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ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Shu-You Peng, FACS, FRCP (Hon), MD, Full Professor, Department of Surgery, Medical School of Zhejiang University, Hangzhou 310009, Zhejiang Province, China. zrwkpsy@zju.edu.cn

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MINIREVIEWS

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

Raphael L C Araujo, Camila G C Y Carvalho, Carlos T Maeda, Jean Michel Milani, Diogo G Bugano, Pedro Henrique Z de Moraes, Marcelo M Linhares

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Raphael L C Araujo, Carlos T Maeda, Jean Michel Milani, Marcelo M Linhares, Department of Surgery, Universidade Federal de São Paulo, São Paulo 04024-002, Brazil

Raphael L C Araujo, Diogo G Bugano, Pedro Henrique Z de Moraes, Department of Oncology, Hospital Israelita Albert Einstein, São Paulo 05652-900, Brazil

Raphael L C Araujo, Camila G C Y Carvalho, Department of Surgical Oncology, Hospital e Maternidade Brasil Rede D'Or São Luiz, Santo André 09030-590, São Paulo, Brazil

Corresponding author: Raphael L C Araujo, MD, PhD, Adjunct Professor, Surgical Oncologist, Department of Surgery, Universidade Federal de São Paulo, Rua Napoleão de Barros, 715 Second Floor Vila Clementino, São Paulo 04024-002, Brazil. raphael.l.c.araujo@gmail.com

Abstract

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

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

resection; Hepatectomy

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

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INTRODUCTION

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

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

LIVER RESECTION FOR CRLM

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

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

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

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

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

PERIOPERATIVE CHEMOTHERAPY IN INITIALLY RESECTABLE PATIENTS

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

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

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

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

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

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

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

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

PERIOPERATIVE CHEMOTHERAPY IN INITIALLY UNRESECTABLE PATIENTS

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

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

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

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

EVALUATION OF RESPONSE TO PREOPERATIVE CHEMOTHERAPY

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

ROLE OF SURGERY IN PATIENTS PROGRESSING WHILE ON CHEMOTHERAPY

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

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

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

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

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

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

[1]Total *per* study.

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

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

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

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

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

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

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

CONCLUSION

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

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

FOOTNOTES

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Country/Territory of origin: Brazil

ORCID number: Raphael L C Araujo 0000-0002-7834-5944; Camila G C Y Carvalho 0000-0003-2661-103X; Carlos T Maeda 0000-0002-0824-7599; Jean Michel Milani 0000-0002-8604-8042; Diogo G Bugano 0000-0001-5284-1555; Pedro Henrique Z de Moraes 0000-0001-7221-7821; Marcelo M Linhares 0000-0001-9562-0058.

Corresponding Author's Membership in Professional Societies: Society for Surgery of the Alimentary Tract; American Hepato-Pancreato-Biliary Association; International Hepato-Pancreato-Biliary Association; International Laparoscopic Liver Society.

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REFERENCES

1 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]

2 **Neumann UP**, Thelen A, Röcken C, Seehofer D, Bahra M, Riess H, Jonas S, Schmeding M, Pratschke J, Bova R, Neuhaus P. Nonresponse to pre-operative chemotherapy does not preclude long-term survival after liver resection in patients with colorectal liver metastases. *Surgery* 2009; **146**: 52-59 [PMID: 19541010 DOI: 10.1016/j.surg.2009.02.004]

3 **Araujo RL**, Riechelmann RP, Fong Y. Patient selection for the surgical treatment of resectable colorectal liver metastases. *J Surg Oncol* 2017; **115**: 213-220 [PMID: 27778357 DOI: 10.1002/jso.24482]

4 **Tomlinson JS**, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, Kemeny N, Brennan MF, Blumgart LH,

D'Angelica M. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol* 2007; **25**: 4575-4580 [PMID: 17925551 DOI: 10.1200/JCO.2007.11.0833]

5 **de Haas RJ**, Wicherts DA, Flores E, Azoulay D, Castaing D, Adam R. R1 resection by necessity for colorectal liver metastases: is it still a contraindication to surgery? *Ann Surg* 2008; **248**: 626-637 [PMID: 18936576 DOI: 10.1097/SLA.0b013e31818a07f1]

6 **Fong Y**, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; **230**: 309-18; discussion 318 [PMID: 10493478 DOI: 10.1097/00000658-199909000-00004]

7 **Giuliante F**, Ardito F, Ferrero A, Aldrighetti L, Ercolani G, Grande G, Ratti F, Giovannini I, Federico B, Pinna AD, Capussotti L, Nuzzo G. Tumor progression during preoperative chemotherapy predicts failure to complete 2-stage hepatectomy for colorectal liver metastases: results of an Italian multicenter analysis of 130 patients. *J Am Coll Surg* 2014; **219**: 285-294 [PMID: 24933714 DOI: 10.1016/j.jamcollsurg.2014.01.063]

8 **Charnsangavej C**, Clary B, Fong Y, Grothey A, Pawlik TM, Choti MA. Selection of patients for resection of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol* 2006; **13**: 1261-1268 [PMID: 16947009 DOI: 10.1245/s10434-006-9023-y]

9 **Adam R**, Yi B, Innominato PF, Barroso E, Laurent C, Giuliante F, Capussotti L, Lapointe R, Regimbeau JM, Lopez-Ben S, Isoniemi H, Hubert C, Lin JK, Gruenberger T, Elias D, Skipenko OG, Guglielmi A; LiverMetSurvey International Contributing Centers. Resection of colorectal liver metastases after second-line chemotherapy: is it worthwhile? *Eur J Cancer* 2017; **78**: 7-15 [PMID: 28407529 DOI: 10.1016/j.ejca.2017.03.009]

10 **Adam R**, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, Giacchetti S, Paule B, Kunstlinger F, Ghémard O, Levi F, Bismuth H. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg* 2004; **240**: 644-57; discussion 657 [PMID: 15383792 DOI: 10.1097/01.sla.0000141198.92114.f6]

11 **Viganò L**, Russolillo N, Ferrero A, Langella S, Sperti E, Capussotti L. Evolution of long-term outcome of liver resection for colorectal metastases: analysis of actual 5-year survival rates over two decades. *Ann Surg Oncol* 2012; **19**: 2035-2044 [PMID: 22219066 DOI: 10.1245/s10434-011-2186-1]

12 **Ciliberto D**, Prati U, Roveda L, Barbieri V, Staropoli N, Abbruzzese A, Caraglia M, Di Maio M, Flotta D, Tassone P, Tagliaferri P. Role of systemic chemotherapy in the management of resected or resectable colorectal liver metastases: a systematic review and meta-analysis of randomized controlled trials. *Oncol Rep* 2012; **27**: 1849-1856 [PMID: 22446591 DOI: 10.3892/or.2012.1740]

13 **Nordlinger B**, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Collette L, Praet M, Bethe U, Van Cutsem E, Scheithauer W, Gruenberger T; EORTC Gastro-Intestinal Tract Cancer Group; Cancer Research UK; Arbeitsgruppe Lebermetastasen und-tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO); Australasian Gastro-Intestinal Trials Group (AGITG); Fédération Francophone de Cancérologie Digestive (FFCD). Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008; **371**: 1007-1016 [PMID: 18358928 DOI: 10.1016/S0140-6736(08)60455-9]

14 **Araujo R**, Gonen M, Allen P, Blumgart L, DeMatteo R, Fong Y, Kemeny N, Jarnagin W, D'Angelica M. Comparison between perioperative and postoperative chemotherapy after potentially curative hepatic resection for metastatic colorectal cancer. *Ann Surg Oncol* 2013; **20**: 4312-4321 [PMID: 23897009 DOI: 10.1245/s10434-013-3162-8]

15 **Araujo RL**, Gönen M, Herman P. Chemotherapy for patients with colorectal liver metastases who underwent curative resection improves long-term outcomes: systematic review and meta-analysis. *Ann Surg Oncol* 2015; **22**: 3070-3078 [PMID: 25586244 DOI: 10.1245/s10434-014-4354-6]

16 **Kanemitsu Y**, Shimizu Y, Mizusawa J, Inaba Y, Hamaguchi T, Shida D, Ohue M, Komori K, Shiomi A, Shiozawa M, Watanabe J, Suto T, Kinugasa Y, Takii Y, Bando H, Kobatake T, Inomata M, Shimada Y, Katayama H, Fukuda H; JCOG Colorectal Cancer Study Group. Hepatectomy Followed by mFOLFOX6 Versus Hepatectomy Alone for Liver-Only Metastatic Colorectal Cancer (JCOG0603): A Phase II or III Randomized Controlled Trial. *J Clin Oncol* 2021; **39**: 3789-3799 [PMID: 34520230 DOI: 10.1200/JCO.21.01032]

17 **Bridgewater JA**, Pugh SA, Maishman T, Eminton Z, Mellor J, Whitehead A, Stanton L, Radford M, Corkhill A, Griffiths GO, Falk S, Valle JW, O'Reilly D, Siriwardena AK, Hornbuckle J, Rees M, Iveson TJ, Hickish T, Garden OJ, Cunningham D, Maughan TS, Primrose JN; New EPOC investigators. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis (New EPOC): long-term results of a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol* 2020; **21**: 398-411 [PMID: 32014119 DOI: 10.1016/S1470-2045(19)30798-3]

18 **Tamandl D**, Gruenberger B, Herberger B, Kaczirek K, Gruenberger T. Surgery after neoadjuvant chemotherapy for colorectal liver metastases is safe and feasible in elderly patients. *J Surg Oncol* 2009; **100**: 364-371 [PMID: 19235181 DOI: 10.1002/jso.21259]

19 **Adam R**, Wicherts DA, de Haas RJ, Ciacio O, Lévi F, Paule B, Ducreux M, Azoulay D, Bismuth H, Castaing D. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? *J Clin Oncol* 2009; **27**: 1829-1835 [PMID: 19273699 DOI: 10.1200/JCO.2008.19.9273]

20 **Van Cutsem E**, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D'Hoore A, Diaz-Rubio E, Douillard JY, Ducreux M, Falcone A, Grothey A, Gruenberger T, Haustermans K, Heinemann V, Hoff P, Köhne CH, Labianca R, Laurent-Puig P, Ma B, Maughan T, Muro K, Normanno N, Österlund P, Oyen WJ, Papamichael D, Pentheroudakis G, Pfeiffer P, Price TJ, Punt C, Ricke J, Roth A, Salazar R, Scheithauer W, Schmoll HJ, Tabernero J, Taïeb J, Tejpar S, Wasan H, Yoshino T, Zaanan A, Arnold D. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016; **27**: 1386-1422 [PMID: 27380959 DOI: 10.1093/annonc/mdw235]

21 **Petrelli F**, Barni S; Anti-EGFR agents for liver metastases. Resectability and outcome with anti-EGFR agents in patients with KRAS wild-type colorectal liver-limited metastases: a meta-analysis. *Int J Colorectal Dis* 2012; **27**: 997-1004 [PMID: 22358385 DOI: 10.1007/s00384-012-1438-2]

22 **Van Cutsem E**, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pintér T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J, Rougier P. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009; **360**: 1408-1417 [PMID: 19339720 DOI: 10.1056/NEJMoa0805019]

23 **Heinemann V**, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, Lerchenmüller C, Kahl C, Seipelt G, Kullmann F, Stauch M, Scheithauer W, Hielscher J, Scholz M, Müller S, Link H, Niederle N, Rost A, Höffkes HG, Moehler M, Lindig RU, Modest DP, Rossius L, Kirchner T, Jung A, Stintzing S. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014; **15**: 1065-1075 [PMID: 25088940 DOI: 10.1016/S1470-2045(14)70330-4]

24 **Stintzing S**, Modest DP, Rossius L, Lerch MM, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, Lerchenmüller C, Kahl C, Seipelt G, Kullmann F, Stauch M, Scheithauer W, Held S, Giessen-Jung C, Moehler M, Jagenburg A, Kirchner T, Jung A, Heinemann V; FIRE-3 investigators. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final RAS wild-type subgroup of this randomised open-label phase 3 trial. *Lancet Oncol* 2016; **17**: 1426-1434 [PMID: 27575024 DOI: 10.1016/S1470-2045(16)30269-8]

25 **Tejpar S**, Stintzing S, Ciardiello F, Tabernero J, Van Cutsem E, Beier F, Esser R, Lenz HJ, Heinemann V. Prognostic and Predictive Relevance of Primary Tumor Location in Patients With RAS Wild-Type Metastatic Colorectal Cancer: Retrospective Analyses of the CRYSTAL and FIRE-3 Trials. *JAMA Oncol* 2017; **3**: 194-201 [PMID: 27722750 DOI: 10.1001/jamaoncol.2016.3797]

26 **Xu R**, Xu C, Liu C, Cui C, Zhu J. Efficacy and safety of bevacizumab-based combination therapy for treatment of patients with metastatic colorectal cancer. *Onco Targets Ther* 2018; **11**: 8605-8621 [PMID: 30584320 DOI: 10.2147/OTT.S171724]

27 **Blazer DG 3rd**, Kishi Y, Maru DM, Kopetz S, Chun YS, Overman MJ, Fogelman D, Eng C, Chang DZ, Wang H, Zorzi D, Ribero D, Ellis LM, Glover KY, Wolff RA, Curley SA, Abdalla EK, Vauthey JN. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. *J Clin Oncol* 2008; **26**: 5344-5351 [PMID: 18936472 DOI: 10.1200/JCO.2008.17.5299]

28 **Allen PJ**, Kemeny N, Jarnagin W, DeMatteo R, Blumgart L, Fong Y. Importance of response to neoadjuvant chemotherapy in patients undergoing resection of synchronous colorectal liver metastases. *J Gastrointest Surg* 2003; **7**: 109-117 [PMID: 12559192 DOI: 10.1016/S1091-255X(02)00121-X]

29 **Adam R**, Pascal G, Castaing D, Azoulay D, Delvart V, Paule B, Levi F, Bismuth H. Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases? *Ann Surg* 2004; **240**: 1052-61; discussion 1061 [PMID: 15570210 DOI: 10.1097/01.sla.0000145964.08365.01]

30 **Gallagher DJ**, Zheng J, Capanu M, Haviland D, Paty P, Dematteo RP, D'Angelica M, Fong Y, Jarnagin WR, Allen PJ, Kemeny N. Response to neoadjuvant chemotherapy does not predict overall survival for patients with synchronous colorectal hepatic metastases. *Ann Surg Oncol* 2009; **16**: 1844-1851 [PMID: 19224284 DOI: 10.1245/s10434-009-0348-1]

31 **Brouquet A**, Overman MJ, Kopetz S, Maru DM, Loyer EM, Andreou A, Cooper A, Curley SA, Garrett CR, Abdalla EK, Vauthey JN. Is resection of colorectal liver metastases after a second-line chemotherapy regimen justified? *Cancer* 2011; **117**: 4484-4492 [PMID: 21446046 DOI: 10.1002/cncr.26036]

32 **Jouffret L**, Ewald J, Marchese U, Garnier J, Gilabert M, Mokart D, Piana G, Delpero JR, Turrini O. Is progression in the future liver remnant a contraindication for second-stage hepatectomy? *HPB (Oxford)* 2019; **21**: 1478-1484 [PMID: 30962135 DOI: 10.1016/j.hpb.2019.03.357]

33 **Vigano L**, Darwish SS, Rimassa L, Cimino M, Carnaghi C, Donadon M, Procopio F, Personeni N, Del Fabbro D, Santoro A, Torzilli G. Progression of Colorectal Liver Metastases from the End of Chemotherapy to Resection: A New Contraindication to Surgery? *Ann Surg Oncol* 2018; **25**: 1676-1685 [PMID: 29488188 DOI: 10.1245/s10434-018-6387-8]

34 **Benson AB**, Venook AP, Al-Hawary MM, Arain MA, Chen YJ, Ciombor KK, Cohen S, Cooper HS, Deming D, Farkas L, Garrido-Laguna I, Grem JL, Gunn A, Hecht JR, Hoffe S, Hubbard J, Hunt S, Johung KL, Kirilcuk N, Krishnamurthi S, Messersmith WA, Meyerhardt J, Miller ED, Mulcahy MF, Nurkin S, Overman MJ, Parikh A, Patel H, Pedersen K, Saltz L, Schneider C, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Gregory KM, Gurski LA. Colon Cancer, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2021; **19**: 329-359 [PMID: 33724754 DOI: 10.6004/jnccn.2021.0012]

35 **de Haas RJ**, Wicherts DA, Flores E, Ducreux M, Lévi F, Paule B, Azoulay D, Castaing D, Lemoine A, Adam R. Tumor marker evolution: comparison with imaging for assessment of response to chemotherapy in patients with colorectal liver metastases. *Ann Surg Oncol* 2010; **17**: 1010-1023 [PMID: 20052553 DOI: 10.1245/s10434-009-0887-5]

36 **Pugh SA**, Bowers M, Ball A, Falk S, Finch-Jones M, Valle JW, O'Reilly DA, Siriwardena AK, Hornbuckle J, Rees M, Rees C, Iveson T, Hickish T, Maishman T, Stanton L, Dixon E, Corkhill A, Radford M, Garden OJ, Cunningham D, Maughan TS, Bridgewater JA, Primrose JN. Patterns of progression, treatment of progressive disease and post-progression survival in the New EPOC study. *Br J Cancer* 2016; **115**: 420-424 [PMID: 27434036 DOI: 10.1038/bjc.2016.208]

37 **Lim E**, Wiggans MG, Shahtahmassebi G, Aroori S, Bowles MJ, Briggs CD, Stell DA. Rebound growth of hepatic colorectal metastases after neo-adjuvant chemotherapy: effect on survival after resection. *HPB (Oxford)* 2016; **18**: 586-592 [PMID: 27346139 DOI: 10.1016/j.hpb.2016.04.006]

38 **Imai K**, Allard MA, Benitez CC, Vibert E, Sa Cunha A, Cherqui D, Castaing D, Bismuth H, Baba H, Adam R. Early Recurrence After Hepatectomy for Colorectal Liver Metastases: What Optimal Definition and What Predictive Factors? *Oncologist* 2016; **21**: 887-894 [PMID: 27125753 DOI: 10.1634/theoncologist.2015-0468]

39 **Ruzzenente A**, Bagante F, Ratti F, Beal EW, Alexandrescu S, Merath K, Makris EA, Poultsides GA, Margonis GA, Weiss MJ, Popescu I, Aldrighetti L, Guglielmi A, Pawlik TM. Response to preoperative chemotherapy: impact of change in total burden score and mutational tumor status on prognosis of patients undergoing resection for colorectal liver metastases. *HPB (Oxford)* 2019; **21**: 1230-1239 [PMID: 30792047 DOI: 10.1016/j.hpb.2019.01.014]

40 **Brunsell TH**, Cengija V, Sveen A, Bjørnbeth BA, Røsok BI, Brudvik KW, Guren MG, Lothe RA, Abildgaard A, Nesbakken A. Heterogeneous radiological response to neoadjuvant therapy is associated with poor prognosis after resection

of colorectal liver metastases. *Eur J Surg Oncol* 2019; **45**: 2340-2346 [PMID: 31350075 DOI: 10.1016/j.ejso.2019.07.017]

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MINIREVIEWS

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

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

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Jing-Yi Jiao, Peng Wang, Department of Hepatobiliary and Pancreatic Surgery, Affiliated Hospital of Nantong University, Nantong 226001, Jiangsu Province, China

Jing-Yi Jiao, Medical School, Nantong University, Nantong 226001, Jiangsu Province, China

Xiao-Jun Zhu, Department of Hepatobiliary Surgery, Nantong First People's Hospital, Nantong 226001, Jiangsu Province, China

Chun Zhou, Department of General Practitioner, Affiliated Hospital of Nantong University, Nantong 226001, Jiangsu Province, China

Corresponding author: Peng Wang, MD, PhD, Chief Physician, Department of Hepatobiliary and Pancreatic Surgery, Affiliated Hospital of Nantong University, No. 20 West Temple Road, Nantong 226001, Jiangsu Province, China. dankongwang@ntu.edu.cn

Abstract

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

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

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

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INTRODUCTION

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

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

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

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

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

IMMUNE DISORDERS LEAD TO CHOLESTEROL GALLSTONES

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

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

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

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

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

ROLE OF INTESTINAL FLORA DYSREGULATION IN CHOLESTEROL GALLSTONES

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

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

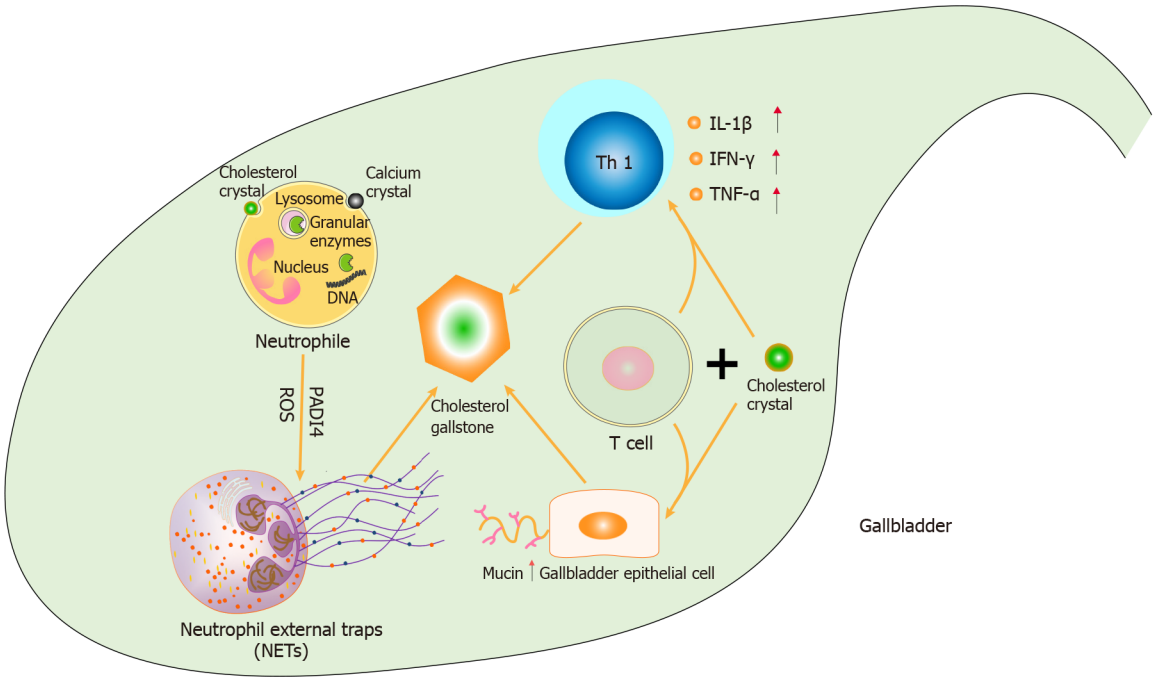

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Figure 1 Role of neutrophils and T cells in cholesterol gallstone formation. In gallbladder bile, cholesterol or calcium crystals are ingested by neutrophils as pinocytosis, inducing leakage of lysosomes and granular enzymes in neutrophils. The intracellular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

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

GENETIC SUSCEPTIBILITY TO CHOLESTEROL GALLSTONES

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

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

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

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

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

CHOLESTEROL GALLSTONE FORMATION BY IMPAIRED GALLBLADDER MOTILITY

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

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

CONCLUSION

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

FOOTNOTES

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Country/Territory of origin: China

ORCID number: Jing-Yi Jiao 0000-0002-9560-4725; Xiao-Jun Zhu 0000-0001-5265-6800; Chun Zhou 0000-0003-2640-5842; Peng Wang 0000-0003-3735-1229.

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REFERENCES

1 **Wang Y**, Qi M, Qin C, Hong J. Role of the biliary microbiome in gallstone disease. *Expert Rev Gastroenterol Hepatol* 2018; **12**: 1193-1205 [PMID: 30791792 DOI: 10.1080/17474124.2018.1533812]
2 **Lammert F**, Gurusamy K, Ko CW, Miquel JF, Méndez-Sánchez N, Portincasa P, van Erpecum KJ, van Laarhoven CJ, Wang DQ. Gallstones. *Nat Rev Dis Primers* 2016; **2**: 16024 [PMID: 27121416 DOI: 10.1038/nrdp.2016.24]
3 **Rudling M**, Laskar A, Straniero S. Gallbladder bile supersaturated with cholesterol in gallstone patients preferentially develops from shortage of bile acids. *J Lipid Res* 2019; **60**: 498-505 [PMID: 30610083 DOI: 10.1194/jlr.S091199]
4 **Dosch AR**, Imagawa DK, Jutric Z. Bile Metabolism and Lithogenesis: An Update. *Surg Clin North Am* 2019; **99**: 215-229 [PMID: 30846031 DOI: 10.1016/j.suc.2018.12.003]
5 **Wang F**, Wang J, Li Y, Yuan J, Yao P, Wei S, Guo H, Zhang X, Yang H, Wu T, He M. Gallstone Disease and Type 2 Diabetes Risk: A Mendelian Randomization Study. *Hepatology* 2019; **70**: 610-620 [PMID: 30515881 DOI: 10.1002/hep.30403]
6 **Camilleri M**, Malhi H, Acosta A. Gastrointestinal Complications of Obesity. *Gastroenterology* 2017; **152**: 1656-1670 [PMID: 28192107 DOI: 10.1053/j.gastro.2016.12.052]
7 **Di Ciaula A**, Garruti G, Frühbeck G, De Angelis M, de Bari O, Wang DQ, Lammert F, Portincasa P. The Role of Diet in the Pathogenesis of Cholesterol Gallstones. *Curr Med Chem* 2019; **26**: 3620-3638 [PMID: 28554328 DOI: 10.2174/0929867324666170530080636]
8 **Mark-Christensen A**, Brandsborg S, Laurberg S, Johansen N, Pachler JH, Thorlacius-Ussing O, Kjær MD, Qvist N, Preisler L, Hillingsø J, Rosenberg J, Jepsen P. Increased Risk of Gallstone Disease Following Colectomy for Ulcerative Colitis. *Am J Gastroenterol* 2017; **112**: 473-478 [PMID: 28117363 DOI: 10.1038/ajg.2016.564]
9 **Moschetta A**, Stolk MF, Rehfeld JF, Portincasa P, Slee PH, Koppeschaar HP, Van Erpecum KJ, Vanberge-Henegouwen GP. Severe impairment of postprandial cholecystokinin release and gall-bladder emptying and high risk of gallstone formation in acromegalic patients during Sandostatin LAR. *Aliment Pharmacol Ther* 2001; **15**: 181-185 [PMID: 11148435

DOI: 10.1046/j.1365-2036.2001.00924.x]

10 **Barahona Ponce C**, Scherer D, Brinster R, Boekstegers F, Marcelain K, Gárate-Calderón V, Müller B, de Toro G, Retamales J, Barajas O, Ahumada M, Morales E, Rojas A, Sanhueza V, Loader D, Rivera MT, Gutiérrez L, Bernal G, Ortega A, Montalvo D, Portiño S, Bertrán ME, Gabler F, Spencer L, Olloquequi J, Fischer C, Jenab M, Aleksandrova K, Katzke V, Weiderpass E, Bonet C, Moradi T, Fischer K, Bossers W, Brenner H, Hveem K, Eklund N, Völker U, Waldenberger M, Fuentes Guajardo M, Gonzalez-Jose R, Bedoya G, Bortolini MC, Canizales-Quinteros S, Gallo C, Ruiz-Linares A, Rothhammer F, Lorenzo Bermejo J. Gallstones, Body Mass Index, C-Reactive Protein, and Gallbladder Cancer: Mendelian Randomization Analysis of Chilean and European Genotype Data. *Hepatology* 2021; **73**: 1783-1796 [PMID: 32893372 DOI: 10.1002/hep.31537]

11 **Boxhoorn L**, Voermans RP, Bouwense SA, Bruno MJ, Verdonk RC, Boermeester MA, van Santvoort HC, Besselink MG. Acute pancreatitis. *Lancet* 2020; **396**: 726-734 [PMID: 32891214 DOI: 10.1016/S0140-6736(20)31310-6]

12 **Everhart JE**, Ruhl CE. Burden of digestive diseases in the United States Part III: Liver, biliary tract, and pancreas. *Gastroenterology* 2009; **136**: 1134-1144 [PMID: 19245868 DOI: 10.1053/j.gastro.2009.02.038]

13 **Reynoso-Paz S**, Coppel RL, Mackay IR, Bass NM, Ansari AA, Gershwin ME. The immunobiology of bile and biliary epithelium. *Hepatology* 1999; **30**: 351-357 [PMID: 10421640 DOI: 10.1002/hep.510300218]

14 **Harvey PR**, Upadhya GA, Strasberg SM. Immunoglobulins as nucleating proteins in the gallbladder bile of patients with cholesterol gallstones. *J Biol Chem* 1991; **266**: 13996-14003 [PMID: 1856228]

15 **Harvey PR**, Upadhya GA. A rapid, simple high capacity cholesterol crystal growth assay. *J Lipid Res* 1995; **36**: 2054-2058 [PMID: 8558092]

16 **Upadhya GA**, Harvey PR, Strasberg SM. Effect of human biliary immunoglobulins on the nucleation of cholesterol. *J Biol Chem* 1993; **268**: 5193-5200 [PMID: 8444895]

17 **Lee SP**, LaMont JT, Carey MC. Role of gallbladder mucus hypersecretion in the evolution of cholesterol gallstones. *J Clin Invest* 1981; **67**: 1712-1723 [PMID: 7240416 DOI: 10.1172/jci110209]

18 **Lammert F**, Wang DQ, Wittenburg H, Bouchard G, Hillebrandt S, Taenzler B, Carey MC, Paigen B. Lith genes control mucin accumulation, cholesterol crystallization, and gallstone formation in A/J and AKR/J inbred mice. *Hepatology* 2002; **36**: 1145-1154 [PMID: 12395324 DOI: 10.1053/jhep.2002.36821]

19 **LaMont JT**, Smith BF, Moore JR. Role of gallbladder mucin in pathophysiology of gallstones. *Hepatology* 1984; **4**: 51S-56S [PMID: 6546237 DOI: 10.1002/hep.1840040809]

20 **Lee KT**, Liu TS. Mucin gene expression in gallbladder epithelium. *J Formos Med Assoc* 2002; **101**: 762-768 [PMID: 12517055]

21 **Wang HH**, Afdhal NH, Gendler SJ, Wang DQ. Targeted disruption of the murine mucin gene 1 decreases susceptibility to cholesterol gallstone formation. *J Lipid Res* 2004; **45**: 438-447 [PMID: 14703511 DOI: 10.1194/jlr.M300468-JLR200]

22 **Wang HH**, Afdhal NH, Gendler SJ, Wang DQ. Evidence that gallbladder epithelial mucin enhances cholesterol cholelithogenesis in MUC1 transgenic mice. *Gastroenterology* 2006; **131**: 210-222 [PMID: 16831603 DOI: 10.1053/j.gastro.2006.04.011]

23 **Hu FL**, Chen HT, Guo FF, Yang M, Jiang X, Yu JH, Zhang FM, Xu GQ. Biliary microbiota and mucin 4 impact the calcification of cholesterol gallstones. *Hepatobiliary Pancreat Dis Int* 2021; **20**: 61-66 [PMID: 33341401 DOI: 10.1016/j.hbpd.2020.12.002]

24 **Andrianifahanana M**, Moniaux N, Batra SK. Regulation of mucin expression: mechanistic aspects and implications for cancer and inflammatory diseases. *Biochim Biophys Acta* 2006; **1765**: 189-222 [PMID: 16487661 DOI: 10.1016/j.bbcan.2006.01.002]

25 **Zen Y**, Harada K, Sasaki M, Tsuneyama K, Katayanagi K, Yamamoto Y, Nakanuma Y. Lipopolysaccharide induces overexpression of MUC2 and MUC5AC in cultured biliary epithelial cells: possible key phenomenon of hepatolithiasis. *Am J Pathol* 2002; **161**: 1475-1484 [PMID: 12368220 DOI: 10.1016/S0002-9440(10)64423-9]

26 **Ikeda H**, Sasaki M, Ishikawa A, Sato Y, Harada K, Zen Y, Kazumori H, Nakanuma Y. Interaction of Toll-like receptors with bacterial components induces expression of CDX2 and MUC2 in rat biliary epithelium in vivo and in culture. *Lab Invest* 2007; **87**: 559-571 [PMID: 17417665 DOI: 10.1038/labinvest.3700556]

27 **Finzi L**, Barbu V, Burgel PR, Mergey M, Kirkwood KS, Wick EC, Scoazec JY, Peschaud F, Paye F, Nadel JA, Housset C. MUC5AC, a gel-forming mucin accumulating in gallstone disease, is overproduced *via* an epidermal growth factor receptor pathway in the human gallbladder. *Am J Pathol* 2006; **169**: 2031-2041 [PMID: 17148666 DOI: 10.2353/ajpath.2006.060146]

28 **Feingold KR**, Pollock AS, Moser AH, Shigenaga JK, Grunfeld C. Discordant regulation of proteins of cholesterol metabolism during the acute phase response. *J Lipid Res* 1995; **36**: 1474-1482 [PMID: 7595071]

29 **Hardardóttir I**, Moser AH, Memon R, Grünfeld C, Feingold KR. Effects of TNF, IL-1, and the combination of both cytokines on cholesterol metabolism in Syrian hamsters. *Lymphokine Cytokine Res* 1994; **13**: 161-166 [PMID: 7948424]

30 **Feingold KR**, Hardardottir I, Memon R, Krul EJ, Moser AH, Taylor JM, Grunfeld C. Effect of endotoxin on cholesterol biosynthesis and distribution in serum lipoproteins in Syrian hamsters. *J Lipid Res* 1993; **34**: 2147-2158 [PMID: 8301233]

31 **Feingold KR**, Spady DK, Pollock AS, Moser AH, Grunfeld C. Endotoxin, TNF, and IL-1 decrease cholesterol 7 alpha-hydroxylase mRNA levels and activity. *J Lipid Res* 1996; **37**: 223-228 [PMID: 9026521]

32 **Memon RA**, Moser AH, Shigenaga JK, Grunfeld C, Feingold KR. In vivo and in vitro regulation of sterol 27-hydroxylase in the liver during the acute phase response. potential role of hepatocyte nuclear factor-1. *J Biol Chem* 2001; **276**: 30118-30126 [PMID: 11406622 DOI: 10.1074/jbc.M102516200]

33 **Wan JF**, Chu SF, Zhou X, Li YT, He WB, Tan F, Luo P, Ai QD, Wang Q, Chen NH. Ursodeoxycholic acid protects interstitial Cajal-like cells in the gallbladder from undergoing apoptosis by inhibiting TNF-α expression. *Acta Pharmacol Sin* 2018; **39**: 1493-1500 [PMID: 29770794 DOI: 10.1038/aps.2017.206]

34 **Maurer KJ**, Rao VP, Ge Z, Rogers AB, Oura TJ, Carey MC, Fox JG. T-cell function is critical for murine cholesterol gallstone formation. *Gastroenterology* 2007; **133**: 1304-1315 [PMID: 17919501 DOI: 10.1053/j.gastro.2007.07.005]

35 **Whary MT**, Morgan TJ, Dangler CA, Gaudes KJ, Taylor NS, Fox JG. Chronic active hepatitis induced by Helicobacter hepaticus in the A/JCr mouse is associated with a Th1 cell-mediated immune response. *Infect Immun* 1998; **66**: 3142-3148

[PMID: 9632578 DOI: 10.1128/IAI.66.7.3142-3148.1998]

36 **Fox JG**, Beck P, Dangler CA, Whary MT, Wang TC, Shi HN, Nagler-Anderson C. Concurrent enteric helminth infection modulates inflammation and gastric immune responses and reduces helicobacter-induced gastric atrophy. *Nat Med* 2000; **6**: 536-542 [PMID: 10802709 DOI: 10.1038/75015]

37 **Muñoz LE**, Boeltz S, Bilyy R, Schauer C, Mahajan A, Widulin N, Grüneboom A, Herrmann I, Boada E, Rauh M, Krenn V, Biermann MHC, Podolska MJ, Hahn J, Knopf J, Maueröder C, Paryzhak S, Dumych T, Zhao Y, Neurath MF, Hoffmann MH, Fuchs TA, Leppkes M, Schett G, Herrmann M. Neutrophil Extracellular Traps Initiate Gallstone Formation. *Immunity* 2019; **51**: 443-450.e4 [PMID: 31422870 DOI: 10.1016/j.immuni.2019.07.002]

38 **Nishimoto S**, Fukuda D, Higashikuni Y, Tanaka K, Hirata Y, Murata C, Kim-Kaneyama JR, Sato F, Bando M, Yagi S, Soeki T, Hayashi T, Imoto I, Sakaue H, Shimabukuro M, Sata M. Obesity-induced DNA released from adipocytes stimulates chronic adipose tissue inflammation and insulin resistance. *Sci Adv* 2016; **2**: e1501332 [PMID: 27051864 DOI: 10.1126/sciadv.1501332]

39 **Celec P**, Janovičová Ľ, Gurecká R, Koborová I, Gardlík R, Šebeková K. Circulating extracellular DNA is in association with continuous metabolic syndrome score in healthy adolescents. *Physiol Genomics* 2021; **53**: 309-318 [PMID: 34097532 DOI: 10.1152/physiolgenomics.00029.2021]

40 **Frey C**, Thorpe C, Abrams G. Gallstone formation in the germ-free mouse. *Am J Surg* 1968; **115**: 75-81 [PMID: 5634678 DOI: 10.1016/0002-9610(68)90132-3]

41 **Maurer KJ**, Ihrig MM, Rogers AB, Ng V, Bouchard G, Leonard MR, Carey MC, Fox JG. Identification of cholelithogenic enterohepatic helicobacter species and their role in murine cholesterol gallstone formation. *Gastroenterology* 2005; **128**: 1023-1033 [PMID: 15825083 DOI: 10.1053/j.gastro.2005.01.008]

42 **Feng R**, Zhang T, Kayani MUR, Wang Z, Shen Y, Su KL, Bielike K, Chen L. Patients with Primary and Secondary Bile Duct Stones Harbor Distinct Biliary Microbial Composition and Metabolic Potential. *Front Cell Infect Microbiol* 2022; **12**: 881489 [PMID: 35548466 DOI: 10.3389/fcimb.2022.881489]

43 **Wang Q**, Jiao L, He C, Sun H, Cai Q, Han T, Hu H. Alteration of gut microbiota in association with cholesterol gallstone formation in mice. *BMC Gastroenterol* 2017; **17**: 74 [PMID: 28599622 DOI: 10.1186/s12876-017-0629-2]

44 **Wu T**, Zhang Z, Liu B, Hou D, Liang Y, Zhang J, Shi P. Gut microbiota dysbiosis and bacterial community assembly associated with cholesterol gallstones in large-scale study. *BMC Genomics* 2013; **14**: 669 [PMID: 24083370 DOI: 10.1186/1471-2164-14-669]

45 **Thomas LA**, Veysey MJ, Murphy GM, Russell-Jones D, French GL, Wass JA, Dowling RH. Octreotide induced prolongation of colonic transit increases faecal anaerobic bacteria, bile acid metabolising enzymes, and serum deoxycholic acid in patients with acromegaly. *Gut* 2005; **54**: 630-635 [PMID: 15831907 DOI: 10.1136/gut.2003.028431]

46 **Qin J**, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, Zhang W, Guan Y, Shen D, Peng Y, Zhang D, Jie Z, Wu W, Qin Y, Xue W, Li J, Han L, Lu D, Wu P, Dai Y, Sun X, Li Z, Tang A, Zhong S, Li X, Chen W, Xu R, Wang M, Feng Q, Gong M, Yu J, Zhang Y, Zhang M, Hansen T, Sanchez G, Raes J, Falony G, Okuda S, Almeida M, LeChatelier E, Renault P, Pons N, Batto JM, Zhang Z, Chen H, Yang R, Zheng W, Yang H, Wang J, Ehrlich SD, Nielsen R, Pedersen O, Kristiansen K. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 2012; **490**: 55-60 [PMID: 23023125 DOI: 10.1038/nature11450]

47 **Hu H**, Shao W, Liu Q, Liu N, Wang Q, Xu J, Zhang X, Weng Z, Lu Q, Jiao L, Chen C, Sun H, Jiang Z, Gu A. Gut microbiota promotes cholesterol gallstone formation by modulating bile acid composition and biliary cholesterol secretion. *Nat Commun* 2022; **13**: 252 [PMID: 35017486 DOI: 10.1038/s41467-021-27758-8]

48 **Petersen C**, Bell R, Klag KA, Lee SH, Soto R, Ghazaryan A, Buhrke K, Ekiz HA, Ost KS, Boudina S, O'Connell RM, Cox JE, Villanueva CJ, Stephens WZ, Round JL. T cell-mediated regulation of the microbiota protects against obesity. *Science* 2019; **365** [PMID: 31346040 DOI: 10.1126/science.aat9351]

49 **Sun H**, Warren J, Yip J, Ji Y, Hao S, Han W, Ding Y. Factors Influencing Gallstone Formation: A Review of the Literature. *Biomolecules* 2022; **12** [PMID: 35454138 DOI: 10.3390/biom12040550]

50 **Katsika D**, Grjibovski A, Einarsson C, Lammert F, Lichtenstein P, Marschall HU. Genetic and environmental influences on symptomatic gallstone disease: a Swedish study of 43,141 twin pairs. *Hepatology* 2005; **41**: 1138-1143 [PMID: 15747383 DOI: 10.1002/hep.20654]

51 **Gerloff T**, Stieger B, Hagenbuch B, Madon J, Landmann L, Roth J, Hofmann AF, Meier PJ. The sister of P-glycoprotein represents the canalicular bile salt export pump of mammalian liver. *J Biol Chem* 1998; **273**: 10046-10050 [PMID: 9545351 DOI: 10.1074/jbc.273.16.10046]

52 **Smit JJ**, Schinkel AH, Oude Elferink RP, Groen AK, Wagenaar E, van Deemter L, Mol CA, Ottenhoff R, van der Lugt NM, van Roon MA. Homozygous disruption of the murine mdr2 P-glycoprotein gene leads to a complete absence of phospholipid from bile and to liver disease. *Cell* 1993; **75**: 451-462 [PMID: 8106172 DOI: 10.1016/0092-8674(93)90380-9]

53 **Yu L**, Hammer RE, Li-Hawkins J, Von Bergmann K, Lutjohann D, Cohen JC, Hobbs HH. Disruption of Abcg5 and Abcg8 in mice reveals their crucial role in biliary cholesterol secretion. *Proc Natl Acad Sci U S A* 2002; **99**: 16237-16242 [PMID: 12444248 DOI: 10.1073/pnas.252582399]

54 **Wang HH**, Portincasa P, Liu M, Wang DQ. Genetic Analysis of *ABCB4* Mutations and Variants Related to the Pathogenesis and Pathophysiology of Low Phospholipid-Associated Cholelithiasis. *Genes (Basel)* 2022; **13** [PMID: 35741809 DOI: 10.3390/genes13061047]

55 **Buch S**, Schafmayer C, Völzke H, Becker C, Franke A, von Eller-Eberstein H, Kluck C, Bässmann I, Brosch M, Lammert F, Miquel JF, Nervi F, Wittig M, Rosskopf D, Timm B, Höll C, Seeger M, ElSharawy A, Lu T, Egberts J, Fändrich F, Fölsch UR, Krawczak M, Schreiber S, Nürnberg P, Tepel J, Hampe J. A genome-wide association scan identifies the hepatic cholesterol transporter ABCG8 as a susceptibility factor for human gallstone disease. *Nat Genet* 2007; **39**: 995-999 [PMID: 17632509 DOI: 10.1038/ng2101]

56 **Berge KE**, von Bergmann K, Lutjohann D, Guerra R, Grundy SM, Hobbs HH, Cohen JC. Heritability of plasma noncholesterol sterols and relationship to DNA sequence polymorphism in ABCG5 and ABCG8. *J Lipid Res* 2002; **43**: 486-494 [PMID: 11893785]

57 **Acalovschi M**, Ciocan A, Mostean O, Tirziu S, Chiorean E, Keppeler H, Schirin-Sokhan R, Lammert F. Are plasma lipid levels related to ABCG5/ABCG8 polymorphisms? *Eur J Intern Med* 2006; **17**: 490-494 [PMID: 17098593 DOI: 10.1016/j.ejim.2006.04.012]

58 **Joshi AD**, Andersson C, Buch S, Stender S, Noordam R, Weng LC, Weeke PE, Auer PL, Boehm B, Chen C, Choi H, Curhan G, Denny JC, De Vivo I, Eicher JD, Ellinghaus D, Folsom AR, Fuchs C, Gala M, Haessler J, Hofman A, Hu F, Hunter DJ, Janssen HL, Kang JH, Kooperberg C, Kraft P, Kratzer W, Lieb W, Lutsey PL, Darwish Murad S, Nordestgaard BG, Pasquale LR, Reiner AP, Ridker PM, Rimm E, Rose LM, Shaffer CM, Schafmayer C, Tamimi RM, Uitterlinden AG, Völker U, Völzke H, Wakabayashi Y, Wiggs JL, Zhu J, Roden DM, Stricker BH, Tang W, Teumer A, Hampe J, Tybjærg-Hansen A, Chasman DI, Chan AT, Johnson AD. Four Susceptibility Loci for Gallstone Disease Identified in a Meta-analysis of Genome-Wide Association Studies. *Gastroenterology* 2016; **151**: 351-363.e28 [PMID: 27094239 DOI: 10.1053/j.gastro.2016.04.007]

59 **Qayyum F**, Lauridsen BK, Frikke-Schmidt R, Kofoed KF, Nordestgaard BG, Tybjærg-Hansen A. Genetic variants in CYP7A1 and risk of myocardial infarction and symptomatic gallstone disease. *Eur Heart J* 2018; **39**: 2106-2116 [PMID: 29529257 DOI: 10.1093/eurheartj/ehy068]

60 **Lauridsen BK**, Stender S, Tybjærg-Hansen A. Genetic Variation in NPC1L1 and Risk of Gallstone Disease. *J Am Coll Cardiol* 2015; **66**: 1086 [PMID: 26314540 DOI: 10.1016/j.jacc.2015.05.076]

61 **Gellert-Kristensen H**, Dalila N, Fallgaard Nielsen S, Grønne Nordestgaard B, Tybjaerg-Hansen A, Stender S. Identification and Replication of Six Loci Associated With Gallstone Disease. *Hepatology* 2019; **70**: 597-609 [PMID: 30325047 DOI: 10.1002/hep.30313]

62 **Krawczyk M**, Müllenbach R, Weber SN, Zimmer V, Lammert F. Genome-wide association studies and genetic risk assessment of liver diseases. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 669-681 [PMID: 21045792 DOI: 10.1038/nrgastro.2010.170]

63 **van Erpecum KJ**, Venneman NG, Portincasa P, Vanberge-Henegouwen GP. Review article: agents affecting gall-bladder motility--role in treatment and prevention of gallstones. *Aliment Pharmacol Ther* 2000; **14** Suppl 2: 66-70 [PMID: 10903008 DOI: 10.1046/j.1365-2036.2000.014s2066.x]

64 **Haal S**, Guman MSS, Bruin S, Schouten R, van Veen RN, Fockens P, Dijkgraaf MGW, Hutten BA, Gerdes VEA, Voermans RP. Risk Factors for Symptomatic Gallstone Disease and Gallstone Formation After Bariatric Surgery. *Obes Surg* 2022; **32**: 1270-1278 [PMID: 35143012 DOI: 10.1007/s11695-022-05947-8]

65 **Haal S**, Guman MSS, Boerlage TCC, Acherman YIZ, de Brauw LM, Bruin S, de Castro SMM, van Hooft JE, van de Laar AWJM, Moes DE, Schouten M, Schouten R, van Soest EJ, van Veen RN, de Vries CEE, Fockens P, Dijkgraaf MGW, Gerdes VEA, Voermans RP. Ursodeoxycholic acid for the prevention of symptomatic gallstone disease after bariatric surgery (UPGRADE): a multicentre, double-blind, randomised, placebo-controlled superiority trial. *Lancet Gastroenterol Hepatol* 2021; **6**: 993-1001 [PMID: 34715031 DOI: 10.1016/S2468-1253(21)00301-0]

66 **Sitzmann JV**, Pitt HA, Steinborn PA, Pasha ZR, Sanders RC. Cholecystokinin prevents parenteral nutrition induced biliary sludge in humans. *Surg Gynecol Obstet* 1990; **170**: 25-31 [PMID: 2104681]

67 **Gebhard RL**, Prigge WF, Ansel HJ, Schlasner L, Ketover SR, Sande D, Holtmeier K, Peterson FJ. The role of gallbladder emptying in gallstone formation during diet-induced rapid weight loss. *Hepatology* 1996; **24**: 544-548 [PMID: 8781321 DOI: 10.1002/hep.510240313]

68 **Wang HH**, Liu M, Portincasa P, Tso P, Wang DQ. Lack of endogenous cholecystokinin promotes cholelithogenesis in mice. *Neurogastroenterol Motil* 2016; **28**: 364-375 [PMID: 26604077 DOI: 10.1111/nmo.12734]

69 **Wang DQ**, Schmitz F, Kopin AS, Carey MC. Targeted disruption of the murine cholecystokinin-1 receptor promotes intestinal cholesterol absorption and susceptibility to cholesterol cholelithiasis. *J Clin Invest* 2004; **114**: 521-528 [PMID: 15314689 DOI: 10.1172/JCI16801]

70 **Pasternak A**, Gajda M, Gil K, Matyja A, Tomaszewski KA, Walocha JA, Kulig J, Thor P. Evidence of interstitial Cajal-like cells in human gallbladder. *Folia Histochem Cytobiol* 2012; **50**: 581-585 [PMID: 23264222 DOI: 10.5603/19673]

71 **Ahmadi O**, Nicholson Mde L, Gould ML, Mitchell A, Stringer MD. Interstitial cells of Cajal are present in human extrahepatic bile ducts. *J Gastroenterol Hepatol* 2010; **25**: 277-285 [PMID: 19793166 DOI: 10.1111/j.1440-1746.2009.05980.x]

72 **Pasternak A**, Gil K, Gajda M, Tomaszewski KA, Matyja A, Walocha JA. Interstitial cajal-like cell: a new player in cholelithiasis? *Am J Gastroenterol* 2014; **109**: 603-604 [PMID: 24698872 DOI: 10.1038/ajg.2013.251]

73 **Franks I**. Gallbladder: Loss of interstitial Cajal-like cells in the gallbladder might contribute to gallstone formation. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 689 [PMID: 23165238 DOI: 10.1038/nrgastro.2012.224]

74 **Pasternak A**, Gil K, Matyja A, Gajda M, Sztefko K, Walocha JA, Kulig J, Thor P. Loss of gallbladder interstitial Cajal-like cells in patients with cholelithiasis. *Neurogastroenterol Motil* 2013; **25**: e17-e24 [PMID: 23121223 DOI: 10.1111/nmo.12037]

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ORIGINAL ARTICLE

Retrospective Study

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

Yi-Wen Chen, Jian Xu, Xiang Li, Wei Chen, Shun-Liang Gao, Yan Shen, Min Zhang, Jian Wu, Ri-Sheng Que, Jun Yu, Ting-Bo Liang, Xue-Li Bai

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Yi-Wen Chen, Jian Xu, Xiang Li, Wei Chen, Shun-Liang Gao, Yan Shen, Min Zhang, Jian Wu, Ri-Sheng Que, Jun Yu, Ting-Bo Liang, Xue-Li Bai, Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310000, Zhejiang Province, China

Ting-Bo Liang, Xue-Li Bai, Department of Pancreatic Disease, Zhejiang Provincial Key Laboratory, Hangzhou 310000, Zhejiang Province, China

Ting-Bo Liang, Xue-Li Bai, The Study of Pancreatic Disease, Zhejiang Provincial Innovation Center, Hangzhou 310000, Zhejiang Province, China

Ting-Bo Liang, Xue-Li Bai, The Study of Hepatobiliary & Pancreatic Diseases, Zhejiang Provincial Clinical Research Center, Hangzhou 310003, Zhejiang Province, China

Ting-Bo Liang, Cancer Center, Zhejiang University, Hangzhou 310058, Zhejiang Province, China

Corresponding author: Xue-Li Bai, Doctor, MD, PhD, Chief Doctor, Professor, Surgeon, Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, No. 79 Qingchun Road, Hangzhou 310000, Zhejiang Province, China. shirleybai@zju.edu.cn

Abstract

BACKGROUND

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

AIM

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

METHODS

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

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

RESULTS

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

CONCLUSION

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

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

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

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INTRODUCTION

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

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

MATERIALS AND METHODS

Study design and data collection

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

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

Postoperative complications

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

Evaluation of endocrine and exocrine functions

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

Statistical analyses

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

RESULTS

Demographic characteristics of the patients

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

Perioperative outcomes

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

Table 1 Demographic and clinical characteristics of the patients

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

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

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

Pancreatic endocrine and exocrine functions

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

DISCUSSION

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

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

Table 2 Perioperative outcomes of the patients

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

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

Table 3 Endocrine and exocrine function of the pancreas after surgery

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

Data are presented as *n* (%).

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

POPF than DP[5,7,9].

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

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

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

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

CONCLUSION

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

ARTICLE HIGHLIGHTS

Research background

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

Research motivation

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

Research objectives

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

Research methods

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

Research results

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

Research conclusions

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

Research perspectives

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

FOOTNOTES

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

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ORCID number: Yi-Wen Chen 0000-0003-4525-0954; Jian Xu 0000-0001-8132-8988; Xiang Li 0000-0002-5942-7282; Wei Chen 0000-0002-4395-6649; Shun-Liang Gao 0000-0002-4330-7139; Jian Wu 0000-0002-6325-0766; Ri-Sheng Que 0000-0003-3242-5639; Ting-Bo Liang 0000-0003-0143-3353; Xue-Li Bai 0000-0002-2934-0880.

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REFERENCES

1 **Sera N**, Nakamura T, Horie I, Higashi R, Tominaga R, Yamamoto H, Nozaki A, Natsuda S, Takashima H, Kamada A, Abiru N, Nagayasu T, Eguchi S, Kawakami A. Characteristics of patients who developed glucose intolerance in the early period after partial pancreatectomy. *Diabetol Int* 2021; **12**: 140-144 [PMID: 33479591 DOI: 10.1007/s13340-020-00440-y]

2 **King J**, Kazanjian K, Matsumoto J, Reber HA, Yeh MW, Hines OJ, Eibl G. Distal pancreatectomy: incidence of postoperative diabetes. *J Gastrointest Surg* 2008; **12**: 1548-1553 [PMID: 18543045 DOI: 10.1007/s11605-008-0560-5]

3 **Guillemin P**, Bessot M. [Chronic calcifying pancreatitis in renal tuberculosis: pancreatojejunostomy using an original technic]. *Mem Acad Chir (Paris)* 1957; **83**: 869-871 [PMID: 13503655]

4 **Roggin KK**, Rudloff U, Blumgart LH, Brennan MF. Central pancreatectomy revisited. *J Gastrointest Surg* 2006; **10**: 804-812 [PMID: 16769536 DOI: 10.1016/j.gassur.2005.11.012]

5 **Paiella S**, De Pastena M, Faustini F, Landoni L, Pollini T, Bonamini D, Giuliani T, Bassi C, Esposito A, Tuveri M, Salvia R. Central pancreatectomy for benign or low-grade malignant pancreatic lesions - A single-center retrospective analysis of 116 cases. *Eur J Surg Oncol* 2019; **45**: 788-792 [PMID: 30527222 DOI: 10.1016/j.ejso.2018.11.021]

6 **Umemura A**, Nitta H, Takahara T, Hasegawa Y, Sasaki A. Current status of laparoscopic pancreaticoduodenectomy and pancreatectomy. *Asian J Surg* 2018; **41**: 106-114 [PMID: 27688035 DOI: 10.1016/j.asjsur.2016.09.003]

7 **Li Y**, Li Y. Central *versus* Distal Pancreatectomy for Benign or Low-Grade Malignant Lesions in the Pancreatic Neck and Proximal Body. *Am Surg* 2019; **85**: 1239-1245 [PMID: 31775965]

8 **Hirono S**, Tani M, Kawai M, Ina S, Nishioka R, Miyazawa M, Shimizu A, Uchiyama K, Yamaue H. A central pancreatectomy for benign or low-grade malignant neoplasms. *J Gastrointest Surg* 2009; **13**: 1659-1665 [PMID: 19488821 DOI: 10.1007/s11605-009-0934-3]

9 **Lee DH**, Han Y, Byun Y, Kim H, Kwon W, Jang JY. Central Pancreatectomy Versus Distal Pancreatectomy and Pancreaticoduodenectomy for Benign and Low-Grade Malignant Neoplasms: A Retrospective and Propensity Score-Matched Study with Long-Term Functional Outcomes and Pancreas Volumetry. *Ann Surg Oncol* 2020; **27**: 1215-1224 [PMID: 31898101 DOI: 10.1245/s10434-019-08095-z]

10 **Lv A**, Qian HG, Qiu H, Wu JH, Hao CY. Is Central Pancreatectomy Truly Recommendable? *Dig Surg* 2018; **35**: 532-538 [PMID: 29275422 DOI: 10.1159/000485806]

11 **Efron DT**, Lillemoe KD, Cameron JL, Yeo CJ. Central pancreatectomy with pancreaticogastrostomy for benign pancreatic pathology. *J Gastrointest Surg* 2004; **8**: 532-538 [PMID: 15239986 DOI: 10.1016/s0016-5085(03)84152-5]

12 **Du ZY**, Chen S, Han BS, Shen BY, Liu YB, Peng CH. Middle segmental pancreatectomy: a safe and organ-preserving option for benign and low-grade malignant lesions. *World J Gastroenterol* 2013; **19**: 1458-1465 [PMID: 23539545 DOI: 10.3748/wjg.v19.i9.1458]

13 **Shin YC**, Jang JY, Chang YR, Jung W, Kwon W, Kim H, Kim E, Kim SW. Comparison of long-term clinical outcomes of external and internal pancreatic stents in pancreaticoduodenectomy: randomized controlled study. *HPB (Oxford)* 2019; **21**: 51-59 [PMID: 30093143 DOI: 10.1016/j.hpb.2018.06.1795]

14 **Song KB**, Kim SC, Park KM, Hwang DW, Lee JH, Lee DJ, Lee JW, Jun ES, Shin SH, Kim HE, Lee YJ. Laparoscopic central pancreatectomy for benign or low-grade malignant lesions in the pancreatic neck and proximal body. *Surg Endosc* 2015; **29**: 937-946 [PMID: 25149632 DOI: 10.1007/s00464-014-3756-7]

15 **Song KB**, Kim SC, Park JB, Kim YH, Jung YS, Kim MH, Lee SK, Seo DW, Lee SS, Park DH, Han DJ. Single-center experience of laparoscopic left pancreatic resection in 359 consecutive patients: changing the surgical paradigm of left pancreatic resection. *Surg Endosc* 2011; **25**: 3364-3372 [PMID: 21556993 DOI: 10.1007/s00464-011-1727-9]

16 **Matsumoto I**, Kamei K, Satoi S, Murase T, Matsumoto M, Kawaguchi K, Yoshida Y, Iwasaki T, Takebe A, Nakai T, Takeyama Y. Laparoscopic versus open distal pancreatectomy for benign and low-grade malignant lesions of the pancreas: a single-center comparative study. *Surg Today* 2019; **49**: 394-400 [PMID: 30467718 DOI: 10.1007/s00595-018-1743-7]

17 **Mardin WA**, Schleicher C, Senninger N, Mees ST. Laparoscopic versus open left pancreatectomy: can preoperative factors indicate the safer technique? *Ann Surg* 2014; **259**: e60 [PMID: 24263306 DOI: 10.1097/SLA.0000000000000400]

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ORIGINAL ARTICLE

Retrospective Study

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

Wei Liu, Feng-Lin Chen, Kun Wang, Quan Bao, Hong-Wei Wang, Ke-Min Jin, Bao-Cai Xing

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Wei Liu, Feng-Lin Chen, Department of Hepatopancreatobiliary Surgery, Peking University School of Oncology, Beijing Cancer Hospital, Beijing 100142, China

Kun Wang, Quan Bao, Hong-Wei Wang, Ke-Min Jin, Bao-Cai Xing, Department of Hepatopancreatobiliary Surgery, Key Laboratory of Carcinogenesis and Translational Research, Ministry of Education, Peking University School of Oncology, Beijing Cancer Hospital and Institute, Beijing 100142, China

Corresponding author: Bao-Cai Xing, Department of Hepatopancreatobiliary Surgery, Key Laboratory of Carcinogenesis and Translational Research, Ministry of Education, Peking University School of Oncology, Beijing Cancer Hospital and Institute, No. 52 Fucheng Road, Haidian District, Beijing 100142, China. xingbaocai88@sina.com

Abstract

BACKGROUND

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

AIM

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

METHODS

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

RESULTS

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

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

CONCLUSION

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

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

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

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INTRODUCTION

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

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

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

MATERIALS AND METHODS

Patient eligibility

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

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

Pretreatment evaluation

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

Treatment

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

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

Statistical analysis

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

RESULTS

Comparison of irinotecan- and oxaliplatin-treated patients before PSM

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

Long-term outcomes before PSM

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

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

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

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

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

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

Comparison of irinotecan- and oxaliplatin-treated patients after PSM

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

Long-term outcomes after PSM

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

Building Cox proportional hazards model

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

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

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

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

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

DISCUSSION

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

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

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

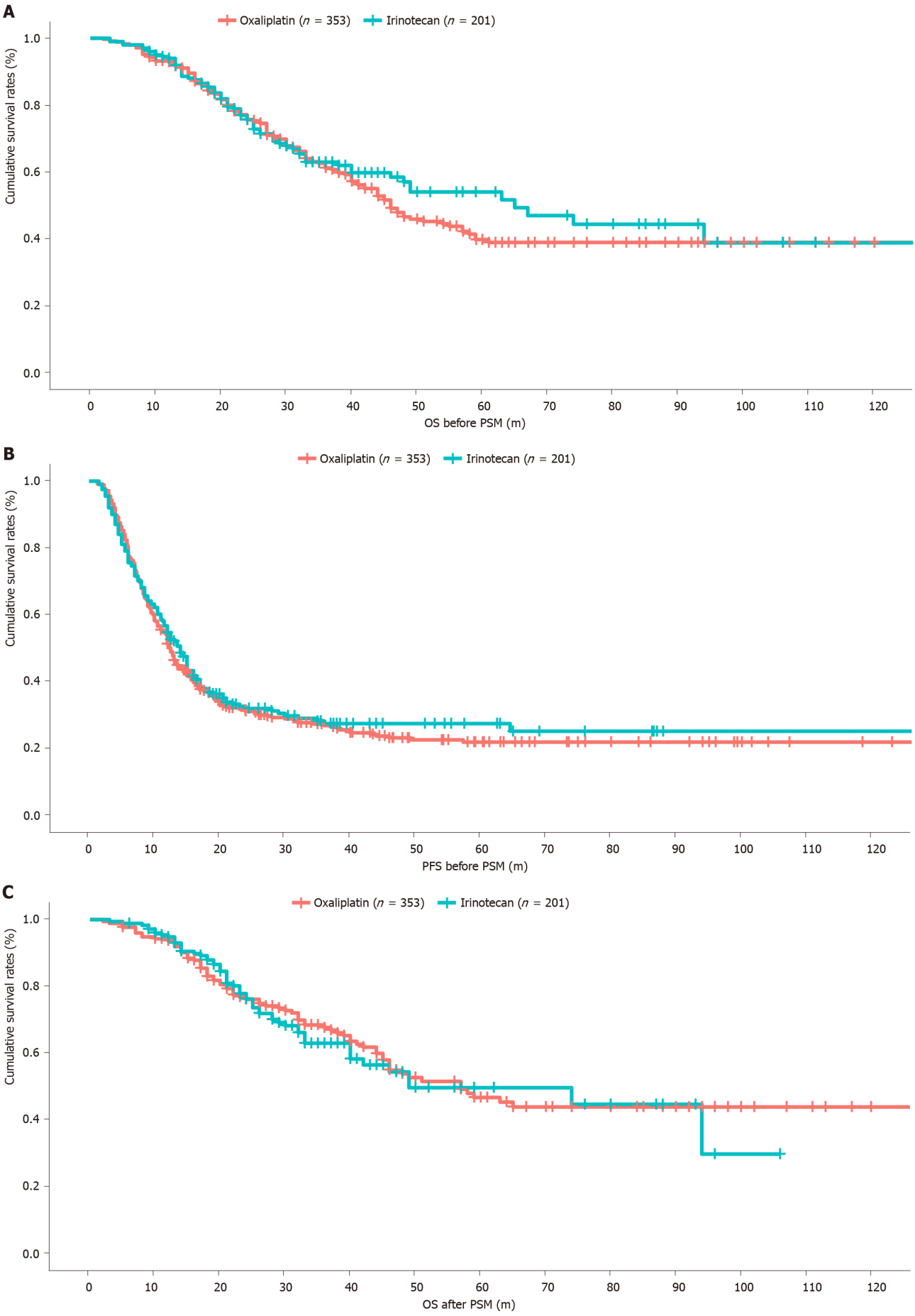
Table 3 Univariable and multivariable analyses of factors associated with progression-free survival

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

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

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

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


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

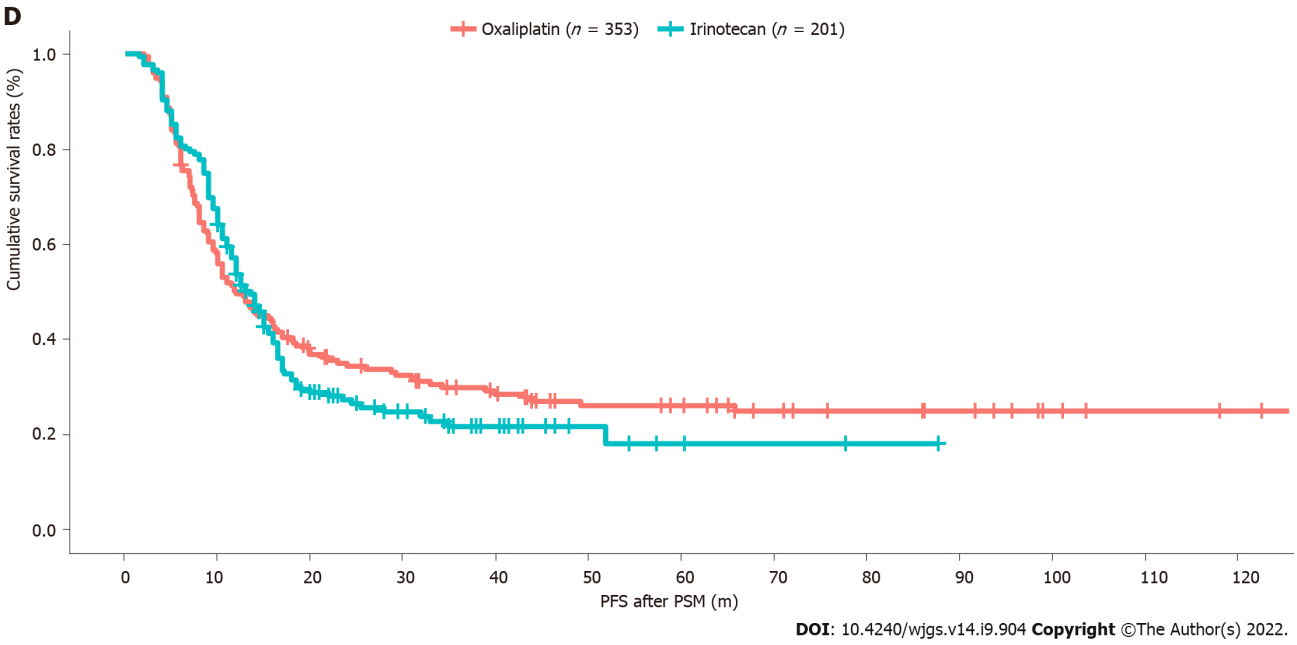


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Figure 1 Overall survival and progression-free survival of patients treated with irinotecan or oxaliplatin before and after propensity score matching. A: Overall survival (OS) of patients treated with irinotecan or oxaliplatin before propensity score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

postoperative liver failure[18,19].

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

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

CONCLUSION

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

ARTICLE HIGHLIGHTS

Research background

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

Research motivation

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

Research objectives

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

Research methods

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

Research results

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

Research conclusions

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

Research perspectives

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

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FOOTNOTES

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

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of Helsinki.

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

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ORCID number: Wei Liu 0000-0003-1871-8478; Feng-Lin Chen 0000-0003-3085-8676; Kun Wang 0000-0002-9778-9479; Quan Bao 0000-0003-0097-8159; Hong-Wei Wang 0000-0002-5571-7688; Ke-Min Jin 0000-0001-8348-7261; Bao-Cai Xing 0000-0002-9908-8588.

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REFERENCES

1 **Torre LA**, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262]
2 **Adam R**, Kitano Y. Multidisciplinary approach of liver metastases from colorectal cancer. *Ann Gastroenterol Surg* 2019; **3**: 50-56 [PMID: 30697610 DOI: 10.1002/ags3.12227]
3 **Leung U**, Gönen M, Allen PJ, Kingham TP, DeMatteo RP, Jarnagin WR, D'Angelica MI. Colorectal Cancer Liver Metastases and Concurrent Extrahepatic Disease Treated With Resection. *Ann Surg* 2017; **265**: 158-165 [PMID: 28009741 DOI: 10.1097/SLA.0000000000001624]
4 **Breitenstein S**, DeOliveira ML, Raptis DA, Slankamenac K, Kambakamba P, Nerl J, Clavien PA. Novel and simple preoperative score predicting complications after liver resection in noncirrhotic patients. *Ann Surg* 2010; **252**: 726-734 [PMID: 21037427 DOI: 10.1097/SLA.0b013e3181fb8c1a]
5 **Liu W**, Zhang W, Xu Y, Li YH, Xing BC. A Prognostic Scoring System to Predict Survival Outcome of Resectable Colorectal Liver Metastases in this Modern Era. *Ann Surg Oncol* 2021; **28**: 7709-7718 [PMID: 34023948 DOI: 10.1245/s10434-021-10143-6]
6 **Rubbia-Brandt L**, Audard V, Sartoretti P, Roth AD, Brezault C, Le Charpentier M, Dousset B, Morel P, Soubrane O, Chaussade S, Mentha G, Terris B. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. *Ann Oncol* 2004; **15**: 460-466 [PMID: 14998849 DOI: 10.1093/annonc/mdh095]
7 **Vauthey JN**, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, Xiong HQ, Eng C, Lauwers GY, Mino-Kenudson M, Risio M, Muratore A, Capussotti L, Curley SA, Abdalla EK. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol* 2006; **24**: 2065-2072 [PMID: 16648507 DOI: 10.1200/JCO.2005.05.3074]
8 **Samura H**, Oki E, Okumura H, Yoshida T, Kai S, Kobayashi K, Kinjo T, Mori S, Tohyama T, Ohgaki K, Kawanaka H, Makiyama A, Ureshino N, Kotaka M, Shimose T, Ando K, Saeki H, Baba H, Maehara Y, Mori M. A phase I/II study of S-1 and irinotecan (IRIS) combined with cetuximab in patients with RAS wild-type metastatic colorectal cancer (KSCC1401). *Cancer Chemother Pharmacol* 2020; **86**: 285-294 [PMID: 32734398 DOI: 10.1007/s00280-020-04108-x]
9 **Adams RB**, Aloia TA, Loyer E, Pawlik TM, Taouli B, Vauthey JN; Americas Hepato-Pancreato-Biliary Association; Society of Surgical Oncology; Society for Surgery of the Alimentary Tract. Selection for hepatic resection of colorectal liver metastases: expert consensus statement. *HPB (Oxford)* 2013; **15**: 91-103 [PMID: 23297719 DOI: 10.1111/j.1477-2574.2012.00557.x]
10 **Fong Y**, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; **230**: 309-18; discussion 318 [PMID: 10493478 DOI: 10.1097/00000658-199909000-00004]
11 **Nordlinger B**, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Mauer M, Tanis E, Van Cutsem E, Scheithauer W, Gruenberger T; EORTC Gastro-Intestinal Tract Cancer Group; Cancer Research UK; Arbeitsgruppe Lebermetastasen und–tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO); Australasian Gastro-Intestinal Trials Group (AGITG); Fédération Francophone de Cancérologie Digestive (FFCD). Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; **14**: 1208-1215 [PMID: 24120480 DOI: 10.1016/S1470-2045(13)70447-9]
12 **Douillard JY**, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M,

Gruia G, Awad L, Rougier P. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000; **355**: 1041-1047 [PMID: 10744089 DOI: 10.1016/s0140-6736(00)02034-1]

13 **de Gramont A**, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, de Braud F, Wilson C, Morvan F, Bonetti A. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; **18**: 2938-2947 [PMID: 10944126 DOI: 10.1200/JCO.2000.18.16.2938]

14 **Behrenbruch C**, Prabhakaran S, Udayasiri D, Hollande F, Michael M, Hayes I, Heriot A, Knowles B, Thomson B. Survival benefit of neoadjuvant chemotherapy and surgery versus surgery first for resectable colorectal liver metastases: a cohort study. *ANZ J Surg* 2021; **91**: 1196-1202 [PMID: 33543551 DOI: 10.1111/ans.16613]

15 **Bacalbasa N**, Balescu I, Cretoiu D, Halmaciu I, Dimitriu M, Socea B, Diaconu C, Iliescu L, Savu C, Filipescu A, Stoica C, Stiru O. Determination of whether HIPEC is beneficial in patients with synchronous peritoneal and liver metastases from colorectal cancer (Review). *Exp Ther Med* 2021; **22**: 1267 [PMID: 34594404 DOI: 10.3892/etm.2021.10702]

16 **Predescu D**, Boeriu M, Constantin A, Socea B, Costea D, Constantinoiu S. Pregnancy and Colorectal Cancer, from Diagnosis to Therapeutical Management - Short Review. *Chirurgia (Bucur)* 2020; **115**: 563-578 [PMID: 33138893 DOI: 10.21614/chirurgia.115.5.563]

17 **Nakano H**, Oussoultzoglou E, Rosso E, Casnedi S, Chenard-Neu MP, Dufour P, Bachellier P, Jaeck D. Sinusoidal injury increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy. *Ann Surg* 2008; **247**: 118-124 [PMID: 18156931 DOI: 10.1097/SLA.0b013e31815774de]

18 **Pathak S**, Tang JM, Terlizzo M, Poston GJ, Malik HZ. Hepatic steatosis, body mass index and long term outcome in patients undergoing hepatectomy for colorectal liver metastases. *Eur J Surg Oncol* 2010; **36**: 52-57 [PMID: 19879103 DOI: 10.1016/j.ejso.2009.09.004]

19 **Wicherts DA**, de Haas RJ, Sebagh M, Ciacio O, Lévi F, Paule B, Giacchetti S, Guettier C, Azoulay D, Castaing D, Adam R. Regenerative nodular hyperplasia of the liver related to chemotherapy: impact on outcome of liver surgery for colorectal metastases. *Ann Surg Oncol* 2011; **18**: 659-669 [PMID: 20976564 DOI: 10.1245/s10434-010-1385-5]

20 **Zorzi D**, Laurent A, Pawlik TM, Lauwers GY, Vauthey JN, Abdalla EK. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. *Br J Surg* 2007; **94**: 274-286 [PMID: 17315288 DOI: 10.1002/bjs.5719]

21 **Soubrane O**, Brouquet A, Zalinski S, Terris B, Brézault C, Mallet V, Goldwasser F, Scatton O. Predicting high grade lesions of sinusoidal obstruction syndrome related to oxaliplatin-based chemotherapy for colorectal liver metastases: correlation with post-hepatectomy outcome. *Ann Surg* 2010; **251**: 454-460 [PMID: 20160638 DOI: 10.1097/SLA.0b013e3181c79403]

22 **Overman MJ**, Maru DM, Charnsangavej C, Loyer EM, Wang H, Pathak P, Eng C, Hoff PM, Vauthey JN, Wolff RA, Kopetz S. Oxaliplatin-mediated increase in spleen size as a biomarker for the development of hepatic sinusoidal injury. *J Clin Oncol* 2010; **28**: 2549-2555 [PMID: 20406923 DOI: 10.1200/JCO.2009.27.5701]

23 **Rubbia-Brandt L**, Lauwers GY, Wang H, Majno PE, Tanabe K, Zhu AX, Brezault C, Soubrane O, Abdalla EK, Vauthey JN, Mentha G, Terris B. Sinusoidal obstruction syndrome and nodular regenerative hyperplasia are frequent oxaliplatin-associated liver lesions and partially prevented by bevacizumab in patients with hepatic colorectal metastasis. *Histopathology* 2010; **56**: 430-439 [PMID: 20459550 DOI: 10.1111/j.1365-2559.2010.03511.x]

24 **Deleve LD**, Wang X, Tsai J, Kanel G, Strasberg S, Tokes ZA. Sinusoidal obstruction syndrome (veno-occlusive disease) in the rat is prevented by matrix metalloproteinase inhibition. *Gastroenterology* 2003; **125**: 882-890 [PMID: 12949732 DOI: 10.1016/s0016-5085(03)01056-4]

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ORIGINAL ARTICLE

Retrospective Study

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

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

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Yu-Ping Wang, Hong Xu, Yuan Chu, Ben-Song Duan, Jing-Jing Lian, Hai-Bin Zhang, Li Zhang, Mei-Dong Xu, Jia Cao, Endoscopy Center, Department of Gastroenterology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai 200120, China

Yu-Ping Wang, Jia-Xin Shen, Wen-Ming Liu, Endoscopy Center, The First Affiliated Hospital of Fujian Medical University, Fuzhou 350004, Fujian Province, China

Hong Xu, Department of Gastroenterology and Hepatology, Hangzhou Red Cross Hospital, Hangzhou 310003, Zhejiang Province, China

Corresponding author: Jia Cao, MD, Endoscopy Center, Department of Gastroenterology, Shanghai East Hospital, Tongji University School of Medicine, No. 150 Jimo Road, Shanghai 200120, China. jia_cao@yeah.net

Abstract

BACKGROUND

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

AIM

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

METHODS

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

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

RESULTS

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

CONCLUSION

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

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

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

Citation: Wang YP, Xu H, Shen JX, Liu WM, Chu Y, Duan BS, Lian JJ, Zhang HB, Zhang L, Xu MD, Cao J. Predictors of difficult endoscopic resection of submucosal tumors originating from the muscularis propria layer at the esophagogastric junction. *World J Gastrointest Surg* 2022; 14(9): 918-929
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INTRODUCTION

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

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

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

MATERIALS AND METHODS

Patients

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

Definitions

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

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

Endoscopic equipment and accessories

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

Procedures of endoscopic resection

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

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

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

Postoperative management

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

Histopathological assessment

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

Follow-up

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

Statistical analysis

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

RESULTS

Clinical characteristics

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

Therapeutic outcomes and complications

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

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

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

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

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

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

Resection rate, procedure time and intraoperative bleeding

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

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

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

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

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

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

Follow-up

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

DISCUSSION

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

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

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

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

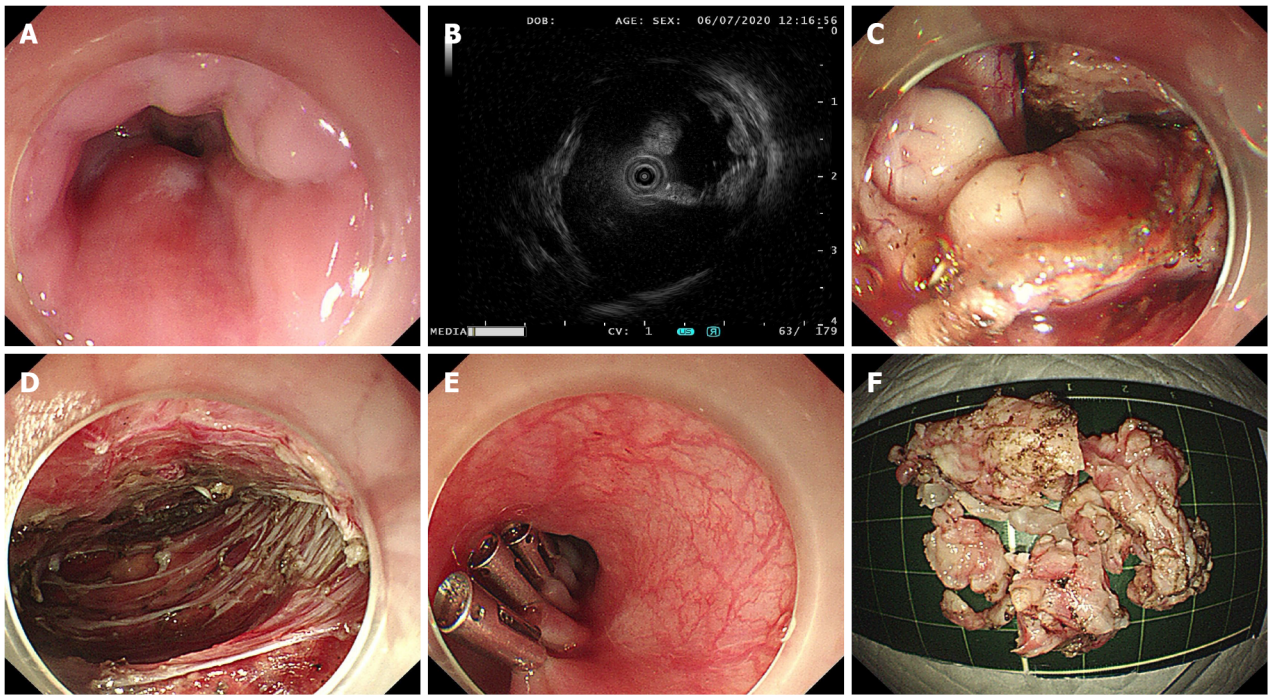

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Figure 1 The procedure of submucosal tunneling endoscopic resection. A: Endoscopic view of the tumor; B: Endoscopic ultrasonography view of the tumor; C: The submucosal tumor exposed using the submucosal tunnel technique; D: Endoscopic view of the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

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

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

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

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

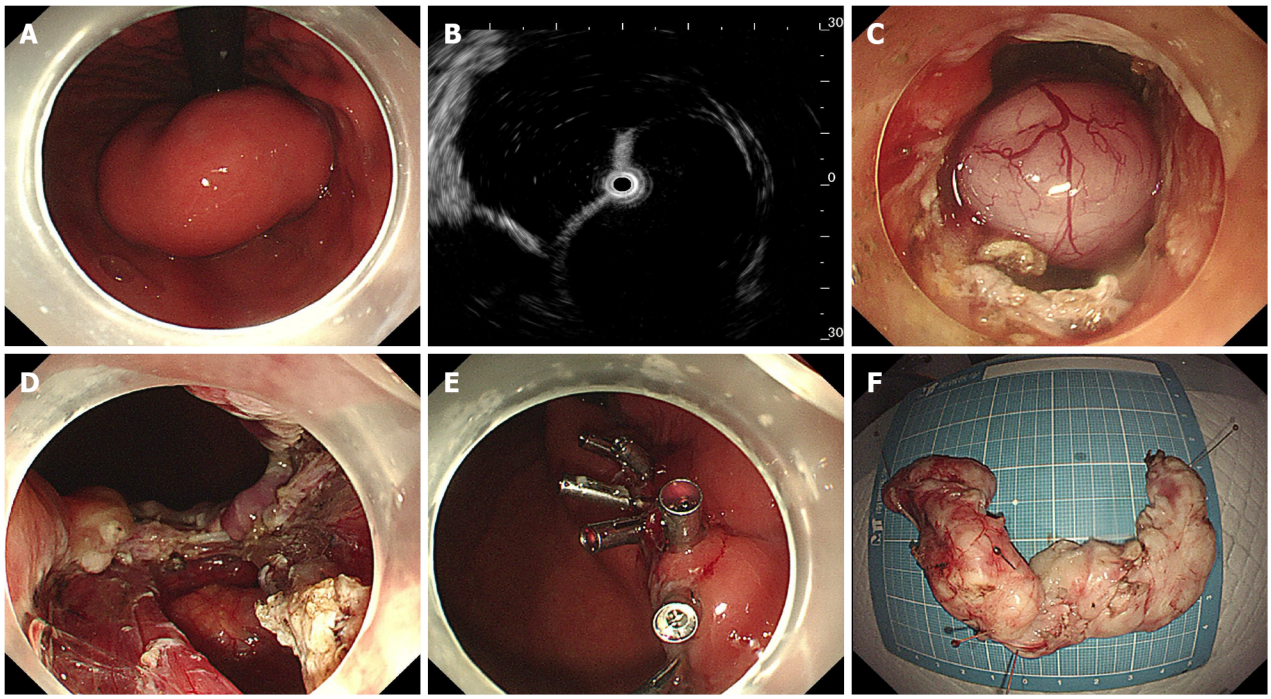

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Figure 2 Case illustration of endoscopic full-thickness resection. A: Endoscopic view of the tumor; B: Endoscopic ultrasonography view of the tumor; C: The submucosal tumor exposed by full-thickness resection; D: The wound surface after removal of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

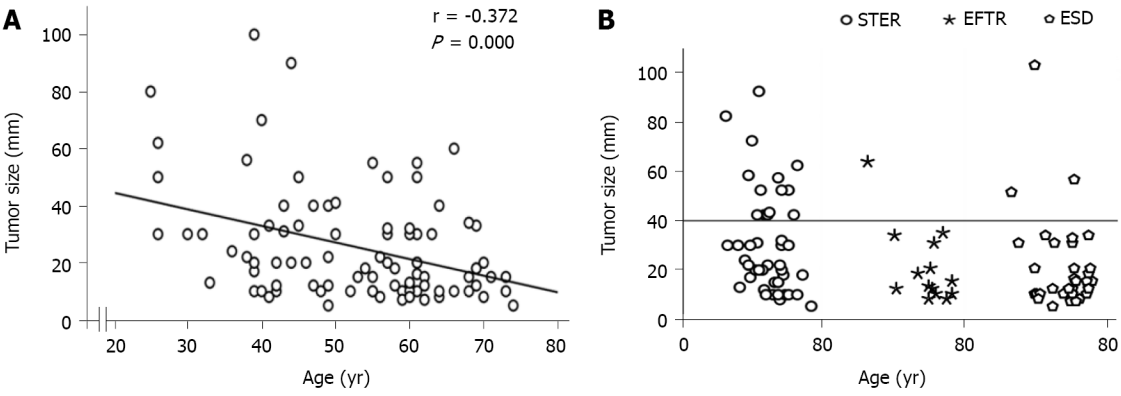

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Figure 3 Tumor size. A: There was a significant negative correlation between age and tumor size; B: Tumor size at different ages in the submucosal tunneling endoscopic resection group, endoscopic full-thickness resection group and endoscopic submucosal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

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

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

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

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

CONCLUSION

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

ARTICLE HIGHLIGHTS

Research background

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

Research motivation

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

Research objectives

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

Research methods

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

Research results

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

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

Research conclusions

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

Research perspectives

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

FOOTNOTES

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

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Country/Territory of origin: China

ORCID number: Jia Cao 0000-0002-9207-9822.

