomy; Bibliometric; Scopus; VOSviewer; Bariatric surgery

Core Tip: One of the most popular bariatric procedures is sleeve gastrectomy, and it has become significantly more common in recent years. Therefore, this study intends to evaluate the research activity in sleeve gastrectomy over the last two decades and quantitatively estimate the hot spots and emerging trends in this type of bariatric surgery with bibliometric methods and enable researchers to identify new areas for potential development. The current literature on sleeve gastrectomy was directed toward several themes such as morbidity and potential complications, the complexity of the procedure and different surgical approaches, and diabetes mellitus and body mass index in correlation with sleeve gastrectomy.

Citation: Barqawi A, Abushamma FA, Akkawi M, Al-Jabi SW, Shahwan MJ, Jairoun AA, Zyoud SH. Global trends in research related to sleeve gastrectomy: A bibliometric and visualized study. *World J Gastrointest Surg* 2021; 13(11): 1509-1522
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INTRODUCTION

Bariatric surgery has been trending since the twentieth century as hundreds of articles discussed different surgical approaches in the prospect of feasibility, complication rate, and long-term outcomes[1]. Bariatric surgery is a broad term that does entail different surgical approaches, including open and laparoscopic surgery. In 2018, 696191 surgical and endoluminal procedures were performed under the umbrella of bariatric surgery [2]. Most of the procedures were surgical approaches rather than endoluminal, such as sleeve gastrectomy (SG), one anastomosis gastric bypass (OAGB), and Roux-en-Y gastric bypass (RYGB). Sleeve gastrectomy remains the most popular procedure worldwide, with thousands of articles and reviews debating its benefits, complications, and long-term outcomes[3-10]. The reasons behind sleeve gastrectomy being a trending topic over the last twenty years are that sleeve gastrectomy is technically less demanding, the learning curve is shorter than other surgical approaches, and it is purely physiological as no anastomosis or bypass is required. The previously mentioned facts support sleeve gastrectomy as it should be associated with less nutritional deficiency and low short-term complications[11-13].

The volume of scientific evidence related to sleeve gastrectomy is enormous, and the annually published article curve is steeply growing[14,15]. Still, it is poorly correlated and not connected to a simple algorithm or graph to explain the pattern and to display the topics that still demand more scientific input so researchers can work on them. Bibliometric analysis revealed that surgical activity and scientific publications in bariatric surgery is a rapidly developing research field[14-18]. However, a quantitative analysis of sleeve gastrectomy has not yet been conducted. Therefore, this study intends to evaluate the research activity in sleeve gastrectomy over the last two decades and quantitatively estimate the hot spots and emerging trends in this type of bariatric surgery with bibliometric methods and enable researchers to identify new areas for potential development.

MATERIALS AND METHODS

Sources of the Data

We downloaded and extracted the publications from the Scopus database. All data were acquired on January 9, 2021. Despite the fact that there are many databases available for worldwide research evaluation, the current study selected the Scopus database because it included rich information such as country distribution and citation analysis. It has been widely used in the field of bibliometric studies[19-22].

Search strategy

The published papers were searched in the recent twenty years (from 2001 to 2020). We used the keyword “Sleeve gastrectomy” or "Gastric Sleeve" in the title and/or abstracts because we are concerned with sleeve gastrectomy per se rather than related terminology. The search strategy was as follows: (TITLE-ABS ("Sleeve gastrectomy") OR TITLE-ABS ("Gastric Sleeve")) AND PUBYEAR > 2000 AND PUBYEAR < 2021.

Bibliometric Analysis

In this analysis, descriptive statistics are primarily used. Scopus's intrinsic role categorized and analyzed research trends and publication features, such as the distribution of countries, organizations, journals, and citation pattern areas. Besides, the top 20 most cited articles were also listed.

Statistical analysis

The Visualization of Similarity viewer (VOSviewer 1.6.16) software[23] was used to create collaboration network maps regarding the cooccurrences of all terms in the title and abstract to determine the hotspots related to sleeve gastrectomy research. The visualization of international collaboration to identify the most prominent countries visualizing their relationships was also accomplished using VOSviewer. The data are compared over three 20-year time spans to see how the term used has evolved over time.

