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EDITORIAL

Has the open surgical approach in colorectal cancer really become uncommon?

Maria Cariati, Giuseppe Brisinda, Maria Michela Chiarello

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Abstract

Colorectal cancer is the third most common cancer in the world. Surgery is mandatory to treat patients with colorectal cancer. Can colorectal cancer be treated in laparoscopy? Scientific literature has validated the oncological quality of laparoscopic approach for the treatment of patients with colorectal cancer. Randomized non-inferiority trials with good remote control have answered positively to this long-debated question. Early as 1994, first publications demonstrated technical feasibility and compliance with oncological imperatives and, as far as short-term outcomes are concerned, there is no difference in terms of mortality and post-operative morbidity between open and minimally invasive surgical approaches, but only longer operating times at the beginning of the experience. Subsequently, from 2007 onwards, long-term results were published that demonstrated the absence of a significant difference regarding overall survival, disease-free survival, quality of life, local and distant recurrence rates between open and minimally invasive surgery. In this editorial, we aim to summarize the clinical and technical aspects which, even today, make the use of open surgery relevant and necessary in the treatment of patients with colorectal cancer.

Key Words: Colorectal cancer; Laparoscopy; Laparoscopic colorectal resection; Bowel obstruction; Bowel perforation; Advanced colorectal cancer

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Core Tip: In terms of oncological outcomes and quality of resection, laparoscopic approach allows to do just as well as open surgery, in particular the number of the lymph nodes removed is identical, regardless of the access. However, the laparoscopic approach is not recommended when the neoplasm presents with urgency, in the occlusive or perforated phase, as well as it is not recommended for locally advanced tumors. When the tumor involved the serosal layer or invades an adjacent organ, open "*en-bloc*" excision is recommended.

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INTRODUCTION

Colorectal cancer is the third most common cancer in the world. In 2019, new cases of colorectal cancer in the world were 1931590, corresponding to 10% of new cancer diagnoses, and is responsible for approximately 750000 cancer-related deaths annually[1]; in Italy there are estimated around 51000 cases/year, representing overall the 15% of new cancer diagnoses[2]. Surgery is mandatory to treat patients with colorectal cancer. In the case of primary non-metastatic disease, surgery guarantees a better long-term prognosis, both in terms of overall survival, disease-free survival and patient quality of life[3-5].

Curative resection aims to radically remove the segment of intestine in which the tumor is located. The resection must include at least 5 cm of healthy colon upstream and downstream of the lesion[6,7]. Furthermore, lymphadenectomy is fundamental for a systematic lymph node dissection and for removing all potentially metastatic lymph nodes[8-11]. International guidelines have established that a number equal or greater than 12 lymph nodes must be removed to guarantee an adequate lymphadenectomy and, at the same time, the possibility of staging the neoplastic disease more accurately[9,10,12]. It is therefore established as an oncologically appropriate resection influences the prognosis of patients with colorectal cancer.

In recent decades, the traditional surgical approach *via* laparotomy and direct access to the patient's abdominal cavity has been joined by new minimally invasive surgical techniques. Laparoscopic surgery has now been validated through large randomized controlled studies conducted throughout the world. In this editorial, we aim to summarize the clinical and technical aspects which, even today, make the use of laparotomy relevant and necessary in the treatment of patients with colorectal cancer.

LAPAROSCOPIC TREATMENT

Laparoscopic surgery in colorectal cancer represents a correct alternative to open surgery, if performed by surgeons with adequate training in this specific procedure[13]. Even in laparoscopic surgery the proximal and distal resection margins are appropriate and proximal vessel ligation is performed safely. Curative resections are therefore obtained, with *en-bloc* removals and tumor-free radial margins (R0)[14].

The United Kingdom Medical Research Counsel (MRC) trial of conventional *vs* laparoscopic assisted surgery in colorectal cancer, published in 2005, which included patients with both colon and rectal cancer was the first randomized controlled trial to investigate the role of laparoscopy in colorectal cancer[15]. After this trial there were four subsequent randomized controlled trials comparing laparoscopy to open surgery in colorectal cancer. All these studies - the Comparison of Open *vs* Laparoscopic Surgery for Mid and Low Rectal Cancer After Neoadjuvant Chemoradiotherapy[16], the Colorectal Cancer Laparoscopic or Open (COLOR II)[17], the American College of Surgeons Oncology Group Z6051[18], and the Australasian Laparoscopic Cancer of the Rectum Randomized Clinical Trial (ALaCart)[19] - were designed to assess the non-inferiority of laparoscopic surgery compared to open surgery. In all these studies, patients with T4 tumors were excluded from inclusion. The COLOR II study also excluded T3 tumors within 2 mm of the endopelvic fascia. The laparoscopic approach was associated with longer operative times, lower estimated blood loss, and faster recovery of bowel function in all of these studies. These randomized trials evaluating the oncologic outcomes of laparoscopic colectomy showed no significant differences in proximal and distal margins, number of lymph nodes retrieved, and perpendicular length of the primary vascular pedicle compared with open surgery[14,15,17,20-22]. Furthermore, long-term survival and recurrence were no different for patients treated with open and laparoscopic surgery in these studies[15,21,23,24].