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REFERENCES

1 **Stein HJ**, Feith M, Siewert JR. Cancer of the esophagogastric junction. *Surg Oncol* 2000; **9**: 35-41 [PMID: 11525305 DOI: 10.1016/s0960-7404(00)00021-9]
2 **Ponsaing LG**, Kiss K, Hansen MB. Classification of submucosal tumors in the gastrointestinal tract. *World J Gastroenterol* 2007; **13**: 3311-3315 [PMID: 17659669 DOI: 10.3748/wjg.v13.i24.3311]
3 **Nishida T**, Hirota S, Yanagisawa A, Sugino Y, Minami M, Yamamura Y, Otani Y, Shimada Y, Takahashi F, Kubota T; GIST Guideline Subcommittee. Clinical practice guidelines for gastrointestinal stromal tumor (GIST) in Japan: English version. *Int J Clin Oncol* 2008; **13**: 416-430 [PMID: 18946752 DOI: 10.1007/s10147-008-0798-7]
4 **Lee IL**, Lin PY, Tung SY, Shen CH, Wei KL, Wu CS. Endoscopic submucosal dissection for the treatment of intraluminal gastric subepithelial tumors originating from the muscularis propria layer. *Endoscopy* 2006; **38**: 1024-1028 [PMID: 17058168 DOI: 10.1055/s-2006-944814]
5 **Park JJ**. Long-Term Outcomes after Endoscopic Treatment of Gastric Gastrointestinal Stromal Tumor. *Clin Endosc* 2016; **49**: 232-234 [PMID: 27196737 DOI: 10.5946/ce.2016.052]
6 **Chen T**, Lin ZW, Zhang YQ, Chen WF, Zhong YS, Wang Q, Yao LQ, Zhou PH, Xu MD. Submucosal Tunneling Endoscopic Resection *vs* Thoracoscopic Enucleation for Large Submucosal Tumors in the Esophagus and the Esophagogastric Junction. *J Am Coll Surg* 2017; **225**: 806-816 [PMID: 28923691 DOI: 10.1016/j.jamcollsurg.2017.09.002]
7 **Peng W**, Tan S, Huang S, Ren Y, Li H, Peng Y, Fu X, Tang X. Efficacy and safety of submucosal tunneling endoscopic resection for upper gastrointestinal submucosal tumors with more than 1-year' follow-up: a systematic review and meta-analysis. *Scand J Gastroenterol* 2019; **54**: 397-406 [PMID: 30925071 DOI: 10.1080/00365521.2019.1591500]

8 **Hwang JC**, Kim JH, Shin SJ, Cheong JY, Lee KM, Yoo BM, Lee KJ, Cho SW. Endoscopic resection for the treatment of gastric subepithelial tumors originated from the muscularis propria layer. *Hepatogastroenterology* 2009; **56**: 1281-1286 [PMID: 19950778]

9 **Xu HW**, Zhao Q, Yu SX, Jiang Y, Hao JH, Li B. Comparison of different endoscopic resection techniques for submucosal tumors originating from muscularis propria at the esophagogastric junction. *BMC Gastroenterol* 2019; **19**: 174 [PMID: 31694564 DOI: 10.1186/s12876-019-1099-5]

10 **Wang Z**, Zheng Z, Wang T, Wang X, Cao Y, Wang Y, Wang B. Submucosal tunneling endoscopic resection of large submucosal tumors originating from the muscularis propria layer in the esophagus and gastric cardia. *Z Gastroenterol* 2019; **57**: 952-959 [PMID: 31398766 DOI: 10.1055/a-0905-3173]

11 **Li B**, Liu J, Lu Y, Hao J, Liu H, Jiang J, Jiang Y, Qin C, Xu H. Submucosal tunneling endoscopic resection for tumors of the esophagogastric junction. *Minim Invasive Ther Allied Technol* 2016; **25**: 141-147 [PMID: 27049345 DOI: 10.3109/13645706.2016.1167085]

12 **Chen T**, Zhou PH, Chu Y, Zhang YQ, Chen WF, Ji Y, Yao LQ, Xu MD. Long-term Outcomes of Submucosal Tunneling Endoscopic Resection for Upper Gastrointestinal Submucosal Tumors. *Ann Surg* 2017; **265**: 363-369 [PMID: 28059965 DOI: 10.1097/SLA.0000000000001650]

13 **Jeon SW**, Jung MK, Cho CM, Tak WY, Kweon YO, Kim SK, Choi YH. Predictors of immediate bleeding during endoscopic submucosal dissection in gastric lesions. *Surg Endosc* 2009; **23**: 1974-1979 [PMID: 18553202 DOI: 10.1007/s00464-008-9988-7]

14 **Xu MD**, Cai MY, Zhou PH, Qin XY, Zhong YS, Chen WF, Hu JW, Zhang YQ, Ma LL, Qin WZ, Yao LQ. Submucosal tunneling endoscopic resection: a new technique for treating upper GI submucosal tumors originating from the muscularis propria layer (with videos). *Gastrointest Endosc* 2012; **75**: 195-199 [PMID: 22056087 DOI: 10.1016/j.gie.2011.08.018]

15 **Li ZS**, Li Q. [The latest 2010 WHO classification of tumors of digestive system]. *Zhonghua Bing Li Xue Za Zhi* 2011; **40**: 351-354 [PMID: 21756837]

16 **Mao XL**, Ye LP, Zheng HH, Zhou XB, Zhu LH, Zhang Y. Submucosal tunneling endoscopic resection using methylene-blue guidance for cardial subepithelial tumors originating from the muscularis propria layer. *Dis Esophagus* 2017; **30**: 1-7 [PMID: 27671744 DOI: 10.1111/dote.12536]

17 **Song S**, Feng M, Zhou H, Liu M, Sun M. Submucosal Tunneling Endoscopic Resection for Large and Irregular Submucosal Tumors Originating from Muscularis Propria Layer in Upper Gastrointestinal Tract. *J Laparoendosc Adv Surg Tech A* 2018; **28**: 1364-1370 [PMID: 30256158 DOI: 10.1089/lap.2017.0607]

18 **Li Z**, Gao Y, Chai N, Xiong Y, Ma L, Zhang W, Du C, Linghu E. Effect of submucosal tunneling endoscopic resection for submucosal tumors at esophagogastric junction and risk factors for failure of en bloc resection. *Surg Endosc* 2018; **32**: 1326-1335 [PMID: 28812158 DOI: 10.1007/s00464-017-5810-8]

19 **Lv XH**, Wang CH, Xie Y. Efficacy and safety of submucosal tunneling endoscopic resection for upper gastrointestinal submucosal tumors: a systematic review and meta-analysis. *Surg Endosc* 2017; **31**: 49-63 [PMID: 27287907 DOI: 10.1007/s00464-016-4978-7]

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ORIGINAL ARTICLE

Retrospective Study

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

Hsiu-Lung Fan, Chung-Bao Hsieh, Shih-Ming Kuo, Teng-Wei Chen

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Hsiu-Lung Fan, Chung-Bao Hsieh, Teng-Wei Chen, Division of General Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei 11409, Taiwan

Shih-Ming Kuo, Division of Pediatric Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei 11409, Taiwan

Corresponding author: Teng-Wei Chen, MD, Associate Professor, Division of General Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, No. 325, Sec 2, Chen-Kung Road, Neihu 114, Taipei 11409, Taiwan. tengweichen@yahoo.com.tw

Abstract

BACKGROUND

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

AIM

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

METHODS

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

RESULTS

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

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

CONCLUSION

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

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

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

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INTRODUCTION

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

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

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

MATERIALS AND METHODS

Patients

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

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

Post-LT follow-up

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

Statistical analysis

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

RESULTS

Patients' characteristics

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

Outcomes

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

Table 1 Patients' characteristics

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

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

[a]$P < 0.05$.

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

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

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

DISCUSSION

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

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

Table 2 Cox proportional hazard model for cancer-free survival

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

[a]$P < 0.05$.

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

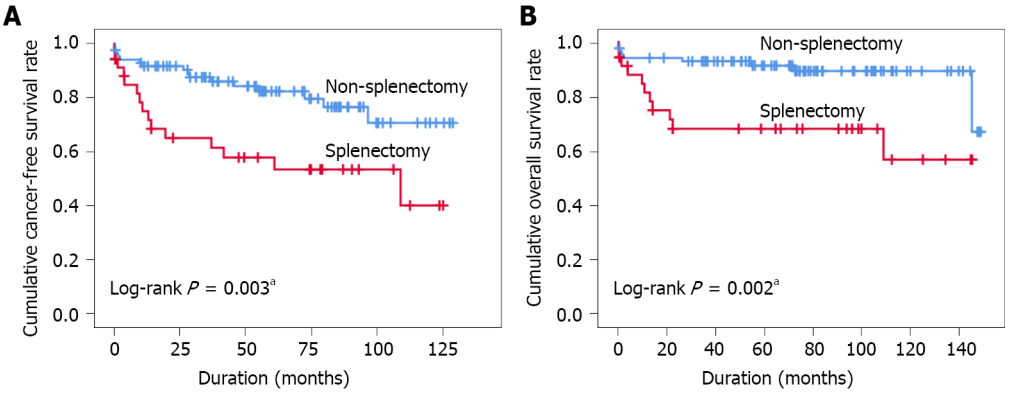

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Figure 1 Kaplan–Meier curves. A: Cancer-free survival in 120 patients. The rates were significantly different between the splenectomy and nonsplenectomy groups ($P = 0.003$); B: Overall survival in 120 patients. The rates were significantly different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

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

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

Table 3 Cox proportional hazard model for mortality

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

[a]$P < 0.05$.

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

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

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

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

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

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

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

CONCLUSION

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

ARTICLE HIGHLIGHTS

Research background

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

Research motivation

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

Research objectives

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

Research methods

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

Research results

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

Research conclusions

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

Research perspectives

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

FOOTNOTES

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

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Country/Territory of origin: Taiwan

ORCID number: Chung-Bao Hsieh 0000-0003-2359-5839; Teng-Wei Chen 0000-0002-4702-5411.

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REFERENCES

1 **Torre LA**, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262]
2 **Forner A**, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018; **391**: 1301-1314 [PMID: 29307467 DOI: 10.1016/S0140-6736(18)30010-2]
3 **Zhang JA**, Kwee SA, Wong LL. Late recurrence of hepatocellular carcinoma after liver transplantation. *Hepatoma Res* 2017; **3**: 58-66 [PMID: 28966983 DOI: 10.20517/2394-5079.2017.05]
4 **Mazzola A**, Costantino A, Petta S, Bartolotta TV, Raineri M, Sacco R, Brancatelli G, Cammà C, Cabibbo G. Recurrence of hepatocellular carcinoma after liver transplantation: an update. *Future Oncol* 2015; **11**: 2923-2936 [PMID: 26414336 DOI: 10.2217/fon.15.239]
5 **Yoon YI**, Lee SG. Living Donor Liver Transplantation for Hepatocellular Carcinoma: An Asian Perspective. *Dig Dis Sci* 2019; **64**: 993-1000 [PMID: 30895483 DOI: 10.1007/s10620-019-05551-4]
6 **Mellemkjoer L**, Olsen JH, Linet MS, Gridley G, McLaughlin JK. Cancer risk after splenectomy. *Cancer* 1995; **75**: 577-583 [PMID: 7812926 DOI: 10.1002/1097-0142(19950115)75:2<577::aid-cncr2820750222>3.0.co;2-k]
7 **Linet MS**, Nyrén O, Gridley G, Mellemkjaer L, McLaughlin JK, Olsen JH, Adami HO, Fraumeni JF Jr. Risk of cancer following splenectomy. *Int J Cancer* 1996; **66**: 611-616 [PMID: 8647621 DOI: 10.1002/(SICI)1097-0215(19960529)66:5<611::AID-IJC5>3.0.CO;2-W]
8 **Sun LM**, Chen HJ, Jeng LB, Li TC, Wu SC, Kao CH. Splenectomy and increased subsequent cancer risk: a nationwide population-based cohort study. *Am J Surg* 2015; **210**: 243-251 [PMID: 25986002 DOI: 10.1016/j.amjsurg.2015.01.017]
9 **Yoshizumi T**, Itoh S, Shimokawa M, Inokuchi S, Harada N, Takeishi K, Mano Y, Yoshiya S, Kurihara T, Nagao Y, Ikegami T, Soejima Y, Mori M. Simultaneous splenectomy improves outcomes after adult living donor liver transplantation. *J Hepatol* 2021; **74**: 372-379 [PMID: 32827564 DOI: 10.1016/j.jhep.2020.08.017]
10 **Usui M**, Isaji S, Mizuno S, Sakurai H, Uemoto S. Experiences and problems pre-operative anti-CD20 monoclonal antibody infusion therapy with splenectomy and plasma exchange for ABO-incompatible living-donor liver transplantation. *Clin Transplant* 2007; **21**: 24-31 [PMID: 17302588 DOI: 10.1111/j.1399-0012.2006.00572.x]
11 **Yoshizumi T**, Mori M. Portal flow modulation in living donor liver transplantation: review with a focus on splenectomy. *Surg Today* 2020; **50**: 21-29 [PMID: 31555908 DOI: 10.1007/s00595-019-01881-y]
12 **Jiang WT**, Yang J, Xie Y, Guo QJ, Tian DZ, Li JJ, Shen ZY. Simultaneous partial splenectomy during liver transplantation for advanced cirrhosis patients combined with severe splenomegaly and hypersplenism. *World J Gastroenterol* 2021; **27**: 654-665 [PMID: 33642835 DOI: 10.3748/wjg.v27.i7.654]
13 **Kristinsson SY**, Gridley G, Hoover RN, Check D, Landgren O. Long-term risks after splenectomy among 8,149 cancer-free American veterans: a cohort study with up to 27 years follow-up. *Haematologica* 2014; **99**: 392-398 [PMID: 24056815 DOI: 10.3324/haematol.2013.092460]
14 **Hull CC**, Galloway P, Gordon N, Gerson SL, Hawkins N, Stellato TA. Splenectomy and the induction of murine colon cancer. *Arch Surg* 1988; **123**: 462-464 [PMID: 3348737 DOI: 10.1001/archsurg.1988.01400280072012]

15 **Higashijima J**, Shimada M, Chikakiyo M, Miyatani T, Yoshikawa K, Nishioka M, Iwata T, Kurita N. Effect of splenectomy on antitumor immune system in mice. *Anticancer Res* 2009; **29**: 385-393 [PMID: 19331177]

16 **Hwang HK**, Murakami T, Kiyuna T, Kim SH, Lee SH, Kang CM, Hoffman RM, Bouvet M. Splenectomy is associated with an aggressive tumor growth pattern and altered host immunity in an orthotopic syngeneic murine pancreatic cancer model. *Oncotarget* 2017; **8**: 88827-88834 [PMID: 29179479 DOI: 10.18632/oncotarget.21331]

17 **Hwang HK**, Kang CM, Lee SH, Murakami T, Kiyuna T, Kim SH, Hoffman RM, Bouvet M. Fluorescence-guided Surgery with Splenic Preservation Prevents Tumor Recurrence in an Orthotopic Nude-mouse Model of Human Pancreatic Cancer. *Anticancer Res* 2018; **38**: 665-670 [PMID: 29374688 DOI: 10.21873/anticanres.12270]

18 **Chen XP**, Wu ZD, Huang ZY, Qiu FZ. Use of hepatectomy and splenectomy to treat hepatocellular carcinoma with cirrhotic hypersplenism. *Br J Surg* 2005; **92**: 334-339 [PMID: 15672441 DOI: 10.1002/bjs.4776]

19 **Zhang X**, Li C, Wen T, Peng W, Yan L, Li B, Yang J, Wang W, Xu M, Zeng Y. Synchronous splenectomy and hepatectomy for patients with small hepatocellular carcinoma and pathological spleen: neutrophil to lymphocyte ratio changes can predict the prognosis. *Oncotarget* 2017; **8**: 46298-46311 [PMID: 28549349 DOI: 10.18632/oncotarget.17758]

20 **Zhang XY**, Li C, Wen TF, Yan LN, Li B, Yang JY, Wang WT, Jiang L. Synchronous splenectomy and hepatectomy for patients with hepatocellular carcinoma and hypersplenism: A case-control study. *World J Gastroenterol* 2015; **21**: 2358-2366 [PMID: 25741142 DOI: 10.3748/wjg.v21.i8.2358]

21 **Zhang XF**, Liu Y, Li JH, Lei P, Zhang XY, Wan Z, Lei T, Zhang N, Wu XN, Long ZD, Li ZF, Wang B, Liu XM, Wu Z, Chen X, Wang JX, Yuan P, Li Y, Zhou J, Pawlik M, Lyu Y. Effect of splenectomy on the right of hepatocellular carcinoma development amoung patients with liver cirrhosis and portal hypertension: a multi-institutional cohort study. *Zhonghua Waike Zazhi* 2021; **59**: 821-828 [DOI: 10.21203/rs.3.rs-53468/v1]

22 **Eiján AM**, Jasnis MA, Kohan SS, Oisgold-Dagá S. Nature of the spleen cell populations capable of releasing tumor enhancing factor. *J Surg Oncol* 1987; **36**: 161-165 [PMID: 3500369 DOI: 10.1002/jso.2930360303]

23 **Davel L**, Miguez M, Jasnis MA, Eiján AM, Oisgold-Dagá S, Sacerdote de Lustig E. Angiogenic activity by spleen cell supernatants from tumor-bearing and tumor-resected mice. *J Surg Oncol* 1988; **37**: 44-48 [PMID: 2447442 DOI: 10.1002/jso.2930370113]

24 **Klein S**, de Bonaparte YP, de D'Elia I. Enhancement of the incidence of metastasis in tumor-resected mice. Influence of soluble tumor extract and splenectomy. *Invasion Metastasis* 1985; **5**: 309-316 [PMID: 4030247]

25 **Shi R**, Zhang YM, Zhu ZJ, Deng YL, Pan C, Zheng H, Shen ZY. Synchronous splenectomy and hepatectomy in patients with hepatocellular carcinoma, hypersplenism and liver cirrhosis. *Hepatogastroenterology* 2014; **61**: 1363-1367 [PMID: 25436312]

26 **Wang C**, Li C, Wen TF, Yan LN, Li B, Liang GL, Li KW. Safety of synchronous hepatectomy and splenectomy for patients with hepatocellular carcinoma and hypersplenism. *Hepatogastroenterology* 2012; **59**: 526-528 [PMID: 22353518 DOI: 10.5754/hge11260]

27 **Ito K**, Akamatsu N, Ichida A, Ito D, Kaneko J, Arita J, Sakamoto Y, Hasegawa K, Kokudo N. Splenectomy is not indicated in living donor liver transplantation. *Liver Transpl* 2016; **22**: 1526-1535 [PMID: 27253521 DOI: 10.1002/lt.24489]

28 **He C**, Liu X, Peng W, Li C, Wen TF. Evaluation the efficacy and safety of simultaneous splenectomy in liver transplantation patients: A meta-analysis. *Medicine (Baltimore)* 2018; **97**: e0087 [PMID: 29517676 DOI: 10.1097/MD.0000000000010087]

29 **Badawy A**, Hamaguchi Y, Satoru S, Kaido T, Okajima H, Uemoto S. Evaluation of safety of concomitant splenectomy in living donor liver transplantation: a retrospective study. *Transpl Int* 2017; **30**: 914-923 [PMID: 28512755 DOI: 10.1111/tri.12985]

30 **Wang P**, Wang C, Li H, Shi B, Wang J, Zhong L. Impact of age on the prognosis after liver transplantation for patients with hepatocellular carcinoma: a single-center experience. *Onco Targets Ther* 2015; **8**: 3775-3781 [PMID: 26719705 DOI: 10.2147/OTT.S93939]

31 **Wai CT**, Woon WA, Tan YM, Lee KH, Tan KC. Younger age and presence of macrovascular invasion were independent significant factors associated with poor disease-free survival in hepatocellular carcinoma patients undergoing living donor liver transplantation. *Transplant Proc* 2012; **44**: 516-519 [PMID: 22410059 DOI: 10.1016/j.transproceed.2012.01.032]

32 **Martínez-Saldivar B**, Prieto J, Berenguer M, de la Mata M, Pons JA, Serrano T, Rafael-Valdivia L, Aguilera V, Barrera P, Parrilla P, Lorente S, Rubin A, Fraga E, Rimola A. Control of blood pressure in liver transplant recipients. *Transplantation* 2012; **93**: 1031-1037 [PMID: 22411562 DOI: 10.1097/TP.0b013e31824cd5e6]

33 **Albeldawi M**, Aggarwal A, Madhwal S, Cywinski J, Lopez R, Eghtesad B, Zein NN. Cumulative risk of cardiovascular events after orthotopic liver transplantation. *Liver Transpl* 2012; **18**: 370-375 [PMID: 22140067 DOI: 10.1002/lt.22468]

34 **Watt KD**, Pedersen RA, Kremers WK, Heimbach JK, Charlton MR. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. *Am J Transplant* 2010; **10**: 1420-1427 [PMID: 20486907 DOI: 10.1111/j.1600-6143.2010.03126.x]

35 **Jiménez-Pérez M**, González-Grande R, Omonte Guzmán E, Amo Trillo V, Rodrigo López JM. Metabolic complications in liver transplant recipients. *World J Gastroenterol* 2016; **22**: 6416-6423 [PMID: 27605877 DOI: 10.3748/wjg.v22.i28.6416]

36 **Kelly DM**, Miller C. Understanding the splenic contribution to portal flow: the role of splenic artery ligation as inflow modification in living donor liver transplantation. *Liver Transpl* 2006; **12**: 1186-1188 [PMID: 16868947 DOI: 10.1002/Lt.20880]

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ORIGINAL ARTICLE

Retrospective Study

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

Shi-Hao Guan, Qiong Wang, Xiao-Ming Ma, Wen-Jie Qiao, Ming-Zheng Li, Ming-Gui Lai, Cheng Wang

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Shi-Hao Guan, Department of General Surgery, Qingpu Branch of Zhongshan Hospital Affiliated to Fudan University, Shanghai 201700, China

Shi-Hao Guan, Medical College, Qinghai University, Xining 810001, Qinghai Province, China

Qiong Wang, Department of Medical Oncology, The Affiliated Hospital of Qinghai University, Xining 810001, Qinghai Province, China

Xiao-Ming Ma, Wen-Jie Qiao, Ming-Zheng Li, Ming-Gui Lai, Cheng Wang, Department of Gastrointestinal Tumor Surgery, The Affiliated Hospital of Qinghai University, Xining 810001, Qinghai Province, China

Corresponding author: Cheng Wang, MM, Chief Doctor, Professor, Department of Gastrointestinal Tumor Surgery, The Affiliated Hospital of Qinghai University, No. 29 Tongren Road, Xining 810001, Qinghai Province, China. cheng_wang_vip@163.com

Abstract

BACKGROUND

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

AIM

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

METHODS

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

RESULTS

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

CONCLUSION

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

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

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

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INTRODUCTION

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

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

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

postoperative pathological features and general clinical data.

MATERIALS AND METHODS

Patients

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

Postoperative survival and follow-up

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

Statistical analysis

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

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

RESULTS

Patient characteristics

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

Factor selection

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

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

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

NIH: National Institutes of Health.

Development of an individualized prediction model

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

Table 2 Prediction factors for recurrence of gastrointestinal stromal tumor

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

β: The regression coefficient.

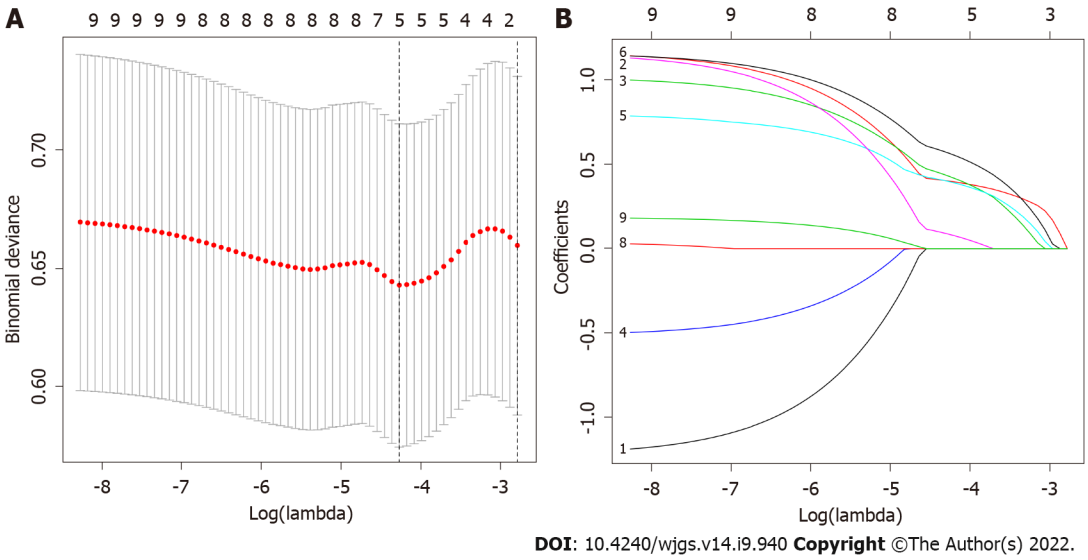

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Figure 1 Clinicopathologic characteristics selection using the least absolute shrinkage and selection operator regression model. A: Optimal parameter (lambda) selection in the least absolute shrinkage and selection operator (LASSO) regression model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

(Figure 2).

Apparent performance of the recurrence risk nomogram in the cohort

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

Clinical use

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

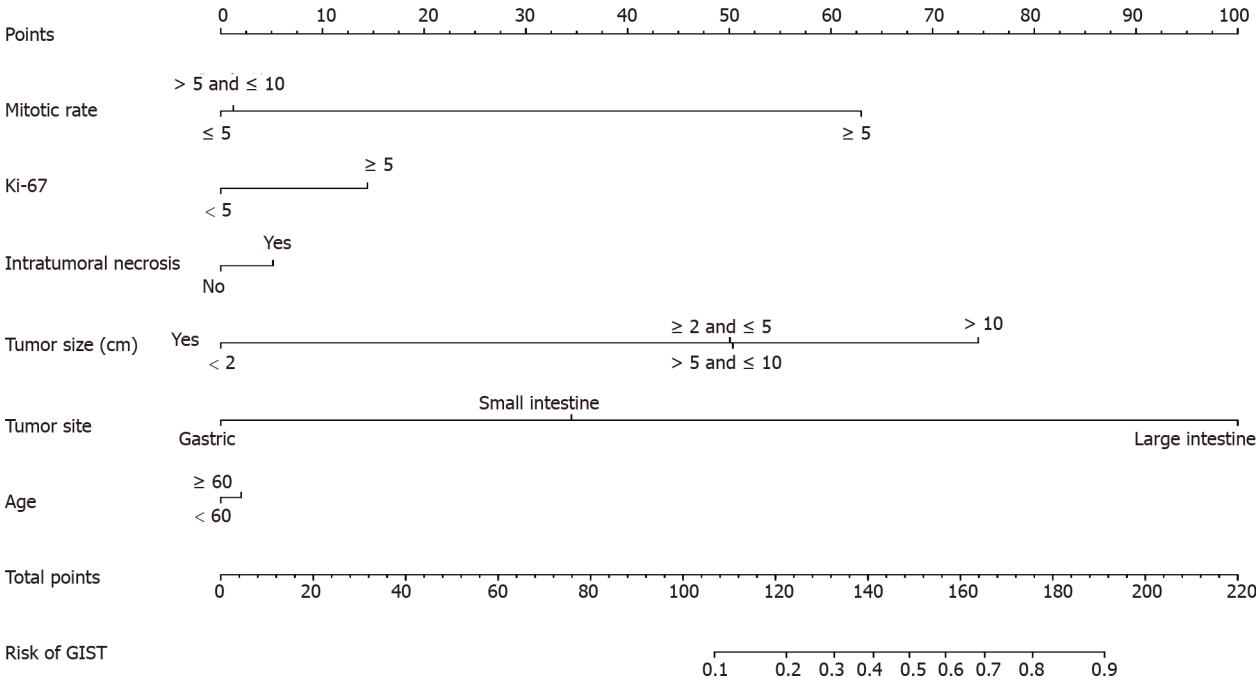

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Figure 2 Developed recurrence nomogram. The recurrence nomogram includes mitotic rate, Ki-67, intratumoral necrosis, tumor size, tumor site and age. GIST: Gastrointestinal stromal tumors.

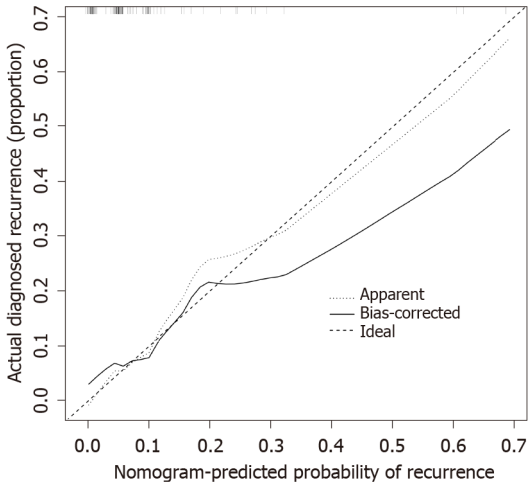

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Figure 3 Calibration curves of the recurrence nomogram prediction. The x-axis represents a possible risk of recurrence of gastrointestinal stromal tumor. The y-axis represents the actual recurrence. Diagonal dotted lines indicate predictions under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

DISCUSSION

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

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

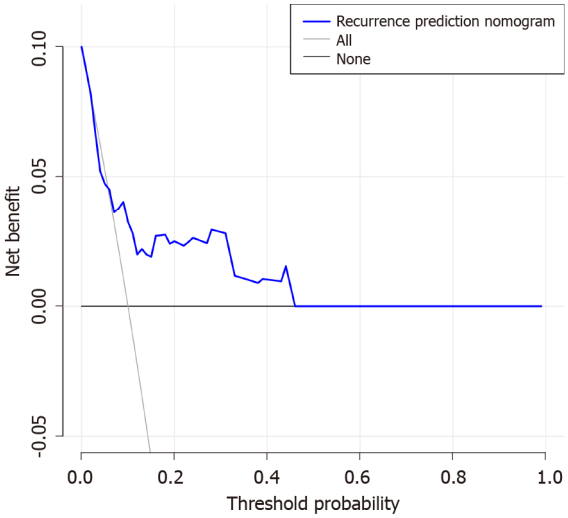

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Figure 4 Decision curve analysis of the recurrence nomogram. The y-axis represents the net benefit. The blue line represents the gastrointestinal stromal tumor (GIST) recurrence risk nomogram. The solid line indicates the hypothesis that all patients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

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

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

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

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

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

CONCLUSION

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

ARTICLE HIGHLIGHTS

Research background

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

Research motivation

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

Research objectives

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

Research methods

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

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

Research results

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

Research conclusions

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

Research perspectives

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

FOOTNOTES

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

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Informed consent statement: All patients signed informed consent forms.

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

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ORCID number: Shi-Hao Guan 0000-0003-3520-7370; Qiong Wang 0000-0001-5923-2779; Xiao-Ming Ma 0000-0002-2659-4092; Wen-Jie Qiao 0000-0001-5302-2009; Ming-Zheng Li 0000-0003-1974-6112; Ming-Gui Lai 0000-0001-8419-9317; Cheng Wang 0000-0003-4942-7833.

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REFERENCES

1 **Wang MX**, Devine C, Segaran N, Ganeshan D. Current update on molecular cytogenetics, diagnosis and management of gastrointestinal stromal tumors. *World J Gastroenterol* 2021; **27**: 7125-7133 [PMID: 34887632 DOI: 10.3748/wjg.v27.i41.7125]
2 **Tan AD**, Willemsma K, MacNeill A, DeVries K, Srikanthan A, McGahan C, Hamilton T, Li H, Blanke CD, Simmons CE. Tyrosine kinase inhibitors significantly improved survival outcomes in patients with metastatic gastrointestinal stromal tumour: a multi-institutional cohort study. *Curr Oncol* 2020; **27**: e276-e282 [PMID: 32669934 DOI: 10.3747/co.27.5869]
3 **Blay JY**, Kang YK, Nishida T, von Mehren M. Gastrointestinal stromal tumours. *Nat Rev Dis Primers* 2021; **7**: 22 [PMID: 33737510 DOI: 10.1038/s41572-021-00254-5]
4 **Bae JH**, Lee CS, Han SR, Park SM, Lee YS, Lee IK. Differences in the prognostic impact of post-operative systemic inflammation and infection in colorectal cancer patients: Using white blood cell counts and procalcitonin levels. *Surg Oncol* 2020; **35**: 374-381 [PMID: 33035785 DOI: 10.1016/j.suronc.2020.09.017]
5 **Joensuu H**. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. *Hum Pathol* 2008; **39**: 1411-1419

[PMID: 18774375 DOI: 10.1016/j.humpath.2008.06.025]
6 **Kallen ME**, Hornick JL. The 2020 WHO Classification: What's New in Soft Tissue Tumor Pathology? *Am J Surg Pathol* 2021; **45**: e1-e23 [PMID: 32796172 DOI: 10.1097/PAS.0000000000001552]
7 **Zhao WY**, Zhao G, Wang M. [Updates and interpretations of the NCCN Clinical Practice Guidelines (2019 6th version) on gastrointestinal stromal tumor]. *Zhonghua Wei Chang Wai Ke Za Zhi* 2020; **23**: 866-871 [PMID: 32927511 DOI: 10.3760/cma.j.cn.441530-20200731-00454]
8 **Khoo CY**, Chai X, Quek R, Teo MCC, Goh BKP. Systematic review of current prognostication systems for primary gastrointestinal stromal tumors. *Eur J Surg Oncol* 2018; **44**: 388-394 [PMID: 29422251 DOI: 10.1016/j.ejso.2017.12.006]
9 **Joensuu H**, Vehtari A, Riihimäki J, Nishida T, Steigen SE, Brabec P, Plank L, Nilsson B, Cirilli C, Braconi C, Bordoni A, Magnusson MK, Linke Z, Sufliarsky J, Federico M, Jonasson JG, Dei Tos AP, Rutkowski P. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. *Lancet Oncol* 2012; **13**: 265-274 [PMID: 22153892 DOI: 10.1016/S1470-2045(11)70299-6]
10 **Zhang J**, Jiang L, Zhu X. A Novel Nomogram for Prediction of Early Postoperative Complications of Total Gastrectomy for Gastric Cancer. *Cancer Manag Res* 2021; **13**: 7579-7591 [PMID: 34629904 DOI: 10.2147/CMAR.S333172]
11 **Wang Z**, Li H, Liu T, Sun Z, Yang F, Jiang G. Development and External Validation of a Nomogram for Predicting Cancer-Specific Survival of Non-Small Cell Lung Cancer Patients With Ipsilateral Pleural Dissemination. *Front Oncol* 2021; **11**: 645486 [PMID: 34350108 DOI: 10.3389/fonc.2021.645486]
12 **Friedman J**, Hastie T, Tibshirani R. Regularization Paths for Generalized Linear Models *via* Coordinate Descent. *J Stat Softw* 2010; **33**: 1-22 [PMID: 20808728]
13 **Sauerbrei W**, Royston P, Binder H. Selection of important variables and determination of functional form for continuous predictors in multivariable model building. *Stat Med* 2007; **26**: 5512-5528 [PMID: 18058845 DOI: 10.1002/sim.3148]
14 **Kidd AC**, McGettrick M, Tsim S, Halligan DL, Bylesjo M, Blyth KG. Survival prediction in mesothelioma using a scalable Lasso regression model: instructions for use and initial performance using clinical predictors. *BMJ Open Respir Res* 2018; **5**: e000240 [PMID: 29468073 DOI: 10.1136/bmjresp-2017-000240]
15 **Pencina MJ**, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. *Stat Med* 2004; **23**: 2109-2123 [PMID: 15211606 DOI: 10.1002/sim.1802]
16 **Vickers AJ**, Cronin AM, Elkin EB, Gonen M. Extensions to decision curve analysis, a novel method for evaluating diagnostic tests, prediction models and molecular markers. *BMC Med Inform Decis Mak* 2008; **8**: 53 [PMID: 19036144 DOI: 10.1186/1472-6947-8-53]
17 **Li M**, Zhang J, Dan Y, Yao Y, Dai W, Cai G, Yang G, Tong T. A clinical-radiomics nomogram for the preoperative prediction of lymph node metastasis in colorectal cancer. *J Transl Med* 2020; **18**: 46 [PMID: 32000813 DOI: 10.1186/s12967-020-02215-0]
18 **Mantese G**. Gastrointestinal stromal tumor: epidemiology, diagnosis, and treatment. *Curr Opin Gastroenterol* 2019; **35**: 555-559 [PMID: 31577561 DOI: 10.1097/MOG.0000000000000584]
19 **Yin XN**, Tang SM, Yin Y, Shen CY, Zhang B, Chen ZX. [Associations of Preoperative Platelet-to-lymphocyte Ratio and Derived Neutrophil-to-lymphocyte Ratio with thePrognosis of Gastrointestinal Stromal Tumor]. *Sichuan Da Xue Xue Bao Yi Xue Ban* 2017; **48**: 239-243 [PMID: 28612534]
20 **Lou S**, Meng F, Yin X, Zhang Y, Han B, Xue Y. Comprehensive Characterization of RNA Processing Factors in Gastric Cancer Identifies a Prognostic Signature for Predicting Clinical Outcomes and Therapeutic Responses. *Front Immunol* 2021; **12**: 719628 [PMID: 34413861 DOI: 10.3389/fimmu.2021.719628]
21 **Cao R**, Yuan L, Ma B, Wang G, Qiu W, Tian Y. An EMT-related gene signature for the prognosis of human bladder cancer. *J Cell Mol Med* 2020; **24**: 605-617 [PMID: 31657881 DOI: 10.1111/jcmm.14767]
22 **Sugiyama Y**, Sasaki M, Kouyama M, Tazaki T, Takahashi S, Nakamitsu A. Current treatment strategies and future perspectives for gastrointestinal stromal tumors. *World J Gastrointest Pathophysiol* 2022; **13**: 15-33 [PMID: 35116177 DOI: 10.4291/wjgp.v13.i1.15]
23 **Qi Y**, Zhao W, Wang Z, Li T, Meng X. Tumor sites and microscopic indicators are independent prognosis predictors of gastrointestinal stromal tumors. *Tohoku J Exp Med* 2014; **233**: 65-72 [PMID: 24827382 DOI: 10.1620/tjem.233.65]
24 **Roşulescu A**, Pechianu N, Hortopan M, Mihai M, Dima S, Stroescu C, Zamfir R, Braşoveanu V, Leonard D, Vasilescu C, Popescu I, Herlea V. Gastrointestinal stromal tumors of the colon and rectum. *Pol J Pathol* 2020; **71**: 200-206 [PMID: 33112110 DOI: 10.5114/pjp.2020.99786]
25 **Serrano C**, George S. Gastrointestinal Stromal Tumor: Challenges and Opportunities for a New Decade. *Clin Cancer Res* 2020; **26**: 5078-5085 [PMID: 32601076 DOI: 10.1158/1078-0432.CCR-20-1706]
26 **Zemła P**, Stelmach A, Jabłońska B, Gołka D, Mrowiec S. A Retrospective Study of Postoperative Outcomes in 98 Patients Diagnosed with Gastrointestinal Stromal Tumor (GIST) of the Upper, Middle, and Lower Gastrointestinal Tract Between 2009 and 2019 at a Single Center in Poland. *Med Sci Monit* 2021; **27**: e932809 [PMID: 34645778 DOI: 10.12659/MSM.932809]
27 **Catena F**, Di Battista M, Ansaloni L, Pantaleo M, Fusaroli P, Di Scioscio V, Santini D, Nannini M, Saponara M, Ponti G, Persiani R, Delrio P, Coccolini F, Di Saverio S, Biasco G, Lazzareschi D, Pinna A; GISTologist Study Group. Microscopic margins of resection influence primary gastrointestinal stromal tumor survival. *Onkologie* 2012; **35**: 645-648 [PMID: 23147540 DOI: 10.1159/000343585]
28 **Cavnar MJ**, Seier K, Curtin C, Balachandran VP, Coit DG, Yoon SS, Crago AM, Strong VE, Tap WD, Gönen M, Antonescu CR, Brennan MF, Singer S, DeMatteo RP. Outcome of 1000 Patients With Gastrointestinal Stromal Tumor (GIST) Treated by Surgery in the Pre- and Post-imatinib Eras. *Ann Surg* 2021; **273**: 128-138 [PMID: 30946076 DOI: 10.1097/SLA.0000000000003277]
29 **Zhu X**, Chen L, Huang B, Wang Y, Ji L, Wu J, Di G, Liu G, Yu K, Shao Z, Wang Z. The prognostic and predictive potential of Ki-67 in triple-negative breast cancer. *Sci Rep* 2020; **10**: 225 [PMID: 31937819 DOI: 10.1038/s41598-019-57094-3]
30 **Kadado KJ**, Abernathy OL, Salyers WJ, Kallail KJ. Gastrointestinal Stromal Tumor and Ki-67 as a Prognostic Indicator. *Cureus* 2022; **14**: e20868 [PMID: 35145775 DOI: 10.7759/cureus.20868]

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ORIGINAL ARTICLE

Retrospective Study

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

Rui-Yang Zhao, Hang-Hang Li, Ke-Cheng Zhang, Hao Cui, Huan Deng, Jing-Wang Gao, Bo Wei

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Rui-Yang Zhao, Hang-Hang Li, Ke-Cheng Zhang, Huan Deng, Jing-Wang Gao, Bo Wei, Department of General Surgery, First Medical Center, Chinese PLA General Hospital, Beijing 100853, China

Rui-Yang Zhao, Hang-Hang Li, Huan Deng, Jing-Wang Gao, Bo Wei, Medical School of Chinese PLA, Chinese PLA General Hospital, Beijing 100853, China

Hao Cui, School of Medicine, Nankai University, Tianjin 300071, China

Corresponding author: Bo Wei, MD, PhD, Chief Doctor, Department of General Surgery, First Medical Center, Chinese PLA General Hospital, No. 28 Fuxing Road, Beijing 100853, China. weibo@301hospital.com.cn

Abstract

BACKGROUND

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

AIM

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

METHODS

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

RESULTS

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

CONCLUSION

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

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

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

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INTRODUCTION

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

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

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

proof for the application of TLG for elderly patients by comparing the short-term efficacy and QOL between elderly GC patients who received TLG or LAG.

MATERIALS AND METHODS

Patients

The inclusion criteria were as follows: (1) Age ≥ 70 years; (2) Gastric adenocarcinoma confirmed by preoperative gastroscopic pathology, endoscopic ultrasonography, abdominal computed tomography (CT) or positron emission tomography-CT; and (3) Postoperative pathological staging of Ia-IIIc. The exclusion criteria were as follows: (1) Intraoperative conversion to open surgery for any reason; (2) American Society of Anesthesiologists (ASA) classification > grade III; (3) Gastric stump cancer treated by gastric surgery; (4) Previous proximal gastrectomy; and (5) Absence of clinical and pathological data.

Based on the above criteria, clinical and pathological data were retrospectively collected from 462 elderly GC patients who underwent TLG or LAG at the Department of General Surgery, First Medical Center, Chinese PLA General Hospital between January 2017 and January 2022, including 230 patients in the TLG group and 232 patients in the LAG group. The clinicopathological characteristics of the patients are provided in Table 1. This study meets the requirements of the Declaration of Helsinki and has been approved by the Research Ethics Committee of Chinese PLA General Hospital (Approval Number: S2021-605-01).

Surgical approach

The surgical procedure was performed in accordance with the *Chinese Guidelines for laparoscopic gastrectomy for gastric cancer* (2016 edition). The scope of surgical resection and lymph node dissection was based on the standard criteria established by the *Japanese gastric cancer treatment guidelines 2018* (5th edition)[11]. D2 Lymph node dissection was performed for all patients who underwent distal or total gastrectomy. The intracorporeal gastrointestinal reconstruction procedure in the TLG group was performed in accordance with the *Chinese Expert consensus and surgical operation guidelines for gastrointestinal reconstruction in totally laparoscopic gastrectomy* (2018 edition). After completing intracorporeal reconstruction, a small upper abdominal median incision (length of incision ≤ 7 cm) was made for specimen removal only. After lymph node dissection in the LAG group, the upper abdominal median incision (incision length ≤ 10 cm) was used to remove the specimens, and the extracorporeal gastrointestinal reconstruction was performed. A circular anastomosis was performed at the esophagojejunal anastomotic site in laparoscopic assisted total gastrectomy (LATG). In totally laparoscopic total gastrectomy (TLTG), a linear anastomosis, including overlap or π anastomosis, was performed at the esophagojejunal anastomotic site. The methods for gastrointestinal reconstruction were selected based on the surgeon's preferences and executed in accordance with standardized procedures.

Definition and classification of postoperative complications

The incidence and severity of complications within 30 d after surgery were assessed[12] using the Clavien–Dindo classification. The evaluation criteria mainly included the following: (1) Grade I: Any deviation from the normal postoperative recovery process but without the need for drugs, surgical intervention, endoscopy or interventional therapy; (2) Grade II: A need for drug therapy including blood transfusion, or total parenteral nutrition (except antiemetic, antipyretic, analgesic, diuretic, rehydration and other symptomatic drug therapy); (3) Grade III: Surgical intervention, endoscopy or interventional treatment needed (Grade IIIa, does not require general anesthesia; Grade IIIb, requires general anesthesia); (4) Grade IV: Life-threatening condition with treatment needed in the intensive care unit (Grade IVa, single organ failure; Grade IVb, multiple organ failure); and (5) Grade V: Death. In this study, complications within 30 d after surgery were defined as Clavien–Dindo grade ≥ II, and severe complications within 30 d after surgery were defined as Clavien–Dindo grade ≥ IIIa because of the limitation associated with a retrospective study design.

QOL questionnaire and scoring method

In this study, the Chinese versions of the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30)[13] and QLQ-ST022[14] were used to assess the QOL of patients before and 3 mo after surgery. The EORTC QLQ-C3O is a core scale for all cancer patients, with a total of 30 items. Among them, items 29 and 30 are scored using 7 grade options, which are assigned 1 to 7 points based on the answer options. Other items are scored using 4 grade options, *i.e.*, not at all, a little, quite a bit, and very much, and are assigned 1 to 4 points when scoring. The QLQ-C30 questionnaire is divided into 15 domains, including 5 functional domains (physical, role, cognitive, emotional, and social functioning), 3 symptom domains (fatigue, pain and nausea and vomiting), 1 overall QOL domain and 6 single items (each as a domain). The QLQ-STO22 includes 22 items related to the QOL of GC patients and consists of 9 scales, including dysphagia, pain, reflux, eating restriction, anxiety, dry mouth, taste, body shape and hair loss.

Table 1 Clinical and pathological characteristics of laparoscopic assisted gastrectomy and totally laparoscopic gastrectomy group for elderly patients (mean ± SD)

Characteristics	LAG group (*n* = 232)	TLG group (*n* = 230)	*P* value
Gender			0.472
Male	183	175	
Female	49	55	
Age (yr)	74.62 ± 3.80	74.69 ± 4.10	0.848
BMI (kg/m^2)	23.31 ± 3.08	23.64 ± 3.46	0.285
aCCI score, *n* (%)			0.608
0-4	188	182	
> 4	44	48	
ASA score, *n* (%)			0.426
I	1	1	
II	177	168	
III	54	61	
History of abdominal surgery			0.232
No	189	177	
Yes	43	53	
Tumor resection			0.163
Distal	125	109	
Total	107	121	
Neoadjuvant chemotherapy			0.201
No	223	215	
Yes	9	15	
Tumor diameters (cm) (median, IQR)	4.00 (2.58-6.00)	4.00 (2.65-5.5)	0.230
pT			0.895
T0	2	0	
T1	38	43	
T2	36	37	
T3	116	107	
T4	40	43	
pN			0.544
N0	83	77	
N1	33	33	
N2	49	48	
N3	67	72	
pTNM			0.857
0	2	0	
I	52	60	
II	65	57	
III	113	113	
Nerve invasion			0.249
Yes	71	82	

No	161	148	
Vascular invasion			0.685
Yes	91	86	
No	141	144	
Differentiation			0.945
Well/moderate	151	149	
Poor/undifferentiated	81	81	

LAG: Laparoscopic assisted gastrectomy; TLG: Totally laparoscopic gastrectomy; aCCI: Age-adjusted Charlson Comorbidity Index; BMI: Body mass index; ASA: American Society of Anesthesiologists; SD: Standard deviation; IQR: Interquartile range.

Statistical analysis

SPSS 26.0 statistical software was used for analysis. Normally distributed measurement data are expressed as the mean ± SD. Categorical data are expressed as *n* (%). Data with a skewed distribution are expressed as the median (interquartile range). Binary logistic regression was used to analyze the relationships between postoperative complications and clinical and pathological factors. Factors with $P < 0.20$ in the univariate analysis were included in the multivariate analysis. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical and pathological characteristics

Among the 462 patients, 183 males and 49 females were included in the TLG group, with an average age of 74.69 ± 4.10 years, and 175 males and 55 females were included in the LAG group, with an average age of 74.62 ± 3.80 years. No significant differences in clinical characteristics, such as age, sex, body mass index, age-adjusted Charlson comorbidity index score, ASA score, a history of abdominal surgery and the range of surgical resection, were identified between 2 groups ($P > 0.05$). In terms of pathological characteristics, no significant differences in pathologic T stage, pathologic N stage, pTNM stage, tumor size, nerve invasion, vascular invasion or tumor differentiation were found between the 2 groups, suggesting that the baseline characteristics of the 2 groups were comparable (Table 1).

In the subgroup analysis, we compared the baseline characteristics between the TLTG group and LATG groups and between the TLDG and LADG groups. The results suggested that the tumor diameter in the TLDG group was smaller than that in the LADG group ($P = 0.035$). No significant differences were noted between other clinicopathological indicators ($P > 0.05$, Supplementary Table 1).

Perioperative outcomes and postoperative recovery

The perioperative outcomes are presented in Table 2. Compared with those in the LAG group, intraoperative blood loss in the LTG group was significantly lower [100 (50-100) mL *vs* 100 (50-200) mL] ($P < 0.001$), the time to first flatus was significantly shorter [(3.79 ± 1.15) d *vs* (4.43 ± 1.20) d] ($P < 0.001$), and the postoperative hospitalization time was shorter [7.75 (6.0-9.0) d *vs* 8.0 (7.0-10.0) d] ($P < 0.001$). No significant differences in the operation time, anastomosis methods, numbers of retrieved lymph nodes or R0 resection rates were observed between the 2 groups ($P > 0.05$). In terms of postoperative complications, the overall incidence of postoperative complications in the TLG group was significantly lower than that in the LAG group (16.5% *vs* 26.3%, $P = 0.01$). Additionally, no significant differences in the incidence of anastomotic-related complications (2.6% *vs* 3.4%, $P = 0.599$) or the incidence of severe complications (3.9% *vs* 4.3%, $P = 0.830$) were found between the TLG and LAG groups.

The results of the subgroup analysis indicated that the operation time in the TLDG group was significantly shorter than that in the LADG group [(201.82 ± 45.35) min *vs* (217.88 ± 49.08) min, $P = 0.01$]. In terms of intraoperative blood loss, the time to first flatus, and postoperative hospitalization time, TLG showed significant advantages over LAG in either distal or total gastrectomy (Supplementary Table 2).

We further explored risk factors for postoperative complications (Table 3). Univariate analysis indicated that TLG and LAG were associated with postoperative complications ($P = 0.011$). We included factors with $P < 0.02$ in the multivariate analysis. The results indicated that LAG and an operation time > 220 min were independent risk factors for postoperative complications in elderly patients with GC ($P < 0.05$). For the comparisons between LDG and LTG, the results suggested that a long tumor diameter > 3 cm and an operation time > 220 min were independent risk factors for postoperative complications in the LDG group ($P < 0.05$). No independent risk factors for postoperative complications were observed in the LTG group, as shown in Supplementary Table 3.

Table 2 Perioperative outcomes between laparoscopic assisted gastrectomy and totally laparoscopic gastrectomy group for elderly patients (mean ± SD)

Variable	LAG group (*n* = 232)	TLG group (*n* = 230)	*P* value
Surgical time, min	221.34 ± 54.96	216.48 ± 52.53	0.332
Blood loss, ml (median, IQR)	100.0 (50.0-200.0)	100.0 (50.0-100.0)	0.000
Anastomotic approach			
B1	17	14	
B2 (+Braun)	39	36	
Roux-en-Y	176	180	
Retrieved lymph nodes, *n*	29.32 ± 11.27	30.69 ± 12.65	0.218
Extent of resection			
R0	218	215	
R1/R2	14	15	
Time to first flatus, d	4.43 ± 1.20	3.79 ± 1.15	0.000
Postoperative day, d (median, IQR)	8.0 (7.0-10.0)	7.75 (6.0-9.0)	0.000
Total complication rate (%)	61 (26.3)	38 (16.5)	0.010
Anastomotic-related complication rate (%)	8 (3.4)	6 (2.6)	0.599
Clavien-Dindo classification			
Grade II			
Deep venous thrombosis	1	1	
Lymphatic leakage	1	0	
Gastroplegia	1	2	
Anaphylaxis	1	1	
Ileus	0	1	
Cardiac failure	1	0	
Hypoproteinemia	10	7	
Anemia	12	7	
Cholecystitis	2	0	
Incision infection	2	1	
Atrial fibrillation	4	2	
Pneumonia	8	2	
Anastomotic leakage	5	2	
Anastomotic bleeding	0	2	
Anastomotic stenosis	1	0	
Duodenal trump leakage	2	1	
Grade IIIa			
Deep venous thrombosis	0	0	
Pleural effusion	4	3	
Anastomotic leakage	2	2	
Duodenal trump leakage	1	1	
Abdominal bleeding	0	1	
Grade IV			
Cardiac failure	2	0	

Abdominal bleeding	1	1	
Acute cerebral infarction	0	1	
Severe complication rate (%)	10 (4.3)	9 (3.9)	0.830

Statistically significant *P* values are in bold ($P < 0.05$). LAG: Laparoscopic assisted gastrectomy; TLG: Totally laparoscopic gastrectomy; SD: Standard deviation; IQR: Interquartile range.

For the subgroup analysis based on surgical resection range, patients who underwent TLG had lower risks of postoperative complications in both the LTG (odds ratio (OR) = 0.612; 95% confidence interval (CI): 0.313-1.198) and LDG (OR = 0.619; 95%CI: 0.313-1.224) groups compared with patients who received LAG, although the differences were not statistically significant.

QOL using the EORTC QLQ-C30 and STO-22

We collected preoperative and 3-mo postoperative QOL questionnaire data from the 462 patients and compared changes in QOL between the LAG and LTG groups (Table 4). The results showed no statistically significant differences in symptom indicators, overall health indicators or functional indicators between the LAG and LTG groups before surgery ($P > 0.05$). Postoperative patients in the TLG group reported greater relief from nausea, vomiting and constipation than those in the LAG group. Patients in the TLG group were more satisfied with their body image.

Furthermore, the subgroup analysis (Supplementary Tables 4 and 5) showed that patients in the TLTG group had lower scores in the nausea and vomiting domains than those in the LATG group [0 (0-0) *vs* 0 (0-16.6), $P = 0.016$]. Patients who underwent TLTG were more satisfied with their body image than those who received LAGT [0 (0-0) *vs* 0 (0-33.3)] ($P = 0.027$). Among patients who received distal gastrectomy, the TLDG group showed more satisfaction with their body image than the LADG group [0 (0-0) *vs* 0 (0-33.3)] ($P = 0.002$).

DISCUSSION

The advantages of TLG have been confirmed by many studies. These advantages include less surgical blood loss, faster postoperative recovery of gastrointestinal functions, a shorter postoperative hospital stay, a smaller incision and improved QOL[8,15,16]. However, no studies have evaluated the short-term efficacy of TLG and LAG in elderly patients.

In this study, we found that intraoperative blood loss in the TLG group was lower than that in the LAG group. However, no significant difference in the operation time was found between the 2 groups. In the subgroup analysis, the operation time for the TLDG group was significantly shorter than that for the LADG group, which is similar to previous results[17]. These results indicate that under the limitation of a small abdominal incision, extracorporeal anastomosis may reduce the surgical efficiency, while intracorporeal anastomosis is more convenient and seems to be easier to execute. Elderly patients have an increased risk of surgical complications due to underlying diseases, decreased physical performance and malnutrition. Therefore, choosing a reasonable surgical strategy is very important[18]. Previous results have shown that the incidence of postoperative complications in elderly patients undergoing LG is comparable with that in younger patients, confirming that laparoscopic surgery is a safe method for elderly patients with GC[19,20]. The results from this study indicate that the overall incidence of postoperative complications in the TLG group was significantly lower than that in the LAG group (16.5% *vs* 26.3%, $P = 0.010$) and that the incidence of severe complications was comparable (3.9% *vs* 4.3%, $P = 0.830$). Further analysis revealed that LAG and operation time were independent risk factors for complications in elderly patients. The following reasons may potentially explain these results. For experienced surgeons, anastomosis (especially esophagojejunal anastomosis) under laparoscopy may offer a clearer view and facilitate more precise and accurate manipulation. It may reduce the risk of postoperative complications for patients[21]. Moreover, the longer operation time is mainly due to obesity, advanced tumor stages, intraoperative erroneous injury and difficulties in gastrointestinal reconstruction, which potentially increase the risk of postoperative complications. Based on these results, TLG is a more suitable approach for elderly patients with GC. However, the operation time must be controlled to reduce the occurrence of postoperative complications.

Anastomosis-related complications are crucial indicators when assessing the safety of gastrointestinal reconstruction methods. A meta-analysis of 10 studies by Zhao *et al*[22] showed that the incidence of anastomotic site-related complications after TLTG was similar to that after LATG[22]. Han *et al*[23] demonstrated that the incidence of anastomotic leakage after TLTG was higher than that after LATG. This phenomenon may be due to the difficulty of dissociating the distal esophagus by intracorporeal anastomosis, which increases the risk of anastomotic ischemia[23]. On the other hand, the physician's proficiency in intracorporeal anastomosis is also an important determinant of surgical safety[24]. In the

Table 3 Uni- and multivariate analysis of postoperative complications for elderly patients

Factor	Univariate analysis		*P* value	Multivariate analysis		*P* value
	OR	95%CI		OR	95%CI	
Sex			0.462			
Male	1.000					
Female	1.215	0.724-2.038				
Age (yr)			0.027			0.157
< 75	1.000			1.000		
≥ 75	1.655	1.058-2.587		1.422	0.874-2.313	
BMI (kg/m^2)			0.321			
< 25	1.000					
≥ 25	0.779	0.475-1.276				
Surgical approach			0.011			**0.011**
LAG	1.000			1.000		
TLG	0.555	0.352-0.874		0.539	0.335-0.865	
aCCI score			0.074			0.416
0-4	1.000			1.000		
> 4	1.603	0.952-2.699		1.276	0.709-2.294	
ASA score			0.030			0.069
≤ II	1.000			1.000		
> II	1.713	1.055-2.783		1.626	0.963-2.744	
Tumor resection			0.846			
Distal	1.000					
Total	0.957	0.613-1.493				
Neoadjuvant chemotherapy			0.752			
No	1.000					
Yes	1.165	0.452-3.000				
pTNM stage			0.918			
0-I	1.000					
II	1.072	0.571-2.012				
III	1.124	0.645-1.958				
Tumor diameter (cm)			0.020			0.116
≤ 3	1.000			1.000		
> 3	1.815	1.101-2.995		1.535	0.900-2.618	
Operation time (min)			0.031			**0.039**
≤ 220	1.000			1.000		
> 220	1.636	1.047-2.558		1.671	1.027-2.718	
Estimated blood loss (mL)			0.120			0.895
≤ 200	1.000			1.000		
> 200	1.628	0.880-3.012		1.047	0.530-2.070	
Vascular invasion			0.035			0.223
No	1.000			1.000		
Yes	1.620	1.034-2.538		1.349	0.834-2.185	

Nerve invasion			0.667			
No	1.000					
Yes	0.901	0.559-1.451				
Differentiation			0.760			
Well/moderate	1.000					
Poor/undifferentiated	1.075	0.676-1.708				
R0 resection			0.197			0.263
No	1.000			1.000		
Yes	1.715	0.755-3.895		1.639	0.690-3.892	

Statistically significant *P* values are in bold ($P < 0.05$). LAG: Laparoscopic assisted gastrectomy; TLG: Totally laparoscopic gastrectomy; aCCI: Age-adjusted Charlson Comorbidity Index; BMI: Body mass index; ASA: American Society of Anesthesiologists; OR: Odd ratio.

group of elderly patients, we found no significant differences in the incidence of anastomotic site-related complications (anastomotic leakage, bleeding and stenosis) between the LTG and LAG groups ($P > 0.05$). The results of the subgroup analysis also suggest that intracorporeal anastomosis is as safe as extracorporeal anastomosis for both distal and total gastrectomy and does not significantly increase the risks of anastomotic complications.

When addressing postoperative complications, the impact of surgical methods on the QOL of GC patients has become a key factor for surgeons when selecting an appropriate surgical approach. The EORTC QLQ-C30 and STO-22 questionnaires have been commonly used to assess the QOL of GC patients in recent years[25]. The QOL of patients can be assessed based on overall health, cognition, social interaction and symptoms. Whether TLG can improve the QOL of patients after surgery is still controversial. Park *et al*[7] compared QOL within 1 year after TLTG and LATG, and the results indicated that postoperative dysphagia, pain, eating and odynophagia were significantly improved in the TLTG group compared with the LATG group[7]. Wei *et al*[26] used circular anastomosis and found that postoperative constipation, dysphagia and anastomotic complications were significantly improved in TLTG group patients compared with LATG group patients[26]. In a study by Woo, no significant difference in QOL was found between patients after TLDG and LADG, and various parameters could not reflect subtle differences in surgical invasiveness between TLDG and LADG[27]. Which may be due to the high expectations of changes in QOL in patients undergoing TLDG, potentially affecting their judgment of subjective symptoms[28]. Postoperative QOL changes in elderly patients are different from those in young patients, and the effects on their physical and role functions are more obvious[29]. Physical function significantly varies with age, and changes in the QOL of elderly GC patients after surgery require close attention. Kim *et al*[30] found that in patients who underwent TLG, the postoperative return of bowel movements was slower in elderly patients[30]. In this study, we found no significant difference in preoperative QOL parameters between the TLG group and the LAG group. The 3-mo follow-up results indicated that the scores for nausea, vomiting and constipation in the TLG group were significantly lower than those in the LAG group, which is similar to the results of previous studies. In addition, in terms of body image, patients in the TLG group seemed to be more satisfied with their postoperative body image changes, which may be related to the smaller length of the incision in TLG. The above results suggest that for elderly patients, TLG may be a key factor in improving postoperative QOL.

This study has some limitations. First, this study did not include patients who underwent proximal gastrectomy, mainly because most patients who underwent proximal gastrectomy in our center received extracorporeal anastomosis, and the variety of intracorporeal anastomosis methods may cause potential bias. Second, this study followed up on the QOL of the patients only at 3 mo after surgery, with no complete follow-up for 1 year. Further follow-up is needed to compare the effects of TLG and LAG on the QOL of elderly patients. Third, we retrospectively established the short-term efficacy of TLG for elderly GC patients. Further studies, such as multicenter prospective studies, need to be conducted to evaluate the clinical value of TLG for elderly patients with GC.

In summary, this study found that TLG is safe and feasible for elderly patients with GC. TLG has significant advantages over LAG in terms of intraoperative bleeding, postoperative exsufflation and hospitalization and the overall postoperative complication rate. We found that LAG and an operation time > 220 min were independent risk factors for postoperative complications. Therefore, we recommend that experienced surgeons preferentially choose intracorporeal anastomosis during gastrectomy for elderly GC patients under the premise of ensuring a shorter operation time.

Table 4 Quality of life using European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire and STO-22 questionnaire between laparoscopic assisted gastrectomy and totally laparoscopic gastrectomy group

Factor	Baseline		*P* value	Postoperative 3 mo		*P* value
	LAG group	TLG group		LAG group	TLG group	
QLQ-C30 questionnaire						
Global status	91.6 (91.6-100)	91.6 (91.6-100)	0.096	91.6 (91.6-100)	91.6 (91.6-100)	0.934
Physical functioning	100 (93.3-100)	100 (93.3-100)	0.863	100 (93.3-100)	96.7(93.3-100)	0.777
Role functioning	100 (83.3-100)	100 (83.3-100)	0.269	100 (83.3-100)	83.3 (83.3-100)	0.804
Emotional functioning	91.6 (91.6-100)	91.6 (91.6-100)	0.343	91.6 (91.6-100)	91.6 (91.6-100)	0.880
Cognitive functioning	100 (83.3-100)	100 (83.3-100)	0.962	100 (83.3-100)	100 (83.3-100)	0.925
Social functioning	100 (83.3-100)	100 (83.3-100)	0.853	100 (83.3-100)	100 (83.3-100)	0.925
Fatigue	0 (0-0)	0 (0-0)	0.471	0 (0-0)	0 (0-11)	0.170
Nausea and vomiting	0 (0-0)	0 (0-0)	0.133	0 (0-12.5)	0 (0-0)	0.043
Pain	0 (0-0)	0 (0-0)	0.507	0 (0-0)	0 (0-0)	0.772
Dyspnea	0 (0-0)	0 (0-0)	0.165	0 (0-0)	0 (0-0)	0.880
Insomnia	0 (0-33.3)	0 (0-33.3)	0.428	0 (0-33.3)	0 (0-33.3)	0.984
Appetite loss	0 (0-0)	0 (0-33.3)	0.494	0 (0-33.3)	0 (0-33.3)	0.899
Constipation	0 (0-33.3)	0 (0-33.3)	0.529	33.3 (0-33.3)	0 (0-33.3)	0.024
Diarrhea	0 (0-0)	0 (0-0)	0.122	0 (0-0)	0 (0-0)	0.705
Financial difficulties	0 (0-33.3)	0 (0-33.3)	0.081	0 (0-33.3)	0 (0-33.3)	0.355
STO-22 questionnaire						
Dysphagia	0 (0-0)	0 (0-0)	0.547	0 (0-22)	0 (0-11)	0.169
Pain	0 (0-0)	0 (0-0)	0.793	0 (0-14.6)	0 (0-8.3)	0.389
Reflux	0 (0-11)	0 (0-11)	0.444	0 (0-22)	0 (0-22)	0.548
Eating restrictions	0 (0-0)	0 (0-0)	0.441	0 (0-8.3)	0 (0-8.3)	0.848
Anxiety	0 (0-11)	0 (0-11)	0.952	0 (0-22)	0 (0-22)	0.214
Dry mouth	0 (0-0)	0 (0-0)	0.681	0 (0-0)	0 (0-0)	0.982
Taste	0 (0-0)	0 (0-0)	0.609	0 (0-0)	0 (0-0)	0.858
Body image	0 (0-0)	0 (0-0)	0.573	0 (0-33.3)	0 (0-0)	0.000
Hair loss	0 (0-0)	0 (0-0)	0.442	0 (0-0)	0 (0-0)	0.077

Statistically significant *P* values are in bold ($P < 0.05$). TLG: Totally laparoscopic gastrectomy; LAG: laparoscopic assisted gastrectomy.

CONCLUSION

TLG is safe and feasible for elderly patients with GC and has outstanding advantages in reducing surgical bleeding, promoting postoperative recovery and improving QOL. We recommend that experienced surgeons prioritize TLG as a gastrectomy approach for elderly patients due to the shorter operation time.

ARTICLE HIGHLIGHTS

Research background

The outstanding advantages of totally laparoscopic gastrectomy (TLG) over laparoscopic assisted gastrectomy (LAG) has been proved in many studies.

Research motivation

The safety and reliability of TLG for elderly patients with gastric cancer (GC) remain unclear.

Research objectives

To evaluate the short-term efficiency and quality of life (QOL) of TLG for elderly patients with GC.

Research methods

The clinicopathological data of 462 elderly patients aged ≥ 70 years who underwent LAG or TLG between January 2017 and January 2022 at Department of General Surgery, First Medical Center, PLA General Hospital were retrospectively collected. We compared the perioperative outcomes between TLG and LAG groups, and used univariate and multivariate analysis to figure out the independent risk factors of LG in elderly patients. QOL data before and 3 mo after surgery were collected to evaluate whether TLG is equally safe and feasible in elderly patients.

Research results

The overall incidence of postoperative complications in the TLG group was significantly lower than that in the LAG group (16.5% *vs* 26.3%, $P = 0.01$). Furthermore, there was no significant difference in the incidence of anastomotic site-related complications or the incidence of severe complications between the TLG group and the LAG group ($P = 0.599$, $P = 0.830$). Binary logistic regression results indicated that LAG and operation time > 220 min were independent risk factors for postoperative complications in elderly patients with GC ($P < 0.05$). In terms of QOL, there were no statistically significant differences in various preoperative indicators between the LAG group and the LTG group ($P > 0.05$). Three months after surgery, patients in the TLG group were more satisfied with their body image.

Research conclusions

TLG is safe and feasible for elderly GC patients, especially in reducing surgical bleeding, promoting postoperative recovery and improving QOL.

Research perspectives

In the further study, we will refine the complete one-year follow-up of patients and conduct a multicenter collaborative prospective study to evaluate the clinical value of TLG more thoroughly for elderly patients with GC.

FOOTNOTES

Author contributions: Zhao RY, Li HH and Zhang KC equally contributed to this work; Zhao RY, Li HH, Zhang KC, Cui H, Deng H and Gao JW participated in the patient information collection; Zhao RY, Li HH and Zhang KC cleaned, analyzed the data and wrote the manuscript; Zhao RY, Li HH and Wei B revised the manuscript; Wei B designed and conceived this project; All authors have read and approved the final manuscript.

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Country/Territory of origin: China

ORCID number: Rui-Yang Zhao 0000-0001-6619-9532; Hang-Hang Li 0000-0002-9117-7156; Ke-Cheng Zhang 0000-0002-9257-5607; Hao Cui 0000-0003-1185-5322; Huan Deng 0000-0002-6144-2289; Jing-Wang Gao 0000-0001-5388-3626; Bo Wei

0000-0001-7386-2689.

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REFERENCES

1 **He Y**, Wang Y, Luan F, Yu Z, Feng H, Chen B, Chen W. Chinese and global burdens of gastric cancer from 1990 to 2019. *Cancer Med* 2021; **10**: 3461-3473 [PMID: 33931958 DOI: 10.1002/cam4.3892]
2 **Sekiguchi M**, Oda I, Matsuda T, Saito Y. Epidemiological Trends and Future Perspectives of Gastric Cancer in Eastern Asia. *Digestion* 2022; **103**: 22-28 [PMID: 34515086 DOI: 10.1159/000518483]
3 **Kitano S**, Iso Y, Moriyama M, Sugimachi K. Laparoscopy-assisted Billroth I gastrectomy. *Surg Laparosc Endosc* 1994; **4**: 146-148 [PMID: 8180768]
4 **Yu J**, Huang C, Sun Y, Su X, Cao H, Hu J, Wang K, Suo J, Tao K, He X, Wei H, Ying M, Hu W, Du X, Hu Y, Liu H, Zheng C, Li P, Xie J, Liu F, Li Z, Zhao G, Yang K, Liu C, Li H, Chen P, Ji J, Li G; Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) Group. Effect of Laparoscopic *vs* Open Distal Gastrectomy on 3-Year Disease-Free Survival in Patients With Locally Advanced Gastric Cancer: The CLASS-01 Randomized Clinical Trial. *JAMA* 2019; **321**: 1983-1992 [PMID: 31135850 DOI: 10.1001/jama.2019.5359]
5 **Kim HH**, Han SU, Kim MC, Kim W, Lee HJ, Ryu SW, Cho GS, Kim CY, Yang HK, Park DJ, Song KY, Lee SI, Ryu SY, Lee JH, Hyung WJ; Korean Laparoendoscopic Gastrointestinal Surgery Study (KLASS) Group. Effect of Laparoscopic Distal Gastrectomy *vs* Open Distal Gastrectomy on Long-term Survival Among Patients With Stage I Gastric Cancer: The KLASS-01 Randomized Clinical Trial. *JAMA Oncol* 2019; **5**: 506-513 [PMID: 30730546 DOI: 10.1001/jamaoncol.2018.6727]
6 **Liu F**, Huang C, Xu Z, Su X, Zhao G, Ye J, Du X, Huang H, Hu J, Li G, Yu P, Li Y, Suo J, Zhao N, Zhang W, Li H, He H, Sun Y; Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) Group. Morbidity and Mortality of Laparoscopic *vs* Open Total Gastrectomy for Clinical Stage I Gastric Cancer: The CLASS02 Multicenter Randomized Clinical Trial. *JAMA Oncol* 2020; **6**: 1590-1597 [PMID: 32815991 DOI: 10.1001/jamaoncol.2020.3152]
7 **Park SH**, Suh YS, Kim TH, Choi YH, Choi JH, Kong SH, Park DJ, Lee HJ, Yang HK. Postoperative morbidity and quality of life between totally laparoscopic total gastrectomy and laparoscopy-assisted total gastrectomy: a propensity-score matched analysis. *BMC Cancer* 2021; **21**: 1016 [PMID: 34511059 DOI: 10.1186/s12885-021-08744-1]
8 **Meng X**, Wang L, Zhu B, Sun T, Guo S, Wang Y, Zhang J, Yang D, Zheng G, Zhang T, Zheng Z, Zhao Y. Totally Laparoscopic Gastrectomy Versus Laparoscopic-Assisted Gastrectomy for Gastric Cancer: A Systematic Review and Meta-Analysis. *J Laparoendosc Adv Surg Tech A* 2021; **31**: 676-691 [PMID: 32955988 DOI: 10.1089/lap.2020.0566]
9 **Xing J**, Wang Y, Shan F, Li S, Jia Y, Ying X, Zhang Y, Li Z, Ji J. Comparison of totally laparoscopic and laparoscopic assisted gastrectomy after neoadjuvant chemotherapy in locally advanced gastric cancer. *Eur J Surg Oncol* 2021; **47**: 2023-2030 [PMID: 33663942 DOI: 10.1016/j.ejso.2021.02.002]
10 **Lee CM**, Park JH, In Choi C, Lee HH, Min JS, Jee YS, Jeong O, Chae H, Choi SI, Huang H, Park S. A multi-center prospective randomized controlled trial (phase III) comparing the quality of life between laparoscopy-assisted distal gastrectomy and totally laparoscopic distal gastrectomy for gastric Cancer (study protocol). *BMC Cancer* 2019; **19**: 206 [PMID: 30845995 DOI: 10.1186/s12885-019-5396-8]
11 **Japanese Gastric Cancer Association**. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer* 2021; **24**: 1-21 [PMID: 32060757 DOI: 10.1007/s10120-020-01042-y]
12 **Katayama H**, Kurokawa Y, Nakamura K, Ito H, Kanemitsu Y, Masuda N, Tsubosa Y, Satoh T, Yokomizo A, Fukuda H, Sasako M. Extended Clavien-Dindo classification of surgical complications: Japan Clinical Oncology Group postoperative complications criteria. *Surg Today* 2016; **46**: 668-685 [PMID: 26289837 DOI: 10.1007/s00595-015-1236-x]
13 **Zhao H**, Kanda K. Translation and validation of the standard Chinese version of the EORTC QLQ-C30. *Qual Life Res* 2000; **9**: 129-137 [PMID: 10983477 DOI: 10.1023/a:1008981520920]
14 **Huang CC**, Lien HH, Sung YC, Liu HT, Chie WC. Quality of life of patients with gastric cancer in Taiwan: validation and clinical application of the Taiwan Chinese version of the EORTC QLQ-C30 and EORTC QLQ-STO22. *Psychooncology* 2007; **16**: 945-949 [PMID: 17279609 DOI: 10.1002/pon.1158]
15 **Liao G**, Wang Z, Zhang W, Qian K, Mariella Mac S, Li H, Huang Z. Comparison of the short-term outcomes between totally laparoscopic total gastrectomy and laparoscopic-assisted total gastrectomy for gastric cancer: a meta-analysis. *Medicine (Baltimore)* 2020; **99**: e19225 [PMID: 32049863 DOI: 10.1097/MD.0000000000019225]
16 **Han WH**, Yehuda AB, Kim DH, Yang SG, Eom BW, Yoon HM, Kim YW, Ryu KW. A comparative study of totally laparoscopic distal gastrectomy *vs* laparoscopic-assisted distal gastrectomy in gastric cancer patients: Short-term operative outcomes at a high-volume center. *Chin J Cancer Res* 2018; **30**: 537-545 [PMID: 30510365 DOI: 10.21147/j.issn.1000-9604.2018.05.07]
17 **Lee J**, Kim D, Kim W. Comparison of laparoscopy-assisted and totally laparoscopic Billroth-II distal gastrectomy for gastric cancer. *J Korean Surg Soc* 2012; **82**: 135-142 [PMID: 22403746 DOI: 10.4174/jkss.2012.82.3.135]
18 **Kawaguchi Y**, Akaike H, Shoda K, Furuya S, Hosomura N, Amemiya H, Kawaida H, Kono H, Ichikawa D. Is surgery the best treatment for elderly gastric cancer patients? *World J Gastrointest Surg* 2021; **13**: 1351-1360 [PMID: 34950425 DOI: 10.4240/wjgs.v13.i11.1351]
19 **Li ZY**, Chen J, Bai B, Xu S, Song D, Lian B, Li JP, Ji G, Zhao QC. Laparoscopic gastrectomy for elderly gastric-cancer patients: comparisons with laparoscopic gastrectomy in non-elderly patients and open gastrectomy in the elderly. *Gastroenterol Rep (Oxf)* 2021; **9**: 146-153 [PMID: 34026222 DOI: 10.1093/gastro/goaa041]

20 **Pan Y**, Chen K, Yu WH, Maher H, Wang SH, Zhao HF, Zheng XY. Laparoscopic gastrectomy for elderly patients with gastric cancer: A systematic review with meta-analysis. *Medicine (Baltimore)* 2018; **97**: e0007 [PMID: 29465537 DOI: 10.1097/MD.0000000000010007]

21 **Dulucq JL**, Wintringer P, Perissat J, Mahajna A. Completely laparoscopic total and partial gastrectomy for benign and malignant diseases: a single institute's prospective analysis. *J Am Coll Surg* 2005; **200**: 191-197 [PMID: 15664093 DOI: 10.1016/j.jamcollsurg.2004.10.004]

22 **Zhao S**, Zheng K, Zheng JC, Hou TT, Wang ZN, Xu HM, Jiang CG. Comparison of totally laparoscopic total gastrectomy and laparoscopic-assisted total gastrectomy: A systematic review and meta-analysis. *Int J Surg* 2019; **68**: 1-10 [PMID: 31189084 DOI: 10.1016/j.ijsu.2019.05.020]

23 **Han WH**, Oh YJ, Eom BW, Yoon HM, Kim YW, Ryu KW. A comparative study of the short-term operative outcome between intracorporeal and extracorporeal anastomoses during laparoscopic total gastrectomy. *Surg Endosc* 2021; **35**: 1602-1609 [PMID: 32270275 DOI: 10.1007/s00464-020-07539-y]

24 **Kodera Y**, Yoshida K, Kumamaru H, Kakeji Y, Hiki N, Etoh T, Honda M, Miyata H, Yamashita Y, Seto Y, Kitano S, Konno H. Introducing laparoscopic total gastrectomy for gastric cancer in general practice: a retrospective cohort study based on a nationwide registry database in Japan. *Gastric Cancer* 2019; **22**: 202-213 [PMID: 29427039 DOI: 10.1007/s10120-018-0795-0]

25 **Kobayashi D**, Kodera Y, Fujiwara M, Koike M, Nakayama G, Nakao A. Assessment of quality of life after gastrectomy using EORTC QLQ-C30 and STO22. *World J Surg* 2011; **35**: 357-364 [PMID: 21104250 DOI: 10.1007/s00268-010-0860-2]

26 **Wei M**, Wang N, Yin Z, Wu T, Zhou S, Dang L, Zhang Z, Wu D, Gao P, Zhang B, Yang Y, Jia G, Wang K, Qiao Q, He X. Short-Term and Quality of Life Outcomes of Patients Using Linear or Circular Stapling in Esophagojejunostomy after Laparoscopic Total Gastrectomy. *J Gastrointest Surg* 2021; **25**: 1667-1676 [PMID: 32989689 DOI: 10.1007/s11605-020-04806-0]

27 **Woo J**, Lee JH, Shim KN, Jung HK, Lee HM, Lee HK. Does the Difference of Invasiveness between Totally Laparoscopic Distal Gastrectomy and Laparoscopy-Assisted Distal Gastrectomy Lead to a Difference in Early Surgical Outcomes? *Ann Surg Oncol* 2015; **22**: 1836-1843 [PMID: 25395149 DOI: 10.1245/s10434-014-4229-x]

28 **Lee SS**, Ryu SW, Kim IH, Sohn SS. Quality of life beyond the early postoperative period after laparoscopy-assisted distal gastrectomy: the level of patient expectation as the essence of quality of life. *Gastric Cancer* 2012; **15**: 299-304 [PMID: 22083419 DOI: 10.1007/s10120-011-0113-6]

29 **Han DS**, Ahn J, Ahn HS. Are the elderly patient's changes in the health-related quality of life one year after gastrectomy for stomach cancer different from those in young patients? *Ann Surg Treat Res* 2021; **100**: 8-17 [PMID: 33457392 DOI: 10.4174/astr.2021.100.1.8]

30 **Kim MG**, Kim HS, Kim BS, Kwon SJ. The impact of old age on surgical outcomes of totally laparoscopic gastrectomy for gastric cancer. *Surg Endosc* 2013; **27**: 3990-3997 [PMID: 23877760 DOI: 10.1007/s00464-013-3073-6]

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ORIGINAL ARTICLE

Retrospective Study

Personal predictive model based on systemic inflammation markers for estimation of postoperative pancreatic fistula following pancreaticoduodenectomy

Zhi-Da Long, Chao Lu, Xi-Gang Xia, Bo Chen, Zhi-Xiang Xing, Lei Bie, Peng Zhou, Zhong-Lin Ma, Rui Wang

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Zhi-Da Long, Chao Lu, Xi-Gang Xia, Bo Chen, Zhi-Xiang Xing, Lei Bie, Peng Zhou, Rui Wang, Department of Hepatobiliary and Pancreaticosplenic Surgery, Jingzhou Hospital, Yangtze University, Jingzhou 434020, Hubei Province, China

Zhong-Lin Ma, Department of Hepatobiliary Surgery, Lu'an Hospital of AnHui Medical University, Hefei 237006, Anhui Province, China

Corresponding author: Rui Wang, MD, Surgical Oncologist, Department of Hepatobiliary and Pancreaticosplenic Surgery, Jingzhou Hospital, Yangtze University, No. 60 Chuyuan Road, Jingzhou District, Jingzhou 434020, Hubei Province, China. wangrui_20222022@163.com

Abstract

BACKGROUND

Postoperative pancreatic fistula (PF) is a serious life-threatening complication after pancreaticoduodenectomy (PD). Our research aimed to develop a machine learning (ML)-aided model for PF risk stratification.

AIM

To develop an ML-aided model for PF risk stratification.

METHODS

We retrospectively collected 618 patients who underwent PD from two tertiary medical centers between January 2012 and August 2021. We used an ML algorithm to build predictive models, and subject prediction index, that is, decision curve analysis, area under operating characteristic curve (AUC) and clinical impact curve to assess the predictive efficiency of each model.

RESULTS

A total of 29 variables were used to build the ML predictive model. Among them, the best predictive model was random forest classifier (RFC), the AUC was [0.897, 95% confidence interval (CI): 0.370–1.424], while the AUC of the artificial neural network, eXtreme gradient boosting, support vector machine, and decision tree were between 0.726 (95%CI: 0.191–1.261) and 0.882 (95%CI: 0.321–1.443).

CONCLUSION

Fluctuating serological inflammatory markers and prognostic nutritional index

can be used to predict postoperative PF.

Key Words: Pancreatoduodenectomy; Pancreatic fistula; Machine learning algorithm; Systemic inflammatory biomarker; Risk prediction

Core tip: Our research is based on machine learning (ML) algorithms and integrates the correlation between serum inflammatory factors and high risk of postoperative pancreatic fistula (PF), and constructs early warning models that can predict postoperative PF, and the predictive efficiency of these ML-based models may be at the population-based level. In the future, we expect these findings to expand external research to strengthen valuable supporting information and guide treatment decisions.

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INTRODUCTION

Pancreaticoduodenectomy (PD), also known as a Whipple procedure, is one of the most difficult and complex surgeries that carries a high rate of major complications[1]. Post-operative pancreatic fistula (PF), as one of the most difficult complications after PD, can seriously endanger the lives of patients, so it has become a field of continuous concern for pancreatic surgeons[1,2]. Although the safety of PD has improved significantly in the past three decades[3,4]. Alarmingly, previous prospective studies have reported that postoperative PF occupied an incidence of > 10%[5-7].

In recent years, people have studied different styles of surgery and perioperative attempts to reduce the incidence of postoperative PF. However, regardless of the type of surgery, PF is still the most common fatal complication after pancreatectomy. Understanding the potential complications and early warning of these complications is important for the care of these severe patients.

Previous studies have utilized preoperative radiology and clinical variables combined with specific intraoperative factors to predict the risk of postoperative PF[8-11]. Despite advances in predictive platforms for postoperative PF, they have undergone a constantly changing approach. However, because of its unsatisfactory predictive performance, an improved delivery system is deemed necessary. Therefore, exploring an optimal risk score range model may contribute to eliminating potential life-threatening complications, and stratifying patients with postoperative PF risk, which can be better applied to clinical management.

Nowadays, a series of serum markers suggest that detecting systemic inflammation may be associated with the risk of benign and malignant disease progression[12-14]. At the same time, the systemic reaction stimulated by local inflammation is closely related to the complications after gastrointestinal surgery[15,16]. In addition, machine learning (ML) algorithms have been widely used in the field of medicine. These unceasing new algorithms and iterative analyses might be useful for prognostication in cases and optimize individual treatment decisions[17]. Collectively, this combination has facilitated elevated predictive performance while minimizing the prediction error.

Given this situation, we searched for the help of inflammatory factors and ML-based algorithms to optimize the predictive accuracy for postoperative PF. In this study, we tried to identify alternative predictors independently related to postoperative PF and develop an optimal risk stratification model that can accurately identify high-risk patients with postoperative PF.

MATERIALS AND METHODS

Patients selection

Patients who underwent PD to treat various periampullary tumors from two tertiary medical centers (Jingzhou Hospital and Lu'an Hospital of Anhui Medical University) between January 2012 and August 2021 were retrospectively reviewed. The inclusion criteria were: (1) Resected tumor specimens were confirmed to be malignant by pathological examination; (2) Blood routine examination and liver function examination results were found within 3 d before surgery; and (3) The patient had complete

case data and relevant indicators of imaging, pathology and laboratory examination. The exclusion criteria were: (1) Patients receiving preoperative treatment, such as thermal ablation, neoadjuvant chemotherapy or radiotherapy; (2) Severe respiratory and circulatory diseases; (3) Severe acute cholangitis or infection in other parts of the body before surgery; (4) Metastasis from other parts of the primary tumor or direct invasion of adjacent organs from the primary tumor; and (5) Parathyroid diseases or other factors interfering with abnormal changes of procalcitonin (PCT). This study was a retrospective cohort study, which was approved by the Ethics Committee of Jingzhou Central Hospital (Reference: 2021-JH005) and conformed to the Declaration of Helsinki. Because this study adopted anonymous follow-up, the patients' personal privacy information was strictly confidential. The detailed research flow chart is shown in Figure 1.