RESULTS

Volume and types of publications

The search strategy yielded a total of 6,508 publications on sleeve gastrectomy from 2001 to 2020. As regards the document type, the majority were articles (n = 5230; 80.36%), followed by reviews (n = 544; 8.36%), letters (n = 250; 3.84%), editorials (n = 172; 2.64%). Other document types such as notes, conferences, papers, or errata amounted to 312 (4.79%) publications. The growth track over the last 20 years (Figure 1) has seen two stages: the first (2001–2010), which had a very slow development period, and the second (2011–2020), which had a very fast development

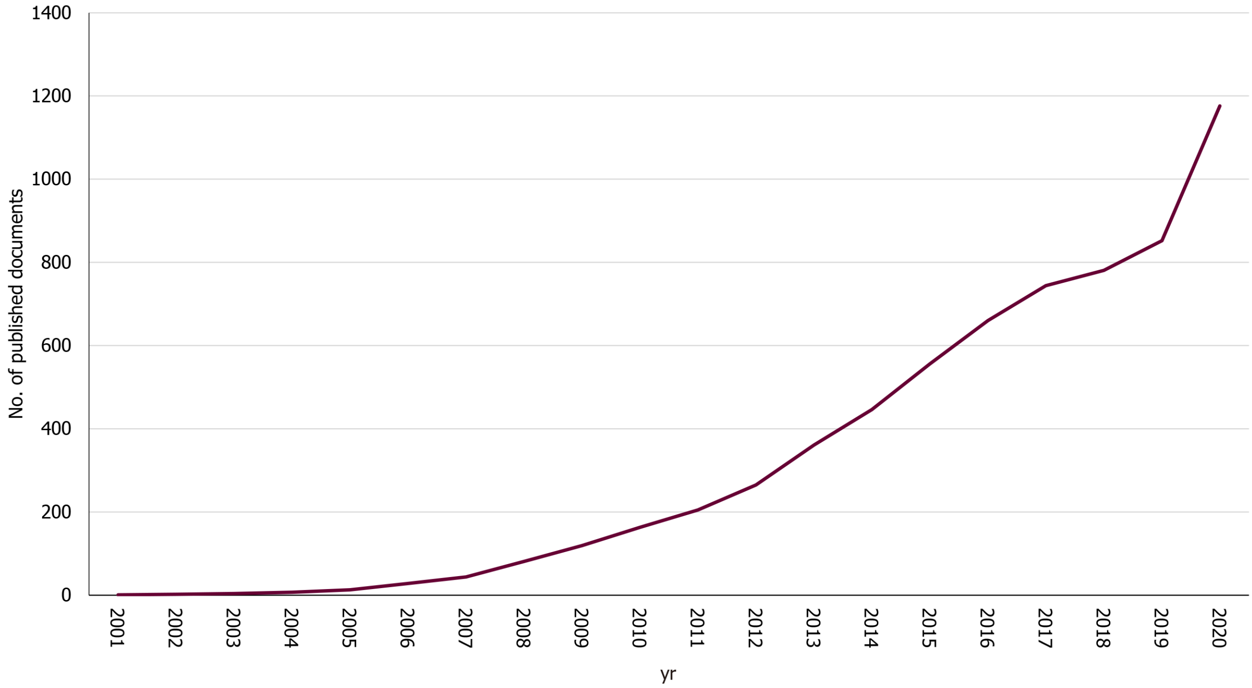

Figure 1 Number of publications on sleeve gastrectomy per year (2001-2020).

period. The average publication output increased from 46.2 publications per year in the initial period to 604.6 publications per year in the development period. Furthermore, the number of publication outputs during the development period increased from 205 publications in 2011 to 1,176 publications in 2020.