Diagnostic criteria for postoperative PF

According to the standards defined by the International Study Group for Pancreatic Fistula (ISGPF) in 2016, that is, drainage flow > 30 mL for ≥ 72 h after an operation, the amylase content of the drainage fluid is measured. If it exceeds ≥ 3 times the upper limit of normal and had a clinical impact (such as abdominal pain or fever) and needed clinical treatment, it is judged that PF has occurred. The grade of PF updated by ISGPF in 2016 removes the diagnosis of grade A PF. The increase in amylase in asymptomatic drainage fluid is considered biochemical leakage, *i.e.*, non-real PF. The occurrence of significant clinical symptoms based on biochemical leakage and the change of treatment strategy (such as puncture and drainage, interventional hemostasis, indwelling abdominal drainage tube for > 3 wk, infection, *etc.*) is defined as grade B PF. If grade B PF needs surgical treatment, or is complicated with organ failure or even death, the grade of PF increases to grade C. Therefore, grades B and C PF are also known as clinical postoperative PF[18,19].

Blood sample collection

We chose to collect 3–5 mL blood samples from each patient on an empty stomach in the morning of 3 d before the operation, and included the latest blood routine and liver function tests in this study. Peripheral venous blood was taken in the morning of d 1, 3 and 5 after the operation, and the changes in C-reactive protein (CRP), serum PCT, and white blood cells were continuously observed.

Data collection and quality assessment

We obtained population baseline data and clinical pathological data from the patients' medical records. For instance, the pancreatic texture was evaluated by the surgeon during the operation (soft 1, hard 0), and the diameter of the main pancreatic was obtained by computed tomography or magnetic resonance imaging before the operation. We also collected routine laboratory measurement results, and when the missing value was ≥ 10% of the bias of the total variable, the variable was directly discarded and not included in the final model variable screening[20]. Finally, a total of 29 variables that met the inclusion criteria were used to build ML-based models.

Construction and verification of ML-based models

At the beginning of building the model, we randomly divided the population data into two parts, namely, the training queue and the verification queue. The training queue was used to construct the predictive model, and the validation queue was used as the internal validation of the model to evaluate the robustness of the model. When screening candidate variables, we adopted the "two-step segmentation evaluation", that is, the principle of random sorting to obtain the intersection[21]. In short, by sorting the intersection of variable sets, the optimal subset modeling was obtained. Finally, these models were evaluated through inspection, discrimination and calibration.

Statistical analysis

As for descriptive variables (*i.e.* continuous or classified variables), the median (interquartile range) or frequency (percentage) were used for statistical analysis. The χ^2 test or Mann–Whitney test was used to calculate the variables between groups to evaluate whether there was a statistical difference. Stepwise regression based on the minimum value of the Akaike information standard was used to select the variables. All data analysis was completed with the help of R language software (version 4.0.4, http://www.r-project.org/). All P values were double tailed, and $P < 0.05$ was statistically significant.

RESULTS

Clinicopathological baseline characteristics of patients

In this study, all patients were randomly divided into a training set (n = 432, 70%) and validation set (n = 186, 30%) *via* the caret package. Seventy-eight (18.06%) and 20 (10.75%) patients developed postoperative PF in the training and validation group, respectively, as shown in Table 1. There were 76 (12.3%) grade B and 22 (3.6%) grace C. One patient died of multiple organ failure due to drug-resistant

Table 1 Baseline demographic and clinicopathological characteristics of patients

Variables	Training set				Testing set			
	Overall (*n* = 432)	Non-POPF (*n* = 354)	POPF (*n* = 78)	*P* value	Overall (*n* = 186)	Non-POPF (*n* = 166)	POPF (*n* = 20)	*P* value
Age, median (IQR)	55.0 (49.0–61.0)	55.0 (49.0–61.0)	53.0 (47.25–61.0)	0.147	55.0 (50.0–60.0)	55.0 (50.0–60.0)	51.50 (45.75–59.50)	0.182
BMI, median (IQR)	23.10 (21.80–24.60)	22.80 (21.50–24.20)	25.0 (23.33–26.92)	< 0.001	22.85 (21.72–24.30)	22.70 (21.52–23.98)	24.35 (22.88–26.13)	< 0.001
Gender (%)								
Male	283 (65.5)	227 (64.1)	56 (71.8)	0.247	127 (68.3)	110 (66.3)	17 (85.0)	0.148
Female	149 (34.5)	127 (35.9)	22 (28.2)		59 (31.7)	56 (33.7)	3 (15.0)	
Smoking (%)								
Yes	198 (45.8)	143 (40.4)	55 (70.5)	< 0.001	89 (47.8)	76 (45.8)	13 (65.0)	0.165
No	234 (54.2)	211 (59.6)	23 (29.5)		97 (52.2)	90 (54.2)	7 (35.0)	
Drinking history (%)								
Yes	129 (29.9)	78 (22.0)	51 (65.4)	< 0.001	54 (29.0)	40 (24.1)	14 (70.0)	< 0.001
No	303 (70.1)	276 (78.0)	27 (34.6)		132 (71.0)	126 (75.9)	6 (30.0)	
Diabetes (%)								
Yes	110 (25.5)	49 (13.8)	61 (78.2)	< 0.001	44 (23.7)	30 (18.1)	14 (70.0)	< 0.001
No	322 (74.5)	305 (86.2)	17 (21.8)		142 (76.3)	136 (81.9)	6 (30.0)	
Hypertension (%)								
Yes	164 (38.0)	129 (36.4)	35 (44.9)	0.208	59 (31.7)	49 (29.5)	10 (50.0)	0.108
No	268 (62.0)	225 (63.6)	43 (55.1)		127 (68.3)	117 (70.5)	10 (50.0)	
Abdominal operation (%)								
Yes	130 (30.1)	103 (29.1)	27 (34.6)	0.409	53 (28.5)	47 (28.3)	6 (30.0)	1
No	302 (69.9)	251 (70.9)	51 (65.4)		133 (71.5)	119 (71.7)	14 (70.0)	
Remnant texture (%)								
Soft	121 (28.0)	62 (17.5)	59 (75.6)	< 0.001	44 (23.7)	27 (16.3)	17 (85.0)	< 0.001
Hard	311 (72.0)	292 (82.5)	19 (24.4)		142 (76.3)	139 (83.7)	3 (15.0)	
Blood transfusion (%)								
Yes	232 (53.7)	188 (53.1)	44 (56.4)	0.686	96 (51.6)	84 (50.6)	12 (60.0)	0.577
No	200 (46.3)	166 (46.9)	34 (43.6)		90 (48.4)	82 (49.4)	8 (40.0)	
Anemia (%)								
Yes	218 (50.5)	179 (50.6)	39 (50.0)	1	84 (45.2)	69 (41.6)	15 (75.0)	0.009
No	214 (49.5)	175 (49.4)	39 (50.0)		102 (54.8)	97 (58.4)	5 (25.0)	
Lesion size (%), cm								
> 3	182 (42.1)	125 (35.3)	57 (73.1)	< 0.001	67 (36.0)	54 (32.5)	13 (65.0)	0.009
≤ 3	250 (57.9)	229 (64.7)	21 (26.9)		119 (64.0)	112 (67.5)	7 (35.0)	
Pancreatic duct diameter (%), mm								
< 3	154 (35.6)	93 (26.3)	61 (78.2)	< 0.001	63 (33.9)	49 (29.5)	14 (70.0)	0.001

≥ 3	278 (64.4)	261 (73.7)	17 (21.8)		123 (66.1)	117 (70.5)	6 (30.0)	
ASA classification (%)								
I + II	231 (53.5)	188 (53.1)	43 (55.1)	0.843	85 (45.7)	78 (47.0)	7 (35.0)	0.436
III + IV	201 (46.5)	166 (46.9)	35 (44.9)		101 (54.3)	88 (53.0)	13 (65.0)	
CRP, median (IQR), mg/L	32.0 (22.0–44.0)	29.0 (21.0–38.0)	88.50 (56.0–120.0)	< 0.001	30.0 (22.0–40.0)	29.0 (21.0–38.0)	84.50 (42.25–109.25)	< 0.001
WBC, median (IQR), 10^9	5.70 (5.30–6.30)	5.70 (5.20–6.20)	6.0 (5.60–6.60)	< 0.001	5.70 (5.20–6.30)	5.60 (5.20–6.20)	6.40 (5.52–6.82)	0.002
PCT, median (IQR), μg/L	0.54 (0.37–0.68)	0.49 (0.34–0.61)	1.06 (0.78–1.21)	< 0.001	0.52 (0.37–0.67)	0.49 (0.35–0.63)	0.84 (0.68–1.09)	< 0.001
AGR, median (IQR)	1.50 (1.30–1.60)	1.50 (1.40–1.60)	1.35 (1.20–1.40)	< 0.001	1.50 (1.30–1.60)	1.50 (1.40–1.60)	1.35 (1.17–1.52)	0.003
PNI, median (IQR)	49.60 (48.10–51.23)	49.90 (48.32–51.60)	48.60 (47.35–49.60)	< 0.001	50.10 (48.40–51.48)	50.30 (48.42–51.60)	49.30 (46.85–50.37)	0.02
Neutrophil count, median (IQR), 10^9	4.02 (3.49–4.59)	4.18 (3.70–4.68)	3.36 (3.03–3.74)	< 0.001	3.94 (3.51–4.54)	4.03 (3.57–4.57)	3.46 (3.11–3.76)	< 0.001
Lymphocyte count, median (IQR), 10^9	1.64 (1.51–1.78)	1.63 (1.50–1.76)	1.79 (1.60–1.94)	< 0.001	1.64 (1.53–1.76)	1.63 (1.52–1.73)	1.83 (1.69–1.98)	< 0.001
Platelet count, median (IQR), 10^9	230.0 (208.0–252.0)	236.0 (213.0–255.0)	206.0 (185.25–229.75)	< 0.001	229.0 (206.0–253.75)	232.0 (208.25–257.75)	200.0 (182.50–225.0)	< 0.001
Monocyte count, median (IQR), 10^9	0.52 (0.45–0.60)	0.55 (0.47–0.62)	0.44 (0.39–0.49)	< 0.001	0.53 (0.46–0.61)	0.54 (0.47–0.62)	0.48 (0.42–0.52)	0.003
Hemoglobin, median (IQR), g/L	132.0 (124.0–139.0)	130.0 (121.25–138.0)	138.0 (133.0–142.75)	< 0.001	132.0 (126.0–140.0)	132.0 (126.0–139.75)	134.50 (130.0–141.0)	0.026
NLR, median (IQR)	2.0 (1.70–2.30)	1.90 (1.70–2.20)	2.70 (2.22–3.10)	< 0.001	2.0 (1.70–2.30)	1.90 (1.60–2.20)	2.80 (2.42–3.05)	< 0.001
NAR, median (IQR)	0.08 (0.07–0.09)	0.08 (0.07–0.09)	0.60 (0.30–0.88)	< 0.001	0.08 (0.07–0.09)	0.08 (0.07–0.09)	0.65 (0.38–0.80)	< 0.001
PLR, median (IQR)	136.20 (116.68–157.43)	143.85 (123.23–161.70)	113.15 (102.58–128.0)	< 0.001	136.45 (120.62–155.80)	141.0 (121.22–159.78)	120.15 (104.78–128.57)	< 0.001
LMR, median (IQR)	3.40 (2.90–3.80)	3.30 (2.80–3.70)	3.90 (3.52–4.70)	< 0.001	3.50 (3.0–3.80)	3.40 (2.90–3.70)	4.15 (3.75–4.48)	< 0.001
HALP, median (IQR)	53.95 (51.08–56.50)	52.90 (50.50–55.20)	72.75 (69.32–75.25)	< 0.001	52.45 (50.40–55.18)	51.95 (50.10–54.30)	70.10 (68.18–72.62]	< 0.001

POPF: Postoperative pancreatic fistula; IQR: Inter-quartile range; BMI: Body mass index; ASA: American Society of Anesthesiologists; CRP: C-reactive protein; WBC: White blood cell; PCT: Procalcitonin; AGR: Albumin-to-globulin ratio; PNI: Prognostic nutrition index; NLR: Neutrophil-to-lymphocyte ratio; NAR: Neutrophil-to-albumin ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; HALP: Hemoglobin level × albumin level × lymphocyte count/platelet count ratio.

bacterial infection; five underwent reoperation because of continuous blood drainage *via* the drainage tube, which was confirmed to be abdominal bleeding caused by intraoperative PF; and two were transferred to intensive care.

Selection of candidate variables

Feature selection is a universal problem in ML[22]. We performed an iterative analysis of 29 potential candidate variables, and the correlation matrix showed that there was a significant correlation between postoperative PF and inflammatory factors and some clinical variables (Figure 2A), including CRP, PCT, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and hemoglobin level × albumin level × lymphocyte count/platelet count ratio (HALP). As shown in Figure 2B, HALP, PCT, neutrophil-to-albumin ratio (NAR), PLR and PNI were the top important predictors. Meanwhile, the seven top-ranked predictors were HALP, remnant texture, PCT, NAR, PLR, PNI, and body mass index (BMI).

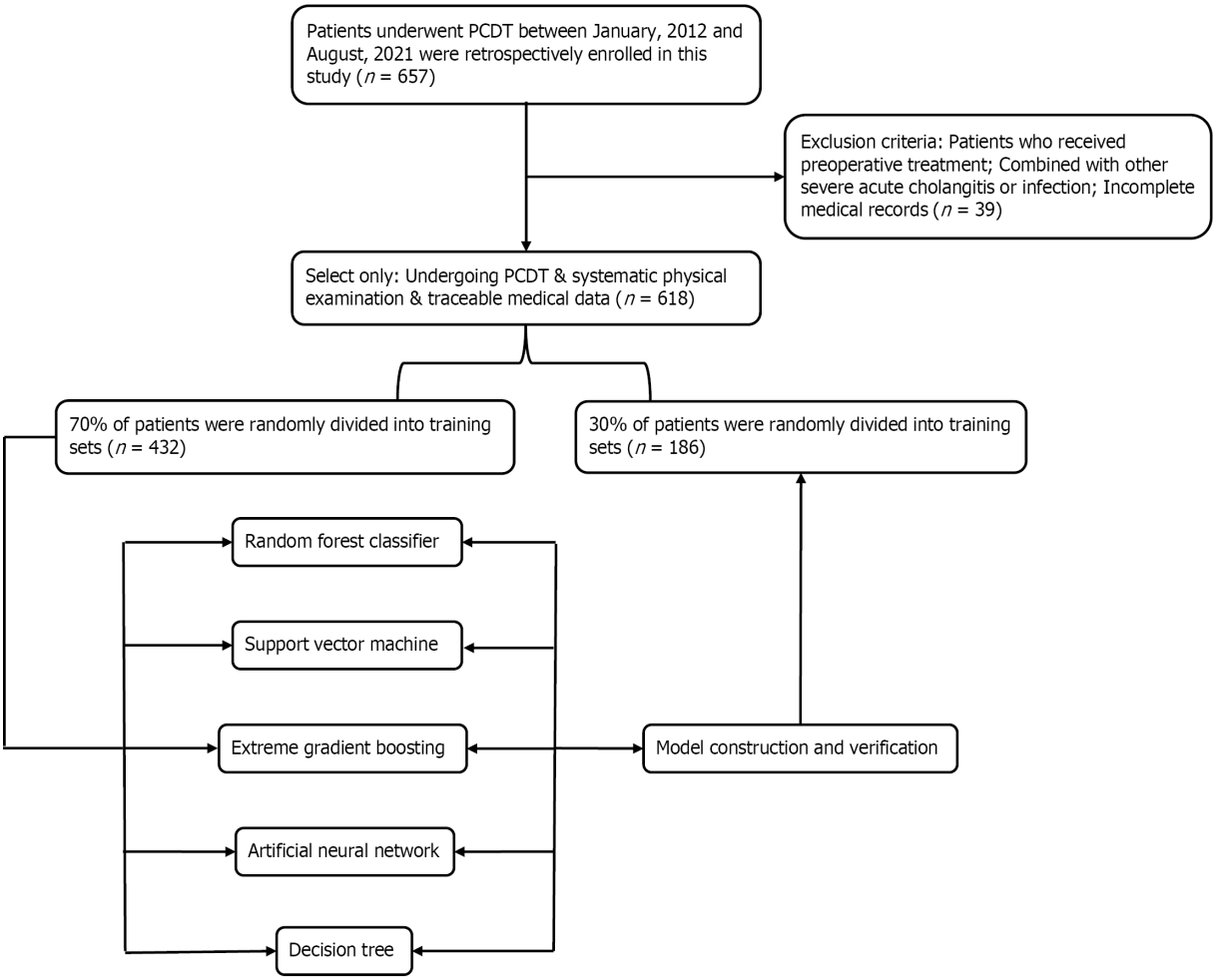

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Figure 1 The flow chart. PD: Pancreatoduodenectomy.

Construction of PF predictive model based on ML algorithm

In the training queue, each patient could use positive or negative training and output the final judgment results. For example, a random forest classifier (RFC) algorithm could be used to effectively navigate the free parameter space to obtain a robust model (Figure 3A). The variable Gini index in the RFC model is shown in Supplementary Table 1. In addition, data mining through the decision tree (DT) model was useful, as shown in Figure 3B, among the candidate variables related to inflammatory factors, PCT and BMI also played an important role in DT as branch weight, which could be used as an important predictor of postoperative PF. The artificial neural network (ANN) model also showed relatively robust predictive performance, but slightly lower than that of RFC (Figure 4). We also constructed nomographs, which depended on the parameters obtained by LR, as shown in Supplementary Table 2. Compared with traditional predictive models, inflammatory factors also accounted for an important proportion.

Comparison between ML-based models

To explore the effectiveness of five supervised learning models for postoperative PF evaluation, we used decision curve analysis (DCA) for evaluation, which was consistent with the results of the included candidate variables. Even if different predictive models included the same variables, there were certain differences in their predictive effectiveness, as shown in Figure 5. In addition, as shown in Table 2, the predictive efficiency of RFC was the best [0.897, 95% confidence interval (CI): 0.370–1.424] compared with the other four predictive models, followed by ANN (0.882, 95%CI: 0.321–1.443), DT (0.807, 95%CI: 0.250–1.364), extreme gradient boosting (XGboost) (0.793, 95%CI: 0.270–1.316), and support vector machine (SVM) (0.726, 95%CI: 0.191–1.261). In conclusion, the iterative algorithm analysis using supervised learning, RFC and ANN, as well as DT (ML-aided decision support) models were properly used to guide postoperative PF prediction.

Table 2 The operating characteristic curve analyses for each machine learning-based model

Model	AUC		No. of candidate variables
	Mean	95%CI	
RFC	0.897	0.370–1.424	7
SVM	0.726	0.191–1.261	8
DT	0.807	0.250–1.364	8
ANN	0.882	0.321–1.443	7
XGboost	0.793	0.270–1.316	9

95%CI: 95% confidence interval; RFC: Random forest classifier; SVM: Support vector machine; DT: Decision tree; ANN: Artificial neutral network; XGboost: Extreme gradient boosting; AUC: Area under curve.

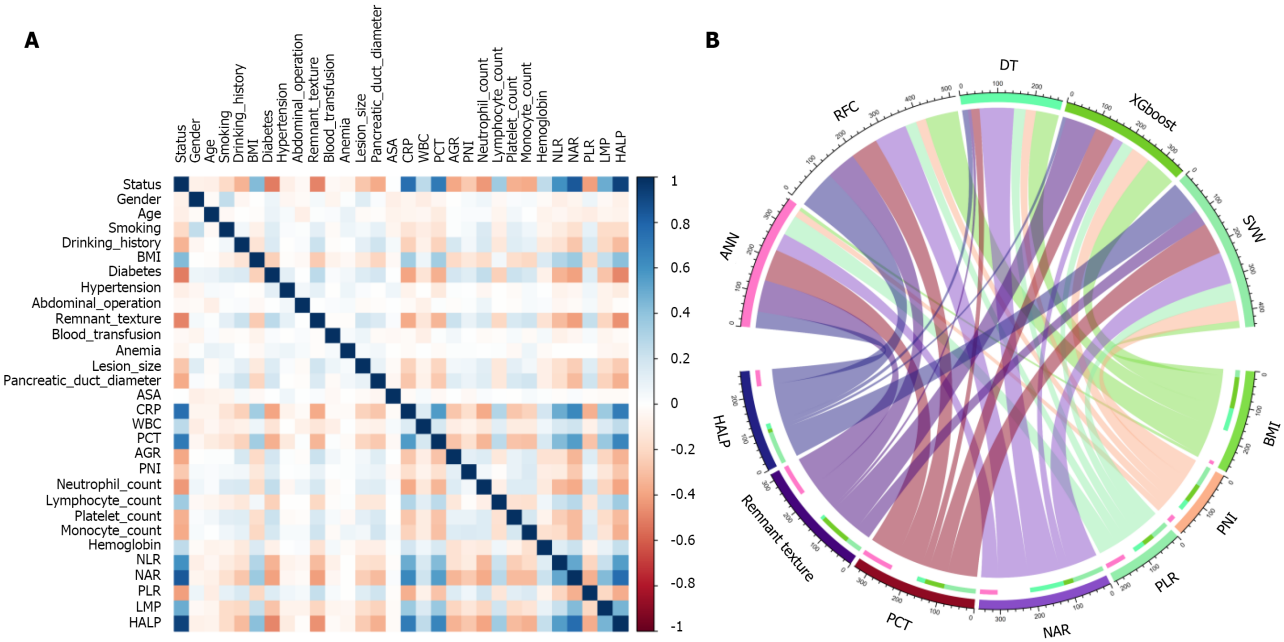

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Figure 2 Variable filtering and weight allocation. A: Correlation matrix analysis; B: Weight distribution of the candidate variables. BMI: Body mass index; ASA: American Society of Anesthesiologists; CRP: C-reactive protein; WBC: White blood cell; PCT: Procalcitonin; AGR: Albumin-to-globulin ratio; PNI: Prognostic nutrition index; NLR: Neutrophil-to-lymphocyte ratio; NAR: Neutrophil-to-albumin ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; HALP: Hemoglobin level × albumin level × lymphocyte count/platelet count ratio; RFC: Random forest classifier; SVM: Support vector machine; DT: Decision tree; ANN: Artificial neural network; XGboost: Extreme gradient boosting.

Internal validation of the optimal postoperative PF predictive model

We evaluated the clinical predictive efficiency of the optimal prediction model (RFC), as shown in Supplementary Figure 1. RFC can be used to achieve accurate stratification of patients' postoperative PF *via* clinical impact curve (CIC). In general, RFC performed best in the construction of prediction models by fusing inflammatory markers.

DISCUSSION

Our study revealed two major findings. First, accurate risk stratification of postoperative PF in patients who received PD, which mainly depended on the added value of systemic inflammation markers. Second, the ML-based predictive model is better than the traditional predictive algorithm model, which is suitable for identifying whether patients have postoperative PF.

Several risk factors leading to such complications have been reported in the relevant literature, including pancreas texture, BMI, intraoperative blood loss, blood transfusion, and operating time[9,23, 24]. We summarize updated literature on predicting postoperative PF, in combination with various

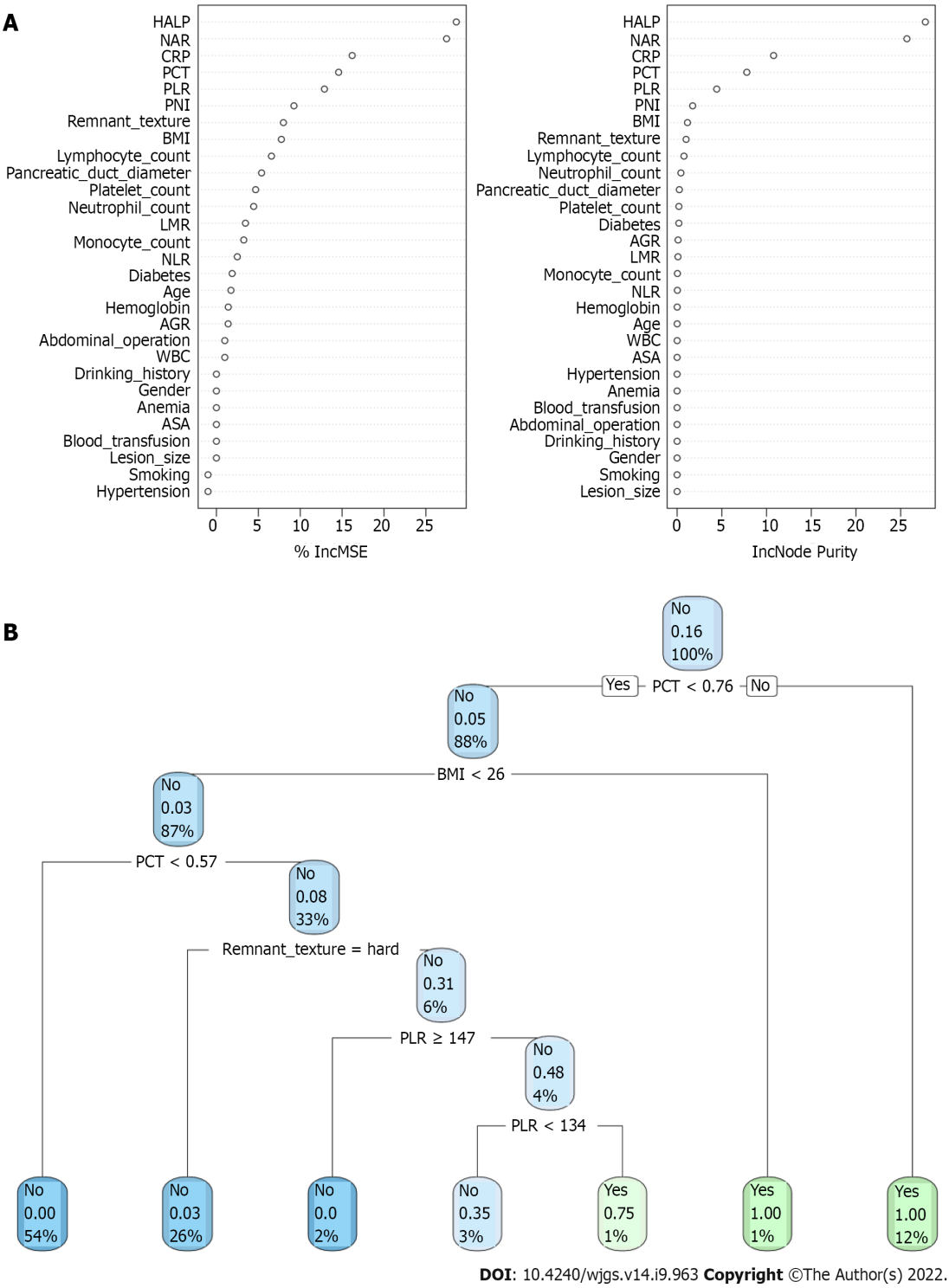

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Figure 3 Visualization of predictive model based on machine learning algorithm. A: Random forest classifier model; B: Decision tree (DT) model. The candidate factors associated with postoperative pancreatic fistula were ordered *via* RFC algorithm (A) and (B) prediction node and weight were allocated *via* DT algorithm. BMI: Body mass index; ASA: American Society of Anesthesiologists; CRP: C-reactive protein; WBC: White blood cell; PCT: Procalcitonin; AGR: Albumin-to-globulin ratio; PNI: Prognostic nutrition index; NLR: Neutrophil-to-lymphocyte ratio; NAR: Neutrophil-to-albumin ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; HALP: Hemoglobin level × albumin level × lymphocyte count/platelet count ratio; RFC: Random forest classifier; SVM: Support vector machine; DT: Decision tree; ANN: Artificial neural network.

candidate predictive markers in Supplementary Table 3. Guo *et al*[25] reported that the texture of pancreas, size of the main pancreatic duct, portal vein invasion and confirmed pathology are the risk factors of postoperative PF. Tajima *et al*[26] summarized that preoperative imaging evaluation of pancreatic pathologies would be also beneficial for stratifying. Not surprisingly, systemic inflammatory markers such as neutrophils, lymphocytes, platelets, CRP, albumin, and biomarkers may help predict postoperative PF. The systemic response to postoperative local inflammatory stimulation is tightly

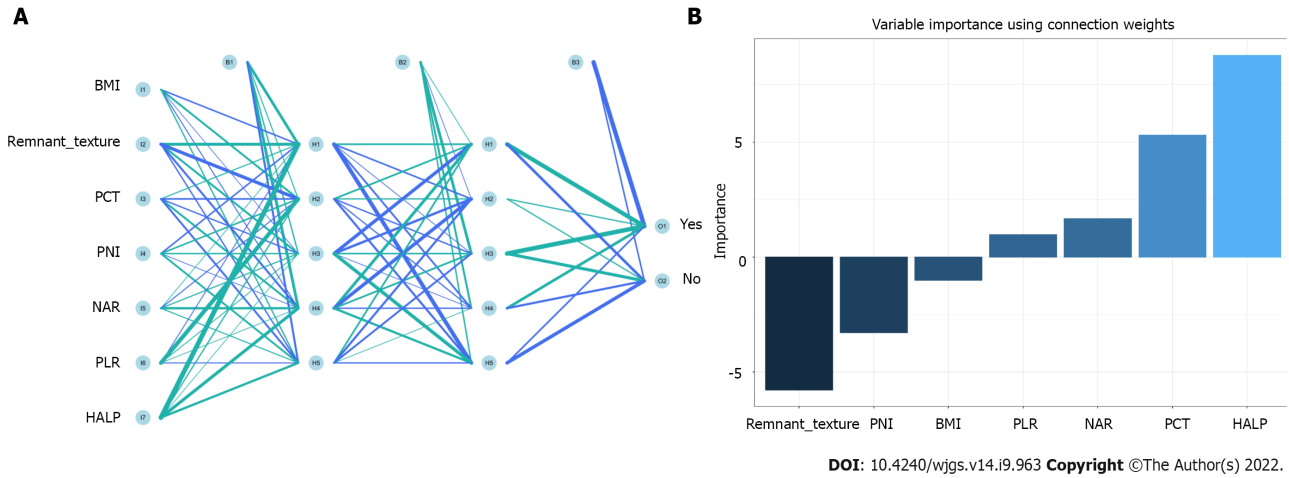

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Figure 4 Visualization of predictive model based on artificial neural network algorithm. A: Artificial neural network model; B: Variable importance using connection weight. BMI: Body mass index; PCT: Procalcitonin; PNI: Prognostic nutrition index; NAR: Neutrophil-to-albumin ratio; PLR: Platelet-to-lymphocyte ratio; HALP: Hemoglobin level × albumin level × lymphocyte count/platelet count ratio.

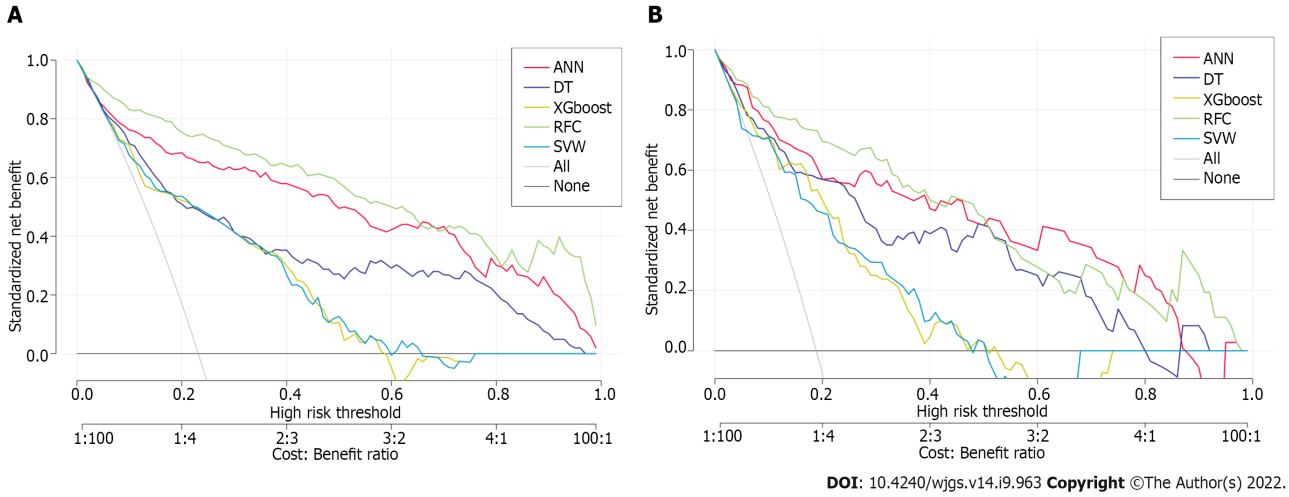

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Figure 5 Efficiency evaluation of machine learning-based prediction model. A: Decision curve analysis (DCA) of training set; B: DCA of testing set. SVM: Support vector machine; DT: Decision tree; ANN: Artificial neural network; RFC: Random forest classifier; XGboost: Extreme gradient boosting.

related to the complications after gastrointestinal surgery[27]. Gasteiger *et al*[15] reported that postoperative pancreatitis and inflammatory reaction are the main determinants of postoperative PF [15]. Intriguingly, our calculated risk factors for postoperative PF and inflammatory factors accounted for an irreplaceable weight in the predictive model.

In this study, an attempt was made to improve early postoperative risk stratification by combining local pancreatic residual inflammatory status and systemic response. We found that abnormal HALP, PCT, NAR, PLR and PNI showed reliable predictive value for postoperative PF. Previous studies have confirmed that neutrophils, as the source of vascular endothelial growth factor and tissue inhibitor protease, can promote tumor infiltration and distant metastasis[28-30]. Additionally, the number of lymphocytes in cancer patients changes frequently, which seriously affects the prognosis and survival rate[31,32]. As noted above, it appears that inflammatory factors were highly related to the presence of postoperative PF. Combined with these findings, our analysis showed that systemic inflammatory markers are of value in predicting postoperative PF.

Our ML-based model was based on clinical parameters and laboratory test results, which were consistent with previous research results. Clinical indicators including preoperative serum albumin, lipase level, and amount of intraoperative fluid infusion were independent risk factors of postoperative PF[23,24,33]. Therefore, we further analyzed the accuracy of the predictive model constructed between clinical parameters and systemic inflammatory markers based on an ML-based algorithm. Not surprisingly, we found that systemic inflammatory markers accounted for a high weight in each model. Among these predictive models, RFC allowed the calculation of risk level based on candidate variables, so the best predictive efficiency was obtained. It is not surprising that RFC adopted the resampling

technique of bootstrapping to repeatedly focus on the "bagging" procedure[34]. To detect the discrimination of the ML-based model, the DCA and CIC methods were used to evaluate the predictive performance, and the results were consistent with the expected goal. Taken together, our model may apply to patients who intended to receive PD, especially to help surgeons decide whether to prevent postoperative PF after surgery.

Despite several strengths, there were some noteworthy limitations to this study. First, patients included were from two tertiary referral hospitals, which may have resulted in selection bias. Second, although we have established a perfect predictive model through an ML-based algorithm, our model still needs to be confirmed in other hospital settings. Although we adopted internal data cross-validation, we still need more external data to verify its feasibility in the future. Third, we only adopted simple data obtained from classification, missing clinical data were not considered throughout the study. Hence, incorporating specific new technologies such as immunodiagnostic biomarkers may help to improve the accuracy of predictive models.

CONCLUSION

Our results provide new insights into candidate predictive markers associated with high risk of PF. With the help of HALP, NAR, CRP, PCT and PLR, we developed ML-based predictive models, and the performance of these unsupervised integrated models was superior to that of traditional predictive models. We expect these findings to extend research to strengthen clinical decision-making and guide treatment.

ARTICLE HIGHLIGHTS

Research background

We provide insights into the candidate predictive markers associated with a high risk of postoperative pancreatic fistula (PF) *via* serum inflammatory secretion. With the help of hemoglobin level × albumin level × lymphocyte count/platelet count ratio, neutrophil-to-albumin ratio, C-reactive protein, procalcitonin and platelet-to-lymphocyte ratio, we develop machine learning (ML)-based predictive models, and the predictive performance of these unsupervised integrated models was superior to that of traditional predictive models. We expect these findings to extend research to strengthen clinical decision-making and guide treatment.

Research motivation

Fluctuating serological inflammation markers and prognostic nutritional index can be detected in the early postoperative period, and clinically well established to predict postoperative PF; in particular, random forest classifier (RFC) performed best, which can guide optimal treatment, clinical management and prevent or mitigate adverse consequences.

Research objectives

A total of 29 variables were used to build the ML predictive model. Among them, the best predictive model was RFC, the area under the curve (AUC) was [0.897, 95% confidence interval (CI): 0.370–1.424], while the AUC of the artificial neural network, eXtreme gradient boosting, support vector machine, and decision tree were between 0.726 (95%CI: 0.191–1.261) and 0.882 (95%CI: 0.321–1.443).

Research methods

As for descriptive variables (*i.e.*, continuous or classified variables), the median (interquartile range) or frequency (percentage) were used for statistics in this study. The χ^2 test or Mann–Whitney test was used to calculate the variables between groups to evaluate whether there was a statistical difference. Stepwise regression based on the minimum value of the Akaike information standard was used to select the variables. All data analysis was completed with the help of R language software (version 4.0.4, http://www.r-project.org/). All P values were double tailed, and $P < 0.05$ was statistically significant.

Research results

A total of 29 variables were used to build the ML predictive model. Among them, the best predictive model was RFC, the area under the curve (AUC) was [0.897, 95% confidence interval (CI): 0.370–1.424], while the AUC of the artificial neural network, eXtreme gradient boosting, support vector machine, and decision tree were between 0.726 (95%CI: 0.191–1.261) and 0.882 (95%CI: 0.321–1.443).

Research conclusions

Fluctuating serological inflammatory markers and prognostic nutritional index (PNI) can be detected in

the early postoperative period, which has been clinically proved to predict postoperative PF. In particular, RFC performed best, which can guide optimal treatment, clinical management, and prevent or mitigate adverse consequences.

Research perspectives

PD, also known as a Whipple procedure, is one of the most difficult and complex surgeries that carries a high rate of major complications. Postoperative PF, as one of the most difficult complications after PD, can seriously endanger the lives of patients, so it has become an area of continuous concern for pancreatic surgeons. Although the safety of PD has improved significantly in the past three decades, previous prospective studies have reported that postoperative PF has an incidence of > 10%. Understanding the potential complications and early warning of these complications is important for the care of these patients.

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FOOTNOTES

Author contributions: Long ZD, Lu C, Xia XG, Chen B, Xing ZX, Bie L, Zhou P, Ma ZL, and Wang R designed the research study; Long ZD, Lu C, Xia XG, and Chen B performed the research; Xia XG, Chen B, and Xing ZX contributed new reagents and analytic tools; Long ZD, Lu C, Xia XG, Chen B, Xing ZX, Bie L, Zhou P, Ma ZL, and Wang R analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

Institutional review board statement: This retrospective study was following the declaration of Helsinki, and was ethically reviewed and approved by the Institutional Ethics Committee of Jingzhou Hospital, No. 2021-JH005.

Informed consent statement: Since the patient information contained in this study was anonymous, written informed consent was not obtained from all participants.

Conflict-of-interest statement: All authors declare that there is no conflict of interest.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Zhi-Da Long 0000-0002-6956-2567; Chao Lu 0000-0002-6236-1550; Xi-Gang Xia 0000-0002-4573-2387; Bo Chen 0000-0002-2017-1235; Zhi-Xiang Xing 0000-0002-1789-0078; Lei Bie 0000-0002-1078-2022; Peng Zhou 0000-0002-1456-1378; Zhong-Lin Ma 0000-0002-1287-0987; Rui Wang 0000-0002-6992-2287.

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REFERENCES

1 **Karim SAM**, Abdulla KS, Abdulkarim QH, Rahim FH. The outcomes and complications of pancreaticoduodenectomy (Whipple procedure): Cross sectional study. *Int J Surg* 2018; **52**: 383-387 [PMID: 29438817 DOI: 10.1016/j.ijsu.2018.01.041]
2 **Xiang Y**, Wu J, Lin C, Yang Y, Zhang D, Xie Y, Yao X, Zhang X. Pancreatic reconstruction techniques after pancreaticoduodenectomy: a review of the literature. *Expert Rev Gastroenterol Hepatol* 2019; **13**: 797-806 [PMID: 31282769 DOI: 10.1080/17474124.2019.1640601]
3 **Narayanan S**, Martin AN, Turrentine FE, Bauer TW, Adams RB, Zaydfudim VM. Mortality after pancreaticoduodenectomy: assessing early and late causes of patient death. *J Surg Res* 2018; **231**: 304-308 [PMID: 30278945 DOI: 10.1016/j.jss.2018.05.075]

4 **Kawaida H**, Kono H, Hosomura N, Amemiya H, Itakura J, Fujii H, Ichikawa D. Surgical techniques and postoperative management to prevent postoperative pancreatic fistula after pancreatic surgery. *World J Gastroenterol* 2019; **25**: 3722-3737 [PMID: 31391768 DOI: 10.3748/wjg.v25.i28.3722]

5 **Wellner UF**, Brett S, Bruckner T, Limprecht R, Rossion I, Seiler C, Sick O, Wegener I, Hopt UT, Keck T; RECOPANC Trial Group. Pancreatogastrostomy *versus* pancreatojejunostomy for RECOnstruction after partial PANCreatoduodenectomy (RECOPANC): study protocol of a randomized controlled trial UTN U1111-1117-9588. *Trials* 2012; **13**: 45 [PMID: 22540372 DOI: 10.1186/1745-6215-13-45]

6 **Chen BP**, Bennett S, Bertens KA, Balaa FK, Martel G. Use and acceptance of the International Study Group for Pancreatic Fistula (ISGPF) definition and criteria in the surgical literature. *HPB (Oxford)* 2018; **20**: 69-75 [PMID: 28927654 DOI: 10.1016/j.hpb.2017.08.022]

7 **Fu SJ**, Shen SL, Li SQ, Hu WJ, Hua YP, Kuang M, Liang LJ, Peng BG. Risk factors and outcomes of postoperative pancreatic fistula after pancreatico-duodenectomy: an audit of 532 consecutive cases. *BMC Surg* 2015; **15**: 34 [PMID: 25887526 DOI: 10.1186/s12893-015-0011-7]

8 **Akgul O**, Merath K, Mehta R, Hyer JM, Chakedis J, Wiemann B, Johnson M, Paredes A, Dillhoff M, Cloyd J, Pawlik TM. Postoperative Pancreatic Fistula Following Pancreaticoduodenectomy-Stratification of Patient Risk. *J Gastrointest Surg* 2019; **23**: 1817-1824 [PMID: 30478529 DOI: 10.1007/s11605-018-4045-x]

9 **Callery MP**, Pratt WB, Kent TS, Chaikof EL, Vollmer CM Jr. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. *J Am Coll Surg* 2013; **216**: 1-14 [PMID: 23122535 DOI: 10.1016/j.jamcollsurg.2012.09.002]

10 **You Y**, Han IW, Choi DW, Heo JS, Ryu Y, Park DJ, Choi SH, Han S. Nomogram for predicting postoperative pancreatic fistula. *HPB (Oxford)* 2019; **21**: 1436-1445 [PMID: 30982739 DOI: 10.1016/j.hpb.2019.03.351]

11 **Mungroop TH**, van Rijssen LB, van Klaveren D, Smits FJ, van Woerden V, Linnemann RJ, de Pastena M, Klompmaker S, Marchegiani G, Ecker BL, van Dieren S, Bonsing B, Busch OR, van Dam RM, Erdmann J, van Eijck CH, Gerhards MF, van Goor H, van der Harst E, de Hingh IH, de Jong KP, Kazemier G, Luyer M, Shamali A, Barbaro S, Armstrong T, Takhar A, Hamady Z, Klaase J, Lips DJ, Molenaar IQ, Nieuwenhuijs VB, Rupert C, van Santvoort HC, Scheepers JJ, van der Schelling GP, Bassi C, Vollmer CM, Steyerberg EW, Abu Hilal M, Groot Koerkamp B, Besselink MG; Dutch Pancreatic Cancer Group. Alternative Fistula Risk Score for Pancreatoduodenectomy (a-FRS): Design and International External Validation. *Ann Surg* 2019; **269**: 937-943 [PMID: 29240007 DOI: 10.1097/SLA.0000000000002620]

12 **Singh N**, Baby D, Rajguru JP, Patil PB, Thakkannavar SS, Pujari VB. Inflammation and cancer. *Ann Afr Med* 2019; **18**: 121-126 [PMID: 31417011 DOI: 10.4103/aam.aam_56_18]

13 **Lontchi-Yimagou E**, Sobngwi E, Matsha TE, Kengne AP. Diabetes mellitus and inflammation. *Curr Diab Rep* 2013; **13**: 435-444 [PMID: 23494755 DOI: 10.1007/s11892-013-0375-y]

14 **Hotamisligil GS**. Inflammation, metaflammation and immunometabolic disorders. *Nature* 2017; **542**: 177-185 [PMID: 28179656 DOI: 10.1038/nature21363]

15 **Gasteiger S**, Primavesi F, Göbel G, Braunwarth E, Cardini B, Maglione M, Sopper S, Öfner D, Stättner S. Early Post-Operative Pancreatitis and Systemic Inflammatory Response Assessed by Serum Lipase and IL-6 Predict Pancreatic Fistula. *World J Surg* 2020; **44**: 4236-4244 [PMID: 32901324 DOI: 10.1007/s00268-020-05768-9]

16 **van Hilst J**, Brinkman DJ, de Rooij T, van Dieren S, Gerhards MF, de Hingh IH, Luyer MD, Marsman HA, Karsten TM, Busch OR, Festen S, Heger M, Besselink MG; Dutch Pancreatic Cancer Group. The inflammatory response after laparoscopic and open pancreatoduodenectomy and the association with complications in a multicenter randomized controlled trial. *HPB (Oxford)* 2019; **21**: 1453-1461 [PMID: 30975599 DOI: 10.1016/j.hpb.2019.03.353]

17 **LeCun Y**, Bengio Y, Hinton G. Deep learning. *Nature* 2015; **521**: 436-444 [PMID: 26017442 DOI: 10.1038/nature14539]

18 **Bassi C**, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M; International Study Group on Pancreatic Fistula Definition. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 2005; **138**: 8-13 [PMID: 16003309 DOI: 10.1016/j.surg.2005.05.001]

19 **Bassi C**, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, Allen P, Andersson R, Asbun HJ, Besselink MG, Conlon K, Del Chiaro M, Falconi M, Fernandez-Cruz L, Fernandez-Del Castillo C, Fingerhut A, Friess H, Gouma DJ, Hackert T, Izbicki J, Lillemoe KD, Neoptolemos JP, Olah A, Schulick R, Shrikhande SV, Takada T, Takaori K, Traverso W, Vollmer CR, Wolfgang CL, Yeo CJ, Salvia R, Buchler M; International Study Group on Pancreatic Surgery (ISGPS). The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. *Surgery* 2017; **161**: 584-591 [PMID: 28040257 DOI: 10.1016/j.surg.2016.11.014]

20 **Miot HA**. Anomalous values and missing data in clinical and experimental studies. *J Vasc Bras* 2019; **18**: e20190004 [PMID: 31320882 DOI: 10.1590/1677-5449.190004]

21 **Fan J**, Lv J. A Selective Overview of Variable Selection in High Dimensional Feature Space. *Stat Sin* 2010; **20**: 101-148 [PMID: 21572976]

22 **Deo RC**. Machine Learning in Medicine. *Circulation* 2015; **132**: 1920-1930 [PMID: 26572668 DOI: 10.1161/CIRCULATIONAHA.115.001593]

23 **Peng YP**, Zhu XL, Yin LD, Zhu Y, Wei JS, Wu JL, Miao Y. Risk factors of postoperative pancreatic fistula in patients after distal pancreatectomy: a systematic review and meta-analysis. *Sci Rep* 2017; **7**: 185 [PMID: 28298641 DOI: 10.1038/s41598-017-00311-8]

24 **Han IW**, Cho K, Ryu Y, Shin SH, Heo JS, Choi DW, Chung MJ, Kwon OC, Cho BH. Risk prediction platform for pancreatic fistula after pancreatoduodenectomy using artificial intelligence. *World J Gastroenterol* 2020; **26**: 4453-4464 [PMID: 32874057 DOI: 10.3748/wjg.v26.i30.4453]

25 **Guo CX**, Shen YN, Zhang Q, Zhang XZ, Wang JL, Gao SL, Lou JY, Que RS, Ma T, Liang TB, Bai XL. Prediction of postoperative pancreatic fistula using a nomogram based on the updated definition. *Ann Surg Treat Res* 2020; **98**: 72-81 [PMID: 32051815 DOI: 10.4174/astr.2020.98.2.72]

26 **Tajima Y**, Kawabata Y, Hirahara N. Preoperative imaging evaluation of pancreatic pathologies for the objective prediction of pancreatic fistula after pancreaticoduodenectomy. *Surg Today* 2018; **48**: 140-150 [PMID: 28421350 DOI: 10.1007/s00595-017-1529-3]

27 **Rettig TC**, Verwijmeren L, Dijkstra IM, Boerma D, van de Garde EM, Noordzij PG. Postoperative Interleukin-6 Level and Early Detection of Complications After Elective Major Abdominal Surgery. *Ann Surg* 2016; **263**: 1207-1212 [PMID: 26135695 DOI: 10.1097/SLA.0000000000001342]

28 **Strieter RM**, Burdick MD, Mestas J, Gomperts B, Keane MP, Belperio JA. Cancer CXC chemokine networks and tumour angiogenesis. *Eur J Cancer* 2006; **42**: 768-778 [PMID: 16510280 DOI: 10.1016/j.ejca.2006.01.006]

29 **Balestrieri ML**, Balestrieri A, Mancini FP, Napoli C. Understanding the immunoangiostatic CXC chemokine network. *Cardiovasc Res* 2008; **78**: 250-256 [PMID: 18252760 DOI: 10.1093/cvr/cvn029]

30 **Ocana A**, Nieto-Jiménez C, Pandiella A, Templeton AJ. Neutrophils in cancer: prognostic role and therapeutic strategies. *Mol Cancer* 2017; **16**: 137 [PMID: 28810877 DOI: 10.1186/s12943-017-0707-7]

31 **Ménétrier-Caux C**, Ray-Coquard I, Blay JY, Caux C. Lymphopenia in Cancer Patients and its Effects on Response to Immunotherapy: an opportunity for combination with Cytokines? *J Immunother Cancer* 2019; **7**: 85 [PMID: 30922400 DOI: 10.1186/s40425-019-0549-5]

32 **Blankenstein T**, Coulie PG, Gilboa E, Jaffee EM. The determinants of tumour immunogenicity. *Nat Rev Cancer* 2012; **12**: 307-313 [PMID: 22378190 DOI: 10.1038/nrc3246]

33 **Ellis RJ**, Brock Hewitt D, Liu JB, Cohen ME, Merkow RP, Bentrem DJ, Bilimoria KY, Yang AD. Preoperative risk evaluation for pancreatic fistula after pancreaticoduodenectomy. *J Surg Oncol* 2019; **119**: 1128-1134 [PMID: 30951614 DOI: 10.1002/jso.25464]

34 **Rigatti SJ**. Random Forest. *J Insur Med* 2017; **47**: 31-39 [PMID: 28836909 DOI: 10.17849/insm-47-01-31-39.1]

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ORIGINAL ARTICLE

Retrospective Study

Feasible management of median arcuate ligament syndrome in orthotopic liver transplantation recipients

Shu-Xuan Li, Ye-Hui Fan, Guang-Yao Tian, Guo-Yue Lv

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Shu-Xuan Li, Guang-Yao Tian, Guo-Yue Lv, Department of Hepatobiliary and Pancreatic Surgery, The First Hospital of Jilin University, Changchun 130021, Jilin Province, China

Ye-Hui Fan, Department of The First Operation Room, The First Hospital of Jilin University, Changchun 130021, Jilin Province, China

Corresponding author: Guo-Yue Lv, PhD, Dean, Professor, Surgeon, Department of Hepatobiliary and Pancreatic Surgery, The First Hospital of Jilin University, No. 1 Xinmin Street, Changchun 130021, Jilin Province, China. lvgy@jlu.edu.cn

Abstract

BACKGROUND

In orthotopic liver transplantation (OLT) recipients, median arcuate ligament syndrome (MALS) is considered a risk factor for hepatic arterial thrombosis (HAT), which is dreadful for OLT recipients. Different alternative surgical procedures have been proposed to overcome the impact of MALS on transplantation, but clinical evidence is still scarce.

AIM

To evaluate the feasible surgical management of MALS to reduce complications in OLT patients.

METHODS

Data for 288 consecutive patients who underwent OLT at The First Hospital of Jilin University between January 2017 and July 2020 were retrospectively reviewed. The surgical management of median arcuate ligament (MAL) and modifications to the arterial anastomosis were recorded. The perioperative and long-term prognosis of MALS recipients were noted. Detailed preoperative and postoperative data of patients were analyzed in a descriptive manner.

RESULTS

Eight patients with MALS were included in this study. The first patient with MALS received no intervention during the primary surgery and developed postoperative HAT. Salvage liver transplantation with MAL division was successfully performed. Gastroduodenal artery (GDA) preservation with splenic artery ligation was performed on three patients, only GDA preservation was performed on two patients, and no intervention was performed on two patients. No patient developed HAT after surgery and postoperative recovery was

satisfactory.

CONCLUSION
The preservation of collateral circulation between the superior mesenteric artery and celiac trunk *via* the GDA with or without splenic artery ligation is a safe and feasible alternative to MAL division.

Key Words: Orthotopic liver transplantation; Median arcuate ligament syndrome; Surgical complications; Surgical management; Hepatic artery thrombosis

Core Tip: This retrospective single-center study analyzed diagnosis, surgical procedure and outcome of 8 patients with median arcuate ligament syndrome (MALS). In eight patients with MALS, orthotopic liver transplantation without median arcuate ligament (MAL) division and celiac trunk-aorta bypass ensured adequate hepatic arterial blood flow. No new onset hepatic arterial thrombosis was observed. The study suggests that without intraoperative MAL release, one cannot ensure adequate hepatic artery flow and prevent hepatic arterial thrombosis.

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INTRODUCTION

Orthotopic liver transplantation (OLT) is the most effective treatment for end-stage liver disease[1]. Although the operative technique for OLT has been standardized, postoperative hepatic arterial thrombosis (HAT) remains a rare but dreadful complication[2-4]. Previous studies have demonstrated that factors associated with HAT include anastomotic stenosis, anastomosis inversion, arterial tortuosity, acute cellular rejection, transfusion and other rare factors. Median arcuate ligament syndrome (MALS) is one of the rare causes of HAT[5-7]. MALS refers to an extrinsic compression of the celiac axis caused by the fibrous ligament known as the MAL and periaortic ganglionic tissue[8]. The condition was first reported as a post-mortem finding by Lipshutz[9] in 1917. Harjola[10] and Dunbar *et al*[11] successfully performed median arcuate ligament (MAL) release operations in 1963 and 1965, respectively. MALS can reduce the hepatic blood flow velocity from 425 cm/s to 200 cm/s[12]. This indicates that MALS can disrupt the hepatic artery hemodynamics, which is considered a high-risk factor for HAT in OLT recipients[12,13]. Thus, timely recognition and management of MALS is of major importance for transplant surgeons. Different surgical procedures have been proposed to overcome the impact of MALS on transplantation, but clinical evidence is still scarce with regard to the surgical treatment of MALS. In this retrospective study, we evaluated the surgical management of MALS to reduce complications in OLT patients.

MATERIALS AND METHODS

Patients

The data for 288 consecutive patients who underwent OLT at The First Hospital of Jilin University between January 2017 and July 2020 were retrospectively reviewed. All patients received liver grafts from cardiac death donors. Patients without adequate preoperative images as well as those who received simultaneous liver-kidney transplantation and pediatric liver transplantations were excluded. The collected data included preoperative data on celiac truck stenosis and MALS, surgical procedures for MALS as well as postoperative short- and long-term follow-up details. The investigators obtained approval from the Ethics Committee of The First Hospital of Jilin University. All patients provided written informed consent for the procedures.

Preoperative computed tomographic angiography

All OLT recipients underwent preoperative computed tomographic angiography (CTA) (Figure 1). End-inspiratory arterial phase, end-expiratory portal venous phase and sagittal arterial reconstruction were

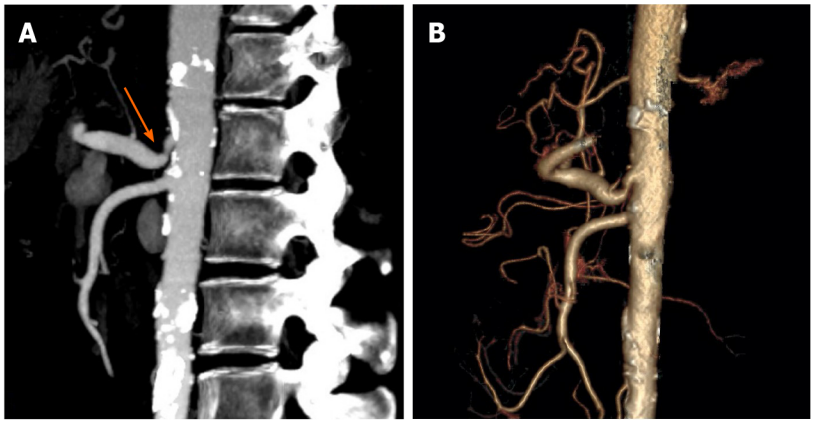

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Figure 1 Computed tomography images of orthotopic liver transplantation recipients with median arcuate syndrome in the sagittal plane.
A: Patient with median arcuate ligament syndrome showing stenosis of the celiac trunk due to compression by the median arcuate ligament and the post-stenotic dilation (arrow); B: Abundant collateral circulation between the superior mesenteric artery and the celiac trunk (arrow).

examined. Vascular abnormalities were evaluated by a senior staff radiologist and the transplant surgeon to determine the operative approach. According to stenosis rate, length of stenosis and distance from aorta, Sugae *et al*[14] classified MALS to three types. The rate of type A stenosis should be less than 50%, its length should be less than 3 mm, and its position should be more than 5 mm from the aorta. The rate of type B stenosis should be between 50 and 80 percent, its length should be between 3 and 8 mm, and its position should be greater than 5 mm from the aorta. The rate of type C stenosis should exceed 80%, its length should exceed 8 mm, and its position should be less than 5 mm from the aorta. MALS was defined based on extrinsic compression on the celiac trunk due to MAL, post-stenotic dilatation, and patients diagnosed with MALS should exhibit at least one or more of the following symptoms postprandial pain, weight loss and small meals as described previously[8,15].

Surgical management of MALS

OLT recipients with suspected or confirmed MALS on pre-operative imaging underwent detailed evaluation of the collateral circulation between the superior mesenteric artery and the celiac trunk based on the pre-operative imaging and intraoperative findings. Gastroduodenal arteries (GDAs) with abundant collateral branches were clamped to determine whether the hepatic arterial flow or pulse was reduced. If clamping decreased the hepatic arterial flow, then the GDA and collateral branches were preserved. The hepatic artery/splenic artery patch from the donor and right/left hepatic artery patch from the recipient were used for branch patch anastomosis (Figure 2). If hepatic arterial flow was not affected by GDA clamping, the hepatic artery/GDA patch from the recipient and hepatic artery/splenic artery patch from the donor was used for branch patch anastomosis as a standard arterial revascularization method (Figure 3). After the anastomosis, the intrahepatic arterial blood flow was evaluated using Doppler ultrasound. If the blood flow was not satisfactory (hepatic arterial blood flow rate < 50 cm/s), after assessing the potential for splenic artery steal syndrome, the splenic artery was ligated and the hepatic arterial flow and pulse was tested again. Surgical division of MAL or celiac trunk-aorta bypass was performed when the hepatic arterial flow remained poor despite all the above measures.

Postoperatively, Doppler ultrasound was used periodically: every 12 h during the first week, twice per week until discharged, and once a week for 3 mo to monitor hepatic artery anastomosis. If Doppler ultrasound revealed any abnormal findings, such as HAT as defined by resistive index (RI) < 0.5 and hepatic artery blood flow < 39 cm/s[16] combined with elevated liver enzymes and bilirubin suggestive of hepatocellular injury, CTA was performed immediately to determine the status of hepatic artery anastomosis and initiate the timely salvage of the liver graft if required.

If there were no other signs, the patients received standard prophylaxis of thromboembolism for 6 wk post-OLT and no anticoagulant therapy was used.

RESULTS

Patient characteristics and perioperative outcomes

Among 288 patients who received OLT, eight were diagnosed with MALS (Figure 1). The mean recipient age was 59 years. There were four men and four women. The warm ischemia time for the liver graft ranged from 12 s to 41 s and the cold ischemia time ranged from 452 min to 632 min. The median follow-up was 20 mo. Other patient characteristics are presented in Table 1. The surgical details for the

Table 1 Characteristics and prognoses of patients with median arcuate ligament syndrome who received orthotopic liver transplantation

Characteristics and prognoses	1	2	3	4	5	6	7	8
Age, donor/recipient	55/52	54/53	67/66	45/48	62/63	52/62	56/38	50/63
Sex, donor/recipient	F/F	M/F	M/M	F/M	M/M	M/F	M/M	M/F
BMI, donor/recipient	20/19	22/22	22/23	21/19	23/20	26/21	22/20	25/21
Donor cause of death	CVA	CVA	Trauma	CVA	Trauma	CVA	CVA	Trauma
The primary disease	PBC	AIH	AIH	Viral	Viral	Viral	Viral	HCC
MALS type	B	B	B	C	A	B	A	A
Cold ischemic time in min	608	348	461	582	586	510	550	458
Warm ischemic time in s	19	15	41	29	12	26	15	16
Intraoperative blood loss in mL	1800	1500	2850	3000	7000	300	1000	2000
Intra-operative red blood cell transfusions in U	4	20	10.5	22	27	9	8	16.5
Intra-operative fresh frozen plasma transfusions in mL	1000	2350	1200	950	3600	960	420	960
Operation time in min	485	580	526	538	632	556	560	452
Intraoperative hepatic arterial blood flow rate in cm/s	NA	80	90	50	60	65	50	53
Hepatic arterial blood flow rate on discharge in cm/s	80	85	102	64	65	70	60	68
Hospital stay in d	17	28	39	18	21	17	17	15

AIH: Autoimmune hepatitis; BMI: Body mass index; CVA: Cerebrovascular accident; F: Female; HCC: Hepatocellular carcinoma; M: Male; NA: Not available; PBC: Primary biliary cirrhosis.

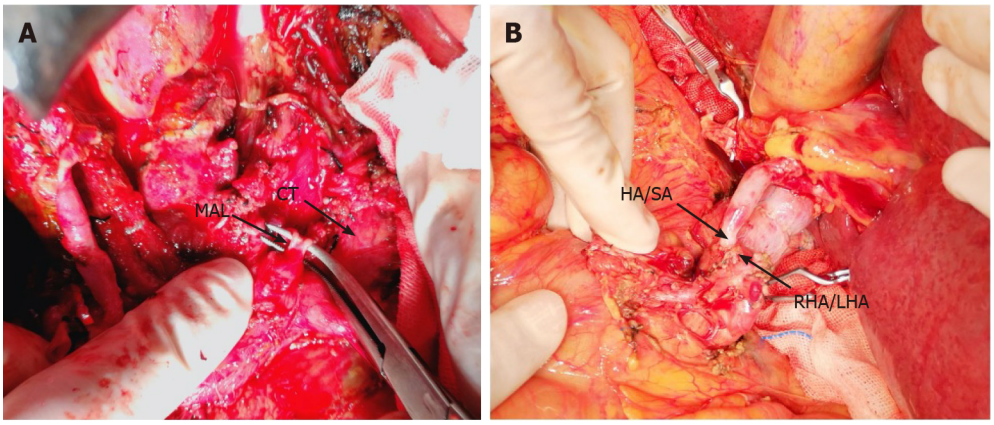

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Figure 2 Intraoperative photograph. A: Median arcuate ligament division; B: The hepatic artery/splenic artery patch from the donor and the right/left hepatic artery patch from the recipient were used for branch patch anastomosis with preservation of the gastroduodenal artery. MAL: Median arcuate ligament; CT: Computed tomography; HA/SA: Hepatic artery/splenic artery; RHA/LHA: Right/left hepatic artery.

recipients with MALS are shown in Table 2.

For the first patient, due to a lack of knowledge about MALS, no intervention for celiac trunk stenosis caused by MAL was performed during the first operation and standard revascularization was performed. On the ninth postoperative day, the total and direct bilirubin reached 210 mmol/L and 130 mmol/L, respectively. Markers of hepatocellular injury increased (alanine aminotransferase 337.5 U/L, aspartate aminotransferase 88.9 U/L). The hepatic flow rate decreased to 10 cm/s and the resistive index dropped to 0.4, suggestive of HAT. On exploratory laparotomy, there was extensive thrombosis in the hepatic artery around the anastomosis. Thrombectomy was performed and hepatic arterial blood flow was restored after re-anastomosis. However, there was no intrahepatic blood flow on Doppler ultrasound, probably due to intrahepatic arterial thrombosis. Thrombolytic therapy with alteplase was

Table 2 Details about hepatic arterial reconstruction

No.	Donor arterial patch	Recipient arterial patch	Ligament lysis	GDA preservation	Splenic artery ligation
1	Celiac truck	Hepatic/gastroduodenal artery patch	Yes	No	No
2	Hepatic/splenic artery patch	Right/left hepatic artery patch	No	Yes	Yes
3	Common hepatic artery	Right/left hepatic artery patch	No	Yes	Yes
4	Hepatic/splenic artery patch	Right/left hepatic artery patch	No	Yes	Yes
5	Common Hepatic artery	Right/left hepatic artery patch	No	Yes	No
6	(1) Gastroduodenal artery; (2) common hepatic artery	(1) Right hepatic artery from the superior mesenteric artery; (2) proper hepatic artery	No	Yes	No
7	Hepatic/splenic artery patch	Hepatic/gastroduodenal artery patch	No	No	No
8	Hepatic/splenic artery patch	Hepatic/gastroduodenal artery patch	No	No	No

GDA: Gastroduodenal artery.

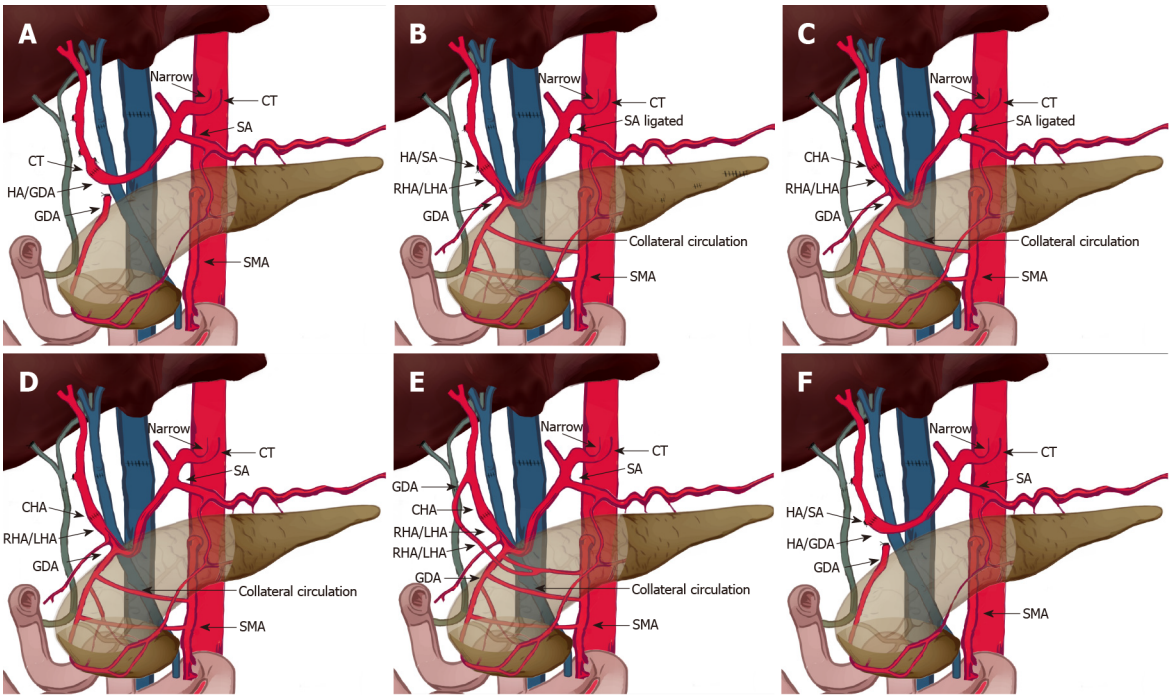

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Figure 3 Schematic diagram showing different types of patch anastomoses performed in this study. A: Donor: celiac trunk; recipient: hepatic/gastroduodenal artery (GDA) patch. Median arcuate ligament (MAL) was divided. Splenic artery was not ligated; B: Donor: hepatic/splenic artery (HA/SA) patch; recipient: right/left hepatic artery (RHA/LHA) patch; MAL was not divided. GDA was preserved. Splenic artery was ligated; C: Donor: common hepatic artery (CHA); recipient: RHA/LHA patch; MAL was not divided. GDA was preserved. Splenic artery was ligated; D: Donor: CHA; recipient: RHA/LHA patch; MAL was not divided. GDA was preserved. Splenic artery was not ligated; E: Donor: (1) GDA; and (2) CHA; recipient: (1) aberrant right hepatic artery; and (2) right/left hepatic artery patch; MAL was not divided. GDA was preserved. Splenic artery was not ligated; F: Donor: HA/SA patch; recipient: hepatic/GDA patch; MAL was not divided. Splenic artery was not ligated. MAL: Median arcuate ligament; CT: Computed tomography; HA/SA: Hepatic artery/splenic artery; RHA/LHA: Right/left hepatic artery; GDA: Gastroduodenal artery; SMA: Superior mesenteric artery; CHA: Common hepatic artery.

given but failed to restore the intrahepatic blood flow. Six hours later, salvage liver transplantation was performed and the MAL was divided (Figure 2A and 3A, Table 1 and 2). Postoperatively, the hepatic blood flow rate increased to 70-87 cm/s.

The remaining six patients had normal preoperative hepatic arterial flow. Four patients had abundant collateral circulation between the superior mesenteric artery and the celiac trunk *via* GDA (Figure 1B), thus GDA was preserved and the hepatic artery/splenic artery patch from the donor and right/left hepatic artery patch from the recipient were used for branch patch anastomosis (Figure 2B).

In three patients, low hepatic arterial flow rate was detected using Doppler ultrasound during the operation with patent anastomosis. Consequently, splenic artery steal syndrome was evaluated when RI was greater than 0.8 and hepatic artery blood flow was less than 35 cm/s[17]. Hepatic artery blood flow returned to normal after splenic artery ligation, and no HAT occurred after surgery (Figures 3B-D).

Another patient with aberrant right hepatic artery received two anastomoses. The first anastomosis was performed between the recipient right hepatic artery from the superior mesenteric artery and the donor GDA. The second anastomosis was done between the recipient's proper hepatic artery and the donor common hepatic artery (Figure 3E).

Two patients received standard arterial revascularization without preservation of the GDA or splenic artery ligation (Figure 3F).

The seven MALS patients without MAL division had satisfactory hepatic arterial blood flow after the operation. All eight patients had adequate hepatic arterial blood flow at discharge, as presented in Table 1.

Long-term outcomes of patients with MALS

The median follow-up was 19 mo (range: 10-29 mo). All the patients are alive. Among these eight patients, seven of them are healthy without complications. One patient developed biliary stricture 2 mo after surgery, which was successfully managed with endoscopic retrograde cholangiography and biliary stenting.

DISCUSSION

In MALS, the coeliac artery gets compressed by the MAL, leading to reduced blood flow in the hepatic artery[12,13,18-20]. Because the blood flow in the hepatic artery is significantly reduced, it predisposes the patients to HAT after OLT, which leads to graft failure in 50% of cases and re-transplantation[2,21-24]. MALS patients with normal hemodynamics usually have no or little clinical symptoms before OLT. However, in the postoperative phase after OLT, patients may develop severe hemodynamic restrictions in hepatic arterial flow, which increases the risk of HAT[25]. Hence, an appropriate preoperative surgical plan should be developed for OLT patients with MALS. The reported incidence of MALS after liver transplantation varies from 2% to 12%[21,26,27]. The low incidence of MALS in previous reports may be due to insufficient awareness of this disease and limited diagnostic methods. Currently, the extensive application of contrast enhance computed tomographic (CECT) has improved the diagnostic rate of MALS.

Recurrent post-prandial epigastric pain, weight loss, nausea or vomiting and abdominal pain after exercise is common symptoms of MALS. Eight patients in this study had a history of epigastric pain and weight loss, but these symptoms were attributed to chronic hepatitis and decompensated liver cirrhosis. Therefore, the diagnosis of MALS is partly clinical and mainly based on radiology. Celiac axis stenosis caused by MAL appears similar to a hook on CECT during sagittal reconstruction[28]. Abundant collateral branches, post-stenotic dilation and thickening of the MAL can also help in the diagnosis of MALS. Angiography used to be a routine test for detecting aberrant arterial vessels but is now used selectively for suspected cases in arterial dynamic studies[21,28]. Gruber *et al*[29] found that the combination of a maximum end-expiratory velocity over 350 cm/s in the celiac trunk and a deflection angle higher than 50°, detected using functional ultrasound, was a reliable diagnostic method for MALS. At our center, we routinely perform CTA on OLT patients to detect vascular variations and MALS.

Sugae *et al*[14] classified MALS into three types according to the stenosis rate, length of stenosis, distance from the aorta and collateral pathways. According to the different types, it has been suggested that type A MALS should not be manipulated, while type B and type C usually require surgery to maintain the blood supply of the hepatic artery.

Cassar *et al*[24] reported the fourth type in which coeliac artery compression from MAL is at the origin of splenic artery and surgical intervention is required to restore hepatic artery flow during liver transplantation. These suggestions are all based on maintaining the hepatic blood to the liver graft, as it is sensitive to hemodynamic changes. Therefore, whether an intervention should be performed for type A needs to be determined carefully. If MAL-related compression is mild with adequate pre- or intraoperative arterial blood flow, surgical division of MAL is not necessary. However, the perioperative hepatic artery flow is determined by various factors, making it difficult to determine whether the blood flow is adequate[8]. Golse *et al*[30] used intraoperative contrast-enhanced Doppler ultrasonography to determine the hepatic blood flow in OLT patients. In their reports, MALS patients who required further treatment and six patients with weak arterial flow without intervention underwent MAL division and the incidence of postoperative vascular complications was significantly reduced. In this study, we determined the hepatic blood flow based on the pulse in the hepatic artery and arterial blood flow rate measured using intraoperative Doppler ultrasonography after anastomosis. In MALS patients, postoperative Doppler ultrasound was used routinely to determine hepatic arterial blood flow.

Currently, there is no consensus on the treatment of MALS in patients who undergo liver transplantation. The various methods reported in the literature are as follows: (1) Endovascular interven-

tional therapy; (2) MLA division to release the extrinsic compression on the celiac axis; (3) Anastomosis of the graft's celiac artery to the recipient's aorta; and (4) Use of gastroduodenal branch-patch anastomosis without MAL division[21].

With the continuous advancements in endovascular interventional therapy, some OLT recipients with MAL have been treated with interventional therapy postoperatively to restore the hepatic blood flow [31,32]. However, the preoperative use of stenting remains controversial, as persistent external compression from the MAL carries a higher risk[21,33].

Recent studies have suggested that regular vascular reconstruction after surgical division of MAL in liver transplant recipients with MALS is safe and effective[13,34]. Czigany *et al*[21] reported a 7-year retrospective study of 34 MALS patients, in which 26 patients received MAL division and four patients required aorto-hepatic conduit construction. Twenty-six patients who underwent surgical division of MAL or alternative reconstruction had no postoperative complications. Three patients with MALS who did not receive any intervention for MALS developed severe vascular complications and one of them required re-transplantation. In their study, preoperative assessment of vascular aberrations and different surgical approaches were planned before the surgery which led to a relatively low HAT rate.

MAL division is a standard treatment for MALS. However, OLT recipients with MALS usually have gastroesophageal varices and extensive collateral vessels between the celiac trunk and superior mesenteric artery, which increases the risk of bleeding during MAL division. The most common collateral circulation is the superior mesenteric artery-pancreaticoduodenal artery-GDA-hepatic artery network. This collateral circulation helps in maintaining hepatic arterial flow in MALS patients after liver transplantation, even without MAL division. Lubrano *et al*[27] reported that one out of 10 patients with MALS underwent MAL division while six patients underwent standard hepatic arterial reconstruction without the division of MAL. None of the 10 patients experienced postoperative vascular complications. In this study, one patient with MALS received standard hepatic arterial reconstruction with GDA ligation. The patient developed HAT during the postoperative period and required a salvage liver transplantation with MAL division. The remaining seven MALS patients were diagnosed with MALS before surgery and had adequate hepatic blood flow preoperatively, determined with Doppler ultrasound. Thus MAL was not divided irrespective of the type. Five patients were found to have abundant collateral circulation between the superior mesenteric artery and the celiac trunk before surgery; therefore, the GDA was preserved intraoperatively. The other two patients had no obvious collateral circulation. Consequently, the GDA was clamped and hepatic arterial blood flow was assessed. Since there was adequate hepatic blood flow despite GDA clamping, GDA ligation with standard hepatic arterial anastomosis was performed. All seven patients had good postoperative hepatic blood flow without HAT. Hence, we believe that in OLT recipients with MALS, preservation of the collateral circulation without MAL division is a safe and feasible procedure. The procedure has fewer complications and makes surgery easier. In addition to collateral preservation, the splenic artery can be ligated if necessary. Additionally, we used the left and right hepatic artery bifurcations to enlarge the anastomosis. If the hepatic artery blood flow is still unsatisfactory with the above measures, the division of MAL may be considered. Hepatic artery-abdominal aorta bypass is the most difficult surgical procedure and can be used as a last resort.

This study has certain limitations. First, this study was a single-center retrospective study. Second, the number of patients was limited. Hence, future studies with larger sample sizes are needed to verify the findings of this study.

CONCLUSION

Preoperative diagnosis of MALS in OLT recipients is important to prevent HAT. Preservation of collateral circulation with or without splenic artery ligation is an easier surgical technique with shorter operation time and a lower risk of intraoperative complications compared to MAL division and celiac trunk-aorta bypass to ensure adequate hepatic arterial blood flow.

ARTICLE HIGHLIGHTS

Research background

In orthotopic liver transplantation (OLT) recipients, median arcuate ligament syndrome (MALS) is regarded as a risk factor for hepatic artery thrombosis (HAT), a devastating complication of OLT. To counteract the influence of MALS on transplantation, a variety of different surgical methods have been proposed, but clinical evidence is still lacking.

Research motivation

To increase the survival rate of MALS patients who receive OLT and decrease postoperative complications.

Research objectives
To evaluate the efficacy of surgical treatment for MALS to reduce complications in OLT patients in order to improve patient survival and decrease the incidence of postoperative complications.

Research methods
A total of 288 consecutive OLT patients at The First Hospital of Jilin University were retrospectively evaluated. Median arcuate ligament (MAL) surgical treatment and arterial anastomosis modification were recorded. Perioperative and long-term MALS prognoses were noted.

Research results
In this investigation, eight patients with MALS were enrolled. The first patient with MALS did not get any intervention during the main operation, and afterward developed HAT. Successful salvage liver transplantation with MAL division was accomplished. Gastroduodenal artery (GDA) preservation with splenic artery ligation was performed on three patients, GDA preservation alone was performed on two patients, and no intervention were performed on two patients. After surgery, no patient got HAT and healing was acceptable.

Research conclusions
The preservation of collateral circulation between the superior mesenteric artery and celiac trunk *via* the GDA, with or without ligation of the splenic artery, provides a safe and practicable alternative to MAL division.

Research perspectives
To provide surgeons with effective and feasible surgical options when they need to perform OLT in MALS patients.

FOOTNOTES

Author contributions: Li SX and Fan YH contributed equally to this work; Li SX wrote the original draft of the manuscript; Fan YH was responsible for the revision and editing of the manuscript; Tian GY was responsible for data curation and software; LV GY was responsible for supervision and methodology; All authors issued final approval for the version submitted.

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Country/Territory of origin: China

ORCID number: Shu-Xuan Li 0000-0001-6809-4283; Ye-Hui Fan 0000-0002-3041-7224; Guang-Yao Tian 0000-0002-1276-5911; Guo-Yue Lv 0000-0001-9115-5945.

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REFERENCES

1 **Starzl TE**, Fung JJ. Themes of liver transplantation. *Hepatology* 2010; **51**: 1869-1884 [PMID: 20235333 DOI: 10.1002/hep.23595]

2 **Oberkofler CE**, Reese T, Raptis DA, Kuemmerli C, de Rougemont O, De Oliveira ML, Schlegel A, Dutkowski P, Clavien PA, Petrowsky H. Hepatic artery occlusion in liver transplantation: What counts more, the type of reconstruction or the severity of the recipient's disease? *Liver Transpl* 2018; **24**: 790-802 [PMID: 29493895 DOI: 10.1002/lt.25044]

3 **Harrison J**, Harrison M, Doria C. Hepatic Artery Pseudoaneurysm Following Orthotopic Liver Transplantation: Increasing Clinical Suspicion for a Rare but Lethal Pathology. *Ann Transplant* 2017; **22**: 417-424 [PMID: 28684726 DOI: 10.12659/aot.903367]

4 **Feltracco P**, Barbieri S, Cillo U, Zanus G, Senzolo M, Ori C. Perioperative thrombotic complications in liver transplantation. *World J Gastroenterol* 2015; **21**: 8004-8013 [PMID: 26185371 DOI: 10.3748/wjg.v21.i26.8004]

5 **Giorgakis E**, Tedeschi M, Bonaccorsi-Riani E, Khorsandi SE, Menon K, Vilca-Melendez H, Jassem W, Srinivasan P, Prachalias A, Heaton N. The Effect of Recipient Body Mass Index and Its Extremes on Survival and Graft Vascular and Biliary Complications After Liver Transplantation: A Single Center Retrospective Study. *Ann Transplant* 2017; **22**: 611-621 [PMID: 29026064 DOI: 10.12659/aot.903475]

6 **Puliti Reigada CH**, de Ataide EC, de Almeida Prado Mattosinho T, Boin IFSF. Hepatic Artery Thrombosis After Liver Transplantation: Five-Year Experience at the State University of Campinas. *Transplant Proc* 2017; **49**: 867-870 [PMID: 28457413 DOI: 10.1016/j.transproceed.2017.01.056]

7 **Gilbo N**, Van Praet L, Jochmans I, Sainz-Barriga M, Verslype C, Maleux G, Laleman W, van der Merwe S, Cassiman D, Nevens F, Monbaliu D, Pirenne J. Pre-operative trans-catheter arterial chemo-embolization increases hepatic artery thrombosis after liver transplantation - a retrospective study. *Transpl Int* 2018; **31**: 71-81 [PMID: 28869805 DOI: 10.1111/tri.13046]

8 **Lainas P**, Fuks D, Gaujoux S, Machroub Z, Fregeville A, Perniceni T, Mal F, Dousset B, Gayet B. Preoperative imaging and prediction of oesophageal conduit necrosis after oesophagectomy for cancer. *Br J Surg* 2017; **104**: 1346-1354 [PMID: 28493483 DOI: 10.1002/bjs.10558]

9 **Lipshutz B**. A composite study of the coeliac axis artery. *Ann Surg* 1917; **65**: 159-169 [PMID: 17863663 DOI: 10.1097/00000658-191702000-00006]

10 **Harjola PT**. A rare obstruction of the coeliac artery. Report of a case. *Ann Chir Gynaecol Fenn* 1963; **52**: 547-550 [PMID: 14083857]

11 **Dunbar JD**, Molnar W, Beman FF, Marable SA. Compression of the celiac trunk and abdominal angina. *Am J Roentgenol Radium Ther Nucl Med* 1965; **95**: 731-744 [PMID: 5844938 DOI: 10.2214/ajr.95.3.731]

12 **Jiang ZJ**, Liang TB, Feng XN, Wang WL, Shen Y, Zhang M, Wu J, Xu X, Zheng SS. Arcuate ligament syndrome inducing hepatic artery thrombosis after liver transplantation. *Hepatobiliary Pancreat Dis Int* 2008; **7**: 433-436 [PMID: 18693183]

13 **Vilatobá M**, Zamora-Valdés D, Guerrero-Hernández M, Romero-Talamás H, Leal-Villalpando RP, Mercado MA. Arcuate ligament compression as a cause of early-onset thrombosis of the hepatic artery after liver transplantation. *Ann Hepatol* 2011; **10**: 88-92 [PMID: 21301017]

14 **Sugae T**, Fujii T, Kodera Y, Kanzaki A, Yamamura K, Yamada S, Sugimoto H, Nomoto S, Takeda S, Nakao A. Classification of the celiac axis stenosis owing to median arcuate ligament compression, based on severity of the stenosis with subsequent proposals for management during pancreatoduodenectomy. *Surgery* 2012; **151**: 543-549 [PMID: 22001637 DOI: 10.1016/j.surg.2011.08.012]

15 **Horton KM**, Talamini MA, Fishman EK. Median arcuate ligament syndrome: evaluation with CT angiography. *Radiographics* 2005; **25**: 1177-1182 [PMID: 16160104 DOI: 10.1148/rg.255055001]

16 **Choi EK**, Lu DS, Park SH, Hong JC, Raman SS, Ragavendra N. Doppler US for suspicion of hepatic arterial ischemia in orthotopically transplanted livers: role of central versus intrahepatic waveform analysis. *Radiology* 2013; **267**: 276-284 [PMID: 23297323 DOI: 10.1148/radiol.12120557]

17 **Pinto S**, Reddy SN, Horrow MM, Ortiz J. Splenic Artery Syndrome after orthotopic liver transplantation: a review. *Int J Surg* 2014; **12**: 1228-1234 [PMID: 25311773 DOI: 10.1016/j.ijsu.2014.09.012]

18 **Agnes S**, Avolio AW, Magalini SC, Frongillo F, Castagneto M. Celiac axis compression syndrome in liver transplantation. *Transplant Proc* 2001; **33**: 1438-1439 [PMID: 11267363 DOI: 10.1016/s0041-1345(00)02544-6]

19 **Sun X**, Fan Z, Qiu W, Chen Y, Jiang C, Lv G. Median arcuate ligament syndrome and arterial anastomotic bleeding inducing hepatic artery thrombosis after liver transplantation: A case report. *Medicine (Baltimore)* 2018; **97**: e10947 [PMID: 29923979 DOI: 10.1097/MD.0000000000010947]

20 **Kazmi SSH**, Safi N, Berge ST, Kazmi M, Sundhagen JO, Hisdal J. Laparoscopic Surgery for Median Arcuate Ligament Syndrome (MALS): A Prospective Cohort of 52 Patients. *Vasc Health Risk Manag* 2022; **18**: 139-151 [PMID: 35356549 DOI: 10.2147/VHRM.S350841]

21 **Czigany Z**, Boecker J, Morales Santana DA, Bednarsch J, Meister FA, Amygdalos I, Isfort P, Liebl M, Neumann UP, Lurje G. Median Arcuate Ligament Compression in Orthotopic Liver Transplantation: Results from a Single-Center Analysis and a European Survey Study. *J Clin Med* 2019; **8** [PMID: 31018577 DOI: 10.3390/jcm8040550]

22 **Fujiki M**, Hashimoto K, Palaios E, Quintini C, Aucejo FN, Uso TD, Eghtesad B, Miller CM. Probability, management, and long-term outcomes of biliary complications after hepatic artery thrombosis in liver transplant recipients. *Surgery* 2017; **162**: 1101-1111 [PMID: 28859949 DOI: 10.1016/j.surg.2017.07.012]

23 **Silva MA**, Jambulingam PS, Gunson BK, Mayer D, Buckels JA, Mirza DF, Bramhall SR. Hepatic artery thrombosis following orthotopic liver transplantation: a 10-year experience from a single centre in the United Kingdom. *Liver Transpl* 2006; **12**: 146-151 [PMID: 16382467 DOI: 10.1002/Lt.20566]

24 **Cassar N**, Gregory S, Menon K. New variation of median arcuate ligament compression causing hepatic arterial hypoperfusion during liver transplantation. *Hepatobiliary Pancreat Dis Int* 2020; **19**: 394-395 [PMID: 31812365 DOI: 10.1016/j.hbpd.2019.11.001]

25 **Warner P**, Fusai G, Glantzounis GK, Sabin CA, Rolando N, Patch D, Sharma D, Davidson BR, Rolles K, Burroughs AK.

Risk factors associated with early hepatic artery thrombosis after orthotopic liver transplantation - univariable and multivariable analysis. *Transpl Int* 2011; **24**: 401-408 [PMID: 21210866 DOI: 10.1111/j.1432-2277.2010.01211.x]

26 **Jurim O**, Shaked A, Kiai K, Millis JM, Colquhoun SD, Busuttil RW. Celiac compression syndrome and liver transplantation. *Ann Surg* 1993; **218**: 10-12 [PMID: 8328823 DOI: 10.1097/00000658-199307000-00003]

27 **Lubrano J**, Scatton O, Randone B, Molinier N, Massault PP, Legmann P, Soubrane O, Dousset B. Median arcuate ligament in orthotopic liver transplantation: relevance to arterial reconstruction. *Transplant Proc* 2008; **40**: 3532-3535 [PMID: 19100431 DOI: 10.1016/j.transproceed.2008.07.133]

28 **Vandermeulen M**, Moïse M, Meurisse N, Honoré P, Meurisse M, Meunier P, Detry O. Image in transplantation surgery: median arcuate ligament in liver transplantation. *Acta Chir Belg* 2020; **120**: 217-219 [PMID: 31696795 DOI: 10.1080/00015458.2019.1689649]

29 **Gruber H**, Loizides A, Peer S, Gruber I. Ultrasound of the median arcuate ligament syndrome: a new approach to diagnosis. *Med Ultrason* 2012; **14**: 5-9 [PMID: 22396932]

30 **Golse N**, Santoni S, Karam V, Ciacio O, Pittau G, Allard MA, Cherqui D, Sa Cunha A, Adam R, Castaing D, Vibert E. Is Routine Intraoperative Contrast-Enhanced Ultrasonography Useful During Whole Liver Transplantation? *World J Surg* 2018; **42**: 1523-1535 [PMID: 29038827 DOI: 10.1007/s00268-017-4295-x]

31 **Yilmaz S**, Ceken K, Gürkan A, Erdoğan O, Demirbaş A, Kabaalioğlu A, Sindel T, Lüleci E. Endovascular treatment of a recipient celiac trunk stenosis after orthotopic liver transplantation. *J Endovasc Ther* 2003; **10**: 376-380 [PMID: 12877627 DOI: 10.1177/152660280301000234]

32 **Sharafuddin MJ**, Olson CH, Sun S, Kresowik TF, Corson JD. Endovascular treatment of celiac and mesenteric arteries stenoses: applications and results. *J Vasc Surg* 2003; **38**: 692-698 [PMID: 14560214 DOI: 10.1016/s0741-5214(03)01030-9]

33 **Björck M**, Koelemay M, Acosta S, Bastos Goncalves F, Kölbel T, Kolkman JJ, Lees T, Lefevre JH, Menyhei G, Oderich G; Esvs Guidelines Committee, Kolh P, de Borst GJ, Chakfe N, Debus S, Hinchliffe R, Kakkos S, Koncar I, Sanddal Lindholt J, Vega de Ceniga M, Vermassen F, Verzini F, Document Reviewers, Geelkerken B, Gloviczki P, Huber T, Naylor R. Editor's Choice - Management of the Diseases of Mesenteric Arteries and Veins: Clinical Practice Guidelines of the European Society of Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg* 2017; **53**: 460-510 [PMID: 28359440 DOI: 10.1016/j.ejvs.2017.01.010]

34 **Ali M**, Patel J. Dunbar syndrome following liver transplantation. *BMJ Case Rep* 2016; **2016** [PMID: 26857586 DOI: 10.1136/bcr-2015-214168]

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ORIGINAL ARTICLE

Retrospective Study

Study of preoperative diagnostic modalities in Chinese patients with superficial esophageal squamous cell carcinoma

Ya-Ting Zeng, Yu-Ying Sun, Wen-Cheng Tan, Shu-Ai Luo, Bi-Hui Zou, Guang-Yu Luo, Chun-Yu Huang

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Ya-Ting Zeng, Yu-Ying Sun, Wen-Cheng Tan, Shu-Ai Luo, Bi-Hui Zou, Guang-Yu Luo, Chun-Yu Huang, State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, Guangzhou 510060, Guangdong Province, China

Ya-Ting Zeng, Yu-Ying Sun, Wen-Cheng Tan, Shu-Ai Luo, Bi-Hui Zou, Guang-Yu Luo, Chun-Yu Huang, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou 510060, Guangdong Province, China

Ya-Ting Zeng, Wen-Cheng Tan, Shu-Ai Luo, Bi-Hui Zou, Guang-Yu Luo, Chun-Yu Huang, Department of Endoscopy, Sun Yat-sen University Cancer Center, Guangzhou 510060, Guangdong Province, China

Yu-Ying Sun, Cancer Prevention Center, Sun Yat-sen University Cancer Center, Guangzhou 510060, Guangdong Province, China

Corresponding author: Chun-Yu Huang, MD, PhD, Professor, State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, No. 651 Dongfeng East Road, Guangzhou 510060, Guangdong Province, China. huangchy@sysucc.org.cn

Abstract

BACKGROUND

Endoscopic ultrasonography (EUS) and magnifying endoscopy (ME) reliably determine indications for endoscopic resection in patients with superficial esophageal squamous cell carcinoma (SESCC). ME is widely accepted for predicting the invasion depth of superficial esophageal cancer with satisfying accuracy. However, the addition of EUS is controversial.

AIM

To evaluate the diagnostic efficiency of ME *vs* EUS for invasion depth prediction and investigate the influencing factors in patients with SESCC to determine the best diagnostic model in China.

METHODS

We retrospectively analyzed patients with suspected SESCC who completed both ME and EUS and then underwent endoscopic or surgical resection at Sun Yat-Sen University Cancer Center between January 2018 and December 2021. We evaluated and compared the diagnostic efficiency of EUS and ME according to histological results, and investigated the influencing factors.

RESULTS

We included 152 lesions from 144 patients in this study. The diagnostic accuracies of ME and EUS in differentiating invasion depth were not significantly different (73.0% and 66.4%, $P = 0.24$); both demonstrated moderate consistency with the pathological results (ME: kappa = 0.58, 95% confidence interval [CI]: 0.48-0.68, $P < 0.01$; EUS: kappa = 0.46, 95%CI: 0.34-0.57, $P < 0.01$). ME was significantly more accurate in the diagnosis of high-grade intraepithelial (HGIN) or carcinoma *in situ* (odds ratio [OR] = 3.62, 95%CI: 1.43-9.16, $P = 0.007$) subgroups. Using a miniature probe rather than conventional EUS can improve the accuracy of lesion depth determination (82.3% *vs* 49.3%, $P < 0.01$). Less than a quarter of circumferential occupation and application of a miniature probe were independent risk factors for the accuracy of tumor invasion depth as assessed by EUS (< 1/4 circumferential occupation: OR = 3.07, 95%CI: 1.04-9.10; application of a miniature probe: OR = 5.28, 95%CI: 2.41-11.59, $P < 0.01$). Of the 41 lesions (41/152, 27.0%) that were misdiagnosed by ME, 24 were corrected by EUS (24/41, 58.5%).

CONCLUSION

Preoperative diagnosis of SESCC should be conducted endoscopically using white light and magnification. In China, EUS can be added after obtaining patient consent. Use of a high-frequency miniature probe or miniature probe combined with conventional EUS is preferable.

Key Words: Superficial esophageal squamous cell carcinoma; Endoscopic ultrasound; Magnifying endoscopy; Endoscopic resection; Japan Esophageal Society classification

Core Tip: Endoscopic ultrasonography (EUS) and magnifying endoscopy (ME) reliably determine indications for endoscopic resection in patients with superficial esophageal squamous cell carcinoma (SESCC). ME is a widely accepted method for predicting the invasion depth. However, the addition of EUS is controversial. We retrospectively analyzed Chinese patients with suspected SESCC who completed both ME and EUS and underwent resection at our facility. We found that EUS and ME demonstrated comparable accuracy and EUS can compensate for deficiencies inherent to ME in some cases. The miniature probe was best suited for detecting early-stage lesions. These findings may further improve diagnostic accuracy.

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INTRODUCTION

Esophageal cancer is the leading malignancy in China, with national morbidity and mortality rankings of third and fourth, respectively, among all malignancies[1]. In China, esophageal squamous cell carcinoma accounts for 90% of esophageal carcinomas[2].

Due to its mild and atypical clinical manifestations, most patients with esophageal carcinoma are diagnosed with advanced-stage disease. This results in a poor prognosis, reduced treatment effectiveness, and low quality of life. This situation underscores the need for better methods for detecting and treating esophageal squamous cell carcinoma during the early disease stages.

Superficial esophageal squamous cell carcinoma (SESCC), considered early-stage cancer, is defined as a tumor confined within the mucosa and submucosa layers of the esophagus, regardless of lymph node metastasis[3]. There are several treatment options for SESCC including traditional surgery or endoscopic resection (ER). Compared to surgery, ER can be curative and less invasive, is generally well tolerated, and is associated with fewer postoperative complications[4]. Identifying patients with SESCC who are ER candidates is, therefore, critical. ER is indicated based on the tumor infiltration depth because the risk of lymph node metastasis increases with the depth of invasion. Lesions confined to the epithelium/lamina propria mucosa (EP/LPM) are rarely accompanied by lymph node metastasis (0-3.3%)[5-7]; in these cases, ER may be curative[8]. Despite their association with an elevated risk of lymph node metastasis, lesions confined to the muscularis mucosa/superficial submucosa (MM/SM1) are also suitable for ER, potentially followed by additional treatments[4,8]. Lesions deeper than the SM1

are contraindicated for ER because of the high rate of lymph node and distant metastases (> 20%)[5-7, 9]; surgery is recommended for these lesions[8].

Accurate determination of tumor infiltration depth before resection is important. To estimate the lesion invasion depth, conventional endoscopy combined with magnification (ME) and endoscopic ultrasound (EUS) are considered the best approaches[10-12]. Currently, ME is more widely accepted than EUS for predicting the invasion depth of SESCC with satisfying accuracy, but the addition of EUS is controversial[13-15].

The endoscopists, access environment, and medical policies differ markedly between China and foreign countries. Chinese physicians require a preoperative diagnosis model that maximizes patient benefit. We, therefore, sought to evaluate the diagnostic efficiency of ME *vs* EUS for invasion depth prediction, to determine the most suitable preoperative diagnostic modality for Chinese patients with SESCC.

MATERIALS AND METHODS

Patients and lesions

We retrospectively analyzed patients with suspected SESCC who underwent examination, including both ME and EUS, and then underwent surgery or ER at Sun Yat-Sen University Cancer Center between January 2018 and December 2021. We included patients with suspected SESCC following white light imaging (WLI) screening or other modalities. All patients were pathologically diagnosed with atypical esophageal hyperplasia or SESCC. We excluded patients who received chemotherapy or radiotherapy as an initial treatment after diagnosis and those who were suspected of having lymph node or organ metastases by imaging. The institutional review board of Sun Yat-Sen University Cancer Center approved this study.

Resected complete specimens obtained during surgery or ER were processed and diagnosed by our Center's pathology department. According to the Paris Endoscopic Classification of Superficial Neoplastic Lesions[16] and the 11th Edition of the Japanese Classification of Esophageal Cancers[3], in the esophageal mucosa (T1a), lesion involvement included the epithelium (EP) (including high-grade intraepithelial neoplasia (HGIN) and carcinoma *in situ)*, the lamina propria mucosa (LPM), and the muscularis mucosa (MM). Submucosal (SM, T1b) lesions were divided into SM1, SM2, and SM3. These lesion layers featured equivalent thickness and were ordered from shallower (SM1) to deeper (SM3). Since the submucosal thickness remained unknown in endoscopically resected specimens, lesions involving the submucosa to 200 μm or less from the MM were classified as T1b-SM1. Those deeper than 200 μm were considered T1b-SM2/SM3. Thus, in our study, lesion invasion depths were categorized pathologically as pEP/LPM, pMM/SM1, and pSM2/SM3.

Examination procedure

The examination procedure was identical to that used in our daily practice. All lesions included were initially examined by conventional endoscopy with WLI. Suspicious lesions were further assessed using magnifying endoscopy with narrow-band or blue laser imaging (ME-NBI/BLI) using a GIF-H260Z (Olympus Corporation, Tokyo, Japan) or EG-L590ZW gastroscope (Fujifilm Corporation, Tokyo, Japan). EUS followed, utilizing 7.5MHz, 10MHz, or 12MHz radical scanning probes (SU 9000, EG-530UR2, Fujifilm; EU-ME2, Olympus) or a 20-MHz miniature probe (UM-DP20-25R, Olympus). Six certified and experienced endoscopists at our center performed all these examinations. The involved endoscopists were divided into junior and senior groups according to their seniority. The senior endoscopist was defined as having a title of Associate Professor or higher with at least 12 years of experience in endoscopy. The junior endoscopist is defined as having a title of Attending Physician or above, with more than 6 years of experience in endoscopy. Residents and trainees did not participate in this study. Each patient's ME-NBI/BLI and EUS were conducted on the same day. The endoscopic findings were later extracted from the electronic medical record.

ME, combined with image-enhanced endoscopy, NBI, or BLI, allows visualization of micro-vessels on the esophageal surface. Intra-papillary capillary loops (IPCL) are basic microvasculature units on the squamous mucosal surface. IPCL forms are used to characterize lesions and predict invasion depth for SESCC. We applied the Japan Esophageal Society (JES) classification scheme, which integrates previous Inoue and Arima classification schemes, presently in widespread clinical use[7,17]. Here, micro-vessels observed by ME were divided into type A and type B. Type A vessels were non-cancerous lesions; type B vessels were abnormal micro-vessels characterized by dilatation, meandering, caliber change, and uneven morphology. These abnormal features were suggestive of cancerous lesions and include three subtypes: B1 (vessels with loop-like formations), B2 (without loops but appearing stretched and markedly elongated), and B3 (highly dilated vessels with calibers more than three times those of B2 vessels). To predict invasion depth, type B1, B2, and B3 vessels corresponded with depths of EP/LPM, MM/SM1, and SM2/SM3, respectively. The subclassification of type B vessels was based upon the indication for ER: Lesions with B1 were absolutely indicated, B2 vessels were relatively indicated, and B3 vessels were contraindicated.

During EUS, a cross-sectional image of the esophageal wall structure was obtained and divided into five layers using a 7.5 MHz radical conventional probe[18]. When using a high-frequency (≥ 20 mHz) miniature probe, the canal wall was depicted as a nine-layer structure if the distance between the probe and mucosa was appropriate. Specifically, the mucosa and submucosa were sonographically divided into an additional four layers. The first and second layers corresponded to the EP/LPM, the third layer to the MM, and the fourth layer to the SM. Specifically, lesions confined to the first and second layers were categorized as EP/LPM; lesions involving the third layer were MM/SM1; lesions that invaded the fourth layer were SM2/SM3. Esophageal cancer usually appears as a hypoechoic lesion that disrupts the normal structure of the esophageal wall, forming images with defects, irregularities, and interruptions.

Statistical analysis

The diagnostic efficiencies of EUS and ME-NBI/BLI for determining exact invasion depth were evaluated by sensitivity, specificity, and accuracy. A paired χ^2 test (McNamar's) was used to assess their differences. P values < 0.05 were considered statistically significant. We applied Cohen's kappa to evaluate the consistency of EUS and ME-NBI/BLI with the final pathological result for determining the depth of tumor infiltration[19,20]. The accuracy of ME-NBI/BLI or EUS concerning the clinicopathologic features was assessed using the χ^2 test or Fisher's exact test. Multivariate logistic regression analysis was performed to identify variables that significantly influenced the performance of ME-NBI/BLI or EUS. SPSS version 25 for Windows software (IBM Inc, Armonk, United States) was used for statistical analyses.

RESULTS

Clinicopathological features of patients and lesions

Of the 146 patients who met our enrollment criterion, two were excluded from the analyses. One was because of hemorrhage during ER, which was later converted to surgical resection; this resulted in an incomplete pathological specimen. Another patient was excluded because we could not obtain a clear view during ME-NBI, preventing micro-vessel characterization.

Ultimately 152 lesions in 144 patients were included in this study. Of these, 108 were male (75%), and 36 were female (25%), with a mean age of 61.3 ± 7.5 years. Most tumors were located in the middle thoracic esophagus (82/152, 53.9%), and the main macroscopic type was flat (90/152, 59.2%). The mean tumor size was 22.9 mm (range 5-60 mm). The average time interval between examinations and resection treatment was 18 d (1-82 d). As for treatment selection, 71 lesions were treated by ER, and 81 were treated by surgery. Pathologically, 78 lesions (51.3%) were diagnosed as pEP/LPM lesions, 28 (22.4%) as pMM/SM1, and 46 (30.3%) as pT1b-SM2/SM3. Detailed clinicopathological features of the patients and lesions are shown in Table 1.

Diagnostic efficiency of ME-NBI/BLI and EUS in estimating invasion depth

The relationships between ME-NBI/BLI or EUS diagnosis and the final pathological result after treatment are listed in Table 2 and Figures 1-3. The overall accuracy of ME-NBI/BLI, based upon the JES classification for determining invasion depth, was 73.0% (111/152), moderately consistent with the pathological results (kappa = 0.58, 95% confidence interval [CI]: 0.48-0.68, P < 0.01). The overall accuracy of EUS for determining invasion depth was 66.4% (101/152), also moderately consistent with the pathological results (kappa = 0.46, CI: 0.34-0.57, P < 0.01).

We also compared the diagnostic efficiency of ME-NBI/BLI and EUS for determining the invasion layer according to the indication for ER (Table 3). There was no significant difference in overall accuracy between ME-NBI/BLI and EUS (73.0% *vs* 66.4%, P = 0.24). For pEP/LPM lesions, ME-NBI/BLI had a higher sensitivity, specificity, and accuracy than EUS (sensitivity 84.6% *vs* 73.1%; specificity 91.9% *vs* 81.1%; accuracy 88.2% *vs* 77.0%), with a significant difference in accuracy (P < 0.01). For pMM/SM1 lesions, ME-NBI/BLI was more sensitive, and EUS had a better specificity (sensitivity 92.9% *vs* 35.7%; specificity 73.4% *vs* 91.1%; P < 0.01 for both); the two techniques demonstrated equivalent accuracy (77.0% *vs* 80.9%, P = 0.51). For pSM2/SM3, ME-NBI/BLI was more specific and EUS was more sensitive (sensitivity 41.3% *vs* 73.9%, P < 0.01; specificity 98.1% *vs* 75.4%, P < 0.01); the techniques had equivalent accuracy (80.9% *vs* 75.0%, P = 0.22). Lastly, of the 41 lesions (41/152, 27.0%) misdiagnosed by ME-NBI/BLI, 24 were corrected by EUS (24/41, 58.5%).

Clinicopathological factors that influence diagnostic accuracy

For ME-NBI/BLI, diagnostic accuracy did not vary significantly according to the tumor location, macroscopic type, circumferential occupation, tumor size, or endoscopist grade (Table 4). The accuracy of ME-NBI/BLI increased significantly for HGIN or carcinoma *in situ* subgroups (P = 0.03). During the multivariate analysis, HGIN and carcinoma *in situ* were independent risk factors for the accuracy of tumor invasion depth, as assessed by ME-NBI/BLI (odds ratio [OR] = 3.62, 95%CI: 1.43-9.16, P = 0.007).

Table 1 Clinicopathological features of patients and lesions

Variable	152 lesions in 144 patients
Sex, *n* (%)	
Male	108 (75.0)
Female	36 (25.0)
Age, average ± SD, yr	61.3 ± 7.5
Location, *n* (%)	
Cervical esophagus	2 (1.3)
Upper thoracic esophagus	13 (8.6)
Middle thoracic esophagus	82 (53.9)
Lower thoracic esophagus	55 (36.2)
Macroscopic type, *n* (%)	
Elevated	60 (39.5)
Flat	90 (59.2)
Depressed	2 (1.3)
Mean tumor size, range, mm	22.9 (5-60)
Circumferential occupation, *n* (%)	
< 1/4	38 (25)
1/4-1/2	51 (33.6)
1/2-3/4	37 (24.3)
≥ 3/4	26 (17.1)
Time interval between examination and resection, d, range	18 (1-82)
Treatment, *n* (%)	
Endoscopic resection	71 (46.7)
Surgery	81 (53.3)
Differentiation degree, *n* (%)	
HGIN or carcinoma *in situ*	60 (39.5)
Poor	13 (8.6)
Moderate	72 (47.4)
Good	7 (4.6)
Depth according to pathological diagnosis, *n* (%)	
EP/LPM	78 (51.3)
MM/SM1	28 (22.4)
SM2/SM3	46 (30.3)

SD: Standard deviation; HGIN: High-grade intraepithelial neoplasia; EP: Epithelium; LPM: Lamina propria mucosa; MM: Muscularis mucosa; SM: Submucosa.

As for EUS, the overall diagnostic accuracy did not vary significantly according to the tumor location, macroscopic type, differentiation degree, and endoscopist grade (Table 4). Increased circumferential occupation and tumors larger than 3 cm were mostly associated with decreased accuracy (P = 0.06 and P = 0.05, respectively). Using a miniature probe instead of conventional EUS improved accuracy (82.3% *vs* 49.3%, P < 0.01). In the multivariate analysis, less than a quarter of circumferential occupation and application of a miniature probe were independent risk factors for the accuracy of tumor invasion depth, as assessed by EUS (< 1/4 circumferential occupation: OR = 3.07, 95%CI: 1.04-9.10; application of a miniature probe: OR = 5.28, 95%CI: 2.41-11.59, P < 0.01).

Table 2 Relationship between magnifying endoscopy or endoscopic ultrasound diagnosis and final pathological results

	Depth according to pathological results			
	EP/LPM (*n* = 78)	MM/SM1 (*n* = 28)	SM2/SM3 (*n* = 46)	Total
ME-NBI/BLI				
B1	66	1	5	72
B2	11	26	22	59
B3	1	1	19	21
EUS				
EP/LPM	57	4	10	71
MM/SM1	9	10	2	21
SM2/SM3	12	14	34	60

ME: Magnifying endoscopy; NBI: Narrow-band imaging; BLI: Blue laser imaging; EUS: Endoscopy ultrasonography; HGIN: High-grade intraepithelial neoplasia; EP: Epithelium; LPM: Lamina propria mucosa; MM: Muscularis mucosa; SM: Submucosa.

Table 3 Diagnostic efficiency of magnifying endoscope or endoscopic ultrasound in dividing specific invasion layer

	EP/LPM			MM/SM1			SM2/SM3		
	ME, %	EUS, %	*P* value	ME, %	EUS, %	*P* value	ME, %	EUS, %	*P* value
Sensitivity	84.60	73.10	0.08	92.90%	35.7	< 0.01	41.30	73.90	< 0.01
Specificity	91.90	81.10	0.06	73.40%	91.10	< 0.01	98.10	75.40	< 0.01
Accuracy	88.20	77.00	< 0.01	77.00%	80.90	0.51	80.90	75.00	0.22

ME: Magnifying endoscopy; EUS: Endoscopy ultrasonography; EP: Epithelium; LPM: Lamina propria mucosa; MM: Muscularis mucosa; SM: Submucosa.

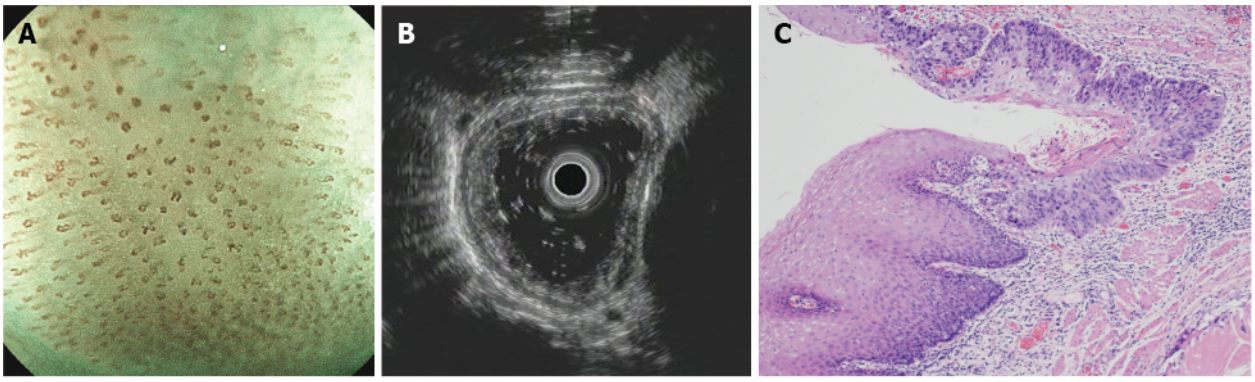

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Figure 1 A typical case of carcinoma *in situ*. A: ME-BLI image shows micro-vessels with a loop-like formation (type B1); B: Ultrasonography image shows hypoechoic thickening confined to the first two layers; C: Hematoxylin-eosin staining (× 40) of an endoscopic resection specimen shows that the squamous cell carcinoma is limited to the epithelium, without invasion.

DISCUSSION

In daily practice, SESCC invasion depth can be diagnosed by observing the micro-vessels using ME-NBI/BLI and is unaffected by biopsy, inflammation, *etc*. However, sometimes visualization is impeded. In contrast, EUS can image deeper lesions and collect vital information that differs from that obtainable by ME. The objective of this study was to evaluate the diagnostic efficiency of ME-NBI/BLI *vs* EUS for diagnosing invasion depth in patients with SESCC based on the indication for ER. We also investigated influencing factors to determine the best model for use during preoperative diagnosis in Chinese patients with SESCC.

Table 4 Diagnostic accuracy of magnifying endoscopy or endoscopic ultrasound according to clinicopathological features

Features	ME-NBI/BLI		EUS	
	Accurately assessed lesions (%)	*P* value	Accurately assessed lesions (%)	*P* value
Location of esophagus				
Cervical	2/2 (100)	0.69	1/2 (50.0)	0.17
Upper thoracic	11/13 (84.6)		9/13 (69.2)	
Middle thoracic	60/82 (73.2)		60/82 (73.2)	
Lower thoracic	38/55 (69.1)		31/55 (56.4)	
Macroscopic type				
Elevated	43/60 (71.1)	0.60	40/60 (66.7)	1.00
Flat	67/90 (74.4)		60/90 (66.7)	
Depressed	1/2 (50.0)		1/2 (50.0)	
Circumferential occupation				
< 1/4	26/38 (68.4)	0.38	31/38 (81.6)	0.06
1/4-1/2	35/51 (68.6)		34/51 (66.7)	
1/2-3/4	31/37 (83.3)		23/37 (62.2)	
≥ 3/4	19/26 (73.1)		13/26 (50.0)	
Tumor size				
≤ 3 cm	87/121 (71.4)	0.54	85/121 (70.2%)	0.05
> 3 cm	24/31 (77.4)		16/31 (51.6)	
Differentiation degree				
HGIN or carcinoma *in situ*	51/60 (85.0)	0.03	43/60 (71.7)	0.54
Good	5/7 (71.4)		4/7 (57.1)	
Moderate	48/72 (66.7)		47/72 (65.3)	
Poor	7/13 (53.8)		7/13 (53.8)	
Endoscopist grade				
Junior	33/41 (80.5)	0.21	23/41 (56.1)	0.10
Senior	78/111 (70.3)		78/111 (70.3)	
EUS probe				
Conventional EUS			36/73 (49.3)	< 0.01
Miniature probe			65/79 (82.3)	

ME: Magnifying endoscopy; NBI: Narrow-band imaging; BLI: Blue laser imaging; EUS: Endoscopy ultrasonography; HGIN: High-grade intraepithelial neoplasia; EP: Epithelium; LPM: Lamina propria mucosa; MM: Muscularis mucosa; SM: Submucosa.

We applied accuracy, sensitivity, and specificity to evaluate diagnostic efficiency. Of these parameters, accuracy is widely used because it combines sensitivity and specificity. We found no significant differences in the diagnostic accuracy of ME-NBI/BLI and EUS for determining invasion depth (73% *vs* 66.4%, $P = 0.24$), and both demonstrated moderate consistency with pathological findings (ME-NBI/BLI: kappa=0.58; EUS: kappa = 0.46). However, both had advantages and limitations for differentiating distinct invasion layers.

We grouped patients according to the indications for ER to optimize clinical decision-making for patients. ME-NBI/BLI presented better diagnostic efficiency than EUS in the prediction of pEP/LPM layer. In addition, tumors confined to EP—including HGIN and carcinoma *in situ*—were more accurately assessed by ME-NBI/BLI than other subgroups (OR = 3.62, 95%CI: 1.43-0.16, $P = 0.007$). Thus, ME-NBI/BLI performed better than EUS for distinguishing EP/LPM invasion; this finding was consistent with current clinical practice and previous research[7,21,22].

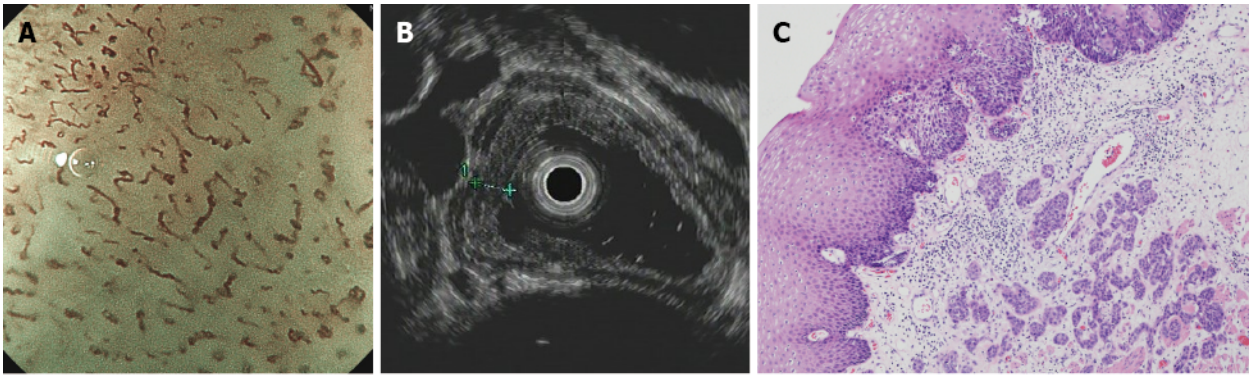

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Figure 2 A typical muscularis mucosal lesion. A: ME-BLI image shows type B2 vessels without loop-like formations but with a stretched and markedly elongated transformation; B: Ultrasonography image shows a hypoechoic lesion invading the third layer with continuous submucosa; C: Hematoxylin-eosin staining (× 40) of a surgical specimen shows a moderately differentiated squamous cell carcinoma invading the muscularis mucosa.

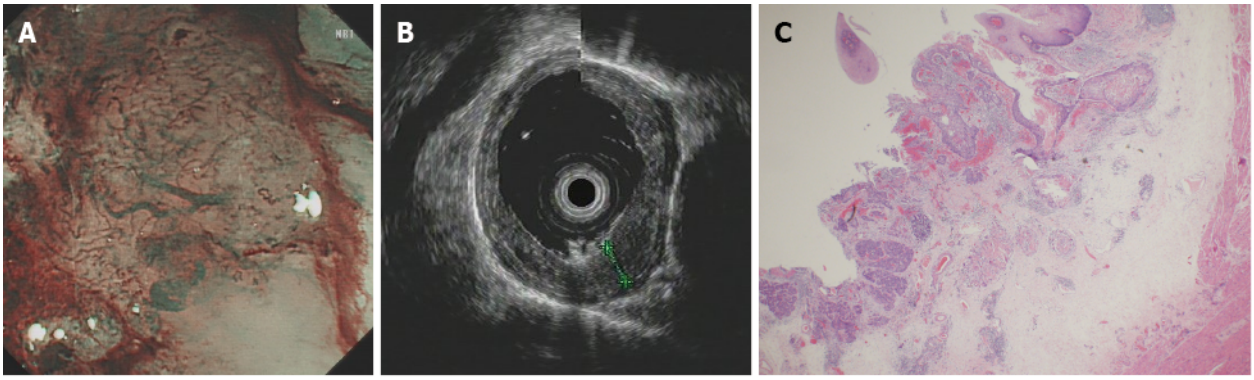

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Figure 3 A typical submucosal lesion. A: ME-NBI image shows micro-vessels dilated more than three times that of B2 vessels (type B3); B: Ultrasonography image shows a hypoechoic lesion invading the fourth layer; C: Hematoxylin-eosin staining (× 20) of a surgical specimen shows a moderately differentiated squamous cell carcinoma infiltrated to the middle third of the submucosa without muscularis propria involvement.

For pT1b-SM2/SM3 lesions, B3 vessels were highly specific for diagnosis (98.1%) but less sensitive (41.3%), consistent with previous reports. Type B3 vessels were negative for 43.1% of the pT1b-SM2/SM3[23]; however, according to our data, EUS can compensate for this deficiency with a significantly higher specificity than ME-NBI/BLI (EUS 73.9% *vs* NBI 41.3%, $P < 0.01$). Therefore, EUS can be a useful supplementary tool to determine if a lesion has invaded the submucosa. Combining ME-NBI/BLI and EUS enables the most comprehensive assessment of lesion infiltration depth.

Considering the lesser diagnostic accuracy for B2 and B3 vessels (77.0% and 80.9%, respectively), the criteria for B2 and B3 vessel characteristics required further refinement[24,25] to improve the accuracy of JES classification. However, this violated the original intention of the JES classification to simplify the items set by previous Inoue and Arima classifications[17], thus increasing the difficulty of memorization and impeding widespread use. Therefore, we tried to find a model of preoperative diagnosis. Surprisingly, we found that when patients were misdiagnosed by ME-NBI/BLI, EUS often determined the correct invasion depth (24/41, 58.5%). These findings may assist clinicians with treatment decision-making and maximize the benefit to the patient.

In our study, EUS was performed using either a miniature probe or conventional EUS. Some lesions were visualized using both probe types according to different detection purposes. Except for depth prediction, EUS can determine the presence of malignant regional lymph nodes with better sensitivity than CT and PET-CT[26], and can sample the suspected lymph nodes to gain pathological confirmation. We compared the accuracy of conventional EUS and the miniature probe for determining lesion infiltration depth. The miniature probe was significantly more accurate than conventional EUS (82.3% *vs* 49.3%, $P < 0.01$). This finding answers questions unanswered by previous data and is consistent with previous study findings[11,27,28]. Because of higher frequencies, the miniature probe can clearly visualize esophageal wall structures. However, as frequency increases, the detection range becomes shallower and more limited, potentially preventing comprehensive exploration of large lesions[29]. Therefore, the miniature probe seems more suitable for small, superficial, and early-stage lesions[27].

This conclusion was further confirmed by our findings. We observed that increased circumferential occupation (P = 0.06) and larger (P = 0.05) tumors were less accurately assessed using EUS. In our clinical practice, we mainly use miniature probes to determine the infiltration depth of early-stage lesions. Conventional EUS is typically used to detect the apparent advanced-stage lesions and determine the presence of lymph nodes or adjacent organ metastases.

Compared with foreign peers, most Chinese endoscopists in tertiary hospitals are proficient in ME-NBI/BLI and EUS. From our data, the diagnostic capacities of junior and senior endoscopists in our center were comparable, and the difference was not significant (ME-NBI/BLI, P = 0.21; EUS, P = 0.10). Additionally, in China, the cost of EUS examinations–including general gastroscopy–is around 150 dollars, much lower than that of developed countries, such as Europe, America, Japan, *etc.* Due to affordability, EUS does not post a substantial financial burden on Chinese patients.

Our findings should be considered within the context of specific limitations. First, all patients were initially examined using ME-NBI/BLI, then EUS. There may be an ordering effect, with ME-NBI/BLI affecting the prediction obtained using EUS. Future studies should alter the order of EUS and ME-NBI/BLI to control for a potential order effect. Second, this was a retrospective study of extracting patients' medical records at a single cancer center in China. As such, selection bias could not be denied. Future prospective multi-center nationwide double-blinded trials are needed to evaluate the clinical validity of EUS and ME-NBI/BLI in patients with SESCC.

CONCLUSION

We recommend that preoperative diagnosis of SESCC be conducted based on the finding of WLI and ME-NBI/BLI. EUS can be added after patient consent in China, preferably utilizing a high-frequency miniature probe or miniature probe combined with conventional radical EUS.

ARTICLE HIGHLIGHTS

Research background

Early-stage detection and treatment of esophageal carcinoma can typically optimize prognosis. Compared with traditional surgery, endoscopic resection is a less invasive and potentially curative treatment for early-stage esophageal cancer. Identification of patients that are candidates for endoscopic resection is crucial. Endoscopic ultrasonography (EUS) and magnifying endoscopy (ME) reliably determine indications for endoscopic resection in patients with superficial esophageal squamous cell carcinoma (SESCC). ME is a widely accepted method for predicting the invasion depth of superficial esophageal cancer with satisfying accuracy. However, the addition of EUS is controversial.

Research motivation

To evaluate the diagnostic efficiency of ME *vs* EUS for invasion depth prediction, and investigate the influencing factors.

Research objectives

To determine the most suitable preoperative diagnostic modality for Chinese patients with SESCC.

Research methods

We retrospectively analyzed patients with suspected SESCC who completed both ME and EUS and then underwent endoscopic or surgical resection at Sun Yat-Sen University Cancer Center between January 2018 and December 2021. We evaluated and compared the diagnostic efficiency of EUS and ME according to histological results, and investigated the influencing factors.

Research results

EUS and ME demonstrated comparable accuracy for determining the depth of invasion of early-stage esophageal cancers, and EUS can compensate for deficiencies inherent to NBI in some cases. The miniature probe was best suited for detecting early-stage lesions

Research conclusions

Preoperative diagnosis of SESCC should be conducted endoscopically using white light and magnification. In China, EUS can be added after obtaining patient consent. Use of a high-frequency miniature probe or miniature probe combined with conventional EUS is preferable.

Research perspectives

Future studies are required to explore how to combine the findings of ME and EUS to make a compre-

hensive preoperative evaluation, instead of solely depending on the experience of endoscopists.

FOOTNOTES

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ORCID number: Ya-Ting Zeng 0000-0002-2654-5979; Yu-Ying Sun 0000-0002-5789-256X; Wen-Cheng Tan 0000-0002-6724-9949; Shu-Ai Luo 0000-0002-7473-8361; Bi-Hui Zou 0000-0003-1166-8850; Guang-Yu Luo 0000-0002-8335-1986; Chun-Yu Huang 0000-0002-1346-5961.

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REFERENCES

1 **Chen W**, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; **66**: 115-132 [PMID: 26808342 DOI: 10.3322/caac.21338]
2 **Abnet CC**, Arnold M, Wei WQ. Epidemiology of Esophageal Squamous Cell Carcinoma. *Gastroenterology* 2018; **154**: 360-373 [PMID: 28823862 DOI: 10.1053/j.gastro.2017.08.023]
3 **Japan Esophageal Society**. Japanese Classification of Esophageal Cancer, 11th Edition: part I. *Esophagus* 2017; **14**: 1-36 [PMID: 28111535 DOI: 10.1007/s10388-016-0551-7]
4 **Ishihara R**, Arima M, Iizuka T, Oyama T, Katada C, Kato M, Goda K, Goto O, Tanaka K, Yano T, Yoshinaga S, Muto M, Kawakubo H, Fujishiro M, Yoshida M, Fujimoto K, Tajiri H, Inoue H; Japan Gastroenterological Endoscopy Society Guidelines Committee of ESD/EMR for Esophageal Cancer. Endoscopic submucosal dissection/endoscopic mucosal resection guidelines for esophageal cancer. *Dig Endosc* 2020; **32**: 452-493 [PMID: 32072683 DOI: 10.1111/den.13654]
5 **Endo M**, Yoshino K, Kawano T, Nagai K, Inoue H. Clinicopathologic analysis of lymph node metastasis in surgically resected superficial cancer of the thoracic esophagus. *Dis Esophagus* 2000; **13**: 125-129 [PMID: 14601903 DOI: 10.1046/j.1442-2050.2000.00100.x]
6 **Araki K**, Ohno S, Egashira A, Saeki H, Kawaguchi H, Sugimachi K. Pathologic features of superficial esophageal squamous cell carcinoma with lymph node and distal metastasis. *Cancer* 2002; **94**: 570-575 [PMID: 11900242 DOI: 10.1002/cncr.10190]
7 **Oyama T**, Inoue H, Arima M, Momma K, Omori T, Ishihara R, Hirasawa D, Takeuchi M, Tomori A, Goda K. Prediction of the invasion depth of superficial squamous cell carcinoma based on microvessel morphology: magnifying endoscopic classification of the Japan Esophageal Society. *Esophagus* 2017; **14**: 105-112 [PMID: 28386209 DOI: 10.1007/s10388-016-0527-7]
8 **Kitagawa Y**, Uno T, Oyama T, Kato K, Kato H, Kawakubo H, Kawamura O, Kusano M, Kuwano H, Takeuchi H, Toh Y, Doki Y, Naomoto Y, Nemoto K, Booka E, Matsubara H, Miyazaki T, Muto M, Yanagisawa A, Yoshida M. Esophageal cancer practice guidelines 2017 edited by the Japan esophageal society: part 2. *Esophagus* 2019; **16**: 25-43 [PMID: 30171414 DOI: 10.1007/s10388-018-0642-8]
9 **Yamashina T**, Ishihara R, Nagai K, Matsuura N, Matsui F, Ito T, Fujii M, Yamamoto S, Hanaoka N, Takeuchi Y, Higashino K, Uedo N, Iishi H. Long-term outcome and metastatic risk after endoscopic resection of superficial esophageal squamous cell carcinoma. *Am J Gastroenterol* 2013; **108**: 544-551 [PMID: 23399555 DOI: 10.1038/ajg.2013.8]

10 **Kitagawa Y**, Uno T, Oyama T, Kato K, Kato H, Kawakubo H, Kawamura O, Kusano M, Kuwano H, Takeuchi H, Toh Y, Doki Y, Naomoto Y, Nemoto K, Booka E, Matsubara H, Miyazaki T, Muto M, Yanagisawa A, Yoshida M. Esophageal cancer practice guidelines 2017 edited by the Japan Esophageal Society: part 1. *Esophagus* 2019; **16**: 1-24 [PMID: 30171413 DOI: 10.1007/s10388-018-0641-9]

11 **Muto M**. Endoscopic diagnostic strategy of superficial esophageal squamous cell carcinoma. *Dig Endosc* 2013; **25** Suppl 1: 1-6 [PMID: 23406378 DOI: 10.1111/den.12025]

12 **Goda K**, Tajiri H, Ikegami M, Yoshida Y, Yoshimura N, Kato M, Sumiyama K, Imazu H, Matsuda K, Kaise M, Kato T, Omar S. Magnifying endoscopy with narrow band imaging for predicting the invasion depth of superficial esophageal squamous cell carcinoma. *Dis Esophagus* 2009; **22**: 453-460 [PMID: 19222533 DOI: 10.1111/j.1442-2050.2009.00942.x]

13 **Lee MW**, Kim GH, I H, Park DY, Baek DH, Lee BE, Song GA. Predicting the invasion depth of esophageal squamous cell carcinoma: comparison of endoscopic ultrasonography and magnifying endoscopy. *Scand J Gastroenterol* 2014; **49**: 853-861 [PMID: 24957951 DOI: 10.3109/00365521.2014.915052]

14 **Ishihara R**, Mizusawa J, Kushima R, Matsuura N, Yano T, Kataoka T, Fukuda H, Hanaoka N, Yoshio T, Abe S, Yamamoto Y, Nagata S, Ono H, Tamaoki M, Yoshida N, Takizawa K, Muto M. Assessment of the Diagnostic Performance of Endoscopic Ultrasonography After Conventional Endoscopy for the Evaluation of Esophageal Squamous Cell Carcinoma Invasion Depth. *JAMA Netw Open* 2021; **4**: e2125317 [PMID: 34524432 DOI: 10.1001/jamanetworkopen.2021.25317]

15 **Mizumoto T**, Hiyama T, Oka S, Yorita N, Kuroki K, Kurihara M, Yoshifuku Y, Sanomura Y, Urabe Y, Arihiro K, Tanaka S, Chayama K. Diagnosis of superficial esophageal squamous cell carcinoma invasion depth before endoscopic submucosal dissection. Diseases of the esophagus: official journal of the International Society for Diseases of the Esophagus. 2018 [DOI: 10.1093/dote/dox142]

16 The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003; S3 [DOI: 10.1016/S0016-5107(03)02159-X]

17 Summaries from the 65th Annual Meeting of the Japan Esophageal Society on September 26, 2011, Sendai. *Esophagus* 2011; 247 [DOI: 10.1007/s10388-011-0301-9]

18 **Akahoshi K**. Radial EUS of the Esophagus and Mediastinum. In: Akahoshi K, Bapaye A, editors. Practical Handbook of Endoscopic Ultrasonography. Tokyo: Springer Japan; 2012: 37-48 [DOI: 10.1007/978-4-431-54014-4_4]

19 **Tang W**, Hu J, Zhang H, Wu P, He H. Kappa coefficient: a popular measure of rater agreement. *Shanghai Jinshen Yixue* 2015; 62 [DOI: 10.5768/JAO201536.0304001]

20 **Landis JR**, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; **33**: 159-174 [PMID: 843571 DOI: 10.2307/2529310]

21 **Kim SJ**, Kim GH, Lee MW, Jeon HK, Baek DH, Lee BE, Song GA. New magnifying endoscopic classification for superficial esophageal squamous cell carcinoma. *World J Gastroenterol* 2017; **23**: 4416-4421 [PMID: 28706424 DOI: 10.3748/wjg.v23.i24.4416]

22 **Katada C**, Tanabe S, Wada T, Ishido K, Yano T, Furue Y, Kondo Y, Kawanishi N, Yamane S, Watanabe A, Azuma M, Koizumi W. Retrospective Assessment of the Diagnostic Accuracy of the Depth of Invasion by Narrow Band Imaging Magnifying Endoscopy in Patients with Superficial Esophageal Squamous Cell Carcinoma. *J Gastrointest Cancer* 2019; **50**: 292-297 [PMID: 29435906 DOI: 10.1007/s12029-018-0075-6]

23 **Ikeda H**, Inoue H, Sato H, Sato C, Onimaru M, Yamaguchi N, Hamatani S, Kudo S. Usefulness of a New Classification by the Japan Esophageal Society to Predict the Depth of Invasion of Esophageal Cancer: Type B3 Vessels. *Stomach Intestine* (Tokyo) 2014: 186 [DOI: 10.1016/j.gie.2014.02.165]

24 **Tanaka I**, Hirasawa D, Saito H, Matsuda T, Nakahori M, Maeda Y, Okuzono T, Suzuki K, Igarashi K, Nawata Y, Ito S, Unno S, Chonan A. The sub-classification of type B2 vessels according to the magnifying endoscopic classification of the Japan Esophageal Society. *Dig Endosc* 2020; **32**: 49-55 [PMID: 31177563 DOI: 10.1111/den.13459]

25 **Kimura H**, Yoshida M, Tanaka M, Kawata N, Kakushima N, Takizawa K, Kishida Y, Imai K, Ito S, Hotta K, Ishiwatari H, Matsubayashi H, Ono H. Preoperative indicators of misdiagnosis in invasion depth staging of esophageal cancer: Pitfalls of magnifying endoscopy with narrow-band imaging. *Dig Endosc* 2020; **32**: 56-64 [PMID: 31206847 DOI: 10.1111/den.13464]

26 **van Vliet EP**, Heijenbrok-Kal MH, Hunink MG, Kuipers EJ, Siersema PD. Staging investigations for oesophageal cancer: a meta-analysis. *Br J Cancer* 2008; **98**: 547-557 [PMID: 18212745 DOI: 10.1038/sj.bjc.6604200]

27 **Mennigen R**, Tuebergen D, Koehler G, Sauerland C, Senninger N, Bruewer M. Endoscopic ultrasound with conventional probe and miniprobe in preoperative staging of esophageal cancer. *J Gastrointest Surg* 2008; **12**: 256-262 [PMID: 17823841 DOI: 10.1007/s11605-007-0300-2]

28 **Menzel J**, Hoepffner N, Nottberg H, Schulz C, Senninger N, Domschke W. Preoperative staging of esophageal carcinoma: miniprobe sonography versus conventional endoscopic ultrasound in a prospective histopathologically verified study. *Endoscopy* 1999; **31**: 291-297 [PMID: 10376454 DOI: 10.1055/s-1999-12]

29 **Vazquez-Sequeiros E**, Wiersema MJ. High-frequency US catheter-based staging of early esophageal tumors. *Gastrointest Endosc* 2002; **55**: 95-99 [PMID: 11756927 DOI: 10.1067/mge.2002.120099]

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ORIGINAL ARTICLE

Observational Study

Oesophageal cancer metastases: An observational study of a more aggressive approach

Lianne Pickett, Mary Dunne, Orla Monaghan, Liam Grogan, Oscar Breathnach, Thomas N Walsh

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Lianne Pickett, Department of Surgery, Connolly Hospital, Blanchardstown, Dublin D15 X40D, Ireland

Mary Dunne, Clinical Trials Resource Unit, St Luke's Radiation Oncology Network, Dublin D06 HH36, Ireland

Orla Monaghan, Department of Radiation Oncology, St Luke's Radiation Oncology Network, Dublin D06 HH36, Ireland

Liam Grogan, Oscar Breathnach, Department of Medical Oncology, Beaumont Hospital, Dublin D09 V2N0, Ireland

Thomas N Walsh, Department of Surgery, RCSI Bahrain, Adliya 15503, Bahrain

Corresponding author: Lianne Pickett, MB, ChB, MCh, Doctor, Department of Surgery, Connolly Hospital, Blanchardstown, Mill Road, Abbots Town, Dublin D15 X40D, Ireland. lianne.pickett@ucdconnect.ie

Abstract

BACKGROUND

The prognosis for oesophageal carcinoma is poor, but once distant metastases emerge the prognosis is considered hopeless. There is no consistent protocol for the early identification and aggressive management of metastases.

AIM

To examine the outcome of a policy of active postoperative surveillance with aggressive treatment of confirmed metastases.

METHODS

A prospectively maintained database of 205 patients diagnosed with oesophageal carcinoma between 1998 and 2019 and treated with curative intent was interrogated for patients with metastases, either at diagnosis or on follow-up surveillance and treated for cure. This cohort was compared with incomplete clinical responders to neoadjuvant chemoradiotherapy (nCRT) who subsequently underwent surgery on their primary tumour. Overall survival was estimated using the Kaplan-Meier method, and the log-rank test was used to compare survival differences between groups.

RESULTS

Of 205 patients, 11 (5.4%) had metastases treated for cure (82% male; median age 60 years; 9 adenocarcinoma and 2 squamous cell carcinomas). All had undergone neoadjuvant chemotherapy or chemoradiotherapy, followed by surgery in all but 1 case. Of the 11 patients, 4 had metastatic disease at diagnosis, of whom 3 were successfully downstaged with nCRT before definitive surgery; 2 of these 4 also developed oligometastatic recurrence and were treated with curative intent. Following definitive treatment, 7 had treatment for metachronous oligometastatic disease; 5 of whom underwent metastasectomy (adrenal × 2; lung × 2; liver × 1). The median overall survival was 10.9 years [95% confidence interval (CI): 0.7-21.0 years], which was statistically significantly longer than incomplete clinical responders undergoing surgery on the primary tumour without metastatic intervention [n = 62; median overall survival = 1.9 (95%CI: 1.1-2.7; P = 0.012]. The cumulative proportion surviving 1, 3, and 5 years was 100%, 91%, and 61%, respectively compared to 71%, 36%, and 25% for incomplete clinical responders undergoing surgery on the primary tumour who did not undergo treatment for metastatic disease.

CONCLUSION

Metastatic oesophageal cancer represents a unique challenge, but aggressive treatment can be rewarded with impressive survival data. In view of recent advances in targeted therapies, intensive follow-up may yield a greater number of patients with curative potential and thus improved long-term survival.

Key Words: Oesophageal metastases; Oligometastases; Active surveillance; Treatment for cure; Metastasectomy; Survival

Core Tip: Modern imaging technologies can detect oligometastatic oesophageal cancer earlier than ever before, and targeted multimodal therapies, combined with innovative surgery, increases the potential for cure. Unfortunately, current guidelines do not reflect these advances and all too often consign patients to palliation. This approach is incongruous with other oligometastatic cancers such as colorectal cancer. Based on the survival outcomes of patients with oligometastatic disease treated for cure at our institution we advocate for more intensive surveillance strategies for earlier identification of patients with curative potential to improve overall long-term survival.

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INTRODUCTION

Oesophageal cancer is an aggressive disease that presents insidiously, disseminates early, and spreads rapidly in most patients. It remains a leading cause of death from cancer worldwide and fewer than 5%-12% will survive 5 years[1,2]. At least 40% of patients present with distant metastasis at initial diagnosis [3], and only 5% of these patients will be alive at 5 years[4]. Even when presenting with early disease, 29%-54% of patients undergoing surgical resection with curative intent will develop locoregional or distant recurrence[5-7]. Of patients with a ypT0N0M0 tumour at resection following neoadjuvant chemoradiotherapy (nCRT), up to 17% will succumb to distant metastases[8-10]. Because of these poor survival outcomes, the role of intensive surveillance post-oesophagectomy and treatment of metastatic disease remains controversial.

The management of oesophageal cancer has undergone major advances over the past 30 years. Specifically, both neoadjuvant chemotherapy and nCRT have been shown to increase survival over surgery alone[11-13]. While neoadjuvant chemotherapy has achieved this increase by targeting occult micrometastases[14], combined CRT has increased survival by both targeting micrometastases and sterilizing locoregional disease, thus up to 50% of patients with squamous cell carcinoma (SCC) and up to 25% of patients with adenocarcinoma (AC) undergoing CRT have a complete pathological response in the resected specimen, depending on the regimen and the disease stage[11,12].

Nevertheless, metastatic oesophageal cancer remains a challenge. Oligometastases are defined as a state of limited metastatic disease characterized by fewer than five metastases[5,15]. Synchronous oligometastases may be detected at the time of diagnosis of the primary cancer, while metachronous

oligometastases are those detected during follow-up[5,16]. Metastasectomy is well-established in the treatment of certain oligometastatic cancers, such as colorectal cancer, where partial hepatectomy and pulmonary resection are well established[5]. Both the United Kingdom's National Institute for Health and Clinical Excellence and the United States' National Comprehensive Cancer Network recommend surveillance strategies to identify recurrence as well as liver and pulmonary metastasectomy where possible[17,18]. In contrast, the National Institute for Health and Clinical Excellence recommends neither routine clinical follow-up nor radiological follow-up be offered to patients who have no symptoms or evidence of residual disease after treatment for oesophagogastric cancer with curative intent for the detection of recurrent disease[19]. The National Comprehensive Cancer Network reco-mmends clinical follow-up alone for asymptomatic patients and palliation alone for patients who develop metastatic recurrence[20].

Over the past decades, efforts have focused on the molecular and biological alterations that lead to oesophageal cancer, specifically the influence of angiogenesis on micrometastatic tumour growth[21,22]. This has resulted in the development of novel molecularly targeted agents that target a variety of relevant pathways, such as vascular endothelial growth factor, cyclooxygenase-2, epidermal growth factor receptor, and mammalian target of rapamycin[23] as well as targeted radiotherapy in the form of stereotactic radiotherapy[24]. Leading the way are HER-2 inhibitors for the treatment of HER-2 expressing metastatic ACs[23]. It is intuitive that aggressive treatment of oligometastatic disease would improve disease control and provide a survival benefit for patients with recurrent cancer detected at its earliest stage. The purpose of this study was to examine survival outcomes in patients who underwent active surveillance and targeted therapy at our institution for their oligometastatic disease.

MATERIALS AND METHODS

Study design and patients

We conducted a retrospective review of a prospectively maintained database of all patients diagnosed with oesophageal carcinoma and treated with curative intent between 1998 and 2019 at Connolly Hospital Blanchardstown, Dublin, Ireland. Patients were treated with either CRT alone, or CRT followed by surgery, or surgery alone.

Patient management and follow-up

Over a 21-year period, 205 patients with oesophageal carcinoma underwent curative management. Following discharge, patients were followed up in the clinic every 3 mo for the first 3 years with esophagogastroduodenoscopy performed every 3 mo and computed tomography (CT) performed every 6 mo. Between 3 years and 5 years they were followed up in the clinic every 6 mo with esophagogastroduodenoscopy every 6 mo and CT scanning performed annually. After 5 years patients were followed up annually with endoscopy and a clinic visit (which was on the same day for patients who had to travel from a distance). In addition, patients had access to their oncology coordinator and were encouraged to call at any time with any concern. On receipt of a call, the coordinator would offer them a clinic visit or an esophagogastroduodenoscopy (or other imaging) depending on their symptoms or concerns.

Patient database

A patient database was maintained over the study period, both by nursing and clinical staff. This was scrutinized for patients with synchronous and metachronous oligometastases. Only patients who underwent curative treatment of oligometastatic disease were included in this study. A second group of patients (with non-metastatic disease) who had an incomplete clinical response to nCRT and subsequently underwent surgery on the primary tumour were identified for comparison of survival outcomes.

Of 205 patients treated with curative intent, 62 had an incomplete response to nCRT for non-metastatic oesophageal cancer and subsequently underwent surgery, and 11 had oligometastases treated for cure. The medical and electronic records of the oligometastatic cohort treated for cure were reviewed for demographic, clinical, and histopathologic variables. Notably, staging of the primary oesophageal cancer was prospectively assigned according to the TNM classification of the American Joint Committee for Cancer Staging, initially the 6th edition and then the 7th following its publication. Each case was assessed with respect to the use of neoadjuvant therapy, history of oesophagectomy, and timing of metastasis. Further details regarding the site and treatment of metastasis were included. Survival data was included for analysis and comparison.

Ethical approval

As this was a retrospective audit ethical approval was not required, but audit approval was sought and granted by the Connolly Hospital Ethics Committee.

Statistical analysis

The statistical analysis of this study was performed by biostatistician Mary Dunne from St Luke's Radiation Oncology Network, Dublin D06 HH36, Ireland. Overall survival was estimated using the Kaplan-Meier method and was defined as the duration from the date of diagnosis until death from any cause or last follow-up at study endpoint on February 26, 2020. The log-rank test was used to compare survival differences between groups (assessed for significance at the 0.05 level). Statistical analysis was performed using IBM SPSS Statistics 25 (Chicago, IL, United States).

RESULTS

Clinical characteristics of patients

Of the 205 patients, 11 (5.4%) patients diagnosed with oesophageal carcinoma [146 (71.0%) male; 135 (65.9%) AC; 68 (33.2%) SCC; 2 adenosquamous)] between 1998 and 2019 and treated with curative intent had metastases treated for cure. Of these, 4 had synchronous oligometastatic oesophageal cancer, 2 of which also had treatment for cure for oligometastatic recurrence. A further 7 had metachronous oligometastatic oesophageal cancer only. The median age of patients with synchronous metastasis was 65 years (range: 53-71 years; AC 75%) and in patients with metachronous carcinoma was 57 years (range: 36-72 years; AC 86%) (Table 1). The majority of both cohorts were male (75% and 86%, respectively).

Treatment of synchronous oligometastatic oesophageal cancer

The 4 patients that had metastatic disease at presentation were treated with nCRT, 3 of whom underwent subsequent oesophagectomy and achieved a margin free R0 resection and 1 of whom declined surgery following a clinical complete response to nCRT (Table 1). Two of these patients subsequently presented with metachronous metastases, which were also treated for cure (Table 2).

Patient 1 had locally advanced SCC at diagnosis (T4N1M1). Despite a complete clinical response to definitive CRT, routine surveillance positron emission tomography–CT (PET-CT) almost 12 mo later (11.5 mo) revealed fluorodeoxyglucose (FDG) avid lung lesions bilaterally. These were subsequently treated with stereotactic radiotherapy. The patient survived for 3 years post metastatic recurrence (36.4 mo). Patient 2 had a 12 mm short-axis FDG-positive lymph node lying immediately to the right of the coeliac axis on staging PET-CT (AC, T3N2M1). The patient was treated with nCRT and radical oesophagogastrectomy for a poorly differentiated junctional/cardia AC (ypT2bN1Mx). Almost 18 mo later (17.9 mo) a radiological work-up for a pulmonary embolus revealed a 1.9 cm left para-aortic node with FDG uptake on PET-CT, which was subsequently treated with chemotherapy (Table 2). Follow-up CT showed a reduction in tumour size and subsequent surveillance with endoscopy and CT revealed stable disease with no evidence of recurrence. The patient was alive and well at the conclusion of this study, 83.3 mo after his initial diagnosis (65.4 mo post-recurrence).

Two further patients (Patient 3 and Patient 4) had treatment for cure of synchronous oligometastatic disease only (Tables 1 and 2). Patient 3 had liver metastasis on staging PET-CT (AC, T3N1M1). Restaging CT post nCRT was negative for liver metastasis, and the patient subsequently underwent oesophagectomy (ypT3N0M0). Patient 4 had a 1 cm FDG avid right supraclavicular node on staging PET-CT (AC, T3N2M0) and underwent nCRT and subsequent oesophagectomy for a moderate to poorly differentiated AC at the oesophagogastric junction (ypT2N0Mx). The patient was alive and well at the conclusion of this study, 8.5 years after his initial diagnosis (102.8 mo).

Treatment of metachronous oligometastatic oesophageal cancer

The remaining 7 patients did not have clinical evidence of metastatic oesophageal cancer at diagnosis. These patients had mostly T3 disease with or without nodal involvement (Table 1; Patient 5-11). All underwent nCRT or neoadjuvant chemotherapy followed by surgery for their primary cancer. Of this cohort (n = 7), 3 developed pulmonary recurrence, 2 adrenal, 1 liver, and 1 patient had biopsy proven retroperitoneal nodal recurrence. All 7 patients underwent targeted treatment for metastatic recurrence with intent to cure, the details of which are summarized in Table 2. The median time from diagnosis to recurrence was 19.2 mo (range: 15.7-33.0 mo), and the median survival post recurrence was 97.4 mo [95% confidence interval (CI): 0-204 mo). The median overall survival (MOS) was 130 mo (95%CI: 3-258 mo), or the MOS was 10.9 years (95%CI: 0.2-21.5 years).

Survival outcomes

The MOS of the 11 patients who underwent curative treatment for synchronous or metachronous metastatic disease or both was 10.9 years (95%CI: 0.7-21) which was statistically significantly longer than patients with an incomplete clinical response following nCRT undergoing surgery [n = 62; MOS = 1.9 years (95%CI: 1.1-2.7); P = 0.012] (Figure 1). Of note, the latter did not undergo curative treatment for any future proven or probable metastatic recurrence. The cumulative proportion of patients with metastatic disease treated for cure surviving 1, 3, and 5 years was 100%, 91%, and 61%, respectively,

Table 1 Clinical characteristics of patients

Patient	Age in yr	Sex	Primary tumour location	Histologic type of tumour	Differentiation	Clinical stage of primary tumour	Neoadjuvant therapy	Oesophagectomy	ypTNM
Synchronous and Metachronous Oligometastatic Disease									
1[1]	62	Female	Upper third	SCC	Moderate	T4N1M1	Walsh Regimen[17]	No	NA
2[2]	53	Male	OGJ	AC	Poor	T3N2M1	Walsh Regimen + CROSS	Yes	T2bN1Mx
Synchronous Oligometastatic Disease Only									
3	71	Male	Lower third/OGJ	AC	Poor	T3N1M1	Carbo5FU; 60Gy	Yes	T3N0M0
4	68	Male	OGJ	AC	Moderate-poor	T3N2M0	Walsh Regimen	Yes	T2N0Mx
Metachronous Oligometastatic Disease Only									
5	56	Male	Middle/lower third	SCC	Moderate	T3N2M0	Walsh Regimen	Yes	T2N1Mx
6	36	Male	Lower	AC	Moderate	T3N1M0	CROSS	Yes	T3N0Mx
7[3]	72	Female	OGJ	AC	Moderate	T3N0M0	CROSS	Yes	T2N0
8	70	Male	OGJ	AC	Poor	Nodal disease/Stage IIIA	MAGIC	Yes	T2N1Mx
9	48	Male	Lower third	AC	Poor	Stage IIB	Walsh Regimen	Yes	T1N0Mx
10[4]	57	Male	Lower third	AC	Poor	T3N0M0	CROSS	Yes	T2N0M0
11	60	Male	OGJ	AC	Poor	T3N0M0	CROSS	Yes	T0N0Mx

[1]Patient 1 had a complete clinical response.
[2]Patient 2 received six cycles of cisplatin and fluorouracil, followed by six cycles of paclitaxel and carboplatin.
[3]Patient 7 underwent salvage surgery after surveillance Positron-emission tomography suggested residual disease despite initial complete clinical response to neoadjuvant chemoradiotherapy.
[4]Patient 10 was diagnosed with a synchronous primary renal cell carcinoma, which was discovered incidentally during staging for his oesophageal cancer. He was referred to a urology service in another hospital and treated with radiofrequency ablation.
ypTNM: Pathologic staging after neoadjuvant therapy; Walsh Regimen[17]: Cisplatin/5-fluorouracil, 40 Gy concurrent radiotherapy; CROSS: The Dutch Chemoradiotherapy for Oesophageal Cancer Followed by Surgery study–weekly carboplatin and paclitaxel with concurrent radiotherapy; Carbo5FU: Carboplatin/5-fluorouracil; MAGIC: Epirubicin, cisplatin, and fluorouracil; NA: Not applicable; OGJ: Oesophagogastric junction; AC: Adenocarcinoma; SCC: Squamous cell carcinoma.

with 6 patients still alive at the end of the study period, compared to 71%, 36%, and 25% for incomplete clinical responders without metastatic disease undergoing surgery on the primary tumour.

Patients that underwent surgical resection for their recurrence (n = 5) had a MOS of 10.9 years (95%CI: 0.6-21.2) from date of diagnosis, 8.1 years (95%CI: 0-16.8 years) post recurrence, and a 5-year survival of 80% from the date of diagnosis.

DISCUSSION

Patients with metastatic oesophageal cancer present a unique challenge. Although solitary metastases of oesophageal cancer are uncommon[25], the evolution of imaging will ensure ever-earlier detection, which challenges oncologists and surgeons to detect and deal with them. Treatment of oligometastatic oesophageal cancer is controversial, and to date formal guidelines are lacking. There are no large randomized multicenter trials, and thus case series, such as ours, remain an important source of information for clinicians managing these challenging patients.

Those patients treated surgically for recurrence in our study had a MOS of 10.9 years, or 130.3 mo and a 5-year survival of 80%. Depypere *et al*[26] conducted a large retrospective study comparing different treatment options for different subtypes of recurrence following curative resection, including single solid organ metastasis and single metastasis at another location. Of 1754 patients that had curative resection, 43.7% had recurrence, 14.4% of whom had clinical solitary solid organ recurrence (liver, lung, brain, or adrenal)[26]. Only 20 patients (1.14%) had their recurrence resected with or without systemic

Table 2 Treatment of synchronous and metachronous oligometastatic oesophageal carcinoma

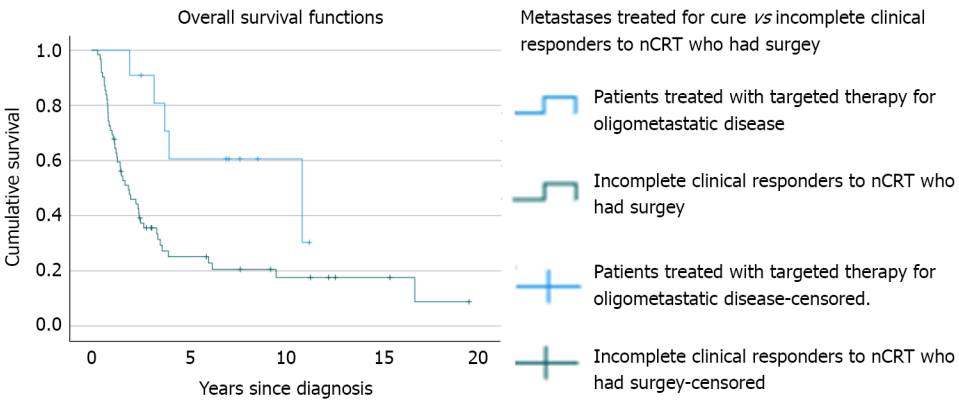
Patient	Synchronous metastases	Type	Treatment	Metachronous metastases	Type	Time to recurrence in mo	Treatment	Survival post recurrence in mo	Alive at study endpoint	Overall survival in mo
1	Yes	Locally advanced[1]	Walsh regimen	Yes	Lung	11.5	Stereotactic radiotherapy	36.4	No	47.9
2	Yes	Coeliac axis	Walsh regimen + CROSS + radial gastrectomy	Yes	Left para-aortic nodes	17.9	Chemotherapy (Epirubicin, Oxaliplatin + Capecitabine)	65.4	Yes	83.3
3	Yes	Liver	Carbo5FU; 60 Gy + oesophagectomy	No	NA	NA	NA	NA	No	23.6
4	Yes	Locally advanced[2]	Walsh regimen + oesophagectomy	No	NA	NA	NA	NA	Yes	102.8
5	No	NA	NA	Yes	Lung	32.9	Left upper lobectomy (VATS)	97.4	No	130.3
6	No	NA	NA	Yes	Lung	16.7	Chemotherapy (*carbo/taxol* + *FOLFOX)*	21.9	No	38.6
7	No	NA	NA	Yes	Lung	19.2	Wedge resection (VATS)	26.1	No	45.3
8	No	NA	NA	Yes	Adrenal	29.7	Adrenalectomy	62.1	Yes	91.8
9	No	NA	NA	Yes	Adrenal	15.9	Adrenalectomy + chemotherapy *(irinotecan)*	118.9	Yes	134.8
10	No	NA	NA	Yes	Liver	33.0	Resection + chemotherapy	51.9	Yes	84.9
11	No	NA	NA	Yes	Paraaortic + Retroperitoneal	15.7	Chemotherapy *(FOLFOX)*	14.9	Yes	30.6

[1]Right innominate artery and pars membrane of the trachea with a right 1 cm subcarinal adenopathy and left 5 mm paratracheal node on staging whole-body positron emission tomography-computed tomography (squamous cell carcinoma, T4N1M1).
[2]1 cm fluorodeoxyglucose avid right supraclavicular node on staging positron emission tomography-computed tomography.
NA: Not applicable; VATS: Video-assisted thoracoscopic surgery; FOLFOX: Folinic acid, fluorouracil, oxaliplatin; CROSS: The Dutch Chemoradiotherapy for Oesophageal Cancer Followed by Surgery study–weekly carboplatin and paclitaxel with concurrent radiotherapy; Carbo5FU: Carboplatin/5-fluorouracil.

therapy and had a significantly better median and 5-year survival than 63 non-surgically treated patients [54.8 mo (5-year survival 43.9%) *vs* 11.6 mo (5-year survival 4.6%)][25,26]. Arguably, those suitable for resection self-select, but the survival statistics for metastatic resection in a disease as aggressive as oesophageal cancer are impressive.

The patients in our study who underwent adrenalectomy were alive at 62.1 and 118.9 mo post recurrence. The oesophagus is the third most frequent site of origin of adrenal metastasis[27], and there are only a few reports of adrenalectomy for recurrence with survival ranging from 28 mo to over 5 years [27-30]. These findings confirm that adrenalectomy for isolated adrenal metastases from oesophageal carcinoma is worthwhile. A disease-free interval of over 6 mo and an AC subtype are reported as predictors of improved survival and should be considered in patient selection[31,32]. As adrenal metastases are clinically silent, intensive surveillance imaging is indicated if they are to be identified early enough for curative resection.

The remaining patients who underwent metastasectomy in our case series had either lung or liver metastases. All had metachronous oligometastases, had received nCRT, and had undergone resection of their primary tumour. Those who underwent pulmonary metastasectomy lived for 26.1 and 97.4 mo post recurrence, while the patient who underwent liver metastasectomy was alive and disease-free at 51.9 mo post recurrence. While hepatectomy and pulmonary resection are universally recommended for colorectal cancer metastases[17,18], they are not recommended for oesophageal cancer[19,20]. A nationwide study by Seesing *et al*[33] of the Dutch national registry for histopathology and cyto-



	Censored	Deaths	Total	Number at risk at each time point			
				5 yr	10 yr	15 yr	20 yr
Patients treated with targeted therapy for oligometastatic disease	6	5	11	6	2	0	0
Patients who had an incomplete clinical response to nCRT and underwent subsequent oesophagectomy	14	48	62	12	6	3	0

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Figure 1 Survival plots for patients undergoing treatment of oligometastatic disease for cure *vs* patients with an incomplete clinical response to neoadjuvant chemoradiotherapy who underwent subsequent oesophagectomy. nCRT: Neoadjuvant chemoradiotherapy.

pathology identified 32057 patients who underwent resection for gastro-oesophageal cancer between 1991 and 2016 and reported that 34 (0.11%) underwent resection for pulmonary (n = 15) or hepatic (n = 19) metastases across 21 hospitals and had an overall 5-year survival of 53% and 31%, respectively[33]. Liu *et al*[34] reported that 26 SCC patients with solitary hepatic metastasis, who underwent liver resection, had 1- and 2-year survival rates of 50.8% and 21.2%, respectively, which was significantly higher than the 31.0% and 7.1% survival rates for the 43 non-surgically treated patients[34].

Oesophageal cancer patients very frequently present with metastases, which almost inevitably consigns them to palliative management. Until recently primary cancer resection in these circumstances was rarely considered. Of the 4 patients who presented with metastatic oesophageal cancer in our case series, 3 underwent surgery to the primary cancer. All 3 had nCRT and all achieved an R0 resection, with a cumulative proportion surviving 2 years of 67%. Zhang *et al*[35] analysed a large population-based cohort of 4367 metastatic oesophageal cancer patients (M1b-stage) from the SEER database[35] and found a significant survival benefit for surgery for the primary tumour with a median survival for the surgery group of 14 mo compared with 9 mo for the no surgery AC group, and a similar significant survival advantage for surgery (11 mo) compared with the no surgery SCC group (7 mo)[35]. Of note, patients who had not received neoadjuvant chemotherapy failed to benefit from resection for either tumour subtype[35]. Thus, when combined with neoadjuvant chemotherapy, surgery for the primary tumour is associated with improved survival in a select group of patients with metastatic oesophageal cancer[35].

Three of the patients in our series received chemotherapy alone for recurrent oligometastatic oesophageal cancer (patients 2, 6, and 11). Although chemotherapy is commonly considered as merely palliative in recurrent metastatic cancer, it also has the potential to cure[36]. Taxanes as single agents have a slightly higher response rate in patients with AC (34%) than in patients with SCC (28%), resulting in an overall survival rate of 13.2 mo[37]. Parry *et al*[38] reported complete tumour regression in 2 patients after chemotherapy alone, with both patients alive at last follow-up (35 and 112 mo)[38]. Developments in proton beam therapy and stereotactic ablative radiation increases its conformality and reduces radiation toxicity[39]. Sachdeva *et al*[40] recently reported on the use of external beam radiotherapy for the treatment of oligometastatic sacral metastases in a 46-year-old male with a rare case of primary oesophageal lymphoma[40]. Moreover, 1-year and 2-year progression-free survival and overall survival rates have been reported at 62% and 48% and 90% and 72%, respectively, following stereotactic ablative therapy for pulmonary metastases[41].

With few predictive factors for survival of metastatic oesophageal cancer in the literature[42], it is unclear which patients or which tumour characteristics predict the best survival outcomes. The current approach to metastatic disease all too often consigns the patient to palliative care and a dismal outcome.

We have previously reported that bone marrow positivity for micrometastases at the time of oesophagectomy is a predictor of increased risk of cancer-related death and can identify patients requiring intensive surveillance for early detection of metastases with intent to treat[43]. Our current findings suggest that a more optimistic approach can be rewarded with impressive survival data. It is intuitive that aggressive treatment can improve survival, but it implies a need for more intensive surveillance strategies, especially in the first 3 years post-resection, to identify salvageable patients and consider curative intent. In an era of molecularly targeted agents, the identification of such patients is more important than ever as identified by the CheckMate 557 trial where the addition of nivolumab for patients with residual disease following CRT provided a median disease-free survival of 22.4 mo *vs* 11.0 mo in the placebo arm, which was significant[44].

The obvious limitation of our study is the small sample size of patients with metastatic oesophageal cancer treated for cure. Moreover, the survival data reported in our study reflects a policy of aggressive treatment of confirmed limited metastases only. Such patients self-select, and our survival data cannot be applied to all patients with metastatic oesophageal cancer.

CONCLUSION

In conclusion, as advances in imaging facilitate earlier metastatic disease detection and advances in multimodal and targeted treatments improve survival outcomes, surveillance strategies must be intensified to diagnose metastatic disease earlier in the recurrence process to institute medical or surgical measures with a greater possibility of success. Future studies are needed to prospectively identify the rate of oligometastatic recurrence in oesophageal carcinoma in the context of today's imaging technologies to update surveillance and treatment guidelines in line with those for cancers of the lower gastrointestinal tract.

ARTICLE HIGHLIGHTS

Research background

The prognosis of metastatic oesophageal cancer is poor. The rate of oligometastatic oesophageal cancer is not well established nor is the survival benefit of intervention. As a result, current guidelines advocate against a proactive approach, which is incongruent with other oligometastatic cancers such as colorectal cancer. Based on a policy of active postoperative surveillance and survival outcomes of patients with oligometastatic disease treated with curative intent at our institution, we advocate for more intensive surveillance strategies to identify patients with curative potential early and thus improve long-term survival.

Research motivation

To evaluate the impact of a policy of active surveillance and aggressive management of confirmed metastases on long-term survival.

Research objectives

To examine survival outcomes in patients who underwent active surveillance and targeted therapy of their oligometastatic disease, either at diagnosis or on follow-up surveillance, at our institution. When compared to incomplete clinical responders to neoadjuvant chemoradiotherapy (nCRT) for non-metastatic oesophageal cancer who underwent surgery on their primary tumour, the median overall survival of the oligometastatic cohort was statistically significantly longer. These findings suggest that aggressive treatment of confirmed metastases can be rewarded with impressive survival data and that a more proactive approach to oesophageal oligometastases should be considered.

Research methods

A prospectively maintained database of patients diagnosed with oesophageal carcinoma and treated with curative intent in a single institution was interrogated for patients with metastases, either at diagnosis or on follow-up surveillance, and treated for cure. This cohort was compared with incomplete clinical responders to nCRT who subsequently underwent surgery on their primary tumour. Overall survival was estimated using the Kaplan-Meier method, and the log-rank test was used to compare survival differences between groups.

Research results

The overall survival of patients with oligometastatic disease who were treated for cure at our institution is impressive and statistically significantly longer than incomplete clinical responders without metastatic disease who subsequently underwent surgery on their primary tumour. These results suggest

that intensive follow-up and aggressive management of confirmed metastases may improve long-term survival. Further studies are needed to prospectively identify the rate of oligometastatic recurrence in oesophageal carcinoma and evaluate the cost-benefit ratio of a policy of active surveillance and aggressive management of confirmed oligometastatic disease.

Research conclusions

In view of recent diagnostic and therapeutic advances, intensive follow-up and aggressive treatment of confirmed metastases may improve long-term survival in patients with oligometastatic oesophageal carcinoma.

Research perspectives

Further research should prospectively establish the rate of oligometastatic recurrence in oesophageal carcinoma to evaluate the cost-benefit ratio of active surveillance and aggressive management and inform future clinical guidelines.

FOOTNOTES

Author contributions: Walsh TN was the guarantor, designed the study, participated in the acquisition of data, and revised and edited the article critically; Pickett L acquired, analysed, and interpreted the data and drafted the initial manuscript; Dunne M statistically analysed the data and edited the manuscript; Monaghan O, Grogan L, and Breathnach O reviewed the article and made critical revisions related to important intellectual content.

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Informed consent statement: As this was a retrospective audit and many patients were not alive at the commencement of this study, written informed consent was not feasible/obtained. This was an observational study, and no patient received treatment as part of the study. Furthermore, we have not included any identifiable patient information in our manuscript. Verbal consent, although not required, was obtained where appropriate/feasible.

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Country/Territory of origin: Ireland

ORCID number: Lianne Pickett 0000-0001-5156-0612; Mary Dunne 0000-0002-3723-6311; Orla Monaghan 0000-0003-2902-528X; Oscar Breathnach 0000-0003-4852-0358; Thomas N Walsh 0000-0002-1600-8029.