Top prolific countries

The contributions from each country were counted. The top ten most profitable countries for sleeve gastrectomy are listed in Table 1, along with the total number of publications for each region. Researchers from the United States of America reported about 1983 publications (30.5%) of the science material relating to sleeve gastrectomy over the last 20 years, resulting in the highest pool of evidence about sleeve gastrectomy. France (n = 600, 9.2%) and Italy (n = 417, 6.4%) are the next two countries. Figure 2 illustrates a network mapping of international research collaboration between countries with a minimum research output of 10 documents on sleeve gastrectomy. The United States and France are the countries with the most active research and collaboration.

Top prolific institutions

Table 2 shows each institution's contribution to the top ten most profitable institutions for sleeve gastrectomy research. The United States and France share six out of the ten most productive institutions for sleeve gastrectomy. The top institution is *Cleveland Clinic Foundation* with a total of 130 publications (2%). The second and third institutions were France-based as both *Inserm institution* and *AP-HP Assistance Publique - Hopitaux de Paris* shared 125 (3.4%) published articles.

Top prolific journals

Concerning the individual journals, *Obesity Surgery* published the largest number of sleeve gastrectomy publications (n = 1744, 27%). This is followed by *Surgery for Obesity and Related Diseases* (n = 1040, 16%). Both journals share the major output of research and articles related to sleeve gastrectomy. Surgical endoscopy is the third on the list with 304 (4.7%) published articles. Table 3 lists the top ten most productive journals for sleeve gastrectomy research.

Top-cited publications

The top 20 most cited papers on sleeve gastrectomy are summarized in Table 4. The top 20 most cited articles had citations ranging from 556 to 1435[1,24-42]. The top-cited article is bariatric surgery *vs* intensive medical therapy in obese patients with diabetes,

Table 1 Top 10 most productive countries in sleeve gastrectomy research

Ranking	Country	Number of publications	%
1st	United States	1983	30.47
2nd	France	600	9.22
3rd	Italy	417	6.41
4th	Spain	356	5.47
5th	United Kingdom	316	4.86
6th	China	297	4.56
7th	Germany	281	4.32
8th	Turkey	272	4.18
9th	Canada	243	3.73
10th	Israel	190	2.92

Table 2 Top 10 most productive institutions in sleeve gastrectomy research

Ranking	Institute	Country	Number of publications	%
1st	*Cleveland Clinic Foundation*	United States	130	2.00
2nd	*Inserm*	France	118	1.81
3rd	*AP-HP Assistance Publique - Hopitaux de Paris*	France	107	1.64
4th	*Università degli Studi di Roma La Sapienza*	Italy	93	1.43
5th	*Tel Aviv University*	Israel	84	1.29
6th	*University of Michigan, Ann Arbor*	United States	82	1.26
7th	*Harvard Medical School*	United States	81	1.24
8th	*Università degli Studi di Napoli Federico II*	Italy	70	1.08
9th	*Centre Hospitalier Universitaire de Nice, Hôpital l'Archet*	France	68	1.04
10th	*Hôpital du Sacré-Cœur-de-Montréal*	Canada	65	1.00

published in 2012 in the *New England Journal of Medicine* with 1435 citations. The second top-cited article is Bariatric surgery *vs* intensive medical therapy for diabetes - 3-Year outcomes, which was published in 2014 in the *New England Journal of Medicine* with 983 citations. The third and fourth top-cited publications were published in *Obesity Surgery* in 2013 and 2015 with 1751 total citations per both documents, retrospectively. A Cochrane review was published in 2014 with total 806 citations discussing surgery for weight loss in adults, which was written by Colquitt JL.

Sleeve gastrectomy research themes, frequent topics, and trends

The visualization of the most frequently found terms in the title and abstracts of the collected documents (a minimum of 50 times) resulted in three major colored clusters (red, green, and blue), which reflect the three research topics as the highest research priority topics (Figure 3). Cluster number 1 (red color) included terms related to morbidity and potential complications topics such as conversion, leak, and fistula; Cluster number 2 (blue color) included terms related to the complexity of the procedure and different surgical approach topics such laparoscopy; and Cluster number 3 (green color) included terms related to diabetes and BMI in correlation to sleeve gastrectomy. Figure 4 shows an overlay visualization in which the VOSviewer was used to add colors to the terms according to the year of publication. Blue terms emerged first, followed by yellow terms later. Most sleeve gastrectomy research centered on terms relating to morbidity and surgical complications before 2016, namely, in the early stages of research in this field. The current trends presented the terms associated with surgical techniques and the correlation of sleeve gastrectomy to diabetes mellitus and body mass index.

Table 3 Top 10 most productive journals in sleeve gastrectomy research

Ranking	Journal	Number of publications	%	IF[a]
1st	*Obesity Surgery*	1744	26.80	3.412
2nd	*Surgery for Obesity and Related Diseases*	1040	15.98	3.812
3rd	*Surgical Endoscopy*	304	4.67	3.149
4th	*Bariatric Surgical Practice and Patient Care*	85	1.31	0.391
5th	*Journal of Laparoendoscopic and Advanced Surgical Techniques*	75	1.15	1.310
6th	*Surgical Laparoscopy Endoscopy and Percutaneous Techniques*	61	0.94	1.382
7th	*International Journal of Surgery*	57	0.88	3.352
8th	*Annals of Surgery*	56	0.86	10.130
9th	*Journal of Gastrointestinal Surgery*	54	0.83	2.573
10th	*International Journal of Surgery Case Reports*	53	0.81	NA

[a]Impact factors based on Journal Citation Reports 2019 from Clarivate Analytics. IF: Impact factors; NA: Not available.

DISCUSSION

This bibliometric analysis presents a comprehensive overview of the growth of the scientific literature regarding sleeve gastrectomy research in the recent twenty years. Sleeve gastrectomy is one of the most common bariatric procedures and one of the most researched[14,15,17,18,43-46]. The global patterns of published papers in sleeve gastrectomy research showed statistically continued growth over time. While the number of publications increased gradually, the year-over-year percentage of publications increased noticeably in the last two years. Thus, sleeve gastrectomy-related research has recently shown considerable growth, which can be recognized by researchers' contributions globally. To evaluate the research contributions at the global level, total research publication output in the field of sleeve gastrectomy has been applied as an indicator for scientific research production. In accordance with the observed increase of research regarding morbidity and surgical complications in general[47-53], our results demonstrated a continued increase of sleeve gastrectomy literature since 2001. This progress was particularly prominent since 2010, which coincided with the shift in focusing on developing tools for surgical techniques[54-57] and the correlation of sleeve gastrectomy with diabetes mellitus and body mass index [58-67].

In the current study, the United States has the highest publication rate in research production with sleeve gastrectomy, which matches what has also been found in other therapeutic approaches to obesity treatment[14,15,18,43-46]. France was ranked as the second in the number of publications in the field of sleeve gastrectomy, followed by Italy. This can be attributed to the development of countries' scientific systems and the number of researchers[68] or due to the high prevalence of overweight and obesity in these countries[69,70].

According to Angrisani *et al*[1] the United States had the largest number of bariatric procedures and the United States is the leading country globally. In addition, according to a review of bariatric practice in the United States, laparoscopic sleeve gastrectomy has become the most commonly performed bariatric procedure[71]. According to data from Europe, France currently has the highest rate of bariatric surgery[72]. Despite the comparatively low prevalence rates of 3.1% and 1.2% for grade II and III obesity, respectively, in France in comparison to other European countries, this may be clarified by a favorable policy contextual and unrestricted access to bariatric surgery in France[73]. France's current distinction in comparison to other European countries is the current and increasing preference for laparoscopic sleeve gastrectomy over other procedures[73].