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REFERENCES

1 **Verhoef C**, van de Weyer R, Schaapveld M, Bastiaannet E, Plukker JT. Better survival in patients with esophageal cancer after surgical treatment in university hospitals: a plea for performance by surgical oncologists. *Ann Surg Oncol* 2007; **14**: 1678-1687 [PMID: 17294070 DOI: 10.1245/s10434-006-9333-0]

2 **Anderson LA**, Tavilla A, Brenner H, Luttmann S, Navarro C, Gavin AT, Holleczek B, Johnston BT, Cook MB, Bannon F, Sant M; EUROCARE-5 Working Group:. Survival for oesophageal, stomach and small intestine cancers in Europe 1999-2007: Results from EUROCARE-5. *Eur J Cancer* 2015; **51**: 2144-2157 [PMID: 26421818 DOI: 10.1016/j.ejca.2015.07.026]

3 **Rustgi AK**, El-Serag HB. Esophageal carcinoma. *N Engl J Med* 2014; **371**: 2499-2509 [PMID: 25539106 DOI: 10.1056/NEJMra1314530]

4 **American Cancer Society [Internet]**. Cancer Facts and Statistics. [cited 22 June 2020]. Available from: https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2020.html

5 **Jamel S**, Tukanova K, Markar S. Detection and management of oligometastatic disease in oesophageal cancer and identification of prognostic factors: A systematic review. *World J Gastrointest Oncol* 2019; **11**: 741-749 [PMID: 31558978 DOI: 10.4251/wjgo.v11.i9.741]

6 **Sugiyama M**, Morita M, Yoshida R, Ando K, Egashira A, Takefumi O, Saeki H, Oki E, Kakeji Y, Sakaguchi Y, Maehara Y. Patterns and time of recurrence after complete resection of esophageal cancer. *Surg Today* 2012; **42**: 752-758 [PMID: 22370963 DOI: 10.1007/s00595-012-0133-9]

7 **Mariette C**, Balon JM, Piessen G, Fabre S, Van Seuningen I, Triboulet JP. Pattern of recurrence following complete resection of esophageal carcinoma and factors predictive of recurrent disease. *Cancer* 2003; **97**: 1616-1623 [PMID: 12655517 DOI: 10.1002/cncr.11228]

8 **Knight WRC**, Zylstra J, Van Hemelrijck M, Griffin N, Jacques AET, Maisey N, Baker CR, Gossage JA, Largergren J, Davies AR. Patterns of recurrence in oesophageal cancer following oesophagectomy in the era of neoadjuvant chemotherapy. *BJS Open* 2017; **1**: 182-190 [PMID: 29951621 DOI: 10.1002/bjs5.30]

9 **Oppedijk V**, van der Gaast A, van Lanschot JJ, van Hagen P, van Os R, van Rij CM, van der Sangen MJ, Beukema JC, Rütten H, Spruit PH, Reinders JG, Richel DJ, van Berge Henegouwen MI, Hulshof MC. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. *J Clin Oncol* 2014; **32**: 385-391 [PMID: 24419108 DOI: 10.1200/JCO.2013.51.2186]

10 **Meguid RA**, Hooker CM, Taylor JT, Kleinberg LR, Cattaneo SM 2nd, Sussman MS, Yang SC, Heitmiller RF, Forastiere AA, Brock MV. Recurrence after neoadjuvant chemoradiation and surgery for esophageal cancer: does the pattern of recurrence differ for patients with complete response and those with partial or no response? *J Thorac Cardiovasc Surg* 2009; **138**: 1309-1317 [PMID: 19931663 DOI: 10.1016/j.jtcvs.2009.07.069]

11 **van Hagen P**, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A; CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012; **366**: 2074-2084 [PMID: 22646630 DOI: 10.1056/NEJMoa1112088]

12 **Bass GA**, Furlong H, O'Sullivan KE, Hennessy TP, Walsh TN. Chemoradiotherapy, with adjuvant surgery for local control, confers a durable survival advantage in adenocarcinoma and squamous cell carcinoma of the oesophagus. *Eur J Cancer* 2014; **50**: 1065-1075 [PMID: 24480403 DOI: 10.1016/j.ejca.2013.12.022]

13 **Shapiro J**, van Lanschot JJB, Hulshof MCCM, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, van Laarhoven HWM, Nieuwenhuijzen GAP, Hospers GAP, Bonenkamp JJ, Cuesta MA, Blaisse RJB, Busch ORC, Ten Kate FJW, Creemers GM, Punt CJA, Plukker JTM, Verheul HMW, Bilgen EJS, van Dekken H, van der Sangen MJC, Rozema T, Biermann K, Beukema JC, Piet AHM, van Rij CM, Reinders JG, Tilanus HW, Steyerberg EW, van der Gaast A; CROSS study group. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol* 2015; **16**: 1090-1098 [PMID: 26254683 DOI: 10.1016/S1470-2045(15)00040-6]

14 **Eguchi T**, Kodera Y, Nakanishi H, Yokoyama H, Ohashi N, Ito Y, Nakayama G, Koike M, Fujiwara M, Nakao A. The effect of chemotherapy against micrometastases and isolated tumor cells in lymph nodes: an in vivo study. *In Vivo* 2008; **22**: 707-712 [PMID: 19180995 DOI: 10.1158/1078-0432.ccr-05-1963]

15 **Weichselbaum RR**, Hellman S. Oligometastases revisited. *Nat Rev Clin Oncol* 2011; **8**: 378-382 [PMID: 21423255 DOI: 10.1038/nrclinonc.2011.44]

16 **Niibe Y**, Chang JY. Novel insights of oligometastases and oligo-recurrence and review of the literature. *Pulm Med* 2012; **2012**: 261096 [PMID: 22966429 DOI: 10.1155/2012/261096]

17 **National Institute for Health and Care Excellence [Internet]**. Colorectal Cancer. NICE Guideline [NG151]. Jan 2020. Updated Dec 2021. [cited 29 May 2022]. Available from: https://www.nice.org.uk/guidance/ng151

18 **National Comprehensive Cancer Network [Internet]**. NCCN Clinical Practice Guidelines in Oncology. Colon Cancer. Feb 2022. [cited 29 May 2022]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

19 **National Institute for Health and Care Excellence [Internet]**. Oesophago-gastric cancer: assessment and management in adults. NICE Guideline [NG83]. Jan 2018. [cited 29 May 2022]. Available from: https://www.nice.org.uk/guidance/ng83/chapter/Recommendations#follow-up

20 **Ajani JA**, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P, Denlinger CS, Enzinger PC, Fanta P, Farjah F, Gerdes H, Gibson M, Glasgow RE, Hayman JA, Hochwald S, Hofstetter WL, Ilson DH, Jaroszewski D, Johung KL, Keswani RN, Kleinberg LR, Leong S, Ly QP, Matkowskyj KA, McNamara M, Mulcahy MF, Paluri RK, Park H, Perry KA, Pimiento J, Poultsides GA, Roses R, Strong VE, Wiesner G, Willett CG, Wright CD, McMillian NR, Pluchino LA. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2019; **17**: 855-883 [PMID: 31319389 DOI: 10.6004/jnccn.2019.0033]

21 **O'sullivan GC**, Sheehan D, Clarke A, Stuart R, Kelly J, Kiely MD, Walsh T, Collins JK, Shanahan F. Micrometastases in esophagogastric cancer: high detection rate in resected rib segments. *Gastroenterology* 1999; **116**: 543-548 [PMID: 10029612 DOI: 10.1016/s0016-5085(99)70175-7]

22 **McDonnell CO**, Hill AD, McNamara DA, Walsh TN, Bouchier-Hayes DJ. Tumour micrometastases: the influence of angiogenesis. *Eur J Surg Oncol* 2000; **26**: 105-115 [PMID: 10744927 DOI: 10.1053/ejso.1999.0753]

23 **Yang YM**, Hong P, Xu WW, He QY, Li B. Advances in targeted therapy for esophageal cancer. *Signal Transduct Target Ther* 2020; **5**: 229 [PMID: 33028804 DOI: 10.1038/s41392-020-00323-3]

24 **Milano MT**, Katz AW, Schell MC, Philip A, Okunieff P. Descriptive analysis of oligometastatic lesions treated with curative-intent stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys* 2008; **72**: 1516-1522 [PMID: 18495378 DOI: 10.1016/j.ijrobp.2008.03.044]

25 **Schizas D**, Lazaridis II, Moris D, Mastoraki A, Lazaridis LD, Tsilimigras DI, Charalampakis N, Liakakos T. The role of surgical treatment in isolated organ recurrence of esophageal cancer-a systematic review of the literature. *World J Surg Oncol* 2018; **16**: 55 [PMID: 29540179 DOI: 10.1186/s12957-018-1357-y]

26 **Depypere L**, Lerut T, Moons J, Coosemans W, Decker G, Van Veer H, De Leyn P, Nafteux P. Isolated local recurrence or solitary solid organ metastasis after esophagectomy for cancer is not the end of the road. *Dis Esophagus* 2017; **30**: 1-8 [PMID: 27704661 DOI: 10.1111/dote.12508]

27 **Fumagalli U**, de Carli S, de Pascale S, Rimassa L, Bignardi M, Rosati R. Adrenal metastases from adenocarcinoma of the esophagogastric junction: adrenalectomy and long-term survival. *Updates Surg* 2010; **62**: 63-67 [PMID: 20845103 DOI: 10.1007/s13304-010-0012-0]

28 **Saito H**, Shuto K, Ota T, Toma T, Ohira G, Natsume T, Uesato M, Akutsu Y, Kono T, Matsubara H. [A case of long-term survival after resection for postoperative solitary adrenal metastasis from esophageal adenocarcinoma]. *Gan To Kagaku Ryoho* 2010; **37**: 2406-2408 [PMID: 21224588]

29 **O'Sullivan KE**, Moriarty AR, Larkin JO, Reynolds JV. Curative surgical management of isolated adrenal recurrence of oesophageal adenocarcinoma. *BMJ Case Rep* 2013; **2013** [PMID: 23632191 DOI: 10.1136/bcr-2013-009657]

30 **Kanaya N**, Noma K, Okada T, Maeda N, Tanabe S, Sakurama K, Shirakawa Y, Fujiwara T. A case of long-term survival after surgical resection for solitary adrenal recurrence of esophageal squamous carcinoma. *Surg Case Rep* 2017; **3**: 61 [PMID: 28477332 DOI: 10.1186/s40792-017-0337-8]

31 **Hess KR**, Varadhachary GR, Taylor SH, Wei W, Raber MN, Lenzi R, Abbruzzese JL. Metastatic patterns in adenocarcinoma. *Cancer* 2006; **106**: 1624-1633 [PMID: 16518827 DOI: 10.1002/cncr.21778]

32 **Howell GM**, Carty SE, Armstrong MJ, Stang MT, McCoy KL, Bartlett DL, Yip L. Outcome and prognostic factors after adrenalectomy for patients with distant adrenal metastasis. *Ann Surg Oncol* 2013; **20**: 3491-3496 [PMID: 23793361 DOI: 10.1245/s10434-013-3050-2]

33 **Seesing MFJ**, van der Veen A, Brenkman HJF, Stockmann HBAC, Nieuwenhuijzen GAP, Rosman C, van den Wildenberg FJH, van Berge Henegouwen MI, van Duijvendijk P, Wijnhoven BPL, Stoot JHMB, Lacle M, Ruurda JP, van Hillegersberg R; Gastroesophageal Metastasectomy Group. Resection of hepatic and pulmonary metastasis from metastatic esophageal and gastric cancer: a nationwide study. *Dis Esophagus* 2019; **32** [PMID: 31220859 DOI: 10.1093/dote/doz034]

34 **Liu J**, Wei Z, Wang Y, Xia Z, Zhao G. Hepatic resection for post-operative solitary liver metastasis from oesophageal squamous cell carcinoma. *ANZ J Surg* 2018; **88**: E252-E256 [PMID: 27764891 DOI: 10.1111/ans.13810]

35 **Zhang R**, Zou J, Li P, Li Q, Qiao Y, Han J, Huang K, Ruan P, Lin H, Song Q, Fu Z. Surgery to the primary tumor is associated with improved survival of patients with metastatic esophageal cancer: propensity score-matched analyses of a large retrospective cohort. *Dis Esophagus* 2020; **33** [PMID: 31175353 DOI: 10.1093/dote/doz051]

36 **Mohamed A**, El-Rayes B, Khuri FR, Saba NF. Targeted therapies in metastatic esophageal cancer: advances over the past decade. *Crit Rev Oncol Hematol* 2014; **91**: 186-196 [PMID: 24582516 DOI: 10.1016/j.critrevonc.2014.01.010]

37 **Ajani JA**, Ilson DH, Daugherty K, Pazdur R, Lynch PM, Kelsen DP. Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. *J Natl Cancer Inst* 1994; **86**: 1086-1091 [PMID: 7912736 DOI: 10.1093/jnci/86.14.1086]

38 **Parry K**, Visser E, van Rossum PS, Mohammad NH, Ruurda JP, van Hillegersberg R. Prognosis and Treatment After Diagnosis of Recurrent Esophageal Carcinoma Following Esophagectomy with Curative Intent. *Ann Surg Oncol* 2015; **22** Suppl 3: S1292-S1300 [PMID: 26334295 DOI: 10.1245/s10434-015-4840-5]

39 **Welsh J**, Amini A, Likhacheva A, Erasmus J J, Gomez D, Davila M, Mehran RJ, Komaki R, Liao Z, Hofstetter WL, Lee H J, Bhutani MS, Ajani JA. Update: modern approaches to the treatment of localized esophageal cancer. *Curr Oncol Rep* 2011; **13**: 157-167 [PMID: 21365188 DOI: 10.1007/s11912-011-0158-z]

40 **Sachdeva S**, Jain A, Dalal A, Puri AS. Primary Esophageal Lymphoma: A Rare Entity. *GE Port J Gastroenterol* 2021 [DOI: 10.1159/000515840]

41 **Jang BS**, Kim HJ, Kim BH, Kim DW, Kim YT, Kim YW, Jang MJ, Wu HG. Clinical outcomes of stereotactic ablative radiotherapy in patients with pulmonary metastasis. *Jpn J Clin Oncol* 2017; **47**: 61-66 [PMID: 28122893 DOI: 10.1093/jjco/hyw147]

42 **Li B**, Wang R, Zhang T, Sun X, Jiang C, Li W, Zou B, Xie P, Meng X, Wang L, Yu J. Development and validation of a nomogram prognostic model for esophageal cancer patients with oligometastases. *Sci Rep* 2020; **10**: 11259 [PMID: 32647289 DOI: 10.1038/s41598-020-68160-6]

43 **Ryan P**, Furlong H, Murphy CG, O'Sullivan F, Walsh TN, Shanahan F, O'Sullivan GC. Prognostic significance of prospectively detected bone marrow micrometastases in esophagogastric cancer: 10-year follow-up confirms prognostic significance. *Cancer Med* 2015; **4**: 1281-1288 [PMID: 25914238 DOI: 10.1002/cam4.470]

44 **Kelly RJ**, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E, Piessen G, Mendez G, Feliciano J, Motoyama S, Lièvre A, Uronis H, Elimova E, Grootscholten C, Geboes K, Zafar S, Snow S, Ko AH, Feeney K, Schenker M, Kocon P, Zhang J, Zhu L, Lei M, Singh P, Kondo K, Cleary JM, Moehler M; CheckMate 577 Investigators. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. *N Engl J Med* 2021; **384**: 1191-1203 [PMID: 33789008 DOI: 10.1056/NEJMoa2032125]

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ORIGINAL ARTICLE

Observational Study

Change of tumor-infiltrating lymphocyte of associating liver partition and portal vein ligation for staged hepatectomy for hepatocellular carcinoma

Wei Wang, Zhen-Feng Deng, Ji-Long Wang, Ling Zhang, Li Bao, Bang-Hao Xu, Hai Zhu, Ya Guo, Zhang Wen

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Wei Wang, Zhen-Feng Deng, Ji-Long Wang, Bang-Hao Xu, Hai Zhu, Ya Guo, Zhang Wen, Department of Hepatobiliary Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China

Wei Wang, Zhen-Feng Deng, Ji-Long Wang, Bang-Hao Xu, Hai Zhu, Ya Guo, Zhang Wen, Guangxi Key Laboratory of Enhanced Recovery after Surgery for Gastrointestinal Cancer, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China

Ling Zhang, Department of Radiology, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China

Li Bao, Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin 300000, China

Corresponding author: Zhang Wen, MD, PhD, Chief Doctor, Department of Hepatobiliary Surgery, The First Affiliated Hospital of Guangxi Medical University, No. 6, Shuangyong Road, Nanning 530021, Guangxi Zhuang Autonomous Region, China. wenzgxmu@163.com

Abstract

BACKGROUND

The role of tumor-infiltrating lymphocytes (TILs) in the growth and progression of hepatocellular carcinoma (HCC) has attracted widespread attention.

AIM

To evaluate the feasibility of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) for massive HCC by exploring the role of TIL in the tumor microenvironment.

METHODS

Fifteen massive HCC patients who underwent ALPPS treatment and 46 who underwent hemi-hepatectomy were selected for this study. Propensity score matching was utilized to match patients in ALPPS and hemi-hepatectomy groups (1:1). Quantitative analysis of TILs in tumor and adjacent tissues between the two groups was performed by immunofluorescence staining and further analyses with oncological characteristics. In the meantime, trends of TILs in peripheral blood

were compared between the two groups during the perioperative period.

RESULTS

Continuous measurement of tumor volume and necrosis volume showed that the proportion of tumor necrosis volume on the seventh day after stage-I ALPPS was significantly higher than the pre-operative value (P = 0.024). In the preoperative period of stage-I ALPPS, the proportion of tumor necrosis volume in the high CD8$^+$ T cell infiltration group was significantly higher than that in the low group (P = 0.048).

CONCLUSION

TIL infiltration level maintained a dynamic balance during the preoperative period of ALPPS. Compared with right hemi-hepatectomy, the ALPPS procedure does not cause severe immunosuppression with the decrease in TIL infiltration and pathological changes in immune components of peripheral blood. Our results suggested that ALPPS is safe and feasible for treating massive HCC from the perspective of immunology. In addition, high CD8$^+$T cell infiltration is associated with increasing tumor necrosis in the perioperative period of ALPPS.

Key Words: Associating liver partition and portal vein ligation for staged hepatectomy; Tumor-infiltrating lymphocytes; Multiplexed immunohistochemistry; Tumor necrosis

Core Tip: This study was conducted to evaluate the feasibility of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) for massive hepatocellular carcinoma by exploring the role of tumor-infiltrating lymphocyte (TIL) subpopulations in the tumor microenvironment. The ALPPS procedure did not cause severe immunosuppression due to reduced TIL infiltration and pathological alterations in peripheral blood immune components. In addition, high perioperative CD8$^+$T cell infiltration with ALPPS was associated with increased tumor necrosis.

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INTRODUCTION

Primary liver cancer is a common digestive system malignancy, with around 906000 new cases and 830000 deaths occurring globally, with the incidence rate and mortality rate increasing yearly. More than 75% of cases of primary liver cancer are hepatocellular carcinoma (HCC)[1]. According to the newly released diagnosis and treatment guidelines, surgery is the primary choice of radical resection of HCC tumors and the principal treatment strategy for prolonging the survival time of patients with HCC [2,3].

In March 2012, Schnitzbauer *et al*[4] were the first to report associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), an innovative hepatectomy, publicly. ALPPS can block part of the blood flow supplying the tumor and completely block the possible collateral circulation between the two hepatic lobes. Thus, ALPPS can effectively stimulate liver hyperplasia and create more favorable conditions for the second-stage surgical resection of the tumor. With the gradual maturity and improvement in ALPPS technology, the clinical application of ALPPS has gone through an early transition, and the incidence of complications and mortality has been gradually reduced. In HCC patients who have undergone rigorous screening for ALPPS treatment, these risks are comparable to those of traditional hepatectomy and portal vein embolization + hepatectomy, which leads to an increase in the resection rate of massive HCC[5]. As a new method of liver surgery, ALPPS is a promising approach to treating HCC patients.

Tumor-infiltrating lymphocytes (TILs) migrate to the tumor microenvironment (TME) after leaving the peripheral blood circulation system, which involve T and B lymphocytes and natural killer (NK) cells. TILs are an integral part of the TME, and their role in HCC tumor growth and progression has attracted widespread attention. Recent studies have focused on the relationship between TILs and the prognosis of liver cancer patients. Anantha *et al*[6] reported for the first time that various immunological components of the future liver remnant (FLR) did not change during the perioperative period of ALPPS.

This shows that FLR proliferates rapidly and relatively expands the formation of various immune cells and components to maintain immune functions. However, in the perioperative period of ALPPS, patients need to withstand two surgical insults. The impact of subsequent stress or inflammatory response on the changes and effects of immune cells residing or recruited in the TME is still unclear. More specifically, to understand whether ALPPS could be used as a viable alternative to traditional hepatectomy techniques, it is necessary to study the potential mechanism of ALPPS complications and the changes and effects of tumor-infiltrating immune cells or components. Here, we investigated the effect of ALPPS surgery on TIL subsets, analyzed the changes in the immune microenvironment of tumor cells during the two-stage ALPPS surgery, and finally evaluated the safety and effectiveness of ALPPS as an alternative to traditional hemi-hepatectomy for the treatment of massive HCC.

MATERIALS AND METHODS

Study design

All subjects were HCC cases from the Department of Hepatobiliary Surgery of a single center from August 2018 to August 2019. Surgical resection was performed in all cases, with the types of tumors confirmed by postoperative pathological examination. These data have been uploaded to the International ALPPS Registry (www.alpps.net). This study followed the declaration of Helsinki and was approved by the ethics committee of the center. Patients were not required to give informed consent for the study because the clinical data were obtained retrospectively after each patient agreed to treatment by written consent.

Patient criteria

The following inclusion criteria were used for the selection of patients: (1) Patients with an FLR/standard liver volume (SLV) ratio < 30%-50% and who have received stage-I ALPPS treatment; (2) Child-Pugh classification A or B; and (3) All subjects were confirmed to be HCC patients by surgery and pathology. The following exclusion criteria were used for rejecting the patients: (1) Incomplete clinical data or histological specimens; (2) Patients without stage-II ALPPS treatment; and (3) Patients undergoing left hemi-hepatectomy.

Multiple immunofluorescence staining

Each specimen was numbered according to the chronological order of the included cases and the site of collection, and hematoxylin-eosin-stained sections of HCC tissues kept in the case specimen library were retrieved. After the pathologists read the slides, paraffin specimens with typical HCC characteristics of cancerous and paracancerous tissues were selected. The screened tissues were then arranged on empty white wax blocks in a certain order using a tissue microarray spotter with the assistance of a pathology technician, and the tissue chip was obtained by serially slicing the wax blocks through a slicer, in which each core spot represented a pathological specimen. The prepared tissue chips were placed in slide boxes and refrigerated at 4 °C for storage. Tissue chips were subjected to antigen repair after dewaxing and dehydration. Subsequently, 3% H_2O_2 was added dropwise to block endogenous peroxidase. Primary antibodies (Abcam, United States) were added and kept at 4 °C overnight. Secondary antibodies were added dropwise at room temperature for 50 min, and then horseradish peroxidase reagent was added dropwise. CD4, CD56, CD3, CD20, CD8, and Foxp3 were stained with different colors of fluorescent dyes. DAPI (Sigma-Aldrich, Germany) was used to stain the nucleus. Dimethyl sulfoxide (1 mL) was added to the tissue chip at room temperature for 5 min, and the slide was covered. Complete images were acquired with the Mantra system (PerkinElmer, Waltham, Massachusetts, United States) to collect multispectral images. The inform image analysis software was used to quantify the amount of fluorescence excitation for each core site and for each fluorophore. The positive expression rate of cells in each sample was calculated as number of positive cells/total number of nucleated cells.

Surgical technique

During stage-I ALPPS, the surgeon first opened the abdominal cavity to exclude extrahepatic metastatic tissues. The right portal vein branch would be ligated in the absence of any metastasis. Intra-operative ultrasound-guided anterior hepatic transection was conducted along the middle hepatic vein, and the blood flow of the hepatic artery was preserved. The interval between stage I and stage II of ALPPS depended on the patient's condition and increased FLR. During stage-II ALPPS, right hepatectomy or enlarged right hepatectomy was performed[7].

Propensity score matching

To add to the control analysis, patients in the ALPPS group were matched 1:1 with those in the right hemicolectomy group using the propensity score matching (PSM) module built into the SPSS 22.0 software. The independent variables of tumor size and number, alpha-fetoprotein (AFP) level, Child-

Pugh score, presence of large vessel cancer thrombi, and presence of distant metastases were used as covariate matching items. Age, gender, body mass index, liver cancer end-stage score, and Barcelona clinic liver cancer (BCLC) staging system were used as balanced matches. The caliper value was set to 0.1.

Volume measurement of the liver and tumor

The liver volume was analyzed using IQQA-3D Liver (EDDA Technology, United States) combined with patient imaging data[8]. SLV was calculated using the Chinese adult standard liver volume estimation formula[9]. FLR/SLV ratio before surgery was used to determine whether FLR was sufficient. The increase in FLR volume confirmed the stage-I ALPPS and stage-II ALPPS. The following conditions were considered acceptable for stage-II ALPPS: (1) FLR/SLV ratio ≥ 50% suggested severe fibrosis or cirrhosis; (2) FLR/SLV ratio ≥ 40% suggested the presence of mild/moderate fibrosis; and (3) FLR/SLV ≥ 30% suggested the absence of liver fibrosis or cirrhosis[10]. A complete tumor image was drawn, and the tumor volume was calculated[11]. The tumor necrosis volume was also calculated. The percentage of tumor necrosis volume was then calculated as tumor necrosis volume/tumor volume × 100%. The tumor size and necrotic volume were analyzed before ALPPS and 3 d and 7 d after stage-I ALPPS.

Follow-up

The patients were followed regularly for 3 mo after discharge and every 3 to 6 mo after that, mainly involving imaging examination (ultrasound, computed tomography, and magnetic resonance imaging), liver function inspection, and AFP level test. After analysis, the overall survival rate of each patient was calculated, with the survival time defined as the time from treatment operation to death. The final events of overall survival included extrahepatic or intrahepatic metastasis, recurrence, and death after primary resection.

Statistical analysis

The data were analyzed and processed with IBM SPSS22.0. The normally distributed measurement data are expressed as the mean ± SD, and the count data are defined as quantity (%). The student's *t*-test was conducted to compare the measurement data between two paired groups. Comparison of counting data was made between two groups using the chi-square test or Fisher's exact test, and the R × C chi-square test was used for comparison among groups. Repeated measurement data were compared by repeated measurement analysis of variance. Kaplan-Meier method was used for survival analysis and fitting survival curves. The Log-rank test was used to compare the differences in survival curves among different groups. $P < 0.05$ was considered statistically significant.

RESULTS

Matching results between the two groups

The clinical data of 90 patients undergoing hepatectomy in a single center were collected. Fifteen HCC patients treated by ALPPS and 46 patients by right hemi-hepatectomy were included for analysis (Figure 1). A 1:1 match was performed between the ALPPS group and the right hemi-hepatectomy group using the PSM module. After matching, the variables such as age, sex, body mass index, liver cancer end-stage score, BCLC stage, tumor size and number, AFP level, Child-Pugh score, presence of macrovascular tumor thrombus, and distant metastasis were found to be similar between the two groups ($P > 0.05$, Table 1). In addition, the average FLR/SLV ratio of the ALPPS group measured before the operation was 36.9% (range, 21.6%-45.4%), and the FLR/SLV value of the right hemi-hepatectomy group was 58.9% (range, 35.3%-77.3%).

Intraoperative and postoperative survey of patients in the two groups

The average operation time of stage-I ALPPS, stage-II ALPPS, and right hemi-hepatectomy was 342 min (range, 229-459 min), 293 min (range, 167-400 min), and 338 (range, 140-515) min, respectively, while the mean intraoperative bleeding volume was 230 (range, 100-500) mL, 619 mL (range, 200-1800 mL), and 344 (range, 190-638) mL, respectively. There was no allogeneic blood transfusion in stage-I ALPPS, while four cases in stage-II ALPPS required allogeneic blood transfusion and one case received leukocyte-depleted red blood cell suspension 2 U after right hemi-hepatectomy. All surgical margins were resected with R0. The median interval between the first stage of ALPPS and the second one was 15 d (range, 9-27 d).

No ALPPS group patients experienced postoperative bile leakage, while two right hemi-hepatectomy group patients underwent postoperative bile leakage. By the Clavien-Dino criteria[12], for stage-I ALPPS, the number of patients with grade I, grade II, and grade III postoperative complications was 13, 1, and 1, respectively. For stage-II ALPPS, the number of patients with grade I, grade II, grade III, and grade IV postoperative complications was 8, 4, 2, and 1, respectively. Whereas, for right hemi-

Table 1 Propensity score matching results of associating liver partition and portal vein ligation for staged hepatectomy group and right hemi-hepatectomy group

Variable	Before matching			After matching		
	ALPPS (15 cases)	Hepatectomy (46 cases)	*P* valve	ALPPS (15 cases)	Hepatectomy (15 cases)	*P* valve
Age (yr)	45.1 ± 11.4	49.4 ± 9.6	0.157	45.1 ± 11.4	49.5 ± 9.9	0.276
Sex (%)			0.795			0.543
Female	2 (13.3%)	5 (10.9%)		2 (13.3%)	1 (6.7%)	
Male	13 (86.7%)	41 (89.1%)		13 (86.7%)	14 (93.3%)	
BMI	22.4 ± 3.2	22.8 ± 3.1	0.644	22.4 ± 3.2	23.0 ± 3.4	0.608
HCC end-stage score	5.8 ± 2.3	5.4 ± 2.6	0.626	5.8 ± 2.3	6.1 ± 3.7	0.815
BCLC stage			0.775			0.915
A	3 (20.0%)	13 (28.3%)		3 (20.0%)	3 (20.0%)	
B	5 (33.3%)	12 (26.0%)		5 (33.3%)	4 (26.7%)	
C	7 (46.7%)	21 (45.7%)		7 (46.7%)	8 (53.3%)	
AFP (%)			0.031			1.000
≥ 400 ng/mL	11 (73.3%)	19 (41.3%)		11 (73.3%)	11 (73.3%)	
< 400ng/mL	4 (26.7%)	27 (58.7%)		4 (26.7%)	4 (26.7%)	
Child-Pugh class (%)			0.984			1.000
A	14 (93.3%)	43 (93.5%)		14 (93.3%)	14 (93.3%)	
B	1 (6.7%)	3 (6.5%)		1 (6.7%)	1 (6.7%)	
Tumor number (%)			0.125			1.000
1	10 (66.7%)	39 (84.8%)		10 (66.7%)	10 (66.67%)	
> 1	5 (33.3%)	7 (15.2%)		5 (33.3%)	5 (33.33%)	
Tumor size (cm)	10.7 ± 4.5	7.7 ± 4.8	0.033	10.7 ± 4.5	9.0 ± 4.9	0.332
Vascular invasion (%)			0.952			0.705
Yes	6 (40.0%)	18 (39.1%)		6 (40.0%)	5 (33.3%)	
No	9 (60.0%)	28 (60.9%)		9 (60.0%)	10 (66.6%)	
Extrahepatic metastasis (%)			1.000			1.000
Yes	0 (0%)	1 (2.2%)		0 (0%)	0 (0%)	
No	15 (100%)	45 (97.8%)		15 (100%)	15 (100%)	

ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; BMI: Body mass index; HCC: Hepatocellular carcinoma; BCLC: Barcelona Clinic Liver Cancer; AFP: Alpha-fetoprotein.

hepatectomy, the number of patients with grade I, grade II, grade III, and grade IV postoperative complications was 9, 4, 1, and 1, respectively. All other complications were cured, except that a stage-II ALPPS patient rated as grade IV due to postoperative liver failure and a right hepatectomy patient with respiratory failure rated as grade IV died during the perioperative period.

The 15 cases of ALPPS patients underwent postoperative liver failure classification by the International Study Group of Liver Surgery standards[13]. After stage-I ALPPS, four were graded as A, 10 as B, and 1 as C and after stage-II ALPPS, 4 were graded as A, 9 as B, and 2 as C. For the right hepatectomy group, the number of cases graded as A, B, and C was 6, 8, and 1, respectively. One patient of the ALPPS group died on the 32nd d after the second stage, while one of the right hepatectomy group died on the 28th d after the operation (Table 2).

Expression of TILs in HCC microenvironment

TILs are an important component of the TME involved in the local immune response, and their degree of infiltration greatly affects tumor growth and progression. In order to determine the infiltration degree

Table 2 Intraoperative and postoperative conditions of patients in associating liver partition and portal vein ligation for staged hepatectomy group and right hemi-hepatectomy group

	ALPPS		Hepatectomy
	Stage-I ALPPS	Stage-II ALPPS	
Surgery time (min)	342 (229-459)	293 (167-400)	338 (140-515)
Intraoperative blood loss (mL)	230 (100-500)	619 (200-1800)	344 (190-638)
Postoperative bile leakage (yes/no)	0/15	0/15	2/13
Postoperative complications, Clavien-Dino (I/II/III/IV)	13/1/1/0	8/4/2/1	9/4/1/1
Classification of postoperative liver failure, ISGLS (A/B/C)	4/10/1	4/9/2	6/8/1
90 d survival after operation (death/alive)	0/15	1/14	1/14

ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; ISGLS: International Study Group of Liver Surgery.

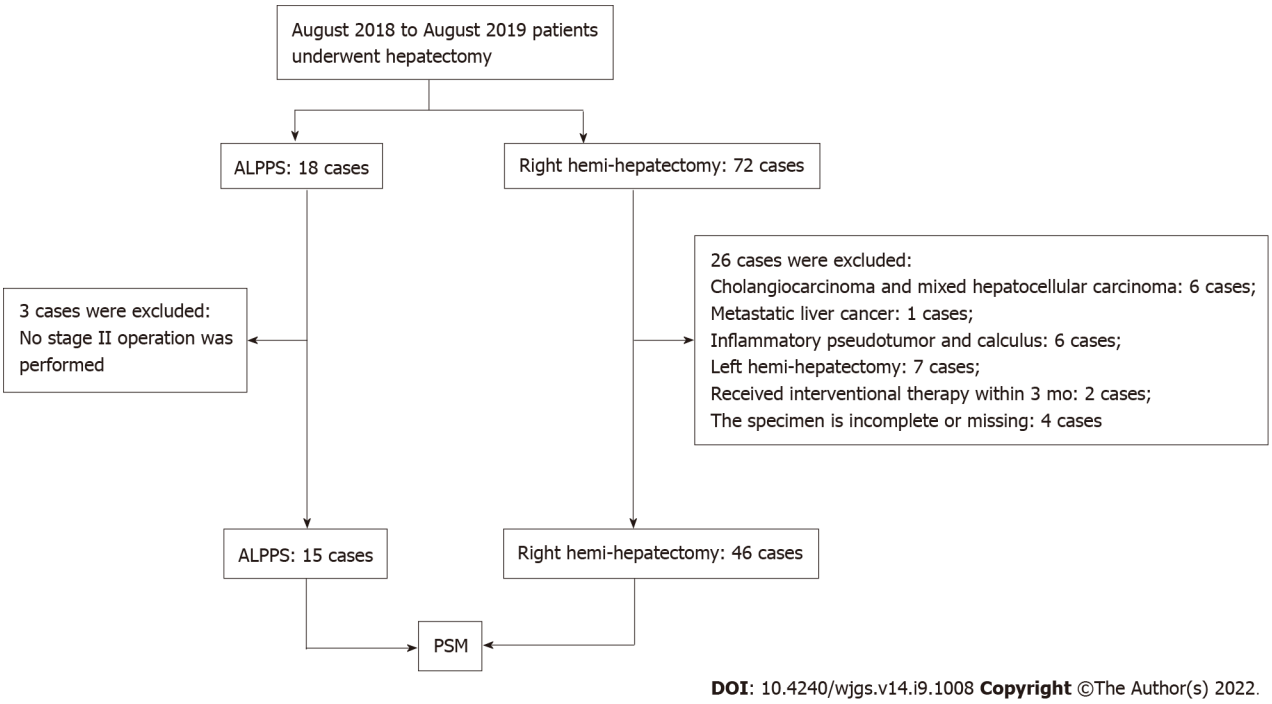

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Figure 1 Flow chart of patient selection. Fifteen hepatocellular carcinoma patients treated by associating liver partition and portal vein ligation for staged hepatectomy and 46 patients by right hemi-hepatectomy were included for analysis. ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; PSM: Propensity score matching.

and trend change of TILs in the HCC microenvironment, we took tissues from 15 cases of ALPPS and 15 matched patients with right hepatectomy. Cancerous tissues and para-cancerous tissues were used to make tissue microarrays. The specific marker molecules of lymphocyte subsets in the TME underwent polychromatic immunohistochemical staining. The results showed that the infiltration pattern of TILs in cancer tissues was significantly different from that in para-cancerous tissues. The infiltration of TILs in cancer tissues was irregular and diffusely distributed. Whereas, in para-cancerous tissues, TILs were mainly concentrated in the connective tissues of the interlobular portal area, often accompanied by three kinds of ducts: Interlobular artery, interlobular vein, and interlobular bile duct (Figure 2).

The quantitative analysis showed the number of target cells and the total number of all nucleated cells. The positive expression levels of six TIL subsets of T cells, $CD8^+$ T cells, $CD4^+$ T cells, Treg cells, B cells, and NK cells in the same spatial tissues were calculated. Furthermore, the TILs of the right hemi-hepatectomy group, ALPPS group (including stages I and II), and cancer or para-cancerous tissues were compared and analyzed (Figure 3). The results showed that the positive expression level of Treg cells in the cancer tissues was significantly higher than that of the adjacent tissues (P = 0.043, Tables 3-6).

Table 3 Comparison of positive expression rates of tumor-infiltrating lymphocyte subpopulations in tumor tissues in stage-I associating liver partition and portal vein ligation for staged hepatectomy, stage-II associating liver partition and portal vein ligation for staged hepatectomy, and right hemi-hepatectomy groups

	ALPPS		Hepatectomy	Variance analysis	
	Stage-I ALPPS	Stage-II ALPPS		*F* valve	*P* valve
Total T cells (%)	3.3 ± 2.9	3.1 ± 2.0	2.8 ± 1.8	0.188	0.829
CD4+ T cells (%)	1.0 ± 0.9	1.2 ± 1.1	0.9 ± 0.5	0.458	0.635
CD8+ T cells (%)	0.8 ± 0.7	1.0 ± 0.9	0.6 ± 0.4	0.546	0.583
Treg cells (‰)	0.2 ± 0.1	0.2 ± 0.2	0.3 ± 0.1	0.166	0.848
B cells (%)	1.7 ± 1.3	1.3 ± 0.7	2.1 ± 0.8	0.726	0.490
NK cells (%)	0.7 ± 0.2	0.4 ± 0.2	0.7 ± 0.2	0.664	0.520

NK: Natural killer; ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy.

Table 4 Comparison of positive expression rates of tumor-infiltrating lymphocyte subpopulations in adjacent tissues in stage-I associating liver partition and portal vein ligation for staged hepatectomy, stage-II associating liver partition and portal vein ligation for staged hepatectomy, and right hemi-hepatectomy groups

	ALPPS			Variance analysis	
	Stage-I ALPPS	Stage-II ALPPS	Hepatectomy	*F* valve	*P* valve
Total T cells (%)	2.0 ± 0.6	1.9 ± 0.9	1.8 ± 1.3	0.129	0.879
CD4+ T cells (%)	0.8 ± 0.3	0.9 ± 0.3	0.9 ± 0.7	0.258	0.774
CD8+ T cells (%)	0.8 ± 0.3	1.0 ± 0.5	1.0 ± 0.7	0.510	0.604
Treg cells (‰)	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.292	0.748
B cells (%)	2.0 ± 1.2	1.8 ± 0.8	1.7 ± 0.5	0.269	0.765
NK cells (%)	0.7 ± 0.7	0.6 ± 0.5	0.8 ± 0.7	0.550	0.581

NK: Natural killer; ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy.

Table 5 Comparison of tumor-infiltrating lymphocyte subpopulations between tumor and adjacent tissues in associating liver partition and portal vein ligation for staged hepatectomy group

	Stage-I ALPPS			Stage-II ALPPS		
	Tumor	Adjacent	*P* valve	Tumor	Adjacent	*P* valve
Total T cells (%)	3.3 ± 2.9	2.0 ± 0.6	0.116	3.1 ± 2.0	1.9 ± 0.9	0.056
CD4+ T cells (%)	1.0 ± 0.9	0.8 ± 0.3	0.403	1.2 ± 1.1	0.9 ± 0.3	0.278
CD8+ T cells (%)	0.8 ± 0.7	0.8 ± 0.3	0.902	1.0 ± 0.9	1.0 ± 0.5	0.792
Treg cells (‰)	0.2 ± 0.1	0.0 ± 0.1	0.056	0.2 ± 0.2	0.0 ± 0.0	0.156
B cells (%)	1.7 ± 1.3	2.0 ± 1.2	0.515	1.3 ± 0.7	1.8 ± 0.8	0.085
NK cells (%)	0.7 ± 0.2	0.7 ± 0.7	0.985	0.4 ± 0.2	0.6 ± 0.5	0.403

NK: Natural killer; ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy.

Perioperative tumor necrosis in stage-I ALPPS and its relationship with TILs

The proportion of tumor necrosis volume was calculated by analyzing the tumor volume and tumor necrosis volume in the perioperative period of stage-I ALPPS (Figure 4). The results showed that the proportion of tumor necrotic volume on the seventh day after stage-I ALPPS was significantly higher than before the operation (P = 0.024, Figure 5). In order to further clarify the relationship between tumor

Table 6 Comparison of tumor-infiltrating lymphocyte subpopulations between tumor and adjacent tissues in right hemi-hepatectomy group

	Right hemi-hepatectomy		
	Tumor tissues	Adjacent tissues	*P* valve
Total T cells (%)	2.8 ± 1.8	1.8 ± 1.3	0.105
CD4+ T cells (%)	0.9 ± 0.5	0.9 ± 0.7	0.840
CD8+ T cells (%)	0.6 ± 0.4	1.0 ± 0.7	0.101
Treg cells (‰)	0.3 ± 0.1	0.0 ± 0.0	0.043
B cells (%)	2.1 ± 0.8	1.7 ± 0.5	0.645
NK cells (%)	0.7 ± 0.2	0.8 ± 0.7	0.678

NK: Natural killer.

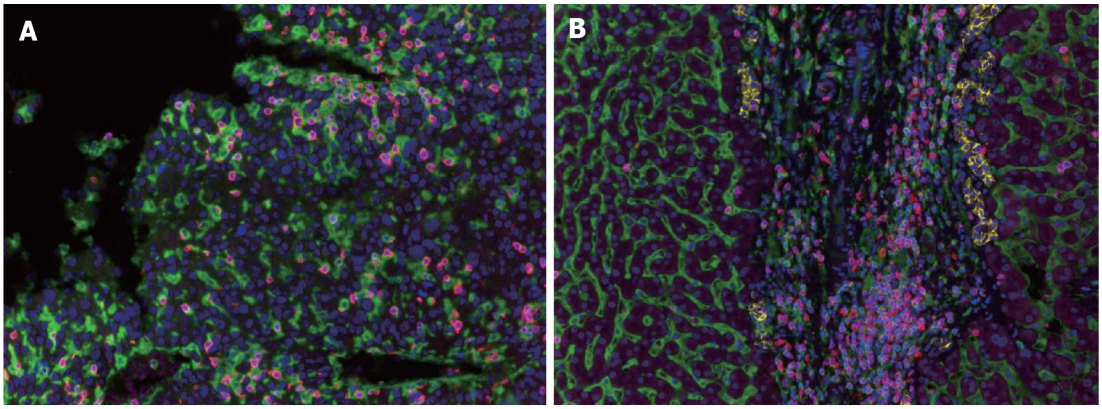

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Figure 2 Expression of tumor-infiltrating lymphocytes in the hepatocellular carcinoma tumor microenvironment. A: Immunohistochemistry image showing the distribution and expression of tumor-infiltrating lymphocyte subpopulations in tumor tissues; B: Immunohistochemistry image showing the distribution and expression of tumor-infiltrating lymphocyte subpopulations in adjacent tissues.

necrosis and TILs in the perioperative period of stage-I ALPPS, the median positive expression level of the six TIL subgroups in stage-I ALPPS cancer tissues was used as the cut-off point. The HCC patients receiving ALPPS treatment were divided into a high-infiltration group and a low-infiltration group. We then compared the difference in the proportion of tumor necrosis volume between the two groups. The results showed that the proportion of tumor necrosis volume in the high $CD8^+$ T cell infiltration group was significantly higher than that in the low $CD8^+$ T cell infiltration group (P = 0.048, Figure 6).

Comparison between immune components in peripheral blood of right hemi-hepatectomy, stage-I ALPPS, and stage-II ALPPS patients

Pairwise comparisons of immune components of peripheral blood were measured between the right hemi-hepatectomy group, stage-I ALPPS group, and stage-II ALPPS group. We found that the components of the complement system, C1q and C3 in peripheral blood in stage-I ALPPS, were significantly higher than those in stage II (C1q: P = 0.007; C3: P = 0.047, Figure 7). In addition, interleukin (IL)-6 levels in the stage-I ALPPS and stage-II ALPPS increased significantly and reached a peak value on the first day after surgery, and then decreased rapidly but were significantly higher than the preoperative level ($P1$ = 0.000, $P2$ = 0.002). NK cells in stage-I and stage-II ALPPS temporarily increased on the first day after surgery and gradually decreased on the second day after surgery to figures lower than the preoperative level (Figure 8). There was no significant difference in other remaining peripheral blood indicators among the groups (P > 0.05, Figure 9, Tables 7-9).

Follow-up results

The ALPPS and right hemi-hepatectomy group patients were followed after the surgery. As of May 20, 2020, the median follow-up time of ALPPS group patients and that of right hemi-hepatectomy group patients were 472 d (279-607 d) and 449 d (267-740 d), respectively. There was no significant difference in follow-up time between the two groups (P = 0.528). The survival rate of the ALPPS group and that of

Table 7 Comparison of immunological data during stage-I associating liver partition and portal vein ligation for staged hepatectomy

Item	Preoperative	Stage-I ALPPS				*F* value	*P* value
		POD1	POD3	POD5	POD7		
T lymphocyte count (cells/μL)	1331.5 ± 600.0	472.8 ± 289.9	682.0 ± 346.9	837.9 ± 383.6	1012.5 ± 444.2	10.095	0.001
Total T lymphocyte percentage (%)	67.8 ± 8.7	59.6 ± 8.5	68.4 ± 12.3	70.5 ± 11.7	68.9 ± 10.3	6.717	0.000
CD4+ T lymphocytes (cells/μL)	806.3 ± 428.2	241.1 ± 202.2	412.3 ± 224.7	520.1 ± 255.1	608.0 ± 266.1	9.049	0.002
CD8+ T lymphocyte (cells/μL)	438.2 ± 194.2	187.6 ± 96.6	238.9 ± 141.0	277.4 ± 143.5	361.2 ± 201.6	11.294	0.001
Natural killer cells (%)	16.5 ± 7.8	27.2 ± 8.6	10.8 ± 6.9	11.0 ± 3.7	11.2 ± 3.7	17.341	0.000
IgA (g/L)	3.11 ± 1.28	2.63 ± 1.64	1.87 ± 0.77	2.08 ± 0.79	2.69 ± 1.24	10.025	0.001
IgG (g/L)	15.11 ± 3.70	10.52 ± 2.89	8.70 ± 2.72	8.89 ± 2.69	9.82 ± 2.70	62.360	0.000
IgM (g/L)	1.27 ± 0.68	0.89 ± 0.40	0.71 ± 0.39	0.82 ± 0.38	1.08 ± 0.53	6.114	0.008
Complement C1q (mg/L)	194.5 ± 28.7	168.9 ± 44.2	140.4 ± 39.6	157.7 ± 45.9	159.17 ± 55.3	6.726	0.000
Complement C3 (g/L)	1.18 ± 0.19	0.87 ± 0.15	0.79 ± 0.19	0.87 ± 0.21	0.91 ± 0.26	44.808	0.000
Complement C4 (g/L)	0.40 ± 0.18	0.26 ± 0.12	0.23 ± 0.11	0.25 ± 0.12	0.28 ± 0.15	8.731	0.002
Interleukin-6 (g/L)	10.7 ± 17.0	177.4 ± 121.6	84.0 ± 62.3	52.6 ± 40.9	41.2 ± 35.1	7.877	0.003
CD19 expression rate (%)	10.5 ± 4.0	9.6 ± 5.62	12.1 ± 5.6	12.7 ± 5.2	13.3 ± 6.1	1.866	0.129

ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; POD: Postoperative day; Ig: Immunoglobulin.

Table 8 Comparison of immunological data during stage-II associating liver partition and portal vein ligation for staged hepatectomy

Item	Preoperative	Stage-II ALPPS				*F* value	*P* value
		POD1	POD3	POD5	POD7		
T lymphocyte count (cells/μL)	1414.4 ± 634.0	455.9 ± 255.4	716.3 ± 311.3	796.3 ± 282.8	913.4 ± 387.1	17.626	0.000
Total T lymphocyte percentage (%)	67.8 ± 8.7	63.7 ± 9.2	72.3 ± 7.5	74.8 ± 6.4	73.6 ± 7.2	8.288	0.000
CD4+ T lymphocytes (cells/μL)	806.3 ± 428.2	246.4 ± 168.2	375.9 ± 170.1	493.9 ± 196.7	537.9 ± 231.3	7.925	0.003
CD8+ T lymphocytes (cells/μL)	438.2 ± 194.2	168.5 ± 89.4	290.3 ± 184.7	291.9 ± 159.0	356.1 ± 210.8	8.775	0.000
Natural killer cells (%)	16.5 ± 7.8	23.0 ± 7.1	12.7 ± 4.6	8.7 ± 4.8	10.2 ± 3.2	15.615	0.000
IgA (g/L)	3.11 ± 1.28	2.37 ± 1.88	2.31 ± 1.41	2.59 ± 1.30	3.40 ± 1.66	8.900	0.002
IgG (g/L)	15.11 ± 3.70	8.71 ± 2.10	8.11 ± 1.90	8.53 ± 1.66	9.68 ± 2.26	12.604	0.000
IgM (g/L)	1.27 ± 0.68	0.70 ± 0.37	0.67 ± 0.28	0.70 ± 0.36	0.83 ± 0.37	1.277	0.001
Complement C1q (mg/L)	194.5 ± 28.7	140.8 ± 33.8	111.1 ± 39.1	118.5 ± 41.3	124.2 ± 42.1	14.422	0.000
Complement C3 (g/L)	1.18 ± 0.19	0.72 ± 0.27	0.54 ± 0.20	0.58 ± 0.20	0.62 ± 0.18	24.345	0.000
Complement C4 (g/L)	0.40 ± 0.18	0.22 ± 0.16	0.15 ± 0.12	0.15 ± 0.14	0.17 ± 0.16	15.305	0.000
Interleukin-6 (pg/mL)	10.7 ± 17.0	210.3 ± 160.9	62.6 ± 27.6	37.1 ± 19.7	41.6 ± 61.3	12.206	0.000
CD19 expression rate (%)	10.5 ± 4.0	9.4 ± 5.1	10.2 ± 4.1	11.2 ± 5.8	11.0 ± 5.6	0.522	0.720

ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; POD: Postoperative day; Ig: Immunoglobulin.

the right hemi-hepatectomy group showed no significant difference (Figure 10, log-rank test $P = 0.733$). During the 90-d follow-up, one person died after stage-II ALPPS, and one died after hemi-hepatectomy; the mortality rate in each group was 6.67% (1/15).

DISCUSSION

As a planned step-by-step hepatectomy, ALPPS involves strict requirements for liver anatomy, degree

Table 9 Comparison of immunological data during conventional hepatectomy

Item	Preoperative	Conventional hepatectomy				*F* value	*P* value
		POD1	POD3	POD5	POD7		
T lymphocyte count (cells/μL)	1194.7 ± 305.4	447.1 ± 240.9	808.8 ± 313.7	835.7 ± 323.7	1032.7 ± 323.6	123.342	0.000
Total T lymphocyte percentage (%)	71.2 ± 5.2	58.9 ± 14.5	65.9 ± 11.7	72.3 ± 9.1	72.8 ± 7.7	17.676	0.000
CD4+ T lymphocytes (cells/μL)	761.1 ± 146.6	244.1 ± 113.9	515.9 ± 155.1	520.7 ± 168.7	644.8 ± 149.1	198.675	0.000
CD8+T lymphocytes (cells/μL)	379.9 ± 119.0	147.9 ± 98.5	226.8 ± 104.5	253.0 ± 110.4	331.8 ± 120.9	106.219	0.000
Natural killer cells (%)	17.9 ± 4.7	25.8 ± 8.4	14.1 ± 3.0	12.9 ± 4.6	13.8 ± 3.8	12.893	0.000
IgA (g/L)	2.67 ± 1.49	2.23 ± 1.34	2.11 ± 1.32	2.44 ± 1.50	2.82 ± 1.60	19.117	0.000
IgG (g/L)	11.78 ± 5.58	8.14 ± 3.97	7.89 ± 3.98	8.09 ± 4.05	8.55 ± 3.95	35.249	0.000
IgM (g/L)	0.91 ± 0.39	0.54 ± 0.31	0.63 ± 0.26	0.66 ± 0.27	0.82 ± 0.30	24.051	0.000
Complement C1q (mg/L)	174.6 ± 51.3	142.8 ± 49.9	121.9 ± 46.9	125.1 ± 52.1	132.2 ± 47.0	39.750	0.000
Complement C3 (g/L)	1.11 ± 0.45	0.84 ± 0.41	0.74 ± 0.37	0.70 ± 0.36	0.73 ± 0.37	31.517	0.000
Complement C4 (g/L)	0.32 ± 0.13	0.24 ± 0.11	0.21 ± 0.11	0.22 ± 0.11	0.24 ± 0.12	37.071	0.000
Interleukin-6 (pg/mL)	16.3 ± 17.7	171.6 ± 119.2	73.3 ± 46.3	43.5 ± 28.8	44.1 ± 31.1	8.981	0.002
CD19 expression rate (%)	13.04 ± 2.21	9.93 ± 3.05	10.68 ± 3.40	12.81 ± 4.37	14.03 ± 3.62	11.115	0.000

ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; POD: Postoperative day; Ig: Immunoglobulin.

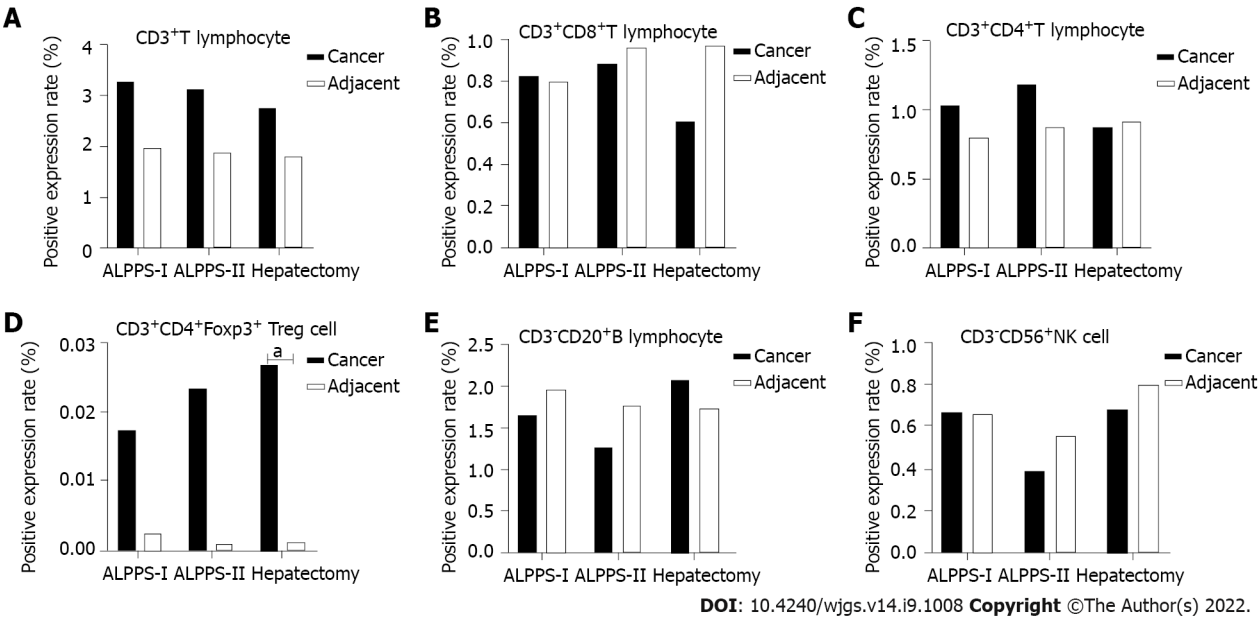

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Figure 3 Expression of each subpopulation of tumor-infiltrating lymphocytes in the associating liver partition and portal vein ligation for staged hepatectomy group (stage I and stage II) and right hemi-hepatectomy group. A: Positive expression level of $CD3^+$ T cells; B: Positive expression level of $CD3^+CD4^+$ T cells; C: Positive expression level of $CD3^+CD8^+$ T cells; D: Positive expression level of $CD3^+CD4^+Foxp3^+$ Treg cells; E: Positive expression level of $CD3^-CD20^+$ B cells; F: Positive expression level of $CD3^-CD56^+$ natural killer cells in different groups and tissues. $^aP < 0.05$.

of FLR hyperplasia, liver volume evaluation, and patient screening. Stage-I ALPPS separates the left hepatic lobe and the right one and ligates the right hepatic vein, resulting in an inflammatory reaction, hypoxia, tumor necrosis, and other factors, thus leading to a unique and complex immune microenvironment of tumor cells. Therefore, it is necessary to understand such immunological effects of the unique TME formed during HCC treatment by ALPPS from an immunological perspective as anti-tumor effect or tumor-induced immunosuppression. HCC treatment by ALPPS, the subsequent recruitment and change of TILs in the TME, and its effect on the tumor are still not completely understood. To verify the safety of ALPPS in treating massive HCC, more in-depth research on TILs in the TME is needed.

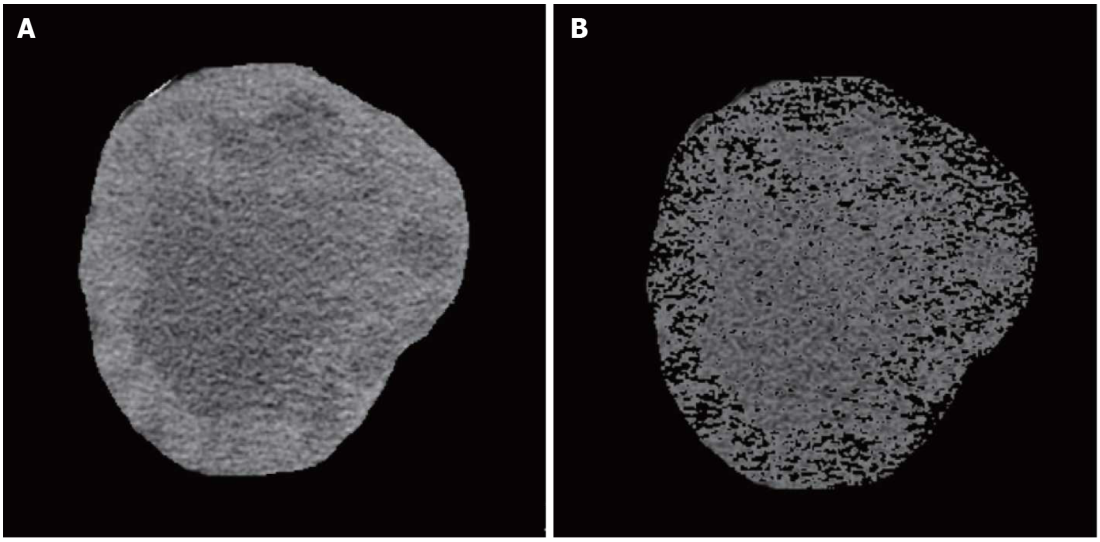

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Figure 4 Diagrammatic representation of tumor volume and tumor necrosis volume measurement. A: Tumor tissue; B: Component of tumor necrosis.

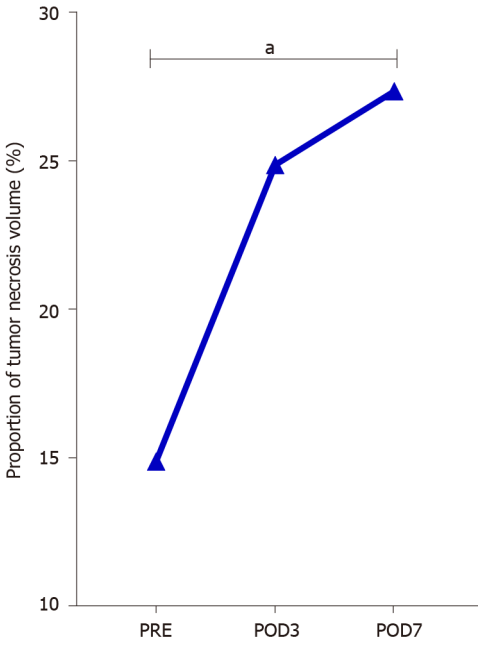

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Figure 5 Change in the proportion of tumor necrosis volume in stage-I associating liver partition and portal vein ligation for staged hepatectomy. The proportion of tumor necrotic volume on the seventh day after stage-I associating liver partition and portal vein ligation for staged hepatectomy was significantly higher than that before the operation. POD: Postoperative day. $^{a}P < 0.05$.

In order to determine the perioperative changes of TILs in patients with massive HCC in the right lobe treated by ALPPS and its effect on the tumor, we used PSM analysis on 15 HCC patients treated by ALPPS and 15 HCC patients treated by right hemi-hepatectomy. The results showed that all clinical baseline and tumor nature trends of the two groups were similar. The PSM method was used to reduce the selection deviation and baseline difference to make the sample data of the two groups more comparable[14]. Meanwhile, cancer and para-cancerous histopathological specimens of the right hemi-hepatectomy group and the ALPPS group were collected. The positive expression levels of TIL subsets were detected by polychromatic immunohistochemical staining. The results showed no significant differences in the six main TIL subsets between the ALPPS and right hepatectomy groups or between the cancerous and adjacent tissues in the same group. Especially during the "isolated" period of tumor-bearing right hepatic lobe between stage-I ALPPS and stage-II ALPPS, the positive expression levels of TIL subsets did not change significantly. It indicated that the degree of TIL infiltration in the TME has

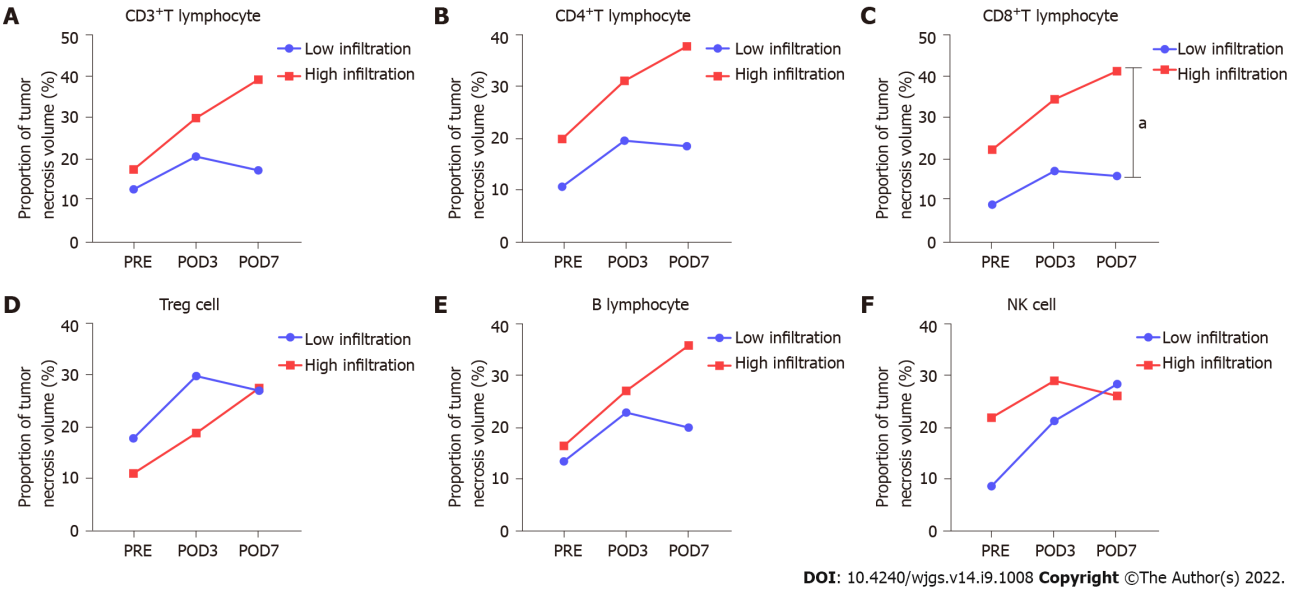

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Figure 6 Relationship between the proportion of tumor necrosis volume and tumor-infiltrating lymphocyte subpopulations in perioperative period of stage-I associating liver partition and portal vein ligation for staged hepatectomy. A: Proportion of tumor necrosis volume between high- and low- infiltration groups divided based on the positive expression level of CD3$^+$ T cells; B: Proportion of tumor necrosis volume between high- and low- infiltration groups divided based on the positive expression level of CD4$^+$ T cells; C: Proportion of tumor necrosis volume between high- and low- infiltration groups divided based on the positive expression level of CD8$^+$ T cells; D: Proportion of tumor necrosis volume between high- and low- infiltration groups divided based on the positive expression level of Treg cells; E: Proportion of tumor necrosis volume between high- and low- infiltration groups divided based on the positive expression level of B cells; F: Proportion of tumor necrosis volume between high- and low- infiltration groups divided based on positive expression level of natural killer cells. $^aP < 0.05$.

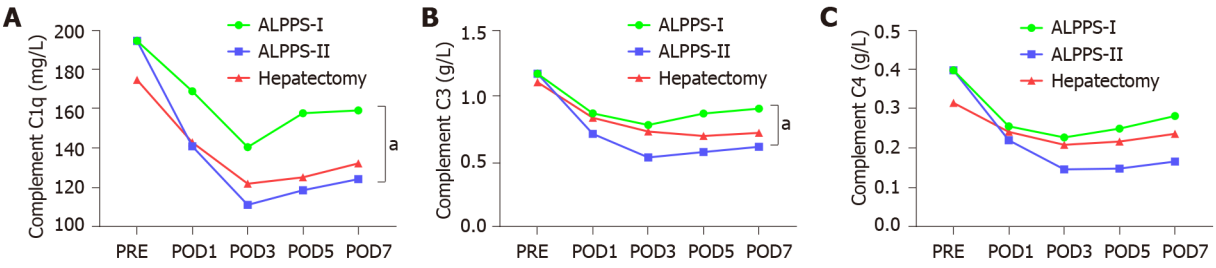

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Figure 7 Changes in peripheral blood complement concentrations after stage-I and II associating liver partition and portal vein ligation for staged hepatectomy and right hemi-hepatectomy. C1q and C3 in peripheral blood in stage-I associating liver partition and portal vein ligation for staged hepatectomy, were significantly higher than those in stage II. A: C1q; B: C3; C: C4. POD: Postoperative day; ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy.

not changed due to the traumatic stress of ALPPS surgery and the persistence of stage-I ALPPS to II tumors, which provides a basis for the operation of tumor local immune function and the body's resistance to tumor invasion. Previous studies have shown that the decrease in the invasion of TILs could promote tumor immune escape and malignant progression and limit the effect of immunotherapy, leading to a poor prognosis. In contrast, the increase in the infiltration degree of TILs produces the opposite result[15-17].

This study showed that the level of TIL infiltration during the perioperative period of ALPPS maintains a dynamic balance, suggesting that there is no adverse effect on TIL infiltration due to the surgical methods of ALPPS. To further verify the correlation between TILs and HCC, we measured the tumor volume and tumor necrotic volume before stage-I ALPPS operation and 3 d and 7 d after the stage-I ALPPS operation. We further calculated the ratio of tumor necrotic volume to tumor volume. We found an increase in tumor necrosis volume proportion, gradually from stage I to stage II of ALPPS, which might be caused by ligation of the right hepatic vein during ALPPS operation[18,19].

TILs play a central role in tumor local immune response, and their infiltration levels largely determine the severity of immune response. This is the main reason for using TILs to evaluate the intensity of immune response induced by ALPPS in this study. T cells not only mediate cellular immune response but also participate in humoral immune response induced by thymus-dependent antigen. CD8$^+$ T cells, also known as cytotoxic T cells, are the primary effector cells of the immune system against

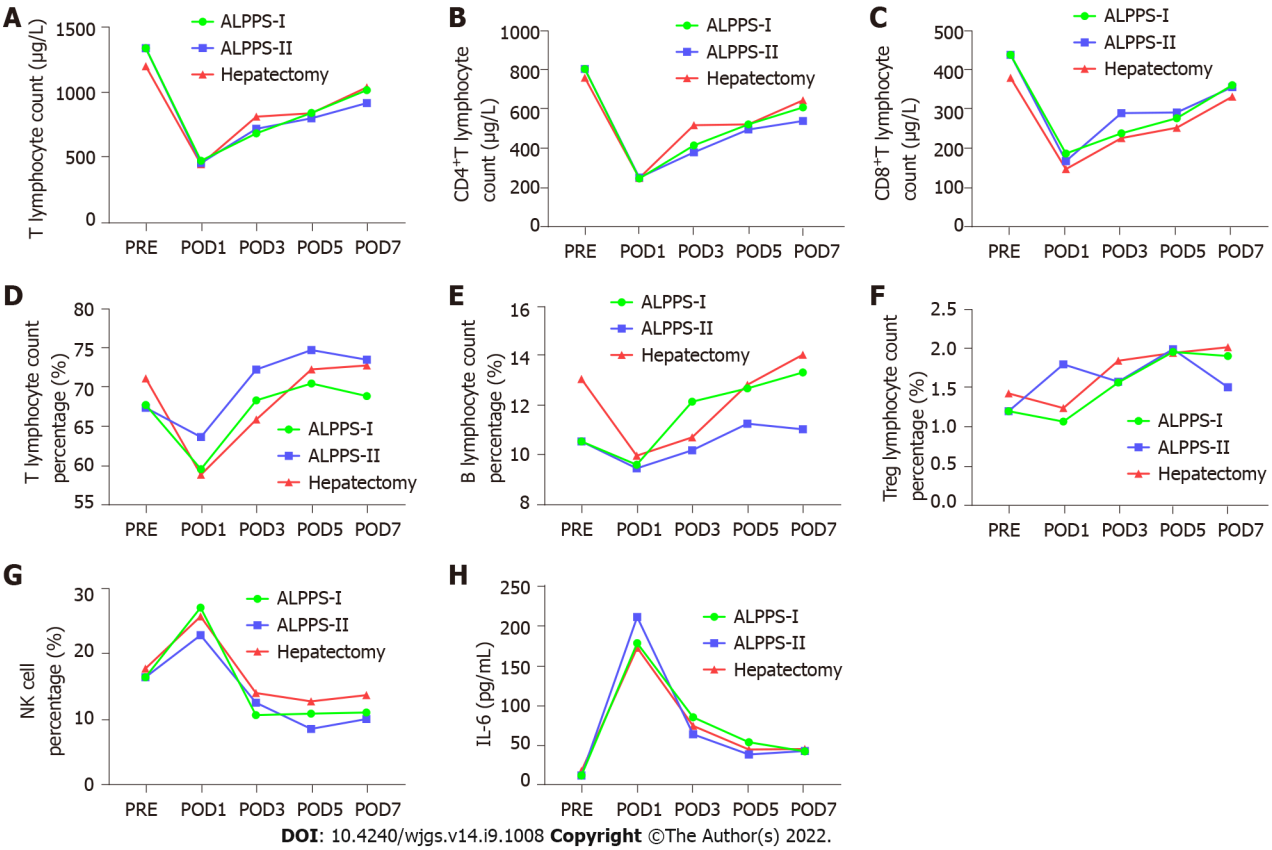

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Figure 8 Changes in peripheral blood lymphocyte subpopulations after stage-I and II associating liver partition and portal vein ligation for staged hepatectomy and right hemi-hepatectomy. Interleukin-6 levels in stage-I associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) and stage-II ALPPS increased significantly and reached a peak value on the first day after surgery. Natural killer cells in stage-I and stage-II ALPPS temporarily increased on the first day after surgery and gradually decreased on the second day after surgery to figures lower than the preoperative level. A: T lymphocyte count (/μL); B: CD4$^+$ T lymphocyte count (/μL); C: CD8$^+$ T lymphocyte count (/μL); D: T lymphocyte percentage (%); E: B lymphocyte percentage (%); F: Treg lymphocyte percentage (%); G: Natural killer cells percentage (%); H: Interleukin-6 (pg/mL). NK: Natural killer; IL: Interleukin; POD: Postoperative day; ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy.

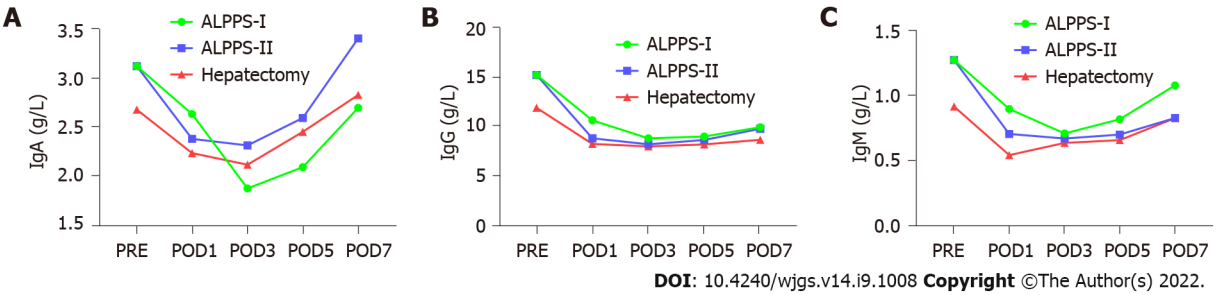

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Figure 9 Changes in peripheral blood immunoglobulins after stage-I and II associating liver partition and portal vein ligation for staged hepatectomy and right hemi-hepatectomy. A: Immunoglobulin (Ig)A (g/L); B: IgG (g/L); C: IgM (g/L). Ig: Immunoglobulin; POD: Postoperative day; ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy.

tumors. They can kill tumor cells efficiently through the perforin-granzyme pathway, Fas-FasL pathway, and tumor necrosis factor (TNF)-TNF receptor pathway[20,21]. Studies have shown that the local low level of CD8$^+$ T cell infiltration makes the tumor grow and progress more rapidly. Here, we found a correlation between the infiltration level of CD8$^+$ T cells and the degree of tumor necrosis. The proportion of tumor necrotic volume in the perioperative stage-I ALPPS gradually increased with time. Moreover, the proportion of tumor necrotic volume in the high CD8$^+$ T cell infiltration group was significantly higher than that in the low infiltration group. Based on the fact that there was no difference in the expression levels of CD8$^+$ T cells between the cancer tissues of the ALPPS group and the right hepatectomy group, it can be inferred that after stage-I ALPPS, the right lobe of the tumor-bearing liver is segregated and the right hepatic vein is ligated, while CD8$^+$ T cells can still effectively infiltrate the

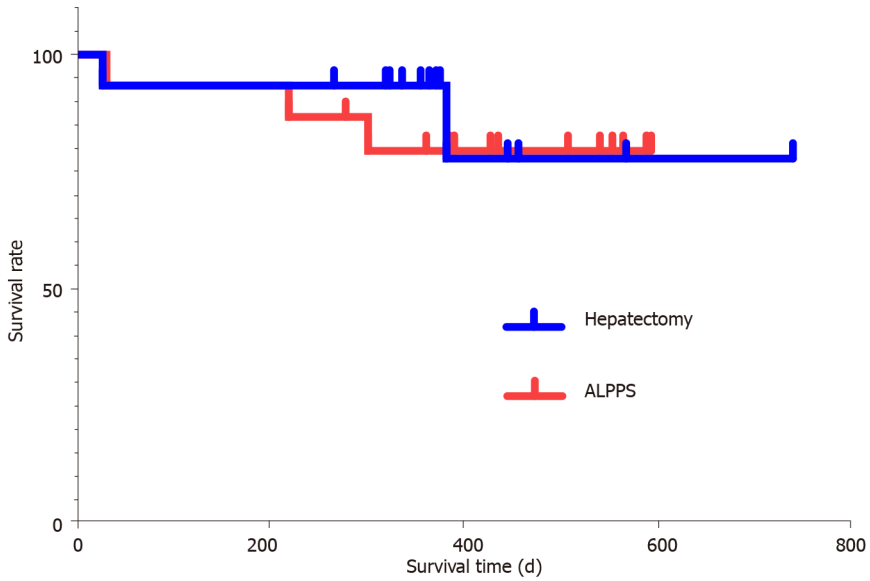

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Figure 10 Comparison of survival rate between associating liver partition and portal vein ligation for staged hepatectomy group and right hemi-hepatectomy group. The survival rate showed no significant difference between the two groups. ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy.

TME, thus exerting cytotoxicity to kill tumor cells. This result also proves that $CD8^+$ T cells do not reduce their infiltration degree due to the ALPPS operation and maintain the stability of the immune system's killing function.

Components of the peripheral blood circulatory system, including T cells, B cells, Treg cells, NK cells, IL-6, complement components (C1q, C3, and C4), and immunoglobulins (IgA, IgG, and IgM) can comprehensively reflect the immune function of the body. NK cells are the primary killer cells in innate immunity and can produce cytotoxic effects on tumor cells[20]. Among the peripheral blood immune indicators tested, NK cells temporarily increased on the first day after stage-I and stage-II ALPPS. They then gradually decreased to a lower level than the preoperative one. This trend may be related to the inhibitory effect of Treg cells on NK cells. One study has shown that higher serum IL-6 levels are associated with an increased risk of adverse HCC[22]. In this study, IL-6 in stage-I and II ALPPS increased significantly on the first postoperative day, and reached a peak. However, their levels were consistently higher than the preoperative levels. The levels after Stage-I and II ALPPS were significantly higher than that before surgery ($P1 = 0.000$, $P2 = 0.002$). This phenomenon might be related to the "waterfall" inflammation and persistent inflammation stimulus caused by surgical strikes. It is reported that the serum complement C1q increases significantly in the occurrence and development of nonalcoholic fatty liver[23]. In addition, complement C3 is involved in the occurrence and development of alcoholic hepatitis, thus inducing liver cancer[24]. In our study, the contents of complement C1q and C3 in peripheral blood after tumor removal in stage-II ALPPS were significantly lower than those in stage-I ALPPS. Finally, there was no significant change in serum IgA, IgG, or IgM levels between stage-I and stage-II ALPPS, indicating that the two-stage surgery performed by ALPPS did not cause excessive physiological stress or inflammation. In summary, comparing the changing trend of peripheral blood immune components in different groups showed that the traumatic stress and inflammatory reaction caused by right hepatectomy and ALPPS are similar. The ALPPS procedure did not cause more severe immunosuppression due to the "radical" surgical strategy, which is consistent with previously reported results[25].

In the past few decades, researchers have gained a deeper understanding of the importance of the TME in the occurrence, development, invasion, and metastasis of HCC[26]. The dynamic changes of the TME significantly affect the tumor biological characteristics of HCC. The TME is thought to have an active interaction with tumors, not just the passive structural support for tumor growth or survival. Therefore, more researchers are actively studying to understand the TME and its interaction with HCC cells. Because each component of the TME plays a complex role and influences one another, targeting a specific component of the TME is usually of little effect. It can be seen that a better understanding of the biological effects and molecular interactions between each component of the TME and tumor cells is crucial for understanding the mechanism and development of tumorigenesis.

In 1988, Rosenberg *et al*[27] invented the TIL therapy. Lymphocytes were isolated and extracted from the patient's body, amplified *in vitro*, and then infused back into the patient's body, opening up a new avenue in the field of tumor treatment. After years of continuous development and improvement, various new therapies based on TIL therapies have come out, such as chimeric antigen receptor T cell

immunotherapy (CAR-T) and T cell receptor chimeric T cell immunotherapy (T cell receptor-modified T cell immunotherapy, TCR-T)[28-30]. CAR-T and TCR-T cells are T cells that have been directionally modified and screened by genetic engineering technology, which strengthens the ability to recognize tumor cells or tumor-associated antigens. They can change the local immune suppression microenvironment induced by tumors and reverse tumor immunity tolerance status, showing good safety and effectiveness in treating various cancers. CAR-T therapy has a significant effect on hematological tumors [31,32], and TCR-T therapy has achieved good results in melanoma[33], multiple myeloma[34], lung cancer[35], and ovarian cancer[36]. The two therapies still face many challenges in treating solid tumors, such as low and uneven treatment response rates, local immunosuppressive effects of the TME, and lack of high-efficiency molecular targets[37,38]. However, the global R&D boom has continued, and several studies on TIL treatment of tumors have entered the clinical trial stage. Given the critical role of TILs in tumor local immunity, various new types of "TIL therapies" have developed rapidly, and significant breakthroughs have been continuously made in the field of tumor treatment. As an essential branch of tumor immunotherapy, TIL therapy is one of the indispensable directions for future medical development. The global multi-center and multi-organization collaboration can promote the standardization of ALPPS surgery and large-scale data statistics. Therefore, it is necessary to deeply understand the trend of TIL changes caused by ALPPS surgery.

From an immunological perspective, this study describes the change in the trend of the TME during the perioperative period of ALPPS. We demonstrate that ALPPS is safe and feasible for massive HCC in the right lobe of the liver. However, this study is a single-center study, with a limited number of patients and clinical data, thus, more in-depth discussion on the conclusions is required.

CONCLUSION

The level of TIL infiltration can maintain a dynamic balance during the perioperative period of ALPPS, which is the basis for the normal tumor local immune response. Compared with the right hepatectomy, ALPPS does not cause a decrease in TIL infiltration and the pathological changes of immune components in peripheral blood, thus resulting in severe immunosuppression. After stage-I ALPPS, $CD8^+$ T cells effectively infiltrate into the TME and play a cytotoxic role in killing tumor cells. Our results suggest that the infiltration of high $CD8^+$ T cells is related to the increase in tumor necrosis.

ARTICLE HIGHLIGHTS

Research background

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is an innovative approach to hepatectomy. The surgical trauma experienced by ALPPS is relatively high. In addition, stage-I ALPPS separates the right and left liver lobes and ligates the right hepatic vein, which causes inflammatory reactions, hypoxia, and tumor necrosis, resulting in a unique and complex immune microenvironment for tumor cells.

Research motivation

The trends and effects of tumor-infiltrating lymphocytes (TIL) residing or recruited in the tumor microenvironment (TME) are still unexplored in studies on ALPPS for hepatocellular carcinoma (HCC).

Research objectives

From an immunological perspective, the immunological effects exerted by the unique TME formed during the treatment of HCC by ALPPS, such as anti-tumor effects or tumor-induced immunosuppression, were investigated to further evaluate the safety and efficacy of ALPPS in treating massive HCC and conduct an in-depth study of TILs in the TME.

Research methods

Patients of the ALPPS and hemi-hepatectomy groups were screened using propensity score matching. Immunofluorescence staining was performed to detect and quantify TILs in tumors and adjacent tissues in these two groups of patients. Trends in TILs in peripheral blood during the perioperative period were compared between the two groups.

Research results

The proportion of tumor necrosis volume at postoperative day 7 after stage-I ALPPS was significantly higher than the pre-operative value (P = 0.024). The proportion of tumor necrosis volume was significantly higher in the high $CD8^+$ T-cell infiltrated group than in the low group before surgery for stage-I ALPPS (P = 0.048).

Research conclusions

From an immunological point of view, ALPPS is safe and feasible for treating right lobe massive HCC. The level of TIL infiltration during the perioperative period is dynamically balanced, and the ALPPS procedure itself does not lead to severe immunosuppression due to reduced TIL infiltration and pathological changes in peripheral blood immune components.

Research perspectives

Many studies on TIL therapy for tumors have entered clinical trials. As an important branch of tumor immunotherapy, TIL therapy is one of the potential directions for the future development of medicine.

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FOOTNOTES

Author contributions: Wang W and Deng ZF contributed equally to this work; Wang W, Deng ZF, Wang JL, Xu BH, Zhu H, Guo Y, and Wen Z designed the research study; Wang W, Deng ZF, Wang JL, Bao L, and Zhang L performed the research; Bao L, Zhang L, Xu BH, Zhu H, Guo Y, and Wen Z contributed reagents and analytic tools; Wang W, Deng ZF, and Wen Z analyzed the data; Wang W and Deng ZF wrote the manuscript; and all authors have read and approved the final manuscript.

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

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Data sharing statement: The data presented in this study are available upon request to the corresponding author.

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ORCID number: Wei Wang 0000-0001-5742-0645; Zhen-Feng Deng 0000-0001-5226-9392; Ji-Long Wang 0000-0001-7626-7199; Ling Zhang 0000-0001-7542-1879; Li Bao 0000-0003-4735-9021; Bang-Hao Xu 0000-0001-7270-3504; Hai Zhu 0000-0003-3697-984X; Ya Guo 0000-0003-0393-7045; Zhang Wen 0000-0003-4268-540X.

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REFERENCES

1 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]

2 **Omata M**, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, Tateishi R, Han KH, Chawla YK, Shiina S, Jafri W, Payawal

DA, Ohki T, Ogasawara S, Chen PJ, Lesmana CRA, Lesmana LA, Gani RA, Obi S, Dokmeci AK, Sarin SK. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatol Int* 2017; **11**: 317-370 [PMID: 28620797 DOI: 10.1007/s12072-017-9799-9]

3 **Forner A**, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018; **391**: 1301-1314 [PMID: 29307467 DOI: 10.1016/S0140-6736(18)30010-2]

4 **Schnitzbauer AA**, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA, Fichtner-Feigl S, Lorf T, Goralcyk A, Hörbelt R, Kroemer A, Loss M, Rümmele P, Scherer MN, Padberg W, Königsrainer A, Lang H, Obed A, Schlitt HJ. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. *Ann Surg* 2012; **255**: 405-414 [PMID: 22330038 DOI: 10.1097/SLA.0b013e31824856f5]

5 **Linecker M**, Björnsson B, Stavrou GA, Oldhafer KJ, Lurje G, Neumann U, Adam R, Pruvot FR, Topp SA, Li J, Capobianco I, Nadalin S, Machado MA, Voskanyan S, Balci D, Hernandez-Alejandro R, Alvarez FA, De Santibañes E, Robles-Campos R, Malagó M, de Oliveira ML, Lesurtel M, Clavien PA, Petrowsky H. Risk Adjustment in ALPPS Is Associated With a Dramatic Decrease in Early Mortality and Morbidity. *Ann Surg* 2017; **266**: 779-786 [PMID: 28806301 DOI: 10.1097/SLA.0000000000002446]

6 **Anantha RV**, Shaler CR, Meilleur CE, Parfitt J, Haeryfar SM, Hernandez-Alejandro R. The Future Liver Remnant in Patients Undergoing the Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy (ALPPS) Maintains the Immunological Components of a Healthy Organ. *Front Med (Lausanne)* 2016; **3**: 32 [PMID: 27556025 DOI: 10.3389/fmed.2016.00032]

7 **Deng Z**, Jin Z, Qin Y, Wei M, Wang J, Lu T, Zhang L, Zeng J, Bao L, Guo Y, Peng M, Xu B, Wen Z. Efficacy of the association liver partition and portal vein ligation for staged hepatectomy for the treatment of solitary huge hepatocellular carcinoma: a retrospective single-center study. *World J Surg Oncol* 2021; **19**: 95 [PMID: 33785022 DOI: 10.1186/s12957-021-02199-1]

8 **He YB**, Bai L, Jiang Y, Ji XW, Tai QW, Zhao JM, Zhang JH, Liu WY, Wen H. Application of a Three-Dimensional Reconstruction Technique in Liver Autotransplantation for End-Stage Hepatic Alveolar Echinococcosis. *J Gastrointest Surg* 2015; **19**: 1457-1465 [PMID: 25967139 DOI: 10.1007/s11605-015-2842-z]

9 **Fu-Gui L**, Lu-Nan Y, Bo L, Yong Z, Tian-Fu W, Ming-Qing X, Wen-Tao W, Zhe-Yu C. Estimation of standard liver volume in Chinese adult living donors. *Transplant Proc* 2009; **41**: 4052-4056 [PMID: 20005340 DOI: 10.1016/j.transproceed.2009.08.079]

10 **Oldhafer KJ**, Stavrou GA, van Gulik TM; Core Group. ALPPS--Where Do We Stand, Where Do We Go? *Ann Surg* 2016; **263**: 839-841 [PMID: 26756771 DOI: 10.1097/SLA.0000000000001633]

11 **Therasse P**, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**: 205-216 [PMID: 10655437 DOI: 10.1093/jnci/92.3.205]

12 **Dindo D**, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205-213 [PMID: 15273542 DOI: 10.1097/01.sla.0000133083.54934.ae]

13 **Rahbari NN**, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, Koch M, Makuuchi M, Dematteo RP, Christophi C, Banting S, Usatoff V, Nagino M, Maddern G, Hugh TJ, Vauthey JN, Greig P, Rees M, Yokoyama Y, Fan ST, Nimura Y, Figueras J, Capussotti L, Büchler MW, Weitz J. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery* 2011; **149**: 713-724 [PMID: 21236455 DOI: 10.1016/j.surg.2010.10.001]

14 **Yang JY**, Webster-Clark M, Lund JL, Sandler RS, Dellon ES, Stürmer T. Propensity score methods to control for confounding in observational cohort studies: a statistical primer and application to endoscopy research. *Gastrointest Endosc* 2019; **90**: 360-369 [PMID: 31051156 DOI: 10.1016/j.gie.2019.04.236]

15 **Garnelo M**, Tan A, Her Z, Yeong J, Lim CJ, Chen J, Lim KH, Weber A, Chow P, Chung A, Ooi LL, Toh HC, Heikenwalder M, Ng IO, Nardin A, Chen Q, Abastado JP, Chew V. Interaction between tumour-infiltrating B cells and T cells controls the progression of hepatocellular carcinoma. *Gut* 2017; **66**: 342-351 [PMID: 26669617 DOI: 10.1136/gutjnl-2015-310814]

16 **Thorsson V**, Gibbs DL, Brown SD, Wolf D, Bortone DS, Ou Yang TH, Porta-Pardo E, Gao GF, Plaisier CL, Eddy JA, Ziv E, Culhane AC, Paull EO, Sivakumar IKA, Gentles AJ, Malhotra R, Farshidfar F, Colaprico A, Parker JS, Mose LE, Vo NS, Liu J, Liu Y, Rader J, Dhankani V, Reynolds SM, Bowlby R, Califano A, Cherniack AD, Anastassiou D, Bedognetti D, Mokrab Y, Newman AM, Rao A, Chen K, Krasnitz A, Hu H, Malta TM, Noushmehr H, Pedamallu CS, Bullman S, Ojesina AI, Lamb A, Zhou W, Shen H, Choueiri TK, Weinstein JN, Guinney J, Saltz J, Holt RA, Rabkin CS; Cancer Genome Atlas Research Network, Lazar AJ, Serody JS, Demicco EG, Disis ML, Vincent BG, Shmulevich I. The Immune Landscape of Cancer. *Immunity* 2018; **48**: 812-830.e14 [PMID: 29628290 DOI: 10.1016/j.immuni.2018.03.023]

17 **Kim HD**, Song GW, Park S, Jung MK, Kim MH, Kang HJ, Yoo C, Yi K, Kim KH, Eo S, Moon DB, Hong SM, Ju YS, Shin EC, Hwang S, Park SH. Association Between Expression Level of PD1 by Tumor-Infiltrating CD8+ T Cells and Features of Hepatocellular Carcinoma. *Gastroenterology* 2018; **155**: 1936-1950.e17 [PMID: 30145359 DOI: 10.1053/j.gastro.2018.08.030]

18 **Zalinski S**, Scatton O, Randone B, Vignaux O, Dousset B. Complete hepatocellular carcinoma necrosis following sequential porto-arterial embolization. *World J Gastroenterol* 2008; **14**: 6869-6872 [PMID: 19058317 DOI: 10.3748/wjg.14.6869]

19 **Chan A**, Zhang WY, Chok K, Dai J, Ji R, Kwan C, Man N, Poon R, Lo CM. ALPPS Versus Portal Vein Embolization for Hepatitis-related Hepatocellular Carcinoma: A Changing Paradigm in Modulation of Future Liver Remnant Before Major Hepatectomy. *Ann Surg* 2021; **273**: 957-965 [PMID: 31305284 DOI: 10.1097/SLA.0000000000003433]

20 **Tahmasebi Birgani M**, Carloni V. Tumor Microenvironment, a Paradigm in Hepatocellular Carcinoma Progression and Therapy. *Int J Mol Sci* 2017; **18**: 405 [PMID: 28216578 DOI: 10.3390/ijms18020405]

21 **Cheng L**, Du X, Wang Z, Ju J, Jia M, Huang Q, Xing Q, Xu M, Tan Y, Liu M, Du P, Su L, Wang S. Hyper-IL-15 suppresses metastatic and autochthonous liver cancer by promoting tumour-specific CD8+ T cell responses. *J Hepatol* 2014; **61**: 1297-1303 [PMID: 25016226 DOI: 10.1016/j.jhep.2014.07.004]

22 **Ohishi W**, Cologne JB, Fujiwara S, Suzuki G, Hayashi T, Niwa Y, Akahoshi M, Ueda K, Tsuge M, Chayama K. Serum interleukin-6 associated with hepatocellular carcinoma risk: a nested case-control study. *Int J Cancer* 2014; **134**: 154-163 [PMID: 23784949 DOI: 10.1002/ijc.28337]

23 **Rensen SS**, Slaats Y, Driessen A, Peutz-Kootstra CJ, Nijhuis J, Steffensen R, Greve JW, Buurman WA. Activation of the complement system in human nonalcoholic fatty liver disease. *Hepatology* 2009; **50**: 1809-1817 [PMID: 19821522 DOI: 10.1002/hep.23228]

24 **Zhong F**, Hu Z, Jiang K, Lei B, Wu Z, Yuan G, Luo H, Dong C, Tang B, Zheng C, Yang S, Zeng Y, Guo Z, Yu S, Su H, Zhang G, Qiu X, Tomlinson S, He S. Complement C3 activation regulates the production of tRNA-derived fragments Gly-tRFs and promotes alcohol-induced liver injury and steatosis. *Cell Res* 2019; **29**: 548-561 [PMID: 31076642 DOI: 10.1038/s41422-019-0175-2]

25 **Joechle K**, Moser C, Ruemmele P, Schmidt KM, Werner JM, Geissler EK, Schlitt HJ, Lang SA. ALPPS (associating liver partition and portal vein ligation for staged hepatectomy) does not affect proliferation, apoptosis, or angiogenesis as compared to standard liver resection for colorectal liver metastases. *World J Surg Oncol* 2017; **15**: 57 [PMID: 28270160 DOI: 10.1186/s12957-017-1121-8]

26 **Sükei T**, Palma E, Urbani L. Interplay between Cellular and Non-Cellular Components of the Tumour Microenvironment in Hepatocellular Carcinoma. *Cancers (Basel)* 2021; **13**: 5586 [PMID: 34771746 DOI: 10.3390/cancers13215586]

27 **Rosenberg SA**, Packard BS, Aebersold PM, Solomon D, Topalian SL, Toy ST, Simon P, Lotze MT, Yang JC, Seipp CA. Use of tumor-infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma. A preliminary report. *N Engl J Med* 1988; **319**: 1676-1680 [PMID: 3264384 DOI: 10.1056/NEJM198812223192527]

28 **Bonini C**, Mondino A. Adoptive T-cell therapy for cancer: The era of engineered T cells. *Eur J Immunol* 2015; **45**: 2457-2469 [PMID: 26202766 DOI: 10.1002/eji.201545552]

29 **Sermer D**, Brentjens R. CAR T-cell therapy: Full speed ahead. *Hematol Oncol* 2019; **37** Suppl 1: 95-100 [PMID: 31187533 DOI: 10.1002/hon.2591]

30 **Ikeda H**. T-cell adoptive immunotherapy using tumor-infiltrating T cells and genetically engineered TCR-T cells. *Int Immunol* 2016; **28**: 349-353 [PMID: 27127191 DOI: 10.1093/intimm/dxw022]

31 **Zhao Z**, Chen Y, Francisco NM, Zhang Y, Wu M. The application of CAR-T cell therapy in hematological malignancies: advantages and challenges. *Acta Pharm Sin B* 2018; **8**: 539-551 [PMID: 30109179 DOI: 10.1016/j.apsb.2018.03.001]

32 **Levin A**, Shah NN. Chimeric antigen receptor modified T cell therapy in B cell non-Hodgkin lymphomas. *Am J Hematol* 2019; **94**: S18-S23 [PMID: 30652353 DOI: 10.1002/ajh.25403]

33 **Hotblack A**, Holler A, Piapi A, Ward S, Stauss HJ, Bennett CL. Tumor-Resident Dendritic Cells and Macrophages Modulate the Accumulation of TCR-Engineered T Cells in Melanoma. *Mol Ther* 2018; **26**: 1471-1481 [PMID: 29628306 DOI: 10.1016/j.ymthe.2018.03.011]

34 **Rapoport AP**, Stadtmauer EA, Binder-Scholl GK, Goloubeva O, Vogl DT, Lacey SF, Badros AZ, Garfall A, Weiss B, Finklestein J, Kulikovskaya I, Sinha SK, Kronsberg S, Gupta M, Bond S, Melchiori L, Brewer JE, Bennett AD, Gerry AB, Pumphrey NJ, Williams D, Tayton-Martin HK, Ribeiro L, Holdich T, Yanovich S, Hardy N, Yared J, Kerr N, Philip S, Westphal S, Siegel DL, Levine BL, Jakobsen BK, Kalos M, June CH. NY-ESO-1-specific TCR-engineered T cells mediate sustained antigen-specific antitumor effects in myeloma. *Nat Med* 2015; **21**: 914-921 [PMID: 26193344 DOI: 10.1038/nm.3910]

35 **Marcinkowski B**, Stevanović S, Helman SR, Norberg SM, Serna C, Jin B, Gkitsas N, Kadakia T, Warner A, Davis JL, Rooper L, Hinrichs CS. Cancer targeting by TCR gene-engineered T cells directed against Kita-Kyushu Lung Cancer Antigen-1. *J Immunother Cancer* 2019; **7**: 229 [PMID: 31455429 DOI: 10.1186/s40425-019-0678-x]

36 **Matsuda T**, Leisegang M, Park JH, Ren L, Kato T, Ikeda Y, Harada M, Kiyotani K, Lengyel E, Fleming GF, Nakamura Y. Induction of Neoantigen-Specific Cytotoxic T Cells and Construction of T-cell Receptor-Engineered T Cells for Ovarian Cancer. *Clin Cancer Res* 2018; **24**: 5357-5367 [PMID: 29720506 DOI: 10.1158/1078-0432.CCR-18-0142]

37 **Johnson LA**, June CH. Driving gene-engineered T cell immunotherapy of cancer. *Cell Res* 2017; **27**: 38-58 [PMID: 28025979 DOI: 10.1038/cr.2016.154]

38 **Ping Y**, Liu C, Zhang Y. T-cell receptor-engineered T cells for cancer treatment: current status and future directions. *Protein Cell* 2018; **9**: 254-266 [PMID: 28108950 DOI: 10.1007/s13238-016-0367-1]

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Blood index panel for gastric cancer detection

Guang-Hong Guo, Yi-Bin Xie, Peng-Jun Zhang, Tao Jiang

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Guang-Hong Guo, Department of Laboratory Medicine, The First Medical Center of Chinese PLA General Hospital, Beijing 100853, China

Yi-Bin Xie, Department of Pancreatic and Gastric Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Peng-Jun Zhang, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Interventional Therapy Department, Peking University Cancer Hospital and Institute, Beijing 100142, China

Tao Jiang, Medicine Innovation Research Division of Chinese PLA General Hospital, Beijing 100853, China

Corresponding author: Tao Jiang, MD, Doctor, Medicine Innovation Research Division of Chinese PLA General Hospital, No. 28 Fuxing Road, Beijing 100853, China.
laoai2915@163.com

Abstract

BACKGROUND

Gastric cancer is a common malignant tumor. Early detection and diagnosis are crucial for the prevention and treatment of gastric cancer.