The current findings are in accord with a previous bibliometric study indicating that the United States were the most productive country in research related to the microbiome related to irritable bowel syndrome[74]. These findings seem to be in agreement with other bibliometric research that found the United States and France were the leading scientific countries on Chagas cardiomyopathy[75]. On the other hand, as revealed by previous bibliometric studies[76-80], the United States took the

Table 4 Top-cited papers from 2001 to 2020 in sleeve gastrectomy research, based on the number of citations in Scopus

Ranking	Authors	Title	Year	Source title	Cited by
1st	Schauer *et al*[42]	"Bariatric surgery versus intensive medical therapy in obese patients with diabetes"	2012	*New England Journal of Medicine*	1435
2nd	Schauer *et al*[41]	"Bariatric surgery versus intensive medical therapy for diabetes – 3 yr outcomes"	2014	*New England Journal of Medicine*	983
3rd	Buchwald and Oien[25]	"Metabolic/bariatric surgery worldwide 2011"	2013	*Obesity Surgery*	902
4th	Angrisani *et al* [1]	"Bariatric Surgery Worldwide 2013"	2015	*Obesity Surgery*	849
5th	Schauer *et al*[40]	"Bariatric surgery versus intensive medical therapy for diabetes – 5 yr outcomes"	2017	*New England Journal of Medicine*	845
6th	Colquitt *et al* [27]	"Surgery for weight loss in adults"	2014	*Cochrane Database of Systematic Reviews*	806
7th	Chang *et al*[26]	"The effectiveness and risks of bariatric surgery an updated systematic review and meta-analysis, 2003-2012"	2014	*JAMA Surgery*	768
8th	Buchwald and Oien[24]	"Metabolic/bariatric surgery worldwide 2008"	2009	*Obesity Surgery*	635
9th	Mechanick *et al* [34]	"Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient-2013 update: Cosponsored by American association of clinical endocrinologists, the obesity society, and American society for metabolic and bariatric surgery"	2013	*Obesity*	634
10th	Picot *et al*[36]	"The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: A systematic review and economic evaluation"	2009	*Health Technology Assessment*	616
11th	Karamanakos *et al*[33]	"Weight loss, appetite suppression, and changes in fasting and postprandial ghrelin and peptide-yy levels after roux-en-y gastric bypass and sleeve gastrectomy a prospective, double blind study"	2008	*Annals of Surgery*	596
12th	Regan *et al*[37]	"Early Experience with Two-Stage Laparoscopic Roux-en-Y Gastric Bypass as an Alternative in the Super-Super Obese Patient"	2003	*Obesity Surgery*	592
13th	Rosenthal *et al* [38]	"International sleeve gastrectomy expert panel consensus statement: Best practice guidelines based on experience of > 12,000 cases"	2012	*Surgery for Obesity and Related Diseases*	556
14th	Ryan *et al*[39]	FXR is a molecular target for the effects of vertical sleeve gastrectomy"	2014	*Nature*	545
15th	Himpens *et al* [30]	"A prospective randomized study between laparoscopic gastric banding and laparoscopic isolated sleeve gastrectomy: Results after 1 and 3 years"	2006	*Obesity Surgery*	500
16th	Himpens *et al* [31]	"Long-term results of laparoscopic sleeve gastrectomy for obesity"	2010	*Annals of Surgery*	498
17th	Colquitt *et al* [28]	"Surgery for obesity"	2009	*Cochrane Database of Systematic Reviews*	489
18th	Cottam *et al*[29]	"Laparoscopic sleeve gastrectomy as an initial weight-loss procedure for high-risk patients with morbid obesity"	2006	*Surgical Endoscopy and Other Interventional Techniques*	473
19th	Hutter *et al*[32]	"First report from the American College of Surgeons Bariatric Surgery Center Network: Laparoscopic sleeve gastrectomy has morbidity and effectiveness positioned between the band and the bypass"	2011	*Annals of Surgery*	438
20th	Peterli *et al*[35]	"Improvement in glucose metabolism after bariatric surgery: Comparison of laparoscopic roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy: A prospective randomized trial"	2009	*Annals of Surgery*	437

first international collaborative articles position. The importance of international collaboration was not only focusing on advancing knowledge and strengthening research capacity[81]; it also might increase citation rates and improve research quality [82,83].

The most cited publication was published in 2012 by Schauer *et al*[42] in the *New England Journal of Medicine* (n = 1435 citations). This publication found that weight loss was greater in the sleeve gastrectomy group than in the medical therapy group. Furthermore, this study demonstrated that 12 mo of medical therapy plus bariatric surgery greatly improved glycemic regulation in obese patients with uncontrolled type 2 diabetes compared with medical therapy alone[42]. The second most cited

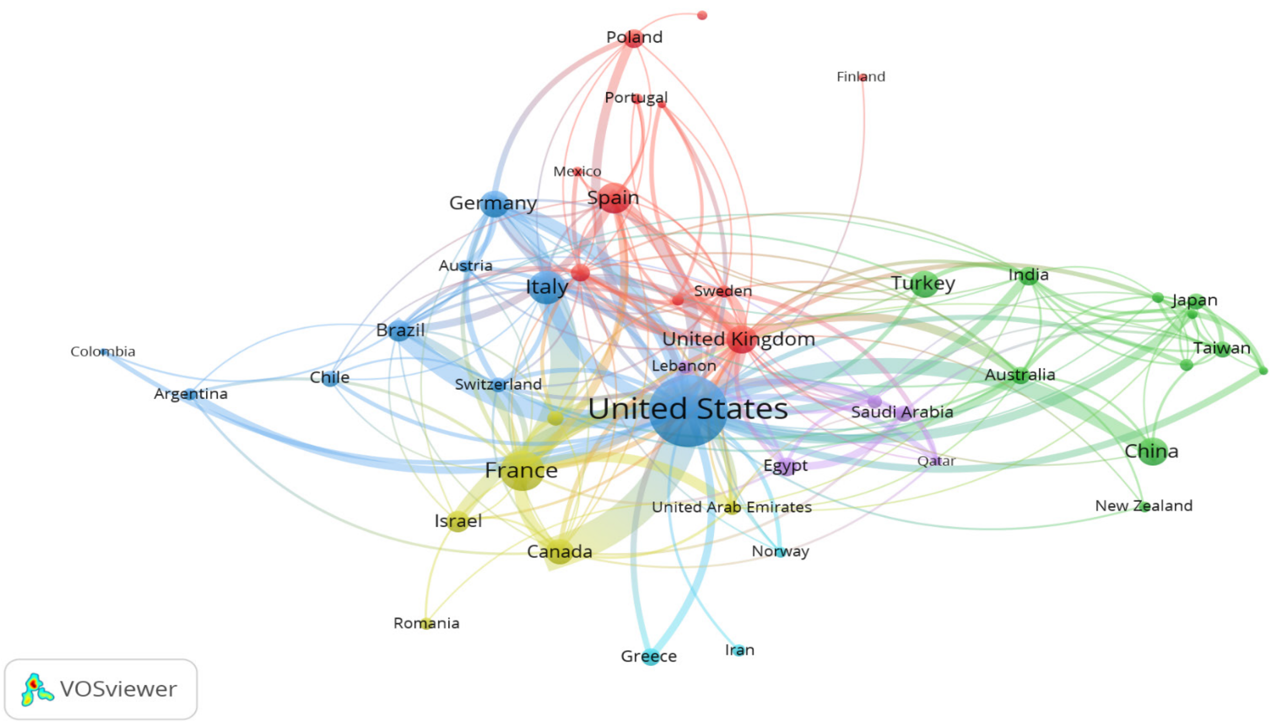

Figure 2 Network visualization map of research collaboration between the top 45 active countries. Each country has a contribution of 20 documents at least.