AIM

To develop a blood index panel that may improve the diagnostic value for discriminating gastric cancer and gastric polyps.

METHODS

Thirteen tumor-related detection indices, 38 clinical biochemical indices and 10 cytokine indices were examined in 139 gastric cancer patients and 40 gastric polyp patients to build the model. An additional 68 gastric cancer patients and 22 gastric polyp patients were enrolled for validation. After area under the curve evaluation and univariate and multivariate analyses.

RESULTS

Five tumor-related detection indices, 12 clinical biochemical indices and 1 cytokine index showed significant differences between the gastric cancer and gastric polyp groups. Carbohydrate antigen (CA) 724, phosphorus (P) and ischemia-modified albumin (IMA) were included in the blood index panel, and the area under the curve (AUC) of the index panel was 0.829 (0.754, 0.905). After validation, the AUC was 0.811 (0.700, 0.923). Compared to the conventional index

CA724, the blood index panel showed significantly increased diagnostic value.

CONCLUSION
We developed an index model that included CA724, P and IMA to discriminate the gastric cancer and gastric polyp groups, which may be a potential diagnostic method for clinical practice.

Key Words: Gastric cancer; Gastric polyp; Blood; Index; Panel

Core Tip: Early diagnosis and early treatment of gastric cancer is the key to improving the survival and cure rates of patients. Therefore, early detection and diagnosis are crucial for the prevention and treatment of gastric cancer. In this study, the we aimed to evaluate the diagnostic value of the blood index panel for gastric cancer.

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INTRODUCTION

Gastric cancer is a common malignant tumor that endangers human health, and it ranks second only to lung cancer in the number of deaths resulting from various malignant tumors[1]. The occurrence and development of gastric cancer is a multistage process involving changes at the gene and molecular levels. There is a period of precancerous lesions in the early stage of gastric cancer, and most of the precancerous lesions remain unchanged, while some develop into cancer[2]. The Correa cascade is a generally recognized model of gastric cancer, which is superficial gastritis-atrophic gastritis-intestinal metaplasia-dysplasia-gastric cancer. In recent years, the incidence of gastrointestinal malignant tumors in China has increased significantly[3]. Because most gastrointestinal malignant tumors have no obvious symptoms during the early stage, they cannot be detected quickly. The postoperative survival rate of malignant tumors is very low[4]. Early diagnosis and early treatment of gastric cancer is the key to improving the survival and cure rates of patients. Therefore, early detection and diagnosis are crucial for the prevention and treatment of gastric cancer[5].

With further research, finding a simple, fast and easy dynamic observation method that can screen high-risk groups of gastric cancer (such as patients with atypical hyperplasia) would be beneficial for early diagnosis, and serum biomarkers (tumor markers, combined screening of cytokines and biochemical indicators) may be new targets for the early diagnosis of gastric cancer. Tumor markers reflect the occurrence and development of tumors and the degree of activation or inactivation of tumor-related genes. Since these substances are secreted by tumor cells and released into the blood and body fluids during tumor proliferation, they can be used to indicate the presence of tumors[6,7]. An ideal tumor marker has the characteristics of high sensitivity and high specificity, is present in body fluids, especially blood, and is easy to detect. In recent years, due to the rapid development of molecular biology, markers related to gastric cancer have been continuously discovered. The cell surface structural antigen carcinoembryonic antigen (CEA) is a tumor-associated antigen that can be extracted from embryonic tissue and detected in a variety of body fluids. As one of the most common tumor markers, it is widely used as a diagnostic and monitoring index for various gastrointestinal tumors (especially gastric adenocarcinoma)[8-10]. Carbohydrate antigen (CA) 724 is a high molecular weight glycoprotein and one of the best tumor markers for the diagnosis of gastric cancer. CA724 is highly specific for gastric cancer and has good application value in digestive system malignant tumors[10-12]. In addition, cytokines also play important roles in the initiation and treatment of cancer. Cytokines produced by tumor cells or the tumor stroma can stimulate the survival, proliferation, and metastasis of cancer cells. These factors were demonstrated to be potential biomarkers for various cancers[13-15].

In our study, we examined 13 tumor-related indices, 38 clinical biochemical indices and 10 cytokines in gastric cancer and gastric polyp patients and aimed to develop an index panel that can improve the diagnostic value of discriminating gastric cancer and gastric polyp patients. This panel may become a detection method for clinical practice.

MATERIALS AND METHODS

Study subjects

Signed informed consent was obtained, and this study was approved by the Ethics Committee of the First Center of Chinese PLA General Hospital. A total of 269 serum samples were collected from patients with gastric cancer and gastric polyps who were admitted to the First Center of Chinese PLA General Hospital. The inclusion criteria for gastric cancer and gastric polyps were as follows: (1) Primary; (2) Confirmed by pathological diagnosis; (3) No radiotherapy or chemotherapy before surgery; (4) Preoperative diagnosis with more than two imaging results; and (5) Complete medical records and follow-up data. The exclusion criteria were as follows: (1) Received radiotherapy, chemotherapy, and immunotherapy; (2) Immune system diseases; (3) Chronic wasting diseases and infectious diseases; and (4) Other types of malignant tumors. A total of 139 gastric cancer patients and 40 gastric polyp patients were enrolled for model building. An additional 68 gastric cancer patients and 22 gastric polyp patients were enrolled for validation. The two groups were age- and sex-matched. Three milliliters of fasting venous blood was collected from the subjects, incubated for 30 min, and centrifuged at 3500 r/min for 7 min to separate the serum, and the specimens without hemolysis or chyle were qualified and stored at -80 °C.

Tumor-related and clinical biochemical index detection

The 13 tumor-related indices included CEA, alpha fetoprotein (AFP), carbohydrate antigen 125 (CA125), CA199, CA153, CA724, cytokeratin fragment 211 (Cyfra211), ferritin (Ferr), neuron-specific enolase (NSE), squamous cell carcinoma (SCC), pepsinogen (PG) I, PG II, and PGI/II. The 38 clinical biochemical indices included alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP), albumin (ALB), total bilirubin (TB), direct bilirubin (DB), total bile acid (TBA), alkaline phosphatase (ALP), γ-glutamyltransferase (GGT), glucose (GLu), urea nitrogen (UN), creatinine (Cr), uric acid (UA), cholesterol (CHO), triglyceride (TG), creatine kinase (CK), lactate dehydrogenase (LDH), isoenzyme of creatine kinase (CKMB), calcium (Ca), phosphorus (P), magnesium (Mg), potassium (K), sodium (Na), chlorine (Cl), carbon dioxide (CO_2), lipoprotein a (LPa), high-density lipoprotein (HDL), low-density lipoprotein (LDL), apolipoprotein A1 (ApoA1), apoB, cysteine (CYS), sialic acid (SA), homocysteine (HCY), C-reactive protein (CRP), amylase (AMY), lipase (LPS), superoxide dismutase (SOD), and ischemia-modified albumin (IMA).

CEA, AFP, CA199, CA724, CA125, CA153, Cyfra211, Ferr, NSE, ALT, AST, TP, ALB, ALP, GGT, Glu, UN, CR, UA, CHO, TG, CK, Ca, P, Mg, K, Na, CL, CO2, HDL, LDL, CRP, AMY, and LPS detection kits, standards and controls were purchased from Roche Diagnostics Ltd. ApoA1, ApoB, CYS, Lp (a), and CKMB detection kits, standards and quality controls were purchased from Beijing Leadman Biochemical Co., Ltd. SCC, PG I and PG II assay kits, standards and controls were purchased from Abbott Laboratories. TBA and HCY detection kits, standards and quality controls were purchased from Beijing Jiuqiang Biotechnology Co., Ltd. TB and DB detection kits, standards and controls were purchased from Hitachi Japan. IMA test kits, standards and quality controls were purchased from Changsha Yikang Technology Development Co., Ltd. SA detection kits, standards and quality controls were purchased from Zhejiang Dongou Diagnostics Products Co., Ltd. SOD detection kits, standards and quality controls were purchased from Fujian Fuyuan Biotechnology Co., Ltd. The serum was collected from the -80 °C serum specimen bank, and after being thawed, 500-1000 μL was dispensed into a centrifuge tube and assigned a new number. The Modular 7600 automatic biochemical analyzer, Roche E170 immunoassay analyzer and Architect i2000 immunoassay system were used to complete quality control and calibrations before the assays. After analysis, the experimental data from each instrument were exported for statistical analysis.

Cytokine detection

The 10 cytokines included granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-γ (IFNγ), interleukin-1β (IL-1β), IL-2, IL-4, IL-6, IL-8, IL-10, monocyte chemoattractant protein (MCP-1), and tumor necrosis factor α (TNFα) and were analyzed by a Luminex Instrument Model 200 Liquid Core Analyzer according to the instructions of the Human Cytokine/Chemokine Detection Kit. All reagents were equilibrated to room temperature (20 °C-25 °C) before the test. A schematic diagram of sample loading in a 96-well plate was drawn on paper (standards, 0, 3.2, 16, 80, 400, 2000, and 10000 ng/mL, QC I, QC II, sample), and duplicate wells were recommended. Then, 200 μL of assay buffer was added to each reaction well, which was sealed and shaken on a horizontal shaking instrument for 10 min (room temperature, 20 °C-25 °C). The excess assay buffer was blotted from the bottom with filter paper or paper towels. Then, 25 μL of analysis buffer was added to the background standard well, 25 μL of buffer was added to each sample well, 25 μL of each standard or quality control was added to the corresponding reaction well, and 25 μL of the appropriate matrix diluent was added to the background wells, standard wells, and quality control wells. When the analyte was serum or plasma, the serum matrix provided by the kit was used. When the analyte was tissue culture fluid or other supernatant, the corresponding medium was used as a diluent. A total of 25 μL of sample was added to the appropriate reaction well, the microspheres were mixed, and 25 μL of the mixed microspheres was added to each

well. The wells were covered with parafilm and aluminum foil and incubated at room temperature (20 °C-25 °C) on a horizontal shaker for 1 h (when the test substance was serum or plasma, overnight incubation at 4 °C can improve the sensitivity). Then, the liquid was gently aspirated, the wells were washed with wash solution (200 μL/well) twice, the liquid was aspirated, and the washing solution at the bottom of the reaction plate was dried with filter paper or paper towel. The detection antibody was added (25 μL/well), and the plates were covered with parafilm and aluminum foil, shaken on a horizontal shaker and incubated at room temperature for 30 min. Streptavidin-PE (25 μL/well) was added, and the plates were covered with parafilm and aluminum foil, shaken on a horizontal shaker and incubated at room temperature for 30 min. Then, the liquid was gently aspirated, the wells were washed with wash solution (200 μL/well) twice, the liquid was aspirated, and the washing solution at the bottom of the reaction plate was blotted with filter paper or paper towel. Sheath fluid (100 μL/well) was added. The plates were covered with aluminum foil and shaken on a horizontal shaker for 5 min to resuspend the microspheres. The microspheres were read on a Luminex instrument, and the results were calculated.

Statistical analysis

SPSS 22.0 was used in this study. Measurement data are expressed as the median (25%, 75%). If the data were normally distributed, they were compared by two independent samples t tests. If not, they were compared by the rank sum test. The area under the curve (AUC) was used to evaluate the diagnostic value. Univariate and multivariate analyses were used to analyze the Exp (B) of the indices. Logistic regression analysis was used to build the index model. *Z* scores were used to compare the AUCs of the two groups.

RESULTS

Comparison of the tumor-related detection indices between the gastric cancer and gastric polyp groups

As shown in Table 1, 13 tumor-related detection indices, including CEA, AFP, CA125, CA199, CA153, CA724, CY211, Ferr, NSE, SCC, PG I/II, PG II, and PG I, were compared between the gastric cancer and gastric polyp groups. Among the 13 tumor-related detection indices, CEA (P = 0.014), CA125 (P = 0.033), CA199 (P = 0.017), CA724 (P = 0.007) and PG I/II (P = 0.008) showed significant differences between the two groups, and the other 8 tumor-related detection indices (AFP, CA153, CY211, Ferr, NSE, SCC, PG II, and PG I) showed no significant differences.

Comparison of the clinical biochemical indices of the gastric cancer and gastric polyp groups

As shown in Table 2, 38 clinical biochemical indices, including ALT, AST, TP, ALB, TB, DB, TBA, ALP, GGT, GLu, UN, Cr, UA, CHO, TG, CK, LDH, CKMB, Ca, P, Mg, K, Na, Cl, CO_2, LP (a), HDL, LDL, ApoA1, ApoB, CYS, SA, HCY, CRP, AMY, LPS, SOD and IMA, were compared between the gastric cancer and gastric polyp groups. ALB (P = 0.007), CHO (P = 0.035), TG (P = 0.017), Ca (P = 0.025), P (P = 0.008), Cl (P = 0.008), HDL (P = 0.004), LDL (P = 0.010), ApoA1 (P = 0.001), ApoB (P = 0.021), SOD (P = 0.001) and IMA (P = 0.001) showed significant differences between the two groups. The other 26 tumor-related detection indices, including ALT, AST, TP, TB, DB, TBA, ALP, GGT, GLu, UN, Cr, UA, CK, LDH, CKMB, Mg, K, Na, CO_2, LP (a), CYS, SA, HCY, CRP, AMY and LPS, showed no significant differences.

Comparison of the cytokine indices in the gastric cancer and gastric polyp groups

As shown in Table 3, 10 tumor-related detection indices, including GM-CSF, IFNγ, IL-10, IL-1β, IL-2, IL-4, IL-6, IL-8, MCP-1, and TNFα, were compared between the gastric cancer and gastric polyp groups. Because IL-2 and IL-4 were lower than the detection limit in most samples, these two cytokine indices were deleted. After analysis, only TNFα (P = 0.001) showed a significant difference between the two groups, and the other 7 tumor-related detection indices, including GM-CSF, IFNγ, IL-10, IL-1β, IL-6, IL-8, and MCP-1, showed no significant differences.

Diagnostic value evaluation of a single differential index for discriminating the gastric cancer and gastric polyp groups

After comparing the tumor-related, clinical biochemical and cytokine indices between the gastric cancer and gastric polyp groups, the diagnostic value of the differential indices for discriminating between the gastric cancer and gastric polyp groups was evaluated. As shown in Table 4, the differential indices of CEA (P = 0.014), CA125 (P = 0.033), CA199 (P = 0.017), CA724 (P = 0.007), PG I/II (P = 0.008), ALB (P = 0.007), CHO (P = 0.035), TG (P = 0.017), Ca (P = 0.025), P (P = 0.008), Cl (P = 0.008), HDL (P = 0.004), LDL (P = 0.010), ApoA1 (P = 0.001), ApoB (P = 0.021), SOD (P = 0.001), IMA (P = 0.001) and TNFα (P = 0.001) were evaluated by the area under the curve. Only CA199 and CHO showed no significant differences. CEA, CA125, CA724, PG I/II, ALB, TG, Ca, P, Cl, HDL, LDL, ApoA1, ApoB, SOD, IMA and TNFα

Table 1 Comparison of tumor related detection index between gastric cancer and gastric polyp group

Indicator	Gastric polyp (*n* = 40)	Gastric cancer (*n* = 139)	*P* value
CEA	1.16 (1.55, 2.11)	1.11 (2.33, 5.11)	0.014
AFP	1.64 (2.63, 3.62)	1.43 (2.24, 3.23)	0.499
CA125	6.86 (9.91, 14.81)	8.56 (13.73, 24.39)	0.033
CA199	4.8 (7.74, 13.91)	5.07 (10.52, 29.36)	0.017
CA153	6.53 (9.3, 12.54)	6.42 (9.03, 13.15)	0.268
CA724	0.84 (1.34, 3.68)	1.43 (3.33, 11)	0.007
CY211	1.32 (1.67, 2.35)	1.7 (2.47, 4.46)	0.390
Ferr	63.86 (144.35, 268.48)	26.19 (79.3, 174.4)	0.176
NSE	8.39 (10.06, 11.87)	7.55 (9.27, 11.57)	0.732
SCC	0.43 (0.7, 1.08)	0.5 (0.7, 1)	0.247
PG1/2	1.3 (4.31, 6.26)	0.67 (2.98, 4.26)	0.008
PG2	7.65 (13.9, 29.68)	9.9 (19.3, 32.4)	0.199
PG1	12.83 (58.5, 115.93)	20.3 (53.8, 82)	0.255

CEA: Carcinoembryonic antigen; AFP: Alpha fetoprotein; CA125: Carbohydrate antigen 125; CY211: Cytokeratin 211; Ferr: Ferritin; NSE: Neuron-specific enolase; SCC: Squamous cell carcinoma; PG: Pepsinogen.

showed significant differences. The AUC of the best indicator, IMA, was 0.790 (0.705, 0.875). The *P* value was < 0.001. The AUC of the conventional index CA724 was 0.702 (0.614, 0.789). The *P* value was <0.001.

Univariate and multivariate analysis of the differential index between gastric cancer and gastric polyp groups

After the diagnostic value evaluation of a single differential index for discriminating the gastric cancer and gastric polyp groups was performed, 16 indices, including CEA, CA125, CA724, PG I/II, ALB, TG, Ca, P, Cl, HDL, LDL, ApoA1, ApoB, SOD, IMA and TNFα, were further analyzed by univariate and multivariate analysis. As shown in Table 5, after the univariate analysis, the 3 indices Exp (B), CA724 (*P* = 0.03), P (*P* = 0.03) and IMA (*P* = 0.03) showed significant differences. The other indices (CEA, CA125, PG I/II, ALB, TG, Ca, Cl, HDL, LDL, ApoA1, ApoB, SOD and TNFα) showed no significant differences. Then, the 3 indices that showed significant differences were further analyzed by multivariate analysis. The Exp (B) of CA724, P and IMA was 1.17 (1.02, 1.34), 0.13 (0.03, 0.58), and 0.85 (0.78, 0.92), respectively.

Diagnostic value evaluation of the index panel for differentiating the gastric cancer and gastric polyp groups

CA724, P and IMA were analyzed by logistic regression analysis to build a diagnostic index panel to differentiate the gastric cancer and gastric polyp groups. As shown in Figure 1A, for discriminating 139 gastric cancer and 40 gastric polyp patients, the AUC index panel was 0.829 (0.754, 0.905), and the conventional index CA724 was 0.704 (0.617, 0.791). The AUC of the index panel showed a significant increase compared to CA724 by z score statistics. After building the index model, as shown in Figure 1B, samples from independent individuals, including 68 gastric cancer patients and 22 gastric polyp patients, were used to validate the model. The AUC of the index panel and CA724 was 0.811 (0.700, 0.923), and that of the conventional index CA724 was 0.779 (0.668, 0.890).

DISCUSSION

The pepsinogen PG is a protein polypeptide chain composed of 375 amino acids, which can be divided into two categories according to biochemical and immunological properties: PG I and PG II. PG I is mainly synthesized by chief cells and cervical mucous cells, while PG II can be synthesized by gastric antrum mucous cells and proximal duodenal Brunner glands, in addition to chief cells and cervical mucous cells[16]. Synthesized PG I and PG II are mainly secreted into the gastric cavity, but a zymogen level of approximately 5% can be reversed and diffuse into the blood, which allows it to be detected in the blood. Studies have shown that the level of PG I can reflect the secretory function of gastric glands to a certain extent, and its level is positively correlated with the maximum secretion of gastric acid but

Table 2 Comparison of clinical biochemical index gastric cancer and gastric polyp group

Indicator	Gastric polyp (*n* = 40)	Gastric cancer (*n* = 139)	*P* value
ALT	11.73 (15.75, 19.35)	10.7 (13.2, 18.3)	0.322
AST	13.93 (17.85, 20.45)	13.1 (15.6, 18.6)	0.252
TP	64.73 (69.4, 72.3)	61.9 (66.2, 69.4)	0.095
ALB	38.9 (41.5, 43.8)	36.5 (38.9, 41)	0.007
TB	8.75 (11.8, 14.95)	6.8 (9.4, 13.7)	0.116
DB	2.33 (3.65, 4.7)	2.4 (3.3, 4.9)	0.248
TBA	2.65 (4.4, 5.98)	2.6 (3.9, 7.4)	0.622
ALP	44.65 (66.85, 77.48)	56.2 (65.2, 81.9)	0.076
GGT	13.13 (16.05, 27.43)	13.3 (16.5, 24)	0.773
GLu	4.74 (5.27, 5.6)	4.72 (5, 5.49)	0.627
UN	4.37 (5.22, 6.49)	4.5 (5.21, 6.23)	0.812
Cr	58.83 (65.3, 75.15)	57.5 (68.2, 77.8)	0.838
UA	261.1 (301.15, 371.9)	228.4 (278.1, 330.5)	0.117
CHO	3.99 (4.34, 5.18)	3.56 (4.16, 4.68)	0.035
TG	1.2 (1.46, 1.81)	0.98 (1.25, 1.48)	0.017
CK	37.68 (55.9, 82.83)	38.6 (56.8, 76.1)	0.740
LDH	139.65 (153.85, 174.43)	118.1 (138, 158.9)	0.792
CKMB	3.15 (6.7, 10.73)	2.4 (6.2, 9.3)	0.357
Ca	2.16 (2.26, 2.34)	2.13 (2.19, 2.26)	0.025
P	1.31 (1.53, 1.81)	1.2 (1.36, 1.51)	0.008
Mg	0.82 (0.87, 0.94)	0.79 (0.85, 0.94)	0.188
K	3.76 (4.05, 4.41)	3.79 (3.99, 4.29)	0.319
Na	141.23 (143.7, 146.35)	141.3 (143.1, 144.5)	0.579
Cl	104.6 (106.6, 108.38)	103.3 (105.3, 106.9)	0.008
CO2	19.75 (22.15, 26.55)	22.3 (24.9, 27.3)	0.281
LP (a)	6.14 (17.34, 35.2)	9.51 (14.82, 26.13)	0.582
HDL	0.95 (1.12, 1.38)	0.83 (1.03, 1.15)	0.004
LDL	2.33 (2.77, 3.34)	1.98 (2.4, 2.93)	0.010
ApoA1	1.08 (1.32, 1.59)	0.96 (1.11, 1.24)	0.001
ApoB	0.7 (0.84, 1.04)	0.66 (0.77, 0.9)	0.021
CYS	0.91 (1, 1.17)	0.84 (0.96, 1.09)	0.816
SA	53.85 (61.4, 65.38)	55.8 (64.5, 70.6)	0.179
HCY	9.85 (13.47, 16.5)	10.63 (13.62, 17.74)	0.414
CRP	0.43 (0.9, 3.78)	0.7 (1.9, 5.4)	0.702
AMY	47.2 (56.9, 77.23)	40.9 (54.8, 68.1)	0.433
LPS	28.25 (34.85, 44.13)	28.2 (35.7, 44.5)	0.291
SOD	141.33 (164.3, 189.5)	108.3 (127.4, 157.4)	0.001
IMA	62.73 (66, 69.35)	56 (60.2, 63.6)	0.001

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TP: Total protein; ALB: Albumin; TB: Total bilirubin; DB: Direct bilirubin; TBA: Total bile acid; ALP: alkaline phosphatase; GGT: γ-glutamyltransferase; Glu: Glucose; UN: Urea nitrogen; Cr: Creatinine; UA: Uric acid; CHO: Cholesterol; TG: Triglyceride; CK: Creatine kinase; LDH: Lactate dehydrogenase; CKMB: Isoenzyme of creatine kinase; Ca: Calcium; P: Phosphorus; Mg: Magnesium; K:

Potassium; Na: Sodium; Cl: Chlorine; CO_2: Carbon dioxide; LPa: Lipoprotein a; HDL: High-density lipoprotein; LDL: Low-density lipoprotein;, ApoA1: Apolipoprotein A1; CYS: Cysteine; SA: Sialic acid; HCY: Homocysteine; CRP: C-reactive protein; AMY: Amylase; LPS: Lipase; SOD: Superoxide dismutase; IMA: Ischemia-modified albumin.

Table 3 Comparison of cytokine index gastric cancer and gastric polyp group

Indicator	Gastric polyp (*n* = 40)	Gastric cancer (*n* = 139)	*P* value
GM-CSF	1.24 (2.7, 6.27)	0.01 (0.53, 2.32)	0.640
IFNγ	0.08 (0.25, 1.08)	0.01 (0, 0.82)	0.585
IL-10	2.14 (3.39, 5.24)	1.63 (4.06, 9.34)	0.326
IL-1β	0.02 (0.31, 1.14)	0.01 (0.08, 0.94)	0.905
IL-6	0.34 (0.94, 2.58)	0.1 (1.98, 7.16)	0.483
IL-8	23.73 (51.11, 112.94)	39.4 (62.55, 138.23)	0.697
MCP-1	321.54 (429.78, 594.82)	310.31 (448.27, 612.02)	0.993
TNFα	5.53 (7.09, 8.72)	5.7 (9.87, 16.6)	0.001

GM-CSF: Granulocyte-macrophage colony-stimulating factor; IFNγ: Interferon-γ; IL: Interleukin; MCP-1: Monocyte chemoattractant protein; TNFα: Tumor necrosis factor α.

Table 4 Diagnostic value evaluation of single differential index for discriminating the gastric cancer and gastric polyp group

Indicator	AUC	*P* value	Lower	Upper
CEA	0.627	0.014	0.543	0.712
CA125	0.637	0.008	0.546	0.729
CA199	0.592	0.078	0.500	0.683
CA724	0.702	< 0.001	0.614	0.789
PG1/2	0.628	0.014	0.517	0.738
ALB	0.687	< 0.001	0.585	0.788
CHO	0.599	0.057	0.499	0.700
TG	0.655	0.003	0.561	0.748
Ca	0.640	0.007	0.534	0.746
P	0.668	0.001	0.566	0.769
Cl	0.635	0.009	0.537	0.733
HDL	0.648	0.004	0.551	0.746
LDL	0.633	0.010	0.532	0.735
ApoA1	0.702	0.000	0.602	0.802
ApoB	0.609	0.036	0.505	0.714
SOD	0.755	< 0.001	0.676	0.834
IMA	0.790	< 0.001	0.705	0.875
TNFα	0.656	0.003	0.575	0d.736

CEA: Carcinoembryonic antigen; CA125: Carbohydrate antigen 125; PG: Pepsinogen; ALB: Albumin; CHO: Cholesterol; TG: Triglyceride; Ca: Calcium; P: Phosphorus; Cl: Chlorine; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; ApoA1: Apolipoprotein A1; SOD: Superoxide dismutase; IMA: Ischemia-modified albumin; TNFα: Tumor necrosis factor α.

Table 5 Univariate and multivariate analysis of the differential index between gastric cancer and gastric polyp groups

Indicator	Univariate analysis					Multivariate analysis				
	Wals	*P* value	Exp (B)	Lower	Upper	Wals	*P* value	Exp (B)	Lower	Upper
CEA	1.02	0.31	1.04	0.97	1.11					
CA125	1.53	0.22	0.99	0.98	1.01					
CA724	4.50	0.03	1.18	1.01	1.38	5.21	0.02	1.17	1.02	1.34
PG12	0.96	0.33	0.91	0.75	1.10					
ALB	0.01	0.93	0.99	0.85	1.16					
TG	0.79	0.37	0.64	0.23	1.72					
Ca	0.01	0.91	0.84	0.04	19.42					
P	4.45	0.03	0.15	0.03	0.88	7.05	0.01	0.13	0.03	0.58
Cl	2.73	0.10	0.85	0.71	1.03					
HDL	0.34	0.56	2.09	0.17	25.09					
LDL	0.10	0.76	0.84	0.27	2.60					
ApoA1	2.42	0.12	0.09	0.00	1.86					
ApoB	0.39	0.53	4.36	0.04	45.13					
SOD	1.22	0.27	0.99	0.98	1.00					
IMA	4.50	0.03	0.89	0.79	0.99	14.77	< 0.001	0.85	0.78	0.92
TNFα	3.07	0.08	1.08	0.99	1.19					

CEA: Carcinoembryonic antigen; CA125: Carbohydrate antigen 125; PG: Pepsinogen; ALB: Albumin; CHO: Cholesterol; TG: Triglyceride; Ca: Calcium; P: Phosphorus; Cl: Chlorine; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; ApoA1: Apolipoprotein A1; SOD: Superoxide dismutase; IMA: Ischemia-modified albumin; TNFα: Tumor necrosis factor α.

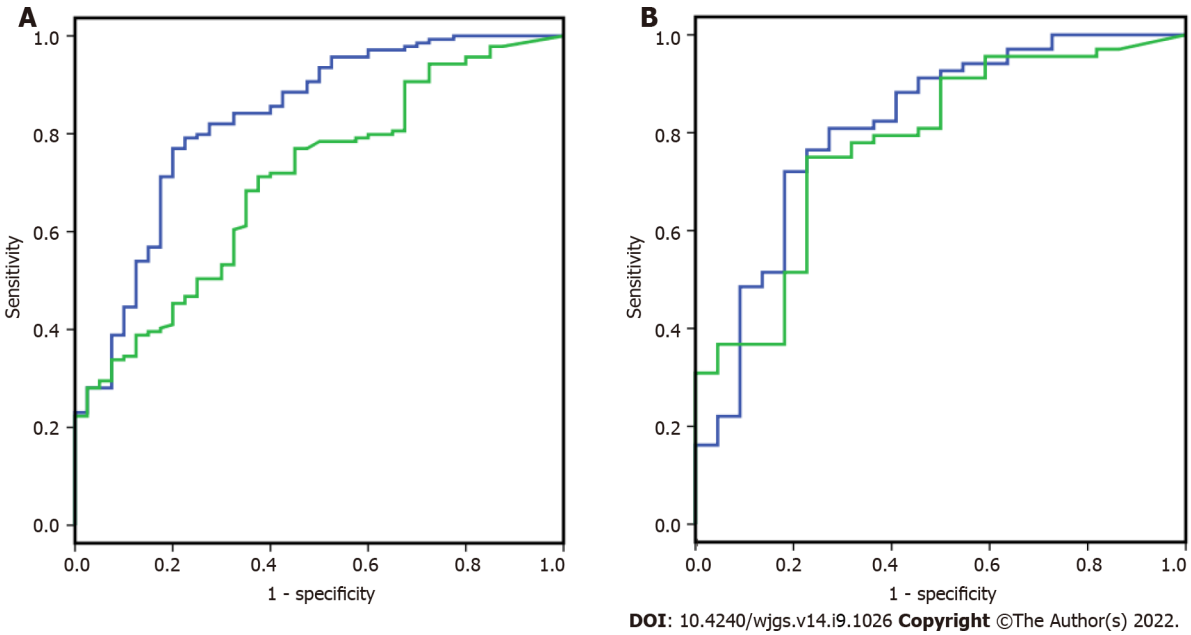

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Figure 1 Diagnostic value evaluation of index panel for discriminating the gastric cancer and gastric polyp group. A: Training model; B: Validation model. Blue line represents index model. Green line represents carbohydrate antigen 724.

negatively correlated with the degree of gastric body inflammation and atrophy[17]. An increase in the level of PG II suggests an inflammatory response in the gastric mucosa, while a decrease in the level of PG I suggests atrophy of the gastric corpus[13]. When the gastric mucosa atrophies and develops severe injury, the number of gastric glands and fundic glands will decrease or be replaced by pyloric glands,

and the pyloric glands lack gastric chief cells and cervical mucous cells, which will lead to a decreases in the level of PG I and the ratio of PG I/II[18]. In our study, the result was 1.3 (4.31, 6.26) in the gastric polyp group and 0.67 (2.98, 4.26) in the gastric cancer group. The AUC was 0.628, which has certain clinical significance in the early diagnosis of gastric cancer.

Cytokines are important in the diagnosis of gastric cancer. Cytokines are small molecular proteins secreted by cells in response to various stimuli that can exert biological effects by binding to specific receptors on target cells[19]. Cytokine production and cellular immune function are important in the occurrence and development of tumors and have certain diagnostic and prognostic value in gastric diseases[20]. The occurrence and development of gastric cancer are biological processes involving multiple stages and multiple factors. A large number of studies have shown that activated inflammatory factors are involved in the occurrence and development of gastric cancer. The immune function of cells is closely related to the occurrence and development of tumors. These inflammatory factors, as multifunctional cytokines, can not only directly damage tumor cells but are also important mediators by which monocytes kill tumor cells[20,21]. Studying the relationship between cytokines and gastric cancer provides a new direction for exploring the pathological mechanism of gastric cancer and provides a theoretical basis for the clinical development of more effective diagnosis and treatment. Studies have confirmed that tumor patients typically have immune function defects, especially cellular immune dysfunction[22]. TNFα is an important mediator of the inflammatory response and a series of pathophysiological processes in vivo. The dysregulation of cytokines and their receptors is closely related to the occurrence and development of tumors[23]. TNFα is known for its ability to significantly induce hemorrhagic necrosis of tumors in mice and is a multifunctional cytokine produced by macrophages and activated T cells. The functions of TNFα mainly include inducing an acute albumin response, activating neutrophils and lymphocytes, regulating the metabolic activity of tissues, and promoting the release of other cytokines[24]. Studies have shown that TNFα can not only kill a variety of tumor cells and enhance antitumor effects but also promote the growth and metastasis of certain tumors. When the concentration is appropriate, TNFα can cause tumor tissue hypoxia and vascular damage around the tumor and promote the cytotoxic effects of NK cells and macrophages, thereby enhancing immunity and inhibiting tumor growth. When TNFα is abnormally elevated in the body, the immune system is disturbed, causing systemic cytotoxicity, and tumor cells evade immune surveillance and continue to grow[25]. TNFα can promote the production of more TNFα in thymic cancer cells cultured in vitro. Tumor cells themselves can also promote the production of TNFα by myeloid cells by secreting versican, and TNFα can promote the accumulation of myeloid cells with a vascular endothelial phenotype to the tumor site, promote the formation of blood vessels, and then promote tumor growth and transfer[26]. In our study, compared to that in the gastric polyp group, the level of TNFα was significantly increased in the gastric cancer group. As an important inflammatory regulator, TNFα may play a role in tumor-associated inflammatory processes, increasing the risk of inflammation-induced tumors.

There are still some limitations in this study. First, the detection indices were only examined in the gastric polyp and gastric cancer groups, and a healthy control group was not evaluated. Second, the stage of gastric cancer was not evaluated and should be evaluated in future studies. Third, the sample size of the gastric polyp group was relatively small, which may cause bias in this study.

CONCLUSION

In summary, we developed an index model that included CA724, P and IMA to distinguish between gastric cancer and gastric polyps. After validation, when compared to the conventional index CA724, the panel showed improvements in detecting gastric cancer and may be a potential discriminating method for use in clinical practice.

ARTICLE HIGHLIGHTS

Research background

Early detection and diagnosis are crucial for the prevention and treatment of gastric cancer in clinical practice.

Research motivation

Blood index panels have been shown to improve the diagnostic value in many studies compared with single indices.

Research objectives

We aimed to develop a blood index panel that can improve the diagnostic value for discriminating gastric cancer and gastric polyps.

Research methods

Tumor-related detection indices, clinical biochemical indices and cytokine indices were analyzed in samples from 139 gastric cancer patients and 40 gastric polyp patients for model building. An additional 68 gastric cancer patients and 22 gastric polyp patients were enrolled for validation.

Research results

Carbohydrate antigen (CA) 724, phosphorus (P) and ischemia-modified albumin were included in the blood index panel, and the area under the curve (AUC) index of the panel was 0.829 (0.754, 0.905). After validation, the AUC index was 0.811 (0.700, 0.923). Compared to the conventional CA724 used in the training and validation, the AUC index was 0.704 (0.617, 0.791) and 0.779 (0.668, 0.890). The blood index panel showed significantly increased diagnostic value.

Research conclusions

We have developed a potential method for differentiating gastric cancer and gastric polyps based on a blood index panel. this tool may be helpful in clinical practice.

Research perspectives

A healthy control group and stage of gastric cancer should be evaluated in future studies, and a larger sample size should be used.

FOOTNOTES

Author contributions: Guo GH and Jiang T designed the study; Guo GH and Zhang PJ performed the research; Guo GH and Xie YB analyzed the date; Guo GH wrote the paper; Jiang T and Zhang PJ revised the manuscript for final submission; Guo GH and Xie YB contributed equally to this study; Zhang PJ and Jiang T are the co-corresponding authors; and all authors have read and agreed to the published version of the manuscript.

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ORCID number: Guang-Hong Guo 0000-0002-0897-0410; Yi-Bin Xie 0000-0002-0255-3018; Peng-Jun Zhang 0000-0002-7391-2495; Tao Jiang 0000-0002-2127-9085.

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REFERENCES

1 **Ang TL**, Fock KM. Clinical epidemiology of gastric cancer. *Singapore Med J* 2014; **55**: 621-628 [PMID: 25630323 DOI: 10.11622/smedj.2014174]

2 **den Hoed CM**, Kuipers EJ. Gastric Cancer: How Can We Reduce the Incidence of this Disease? *Curr Gastroenterol Rep*

2016; **18**: 34 [PMID: 27184043 DOI: 10.1007/s11894-016-0506-0]
3 **Strong VE**. Progress in gastric cancer. *Updates Surg* 2018; **70**: 157-159 [PMID: 29869781 DOI: 10.1007/s13304-018-0543-3]
4 **Petryszyn P**, Chapelle N, Matysiak-Budnik T. Gastric Cancer: Where Are We Heading? *Dig Dis* 2020; **38**: 280-285 [PMID: 32062657 DOI: 10.1159/000506509]
5 **Baretton GB**, Aust DE. [Current biomarkers for gastric cancer]. *Pathologe* 2017; **38**: 93-97 [PMID: 28213714 DOI: 10.1007/s00292-017-0271-3]
6 **Sauerbrei W**, Taube SE, McShane LM, Cavenagh MM, Altman DG. Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK): An Abridged Explanation and Elaboration. *J Natl Cancer Inst* 2018; **110**: 803-811 [PMID: 29873743 DOI: 10.1093/jnci/djy088]
7 **Filik H**, Avan AA. Electrochemical and Electrochemiluminescence Dendrimer-based Nanostructured Immunosensors for Tumor Marker Detection: A Review. *Curr Med Chem* 2021; **28**: 3490-3513 [PMID: 33076797 DOI: 10.2174/0929867327666201019143647]
8 **Feng F**, Tian Y, Xu G, Liu Z, Liu S, Zheng G, Guo M, Lian X, Fan D, Zhang H. Diagnostic and prognostic value of CEA, CA19-9, AFP and CA125 for early gastric cancer. *BMC Cancer* 2017; **17**: 737 [PMID: 29121872 DOI: 10.1186/s12885-017-3738-y]
9 **Shimada H**, Noie T, Ohashi M, Oba K, Takahashi Y. Clinical significance of serum tumor markers for gastric cancer: a systematic review of literature by the Task Force of the Japanese Gastric Cancer Association. *Gastric Cancer* 2014; **17**: 26-33 [PMID: 23572188 DOI: 10.1007/s10120-013-0259-5]
10 **Gong X**, Zhang H. Diagnostic and prognostic values of anti-helicobacter pylori antibody combined with serum CA724, CA19-9, and CEA for young patients with early gastric cancer. *J Clin Lab Anal* 2020; **34**: e23268 [PMID: 32118318 DOI: 10.1002/jcla.23268]
11 **Ding J**, Zhang H, Wu Z. Study on the Differential Value of Tumor Marker CA724 on Primary Gastric Cancer. *J Oncol* 2021; **2021**: 2929233 [PMID: 34608388 DOI: 10.1155/2021/2929233]
12 **Chen XZ**, Zhang WK, Yang K, Wang LL, Liu J, Wang L, Hu JK, Zhang B, Chen ZX, Chen JP, Zhou ZG, Mo XM. Correlation between serum CA724 and gastric cancer: multiple analyses based on Chinese population. *Mol Biol Rep* 2012; **39**: 9031-9039 [PMID: 22752725 DOI: 10.1007/s11033-012-1774-x]
13 **Zeyaullah M**, AlShahrani AM, Ahmad I. Association of *Helicobacter pylori* Infection and Host Cytokine Gene Polymorphism with Gastric Cancer. *Can J Gastroenterol Hepatol* 2021; **2021**: 8810620 [PMID: 34136433 DOI: 10.1155/2021/8810620]
14 **Perez-Perez GI**, Garza-Gonzalez E, Portal C, Olivares AZ. Role of cytokine polymorphisms in the risk of distal gastric cancer development. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 1869-1873 [PMID: 16103428 DOI: 10.1158/1055-9965.EPI-04-0889]
15 **Wong HL**, Rabkin CS, Shu XO, Pfeiffer RM, Cai Q, Ji BT, Yang G, Li HL, Rothman N, Gao YT, Zheng W, Chow WH. Systemic cytokine levels and subsequent risk of gastric cancer in Chinese Women. *Cancer Sci* 2011; **102**: 1911-1915 [PMID: 21740481 DOI: 10.1111/j.1349-7006.2011.02033.x]
16 **Venerito M**, Link A, Rokkas T, Malfertheiner P. Gastric cancer - clinical and epidemiological aspects. *Helicobacter* 2016; **21** Suppl 1: 39-44 [PMID: 27531538 DOI: 10.1111/hel.12339]
17 **Nunobe S**, Ida S. Current status of proximal gastrectomy for gastric and esophagogastric junctional cancer: A review. *Ann Gastroenterol Surg* 2020; **4**: 498-504 [PMID: 33005844 DOI: 10.1002/ags3.12365]
18 **Yuan P**, Lin L, Zheng K, Wang W, Wu S, Huang L, Wu B, Chen T, Li X, Cai L. Risk factors for gastric cancer and related serological levels in Fujian, China: hospital-based case-control study. *BMJ Open* 2020; **10**: e042341 [PMID: 32963075 DOI: 10.1136/bmjopen-2020-042341]
19 **Lippitz BE**. Cytokine patterns in patients with cancer: a systematic review. *Lancet Oncol* 2013; **14**: e218-e228 [PMID: 23639322 DOI: 10.1016/S1470-2045]
20 **Yoo SY**, Lee SY, Yoo NC. Cytokine expression and cancer detection. *Med Sci Monit* 2009; **15**: RA49-RA56 [PMID: 19247257]
21 **Balkwill F**, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet* 2001; **357**: 539-545 [PMID: 11229684 DOI: 10.1016/S0140-6736]
22 **Loo SW**, Pui TS. Cytokine and Cancer Biomarkers Detection: The Dawn of Electrochemical Paper-Based Biosensor. *Sensors (Basel)* 2020; **20** [PMID: 32230808 DOI: 10.3390/s20071854]
23 **Balkwill F**. TNF-alpha in promotion and progression of cancer. *Cancer Metastasis Rev* 2006; **25**: 409-416 [PMID: 16951987 DOI: 10.1007/s10555-006-9005-3]
24 **Balkwill F**. Tumour necrosis factor and cancer. *Nat Rev Cancer* 2009; **9**: 361-371 [PMID: 19343034 DOI: 10.1038/nrc2628]
25 **Salomon BL**, Leclerc M, Tosello J, Ronin E, Piaggio E, Cohen JL. Tumor Necrosis Factor α and Regulatory T Cells in Oncoimmunology. *Front Immunol* 2018; **9**: 444 [PMID: 29593717 DOI: 10.3389/fimmu.2018.00444]
26 **Philipp S**, Sosna J, Adam D. Cancer and necroptosis: friend or foe? *Cell Mol Life Sci* 2016; **73**: 2183-2193 [PMID: 27048810 DOI: 10.1007/s00018-016-2193-2]

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ORIGINAL ARTICLE

Randomized Controlled Trial

Effect of cardiac output - guided hemodynamic management on acute lung injury in pediatric living donor liver transplantation

Xiao-Jing Dou, Qing-Ping Wang, Wei-Hua Liu, Yi-Qi Weng, Ying Sun, Wen-Li Yu

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Xiao-Jing Dou, Qing-Ping Wang, Wei-Hua Liu, Yi-Qi Weng, Ying Sun, Wen-Li Yu, Department of Anesthesiology, Tianjin First Central Hospital, Tianjin 300192, China

Corresponding author: Wen-Li Yu, Doctor, PhD, Chief Doctor, Department of Anesthesiology, Tianjin First Central Hospital, No. 24 Fukang Road, Tianjin 300192, China.
yzxyuwenli@163.com

Abstract

BACKGROUND

Acute lung injury (ALI) after liver transplantation (LT) may lead to acute respiratory distress syndrome, which is associated with adverse postoperative outcomes, such as prolonged hospital stay, high morbidity, and mortality. Therefore, it is vital to maintain hemodynamic stability and optimize fluid management. However, few studies have reported cardiac output-guided (CO-G) management in pediatric LT.

AIM

To investigate the effect of CO-G hemodynamic management on early post-operative ALI and hemodynamic stability during pediatric living donor LT.

METHODS

A total of 130 pediatric patients scheduled for elective living donor LT were enrolled as study participants and were assigned to the control group (65 cases) and CO-G group (65 cases). In the CO-G group, CO was considered the target for hemodynamic management. In the control group, hemodynamic management was based on usual perioperative care guided by central venous pressure, continuous invasive arterial pressure, urinary volume, *etc.* The primary outcome was early postoperative ALI. Secondary outcomes included other early post-operative pulmonary complications, readmission to the intense care unit (ICU) for pulmonary complications, ICU stay, hospital stay, and in-hospital mortality.

RESULTS

The incidence of early postoperative ALI was 27.7% in the CO-G group, which was significantly lower than that in the control group (44.6%) ($P < 0.05$). During the surgery, the incidence of postreperfusion syndrome was lower in the CO-G group ($P < 0.05$). The level of intraoperative positive fluid transfusions was lower and the rate of dobutamine use before portal vein opening was higher, while the usage and dosage of epinephrine during portal vein opening and vasoactive

inotropic score after portal vein opening were lower in the CO-G group ($P < 0.05$). Compared to the control group, serum inflammatory factors (interleukin-6 and tumor necrosis factor-α), cardiac troponin I, and N-terminal pro-brain natriuretic peptide were lower in the CO-G group after the operation ($P < 0.05$).

CONCLUSION

CO-G hemodynamic management in pediatric living-donor LT decreases the incidence of early postoperative ALI due to hemodynamic stability through optimized fluid management and appropriate administration of vasopressors and inotropes.

Key Words: Cardiac output; Hemodynamic management; Child; Liver transplantation; Acute lung injury; Reperfusion injury

Core Tip: This is the first randomized controlled trial to evaluate the effect of cardiac output (CO)-guided hemodynamic therapy in pediatric liver recipients. In this study, hemodynamic parameters, including CO, stroke volume index, stroke volume variation, and the maximum increase in the speed of intraventricular pressure (dp/dt_{max}) obtained through the pressure recording analytical method monitoring were used to guide intraoperative hemodynamic management. The incidence of postoperative acute liver injury was significantly lower in the interventional group. Moreover, the inflammatory factors (interleukin-6 and tumor necrosis factor-α), cardiac troponin I, and N-terminal pro-brain natriuretic peptide levels decreased faster in the intervention group.

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INTRODUCTION

Pediatric liver transplantation (LT) is a life-saving procedure for children with end-stage liver disease caused by biliary atresia or progressive familial intrahepatic cholestasis[1]. The number of LTs performed globally has been reported to be 4-9 per million people < 18 years, with a 10-year survival rate of > 80%[1-3]. The incidence of post-LT acute lung injury (ALI) has been reported to vary between 34.2% and 77.8%[4,5]. ALI may lead to acute respiratory distress syndrome (ARDS), which is associated with adverse postoperative outcomes, such as prolonged hospital stay, high morbidity, and mortality [6]. ARDS is often caused by hemodynamic instability during surgery, which results in liver hypoperfusion and ischemia-reperfusion injury, exaggerating the inflammatory process[7]. Additionally, hemodynamic instability accompanied by excessive administration of fluids and blood products leads to fluid imbalance during LT. Clinical studies have demonstrated that intraoperative fluid overload is the primary risk factor for postoperative pulmonary complications (PPCs)[8]. Effective fluid management strategies can reduce the occurrence of PPCs[9].

In the early stages after LT, ALI may prolong the intubation time and increase the risk of systemic infectious complications. Prolonged mechanical ventilation due to refractory respiratory failure is an extremely morbid event and a marker of poor recipient recovery that predisposes a recipient to long-term ventilator dependency and predicts further complications. Several factors are involved in the onset of postoperative ALI, among which intraoperative hemodynamic instability and fluid overload are the most important[10].

Pediatric patients with poor oxygen reserve capacity are vulnerable to ischemia and hypoxia, leading to ALI. Therefore, it is vital to maintain hemodynamic stability and optimize fluid management. A study on pediatric kidney transplantation showed that the use of the cardiac output-guided (CO-G) algorithm led to excellent renal results, with a trend toward less fluids in favor of norepinephrine[11]. However, few studies have reported CO-G management in pediatric LT. CO monitoring is extremely difficult and limited due to the anatomical characteristics and biomaterial technology in pediatric liver transplant patients. The pressure recording analytical method (PRAM) is a minimally invasive hemodynamic monitoring method that calculates hemodynamic parameters, with the advantages of being invasive, not requiring calibration, and suitable for pediatric patients weighing < 20 kg compared to other devices[12]. In this study, a randomized controlled trial was designed to evaluate the effect of

CO-G algorithm management on reducing ALI events after pediatric LT and intraoperative hemodynamic stability with PRAM.

MATERIALS AND METHODS

Participants

This was a randomized controlled trial conducted at Tianjin First Central Hospital. This study was approved by the Ethics Committee of Tianjin First Center Hospital in China (Approval Number: 2019N180KY), and written informed consent was obtained from eligible guardians. The clinical trial registration number is ChiCTR1900026016. The inclusion criteria were as follows: (1) Pediatric liver recipients 5-24 mo of age; (2) American Society of Anesthesiologists physical status III or IV; and (3) Living donation. The exclusion criteria were as follows: (1) Contraindications to arterial puncture and cannulation; (2) Preoperative incomplete data; (3) Preoperative severe cardiac, renal, and other viral organ failure before LT; and (4) Sepsis and/or pulmonary complications, including pneumonia, atelectasis, pulmonary edema, pleural effusion, and ARDS within 2 wk before surgery. Every case of transplantation passed the ethical review and approval of the Tianjin First Center Hospital.

Anesthesia and surgery

Patients enrolled in this study were routinely monitored for heart rate (HR), non-invasive blood pressure, pulse oximetry, and electrocardiography. Anesthesia was induced using scopolamine (0.01 mg/kg), midazolam (0.15 mg/kg), etomidate (0.15 mg/kg), fentanyl (2-5 μg/kg), and vecuronium (0.2 mg/kg) to maintain analgesia, muscle relaxation, and sedation. After intubation, mechanical ventilation was performed with a fraction of inspired oxygen (FiO_2) of 50%-60%, tidal volume of 8-10 mL/kg, respiratory rate of 20-28/min, an inspiration-to-expiration ratio of (1.0:1.5)-2.0 min, an inspiration-to-expiration ratio of (1.0:1.5)-2.0, and a postapneic end-tidal carbon dioxide pressure of 30-35 mmHg (1 mmHg = 0.133 kPa). Anesthesia maintenance included intravenous infusion of propofol (9-15 mg/kg/h), intermittent intravenous fentanyl (1-3 μg/kg), and intravenous infusion of atracurium besylate (1-2 μg/kg/h).

The operative procedure was performed using both the caval replacement and piggyback techniques. Reperfusion of the liver graft started with opening of the portal vein, followed by opening of the artery. After arterial reperfusion, the bile duct was connected to the recipient's bile duct (choledocho-choledochostomy) or to a small bowel loop (hepaticojejunostomy). A back table biopsy of the donor liver was performed before implantation.

Hemodynamic instrumentation and design

The central venous pressure (CVP) was monitored continuously with a three-lumen central venous catheter placed using ultrasound-guided right internal jugular vein puncture and arterial pressure was monitored invasively in both groups using a catheter placed in the radial artery. The mean arterial blood pressure (MAP), HR, cardiac index (CI), stroke volume index (SVI), stroke volume variation (SVV), and left ventricular contractility index, which is the maximum increase in the speed of intraventricular pressure (dp/dt_{max}), were continuously monitored through PRAM (Most Care monitoring system; Vytech Healthcare, Padova, Italy) *via* a pressure catheter (Pulsion Medical Systems, Munich, Germany) in the CO-G group.

Hemodynamic management included fluid transfusion and use of vasopressors and/or inotropes: (1) Fluid management protocol: In the control group, fluid management was implemented mainly according to CVP, urine volume, bleeding, *etc.* CVP was maintained at a level of 6-12 mmHg, and the urine volume at ≥ 20 mL/h. If the urine volume was < 20 mL/h and/or CVP < 6 mmHg, 4% albumin or crystalloid was infused to expand the volume; if the urine volume was < 20 mL/h and/or CVP > 12 mmHg, 0.5 g/kg furosemide was also administered to decrease fluid load. In the CO-G group, fluid was infused at a rate of 10 mL/kg/h to maintain SVV at 12%-15%. If SVV was > 12%, 4% albumin or crystalloid was administered in combination with CI, SVI, and other parameters; and (2) Vasopressor and/or inotrope protocol: In the control group, if MAP was < 50 mmHg, norepinephrine or dopamine was pumped intravenously, and if MAP fell rapidly below 30 mmHg after the opening of the portal vein, rehydration and/or epinephrine of 1-5 mg/kg was administrated. In the CO-G group, the administration of vasopressors and/or inotropes according to the CO and other hemodynamic parameters is illustrated in the PRAM diagram (Figure 1). Other management: Albumin and blood products were infused to maintain the blood volume and hemoglobin level at ≥ 8 g/L. The electrolyte and acid-base balance were maintained within the normal range during surgery and were kept warm.

Blood assays

Venous blood (3 mL) was collected from the right internal jugular catheter and placed into vacuum tubes containing sodium heparin. Blood samples were collected at four time points: Immediately before the induction of general anesthesia (baseline, T_0), at the end of surgery (T_1), 1 d after surgery (T_2), and 3

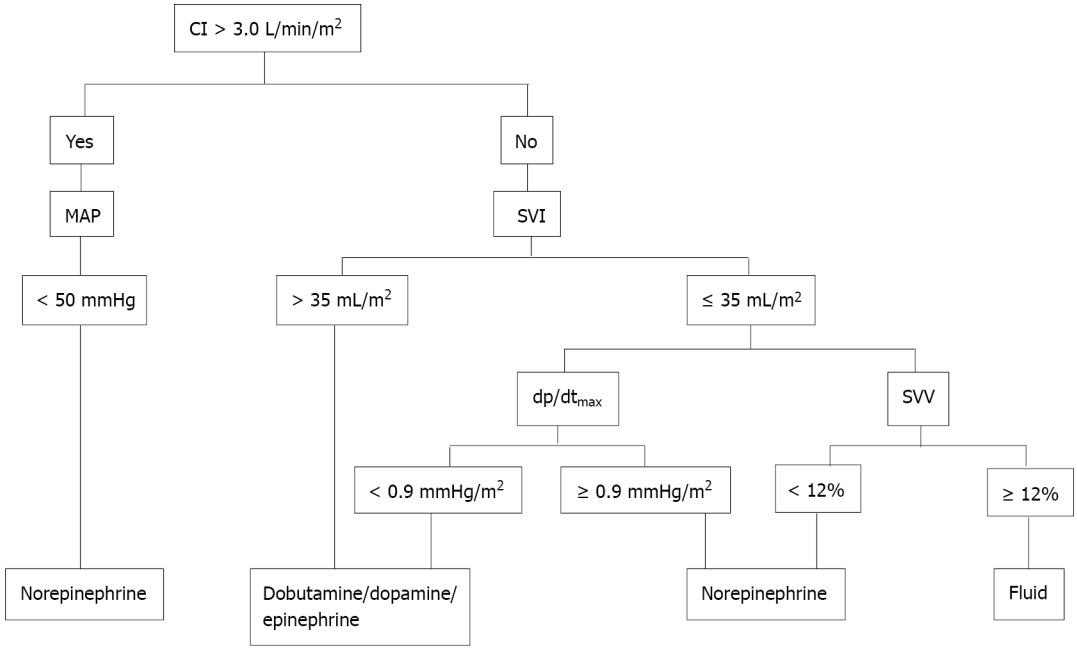

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Figure 1 Pressure recording analytical method. CI: Cardiac index; MAP: Mean arterial blood pressure; SVI: Stroke volume index; SVV: Stroke volume variation.

d after surgery (T_3). The samples were then placed in dry tubes and centrifuged. The serum was removed and stored at -80 °C until analysis. The levels of serum inflammatory factors interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), cardiac troponin I (cTnI), and N-terminal pro-brain natriuretic peptide precursor (NT-pro-BNP) were analyzed at four time points. Wuhan Huamei Biological Technology Company (Wuhan, China) was used to construct the reaction standard curves. The protein levels were calculated by comparing the optical density values of the samples with the standard curve.

Data collection

The following patients and preoperative variables were assessed: Patient characteristics, including age, weight, pediatric end-stage liver disease, and graft characteristics, including graft mass, graft-to-recipient body weight ratio, cold ischemia time of the graft, and preoperative laboratory test results. The intraoperative hemodynamic parameters included baseline values, the maximum and minimum values of HR, MAP, CVP, and the incidence of postreperfusion syndrome (PRS, defined as a sudden drop in MAP of ≥ 30% within 1-5 min of reperfusion)[13], and hemodynamic management, including transfusion of red blood cells, fresh frozen plasma, and fluids (colloids and crystalloids), usage of vasopressor or inotrope agents, and vasoactive drug score (VIS) [VIS = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 10000 × vasopressin dose (μg/kg/min) + 100 × norepinephrine dose (μg/kg/h) + 100 × milrinone dose (μg/kg/min)][14]. The postoperative variables included the occurrence of ALI and pulmonary complications in the first week after surgery, duration of mechanical ventilation, intense care unit (ICU) stay, incidence of readmission to the ICU for pulmonary complications, hospital stay, and in-hospital mortality.

Relevant definitions

ALI was defined according to the following criteria[15]: (1) Acute onset; (2) PaO_2/FiO_2 < 300; (3) Pulmonary artery wedge pressure < 18 mmHg without clinical evidence of left atrial hypertension; and (4) Bilateral infiltrates on chest radiography.

Study outcomes

The primary outcome was early postoperative ALI. The secondary outcomes included early PPCs, ICU stay, readmission to the ICU for pulmonary complications, hospital stay, in-hospital mortality, and intraoperative hemodynamic stability.

Sample size, randomization, and blinding

Sample size: The incidence of ALI in children after LT in the control and intervention groups was 50% and 25%, respectively, based on previous reports[3,4]. The α-error was set to 0.05, β-error to 80%, and the ratio to 1:1. PASS 15 (NCSS, LLC. Kaysville, UT, United States) was used to calculate the sample size, and the results showed that at least 58 patients should be included per group, with an expected

dropout rate of 10%.

Randomization and blinding: Pediatric patients were randomly assigned to the CO-G hemodynamic therapy algorithm (CO-G group) and the control group by a computer-generated random number system and individually sealed in envelopes. One investigator created computer-generated randomization codes and enrolled participants in accordance with the approved study protocol (ChiCTR1900026016), one investigator created computer-generated randomization codes and enrolled the participants. The participants were assigned to different groups based on the codes, which were kept in sequentially numbered opaque envelopes. After anesthetic induction, the envelopes were opened by another investigator, who was an anesthesiologist conducting CO-G hemodynamic management during the LT. An additional third investigator measured the primary and secondary outcomes in a blinded manner. The surgeons were blinded to the group allocation.

Statistical analysis

Outcome analyses were performed using SPSS software package (SPSS; IBM. Corp., Armonk, NY, United States). The Kolmogorov-Smirnov test was used to analyze the distribution of the data. The results are presented as the mean (SD), median (second quartile, third quartile), or number of patients. The patient characteristics and perioperative variables were compared using an independent *t*-test or Fisher's exact test, as appropriate. Changes in the above variables in the group over time were analyzed using repeated ANOVA, followed by an appropriate *post hoc* test. Categorical data were compared using the chi-squared test or Fisher's exact method. The results were evaluated within a 95% reliability index ($P < 0.05$).

RESULTS

Baseline patient characteristics and intraoperative data

A total of 148 patients were screened from December 2019 to October 2020, and 130 patients were enrolled and analyzed in this study. Among whom, 65 patients were randomly allocated to the CO-G group and 65 to the control group (Figure 2, Table 1). The patient characteristics were similar between the study groups (Table 1).

Primary outcome

The incidence of early postoperative ALI was 27.7% in the CO-G group, which was lower than that in the control group (44.6%) ($P < 0.05$) (Table 2). There were no significant differences in other pulmonary complications and ICU stay, readmission to the ICU for pulmonary complications, hospital stay, and in-hospital mortality (Table 2).

Intraoperative hemodynamic changes

Compared to the control group, intraoperative fluid transfusion (865.5 ± 153.1 mL *vs* 1222.7 ± 381.9 mL, $P < 0.001$), and positive fluid balance (598.8 ± 320.7 mL *vs* 1021.4 ± 467.9 mL, $P < 0.001$) were lower in the CO-G group. The utilization of dobutamine before portal vein opening was higher, whereas the usage and dosage of epinephrine during portal vein opening and VIS after portal vein opening [2 (2-3) *vs* 3 (2-7), $P < 0.05$] were lower in the CO-G group. The peak value of CVP was lower (9.46 ± 1.66 mmHg *vs* 11.64 ± 2.1 mmHg, $P < 0.001$) while the bottom value of MAP was higher (43.3 ± 7.4 mmHg *vs* 34.9 ± 5.5 mmHg, $P < 0.001$) in CO-G group. The incidence of PRS in the CO-G group was lower than that in the control group (33.8% *vs* 53.8%, $P = 0.022$) (Table 3).

Differences in inflammatory factors

In both groups, the levels of inflammatory factors (IL-6 and TNF-α) and cTnI increased during the operation, decreased gradually during the following 3 d postoperatively, and returned to preoperative levels (Table 4). The NT-proBNP levels showed the same trend (Table 4). For group comparisons, at T1 and T2, the values of IL-6, TNF-α, and cTnI were significantly lower in the CO-G group (Table 4). At T1, T2, and T3, the NT-proBNP levels were significantly lower in the CO-G group (Table 4).

DISCUSSION

To the best of our knowledge, this is the first randomized controlled trial to evaluate the effect of CO-guided hemodynamic therapy in pediatric liver recipients. In this study, hemodynamic parameters, including CO, SVV, SVI, and dp/dt_{max}, obtained through PRAM monitoring were used to guide intraoperative hemodynamic management. The incidence of postoperative ALI was significantly lower in the interventional group than in the control group. Moreover, the inflammatory factors of IL-6, TNF-α, and cTnI decreased faster in the intervention group than in the control group.

Table 1 Patient demographic and perioperative data

Variables	Control group (*n* = 65)	CO-G group (*n* = 65)	*P* value
Age, mo	7.5 (5.9, 9.6)	7.0 (6.0, 8.5)	0.390
Gender (boy/girl), *n*	31/34	33/32	0.726
Weight of receptor, kg	7.5 (6.5, 9.0)	7.4 (6.5, 8.0)	0.383
Mass of graft, g	220.5 ± 40.7	218.8 ± 39.5	0.736
GRWR, %	3.10 ± 0.76	3.03 ± 0.76	0.631
Pretransplant PELD score	16.5 ± 3.2	17.2 ± 3.5	0.549
Pretransplant INR, IU	1.77 ± 0.86	1.91 ± 0.67	0.300
Pretransplant PTA, %	57.5 ± 20.7	51.4 ± 20.2	0.095
Pretransplant PT, s	20.2 ± 9.9	21.5 ± 8.7	0.454
Pretransplant WBC, 10^9/L	13.3 ± 6.3	12.2 ± 5.6	0.331
Pretransplant hemoglobin, g/L	90.4 ± 13.6	86.8 ± 12.8	0.116
Pretransplant platelets, 10^{12}/L	194.3 ± 87.0	207.3 ± 72.1	0.355
Pretransplant albumin, g/L	34.1 ± 4.4	35.6 ± 5.9	0.088
Pretransplant total bilirubin, μmol/L	271.6 ± 128.3	282.9 ± 122.4	0.607
Pretransplant creatinine, μmol/L	12.7 ± 3.5	11.8 ± 3.0	0.099
Graft cold ischemia time, min	65.9 ± 25.7	60.2 ± 14.8	0.081
Anhepatic time, min	44.4 ± 11.5	47.1 ± 15.8	0.267
Operation time, min	545.0 ± 44.9	559.5 ± 49.6	0.083
Mechanical ventilation after operation, h	3.00 (2.25, 4.50)	2.75 (2.00, 3.88)	0.789

Data are expressed as number (%), mean ± SD, or median (interquartile range), as appropriate. CO-G: Cardiac output-guided; GRWR: Graft-to-recipient body weight ratio; PELD: Pediatric end-stage liver disease; INR: International Normalized Ratio; PTA: Prothrombin activity; PT: Prothrombin time; WBC: White blood cell.

Effects on ALI

The incidence of ALI in the control group was 44.6%, which was close to that used in the sample size calculation (50%). These results are similar to those of previous studies. Hong *et al*[4] reported that the rate of ALI was 34.6% in adult LT, while Yao *et al*[5] showed that the incidence of ALI in a rat LT model was 77.8%. CO-G interventions significantly decreased ALI occurrence after pediatric LT. This might be due to more stable hemodynamic parameters, which can mitigate ischemia-reperfusion injury, as well as optimized vasopressor use and fluid management in the CO-G group.

Effects on inflammatory factors

Inflammatory lung liver interactions, and the activation of nuclear factor-kappa B in particular, may be implicated in the pathogenesis of permeability-type pulmonary edema[16]. It is well accepted known that the inflammatory response is involved in the progression of ALI and that cytokines, such as TNF-α, IL-1β, and IL-6, play important roles in the massive inflammatory response that is a hallmark feature of ALI[17]. In contrast, IL-4 and IL-10 seem to exert protective roles[18].

Therefore, in the present study, we selected TNF-α and IL-6, which are typical factors that reflect inflammation and oxidative stress in the lungs. The results showed that the inflammatory factors mentioned above were elevated from the end of the operation and returned to preoperative levels 3 d after surgery. Compared with the control group, TNF-α and IL-6 levels were significantly lower from the end of the operation to 1 d after surgery in the CO-G group, indicating that CO-G hemodynamic therapy can attenuate lung inflammation during LT.

Effects on hemodynamic stability

Several triggering conditions, including bleeding, blood transfusion, and ischemia-reperfusion, can exaggerate the inflammatory process of ALI. Among them, liver ischemia-reperfusion may be the most notable factor. The greatest hemodynamic disturbance in LT is defined as PRS, which occurs during reperfusion of the donated liver after unclamping of the portal vein. PRS is characterized by marked decreases of > 30% in MAP lasting > 1 min within 5 min after reperfusion and occurring with an

Table 2 Results for primary outcome and secondary outcomes

	Control group (*n* = 65)	CO-G group (*n* = 65)	*P* value
Primary outcomes			
ALI, *n* (%)	29 (44.6)	18 (27.7)	0.045
Others			
Pneumonia, *n* (%)	12 (18.5)	8 (12.3)	0.634
Atelectasis, *n* (%)	18 (27.7)	12 (18.5)	0.687
ARDS, *n* (%)	6 (9.2)	4 (6.2)	0.742
Refractory heart failure, *n* (%)	3 (4.6)	1 (1.5)	0.612
Readmission to ICU for pulmonary complications, *n* (%)	3 (4.6)	2 (3.1)	1.000
ICU stay, d	2 (2, 3)	2 (2, 3)	0.200
Hospital stay, d	28 (22, 39)	27 (20, 37)	0.450
In-hospital mortality, *n* (%)	2 (3.1)	0	0.476

Data are expressed as number (%), mean ± SD, or median (interquartile range), as appropriate. CO-G: Cardiac output-guided; ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit.

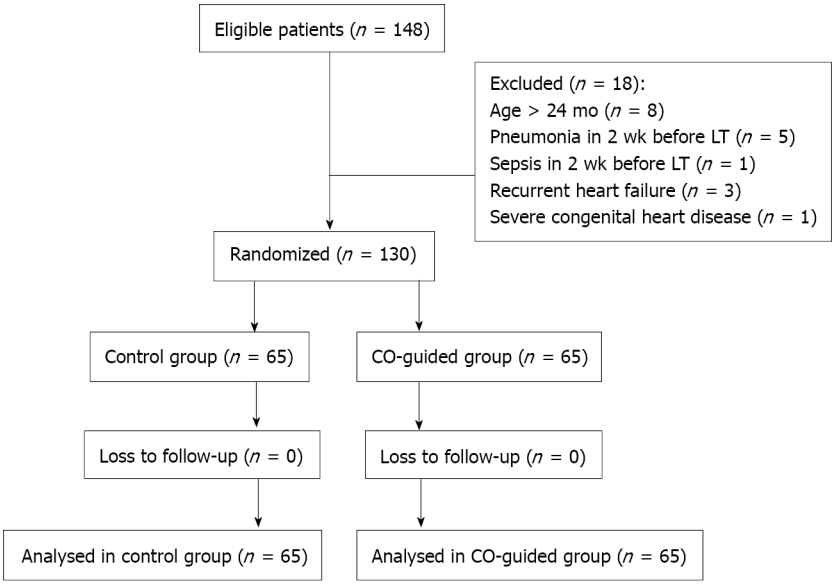

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Figure 2 Trial profile. CO: Cardiac output; LT: Liver transplantation.

incidence of 12.1%-42%[19]. A dramatic drop in blood pressure and myocardial inhibition are manifestations, but are also risk factors for PRS[20]. It is noteworthy that the intraoperative stabilization of arterial pressure through the preventive use of vasopressors during the reperfusion phase is capable of decreasing the incidence of PRS[21]. In our study, the incidence of PRS in the CO-G group was lower than that in the control group, which was attributed to the appropriate cardiotonic and optimized vasopressor by the continuous monitoring of CO.

In our study, the use of dobutamine before portal vein opening was higher than that in the control group, whereas the usage and dosage of epinephrine during portal vein opening and VIS after portal vein opening were lower in the CO-G group. CO-G hemodynamic therapy can reduce hemodynamic fluctuations and prevent the occurrence of PRS by continuously monitoring the intraoperative CO, which can consistently summarize cardiac function, and aid to the appropriate administration of vasopressors and inotropes.

Effects on myocardial injury

Myocardial injury commonly occurs in LT[22], which leads to arrhythmias and myocardial depression,

Table 3 Hemodynamic parameters and hemodynamic management

	Control group (*n* = 65)	CO-G group (*n* = 65)	*P* value
Preoperative hemodynamic parameters			
HR, bpm/min	110 ± 12	108 ± 11	0.325
MAP, mmHg	60.3 ± 8.0	61.6 ± 9.5	0.382
CVP, cmH_2O	6.08 ± 1.37	5.79 ± 1.44	0.241
Intraoperative hemodynamic parameters			
HR_H, bpm/min	123 ± 15	125 ± 18	0.317
HR_L, bpm/min	82 ± 8	86 ± 8	0.003
MAP_H, mmHg	72.3 ± 8.8	71.7 ± 10.4	0.531
MAP_L, mmHg	34.9 ± 5.5	43.3 ± 7.4	< 0.001
CVP_H, cmH_2O	11.64 ± 2.1	9.46 ± 1.66	< 0.001
CVP_L, cmH_2O	4.17 ± 1.49	3.55 ± 1.34	0.013
Intraoperative hemodynamic events			
PRS, *n* (%)	35 (53.8)	22 (33.8)	0.022
Malignant ventricular arrhythmia, *n* (%)	3 (5)	2 (3.1)	1.000
Cardiac arrest, *n* (%)	1 (1.5)	0	1.000
Intraoperative hemodynamic management			
Intraoperative blood transfusions, U	2.5 (2, 3)	2.0 (1.5, 2.5)	0.821
Intraoperative frozen plasma transfusions, mL	0 (0, 200)	0 (0, 110)	0.751
Intraoperative fluid transfusions, mL	1222.7 ± 381.9	865.5 ± 153.1	< 0.001
Intraoperative bleeding volume, mL	300 (200, 500)	300 (200, 400)	0.543
Intraoperative urinary volume, mL	300 (277.5, 400)	400 (200, 510)	0.416
Positive fluid balance, mL	1021.4 ± 467.9	598.8 ± 320.7	< 0.001
VIS before portal vein opening	2 (2, 5)	3 (2, 6.25)	0.565
During portal vein opening			
Bolus injection of epinephrine, *n* (%)	30 (46.2)	18 (27.7)	0.029
Bolus dosage of epinephrine, μg	3 (2, 5)	2.5 (1.75, 4.25)	0.030
VIS after portal vein opening	3 (2, 7)	2 (2, 3)	0.049

Data are expressed as number (%), mean ± SD, or median (interquartile range), as appropriate. CO-G: Cardiac output-guided; HR: Heart rate; MAP: Mean arterial blood pressure; CVP: Central venous pressure; HR_H: Intraoperative maximum heart rate; HR_L: Intraoperative minimum heart rate; MAP_H: Intraoperative maximum mean arterial blood pressure; MAP_L: Intraoperative minimum mean arterial blood pressure; CVP_H: Intraoperative maximum central venous pressure; CVP_L: Intraoperative minimum central venous pressure; PRS: Postreperfusion syndrome; VIS: Vasoactive inotropic score.

severely affecting circulatory stability and aggravating ischemia-reperfusion injury. cTnI is currently recognized as a sensitive and specific gold standard for reflecting the degree of myocardial injury, and mildly elevated cTnI levels (≥ 0.04 ng/mL) are strongly associated with postoperative mortality[23]. Sheng *et al*[24] demonstrated that intraoperative cTnI elevation (≥ 0.07 ng/mL) was a significant prognostic risk factor in ALI after pediatric living-donor LT for children with biliary atresia. NT-proBNP is an early and reliable predictor of myocardial dysfunction onset[25]. BNP levels positively correlated with left ventricular systolic function and required inotropic support[26].

In our study, we analyzed cTnI and NT-pro-BNP levels to identify myocardial injury and cardiac dysfunction. The results showed that cTnI and NT-pro-BNP levels were elevated from the end of the operation and returned to preoperative levels 3 d after surgery. NT-pro-BNP level was lower at 3 d after surgery than at the preoperative level. Compared to the control group, the values of cTnI were significantly lower at the end of surgery and 1 d after surgery in the CO-G group. In the CO-G group, the NT-pro-BNP values from the end of surgery to 3 d after surgery were all lower than those in the control group, indicating that CO-G hemodynamic therapy can attenuate myocardial injury and cardiac

Table 4 Changes in serum interleukin-6, tumor necrosis factor-α, troponin I, and N-terminal pro-brain natriuretic peptide levels at every time point

		IL-6 (pg/mL)	TNF-α (pg/mL)	cTnI (ug/L)	NT-proBNP (ng/L)
Control group (n = 65)	T_0	78.9 ± 23.2	87.5 ± 25.6	0.032 ± 0.015	556.6 ± 251.2
	T_1	170.4 ± 42.3[b]	175.3 ± 43.1[b]	0.383 ± 0.166[b]	1012.4 ± 568.8[b]
	T_2	126.2 ± 33.6[b]	129.5 ± 35.2[b]	0.182 ± 0.067[b]	866.0 ± 283.6[b]
	T_3	80.7 ± 23.2	92.8 ± 26.8	0.030 ± 0.011	667.4 ± 247.7
CO-G group (n = 65)	T_0	80.6 ± 22.5	83.2 ± 23.8	0.029 ± 0.012	562.2 ± 195.8
	T_1	145.5 ± 34.5[a,b]	156.7 ± 36.1[a,b]	0.255 ± 0.128[a,b]	876.7 ± 268.2[a,b]
	T_2	108.6 ± 24.9[a,b]	115.5 ± 25.6[a,b]	0.116 ± 0.070[a,b]	594.0 ± 163.3[a,b]
	T_3	78.6 ± 21.9	86.2 ± 22.6	0.028 ± 0.011	462.6 ± 154.5[a,b]

[a]P < 0.05, compared with control group.
[b]P < 0.05, compared with T_0.
Data are expressed as number (%) or mean ± SD. T_0 before induction of general anesthesia, T_1 at the end of surgery, T_2 1 d after surgery, T_3 3 d after surgery. CO-G: Cardiac output-guided; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; cTnI: Cardiac troponin I; NT-pro-BNP: N-terminal pro-brain natriuretic peptide.

volume load, which could be helpful in circulatory stability and attenuation of pulmonary edema.

Optimizing fluid management

Intraoperative fluid overload can exacerbate pulmonary edema and heart failure, thereby increasing the duration of postoperative mechanical ventilation, pulmonary infection, and mortality. Previous intraoperative volume management is often achieved through empirical rehydration and CVP-directed management; CVP is a pressure-based index that cannot accurately reflect volume status, and CVP-directed fluid management can result in volume overload[27,28]. Compared to pressure-monitoring metrics, volume-monitoring metrics better reflect volume status to guide hemodynamic management, and SVV < 12% and PPV < 13% are more accurate in predicting fluid responsiveness[29]. Shin *et al*[30] showed that the sensitivity of SVV for monitoring blood volume changes during the neohepatic period of LT was 89%, with a specificity of 80%, which was significantly better than that of CVP. In addition, studies have shown that CO-G fluid management reduces postoperative complications by 20% to 30% compared with any infusion strategy[31]. In this study, CO-directed fluid management combined with SVI and SVV showed that intraoperative fluid transfusion and maximum CVP were significantly lower in the CO-G group than in the control group. The incidence of postoperative ALI was also significantly lower, suggesting that CO-G hemodynamic management can reduce fluid overload, decrease the occurrence of pulmonary edema, stabilize cardiopulmonary function, control CVP, and reduce the occurrence of ALI.

Limitations

As this was a single center study, a multicenter study with other monitoring indicators is needed for further analysis.

CONCLUSION

CO-G hemodynamic management in pediatric living donor LT can decrease the incidence of early postoperative ALI due to hemodynamic stability through optimized fluid management and appropriate administration of vasopressors and inotropes achieved by continuous monitoring of CO.

ARTICLE HIGHLIGHTS

Research background

Acute lung injury (ALI) post-liver transplantation (LT) may lead to acute respiratory distress syndrome, which is associated with adverse postoperative outcomes, such as prolonged hospital stay, high morbidity, and mortality. Therefore, it is vital to maintain hemodynamic stability and optimize fluid management. However, few studies have reported cardiac output-guided (CO-G) management in

pediatric LT.

Research motivation

In this study, a randomized controlled trial was designed to evaluate the effect of CO-G algorithm management on reducing ALI events after pediatric LT and intraoperative hemodynamic stability with pressure recording analytical method (PRAM).

Research objectives

To investigate the effect of CO-G hemodynamic management in pediatric living donor LT on early postoperative ALI and its influence on hemodynamic stability during surgery.

Research methods

A total of 130 pediatricians scheduled for elective living donor LT were enrolled as study participants and were assigned to the control group (65 cases) and CO-G group (65 cases). In the CO-G group, CO was considered the target for hemodynamic management. In the control group, hemodynamic management was based on usual perioperative care guided by central venous pressure, continuous invasive arterial pressure, urinary volume, *etc*. The primary outcome was early postoperative ALI. Secondary outcomes included other early postoperative pulmonary complications, readmission to the intense care unit (ICU) for pulmonary complications, ICU stay, hospital stay, and in-hospital mortality.

Research results

The incidence of early postoperative ALI was 27.7% in the CO-G group, which was significantly lower than that in the control group (44.6%) ($P < 0.05$). During the surgery, the incidence of postreperfusion syndrome was lower in the CO-G group ($P < 0.05$). The level of intraoperative positive fluid transfusions was lower and the rate of dobutamine use before portal vein opening was higher, while the usage and dosage of epinephrine when portal vein opening and vasoactive inotropic score after portal vein opening were lower in the CO-G group ($P < 0.05$). Compared to the control group, the serum inflammatory factors interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), cardiac troponin I (cTnI), and N-terminal-pro hormone BNP in the CO-G group were lower after the operation ($P < 0.05$).

Research conclusions

CO-G hemodynamic management in pediatric living-donor LT decreased the incidence of early postoperative ALI, which is considered to benefit from hemodynamic stability through optimized fluid management and appropriate administration of vasopressors and inotropes by continuous monitoring of CO.

Research perspectives

This is the first randomized controlled trial to evaluate the effect of CO-G hemodynamic therapy in pediatric liver recipients. In this study, hemodynamic parameters, including CO, stroke volume index, stroke volume variation, and the maximum increase in the speed of intraventricular pressure (dp/dt_{max}), obtained through the PRAM monitoring were used to guide intraoperative hemodynamic management. The incidence of postoperative ALI was significantly lower in the interventional group. Moreover, the inflammatory factors of IL-6, TNF-α, cTnI, decreased faster in the intervention group.

FOOTNOTES

Author contributions: Dou XJ contributed to acquisition of data, data analysis, and wrote the manuscript; Yu WL provided substantial contribution to the conception and design of the study and corrected the manuscript; Wang QP, Liu WH, Weng YQ, and Sun Y collected the data.

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ORCID number: Wen-Li Yu 0000-0003-1700-4844.