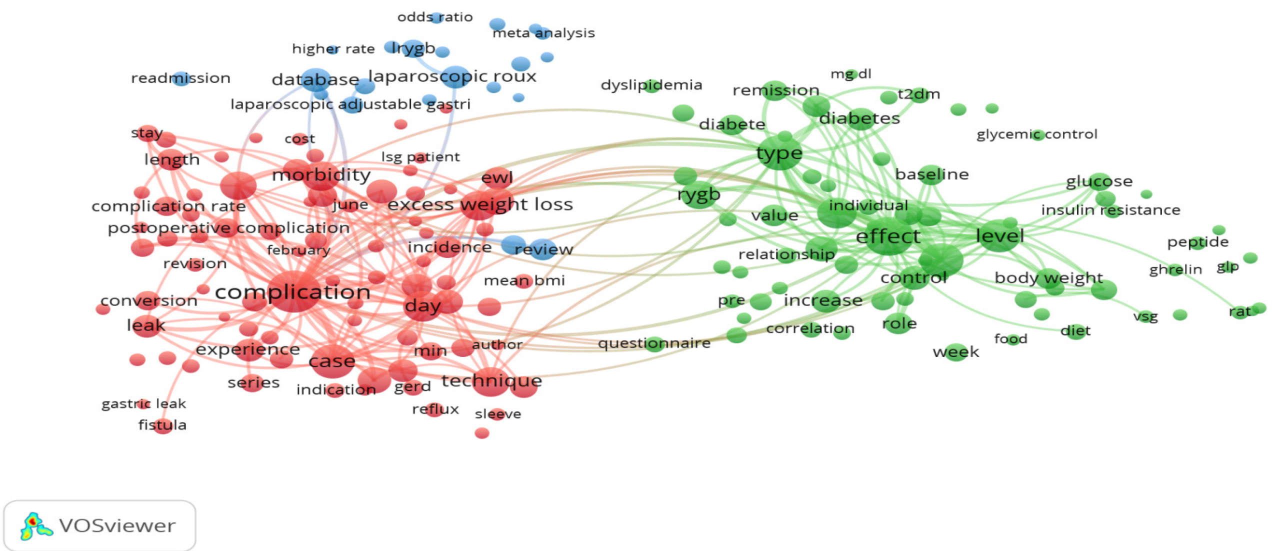

Figure 3 Network visualization map of the most frequent terms in the title and abstracts of the retrieved literature. Of the 72684 terms, 305 terms have occurred at least 100 times. The network visualization term map for sleeve gastrectomy research undertaken globally over the 20 years.

publication (n = 983 citations) was published in 2014 in the *New England Journal of Medicine* by Schauer *et al*[41], it presented the outcomes 3 years obese patients with uncontrolled type 2 diabetes were randomly assigned to undergo either intensive medical therapy alone or intensive medical therapy plus sleeve gastrectomy or Roux-en-Y gastric bypass. This study proved that 3 years of medical therapy plus bariatric surgery greatly improved glycemic regulation in obese patients with uncontrolled type 2 diabetes compared to medical therapy alone[41]. Finally, the third paper (n = 902 citations), published in 2013 in *Obesity Surgery* by Buchwald and Oien[25], found that the most commonly performed bariatric procedures were Roux-en-Y gastric bypass and sleeve gastrectomy.

The major limitation of this study is related to the database used to collect publications related to sleeve gastrectomy. However, the Scopus database does not represent

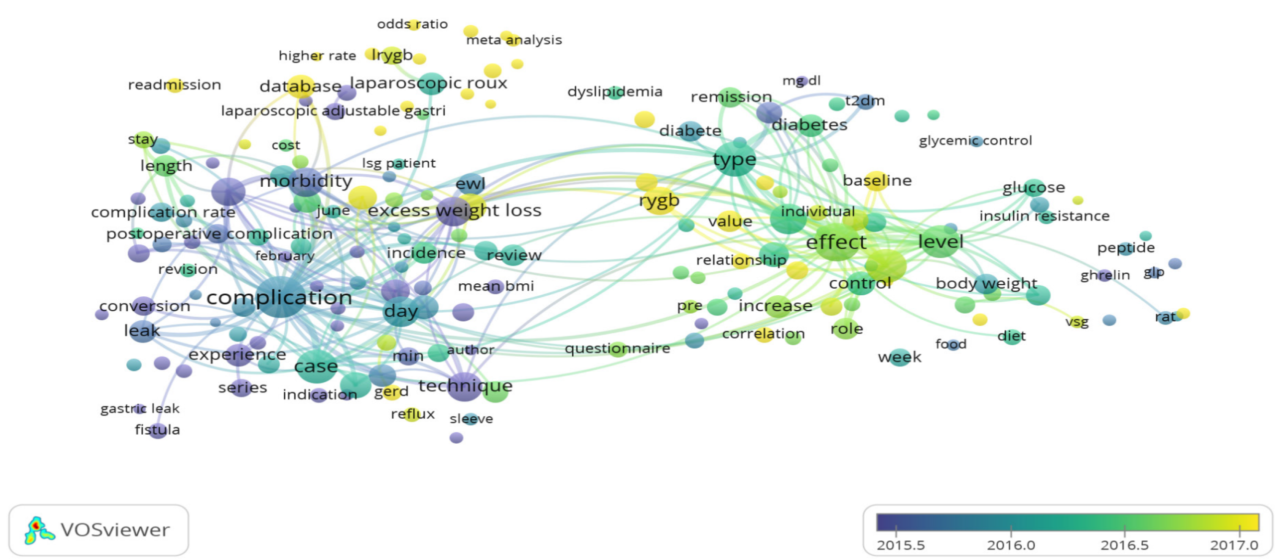

Figure 4 Distribution of terms according to the mean frequency of appearance; terms in blue appeared earlier than those in yellow-colored terms appeared later.

all scientific journals. However, it is the largest database of peer-reviewed scientific journals[84]. Another limitation is that certain articles' titles and abstracts did not include the term "sleeve gastrectomy" or related expressions, so not all articles regarding sleeve gastrectomy might be considered. Furthermore, the majority of publications were published and indexed in 2020, but since new journal issues are still being released and indexed, therefore, the amount of scientific research productivity this year could be higher.

CONCLUSION

The number of sleeve gastrectomy publications has gradually grown over the last 20 years. The current study's findings were biased in favor of high-income countries. In this domain, the United States and France had a significant impact. The current literature on sleeve gastrectomy was directed toward several themes such as morbidity and potential complications, the complexity of the procedure and different surgical approaches, and diabetes mellitus and body mass index in correlation with sleeve gastrectomy. This bibliometric analysis could help researchers better understand the knowledge base and research frontiers surrounding sleeve gastrectomy. In addition, future studies may focus on emerging research hotspots.

ARTICLE HIGHLIGHTS

Research background

Sleeve gastrectomy has grown in popularity among laparoscopic surgeons who do bariatric surgery and has shown to be an effective way of obtaining significant weight loss in a short period of time.

Research motivation

The amount of scientific evidence relating to sleeve gastrectomy is massive, and the annually published article curve is sharply increasing. It is still weakly correlated and unconnected to a simple algorithm or graph to describe the pattern and highlight the issues that require more scientific input so that researchers may work on them.

Research objectives

The goal of this study is to use bibliometric approaches to assess the research activity in sleeve gastrectomy over the last two decades and to visualize the hot areas and developing trends in this type of bariatric surgery.

Research methods

On January 9, 2021, we performed a literature search utilizing the Scopus database to gather papers from 2001 to 2020 for this retrospective research. Bibliometric characteristics such as publication output, countries, institutions, journals, citation frequency, and research hotspots were evaluated by using Excel 2013 and VOSviewer.

Research results

Over the previous 20 years, the number of publications on sleeve gastrectomy has progressively increased. The outcomes of the current study were skewed in favor of high-income nations. The United States and France have a big effect in this sector.

Research conclusions

The present literature on sleeve gastrectomy focused on numerous issues, including morbidity and possible complications, the procedure's complexity and various surgical methods, and diabetes mellitus and body mass index in connection to sleeve gastrectomy.

Research perspectives

This bibliometric study may aid researchers in better understanding the current state of knowledge and research horizons in the field of sleeve gastrectomy.

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