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REFERENCES

1 **Bourdeaux C**, Brunati A, Janssen M, de Magnée C, Otte JB, Sokal E, Reding R. Liver retransplantation in children. A 21-year single-center experience. *Transpl Int* 2009; **22**: 416-422 [PMID: 19040484 DOI: 10.1111/j.1432-2277.2008.00807.x]
2 **Fischler B**, Baumann U, D'Agostino D, D'Antiga L, Dezsofi A, Debray D, Durmaz O, Evans H, Frauca E, Hadzic N, Jahnel J, Loveland J, McLin V, Ng VL, Nobili V, Pawłowska J, Sharif K, Smets F, Verkade HJ, Hsu E, Horslen S, Bucuvalas J. Similarities and Differences in Allocation Policies for Pediatric Liver Transplantation Across the World. *J Pediatr Gastroenterol Nutr* 2019; **68**: 700-705 [PMID: 30676519 DOI: 10.1097/MPG.0000000000002283]
3 **Qin T**, Fu J, Verkade HJ. The role of the gut microbiome in graft fibrosis after pediatric liver transplantation. *Hum Genet* 2021; **140**: 709-724 [PMID: 32920649 DOI: 10.1007/s00439-020-02221-8]
4 **Hong SK**, Hwang S, Lee SG, Lee LS, Ahn CS, Kim KH, Moon DB, Ha TY. Pulmonary complications following adult liver transplantation. *Transplant Proc* 2006; **38**: 2979-2981 [PMID: 17112879 DOI: 10.1016/j.transproceed.2006.08.090]
5 **Yao W**, Luo G, Zhu G, Chi X, Zhang A, Xia Z, Hei Z. Propofol activation of the Nrf2 pathway is associated with amelioration of acute lung injury in a rat liver transplantation model. *Oxid Med Cell Longev* 2014; **2014**: 258567 [PMID: 24669282 DOI: 10.1155/2014/258567]
6 **Chi XJ**, Cai J, Luo CF, Cheng N, Hei ZQ, Li SR, Luo GJ. Relationship between the expression of Toll-like receptor 2 and 4 in mononuclear cells and postoperative acute lung injury in orthotopic liver transplantation. *Chin Med J (Engl)* 2009; **122**: 895-899 [PMID: 19493410]
7 **Nastos C**, Kalimeris K, Papoutsidakis N, Tasoulis MK, Lykoudis PM, Theodoraki K, Nastou D, Smyrniotis V, Arkadopoulos N. Global consequences of liver ischemia/reperfusion injury. *Oxid Med Cell Longev* 2014; **2014**: 906965 [PMID: 24799983 DOI: 10.1155/2014/906965]
8 **Lin YH**, Cai ZS, Jiang Y, Lü LZ, Zhang XJ, Cai QC. Perioperative risk factors for pulmonary complications after liver transplantation. *J Int Med Res* 2010; **38**: 1845-1855 [PMID: 21309501 DOI: 10.1177/147323001003800532]
9 **Carrier FM**, Chassé M, Wang HT, Aslanian P, Iorio S, Bilodeau M, Turgeon AF. Restrictive fluid management strategies and outcomes in liver transplantation: a systematic review. *Can J Anaesth* 2020; **67**: 109-127 [PMID: 31556006 DOI: 10.1007/s12630-019-01480-y]
10 **Feltracco P**, Carollo C, Barbieri S, Pettenuzzo T, Ori C. Early respiratory complications after liver transplantation. *World J Gastroenterol* 2013; **19**: 9271-9281 [PMID: 24409054 DOI: 10.3748/wjg.v19.i48.9271]
11 **Voet M**, Nusmeier A, Lerou J, Luijten J, Cornelissen M, Lemson J. Cardiac output-guided hemodynamic therapy for adult living donor kidney transplantation in children under 20 kg: A pilot study. *Paediatr Anaesth* 2019; **29**: 950-958 [PMID: 31309649 DOI: 10.1111/pan.13705]
12 **Romagnoli S**, Bevilacqua S, Lazzeri C, Ciappi F, Dini D, Pratesi C, Gensini GF, Romano SM. Most Care®: a minimally invasive system for hemodynamic monitoring powered by the Pressure Recording Analytical Method (PRAM). *HSR Proc Intensive Care Cardiovasc Anesth* 2009; **1**: 20-27 [PMID: 23439735]
13 **Bezinover D**, Kadry Z, McCullough P, McQuillan PM, Uemura T, Welker K, Mastro AM, Janicki PK. Release of cytokines and hemodynamic instability during the reperfusion of a liver graft. *Liver Transpl* 2011; **17**: 324-330 [PMID: 21384515 DOI: 10.1002/lt.22227]
14 **McIntosh AM**, Tong S, Deakyne SJ, Davidson JA, Scott HF. Validation of the Vasoactive-Inotropic Score in Pediatric Sepsis. *Pediatr Crit Care Med* 2017; **18**: 750-757 [PMID: 28486385 DOI: 10.1097/PCC.0000000000001191]
15 **Sapru A**, Curley MA, Brady S, Matthay MA, Flori H. Elevated PAI-1 is associated with poor clinical outcomes in pediatric patients with acute lung injury. *Intensive Care Med* 2010; **36**: 157-163 [PMID: 19855955 DOI: 10.1007/s00134-009-1690-2]
16 **Christman JW**, Sadikot RT, Blackwell TS. The role of nuclear factor-kappa B in pulmonary diseases. *Chest* 2000; **117**: 1482-1487 [PMID: 10807839 DOI: 10.1378/chest.117.5.1482]
17 **Bhatia M**, Zemans RL, Jeyaseelan S. Role of chemokines in the pathogenesis of acute lung injury. *Am J Respir Cell Mol Biol* 2012; **46**: 566-572 [PMID: 22323365 DOI: 10.1165/rcmb.2011-0392TR]
18 **Yoshidome H**, Kato A, Edwards MJ, Lentsch AB. Interleukin-10 inhibits pulmonary NF-kappaB activation and lung injury induced by hepatic ischemia-reperfusion. *Am J Physiol* 1999; **277**: L919-L923 [PMID: 10564176 DOI: 10.1152/ajplung.1999.277.5.L919]
19 **Rudnick MR**, Marchi LD, Plotkin JS. Hemodynamic monitoring during liver transplantation: A state of the art review. *World J Hepatol* 2015; **7**: 1302-1311 [PMID: 26052376 DOI: 10.4254/wjh.v7.i10.1302]

20 **Siniscalchi A**, Gamberini L, Laici C, Bardi T, Ercolani G, Lorenzini L, Faenza S. Post reperfusion syndrome during liver transplantation: From pathophysiology to therapy and preventive strategies. *World J Gastroenterol* 2016; **22**: 1551-1569 [PMID: 26819522 DOI: 10.3748/wjg.v22.i4.1551]

21 **Ryu HG**, Jung CW, Lee HC, Cho YJ. Epinephrine and phenylephrine pretreatments for preventing postreperfusion syndrome during adult liver transplantation. *Liver Transpl* 2012; **18**: 1430-1439 [PMID: 22821620 DOI: 10.1002/lt.23511]

22 **Vilchez-Monge AL**, Garutti I, Jimeno C, Zaballos M, Jimenez C, Olmedilla L, Piñeiro P, Duque P, Salcedo M, Asencio JM, Lopez-Baena JA, Maruszewski P, Bañares R, Perez-Peña JM. Intraoperative Troponin Elevation in Liver Transplantation Is Independently Associated With Mortality: A Prospective Observational Study. *Liver Transpl* 2020; **26**: 681-692 [PMID: 31944566 DOI: 10.1002/lt.25716]

23 **Botto F**, Alonso-Coello P, Chan MT, Villar JC, Xavier D, Srinathan S, Guyatt G, Cruz P, Graham M, Wang CY, Berwanger O, Pearse RM, Biccard BM, Abraham V, Malaga G, Hillis GS, Rodseth RN, Cook D, Polanczyk CA, Szczeklik W, Sessler DI, Sheth T, Ackland GL, Leuwer M, Garg AX, Lemanach Y, Pettit S, Heels-Ansdell D, Luratibuse G, Walsh M, Sapsford R, Schünemann HJ, Kurz A, Thomas S, Mrkobrada M, Thabane L, Gerstein H, Paniagua P, Nagele P, Raina P, Yusuf S, Devereaux PJ, McQueen MJ, Bhandari M, Bosch J, Buckley N, Chow CK, Halliwell R, Li S, Lee VW, Mooney J, Furtado MV, Suzumura E, Santucci E, Leite K, Santo JA, Jardim CA, Cavalcanti AB, Guimaraes HP, Jacka MJ, McAlister F, McMurtry S, Townsend D, Pannu N, Bagshaw S, Bessissow A, Duceppe E, Eikelboom J, Ganame J, Hankinson J, Hill S, Jolly S, Lamy A, Ling E, Magloire P, Pare G, Reddy D, Szalay D, Tittley J, Weitz J, Whitlock R, Darvish-Kazim S, Debeer J, Kavsak P, Kearon C, Mizera R, O'Donnell M, McQueen M, Pinthus J, Ribas S, Simunovic M, Tandon V, Vanhelder T, Winemaker M, McDonald S, O'Bryne P, Patel A, Paul J, Punthakee Z, Raymer K, Salehian O, Spencer F, Walter S, Worster A, Adili A, Clase C, Crowther M, Douketis J, Gangji A, Jackson P, Lim W, Lovrics P, Mazzadi S, Orovan W, Rudkowski J, Soth M, Tiboni M, Acedillo R, Garg A, Hildebrand A, Lam N, Macneil D, Roshanov PS, Srinathan SK, Ramsey C, John PS, Thorlacius L, Siddiqui FS, Grocott HP, McKay A, Lee TW, Amadeo R, Funk D, McDonald H, Zacharias J, Cortés OL, Chaparro MS, Vásquez S, Castañeda A, Ferreira S, Coriat P, Monneret D, Goarin JP, Esteve CI, Royer C, Daas G, Choi GY, Gin T, Lit LC, Sigamani A, Faruqui A, Dhanpal R, Almeida S, Cherian J, Furruqh S, Afzal L, George P, Mala S, Schünemann H, Muti P, Vizza E, Ong GS, Mansor M, Tan AS, Shariffuddin II, Vasanthan V, Hashim NH, Undok AW, Ki U, Lai HY, Ahmad WA, Razack AH, Valderrama-Victoria V, Loza-Herrera JD, De Los Angeles Lazo M, Rotta-Rotta A, Sokolowska B, Musial J, Gorka J, Iwaszczuk P, Kozka M, Chwala M, Raczek M, Mrowiecki T, Kaczmarek B, Biccard B, Cassimjee H, Gopalan D, Kisten T, Mugabi A, Naidoo P, Naidoo R, Rodseth R, Skinner D, Torborg A, Urrutia G, Maestre ML, Santaló M, Gonzalez R, Font A, Martínez C, Pelaez X, De Antonio M, Villamor JM, García JA, Ferré MJ, Popova E, Garutti I, Fernández C, Palencia M, Díaz S, Del Castillo T, Varela A, de Miguel A, Muñoz M, Piñeiro P, Cusati G, Del Barrio M, Membrillo MJ, Orozco D, Reyes F, Sapsford RJ, Barth J, Scott J, Hall A, Howell S, Lobley M, Woods J, Howard S, Fletcher J, Dewhirst N, Williams C, Rushton A, Welters I, Pearse R, Ackland G, Khan A, Niebrzegowska E, Benton S, Wragg A, Archbold A, Smith A, McAlees E, Ramballi C, Macdonald N, Januszewska M, Stephens R, Reyes A, Paredes LG, Sultan P, Cain D, Whittle J, Del Arroyo AG, Sun Z, Finnegan PS, Egan C, Honar H, Shahinyan A, Panjasawatwong K, Fu AY, Wang S, Reineks E, Blood J, Kalin M, Gibson D, Wildes T; Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Writing Group, on behalf of The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Investigators; Appendix 1. The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Study Investigators Writing Group; Appendix 2. The Vascular events In noncardiac Surgery patIents cOhort evaluatioN Operations Committee; Vascular events In noncardiac Surgery patIents cOhort evaluatioN VISION Study Investigators. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. *Anesthesiology* 2014; **120**: 564-578 [PMID: 24534856 DOI: 10.1097/ALN.0000000000000113]

24 **Sheng M**, Lin Y, Weng Y, Xu R, Sun Y, Yu W, Du H. Predictive Value of Intraoperative Troponin I Elevation in Pediatric Living Donor Liver Transplant Recipients With Biliary Atresia. *Transplantation* 2017; **101**: 2385-2390 [PMID: 28319568 DOI: 10.1097/TP.0000000000001732]

25 **Papanikolaou J**, Makris D, Mpaka M, Palli E, Zygoulis P, Zakynthinos E. New insights into the mechanisms involved in B-type natriuretic peptide elevation and its prognostic value in septic patients. *Crit Care* 2014; **18**: R94 [PMID: 24887309 DOI: 10.1186/cc13864]

26 **Klouche K**, Pommet S, Amigues L, Bargnoux AS, Dupuy AM, Machado S, Serveaux-Delous M, Morena M, Jonquet O, Cristol JP. Plasma brain natriuretic peptide and troponin levels in severe sepsis and septic shock: relationships with systolic myocardial dysfunction and intensive care unit mortality. *J Intensive Care Med* 2014; **29**: 229-237 [PMID: 23753226 DOI: 10.1177/0885066612471621]

27 **Feng ZY**, Xu X, Zhu SM, Bein B, Zheng SS. Effects of low central venous pressure during preanhepatic phase on blood loss and liver and renal function in liver transplantation. *World J Surg* 2010; **34**: 1864-1873 [PMID: 20372900 DOI: 10.1007/s00268-010-0544-y]

28 **Rogiers X**, Berrevoet F, Troisi R. Comments on Bonney *et al*. "Outcomes on right liver lobe transplantation: a match pair analysis" (Transpl. Int. 2008; 21: 1045-1051). *Transpl Int* 2009; **22**: 588 [PMID: 19055618 DOI: 10.1111/j.1432-2277.2008.00813.x]

29 **Marik PE**, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med* 2009; **37**: 2642-2647 [PMID: 19602972 DOI: 10.1097/CCM.0b013e3181a590da]

30 **Shin YH**, Ko JS, Gwak MS, Kim GS, Lee JH, Lee SK. Utility of uncalibrated femoral stroke volume variation as a predictor of fluid responsiveness during the anhepatic phase of liver transplantation. *Liver Transpl* 2011; **17**: 53-59 [PMID: 21254345 DOI: 10.1002/lt.22186]

31 **Weinberg L**, Banting J, Churilov L, McLeod RL, Fernandes K, Chao I, Ho T, Ianno D, Liang V, Muralidharan V, Christophi C, Nikfarjam M. The effect of a surgery-specific cardiac output-guided haemodynamic algorithm on outcomes in patients undergoing pancreaticoduodenectomy in a high-volume centre: a retrospective comparative study. *Anaesth Intensive Care* 2017; **45**: 569-580 [PMID: 28911286 DOI: 10.1177/0310057x1704500507]

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SYSTEMATIC REVIEWS

Minimally invasive endoscopic repair of rectovaginal fistula

Yi-Xian Zeng, Ying-Hua He, Yun Jiang, Fei Jia, Zi-Ting Zhao, Xiao-Feng Wang

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Yi-Xian Zeng, Ying-Hua He, Yun Jiang, Fei Jia, Zi-Ting Zhao, Xiao-Feng Wang, Department of Proctology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China

Corresponding author: Xiao-Feng Wang, MD, Doctor, Surgeon, Department of Proctology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, No. 5 North Line Pavilion, Xicheng District, Beijing 100053, China. wangxiaofeng74@hotmail.com

Abstract

BACKGROUND

Surgical techniques for repair of rectovaginal fistula (RVF) have been continually developed, but the ideal procedure remains unclear. Endoscopic repair is a novel and minimally invasive technique for RVF repair with increasing reporting.

AIM

To review the current applications and preliminary outcomes of this technique for RVF repair, aiming to give surgeons an alternative in clinical practice.

METHODS

Available articles were searched according to the search strategy. And the sample size, fistula etiology, fistula type, endoscopic repair approaches, operative time and hospital stay, follow-up period, complication and life quality assessment were selected for recording and further analysis.

RESULTS

A total of 11 articles were eventually identified, involving 71 patients with RVFs who had undergone endoscopic repair. The principal causes of RVFs were surgery (n = 51, 71.8%), followed by obstetrics (n = 7, 9.8%), inflammatory bowel disease (n = 5, 7.0%), congenital (n = 3, 4.2%), trauma (n = 2, 2.8%), radiation (n = 1, 1.4%), and in two patients, the cause was unclear. Most fistulas were in a mid or low position. Several endoscopic repair methods were included, namely transanal endoscopic microsurgery, endoscopic clipping, and endoscopic stenting. Most patients underwent > 1-year follow-up, and the success rate was 40%-93%, and all cases reported successful closure. Few complications were mentioned, while postoperative quality of life assessment was only mentioned in one study.

CONCLUSION

In conclusion, endoscopic repair of RVF is novel, minimally invasive and promising with acceptable preliminary effectiveness. Given its unique advantages, endoscopic repair can be an alternative technique for surgeons.

Key Words: Endoscopic repair; Minimal-invasive technique; Rectovaginal fistula

Core Tip: The current status of minimally invasive endoscopic repair for rectovaginal fistulas (RVFs) was reviewed. This is the first review to explore the current application status and evaluate the preliminary outcomes. Endoscopic repair is recommended as a novel and promising technique for RVF and warrants consideration by surgeons. The disappointing quality of published studies on surgical treatment of RVF is discussed, along with the possible role of endoscopic repair in improving the situation.

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INTRODUCTION

Rectovaginal fistula (RVF), a type of chronic gastrointestinal fistula, refers to an abnormal epithelialized-lined connection between the rectum and the vagina, presenting with symptoms including uncontrollable passage of gas and/or fecal discharge from the vagina[1]. Even though it is benign, the distressing and persistent symptoms interfere with daily activities and sexual life, and have a long-term potential detrimental impact on psychological health[2,3]. Obstetric trauma is the primary etiological factor for RVF, but it can also be acquired from local abscess, pelvic floor or rectal surgery, trauma, or radiotherapy[3-5]. Chronic inflammatory bowel disease (most commonly Crohn's disease) is the second most common etiology with rates varying between 6% and 23%[6]. It is reported that RVF occurs in up to 10% of women diagnosed with Crohn's disease[7,8]. Congenital RVF is rare, usually coexists with anal malformation, and can be treated by anal reconstruction at a young age[9].

Standard classification of RVF will benefit to the choice of treatment approach and the comparison of treatment outcomes between studies, and help develop an algorithm for repair. However, there is no generally accepted classification of RVF. Currently, the classification of "simple/complex" or "low/middle/high" according to location, size, and etiology of RVF is most used[10,11]. With the development of diagnostic and therapeutic techniques, the imaging results, endoscopic exploration and gradually defined local anatomical structure will promote a classification consensus[12,13]. The anatomical features are always the principle of classification, which makes it necessary to achieve a more detailed and precise anatomical recognition[14].

Various medical and surgical treatments have been applied for RVF, but treatment is still a challenge for doctors due to the high recurrence rate. Nonoperative methods are recommended for the treatment of fresh and slight symptomatic fistula. Surgical repair is essential, once it occurs and persists[15]. There is still no standard surgical repair technique worldwide for RVF and no evidence can suggest one surgical technique over another since the release of the procedural guidelines in Europe.

Multiple surgical repair techniques, including fistulectomy, advancement flap, muscle transposition, closure with biomaterials, endoscopic repair and transabdominal approaches[16], have been gradually reported in the literature. Fistulectomy is not technically demanding, whose main step is to remove the fistula tract, together with the surrounding scarred and sclerotic tissue. It may fail due to incomplete removal and excessive tissue tension of tissue suture for large excision, and is therefore, mostly used to repair small and simple RVFs[17,18]. Advancement flaps are performed by raising either the rectal mucosa (transrectal) or vaginal mucosa (transvaginal) to cover the fistula tract. Transrectal advancement flap is more commonly adopted compared to the transvaginal approach, and the repair is performed from the high pressure of the rectum side, and has an actual success rate of 50%-70%[1,4]. Even though some studies have recommended transrectal advancement flap as the first-line treatment for low RVFs, it is not as effective as expected if the periorificial tissue is chronically inflamed, or when the fistula is large in diameter and causes anal stenosis[19]. Reconstruction by Martius flap, gracilis muscle flap or bulbocavernosus muscle transposition can be used to introduce healthy vascularized tissues, which has achieved a certain effect for recurrent, Crohn's-disease-related and radiation-related RVFs, with reported overall success rates ranging from 25% to 100%[20,21]. However, given the aggressive incision, tissue damage, prolonged hospital stay and protective stoma diversion routinely required, this technique is demanding and not easily accepted by patients[22,23]. Biomaterials and endoscopic repair are novel and less invasive techniques and constant attempts have been made to apply them for RVF repair. However, given the limited number of publications available, there are currently no relevant recommendations. Transabdominal approaches are recommended for high RVFs resulting from

complications of colorectal anastomosis, and laparoscopic repair has been frequently adopted[15,24]. In clinical practice, protective stoma diversion is generally applied for the treatment of RVF, whereas absence of any reliable efficacy assessment for RVF makes it remain controversial. Theoretically, diversion stoma may help control the symptoms by fecal diversion and support healing of the fistula and surgical success[25]. Corte *et al*[26] claimed that a temporary diversion stoma could significantly improve the success rate of repair. However, Lambertz *et al*[27] found no connection between diversion stoma creation and rate of recurrence, which was supported by other authors[28,29]. Some studies have shown that radiation- and Chron's-disease-related RVFs are indications for diversion stoma[30,31], and stating that once the diversion stoma is made, large invasion, distressing conditions and potential complications can occur[32]. Although the techniques for RVF repair have been developing, the etiology, classification, surrounding tissue condition, prior treatment procedures and the surgeon's preference are always the basis for determining the approach. In addition, individualized, precise, and less-invasive surgical techniques for RVFs repair are gradually being recommended[13,33].

All the surgical interventions performed *via* an endoscope or in the endoscopy unit can be classified as endoscopic repair, which is a novel and minimally invasive surgical technique for RVF. Several endoscopic repair approaches have been applied and reported for RVF surgical treatment. Transanal endoscopic microsurgery (TEMS) is an endoscopic technique performed entirely through the anus and rectum, which was originally developed in the 1980s to treat lower rectal adenomas[34] (Figure 1). Vávra *et al*[35] reported the first case of RVF treatment using TEMS in 2006, which is one of the most reported endoscopic approaches for RVF. Several minimally invasive endoscopic approaches such as the through-the-scope clip (TTSC), over-the-scope clip proctology system (OTSC) and endoscopic stenting have successively proven their role in RVF repair. After more than a decade of development, endoscopic repair for RVF has been continuously advanced and more advantages have been unveiled. Endoscopic repair for RVF is novel but limited by the information available. Therefore, a review of studies on minimally invasive endoscopic repair for RVF was carried out to assess the preliminary outcomes and introduce several endoscopic approaches for RVF surgical repair to surgeons, thereby contributing to developing a more individualized, precise, and less-invasive treatment plan appropriate for each patient.

MATERIALS AND METHODS

A search was performed to identify the existing literature available in PubMed and EMBASE databases in December 2021, without timeframe limitations (Figure 2). The following keywords, including "rectovaginal fistula," "rectovaginal," "fistula," "endoscope", "endoscopic," and "endoscopy", were used for searching. Given that there were only around 184 articles available, every single article was reviewed at the beginning. Exclusion criteria included irrelevancy, not English language, guidelines, or reviews. Articles published by the same author were found a duplication in the inclusion of patients, and the study with the longest follow-up was included. Three independent reviewers extracted and summarized data from the included articles and conducted qualitative assessment in accordance with the Oxford Centre for Evidence-Based Medicine 2011 Level of evidence[36]. All disagreements were settled by consensus. In addition, we conducted a research using Reference Citation Analysis (https://www.referencecitationanalysis.com/) and cited the relevant references.

RESULTS

A total of 11 articles were eventually identified according to the search strategy. Data were extracted by the reviewers and eventually reported using summary statistics, as shown in Table 1. The limited number of available articles and the low evidence of all studies made the primary outcome not sufficiently satisfactory. Besides, there were not enough eligible articles to perform a meta-analysis. In terms of the type of study, case reports seemed to be preferred for this novel technique, and the number of patients in each retrospective study was limited. The etiology was classified as: related to surgery (n = 51) such as rectal surgery, pelvic surgery and the colorectal anastomosis, *etc*., with 22 patients undergoing rectal surgery with a history of radiotherapy; and directly caused by radiotherapy (n = 1), inflammatory bowel diseases (n = 5) including Crohn's disease and ulcerative colitis; congenital (n = 3), obstetric injury (n = 7), trauma (n = 2), with the etiology unclear in two patients. Most fistulas were situated in the middle or low. Most of the patients had undergone previous repairs, even on multiple occasions. Fecal diversion was chosen as part of surgical treatment in some patients. Psychological components regarded as important as the success rate were rarely reported[19,37], with improved sexual function after repair mentioned in only one paper.

Table 2 summarized the details and preliminary outcomes of endoscopic repair of RVFs. A total of 38 patients underwent the conventional surgical procedure with a transrectal endoscopic device, when the layered suture was closed for 24, and mucosal advancement flap was for 14 patients. Endoscopic clip was another commonly used approach for RVF repair, and 18 patients who were treated using this

Table 1 Extract data of studies included

Number	Ref.	Type of study and evidence level	No. of patient(s)	Age of patients (yr)	Fistula etiology	Fistula type	No. of patients with previous repair	Diversion stoma	Life quality assessment (yes or no)
1	D'Ambrosio *et al*[41], 2012	Retrospective, level IV	13	44 (range, 25-70)	Surgery (n = 12); Radiation (n = 1)	Mid-low	13	Yes, 13 patients	No
2	Lamazza *et al* [54], 2016	Retrospective, level IV	15	58 (rang, 36-77)	Surgery with radiation (n = 15)	Mid-low	4	Yes, 4 patients	No
3	van Vledder *et al*[56], 2016	Retrospective, level IV	5	40 (range, 35-73)	Surgery (n = 5)	Mid-low	0	Yes, 3 patients	No
4	Yuan *et al* [42], 2019	Retrospective, level IV	17	46 (range, 10-76)	Surgery (n = 11); Congenital (n = 3); Obstetric (n = 2); IBDs (n = 1)	Mid-low	6	Yes, 9 patients	No
5	Tong *et al* [50], 2019	Prospective, level IV	16	40.1 (range, 27-56)	Surgery with radiation (n = 6); Obstetric (n = 5); IBDs (n = 3); Unclear (n = 2)	Mid-low	13	Yes, 11 patients	No
6	Shibata *et al* [57], 1999	Case report, level IV	1	71	Surgery	Low	0	No	No
7	Darwood *et al* [58], 2008	Case report, level IV	1	71	Surgery with radiation (n = 1)	Unclear	0	Yes	No
8	John *et al*[45], 2008	Case report, level IV	1	77	Infection (n = 1)	Mid	0	No	No
9	Vavra *et al* [59], 2009	Case report, level IV	1	53	Trauma (n = 1)	Mid	0	Yes	Yes
10	Chen *et al* [43], 2016	Case report, level IV	1	22	Trauma (n = 1)	Mid	2	Yes	No
11	Matano *et al* [48], 2019	Case report, level IV	1	71	Surgery (n = 1)	Mid	Multiple times	Yes	No

technique benefited from TTSC (n = 2) and OTSC (n = 16). One retrospective study reported endoscopic repair with placement of a self-expandable metal stent (n = 15). Several other endoscopic repair approaches for RVF such as endoscopic plugs, endoscopic injection and endoscopic–laparoscopic combined approach were noted, which were removed due to no complete references. Operating time and hospital stay were the desired outcomes, but not frequently reported. Most patients underwent > 1 year of follow-up. All case reports reported successful outcomes, but the success rates were different (40%-93%) in retrospective case series. More than half the studies reported no severe complications, and a few reported some minor postoperative complications, such as hematoma or abscess of rectovaginal septum (n = 2), moderate sphincter hypotonia (n = 1), pain (n = 5), minimal vaginal flatus (n = 1).

Minimally invasive endoscopic repair

TEMS: Minimally invasive techniques have been one of the major advancements in surgery in the last few decades, and are also one of the future trends. Such a technique has been almost routinely performed in colorectal resection irrespective of underlying diseases[38]. With the development of surgical instruments, endoscopic surgery is considered a feasible and minimally invasive approach that can facilitate better exposure, direct visualization and precise operation, with an increasing number of surgeons choosing it[39]. TEMS, as a platform for natural orifice transluminal endoscopic surgery, has developed into a well-established method of accurate resection of specimens from the rectum under binocular vision after the initial application for rectal cancer, and has also been adopted as an operative intervention in an extended setting for RVF[40]. After the first case of TEMS for RVF repair reported in 2006[35], the first retrospective review with 13 patients who had undergone layered sutures *via* this repair technique was published in 2012, with a closure rate of 93%[41]. In the present review, more than half of patients (n = 38) underwent conventional surgical repair procedures with transanal endoscopic devices, with a success rate of 40%-93%. The latest study reported a closure rate of 82% of mid-low RVF TEMS with layered sutures and mucosal advancement flaps[42]. Another three cases all reported successful closure. The superior 3D exposure and direct vision were the greatest advantages of TEMS. Under good visualization, comprehensive procedures exploring the anatomical structural relationship

Table 2 Details and results of the endoscopic repair approaches for rectovaginal fistulas

Number	Endoscopic repair	Operative time (min) and hospital-stay (d)	Follow-up (mo)	Results[a]	Complication
1	TEMS + fistulectomy + suturing (n = 13)	130 min (range, 90-150 min); 5 d (range, 3-8 d)	25	93% closed	Hematoma of the septum (n = 1); Abscess of the septum (n = 1); Moderate sphincter hypotonia (n = 1)
2	Endoscopic stenting (n = 15)	Unclear; Unclear	22 (range, 4-39)	80% closed	Pain (n = 1); Too uncomfortable to tolerate the stent (n = 1)
3	TEMS + fistulectomy + suturing (n = 4); TEMS + RAF (n = 1)	Unclear; Unclear	5 (range, 1-68)	40% closed	No complication
4	TEMS + VAF (n = 6); TEMS exploration + VAF (n = 6); TEMS + transvaginal suturing (n = 3); TES exploration + transvaginal suturing (n = 2)	75 min (range, 60-120 min); 8.29 d (range, 2-24 d)	8 (range, 2-24)	82.4% closed	No complication
5	OTSCs (n = 16)	Unclear; Unclear	10.2 (range, 8-36)	43.7% closed	Pain (n = 4); Spontaneous clip detachment (n = 1)
6	Endoscopic injection of fibrin glue (n = 1)	Few min; 0 d	12	Closed successfully	No complication
7	TEMS + RAF (n = 1)	Unclear; 2 d	6	Closed successfully	No complication
8	TTSCs (n = 1)	Unclear; Unclear	12	Closed successfully	Minimal flatus from vaginal (n = 1)
9	TEMS + suturing (n = 1)	125 min; 7d	12	Closed successfully	No complication
10	TEMS + stratified suturing (n = 1)	40 min; 2 d	12	Closed successfully	No complication
11	TTSCs (n = 1)	Unclear; Unclear	13	Closed successfully	No complication

[a]Success rate (%) for retrospective or prospective studies, closed successfully or unsuccessfully for case reports.

TEMS: Transanal endoscopic microsurgery; OTSC: Over-the-scope clip; TTSC: Through-the-scope clip; RAF: Rectal advancement flap; VAF: Vaginal advancement flap.

could be provided preoperatively and intraoperatively. The conventional invasive procedure could be performed more accurately with TEMS equipment, and ensure complete removal of the surrounding scarred or granulomatous tissues, but without significant loss of normal tissue. Therefore, there was a greater certainty of adequate blood supply to the tissue overlaps and/or flaps owing to the fresh tissue with the healthy margins[42]. In addition, the smaller tissue defect and good control of suture tightness enable free-tension repair[43], and make up for the shortcomings of conventional local repair that cannot completely remove surrounding tissue and is subject to insufficient blood supply and prompt healing. Using a natural endoluminal approach with endoscopy, precise operation and visualization can greatly reduce the invasiveness of conventional surgery with less intraoperative bleeding, shorter operating time and hospital stay, and fewer postoperative complications.

Endoscopic clipping: Endoscopic clipping is another technology using endoclips to completely close gastrointestinal leaks and fistulas, initially applied for iatrogenic gastric perforation in 1993[44]. John *et al*[45] reported the first successful closure of an RVF with TTSCs, which was also applied for repair of refractory RVF[33]; Ortiz-Moyano *et al*[46] described a combined approach using TTSCs and tissue adhesive that improved the rate of technical success in the endoscopic clips treatment of RVFs, since clips not only worked in opposing the margins, but acted as a scaffold for the glue. OTSCs for the gastrointestinal tract had greater force and a consistently high mean rate of procedural success of 80%-100%, and a durable clinical success rate of 57%-100%, and was preferred over TTSCs for closure of gastrointestinal fistulas[47]. Regarding colon perforation, small perforations (< 10 mm) could be successfully closed with TTSCs, whereas larger perforations could be successfully closed with OTSCs [48]. The first RVF closure using the OTSC proctology system was performed by Prosst *et al*[49] in 2015. One prospective study in 2019[50] presented the first evaluation of the therapeutic effects and safety of the application of OTSCs in complex RVFs, with a success rate of 43.7%, which was as high as that for gastrointestinal fistulas and convincing for complicated ones. Endoscopic clipping is a minimally invasive technique that involves transrectal placement of endoclips for RVF closure to avoid tissue incision, sphincter damage and intraoperative bleeding[49]. It is considered suitable for small fistulas,

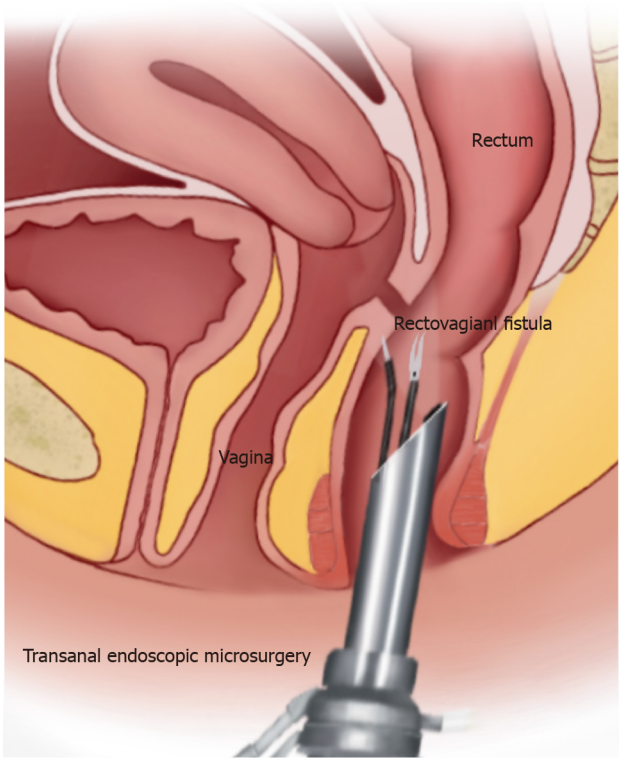

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Figure 1 Transanal endoscopic microsurgery for rectovaginal fistula repair.

and is even recommended to repair high-level fistulas[45,48]. Given limited data and obtained evidence, the role of endoscopic clips in RVF repair remains to be further investigated.

Endoscopic stenting: Endoscopic stenting involves placement of a self-expandable metal stent into the gastrointestinal tract to treat the defects, especially anastomotic leaks or perforation of the upper gastrointestinal tract[51]. Endoscopic placement of the self-expandable metal stent to treat RVFs after colorectal resection for cancer was a useful alternative to divert colostomy for the palliation of malignant rectal obstruction[52]. The team presented the two series outcomes with a success rate of 83% (5 of 6 patients)[53] and 80% (12 of 15 patients)[54], and the fistula size decreased significantly in all remaining patients, indicating that endoscopic placement of self-expandable metal stents may be a valid adjunctive treatment of RVF after colorectal resection for cancer. However, the favorable results may have been due to the low number of patients and selection bias. In the selected cases, the endoscopic placement of the self-expandable metal stent for RVF repair showed that the endoscopic stenting allowed a fast and proper closure of the fistula in a minimally invasive endoscopic way, with minor discomfort for patients and early discharge. A clear indication and results are still required for further in-depth study.

DISCUSSION

Surgical outcomes of RVF repair are mostly measured by the rates of closure and reoperation[37]. The successful closure rates for RVF surgical repair vary in the literature[55]. A similar variation in success rate (20%-93%) was found in this study using different etiologies and endoscopic approaches. We acknowledge that the varying rate of successful closure, limited number of publications available on this novel technique, and the low quality of included studies were limitations of the present review. In addition, the indications for endoscopic repair for RVF are not clear due to the lack of high-quality clinical studies. From a review of the included literature, endoscopic repair for RVF seems to be more commonly used in the treatment of low- and mid-level fistulas. However, it is also used for high-level fistulas with small openings, because transabdominal surgery is an invasive approach for small fistulas; therefore, endoscopic repair is considered a viable minimally invasive approach[48]. Moreover, endoscopic repair is a promising option for primary repair of RVF, and can be recommended for treatment of recurrent fistulas as well[50]. Regarding endoscopic repair is performed locally, it is not suitable for refractory RVFs with large openings and excessive tissue defects. Nevertheless, the minimally invasive endoscopic approach for RVF repair is a promising choice, and more surgical methods could be developed based on the endoscopic technique. As the research progresses, more

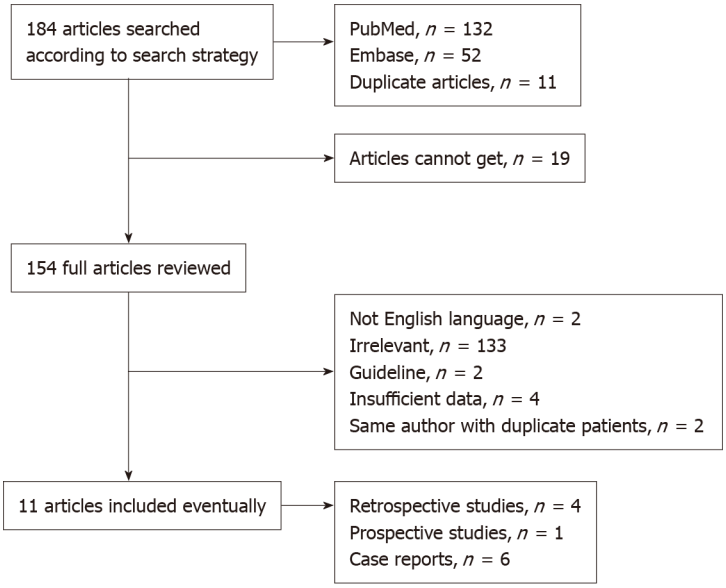

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Figure 2 The search strategy.

indications should be unveiled as well.

A 2014 systematic review claimed that the reason for difficulties in formulating a conclusion about the best surgical technique for RVF repair was the disappointing quality of existing literature surrounding different surgical techniques and outcomes for RVF repair[16]. Such a result not only persisted in the present review, but also in some related to single surgical approaches[8,20]. On the one hand, the limited number of samples and the heterogeneity of etiologies and local conditions made it hard to design large studies. RVF is a benign and chronic disease without a high incidence, but subject to variable and complex causes. There is no doubt that compared to the sample iatrogenic etiologies, IBDs-or radiation-related RVF would make difference in the local condition and the selection of surgical techniques. Therefore, retrospective studies were reviewed carefully to ensure the study sample size and homogeneity. With the continuous advancement of endoscopic techniques, different surgical procedures can be applied and standardized, which may improve the homogeneity of the surgical devices and contribute to designing large studies. On the other hand, in terms of the precise anatomical relationship of the fistula defect and the surrounding tissue, the lack of consensus on classification of RVFs makes it difficult to compare different surgical techniques. It is therefore proposed that further revisions are needed to guide the choice of newly developed treatment approaches[19]. Additionally, some authors claimed that a precise preoperative anatomical relationship assessment allowed better classification of fistulas and comparisons among different techniques[14]. It is believed that diagnostic imaging and endoscopic exploration could play a role in clarifying and developing anatomical relationship standards.

CONCLUSION

Endoscopic repair for RVFs is novel, effective and promising. A precise operation under good visualization through a natural lumen can reduce the invasiveness of conventional procedures. Some endoscopic surgical modes such as clipping and stenting mentioned in this review could even close the fistula without incision, less intraoperative bleeding, fewer complications, and shorter operating time and hospital stay. Surgeons could clarify the anatomical relationship of the fistula and surrounding tissue by endoscopic preoperative exploration and provide patients with a more appropriate treatment approach. However, endoscopic surgical repair for RVFs is technically demanding with a long learning curve and requires sufficient professional experience. Therefore, it is advocated to be performed by professional colorectal surgeons in highly specialized centers. Besides, larger high-quality studies and longer follow-up studies are necessary to unveil the clear indication and advantages of this novel minimally invasive endoscopic technique for RVF repair.

ARTICLE HIGHLIGHTS

Research background

Rectovaginal fistula (RVF) is abnormal connection between the rectum and vagina. Surgical repair is essential, once it occurs and persists. Surgical techniques for repair of rectovaginal fistula have been continually developed, but the ideal procedure remains unclear. Endoscopic repair is a novel and minimally invasive technique for RVF repair with increasing reporting.

Research motivation

To review the current literature of endoscopic repair of RVF and highlight the novel and minimally invasive technique for RVF repair to surgeons.

Research objectives

To evaluate the preliminary outcomes of this technique for RVF repair and analyze the indication and technical superiority.

Research methods

We searched PubMed and EMBASE databases for available studies. Data were extracted and qualitative assessment was conducted.

Research results

The endoscopic repair of RVF is in constant development, including several available approaches. The preliminary effectiveness of endoscopic technique for RVF repair is acceptable.

Research conclusions

Endoscopic repair for RVF is novel, effective and promising with acceptable preliminary effectiveness. In this manuscript, we have provided a detailed review of literatures, summarized its indications and unique technical advantages and made suggestions for its application and future development.

Research perspectives

Endoscopic repair for RVF is effective and safe according to preliminary outcomes. It is a promising technique for the treatment of rectovaginal fistulas and provides a minimally invasive technique selection for surgeons to treat rectovaginal fistulas.

FOOTNOTES

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Country/Territory of origin: China

ORCID number: Yi-Xian Zeng 0000-0002-9219-9103; Ying-Hua He 0000-0002-8970-4519; Yun Jiang 0000-0002-4449-2137; Fei Jia 0000-0002-4114-492X; Zi-Ting Zhao 0000-0003-4023-0006; Xiao-Feng Wang 0000-0001-6053-8177.

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REFERENCES

1 **Kniery KR**, Johnson EK, Steele SR. Operative considerations for rectovaginal fistulas. *World J Gastrointest Surg* 2015; **7**: 133-137 [PMID: 26328032 DOI: 10.4240/wjgs.v7.i8.133]

2 **Baig MK**, Zhao RH, Yuen CH, Nogueras JJ, Singh JJ, Weiss EG, Wexner SD. Simple rectovaginal fistulas. *Int J Colorectal Dis* 2000; **15**: 323-327 [PMID: 11151438 DOI: 10.1007/s003840000253]

3 **Byrnes JN**, Schmitt JJ, Faustich BM, Mara KC, Weaver AL, Chua HK, Occhino JA. Outcomes of Rectovaginal Fistula Repair. *Female Pelvic Med Reconstr Surg* 2017; **23**: 124-130 [PMID: 28106653 DOI: 10.1097/SPV.0000000000000373]

4 **Ommer A**, Herold A, Berg E, Fürst A, Schiedeck T, Sailer M. German S3-Guideline: rectovaginal fistula. *Ger Med Sci* 2012; **10**: Doc15 [PMID: 23255878 DOI: 10.3205/000166]

5 **Rahman MS**, Al-Suleiman SA, El-Yahia AR, Rahman J. Surgical treatment of rectovaginal fistula of obstetric origin: a review of 15 years' experience in a teaching hospital. *J Obstet Gynaecol* 2003; **23**: 607-610 [PMID: 14617459 DOI: 10.1080/01443610310001604349]

6 **Pinto RA**, Peterson TV, Shawki S, Davila GW, Wexner SD. Are there predictors of outcome following rectovaginal fistula repair? *Dis Colon Rectum* 2010; **53**: 1240-1247 [PMID: 20706066 DOI: 10.1007/DCR.0b013e3181e536cb]

7 **Valente MA**, Hull TL. Contemporary surgical management of rectovaginal fistula in Crohn's disease. *World J Gastrointest Pathophysiol* 2014; **5**: 487-495 [PMID: 25400993 DOI: 10.4291/wjgp.v5.i4.487]

8 **Kaimakliotis P**, Simillis C, Harbord M, Kontovounisios C, Rasheed S, Tekkis PP. A Systematic Review Assessing Medical Treatment for Rectovaginal and Enterovesical Fistulae in Crohn's Disease. *J Clin Gastroenterol* 2016; **50**: 714-721 [PMID: 27466166 DOI: 10.1097/MCG.0000000000000607]

9 **Oh C**, Youn JK, Han JW, Yang HB, Kim HY, Jung SE, Park KW. Experiences of Rectovaginal Fistula in Anorectal Malformation. *J Pediatr Surg* 2020; **55**: 1495-1498 [PMID: 31416593 DOI: 10.1016/j.jpedsurg.2019.06.021]

10 **Rothenberger DA**, Goldberg SM. The management of rectovaginal fistulae. *Surg Clin North Am* 1983; **63**: 61-79 [PMID: 6338609 DOI: 10.1016/s0039-6109(16)42930-0]

11 **Abu Gazala M**, Wexner SD. Management of rectovaginal fistulas and patient outcome. *Expert Rev Gastroenterol Hepatol* 2017; **11**: 461-471 [PMID: 28276809 DOI: 10.1080/17474124.2017.1296355]

12 **Rociu E**, Stoker J, Zwamborn AW, Laméris JS. Endoanal MR imaging of the anal sphincter in fecal incontinence. *Radiographics* 1999; **19** Spec No: S171-S177 [PMID: 10517453 DOI: 10.1148/radiographics.19.suppl_1.g99oc02s171]

13 **Komori K**, Kinoshita T, Oshiro T, Ouchi A, Ito S, Abe T, Senda Y, Misawa K, Ito Y, Natsume S, Higaki E, Okuno M, Hosoi T, Nagao T, Kunitomo A, Oki S, Takano J, Suenaga Y, Maeda S, Dei H, Numata Y, Shimizu Y. Surgical Strategy for Rectovaginal Fistula After Colorectal Anastomosis at a High-volume Cancer Center According to Image Type and Colonoscopy Findings. *Anticancer Res* 2019; **39**: 5097-5103 [PMID: 31519621 DOI: 10.21873/anticanres.13704]

14 **Hauch A**, Ramamoorthy S, Zelhart M, Dobke M. Refining Approaches to Surgical Repair of Rectovaginal Fistulas. *Ann Plast Surg* 2020; **84**: S250-S256 [PMID: 31923012 DOI: 10.1097/SAP.0000000000002207]

15 **Vogel JD**, Johnson EK, Morris AM, Paquette IM, Saclarides TJ, Feingold DL, Steele SR. Clinical Practice Guideline for the Management of Anorectal Abscess, Fistula-in-Ano, and Rectovaginal Fistula. *Dis Colon Rectum* 2016; **59**: 1117-1133 [PMID: 27824697 DOI: 10.1097/DCR.0000000000000733]

16 **Göttgens KW**, Smeets RR, Stassen LP, Beets G, Breukink SO. The disappointing quality of published studies on operative techniques for rectovaginal fistulas: a blueprint for a prospective multi-institutional study. *Dis Colon Rectum* 2014; **57**: 888-898 [PMID: 24901691 DOI: 10.1097/DCR.0000000000000147]

17 **Beksac K**, Tanacan A, Ozgul N, Beksac MS. Treatment of Rectovaginal Fistula Using Sphincteroplasty and Fistulectomy. *Obstet Gynecol Int* 2018; **2018**: 5298214 [PMID: 29853904 DOI: 10.1155/2018/5298214]

18 **Fu J**, Liang Z, Zhu Y, Cui L, Chen W. Surgical repair of rectovaginal fistulas: predictors of fistula closure. *Int Urogynecol J* 2019; **30**: 1659-1665 [PMID: 31468097 DOI: 10.1007/s00192-019-04082-w]

19 **Trompetto M**, Realis Luc A, Novelli E, Tutino R, Clerico G, Gallo G. Use of the Martius advancement flap for low rectovaginal fistulas. *Colorectal Dis* 2019; **21**: 1421-1428 [PMID: 31260184 DOI: 10.1111/codi.14748]

20 **Hotouras A**, Ribas Y, Zakeri S, Murphy J, Bhan C, Chan CL. Gracilis muscle interposition for rectovaginal and anovaginal fistula repair: a systematic literature review. *Colorectal Dis* 2015; **17**: 104-110 [PMID: 25284745 DOI: 10.1111/codi.12791]

21 **Lowry AC**. Management of rectovaginal fistula. *Semin Colon Rectal Surg* 2016; **27**: 64-68 [DOI: 10.1053/J.SCRS.2015.12.010]

22 **Lee RC**, Rotmensch J. Rectovaginal radiation fistula repair using an obturator fasciocutaneous thigh flap. *Gynecol Oncol* 2004; **94**: 277-282 [PMID: 15297162 DOI: 10.1016/j.ygyno.2004.03.049]

23 **Lefèvre JH**, Bretagnol F, Maggiori L, Alves A, Ferron M, Panis Y. Operative results and quality of life after gracilis muscle transposition for recurrent rectovaginal fistula. *Dis Colon Rectum* 2009; **52**: 1290-1295 [PMID: 19571707 DOI: 10.1007/DCR.0b013e3181a74700]

24 **Mukwege D**, Mukanire N, Himpens J, Cadière GB. Minimally invasive treatment of traumatic high rectovaginal fistulas. *Surg Endosc* 2016; **30**: 379-387 [PMID: 25847136 DOI: 10.1007/s00464-015-4192-z]

25 **Fu W**, Yi S, An M, Tang Y, Tang L, Wang Y, Yuan Y, Zhou Q, Hu Y, Wen Y. Effect of diverting stoma for rectovaginal fistula: A protocol of systematic review and meta-analysis. *Medicine (Baltimore)* 2020; **99**: e23202 [PMID: 33285694 DOI: 10.1097/MD.0000000000023202]

26 **Corte H**, Maggiori L, Treton X, Lefevre JH, Ferron M, Panis Y. Rectovaginal Fistula: What Is the Optimal Strategy? *Ann Surg* 2015; **262**: 855-60; discussion 860 [PMID: 26583676 DOI: 10.1097/SLA.0000000000001461]

27 **Lambertz A**, Lüken B, Ulmer TF, Böhm G, Neumann UP, Klink CD, Krones CJ. Influence of diversion stoma on surgical outcome and recurrence rates in patients with rectovaginal fistula - A retrospective cohort study. *Int J Surg* 2016; **25**: 114-117 [PMID: 26700197 DOI: 10.1016/j.ijsu.2015.12.005]

28 **Barugola G**, Bertocchi E, Leonardi A, Almoudaris AM, Ruffo G. Post surgical rectovaginal fistula: who really benefits from stoma diversion? *Updates Surg* 2021; **73**: 165-171 [PMID: 32449033 DOI: 10.1007/s13304-020-00810-w]

29 **Tozer PJ**, Balmforth D, Kayani B, Rahbour G, Hart AL, Phillips RK. Surgical management of rectovaginal fistula in a tertiary referral centre: many techniques are needed. *Colorectal Dis* 2013; **15**: 871-877 [PMID: 23331635 DOI: 10.1111/codi.12114]

30 **Piekarski JH**, Jereczek-Fossa BA, Nejc D, Pluta P, Szymczak W, Sek P, Bilski A, Gottwald L, Jeziorski A. Does fecal diversion offer any chance for spontaneous closure of the radiation-induced rectovaginal fistula? *Int J Gynecol Cancer* 2008; **18**: 66-70 [PMID: 17466039 DOI: 10.1111/j.1525-1438.2007.00954.x]

31 **Hannaway CD**, Hull TL. Current considerations in the management of rectovaginal fistula from Crohn's disease. *Colorectal Dis* 2008; **10**: 747-55; discussion 755 [PMID: 18462243 DOI: 10.1111/j.1463-1318.2008.01552.x]

32 **Klink CD**, Lioupis K, Binnebösel M, Kaemmer D, Kozubek I, Grommes J, Neumann UP, Jansen M, Willis S. Diversion stoma after colorectal surgery: loop colostomy or ileostomy? *Int J Colorectal Dis* 2011; **26**: 431-436 [PMID: 21221605 DOI: 10.1007/s00384-010-1123-2]

33 **Shen B**. Exploring endoscopic therapy for the treatment of Crohn's disease-related fistula and abscess. *Gastrointest Endosc* 2017; **85**: 1133-1143 [PMID: 28153572 DOI: 10.1016/j.gie.2017.01.025]

34 **Buess G**, Theiss R, Hutterer F, Pichlmaier H, Pelz C, Holfeld T, Said S, Isselhard W. [Transanal endoscopic surgery of the rectum - testing a new method in animal experiments]. *Leber Magen Darm* 1983; **13**: 73-77 [PMID: 6621245]

35 **Vávra P**, Andel P, Dostalík J, Gunková P, Pelikán A, Gunka I, Martínek L, Vávrová M, Spurný P, Curík R, Koliba P. [The first case of management of the rectovaginal fistule using transanal endocsopic microsurgery]. *Rozhl Chir* 2006; **85**: 82-85 [PMID: 16626017]

36 University of Oxford. OCEBM Levels of Evidence Working Group. "The Oxford Levels of Evidence 2". Centre for Evidence-Based Medicine. [cited 28 May 2022]. Available from: https://www.cebm.ox.ac.uk/resources/Levels-of-evidence/ocebm-levels-of-evidence

37 **Hauch A**, McKee RM, Li WY, Crowley JS, Ramamoorthy S, Dobke M. Rectovaginal Fistula Repair 1 Year Later: Lessons Learned. *Ann Plast Surg* 2021; **87**: 187-193 [PMID: 33346534 DOI: 10.1097/SAP.0000000000002626]

38 **Neumann PA**, Rijcken E. Minimally invasive surgery for inflammatory bowel disease: Review of current developments and future perspectives. *World J Gastrointest Pharmacol Ther* 2016; **7**: 217-226 [PMID: 27158537 DOI: 10.4292/wjgpt.v7.i2.217]

39 **Reavis KM**, Melvin WS. Advanced endoscopic technologies. *Surg Endosc* 2008; **22**: 1533-1546 [PMID: 18401657 DOI: 10.1007/s00464-008-9831-1]

40 **Saclarides TJ**. Transanal Endoscopic Microsurgery. *Clin Colon Rectal Surg* 2015; **28**: 165-175 [PMID: 26491409 DOI: 10.1055/s-0035-1562889]

41 **D'Ambrosio G**, Paganini AM, Guerrieri M, Barchetti L, Lezoche G, Fabiani B, Lezoche E. Minimally invasive treatment of rectovaginal fistula. *Surg Endosc* 2012; **26**: 546-550 [PMID: 22083318 DOI: 10.1007/s00464-011-1917-5]

42 **Yuan X**, Chen H, Chen C, Yang M, Li Q, Gao R, Wu X, Xu W, Sun J, Yin L. Minimally invasive treatment of mid-low rectovaginal fistula: a transanal endoscopic surgery study. *Surg Endosc* 2020; **34**: 3971-3977 [PMID: 31728753 DOI: 10.1007/s00464-019-07174-2]

43 **Chen W**, Chen X, Lin G, Qiu H. Successful repair of recurrent rectovaginal fistula by stratified suture using transanal endoscopic microsurgery: A CARE-compliant case report. *Medicine (Baltimore)* 2016; **95**: e4600 [PMID: 27603349 DOI: 10.1097/MD.0000000000004600]

44 **Binmoeller KF**, Grimm H, Soehendra N. Endoscopic closure of a perforation using metallic clips after snare excision of a gastric leiomyoma. *Gastrointest Endosc* 1993; **39**: 172-174 [PMID: 8495838 DOI: 10.1016/s0016-5107(93)70060-7]

45 **John BK**, Cortes RA, Feinerman A, Somnay K. Successful closure of a rectovaginal fistula by using an endoscopically placed Resolution clip. *Gastrointest Endosc* 2008; **67**: 1192-1195 [PMID: 18402957 DOI: 10.1016/j.gie.2007.12.057]

46 **Ortiz-Moyano C**, Guerrero-Jiménez P, Romero-Gómez M. Endoscopic closure of a rectovaginal fistula combining N-2-butyl-cyanoacrylate (Histoacryl) and Resolution clips. *Endoscopy* 2011; **43** Suppl 2 UCTN: E133-E134 [PMID: 21425012 DOI: 10.1055/s-0030-1256166]

47 **Weiland T**, Fehlker M, Gottwald T, Schurr MO. Performance of the OTSC System in the endoscopic closure of iatrogenic gastrointestinal perforations: a systematic review. *Surg Endosc* 2013; **27**: 2258-2274 [PMID: 23340813 DOI: 10.1007/s00464-012-2754-x]

48 **Matano Y**, Zianne M, Omura H, Hayashi N, Miwa K. Successful endoscopic closure of a refractory postoperative rectovaginal fistula. *Endosc Int Open* 2019; **7**: E796-E799 [PMID: 31198842 DOI: 10.1055/a-0895-5573]

49 **Prosst RL**, Joos AK, Ehni W, Bussen D, Herold A. Prospective pilot study of anorectal fistula closure with the OTSC Proctology. *Colorectal Dis* 2015; **17**: 81-86 [PMID: 25175824 DOI: 10.1111/codi.12762]

50 **Tong Y**, Trilling B, Sage PY, Girard E, Faucheron JL. Short-term outcomes of the over-the-scope clip proctology system for rectovaginal fistula repair: a prospective study. *Tech Coloproctol* 2019; **23**: 245-249 [PMID: 30937645 DOI: 10.1007/s10151-019-01948-5]

51 **El Hajj II**, Imperiale TF, Rex DK, Ballard D, Kesler KA, Birdas TJ, Fatima H, Kessler WR, DeWitt JM. Treatment of esophageal leaks, fistulae, and perforations with temporary stents: evaluation of efficacy, adverse events, and factors associated with successful outcomes. *Gastrointest Endosc* 2014; **79**: 589-598 [PMID: 24125513 DOI: 10.1016/j.gie.2013.08.039]

52 **Baron TH**. Indications and results of endoscopic rectal stenting. *J Gastrointest Surg* 2004; **8**: 266-269 [PMID: 15019920 DOI: 10.1016/j.gassur.2003.11.018]

53 **Lamazza A**, Fiori E, Sterpetti AV. Endoscopic placement of self-expandable metal stents for treatment of rectovaginal fistulas after colorectal resection for cancer. *Gastrointest Endosc* 2014; **79**: 1025-1027 [PMID: 24565070 DOI: 10.1016/j.gie.2014.01.010]

54 **Lamazza A**, Fiori E, Sterpetti AV, Schillaci A, De Cesare A, Lezoche E. Endoscopic placement of self-expandable metallic stents for rectovaginal fistula after colorectal resection: a comparison with proximal diverting ileostomy alone. *Surg Endosc* 2016; **30**: 797-801 [PMID: 26017913 DOI: 10.1007/s00464-015-4246-2]

55 **Zhu YF**, Tao GQ, Zhou N, Xiang C. Current treatment of rectovaginal fistula in Crohn's disease. *World J Gastroenterol* 2011; **17**: 963-967 [PMID: 21448347 DOI: 10.3748/wjg.v17.i8.963]

56 **van Vledder MG**, Doornebosch PG, de Graaf EJ. Transanal endoscopic surgery for complications of prior rectal surgery. *Surg Endosc* 2016; **30**: 5356-5363 [PMID: 27059974 DOI: 10.1007/s00464-016-4888-8]

57 **Shibata**, Mizuguchi, Takeda, Miyashita. Successful closure of a rectovaginal fistula following low anterior resection by endoscopic fibrin glue application. *Colorectal Dis* 1999; **1**: 42-44 [PMID: 23577683 DOI: 10.1046/j.1463-1318.1999.00009.x]

58 **Darwood RJ**, Borley NR. TEMS: an alternative method for the repair of benign recto-vaginal fistulae. *Colorectal Dis* 2008; **10**: 619-620 [PMID: 18294273 DOI: 10.1111/j.1463-1318.2008.01478.x]

59 **Vavra P**, Dostalik J, Vavrova M, Gunkova P, Pai M, El-Gendi A, Habib N, Papaevangelou A. Transanal endoscopic microsurgery: a novel technique for the repair of benign rectovaginal fistula. *Surgeon* 2009; **7**: 126-127 [PMID: 19408806 DOI: 10.1016/s1479-666x(09)80031-0]

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META-ANALYSIS

Laparoscopic appendectomy, stump closure and endoloops: A meta-analysis

Noemi Zorzetti, Augusto Lauro, Maria Irene Bellini, Samuele Vaccari, Barbara Dalla Via, Maurizio Cervellera, Roberto Cirocchi, Salvatore Sorrenti, Vito D'Andrea, Valeria Tonini

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Noemi Zorzetti, Department of General Surgery, Ospedale Civile A Costa, Porretta Terme 40046, Italy

Noemi Zorzetti, Augusto Lauro, Maria Irene Bellini, Samuele Vaccari, Salvatore Sorrenti, Vito D'Andrea, Department of Surgical Sciences, Sapienza University, Rome 00161, Italy

Samuele Vaccari, Department of General Surgery, Ospedale di Bentivoglio, Bologna 40010, Italy

Barbara Dalla Via, Valeria Tonini, Department of Emergency Surgery, St Orsola University Hospital, Bologna 40138, Italy

Maurizio Cervellera, Department of General Surgery, Ospedale Santissima Annunziata, Taranto 74121, Italy

Roberto Cirocchi, Department of General Surgery, Ospedale di Terni, Università di Perugia, Terni 05100, Italy

Corresponding author: Maria Irene Bellini, MD, PhD, Assistant Professor, Senior Lecturer, Department of Surgical Sciences, Sapienza University, Viale Regina Elena, Rome 00161, Italy. mariairene.bellini@uniroma1.it

Abstract

BACKGROUND

Acute appendicitis (AA) is one of the main indications for urgent surgery. Laparoscopic appendectomy (LA) has shown advantages in terms of clinical results and cost-effectiveness, even if there is still controversy about different devices to utilize, especially with regards to the endoloop (EL) *vs* endostapler (ES) when it comes to stump closure.

AIM

To compare safety and cost-effectiveness of EL *vs* ES.

METHODS

From a prospectively maintained database, data of 996 consecutive patients treated by LA with a 3 years-follow up in the department of Emergency General Surgery - St Orsola University Hospital, Bologna (Italy) were retrieved. A meta-analysis was performed in terms of surgical complications, in comparison to the

international literature published from 1995 to 2021.

RESULTS
The meta-analysis showed no evidence regarding wound infections, abdominal abscesses, and total post-operative complications, in terms of superiority of a surgical technique for the stump closure in LA.

CONCLUSION
Even when AA is complicated, the routine use of EL is safe in most patients.

Key Words: Acute appendicitis; Laparoscopic appendectomy; Endoloops; Stapler; Post-operative complications

Core Tip: Stump closure in the acute appendectomy setting could be performed *via* endoloop (EL) or endostapler use. The present meta-analysis assesses the experience of 996 patients consecutively treated in the department of Emergency General Surgery - St Orsola University Hospital, Bologna (Italy) and the evidence published in literature, confirming there is no superiority of a surgical method on how to perform the stump closure, with regards to wound infections, abdominal abscess, and total post-operative complications. Even when acute appendicitis is complicated, the routine use of EL is safe in most patients.

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INTRODUCTION

Acute appendicitis (AA) is one of the most frequent causes of acute abdominal pain and access to emergency care department. The lifetime chance of developing AA is lower in women, and the risk of being subject to surgery is higher in males[1], representing in fact one of the main indications for an urgent operation. Surgery is generally performed *via* a laparoscopic approach, and given the high volume of AA procedures worldwide, it represents a training operation as well[2].

Laparoscopic appendectomy (LA)[3,4] is demonstrated to be superior in terms of clinical results[5-9] and cost-effectiveness[10-14], even if there is still controversy[15-19] about the use of different devices during the operation[20-24]. Currently, it is still debated the use of endostapler (ES) *vs* endoloop (EL) in appendiceal stump closure[25-28]. The routine use of EL is safe in most patients affected by AA, also when it is complicated[29-32], representing a cost-effective device when taking into consideration the additional costs of potential post-operative complications, too[33-37]. We have previously shown money saving as well as the safety of the routine use of ELs[38]. The aim of this study is to meta-analyze the international literature, to compare the outcome of the patients laparoscopically treated in Bologna *via* EL to the data from the international literature.

MATERIALS AND METHODS

Between November 2011 and January 2018, a total of 1045 LAs were performed in the department of Emergency General Surgery - St Orsola University Hospital, Bologna (Italy). Patients who undergone LA until January 2018 were identified retrospectively from a prospectively maintained database, so that a 3-year follow-up was achieved[39,40]. All grades of post-operative complications were collected and examined. Institutional review board for this study was not required, as this is a meta-analysis of already previous published data. At Bologna centre, patients were initially evaluated by a general surgeon, then underwent laboratory tests, and Alvarado or appendicitis inflammatory response (AIR) score (Table 1) were calculated in females and in males respectively[41,42].

Surgery

Surgical procedures were performed by attendants or supervised trainees. Written informed consent

Table 1 Alvarado and appendicitis inflammatory response score

	Alvarado score	AIR score
Likely appendicitis	7-10	9-12
Probably appendicitis	5-6	5-8
Unlikely appendicitis	0-4	0-4

AIR: Appendicitis inflammatory response.

was signed by all the patients before the procedures. Antibiotic prophylaxis was always administered. A supraumbilical 12 mm-Hasson trocar with an open approach was adopted to induce pneumoperitoneum and initiate laparoscopy. Then, 2 other operative trocars were placed in the left flank (10 mm) and suprapubic position (5 mm), with identification of the appendix, cut and coagulation of the mesoappendix.

EL or ES use

The choice of EL *vs* ES to close the base of the appendiceal stump was made by the operating surgeon, after evaluating the inflammatory infiltration of the appendicular base[43]. If an EL was used, the appendicular stump was cut 3-5 mm away from cecum. The surgical specimen was then removed in an endobag through the 12 mm trocar.

Bologna cohort

Patients were divided in two groups (EL and ES) and in three categories (edematous, phlegmonous and gangrenous appendicitis) based on the severity of the histological examination. Cases requiring conversion to open appendectomy were excluded, while 996 LA (95.3%) were included in the meta-analysis.

Meta-analysis

A meta-analysis was performed in terms of surgical complications, comparing the clinical data of the EL group (821 patients) to the international literature retrieved by Pubmed (Figure 1), according to the PRISMA principles[44].

Inclusion and exclusion criteria

Manuscripts were excluded from the analysis if they dealt with pediatric patients (< 15 years of age) or were published before 1995.

Statistical analysis

Data were collected and analyzed with MedCalc software. Statistical expertise was available to the authors. MedCalc 13.0.6.0 (MedCalc Software bvba, Østend, Belgium) was used for the meta-analysis. MedCalc uses a Freeman-Tukey transformation (arcsine square root transformation) to calculate the weighted summary proportion under the fixed and random effects model. The program lists the proportions (expressed as a percentage), with their 95% confidence interval (CI), found in the individual studies included in the meta-analysis. The heterogeneity was evaluated by means of statistics Cohran's Q and I2. The results of the different studies, with 95%CI, and the pooled proportions with 95%CI are shown in a forest plot. Bias was detected using a funnel plot. Publication bias results in asymmetry of the funnel plot. $P < 0.05$ was considered statistically significant.

RESULTS

Meta-analysis of clinical outcome in EL patients and comparative results

The sample of our study consisted of all our patients treated with EL for a total of eight hundred twenty-one patients (Table 2), corresponding to the 78.5% of all LAs. Post-operative complications in this group of interest were collected (Table 3) and reported according to the Clavien-Dindo classification [45,46] (Table 4). These data were then compared to those retrieved from the manuscripts finally considered in the analysis[9,19,26,29-31,47] (Table 5), in fact other four papers that were initially assessed and that were from the last 3 years[48-51], were not included, because of the lack of information and partial numbers and percentages of patients with wound infections, abdominal abscesses and total post-operative complications.

Table 2 Groups and categories of severity of Bologna patients

	EL (*n* = 821)	ES (*n* = 175)	*P* values
Age (yr)	35 (14-94) ± 18	36 (14-91) ± 17	0.50
Male:Female	425:396	111:64	< 0.05
BMI	23.85 (14-44) ± 4.4	24 (17-42) ± 4.5	0.68
CV comorbidities	7.6%	24%	< 0.05
Other comorbidities	13.9%	31.4%	< 0.05
Edematous AA	251	5	0.18
Phlegmonous AA	410	59	0.05
Gangrenous AA	160	111	0.05

EL: Endoloop; ES: Endostapler; BMI: Body mass index; CV: Cardiovascular; AA: Acute appendicitis.

Table 3 Post-operative complications in Bologna endoloop group

	EL (*n* = 821)
Wound infections	2 (0.3%)
Abdominal abscesses	12 (1.5%)
Post-op complications IIIa/IIIb Clavien-Dindo	17 (2%)
Total post-op complications	35 (4.3%)

EL: Endoloop.

Table 4 Post-operative complications in Bologna 996 laparoscopic appendectomy patients

Clavien-Dindo	Number of patients (% of total cohort)
I	3 (0.3)
II	24 (2.4)
IIIa	7 (0.7)
IIIb	16 (1.6)
IVa	0 (0)
IVb	0 (0)
V	0 (0)
Total	50 (5)

Examination of the seven papers involved in the meta-analysis[9,19,26,29-31,47] showed that only Beldi *et al*[26] were in favor of application of an ES for transection and closure of the appendiceal stump in patients with AA. In their report it lowered the risk of postoperative intra-abdominal surgical-site infection and the need for readmission to hospital. All the other 6 papers didn't find a statistically significant difference for intra or postsurgical complications, length of stay (LOS), wound infections, and abdominal abscesses among different groups of patients. Sahm *et al*[29] and Van Rossem *et al*[30] clearly stated that infectious complication rate is not influenced by the type of appendicular stump closure, either if performed by EL or ES, and routine stump closure using an EL is an easy, safe, and cost-effective procedure. Finally, it is important to mention the retrospective cohort study conducted by Swank *et al*[31] that compares the two strategies for closure of the appendiceal stump. The routine use of the ES showed no clinical advantages over the use of ELs.

Statistical data and results showed that our experience followed the trend of the evidence in literature in terms of wound infections (Figure 2 and Table 6), abdominal abscesses (Figure 3 and Table 7) and total post-operative complications (Figure 4 and Table 8). The meta-analysis proved a wide heterogeneity among analyzed groups, as the funnel plots and the forest plots confirmed. Tables 6-8 report

Table 5 Complete data to meta-analyse

Ref.	Number of patients (% of EL)	Wound infection	Abdominal abscesses	Post-op complications
Bologna experience	821 (78.5)	2 (0.3%)	12 (1.5%)	26 (3.2%)
Ortega *et al*[9], 1995	89	4 (4.5%)	4 (4.5%)	14 (15.7%)
Sadat-Safavi *et al*[19], 2016	38 (50)	1 (2.6%)	0 (0%)	0 (0%)
Beldi *et al*[26], 2006	2565 (39.5)	12 (0.5%)	41 (1.6%)	37 (1.4%)
Sahm *et al*[29], 2011	1670 (97.3)	34 (2%)	27 (1.6%)	48 (2.9%)
Van Rossem *et al*[30], 2017	1050 (76.7)	16 (1.5%)	48 (4.5%)	20 (1.9%)
Swank *et al*[31], 2014	465 (44.9)	7 (1.5%)	20 (4.3%)	14 (3.1%)
Klima *et al*[47], 1998	100	3 (3%)	4 (4%)	4 (4%)

EL: Endoloop.

Table 6 Wound infection: Data standard deviation in the meta-analysis

Ref.	Standard deviation	Proportion (%)	95%CI
Our experience	821	0.244	0.0295-0.877
Van Rossem *et al*[30], 2017	1050	1.524	0.873-2.463
Sadat-Safavi *et al*[19], 2016	38	2.632	0.0666-13.810
Swank *et al*[31], 2014	465	1.505	0.607-3.077
Sahm *et al*[29], 2011	1670	2.036	1.414-2.833
Beldi *et al*[26], 2006	2565	0.468	0.242-0.816
Klima *et al*[47], 1998	100	3.000	0.623-8.518
Ortega *et al*[9], 1995	89	4.494	1.238-11.109
Total (fixed effects)	6798	1.064	0.834-1.337
Total (random effects)	6798	1.496	0.759-2.475

CI: Confidence interval.

data related to the standard deviation of wound infection, abdominal abscesses, and post-operative complications, respectively. Figures 2A, 3A and 4A are Funnel Plots showing an asymmetrical distribution of the articles (*dot*) among both sides indicating that bias can be present. In Figures 2A and 4A, few papers are near the middle solid line, indicating the overall effect from the meta-analysis, possibly in relation to the limited size of the samples. Figures 2B, 3B and 4B Forrest Plots prove there is no statistically significant result in favor of ES or EL for the overall incidence of wound infections, abdominal abscess, or post-operative complications.

DISCUSSION

Appendectomy is one of the most performed emergency surgery procedures. The laparoscopic approach is recognized and recommended internationally, but a matter of debate during the operation is the choice of the different available devices to close the appendicular stump, in consideration of the possible consequent leak leading to infection and postoperative complications.

Already previously[38], we evidenced that the routine use of EL is safe in most patients affected by AA, including cases with signs of complications. Furthermore, it is a cost-effective device, even when possible additional costs secondary to the occurrence of adverse events in the post-operative course are included. Conversely, Lasek *et al*[48] assessed *via* a multicenter observational study the stump closure only in patients affected by complicated AA. Their results highlighted some clinical benefits of ES use, but EL was superior in terms of overall morbidity and LOS, with no statistically significant difference in major complication rates and postoperative intra-abdominal abscess formation.

Table 7 Abdominal abscess: Data standard deviation in the meta-analysis

Ref.	Standard deviation	Proportion (%)	95%CI
Our experience	821	1.462	0.757-2.539
Van Rossem *et al*[30], 2017	1050	4.571	3.390-6.016
Sadat-Safavi *et al*[19], 2016	38	0.000	0.000-9.251
Swank *et al*[31], 2014	465	4.301	2.647-6.565
Sahm *et al*[29], 2011	1670	1.617	1.068-2.344
Beldi *et al*[26], 2006	2565	1.598	1.149-2.162
Klima *et al*[47], 1998	100	4.000	1.100-9.926
Ortega *et al*[9], 1995	89	4.494	1.238-11.109
Total (fixed effects)	6798	2.206	1.870-2.583
Total (random effects)	6798	2.699	1.697-3.924

CI: Confidence interval.

Table 8 Post-operative complications: Data standard deviation in the meta-analysis

Ref.	Standard deviation	Proportion (%)	95%CI
Our experience	821	3.167	2.079-4.606
Van Rossem *et al*[30], 2017	1050	1.905	1.167-2.926
Sadat-Safavi *et al*[19], 2016	38	0.000	0.000-9.251
Swank *et al*[31], 2014	465	3.011	1.656-5.000
Sahm *et al*[29], 2011	1670	2.874	2.127-3.793
Beldi *et al*[26], 2006	2565	1.442	1.018-1.983
Klima *et al*[47], 1998	100	4.000	1.100-9.926
Ortega *et al*[9], 1995	89	15.730	8.875-24.982
Total (fixed effects)	6798	2.304	1.961-2.689
Total (random effects)	6798	3.089	1.979-4.437

CI: Confidence interval.

In literature, two papers systematically analyzed the techniques for appendiceal stump closure during LA[49,50]. Ceresoli *et al*[49] meta-analysed randomized trials and cohort studies comparing ES with endoscopic loop ties for the closure of the appendicular stump in LA, including pediatric patients and complicated AA, such as gangrenous/necrotic appendix or the perforated ones. In their analysis, ES was associated with a similar intra-abdominal abscess rate, but a lower incidence of wound infection, while LOS, readmission and reoperation rates were similar. In a subgroup analysis ES significantly reduced the wound infection rate in pediatric patients, while no difference in the main outcomes was observed in patients with complicated AA.

Makaram *et al*[50] performed a systematic review evaluating all methods of stump closure (ELs, polymeric endoclips, metallic endoclips, endosuture and ES). In this study[50], no difference in complication rate, LOS or cost was found. According to their analysis, endoclips provide the most time-efficient method of closure, although not statistically significant; closure by endosuture, represents the cheapest method, but it is hindered by a high complication rate. Current evidence suggests endosuture should then be avoided. ESs appear very safe and effective for stump closure, however they seem to be associated with high postoperative complication rates; furthermore, the consequent cost limits their use to the most severe cases of appendicitis, while instead EL provides a valuable alternative for closure, with a risk of intraoperative complications of 4.61%.

Another recent retrospective cohort study[51], whose subject was to determine the safety and efficiency of the use of EL and ES in complicated and uncomplicated AA, concluded that the systematic use of EL could reduce costs in uncomplicated appendicitis, while in complicated cases both options

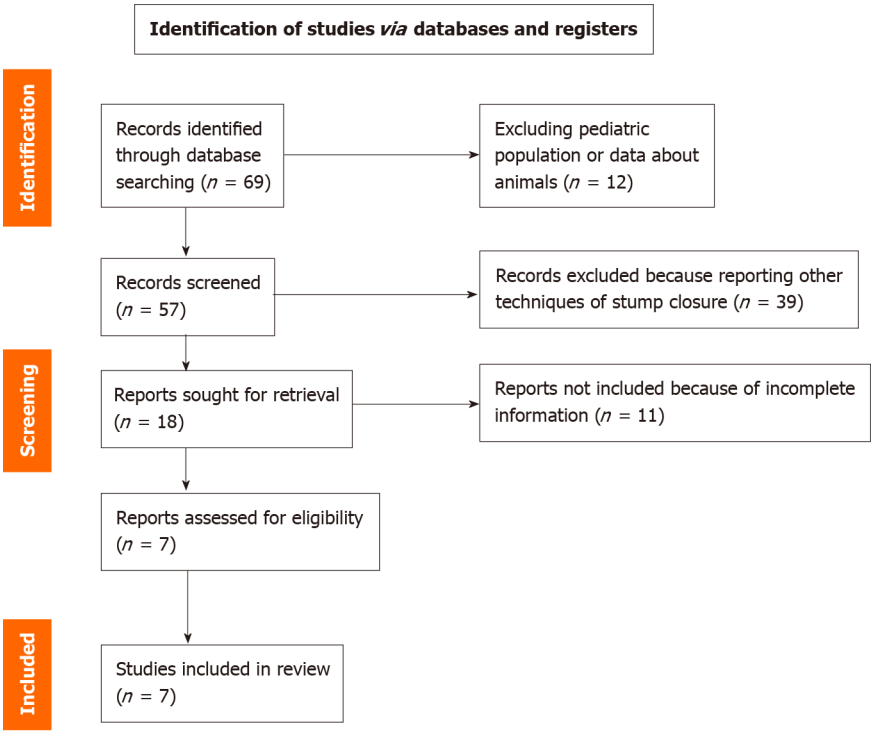

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Figure 1 PRISMA diagram.

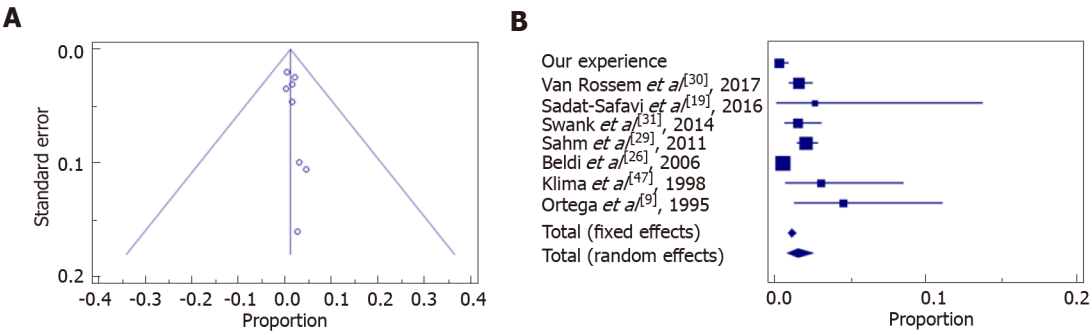

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Figure 2 Wound infection Funnel plot. A: Asymmetrical distribution among both sides indicates that bias can be present; B: The confidence interval (diamond) confirms there is no statistically significant result.

(loop and stapler) are valid. Also a prospective randomized clinical trial[52] and a retrospective study [53] recently analyzed the technical aspects of appendix stump closure: Ihnát *et al*[52] reported similar postoperative morbidity and safety following the use of EL, ES or hem-o-lok and even White *et al*[53] demonstrated non univocal superiority of one technique over the others, too.

Another point indeed to be considered is LA availability together with the fact that the different devices rely upon the resources of the hospital and the country where surgery is performed, pending possible spending reviews carried out by the government. It has been demonstrated that LA is performed more frequently in high-income countries in comparison to low-income countries (67.7% *vs* 8.1%), with better postoperative outcomes[54]. The difference in the costs of the used surgical devices (above all stapler) represented a principal determinant for the overall economic impact of the surgical procedure in some recent reports[33,36,38,50,51], to highlight how important is the cost-effectiveness in the measured outcomes. The medium saving reported in the present paper is relevant, varying from around approximately 300 € to more than 500 € just for the device, which then must be multiplied for the many LA conducted worldwide; further cost-analysis including operative time and LOS could reach major savings.

Our study presents some limitations: The design is a retrospective analysis to investigate the safety of ELs, then the results are pooled with other reports; the comparison between studies is difficult due to heterogenous patient selection and outcomes measured. However, EL seems to have the potential for

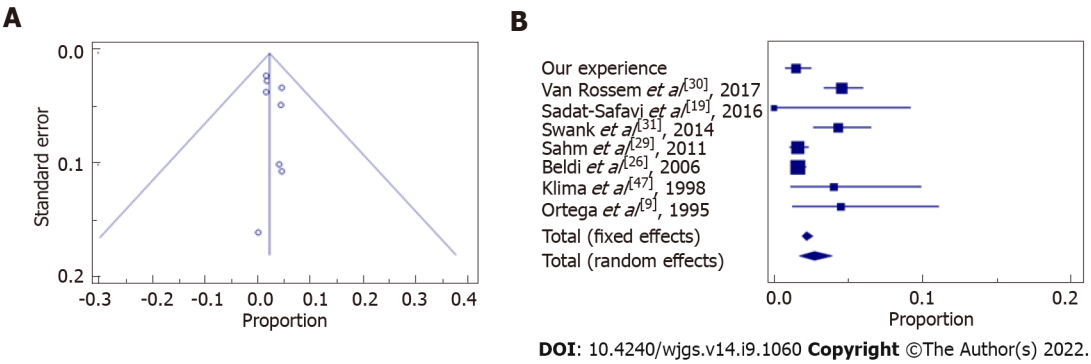

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Figure 3 Abdominal abscess Funnel plot. A: With asymmetrical distribution among both sides, indicating that bias can be present; B: The confidence interval (diamond) confirms there is no statistically significant result favoring endoloop or endostapler.

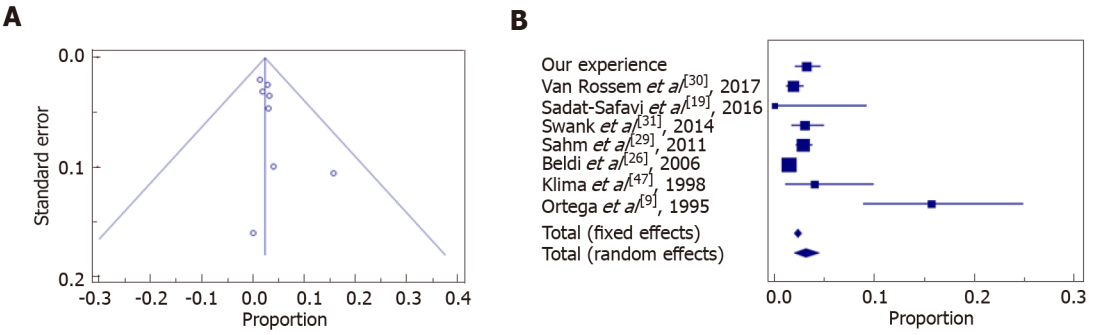

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Figure 4 Post-operative complications Funnel plot. A: Asymmetrical distribution among both sides indicates that bias can be present; B: The confidence interval (diamond) confirms there is not statistically significant difference between endoloop *vs* endostapler.

being a safe and cost-effective device.

CONCLUSION

In conclusion, there is no evidence clearly illustrating a superior surgical method for performing stump closure in LA. Given that comparison between studies is difficult due to heterogeneous patient selection and measured outcomes, our meta-analysis shows that the data of our sample, related to wound infections, post-operative abdominal abscesses, and total post-operative complications, mirror current literature trend. The routine use of EL is safe in most patients affected by AA, even when complicated, and these findings could have above all more relevance in lower resource environments that may not have easy access to ES. Prospective studies are needed to analyze a greater number of patients and taking into account an accurate grading system for AA severity such as Disease Severity Score[55], Alvarado Score[41], AIR Score[42] or imaging severity scoring, such as the CT-Determined Severity Score[56]. Their aim should be first to stratify preoperatively the grade of AA and secondly to observe differences in postoperative complications. Finally, studies aiming at an accurate cost analysis are required, ideally in the form of randomized controlled trials comparing EL to polymeric clips, as both techniques are safe and effective, with favorable outcomes[50,52].

ARTICLE HIGHLIGHTS

Research background

Laparoscopic appendectomy (LA) has shown advantages in terms of clinical results and cost-effectiveness, even if there is still controversy about which surgical device should be preferred to perform it.

Research motivation

To evaluate the safety cost-effectiveness of surgical devices in LA stump closure.

Research objectives
Incidence of wound infections, abdominal abscesses and total post-operative complications according to the Dindo-Clavien classification in LA stump closure with endoloop (EL) or endostapler.

Research methods
A meta-analysis was performed in terms of surgical complications, comparing the clinical data of the EL group (821 patients) to the international literature retrieved by Pubmed, according to the PRISMA principles.

Research results
There is no superiority of one or another technique in terms of surgical complications for LA stump closure.

Research conclusions
Routine use of EL is safe in most patients affected by acute appendectomy, even when complicated.

Research perspectives
Studies of EL performing accurate cost analysis are required, in addition to randomized controlled trials comparing this method to polymeric clips, as both techniques have been proved to have to be safe and effective with favorable outcomes.

FOOTNOTES

Author contributions: Zorzetti L and Bellini MI wrote and revised the article; Lauro A, Dalla Via B, Cervellera M, Tonini V, Sorrenti S, Cirocchi R and D'Andrea V designed the research study; Vaccari S, Zorzetti N, Lauro A, and Bellini MI performed the research; and all authors have read and approve the final manuscript.

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Country/Territory of origin: Italy

ORCID number: Noemi Zorzetti 0000-0002-7466-2336; Augusto Lauro 0000-0002-2292-5595; Maria Irene Bellini 0000-0003-0730-4923; Samuele Vaccari 0000-0001-9741-4303; Barbara Dalla Via 0000-0002-7754-8387; Maurizio Cervellera 0000-0002-8885-7660; Roberto Cirocchi 0000-0002-2457-0636; Salvatore Sorrenti 0000-0003-0427-6648; Vito D'Andrea 0000-0001-5709-2530; Valeria Tonini 0000-0003-3130-2928.

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REFERENCES

1 **Birnbaum BA**, Wilson SR. Appendicitis at the millennium. *Radiology* 2000; **215**: 337-348 [PMID: 10796905 DOI: 10.1148/radiology.215.2.r00ma24337]

2 **Ussia A**, Vaccari S, Gallo G, Grossi U, Ussia R, Sartarelli L, Minghetti M, Lauro A, Barbieri P, Di Saverio S, Cervellera M, Tonini V. Laparoscopic appendectomy as an index procedure for surgical trainees: clinical outcomes and learning curve. *Updates Surg* 2021; **73**: 187-195 [PMID: 33398773 DOI: 10.1007/s13304-020-00950-z]

3 **Costa-Navarro D**, Jiménez-Fuertes M, Illán-Riquelme A. Laparoscopic appendectomy: quality care and cost-effectiveness for today's economy. *World J Emerg Surg* 2013; **8**: 45 [PMID: 24180475 DOI: 10.1186/1749-7922-8-45]

4 **Masoomi H**, Mills S, Dolich MO, Ketana N, Carmichael JC, Nguyen NT, Stamos MJ. Comparison of outcomes of laparoscopic versus open appendectomy in adults: data from the Nationwide Inpatient Sample (NIS), 2006-2008. *J Gastrointest Surg* 2011; **15**: 2226-2231 [PMID: 21725700 DOI: 10.1007/s11605-011-1613-8]

5 **Sajid MS**, Rimple J, Cheek E, Baig MK. Use of endo-GIA versus endo-loop for securing the appendicular stump in laparoscopic appendicectomy: a systematic review. *Surg Laparosc Endosc Percutan Tech* 2009; **19**: 11-15 [PMID:

19238059 DOI: 10.1097/SLE.0b013e31818a66ab]

6 **Coşkun H**, Hasbahçeci M, Bozkurt S, Çipe G, Malya FÜ, Memmi N, Karatepe O, Akçakaya A, Müslümanoğlu M. Is concomitant cholecystectomy with laparoscopic sleeve gastrectomy safe? *Turk J Gastroenterol* 2014; **25**: 624-627 [PMID: 25599771 DOI: 10.5152/tjg.2014.6954]

7 **Sohn M**, Agha A, Bremer S, Lehmann KS, Bormann M, Hochrein A. Surgical management of acute appendicitis in adults: A review of current techniques. *Int J Surg* 2017; **48**: 232-239 [PMID: 29155250 DOI: 10.1016/j.ijsu.2017.11.028]

8 **Di Saverio S**, Mandrioli M, Sibilio A, Smerieri N, Lombardi R, Catena F, Ansaloni L, Tugnoli G, Masetti M, Jovine E. A cost-effective technique for laparoscopic appendectomy: outcomes and costs of a case-control prospective single-operator study of 112 unselected consecutive cases of complicated acute appendicitis. *J Am Coll Surg* 2014; **218**: e51-e65 [PMID: 24559968 DOI: 10.1016/j.jamcollsurg.2013.12.003]

9 **Ortega AE**, Hunter JG, Peters JH, Swanstrom LL, Schirmer B. A prospective, randomized comparison of laparoscopic appendectomy with open appendectomy. Laparoscopic Appendectomy Study Group. *Am J Surg* 1995; **169**: 208-12; discussion 212 [PMID: 7840381 DOI: 10.1016/s0002-9610(99)80138-x]

10 **Lucchi A**, Berti P, Grassia M, Siani LM, Gabbianelli C, Garulli G. Laparoscopic appendectomy: Hem-o-lok versus Endoloop in stump closure. *Updates Surg* 2017; **69**: 61-65 [PMID: 28013455 DOI: 10.1007/s13304-016-0413-9]

11 **Takami T**, Yamaguchi T, Yoshitake H, Hatano K, Kataoka N, Tomita M, Makimoto S. A clinical comparison of laparoscopic versus open appendectomy for the treatment of complicated appendicitis: historical cohort study. *Eur J Trauma Emerg Surg* 2020; **46**: 847-851 [PMID: 30710176 DOI: 10.1007/s00068-019-01086-5]

12 **Shimoda M**, Maruyama T, Nishida K, Suzuki K, Tago T, Shimazaki J, Suzuki S. Comparison of clinical outcome of laparoscopic versus open appendectomy, single center experience. *Heliyon* 2018; **4**: e00635 [PMID: 29872767 DOI: 10.1016/j.heliyon.2018.e00635]

13 **Guadagni S**, Cengeli I, Galatioto C, Furbetta N, Piero VL, Zocco G, Seccia M. Laparoscopic repair of perforated peptic ulcer: single-center results. *Surg Endosc* 2014; **28**: 2302-2308 [PMID: 24609709 DOI: 10.1007/s00464-014-3481-2]

14 **Gorter RR**, Heij HA, Eker HH, Kazemier G. Laparoscopic appendectomy: State of the art. Tailored approach to the application of laparoscopic appendectomy? *Best Pract Res Clin Gastroenterol* 2014; **28**: 211-224 [PMID: 24485267 DOI: 10.1016/j.bpg.2013.11.016]

15 **Antoniou SA**, Mavridis D, Hajibandeh S, Antoniou GA, Gorter R, Tenhagen M, Koutras C, Pointner R, Chalkiadakis GE, Granderath FA, Fragiadakis GF, Philalithis AE, Bonjer HJ. Optimal stump management in laparoscopic appendectomy: A network meta-analysis by the Minimally Invasive Surgery Synthesis of Interventions and Outcomes Network. *Surgery* 2017; **162**: 994-1005 [PMID: 28864100 DOI: 10.1016/j.surg.2017.07.013]

16 **Aziret M**, Çetinkünar S, Erdem H, Kahramanca Ş, Bozkurt H, Dülgeroğlu O, Yıldırım AC, İrkörücü O, Gölboyu EB. Comparison of open appendectomy and laparoscopic appendectomy with laparoscopic intracorporeal knotting and glove endobag techniques: A prospective observational study. *Turk J Surg* 2017; **33**: 258-266 [PMID: 29260130 DOI: 10.5152/turkjsurg.2017.3583]

17 **Partecke LI**, Kessler W, von Bernstorff W, Diedrich S, Heidecke CD, Patrzyk M. Laparoscopic appendectomy using a single polymeric clip to close the appendicular stump. *Langenbecks Arch Surg* 2010; **395**: 1077-1082 [PMID: 20577759 DOI: 10.1007/s00423-010-0671-9]

18 **Al-Temimi MH**, Berglin MA, Kim EG, Tessier DJ, Johna SD. Discussion of: "Endostapler versus Hem-O-Lok clip to secure the appendiceal stump and mesoappendix during laparoscopic appendectomy". *Am J Surg* 2017; **214**: 1149-1150 [PMID: 29054445 DOI: 10.1016/j.amjsurg.2017.10.006]

19 **Sadat-Safavi SA**, Nasiri S, Shojaiefard A, Jafari M, Abdehgah AG, Notash AY Jr, Soroush A. Comparison the effect of stump closure by endoclips versus endoloop on the duration of surgery and complications in patients under laparoscopic appendectomy: A randomized clinical trial. *J Res Med Sci* 2016; **21**: 87 [PMID: 28163733 DOI: 10.4103/1735-1995.192503]

20 **Delibegović S**. The use of a single Hem-o-lok clip in securing the base of the appendix during laparoscopic appendectomy. *J Laparoendosc Adv Surg Tech A* 2012; **22**: 85-87 [PMID: 22145605 DOI: 10.1089/lap.2011.0348]

21 **Bali İ**, Karateke F, Özyazıcı S, Kuvvetli A, Oruç C, Menekşe E, Emir S, Özdoğan M. Comparison of intracorporeal knotting and endoloop for stump closure in laparoscopic appendectomy. *Ulus Travma Acil Cerrahi Derg* 2015; **21**: 446-449 [PMID: 27054634 DOI: 10.5505/tjtes.2015.56798]

22 **Mayir B**, Ensari CÖ, Bilecik T, Aslaner A, Oruç MT. Methods for closure of appendix stump during laparoscopic appendectomy procedure. *Ulus Cerrahi Derg* 2015; **31**: 229-231 [PMID: 26668532 DOI: 10.5152/UCD.2015.2768]

23 **Yıldız I**, Koca S. Is There An Ideal Stump Closure Technique In Laparoscopic Appendectomy? *Surg Technol Int* 2016; **28**: 117-120 [PMID: 27121413]

24 **Delibegović S**, Mehmedovic Z. The influence of the different forms of appendix base closure on patient outcome in laparoscopic appendectomy: a randomized trial. *Surg Endosc* 2018; **32**: 2295-2299 [PMID: 29098432 DOI: 10.1007/s00464-017-5924-z]

25 **Kazemier G**, in't Hof KH, Saad S, Bonjer HJ, Sauerland S. Securing the appendiceal stump in laparoscopic appendectomy: evidence for routine stapling? *Surg Endosc* 2006; **20**: 1473-1476 [PMID: 16823654 DOI: 10.1007/s00464-005-0525-7]

26 **Beldi G**, Vorburger SA, Bruegger LE, Kocher T, Inderbitzin D, Candinas D. Analysis of stapling versus endoloops in appendiceal stump closure. *Br J Surg* 2006; **93**: 1390-1393 [PMID: 16862615 DOI: 10.1002/bjs.5474]

27 **Caglià P**, Tracia A, Borzì L, Amodeo L, Tracia L, Veroux M, Amodeo C. Incisional hernia in the elderly: risk factors and clinical considerations. *Int J Surg* 2014; **12** Suppl 2: S164-S169 [PMID: 25157994 DOI: 10.1016/j.ijsu.2014.08.357]

28 **Sohn M**, Hoffmann M, Pohlen U, Lauscher JC, Zurbuchen U, Holmer C, Buhr HJ, Lehmann KS. [Stump closure in laparoscopic appendectomy. Influence of endoloop or linear stapler on patient outcome]. *Chirurg* 2014; **85**: 46-50 [PMID: 23780410 DOI: 10.1007/s00104-013-2549-1]

29 **Sahm M**, Kube R, Schmidt S, Ritter C, Pross M, Lippert H. Current analysis of endoloops in appendiceal stump closure. *Surg Endosc* 2011; **25**: 124-129 [PMID: 20552371 DOI: 10.1007/s00464-010-1144-5]

30 **van Rossem CC**, van Geloven AA, Schreinemacher MH, Bemelman WA; snapshot appendicitis collaborative study group. Endoloops or endostapler use in laparoscopic appendectomy for acute uncomplicated and complicated appendicitis : No

difference in infectious complications. *Surg Endosc* 2017; **31**: 178-184 [PMID: 27129569 DOI: 10.1007/s00464-016-4951-5]

31 **Swank HA**, van Rossem CC, van Geloven AA, in't Hof KH, Kazemier G, Meijerink WJ, Lange JF, Bemelman WA. Endostapler or endoloops for securing the appendiceal stump in laparoscopic appendectomy: a retrospective cohort study. *Surg Endosc* 2014; **28**: 576-583 [PMID: 24048816 DOI: 10.1007/s00464-013-3207-x]

32 **Beldi G**, Muggli K, Helbling C, Schlumpf R. Laparoscopic appendectomy using endoloops: a prospective, randomized clinical trial. *Surg Endosc* 2004; **18**: 749-750 [PMID: 15026904 DOI: 10.1007/s00464-003-9156-z]

33 **Mehdorn M**, Schürmann O, Mehdorn HM, Gockel I. Intended cost reduction in laparoscopic appendectomy by introducing the endoloop: a single center experience. *BMC Surg* 2017; **17**: 80 [PMID: 28693476 DOI: 10.1186/s12893-017-0277-z]

34 **Rakić M**, Jukić M, Pogorelić Z, Mrklić I, Kliček R, Družijanić N, Perko Z, Patrlj L. Analysis of endoloops and endostaples for closing the appendiceal stump during laparoscopic appendectomy. *Surg Today* 2014; **44**: 1716-1722 [PMID: 24337502 DOI: 10.1007/s00595-013-0818-8]

35 **Kryspin M**, Wyrzykowsk D. Outcomes of Open and Laparoscopic Appendectomy With Single Endoloop Stump Closure. *JSLS* 2018; **22** [PMID: 30607104 DOI: 10.4293/JSLS.2018.00062]

36 **Kim S**, Weireter L. Cost Effectiveness of Different Methods of Appendiceal Stump Closure during Laparoscopic Appendectomy. *Am Surg* 2018; **84**: 1329-1332 [PMID: 30185311 DOI: 10.1177/000313481808400847]

37 **Granados-Romero JJ**, Valderrama-Treviño AI, Barrera-Mera B, Uriarte-Ruíz K, Banegas-Ruiz R, Ceballos-Villalva JC. [Comparación entre ligadura con lazo hemostático y engrapadora mecánica lineal para el cierre de base apendicular]. *Cir Cir* 2018; **86**: 428-431 [PMID: 30226495 DOI: 10.24875/CIRU.18000258]

38 **Zorzetti N**, Lauro A, Vaccari S, Ussia A, Brighi M, D'andrea V, Cervellera M, Tonini V. A systematic review on the cost evaluation of two different laparoscopic surgical techniques among 996 appendectomies from a single center. *Updates Surg* 2020; **72**: 1167-1174 [PMID: 32474801 DOI: 10.1007/s13304-020-00817-3]

39 **Antonacci N**, Ricci C, Taffurelli G, Monari F, Del Governatore M, Caira A, Leone A, Cervellera M, Minni F, Cola B. Laparoscopic appendectomy: Which factors are predictors of conversion? *Int J Surg* 2015; **21**: 103-107 [PMID: 26231996 DOI: 10.1016/j.ijsu.2015.06.089]

40 **Finnerty BM**, Wu X, Giambrone GP, Gaber-Baylis LK, Zabih R, Bhat A, Zarnegar R, Pomp A, Fleischut P, Afaneh C. Conversion-to-open in laparoscopic appendectomy: A cohort analysis of risk factors and outcomes. *Int J Surg* 2017; **40**: 169-175 [PMID: 28285058 DOI: 10.1016/j.ijsu.2017.03.016]

41 **Alvarado A**. A practical score for the early diagnosis of acute appendicitis. *Ann Emerg Med* 1986; **15**: 557-564 [PMID: 3963537 DOI: 10.1016/s0196-0644(86)80993-3]

42 **Kollár D**, McCartan DP, Bourke M, Cross KS, Dowdall J. Predicting acute appendicitis? *World J Surg* 2015; **39**: 104-109 [PMID: 25245432 DOI: 10.1007/s00268-014-2794-6]

43 **Chu T**, Chandhoke RA, Smith PC, Schwaitzberg SD. The impact of surgeon choice on the cost of performing laparoscopic appendectomy. *Surg Endosc* 2011; **25**: 1187-1191 [PMID: 20835717 DOI: 10.1007/s00464-010-1342-1]

44 **Page MJ**, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; **372**: n71 [PMID: 33782057 DOI: 10.1136/bmj.n71]

45 **Dindo D**, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205-213 [PMID: 15273542 DOI: 10.1097/01.sla.0000133083.54934.ae]

46 **Clavien PA**, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009; **250**: 187-196 [PMID: 19638912 DOI: 10.1097/SLA.0b013e3181b13ca2]

47 **Klima S**. [Importance of appendix stump management in laparoscopic appendectomy]. *Zentralbl Chir* 1998; **123** Suppl 4: 90-93 [PMID: 9880884]

48 **Lasek A**, Wysocki M, Mavrikis J, Myśliwiec P, Bobowicz M, Dowgiałło-Wnukiewicz N, Kenig J, Stefura T, Walędziak M, Pędziwiatr M; Pol-LA (Polish Laparoscopic Appendectomy) Collaborative Study Group. Comparison of stump closure techniques during laparoscopic appendectomies for complicated appendicitis - results from Pol-LA (Polish laparoscopic appendectomy) multicenter large cohort study. *Acta Chir Belg* 2020; **120**: 116-123 [PMID: 30747049 DOI: 10.1080/00015458.2019.1573527]

49 **Ceresoli M**, Tamini N, Gianotti L, Braga M, Nespoli L. Are endoscopic loop ties safe even in complicated acute appendicitis? *Int J Surg* 2019; **68**: 40-47 [PMID: 31226406 DOI: 10.1016/j.ijsu.2019.06.011]

50 **Makaram N**, Knight SR, Ibrahim A, Patil P, Wilson MSJ. Closure of the appendiceal stump in laparoscopic appendectomy: A systematic review of the literature. *Ann Med Surg (Lond)* 2020; **57**: 228-235 [PMID: 32802324 DOI: 10.1016/j.amsu.2020.07.058]

51 **Durán Muñoz-Cruzado V**, Anguiano-Diaz G, Tallón Aguilar L, Tinoco González J, Sánchez Arteaga A, Aparicio Sánchez D, Pareja Ciuró F, Padillo Ruiz J. Is the use of endoloops safe and efficient for the closure of the appendicular stump in complicated and uncomplicated acute appendicitis? *Langenbecks Arch Surg* 2021; **406**: 1581-1589 [PMID: 33409584 DOI: 10.1007/s00423-020-02050-3]

52 **Ihnát P**, Tesař M, Tulinský L, Ihnát Rudinská L, Okantey O, Durdík Š. A randomized clinical trial of technical modifications of appendix stump closure during laparoscopic appendectomy for uncomplicated acute appendicitis. *BMC Surg* 2021; **21**: 272 [PMID: 34059039 DOI: 10.1186/s12893-021-01279-z]

53 **White C**, Hardman C, Parikh P, Ekeh AP. Endostapler vs Endoloop closure of the appendiceal stump in laparoscopic appendectomy: Which has better outcomes? *Am J Surg* 2021; **222**: 413-416 [PMID: 33419519 DOI: 10.1016/j.amjsurg.2020.12.047]

54 **GlobalSurg Collaborative**. Laparoscopy in management of appendicitis in high-, middle-, and low-income countries: a multicenter, prospective, cohort study. *Surg Endosc* 2018; **32**: 3450-3466 [PMID: 29623470 DOI:

10.1007/s00464-018-6064-9]

55 **Garst GC**, Moore EE, Banerjee MN, Leopold DK, Burlew CC, Bensard DD, Biffl WL, Barnett CC, Johnson JL, Sauaia A. Acute appendicitis: a disease severity score for the acute care surgeon. *J Trauma Acute Care Surg* 2013; **74**: 32-36 [PMID: 23271074 DOI: 10.1097/TA.0b013e318278934a]

56 **Kim HC**, Yang DM, Lee CM, Jin W, Nam DH, Song JY, Kim JY. Acute appendicitis: relationships between CT-determined severities and serum white blood cell counts and C-reactive protein levels. *Br J Radiol* 2011; **84**: 1115-1120 [PMID: 21123307 DOI: 10.1259/bjr/47699219]

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CASE REPORT

Retrorectal mucinous adenocarcinoma arising from a tailgut cyst: A case report and review of literature

Yan-Shuai Wang, Qing-Yun Guo, Fang-Hong Zheng, Zi-Wei Huang, Jia-Lang Yan, Fu-Xiang Fan, Tian Liu, Shun-Xian Ji, Xiao-Feng Zhao, Yi-Xiong Zheng

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Yan-Shuai Wang, Fang-Hong Zheng, Zi-Wei Huang, Jia-Lang Yan, Fu-Xiang Fan, Yi-Xiong Zheng, Department of General Surgery, The Fourth Affiliated Hospital, School of Medicine, Zhejiang University, Yiwu 322000, Zhejiang Province, China

Qing-Yun Guo, Xiao-Feng Zhao, Department of Gynecology, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou 310006, Zhejiang Province, China

Tian Liu, Department of Intensive Care Unit, The Fourth Affiliated Hospital, School of Medicine, Zhejiang University, Yiwu 322000, Zhejiang Province, China

Shun-Xian Ji, Department of Pathology, The Fourth Affiliated Hospital, School of Medicine, Zhejiang University, Yiwu 322000, Zhejiang Province, China

Corresponding author: Yi-Xiong Zheng, MD, Attending Doctor, Professor, Department of General Surgery, The Fourth Affiliated Hospital, School of Medicine, Zhejiang University, No. 1 Shangcheng Road, Yiwu 322000, Zhejiang Province, China. 2100011@zju.edu.cn

Abstract

BACKGROUND

Tailgut cysts are defined as congenital cysts that develop in the rectosacral space from the residue of the primitive tail. As a congenital disease, caudal cysts are very rare, and their canceration is even rarer, which makes the disease prone to misdiagnosis and delayed treatment. We describe a case of caudal cyst with adenocarcinogenesis and summarize in detail the characteristics of cases with analytical value reported since 1990.

CASE SUMMARY

A 35-year-old woman found a mass in her lower abdomen 2 mo ago. She was asymptomatic at that time and was not treated because of the coronavirus disease 2019 pandemic. Two weeks ago, the patient developed abdominal distension and right waist discomfort and came to our hospital. Except for the high level of serum carcinoembryonic antigen, the medical history and laboratory tests were not remarkable. Magnetic resonance imaging showed a well-defined, slightly lobulated cystic-solid mass with a straight diameter of approximately 10 cm × 9 cm in the presacral space, slightly high signal intensity on T2-weighted imaging, and moderate signal intensity on T1-weighted imaging. The mass was completely removed by laparoscopic surgery. Histopathological examination showed that the lesion was an intestinal mucinous adenocarcinoma, and the multidisciplinary

team decided to implement postoperative chemotherapy. The patient recovered well, the tumor marker levels returned to normal, and tumor-free survival has been achieved thus far.

CONCLUSION
The case and literature summary can help clinicians and researchers develop appropriate examination and therapeutic methods for diagnosis and treatment of this rare disease.

Key Words: Tailgut cysts; Adenocarcinoma; Magnetic resonance imaging; Retrorectal disease; Preoperative biopsy; Case report

Core Tip: Tailgut cysts (TGCs) are rare congenital cysts of the retrorectal space. We report a case of TGC with adenocarcinogenesis and review the literature on caudal cyst adenocarcinogenesis. Magnetic resonance imaging is the most valuable tool for diagnosis and differential diagnosis, and preoperative biopsy is not worth advocating. Early MDT plays an important role in the accurate diagnosis and selection of the most appropriate personalized treatment. Complete resection of TGCs is the key to avoiding postoperative recurrence. We recommend MDT with complete surgical resection as the core and discuss the advantages and disadvantages of various diagnostic and treatment strategies.

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INTRODUCTION

Tailgut cysts (TGCs) are congenital cysts that develop in the retrorectal-presacral space from the remnants of the primitive embryonic hindgut[1,2]. These rare cysts are more common in women. Patients may present with lower abdominal pain and perianal lesions. Due to the risk of complications, such as recurrent perianal suppuration and malignant changes, surgical treatment is necessary. TGCs with malignant transformation are extremely rare[3]. The types of malignant transformation include adenocarcinoma, neuroendocrine tumor, and carcinoid. Most of these tumors are more inert than other epithelial malignant tumors; however, a small number of them are aggressive and resistant to treatment. Adenocarcinoma caused by TGCs is very rare, with only 28 cases with clinical details having been reported in the medical literature since 1990. In this paper, we report a new case and summarize the clinical and pathological features of adenocarcinoma from TGCs with a literature review. The reported cases were retrieved from the PubMed and *Reference Citation Analysis* (https://www.referencecitation-analysis.com/) database, and case summary information was carefully extracted from each article searched by PubMed (Table 1). To the best of our knowledge, a summary of adenocarcinogenesis of TGCs has not been reported before. Here, we focus on the regular characteristics of malignant transformation of TGCs to facilitate clinical diagnosis and treatment.

CASE PRESENTATION

Chief complaints

A 35-year-old Chinese woman complained of a lower abdominal mass for 2 mo and abdominal distension for 2 wk.

History of present illness

The patient accidentally found a mass in her lower abdomen in May 2020 with no related clinical symptoms. She delayed hospitalization for 2 mo due to the coronavirus disease 2019 pandemic. Two months later, due to abdominal distension and right waist discomfort, the patient went to the gynecology clinic to seek medical help. Since the onset of the disease, the patient has had no dysuria or menstrual changes.

Table 1 Summary of disease information on adenocarcinogenesis of tailgut cysts published from 1990-2021

Case	Ref.	Sex	Age	Clinical symptoms	Duration	Size (mm)	MRI/CT	Biopsy	Invasion	Position S4+/S3-	CEA/CA199	Surgery planning
1	Baverez *et al*[19], 2021	F	57	Perianal suppuration	5 yr	55	+/+	+	Anal canal and perianal skin	-	30/UN	Abdominoperineal resection
2	Wang *et al*[3], 2020	F	50	Irregular defecation	2 wk	90 × 80	+/+	-	-	-	79.89/57.60	Trans-sacrococcygeal approach
3	Rachel *et al*[20], 2019	F	73	Anal abscess and associated fistula	40 yr	56 × 46	+/+	+	Anal canal and perianal skin	-	UN	Trans-sacrococcygeal approach
4	Martins *et al*[4], 2020	F	54	Pelvic and perineal pain	1-2 mo	50 × 35	+/+	+	Sacrum	-	UN	Trans-sacrococcygeal approach
5	Li *et al*[21], 2019	M	33	-	-	80 × 59	+/-	-	-	-	26.97/106.50	Trans-sacrococcygeal approach
6	Şahin *et al*[22], 2020	F	55	Swelling of the buttocks	6 mo	21 × 16	+/-	-	-	-	-/204	Trans-sacrococcygeal approach
7	Almeida Costa and Rio [23], 2018	F	53	Defecation and lower abdominal pain	UN	UN	+/+	-	Sacrum	+	UN	Trans-sacrococcygeal approach
8	Zhao *et al*[11], 2015	F	44	Pelvic and perineal pain	6 mo	100	-/+	+	Rectum and surrounding	+	+/UN	Partial resection and drainage of the pelvic tumor
9	Chhabra *et al*[8], 2013	F	56	Hematuria	1 yr	46 × 37	-/+	+	-	-	-/UN	Trans-sacrococcygeal approach
10	Jarboui *et al*[24], 2008	F	49	Pelvic and perineal pain	6 mo	150	-/+	-	-	+	UN	Laparotomy
11	Tampi *et al*[2], 2007	F	57	Low backache	6 mo	120 × 100 × 80	-/+	-	Liver	+	-/-	Laparotomy
12	Andea and Klimstra[25], 2005	F	47	Gluteal pain	3 mo	40 × 40	UN/UN	-	-	UN	-/UN	UN
13	Cho *et al*[26], 2005	F	40	Perianal pain	1 mo	100 × 80 × 70	+/	+	Sacrum	-	159/2270	Abdominoperineal resection and partial sacrectomy
14	Kanthan *et al*[12], 2004	F	76	Perianal pain	UN	65 × 45 × 35	-/+	+	-	-	UN	Trans-sacrococcygeal approach
15	Moreira *et al*[13], 2001 (case-1)	F	64	Constipation and frequent urination	2 mo	120 × 100	+/UN	-	-	UN	UN	UN
16	Moreira *et al*[13], 2001 (case-2)	F	68	Rectal "fullness"	2 yr	180 × 40	+/+	-	-	UN	UN	UN
17	Schwarz *et al*[14], 2000	M	47	Bilateral flank pain, constipation	3 mo	160	-/+	-	-	-	46/-	Abdominoperineal resection and partial sacrectomy
18	Prasad *et al*[27], 2000	F	36	-	UN	95 × 92 × 88	+/+	UN	-	UN	UN	UN
19	Sauer *et al*[28], 2000	F	58	Recurrent perianal fistulas	17	55 × 40 × 35	+/+	-	-	+	6.7/42	Laparotomy
20	Graadt van Roggen *et al*	F	43	-	-	130	+/-	-	UN	+	+/UN	UN

	[7], 1999											
21	Maruyama *et al*[29], 1998	F	66	Perianal pain	6 mo	100 × 90	+/+	-	-		3.8/-	Trans-sacrococcygeal approach
22	Lim *et al*[10], 1998	F	40	Urinary frequency and constipation	8 mo	250 × 100 × 100	+/-	-	-	UN	-/-	Laparotomy
23	Yamaguchi *et al*[30], 2001	M	32	Anal fistula	4 yr	UN	+/+	-	Rectum	UN	UN	Pelvic evisceration
24	Liessi *et al*[31], 1995	M	50	UN	UN	UN	+/+	UN	Sacrum	UN	UN	Trans-sacrococcygeal approach

CT: Computed tomography; MRI: Magnetic resonance imaging; F: Female; M: Male; CEA: Carcinoembryonic antigen.

History of past illness

The patient's past medical history included a loop electrosurgical excision procedure for cervical erosion 10 years ago.

Personal and family history

No family history was identified.

Physical examination

Physical examination showed that the patient's abdomen was flat and soft, with no abnormal bulge, tenderness, or rebound pain. A cystic-solid mass of approximately 10 cm, which was painless and could not be pushed, was palpated slightly higher than the pubic bone. Gynecological bimanual examination showed no abnormalities of the vagina, cervix, or uterus.

Laboratory examinations

Laboratory studies were normal except for an elevation in serum carcinoembryonic antigen (CEA) to 132.69 ng/mL.

Imaging examinations

Gynecological B-mode ultrasonography examination showed that there was a cystic-solid mass close to the surface of the right ovary, mainly cystic, and the sound difference of the internal diaphragm was noisy. The appearance of thick and intense light spots followed by sound shadows, as well as a small blood flow signal in the solid part, allowed us to calculate a resistance index of 0.55. Computed tomography (CT) showed a cystic mass in the posterior rectal pelvis, extending to the level of the sacral promontory but not reaching the bony components of the sacrum or coccyx. The size of the mass was approximately 10 cm × 9 cm, and it showed polycystic changes with a septum and calcification. Contrast-enhanced CT indicated that the septum of the mass could be enhanced. Magnetic resonance imaging (MRI) showed a mass of abnormal signal on the right side of the pelvis measuring approximately 10 cm × 7 cm. Its borders were clear, with mixed high signal on T2-weighted imaging (T2WI) and localized lamellar low signal within. The right adnexal region was a cystic abnormal signal focus with a moderate signal on T1-weighted imaging (T1WI) and a slightly high signal on T2WI, with

nodular ring reinforcement on an enhanced scan. No enlarged lymph nodes or abnormal masses were seen in the pelvis. There was also no abnormal signal in the pelvic wall tissue (Figure 1).

FINAL DIAGNOSIS

Histopathology revealed that the lesion was an intestinal mucinous adenocarcinoma, and the malignant transformation of an embryonic residual enterogenous cyst was considered. The results of pathological sections showed fibrous tissue with a cystic lining; the lesion was rich in cellular mucus and infiltrating the columnar epithelium, and it also showed high-grade atypical cell hyperplasia and mitotic activity. Morphologically, this was consistent with mucinous adenocarcinoma, intestinal type. Immunopathology showed that cytokeratin 20 (CK) 20, CK7, CDX2, and STATB2 were positive (Figure 2). After joint consultation with the Department of Pathology of University of California, Los Angeles, we diagnosed the patient with a TGC with adenocarcinogenesis.

TREATMENT

After a multidisciplinary consultation and evaluation, laparoscopic surgery was performed under general anesthesia on July 14, 2020. During the operation, there was no obvious free fluid in the pelvis and no obvious abnormalities in the uterus, fallopian tubes, or ovaries.

An enlarged cyst, swollen and measuring approximately 10 cm × 9 cm, was found behind the peritoneum in front of the sacrum near the right iliac vessel. Hyperplastic vessels were visible on the smooth surface of the swelling, the ureter was observed to pass through the surface, and the iliac vessels were visible below it, with no adhesion to the surrounding tissues of S2-S4.

The operation was performed by an experienced general surgeon and a gynecologist. With the help of laparoscopy, we successfully removed the cyst completely. After the cyst was removed from the abdominal cavity, we opened the cyst and found that its inner wall was rough; moreover, we found multiple tissue calcifications. The intraoperative frozen pathological results showed a retroperitoneal benign cyst and cyst wall fibrosis and calcification. After flushing the abdominal cavity and retroperitoneal space with distilled water, no residual cysts or enlarged lymph nodes were found, and the peritoneum was closed by suture (Figure 3).

OUTCOME AND FOLLOW-UP

The patient received six cycles of capecitabine and oxaliplatin (CapeOX) chemotherapy, and there were no grade 3-4 side effects during this treatment. After treatment, her CEA level decreased progressively and ultimately fell within the normal range, and no metastatic focus was found on CT. The patient received therapy with high compliance, expressed satisfaction with her recovery, and has been tumor-free for more than 18 mo.

DISCUSSION

TGCs are considered to be congenital cysts that develop in the rectosacral space from the residue of the primitive tail[1,2]. This incomplete degeneration of the extension of the tail from the posterior intestine of the embryo usually occurs at the 8th week of the embryonic stage[4]. The rectosacral space is a potential space located in the deep part of the pelvis, with the posterior rectal fascia in the front and the presacral fascia (Waldeyer fascia) in the back; this space extends upward to the peritoneum and downward to the level of the rectosacral fascia and perineal muscle[5]. The boundaries on both sides are roughly outlined by the ureter, iliac vessels, and sacral nerve roots[6]. This area includes the confluence of the embryonic hindgut, pelvis, and neuroectoderm, and consequently, there are many different tissue types that can lead to retrorectal tumors. Retrorectal tumors can be divided into congenital, inflammatory, neurogenic, and osteogenic tumors. Cystic congenital lesions consist of epidermoid cysts, dermoid cysts, TGCs, enterogenous cysts, teratomas, and teratocarcinomas[7]. Such lesions affect people of all ages from birth to adulthood and are more common in women. Sometimes, patients may have space-occupying symptoms due to the enlargement of deep pelvic masses[1,3]. Clinical manifestations are usually nonspecific, with half of the patients experiencing pain, perianal lesions, changes in defecation habits, dysuria, and neurological symptoms of the lower extremities and perineum[8]. Among congenital cystic lesions, the incidence of TGCs is relatively high, but the incidence of canceration is very rare.

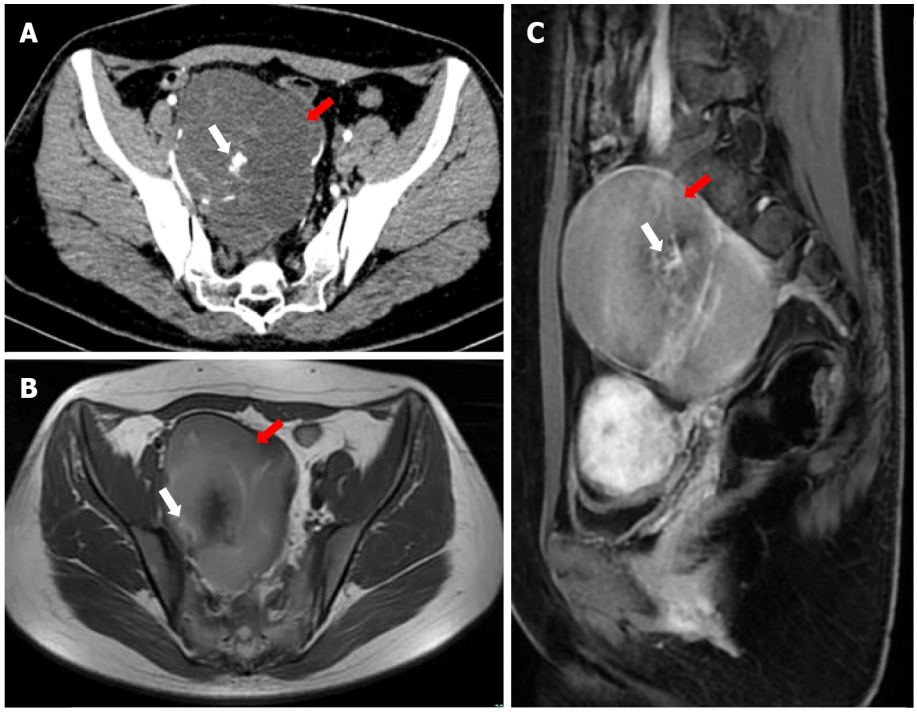

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Figure 1 Imaging examination. A: Computed tomography showed a low-density mass (red arrow) of approximately 10 cm × 9 cm in the pelvis, with cordlike separation and unclear boundaries with the posterior wall and lateral wall. Inhomogeneous enhancement and high-density areas (white arrow) were seen; B and C: Magnetic resonance imaging showed a mass (red arrow) of abnormal signal intensity on the right side of the pelvic cavity, whereas the boundary was still clear. T1-weighted imaging showed a slightly high signal intensity, T2-weighted imaging showed a mixed high signal intensity, and the septal changes in the enhanced scan showed obvious enhancement (white arrow).

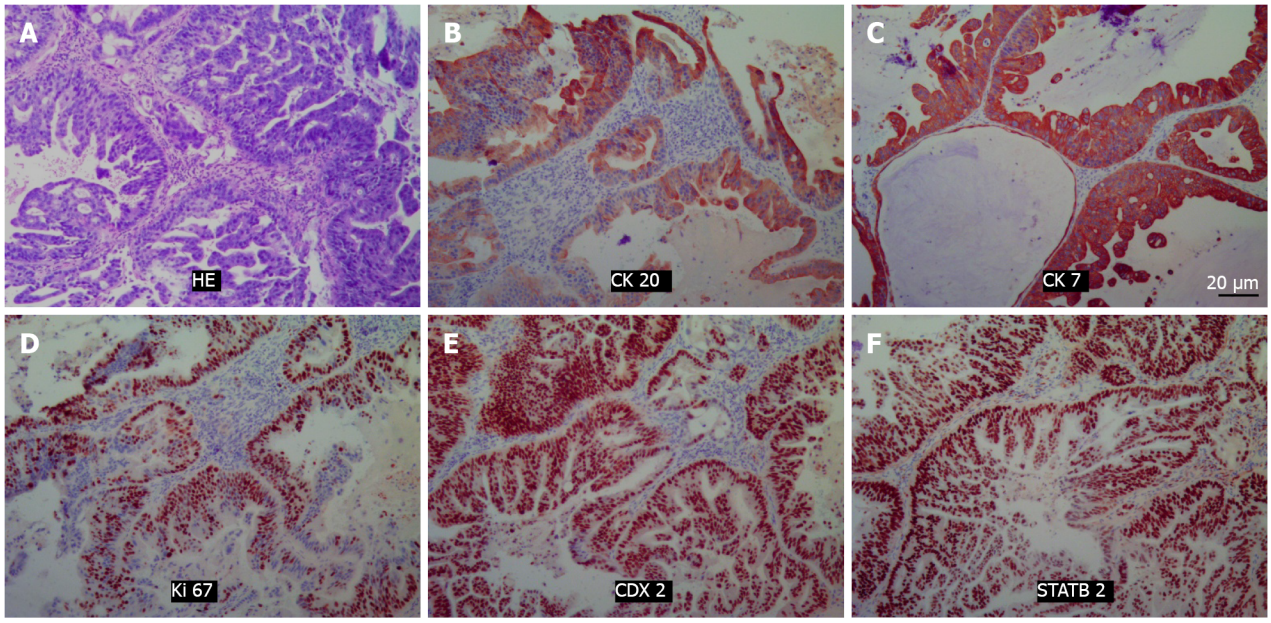

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Figure 2 Hematoxylin-eosin staining and immunohistochemical pictures. Positivity for cytokeratin 20, cytokeratin 7, Ki67, CDX2, and STATB2 was noted. A: Hematoxylin-eosin staining; B: CK20; C: CK7; D: Ki67; E: CDX2; F: STATB2. HE: Hematoxylin-eosin; CK20: Cytokeratin 20; CK7: Cytokeratin 7.

The malignant transformation of TGCs into reported tumors includes adenocarcinoma, carcinoid, neuroendocrine carcinoma, endometrioid carcinoma, adenosquamous carcinoma, squamous cell carcinoma, and sarcoma[2]. Most of them are endocrine tumors and adenocarcinomas, while others, such as carcinoids, are rare. At present, approximately 28 cases of TGC adenocarcinoma have been reported, of which 24 with relatively complete data were retrieved. We describe a new case of TGC with

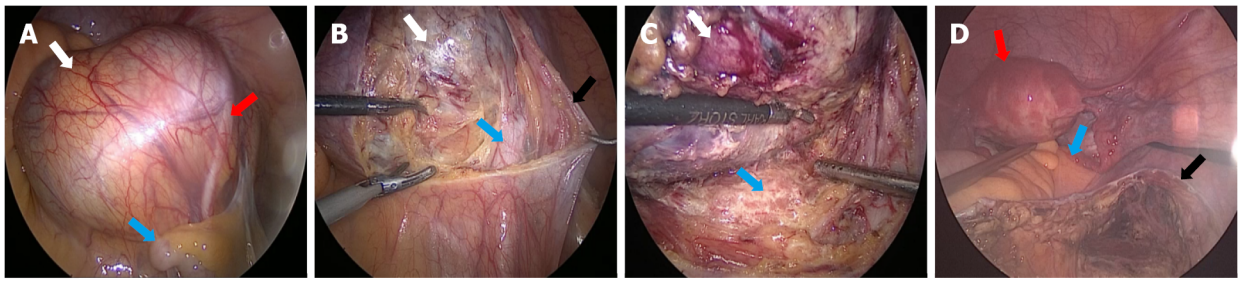

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Figure 3 Surgical pictures. A: Gross view of the mass (white arrow) under laparoscopy. The sigmoid colon (blue arrow) and ureter (red arrow) can be seen; B: Opening of the retroperitoneum (black arrow) and exposure of the mass (white arrow) and external iliac artery (blue arrow); C: Careful separation of the mass (white arrow) from the presacral tissue (blue arrow); D: The operative field after the tumor was removed, and the uterus (red arrow), rectum (blue arrow), and retroperitoneum (black arrow) can be seen.

mucinous cystadenocarcinoma and review the literature reports of TGCs with adenocarcinogenesis to provide a reference for diagnosis and treatment.

We summarize cases of TGC adenocarcinoma reported from 1990 to 2021, as the diagnostic and therapeutic approach is of limited interest due to the low prevalence and accuracy of diagnostic tools such as MRI and CT prior to 1990.

First, we sorted out the historical process of a complete understanding of TGCs. Cancerous TGC was first reported in 1932, and Ballantyne reported the first case of adenocarcinoma with TGCs. That patient developed local recurrence, lung metastasis, and inguinal lymph node metastasis and died 8 mo after cyst resection. Subsequently, doctors began to pay attention to and share the diagnosis and treatment of this rare disease. Through the review of articles related to TGCs, we found that there were two related landmark systematic retrospective studies. The first one was conducted in 1987 when Hjermstad and Helwig[1] evaluated all the pathological specimens of posterior rectal cysts diagnosed by the Institute of Pathology of the Armed Forces of the United States during a period of 35 years, and 53 cases of "tailgut cysts" were selected[1]. Their screening criteria were that the cysts must be partially covered by a columnar or transitional epithelium, but there must be no myenteric plexus or serosa, nor can there be a complete muscular layer. Hjermstad and Helwig's study defined the pathological criteria for the diagnosis of TGCs, allowing doctors to unify the definition of the disease[1]. The second was a retrospective analysis of the clinical and pathological data of patients who underwent colectomy at Mayo Clinic in 2008, conducted by Mathis *et al*[9]. A total of 31 patients were diagnosed, including 28 females, with an average age of 52 years. The median diameter of the cyst was 4.4 cm. There were four patients with malignant transformation, comprising three cases of adenocarcinoma and one case of carcinoid, and the 5-year survival rate was 83%. The work of Mathis *et al*[9] provides a single-center clinical experiential basis for the treatment and prognosis of TGCs. At present, with the progress of medical technology, the surgical methods and chemotherapy schemes have changed, but their principle of complete resection of the tumor remains unaddressed.

The summary of cases of TGCs with adenocarcinogenesis showed that most of the patients were middle-aged adults with a female–male ratio of 10:1, which was much higher than the ratio of 3-4:1 in previous articles on caudal cysts. The clinical manifestations of TGCs are varied and nonspecific. However, by summarizing the cases of caudal cysts with adenocarcinoma, we found that half of the patients complained of an abdominal mass and pain, perianal disease, and changes in stool habits and stool characteristics, while other patients did not have any symptoms. TGC is a rare congenital retrorectal disease in which the residue of the fetal retroanal intestine grows in the retrorectal space. It should be noted that this gap is a potential space, and the mass has considerable room for growth. This can explain the late onset of the disease, and TGC canceration occurs during this process. It is suggested that TGCs should be regarded as a precancerous lesion to explain this phenomenon. More than half of the patients were diagnosed with TGCs within 1 year after the onset of symptoms, and most of them exhibited retrorectal masses by imaging examinations such as CT and MRI. Compared with CT, MRI has the ability of multiplanar imaging and better tissue contrast in presacral masses[10]. MR has more advantages in differential diagnosis. Regarding the differential diagnosis of presacral masses, anal gland cysts, repeated cysts, teratomas, epidermoid cyst chordomas, abscesses, metastatic tumors, and neurofibromas should be considered. Fat content on fat-saturated images indicates dermoid cysts[1]. In presacral cystic masses, epidermoid cysts, dermoid cysts, rectal repeated cysts, and meningoceles are usually monocular. Rectal repetitive cysts, which are located in front of the rectum, often communicate with the rectal cavity. In contrast, TGCs are usually polycystic and can be characterized by large cysts with small peripheral cysts. This polycystic change is very important. Regarding the MRI features of TGCs, low signal intensity is usually shown on T1WI, and high signal intensity is shown on T2WI. However, the internal signal intensity of T1WI and T2WI indicates the protein concentration in the lesion, which increases with age, and the cysts show high signal intensity on T1WI. However, the

consistent feature is that most of the dominant cysts on T2-weighted sequences are hyperintense relative to the pelvic muscles. In addition, we are more concerned about the accuracy of MRI in predicting the nature of tumors. Cystic tumors with smooth, well-defined boundaries and no infiltrative or gadolinium enhancement are generally considered to be benign, whereas cysts with thickened and irregularly enhancing cyst wall boundaries, which may even be surrounded by inflammatory changes, are usually malignant.

MRI is the most valuable tool to meet the needs of diagnosis and differential diagnosis, to help improve preoperative assessments, to estimate the extent of the disease and malignant risk, and to determine the most appropriate treatment strategy. The effect of CT is not as accurate as that of MRI[3]. By pooling the literature, it was found that half of the cases had calcification and that the presence or absence of calcification was not of significant value in the diagnosis of benign or malignant lesions. Enhanced MRI and PET may be good examination methods for the diagnosis of malignant transformation and metastasis of TGCs, which is worth exploring in the future.

Preoperative biopsy of TGCs is considered unnecessary because it cannot confirm or even misconfirm the diagnosis of adenocarcinogenesis or tumor differentiation of TGCs[8]. Some authors believe that in the case of heterogeneous masses with elevated CEA, direct surgery should be performed without biopsy. However, in our statistical table, we can see that among three patients with benign lesions diagnosed by preoperative biopsy, one had a high CEA level (case 8)[11], one had a normal CEA level (case 9)[8], and one had an unknown CEA level (case 14)[12], but postoperative pathology confirmed adenocarcinoma. Therefore, biopsy can provide very limited help in diagnosing heterogeneous masses with normal CEA. Preoperative biopsies may pose major risks, such as malignant cell spillage or needle implantation. After such a biopsy, it is necessary to consider removing the tissue around the needle track during the operation, but in many cases, this is not easy to do. When we make the surgical plan, regardless of the biopsy results, we need to assume that this is a malignant lesion and adhere to the principle of complete resection. The accuracy of preoperative biopsy is in doubt, and this procedure may bring the risk of metastasis and increase the difficulty of operation. However, for patients who are unable or difficult to surgically remove the tumor, it is indeed a good method to determine the nature of the tumor through the pathological results of the biopsy and then perform surgical treatment after neoadjuvant chemotherapy.

Because cases of adenocarcinogenesis of TGCs are very rare, there are no guidelines to follow in the treatment of retrorectal tumors. In view of the strong positive expression of p53 and Ki-67 and the negative expression of p21 in the dysplastic epithelium of tailgut adenocarcinoma, it is speculated that the occurrence order of dysplasia and carcinoma is similar to that of colonic adenocarcinoma[13]. At present, the treatment mainly draws lessons from the clinical treatment guidelines for rectal adenocarcinoma, including European ESMO guidelines and American NCCN guidelines. It is suggested that multidisciplinary treatment should be adopted. Considering the postoperative pathological report and high CEA level, the present patient chose surgery and chemotherapy. The key to such operations is to remove the cyst wall completely. There are three common surgical approaches, namely, the anterior approach (abdomen), posterior approach (perineal approach), and combined abdominal perineal approach[4,14]. MRI will help to determine the margin of resection and identify the relationship between the tumor and the sacral level. For instance, if the tumor is below the middle of S3, the perineal approach can be considered[15]. All tumors extending above S4 usually require an abdominal or combined approach. For small lesions, the surgeon can also use a transvaginal approach. If malignant lesions are confirmed or suspected, the tumor tissue can be cleared more thoroughly *via* the combined abdominal perineal approach. Minimally invasive surgery has great advantages in the fine separation of anatomical hierarchy and reduction of complications[16,17]. In view of the leakage of the cancer and the large mass, it is recommended to use an endobag in the extraction of the specimen through a small incision in the abdominal wall. If there is no R0 resection or residual cyst wall and invasion of the tissue around the tumor leads to postoperative recurrence, comprehensive treatment schemes such as cytoreductive surgery, radiotherapy, chemotherapy, interventional therapy, and molecular targeted drug therapy are recommended. Considering that a small amount of leakage of TGC fluid during the operation might occur and that the postoperative pathology showed mucinous adenocarcinoma with high CEA, we chose to use CapeOX treatment to prevent recurrence. The reason for choosing CapeOX treatment is that it is feasible and widely used in malignant tumors of the digestive tract; the other reason is that the incidence of serious side effects of this regimen is low. In summary, complete resection of TGC masses during surgery is the key to avoiding postoperative recurrence and obtaining long-term survival for patients without metastasis[18].

CONCLUSION

Adenocarcinoma of TGCs is a very rare disease, and complete resection is still the gold standard. We do not recommend preoperative biopsies. Early MDT plays a significant role in the accurate diagnosis and selection of the most appropriate personalized treatment.

FOOTNOTES

Author contributions: Wang YS and Guo QY contributed to the conceptualization; Zheng FH, Huang ZW, and Yan JL contributed to the literature search and data analysis; Wang YS wrote the original draft; Fan FX, Liu T, and Ji SX reviewed and edited the manuscript; Zheng YX and Zhao XF supervised the manuscript.

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ORCID number: Yan-Shuai Wang 0000-0002-2692-2244; Qing-Yun Guo 0000-0003-1465-6185; Fang-Hong Zheng 0000-0001-7524-9511; Zi-Wei Huang 0000-0001-9038-958X; Jia-Lang Yan 0000-0003-0275-049X; Fu-Xiang Fan 0000-0001-6321-1057; Tian Liu 0000-0002-1349-2177; Shun-Xian Ji 0000-0001-9652-2070; Xiao-Feng Zhao 0000-0002-8579-6997; Yi-Xiong Zheng 0000-0002-2729-6417.

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REFERENCES

1 **Hjermstad BM**, Helwig EB. Tailgut cysts. Report of 53 cases. *Am J Clin Pathol* 1988; **89**: 139-147 [PMID: 3277378 DOI: 10.1093/ajcp/89.2.139]
2 **Tampi C**, Lotwala V, Lakdawala M, Coelho K. Retrorectal cyst hamartoma (tailgut cyst) with malignant transformation. *Gynecol Oncol* 2007; **105**: 266-268 [PMID: 17303225 DOI: 10.1016/j.ygyno.2007.01.008]
3 **Wang M**, Liu G, Mu Y, He H, Wang S, Li J. Tailgut cyst with adenocarcinoma transition: A rare case report. *Medicine (Baltimore)* 2020; **99**: e20941 [PMID: 32629697 DOI: 10.1097/MD.0000000000020941]
4 **Martins P**, Canotilho R, Peyroteo M, Afonso M, Moreira A, de Sousa A. Tailgut cyst adenocarcinoma. *Autops Case Rep* 2020; **10**: e2019115 [PMID: 32039057 DOI: 10.4322/acr.2019.115]
5 **Satyadas T**, Davies M, Nasir N, Halligan S, Akle CA. Tailgut cyst associated with a pilonidal sinus: an unusual case and a review. *Colorectal Dis* 2002; **4**: 201-204 [PMID: 12780617 DOI: 10.1046/j.1463-1318.2002.00345.x]
6 **Kildušis E**, Samalavičius NE. Surgical management of a retro-rectal cystic hamartoma (tailgut cyst) using a trans-rectal approach: a case report and review of the literature. *J Med Case Rep* 2014; **8**: 11 [PMID: 24393234 DOI: 10.1186/1752-1947-8-11]
7 **Graadt van Roggen JF**, Welvaart K, de Roos A, Offerhaus GJ, Hogendoorn PC. Adenocarcinoma arising within a tailgut cyst: clinicopathological description and follow up of an unusual case. *J Clin Pathol* 1999; **52**: 310-312 [PMID: 10474528 DOI: 10.1136/jcp.52.4.310]
8 **Chhabra S**, Wise S, Maloney-Patel N, Rezac C, Poplin E. Adenocarcinoma associated with tail gut cyst. *J Gastrointest Oncol* 2013; **4**: 97-100 [PMID: 23450681 DOI: 10.3978/j.issn.2078-6891.2012.043]
9 **Mathis KL**, Dozois EJ, Grewal MS, Metzger P, Larson DW, Devine RM. Malignant risk and surgical outcomes of presacral tailgut cysts. *Br J Surg* 2010; **97**: 575-579 [PMID: 20169572 DOI: 10.1002/bjs.6915]
10 **Lim KE**, Hsu WC, Wang CR. Tailgut cyst with malignancy: MR imaging findings. *AJR Am J Roentgenol* 1998; **170**: 1488-1490 [PMID: 9609159 DOI: 10.2214/ajr.170.6.9609159]
11 **Zhao XR**, Gao C, Zhang Y, Yu YH. The Malignant Transformation of Retrorectal Cystic Hamartomas With Blood Irregular Antibodies Positive: A Case Report. *Medicine (Baltimore)* 2015; **94**: e2253 [PMID: 26656372 DOI: 10.1097/MD.0000000000002253]
12 **Kanthan SC**, Kanthan R. Unusual retrorectal lesion. *Asian J Surg* 2004; **27**: 144-146 [PMID: 15140669 DOI: 10.1016/S1015-9584(09)60330-4]
13 **Moreira AL**, Scholes JV, Boppana S, Melamed J. p53 Mutation in adenocarcinoma arising in retrorectal cyst hamartoma (tailgut cyst): report of 2 cases--an immunohistochemistry/immunoperoxidase study. *Arch Pathol Lab Med* 2001; **125**: 1361-1364 [PMID: 11570917 DOI: 10.5858/2001-125-1361-PMIAAI]
14 **Schwarz RE**, Lyda M, Lew M, Paz IB. A carcinoembryonic antigen-secreting adenocarcinoma arising within a retrorectal tailgut cyst: clinicopathological considerations. *Am J Gastroenterol* 2000; **95**: 1344-1347 [PMID: 10811351 DOI: 10.1111/j.1572-0241.2000.02023.x]
15 **Alsofyani TM**, Aldossary MY, AlQahtani FF, Sabr K, Balhareth A. Successful excision of a retrorectal cyst through trans-

sacral approach: A case report. *Int J Surg Case Rep* 2020; **71**: 307-310 [PMID: 32485636 DOI: 10.1016/j.ijscr.2020.05.023]

16 **Rompen IF**, Scheiwiller A, Winiger A, Metzger J, Gass JM. Robotic-Assisted Laparoscopic Resection of Tailgut Cysts. *JSLS* 2021; **25** [PMID: 34354334 DOI: 10.4293/JSLS.2021.00035]

17 **Inada R**, Watanabe A, Toshima T, Katsura Y, Sato T, Sui K, Oishi K, Okabayashi T, Ozaki K, Shibuya Y, Matsumoto M, Iwata J. Laparoscopic Synchronous Resection for Descending Colon Cancer and Tailgut Cyst. *Acta Med Okayama* 2021; **75**: 529-532 [PMID: 34511622 DOI: 10.18926/AMO/62407]

18 **Baek SK**, Hwang GS, Vinci A, Jafari MD, Jafari F, Moghadamyeghaneh Z, Pigazzi A. Retrorectal Tumors: A Comprehensive Literature Review. *World J Surg* 2016; **40**: 2001-2015 [PMID: 27083451 DOI: 10.1007/s00268-016-3501-6]

19 **Baverez M**, Thibaudeau E, Libois V, Kerdraon O, Senellart H, Raoul JL. Retrorectal Mucinous Adenocarcinoma Arising from a Tailgut Cyst: A Case Report. *Case Rep Oncol* 2021; **14**: 147-151 [PMID: 33776696 DOI: 10.1159/000513028]

20 **Rachel F**, Guzik A, Szczerba D, Kozieł K, Gutterch K. Tailgut cyst and a very rare case of a tailgut cyst with mucinous adenocarcinoma in a 73 year old woman treated for buttock abscess with fistula. *Pol Przegl Chir* 2019; **91**: 38-42 [PMID: 31243172 DOI: 10.5604/01.3001.0013.0810]

21 **Li W**, Li J, Yu K, Zhang K. Retrorectal adenocarcinoma arising from tailgut cysts: a rare case report. *BMC Surg* 2019; **19**: 180 [PMID: 31775691 DOI: 10.1186/s12893-019-0639-9]

22 **Şahin S**, Kepil N, Batur Ş, Çetin SE. Adenocarcinoma in a Tailgut Cyst: A Rare Case Report. *Turk Patoloji Derg* 2020; **36**: 169-172 [PMID: 31026045 DOI: 10.5146/tjpath.2018.01459]

23 **Almeida Costa NA**, Rio G. Adenocarcinoma within a tailgut cyst. *BMJ Case Rep* 2018; **2018** [PMID: 30108121 DOI: 10.1136/bcr-2018-226107]

24 **Jarboui S**, Jarraya H, Mihoub MB, Abdesselem MM, Zaouche A. Retrorectal cystic hamartoma associated with malignant disease. *Can J Surg* 2008; **51**: E115-E116 [PMID: 19057717]

25 **Andea AA**, Klimstra DS. Adenocarcinoma arising in a tailgut cyst with prominent meningothelial proliferation and thyroid tissue: case report and review of the literature. *Virchows Arch* 2005; **446**: 316-321 [PMID: 15731926 DOI: 10.1007/s00428-004-1178-y]

26 **Cho BC**, Kim NK, Lim BJ, Kang SO, Sohn JH, Roh JK, Choi ST, Kim SA, Park SE. A carcinoembryonic antigen-secreting adenocarcinoma arising in tailgut cyst: clinical implications of carcinoembryonic antigen. *Yonsei Med J* 2005; **46**: 555-561 [PMID: 16127782 DOI: 10.3349/ymj.2005.46.4.555]

27 **Prasad AR**, Amin MB, Randolph TL, Lee CS, Ma CK. Retrorectal cystic hamartoma: report of 5 cases with malignancy arising in 2. *Arch Pathol Lab Med* 2000; **124**: 725-729 [PMID: 10782156 DOI: 10.5858/2000-124-0725-RCH]

28 **Sauer J**, Wolf HK, Junginger T. [Adenocarcinoma in a tail-gut cyst: a rare cause of recurrent perianal fistula]. *Chirurg* 2000; **71**: 712-716 [PMID: 10948740 DOI: 10.1007/s001040051125]

29 **Maruyama A**, Murabayashi K, Hayashi M, Nakano H, Isaji S, Uehara S, Kusuda T, Miyahara S, Kondo A, Yabana T. Adenocarcinoma arising in a tailgut cyst: report of a case. *Surg Today* 1998; **28**: 1319-1322 [PMID: 9872560 DOI: 10.1007/BF02482826]

30 **Yamaguchi K**, Okushiba S, Katoh H, Shimizu M, Taneichi H. Tailgut cyst invaded by rectal cancer through an anal fistula: report of a case. *Dis Colon Rectum* 2001; **44**: 447 [PMID: 11289294 DOI: 10.1007/BF02234747]

31 **Liessi G**, Cesari S, Pavanello M, Butini R. Tailgut cysts: CT and MR findings. *Abdom Imaging* 1995; **20**: 256-258 [PMID: 7620420 DOI: 10.1007/BF00200409]

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LETTER TO THE EDITOR

Successful treatment of acute symptomatic extensive portal venous system thrombosis by 7-day systemic thrombolysis

Fang-Bo Gao, Le Wang, Wen-Xiu Zhang, Xiao-Dong Shao, Xiao-Zhong Guo, Xing-Shun Qi

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Fang-Bo Gao, Le Wang, Wen-Xiu Zhang, Xiao-Dong Shao, Xiao-Zhong Guo, Xing-Shun Qi, Department of Gastroenterology, General Hospital of Northern Theater Command, Shenyang 110840, Liaoning Province, China

Fang-Bo Gao, Postgraduate College, Shenyang Pharmaceutical University, Shenyang 110016, Liaoning Province, China

Corresponding author: Xing-Shun Qi, MD, PhD, Associate Professor, Department of Gastroenterology, General Hospital of Northern Theater Command, No. 83 Wenhua Road, Shenyang 110840, Liaoning Province, China. xingshunqi@126.com

Abstract

Acute portal venous system thrombosis (PVST) can cause acute mesenteric ischemia and even intestinal infarction, which are potentially fatal, and requires recanalization in a timely fashion. Herein, we report a 56-year-old man with acute non-cirrhotic symptomatic extensive PVST who achieved portal vein recanalization after systemic thrombolysis combined with anticoagulation. Initially, anticoagulation with enoxaparin sodium for 4 d was ineffective, and then systemic thrombolysis for 7 d was added. After that, his abdominal pain completely disappeared, and portal vein system vessels became gradually patent. Long-term anticoagulation therapy was maintained. In conclusion, 7-d systemic thrombolysis may be an effective and safe choice of treatment for acute symptomatic extensive PVST which does not respond to anticoagulation therapy.

Key Words: Portal vein; Mesenteric vein; Thrombosis; Thrombolysis; Anticoagulation; Deep vein thrombosis

Core Tip: The present case suggests that systemic thrombolysis should be safe and effective for acute extensive portal venous system thrombosis, if it is unresponsive to anticoagulation.

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TO THE EDITOR

Acute portal venous system thrombosis (PVST) is potentially life-threatening and can achieve a good response to agitation thrombolysis combined with catheter-directed thrombolysis[1]. However, it should be acknowledged that systemic thrombolysis, a more convenient treatment approach, has been rarely attempted for the treatment of acute PVST in clinical practice due to its potential bleeding risk. Herein, we report a case of acute symptomatic extensive PVST successfully treated by systemic thrombolysis combined with anticoagulation to strengthen our confidence in its clinical efficacy and safety.

A 56-year-old man with a history of hepatitis B virus infection was admitted to the Department of Gastroenterology due to aggravating severe epigastric pain for nearly half a month. He had no other obvious medical history. On physical examinations, his abdomen was soft without abdominal tenderness, rebound, or tension. On day 1 of admission, laboratory tests were performed (Table 1). Contrast-enhanced computed tomography (CT) showed no contrast agent filling within all vessels of the portal venous system, including the main portal vein (MPV), right portal vein (RPV), left portal vein (LPV), confluence of the superior mesenteric vein (SMV) and splenic vein (SV), SMV, and SV (Figure 1A), suggesting a diagnosis of occlusive PVST. Thus, subcutaneous injection of enoxaparin sodium was immediately initiated at a dose of 5000 IU (62.5 IU/kg) twice daily. On day 5, his abdominal pain was not relieved. Anti-Xa level was 0.05 IU/mL (reference range: 0-0.1 IU/mL). Contrast-enhanced CT showed no significant improvement of PVST (Figure 1B). Thus, systemic thrombolysis was recommended. After obtaining this patient and his relatives' informed consent, intravenous injection of urokinase at a dose of 300000 IU twice daily was added on subcutaneous injection of enoxaparin sodium at a dose of 5000 IU twice daily. On day 10, this patient's abdominal pain improved significantly. Contrast-enhanced CT showed that MPV, LPV, and RPV thromboses were partially recanalized (Figure 1C). On day 12, urokinase was discontinued. No bleeding event occurred during the period of systemic thrombolysis. On day 17, his abdominal pain completely disappeared. Then, he was discharged. Enoxaparin sodium was replaced with oral rivaroxaban 20 mg once daily. After 5-mo anticoagulation with rivaroxaban, contrast-enhanced CT showed that the SMV and SV became patent and fine collateral vessels developed around the RPV without signs of esophageal varices (Figure 1D). Laboratory tests were performed again (Table 1). At the time of writing this paper, rivaroxaban is still continued.

Anticoagulation is the preferred choice of treatment for acute PVST[2], but 18% of patients still develop transmural intestinal necrosis after anticoagulation therapy, and 25%-50% will develop prehepatic portal hypertension[3,4]. Patients with acute PVST who do not respond to anticoagulation therapy may benefit from thrombolytic therapy[5]. However, thrombolytic therapy has a higher risk of bleeding, including upper gastrointestinal bleeding, abdominal bleeding, and epistaxis. Notably, the current evidence on systemic thrombolytic therapy for PVST is scare. In a retrospective cohort study[6], 33 patients with acute PVST were treated with intravenous injection of 750000 IU/d streptokinase or 100-150 mg/6-12 h recombinant tissue-type plasminogen activator (rt-PA) for 2-3 d, followed with heparin infusion, and then received oral anticoagulants for 12 mo after discharge. Thrombosis recanalization was achieved in 23 patients. In a prospective cohort study[7], nine cirrhotic patients with recent PVST received continuous intravenous infusion of rt-PA at a dose of 0.25 mg/kg/d combined with subcutaneous injection of low molecular weight heparin for a maximum duration of 7 d. Thrombosis recanalization was achieved in eight patients. Besides, a stepwise thrombolysis regimen for PVST should be considered. In a study by Benmassaoud *et al*[8], 22 non-cirrhotic patients with acute PVST received systemic thrombolysis, of whom eight achieved portal vein recanalization, and the remaining 14 did not have any improvement of thrombosis or abdominal pain and were then treated with transjugular intrahepatic portosystemic shunt (TIPS) or local thrombolysis. Finally, the overall rate of portal vein recanalization was 86.4%. Notably, local thrombolysis and TIPS were employed in the study by Benmassaoud *et al*[8], but they are more invasive and technically complicated as compared to systemic thrombolysis. In our case, initial anticoagulation was less effective, and thus systemic thrombolysis was given. The symptoms improved significantly after thrombolysis, which avoided further vascular interventional procedures, and even surgery for intestinal infarction and necrosis[9].

Acute PVST is often defined if PVST develops 1-3 wk since the onset of symptoms. Accordingly, our case should be diagnosed with acute PVST. Notably, the timing of antithrombotic therapy for acute PVST is very important. A shorter interval from the diagnosis of PVST to initiation of antithrombotic therapy indicates a higher probability of thrombus recanalization[10]. In our case, the interval was

Table 1 Laboratory tests in this patient

Laboratory tests	Reference range	Before antithrombotic treatment	After 7-d thrombolysis	After 5-mo oral anticoagulants
White blood cell count (10^9/L)	3.5-9.5	9.70	5.20	6.7
Hemoglobin (g/L)	130-175	143	119	164
Platelet count (10^9/L)	125-350	230	242	123
Total bilirubin (μmol/L)	5.1-22.2	16.70	8.1	13.9
Aspartate aminotransferase (U/L)	15-40	17.60	16.29	18.65
Alanine aminotransferase (U/L)	9-50	20.39	20	21.99
International normalized ratio	0.9-1.2	1.19	1.15	0.99
Prothrombin time (s)	11.0-13.7	14.80	14.4	13.1
Activated partial thromboplastin time (s)	31.5-43.5	32.30	38.9	34.6
D-dimer (mg/L)	0-0.55	7.71	4.77	0.27
Antithrombin III (%)	80-120	48	-	55
Fibrinogen (g/L)	2.0-4.0	3.09	4.87	3.09
Protein C (%)	70-140	-	-	89.3
Protein S (%)	75-130	-	-	90.4

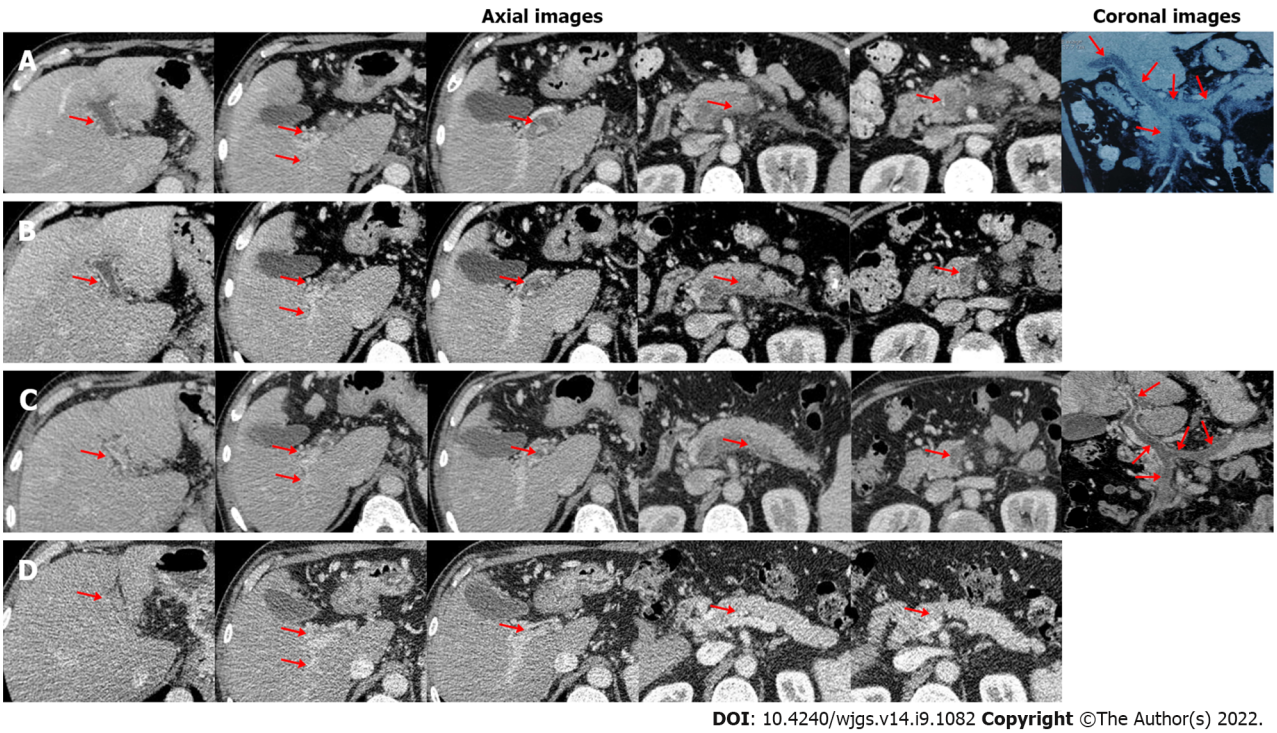

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Figure 1 Axial and coronal computed tomography images in this patient. A: On day 1 of admission, computed tomography (CT) images demonstrated occlusive thrombosis within the main portal vein (MPV), left portal vein (LPV), right portal vein (RPV), confluence of the superior mesenteric vein (SMV) and splenic vein (SV), SMV, and SV, with fine collaterals around the hilum (red arrow); B: On day 5, CT images demonstrated partially recanalized LPV and RPV (red arrow); C: On day 10, CT images demonstrated partially recanalized MPV, LPV, and RPV (red arrow); D: After 5-mo anticoagulation with rivaroxaban, CT images demonstrated completely recanalized SMV and SV (red arrow).

relatively long, which potentially compromised the efficacy of anticoagulation and forced the use of systemic thrombolysis.

In conclusion, systemic thrombolysis should be considered in the cases where anticoagulant therapy fails and interventional therapy is neither available nor feasible. The timing of systemic thrombolytic

therapy and the dose of thrombolytic drugs should be further explored.

FOOTNOTES

Author contributions: Qi XS conceived this manuscript; Zhang WX, Guo XZ, and Qi XS treated this case; Gao FB, Wang L, and Qi XS followed this case; Gao FB and Qi XS drafted the manuscript; Gao FB, Wang L, Zhang WX, Shao XD, Guo XZ, and Qi XS revised the manuscript; all authors have made an intellectual contribution to the manuscript and approved the submission.

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ORCID number: Xiao-Zhong Guo 0000-0002-6397-0501; Xing-Shun Qi 0000-0002-9448-6739.

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REFERENCES

1 **Wang CY**, Wei LQ, Niu HZ, Gao WQ, Wang T, Chen SJ. Agitation thrombolysis combined with catheter-directed thrombolysis for the treatment of non-cirrhotic acute portal vein thrombosis. *World J Gastroenterol* 2018; **24**: 4482-4488 [PMID: 30357003 DOI: 10.3748/wjg.v24.i39.4482]
2 **Wang L**, Xu X, Hou Y, Shao X, Guo X, Qi X. Acute mesenteric vein thrombosis after endoscopic injection sclerotherapy for esophageal varices in a patient with liver cirrhosis. *Drug Discov Ther* 2019; **13**: 118-121 [PMID: 31080203 DOI: 10.5582/ddt.2019.01014]
3 **Plessier A**, Darwish-Murad S, Hernandez-Guerra M, Consigny Y, Fabris F, Trebicka J, Heller J, Morard I, Lasser L, Langlet P, Denninger MH, Vidaud D, Condat B, Hadengue A, Primignani M, Garcia-Pagan JC, Janssen HL, Valla D; European Network for Vascular Disorders of the Liver (EN-Vie). Acute portal vein thrombosis unrelated to cirrhosis: a prospective multicenter follow-up study. *Hepatology* 2010; **51**: 210-218 [PMID: 19821530 DOI: 10.1002/hep.23259]
4 **Condat B**, Pessione F, Helene Denninger M, Hillaire S, Valla D. Recent portal or mesenteric venous thrombosis: increased recognition and frequent recanalization on anticoagulant therapy. *Hepatology* 2000; **32**: 466-470 [PMID: 10960436 DOI: 10.1053/jhep.2000.16597]
5 **Rössle M**, Bettinger D, Trebicka J, Klinger C, Praktiknjo M, Sturm L, Caca K, Mücke VT, Radecke K, Engelmann C, Zipprich A, Heinzow H, Meyer C, Tappe U, Appenrodt B, Schmidt A, Lange C, Strassburg C, Zeuzem S, Grandt D, Schmidt H, Moessner J, Berg T, Lammert F, Thimme R, Schultheiß M. A prospective, multicentre study in acute non-cirrhotic, non-malignant portal vein thrombosis: comparison of medical and interventional treatment. *Aliment Pharmacol Ther* 2020; **52**: 329-339 [PMID: 32506456 DOI: 10.1111/apt.15811]
6 **Malkowski P**, Pawlak J, Michalowicz B, Szczerban J, Wroblewski T, Leowska E, Krawczyk M. Thrombolytic treatment of portal thrombosis. *Hepatogastroenterology* 2003; **50**: 2098-2100 [PMID: 14696472]
7 **De Santis A**, Moscatelli R, Catalano C, Iannetti A, Gigliotti F, Cristofari F, Trapani S, Attili AF. Systemic thrombolysis of portal vein thrombosis in cirrhotic patients: a pilot study. *Dig Liver Dis* 2010; **42**: 451-455 [PMID: 19819770 DOI: 10.1016/j.dld.2009.08.009]
8 **Benmassaoud A**, AlRubaiy L, Yu D, Chowdary P, Sekhar M, Parikh P, Finkel J, See TC, O'Beirne J, Leithead JA, Patch D. A stepwise thrombolysis regimen in the management of acute portal vein thrombosis in patients with evidence of intestinal ischaemia. *Aliment Pharmacol Ther* 2019; **50**: 1049-1058 [PMID: 31489698 DOI: 10.1111/apt.15479]
9 **Kumar S**, Sarr MG, Kamath PS. Mesenteric venous thrombosis. *N Engl J Med* 2001; **345**: 1683-1688 [PMID: 11759648 DOI: 10.1056/NEJMra010076]
10 **Wang L**, Guo X, Xu X, De Stefano V, Plessier A, Noronha Ferreira C, Qi X. Anticoagulation Favors Thrombus Recanalization and Survival in Patients With Liver Cirrhosis and Portal Vein Thrombosis: Results of a Meta-Analysis. *Adv Ther* 2021; **38**: 495-520 [PMID: 33155180 DOI: 10.1007/s12325-020-01550-4]

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LETTER TO THE EDITOR

Prediction factors for ischemia of closed-loop small intestinal obstruction

Efstathios Theodoros Pavlidis, Theodoros Efstathios Pavlidis

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Efstathios Theodoros Pavlidis, Theodoros Efstathios Pavlidis, The Second Propedeutic Department of Surgery, Hippocration Hospital, Aristotle University of Thessaloniki, School of Medicine, Thessaloniki 54642, Greece

Corresponding author: Theodoros Efstathios Pavlidis, Doctor, PhD, Chief Doctor, Full Professor, Surgeon, The Second Propedeutic Department of Surgery, Hippocration Hospital, Aristotle University of Thessaloniki, School of Medicine, Konstantinoupoleos 49, Thessaloniki 54642, Greece. pavlidth@auth.gr

Abstract

A closed-loop type of intestinal obstruction leads to ischemic necrosis. There have been indicators that may predict ischemia and its severity, such as biomarkers and computed tomography scans. In addition to the usual inflammation markers, such as white blood count-neutrophil count and c-reactive protein (CRP), the most accurate predictors that have been proposed are the CRP-to-albumin ratio, the neutrophil/lymphocyte ratio and the platelet/lymphocyte ratio. Endothelin 1 is another promising biomarker of ischemia that must be assessed in daily clinical practice. Advanced age and frailty status were assessed as predictors of mortality. A timely operative procedure without any delay ensures a better outcome.

Key Words: Acute abdomen; Obstructive ileus; Bowel ischemia; Closed loop; Predictive factors; Inflammatory markers

Core Tip: Early recognition of closed loops is important to interrupt ongoing ischemia by prompt surgical intervention, especially for older age patients. In such a case, we achieve avoidance of bowel necrosis and enterectomy as well as septic complications, which ultimately resulted in an improved outcome. Endothelin 1, c-reactive protein and leukocyte-neutrophil count must be more often used in daily practice as a severity marker of small bowel ischemia.

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TO THE EDITOR

It was very interesting to read the recent paper by Toneman *et al*[1]. We were pleased and enlightened by their excellent work. This retrospective trial included 148 patients who underwent surgery for suspected closed-loop small bowel obstruction; the sample size was adequate. After assessing several parameters, the authors concluded that older age and an American Society of Anesthesiologists score ≥ 3 were prediction factors of irreversible ischemia. We completely agree with their conclusions because their conclusions are reasonable in that both conditions are associated with an increased risk of reduced tissue blood supply. Thus, the manifestation and progression of intestinal ischemia is faster. Early surgical operation prevents necrosis that leads to bowel perforation causing severe peritonitis and subsequent severe sepsis. The topic is very interesting, and it prompts certain thoughts and observations.

Intestinal obstruction is a common clinical occurrence in the acute surgical setting, with an incidence ranging from 12% to 16%, and is a causative factor for morbidity and mortality worldwide (2%-8%). The most common causes of obstructive ileus of the small intestine are adhesions (60%-70%) and hernia incarceration (20%). The obstruction may be complete, partial, incarcerated or closed-loop type. Questions, such as whether there is an obstruction, where is it located, what is the cause, whether there is ischemia and which are the management choices? In addition to patient history, clinical examination, laboratory tests and plain abdominal radiogram, computed tomography (CT) is the gold standard, with a sensitivity and specificity up to 95%. CT findings include intestinal wall thickening (> 3 mm) and abnormal enhancement, edema of the mesentery, fluid in the mesentery and/or peritoneal cavity, dilatation of veins, a closed-loop obstruction or volvulus, and in advanced cases, intraperitoneal gas, mesenteric or even portal venous gas[2].

The term closed loop means obstruction of two parts of the intestinal loop at the same point, including the mesentery. The mucosa continues to produce secretions, causing distention and wall edema, followed by blood supply disturbances and ischemia. It is crucial to assess bowel viability during the operation. A pink, edematous and thickened bowel is at low risk for ischemia. Violaceous or cyanotic serosa should be kept warm and observed for 15 to 20 min. If perfusion is not improved and viability remains questionable, Doppler ultrasound or a fluorescein dye should be used to evaluate the blood supply[3].

There has been no preoperative finding of an ideal biomarker for predicting the outcome. C-reactive protein (CRP) is a useful biomarker that may predict the clinical course[4,5]. Levels higher than 50 mg/L indicate moderate inflammation and levels above 150 mg/L indicate potential necrosis. Nevertheless, clinicians should obtain CT scans of obstructive ileus; in such cases, imaging should be performed immediately without delay. However, the ratio of CRP to albumin (CRP/Alb) is the most accurate indicator for predicting the severity of inflammation and the outcome, as recently reported. Values of CRP/Alb > 1.32 have a sensitivity of 94% and specificity of 70% for intestinal ischemia[6]. Other markers, including L-lactate, D-dimers, white blood count, neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR), have no particular prognostic value[4,5,7]. Otherwise, in another study, NLR > 4.5 and PLR > 157 were independent predictors of outcome[8]. The univariate analysis showed that leukocyte and neutrophil counts were predictors of mortality, and the multivariate analysis showed that age was a predictor of mortality[7].

Endothelin 1 (ET-1) is a vasoconstrictive peptide derived from vessel endothelium that has been used as a biomarker of ischemic damage severity in experimental models[9-11] but also occasionally in clinical studies, in which it is increased in mesenteric ischemia[12,13]. ET-1 and CRP must be more often assessed in daily practice as markers of small bowel ischemia.

Other experimental biomarkers of ischemia include tumor necrosis factor-alpha, P-selectin, antithrombin III, and intracellular adhesion molecule-1[9]. Research is focused on these biomarkers and may indicate a future perspective. Treatment to avoid both an unnecessary operation and a missed diagnosis of bowel ischemia must be carefully decided. A prediction model has been introduced for the latter, indicating surgical management instead of conservative management. Surgical management is indicated for CT findings, including intraperitoneal free fluid, mesenteric edema and lack of small bowel feces signs, and a history of vomiting[14]. In conclusion, a closed-loop small intestinal obstruction must be excluded in the initial stage of an investigation. Acute phase proteins and cooperation between surgeons and radiologists is important, since a prompt operation ensures a better outcome.

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Country/Territory of origin: Greece

ORCID number: Efstathios Theodoros Pavlidis 0000-0002-7282-8101; Theodoros Efstathios Pavlidis 0000-0002-8141-1412.

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REFERENCES

1 **Toneman MK**, de Kok BM, Zijta FM, Oei S, van Acker GJD, Westerterp M, van der Pool AEM. Predicting the outcome of closed-loop small bowel obstruction by preoperative characteristics. *World J Gastrointest Surg* 2022; **14**: 556-566 [PMID: 35979424 DOI: 10.4240/wjgs.v14.i6.556]
2 **Paulson EK**, Thompson WM. Review of small-bowel obstruction: the diagnosis and when to worry. *Radiology* 2015; **275**: 332-342 [PMID: 25906301 DOI: 10.1148/radiol.15131519]
3 **Bower KL**, Lollar DI, Williams SL, Adkins FC, Luyimbazi DT, Bower CE. Small Bowel Obstruction. *Surg Clin North Am* 2018; **98**: 945-971 [PMID: 30243455 DOI: 10.1016/j.suc.2018.05.007]
4 **Destek S**, Yabacú A, Abik YN, Gól VO, Deπer KC. Predictive and prognostic value of L-lactate, D-dimer, leukocyte, C-reactive protein and neutrophil/Lymphocyte ratio in patients with acute mesenteric ischemia. *Ulus Travma Acil Cerrahi Derg* 2020; **26**: 86-94 [PMID: 31942740 DOI: 10.14744/tjtes.2019.61580]
5 **El-Awady SI**, El-Nagar M, El-Dakar M, Ragab M, Elnady G. Bacterial translocation in an experimental intestinal obstruction model. C-reactive protein reliability? *Acta Cir Bras* 2009; **24**: 98-106 [PMID: 19377777 DOI: 10.1590/s0102-86502009000200005]
6 **Kaηer é**, Haπlar A, Akúllú NB. The Prognostic Value of C-Reactive Protein/Albumin Ratio in Acute Mesenteric Ischemia. *Am Surg* 2022; 31348221074220 [PMID: 35073777 DOI: 10.1177/00031348221074220]
7 **Vural V**, Ozozan OV. The Usefulness of Inflammation-based Prognostic Scores for the Prediction of Postoperative Mortality in Patients Who Underwent Intestinal Resection for Acute Intestinal Ischemia. *Cureus* 2019; **11**: e6372 [PMID: 31886096 DOI: 10.7759/cureus.6372]
8 **Toptas M**, Akkoc é, Savas Y, Uzman S, Toptas Y, Can MM. Novel hematologic inflammatory parameters to predict acute mesenteric ischemia. *Blood Coagul Fibrinolysis* 2016; **27**: 127-130 [PMID: 26258672 DOI: 10.1097/MBC.0000000000000372]
9 **Guzmαn-de la Garza FJ**, Cαmara-Lemarroy CR, Alarcσn-Galvαn G, Cordero-Pιrez P, Muρoz-Espinosa LE, Fernαndez-Garza NE. Different patterns of intestinal response to injury after arterial, venous or arteriovenous occlusion in rats. *World J Gastroenterol* 2009; **15**: 3901-3907 [PMID: 19701970 DOI: 10.3748/wjg.15.3901]
10 **Pavlidis ET**, Ballas KD, Symeonidis NG, Psarras K, Koliakos G, Kouzi-Koliakos K, Topouridou K, Rafailidis SF, Pavlidis TE, Marakis GN, Sakantamis AK. The effect of bevacizumab on colon anastomotic healing in rats. *Int J Colorectal Dis* 2010; **25**: 1465-1473 [PMID: 20689957 DOI: 10.1007/s00384-010-1039-x]
11 **Irces D**, Nσgrαdy M, Varga G, Szücs S, Mιszαros AT, Fischer-Szatmαri T, Cao C, Okada N, Okada H, Boros M, Kaszaki J. Complement C5a inhibition improves late hemodynamic and inflammatory changes in a rat model of nonocclusive mesenteric ischemia. *Surgery* 2016; **159**: 960-971 [PMID: 26632492 DOI: 10.1016/j.surg.2015.10.020]
12 **Watkins DJ**, Besner GE. The role of the intestinal microcirculation in necrotizing enterocolitis. *Semin Pediatr Surg* 2013; **22**: 83-87 [PMID: 23611611 DOI: 10.1053/j.sempedsurg.2013.01.004]
13 **Groesdonk HV**, Raffel M, Speer T, Bomberg H, Schmied W, Klingele M, Schδfers HJ. Elevated endothelin-1 Level is a risk factor for nonocclusive mesenteric ischemia. *J Thorac Cardiovasc Surg* 2015; **149**: 1436-42.e2 [PMID: 25623906 DOI: 10.1016/j.jtcvs.2014.12.019]
14 **Zielinski MD**, Eiken PW, Bannon MP, Heller SF, Lohse CM, Huebner M, Sarr MG. Small bowel obstruction-who needs an operation? *World J Surg* 2010; **34**: 910-919 [PMID: 20217412 DOI: 10.1007/s00268-010-0479-3]

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