Recently, the short-term results of a multicenter prospective randomized trial conducted in China comparing laparoscopic and open resection have been published[20]. The Laparoscopy-Assisted Surgery for Carcinoma of the Low Rectum study was conducted on a population of over 1000 patients. Specifically, 685 patients in the laparoscopic surgery group and 350 patients in the open surgery group were included. No significant differences in morbidity rate were observed between the two groups. Higher rates of sphincter preservation and shorter length of stay were observed in patients undergoing laparoscopic surgery.

Extraperitoneal rectal carcinoma presents peculiar aspects. While the approach to carcinoma of high rectum does not differ from that of the recto-sigmoid junction and the sigmoid carcinoma, surgery of the mid-lower rectum presents technical difficulties that are best managed in high-volume specialist centers. The cornerstones of this surgery concern the total excision of the mesorectum (Figure 1), the preservation of the sympathetic and parasympathetic innervation (nerve-sparing technique), the distal and circumferential section margin free from neoplasia and, in locally advanced forms (T3-T4 and/or regional lymph node metastases) the use of neoadjuvant therapies. In these patients, laparoscopic total mesorectal excision can be performed safely and adequately as demonstrated in prospective studies and retrospective series [25-29]. Mid and long-term oncological outcomes appear similar between open and laparoscopic approaches[30]. We can therefore conclude that oncologic results of the laparoscopic surgery for rectal cancer are generally comparable to open surgery. Currently, the results reported by numerous studies in the literature highlight that laparoscopic surgery is the therapeutic option of choice for the surgical treatment of rectal cancer.

THE ROLE OF OPEN SURGERY

In colorectal cancer patients, laparoscopic surgery has some controversial aspects. A learning curve appears fundamental in the laparoscopic field. Both the surgeon and the operating room auxiliary staff are required to acquire advanced laparoscopic skills in well-defined time intervals[31,32]. Laparoscopic surgery is very demanding, and can be performed with low morbidity and mortality rates only by a surgeon with above-average experience with this type of surgery and a large caseload of laparoscopic colorectal procedures. The learning curve for such procedures is appreciably longer than for other laparoscopic operations. With increasing experience, technically more demanding operations, including radical oncologic rectal laparoscopic procedures, can be performed with appreciably reduced operating times and conversion rates, but with no increase in morbidity or mortality. At least 20 laparoscopic procedures for colon cancer are required for the individual surgeon to be included in multicenter clinical trials. Studies more carefully examining the learning curve for laparoscopic colectomy have suggested that full surgical autonomy and competence is acquired with at least 50 colorectal resection procedures in a defined time interval[31-33]. Advanced laparoscopic training during residency or fellowship and training on simulators may shorten the learning curve toward proficiency. Mentoring, proctoring, and working with an experienced assistant have each been shown effective in the adoption of techniques new to a surgeon's skill set[34-37].

Furthermore, aspects of laparoscopic surgery have raised some initial concerns in the scientific community. The risk of a potential violation of oncological principles, the possible spread of neoplastic cells linked to carbon dioxide insufflation and the possibility of tumor recurrence in the access sites of the trocars have represented some of the controversial aspects [38,39]. However, it seems right to emphasize that these fears and these controversial aspects were found to be completely unjustified, both by evaluating some aspects of basic scientific research and by analyzing the results of large randomized and controlled studies.

T4 tumors show an incidence of up to 15% in patients with colon cancer. Among patients with rectal cancer, 5% to 12% of patients have tumors adherent to adjacent organs[40-42]. In these patients, is recommended *en-bloc* resection to manage locally advanced colorectal cancer[43,44]. Thus is T4 colorectal cancer still an absolute contraindication to laparoscopic surgery? The answer is that T4 colon cancer is not an absolute contraindication. Obviously, the possibility of treating T4 colorectal cancer laparoscopically depends on local circumstances (*e.g.*, organs involved in the enlarged demolition and factors related to the surgeon (*e.g.*, skill and experience of the individual surgeon in performing a laparoscopic *en-bloc* resection). Intraoperative observation of a T4 lesion often requires conversion to open surgery, especially if the goal of the therapeutic approach is curative resection. This eventuality is necessary because *en-bloc* demolition in the presence of a T4 lesion is not always effective in laparoscopic surgery. However, *en-bloc* resection may not be possible using either technique or, therefore, the surgeon must decide whether conversion is likely to allow curative resection. To date, there have been no randomized trials comparing laparoscopic and open approaches to T4 colonic or rectal cancers.

In the UK MRC-CLASSIC trial, 34% of the patients randomized to the laparoscopic group underwent conversion to an open procedure. In this group of patients, a higher post-operative morbidity rate ($P = 0.002$) and a worsened overall survival have been observed[45,46]. Furthermore, in patients undergoing laparoscopic low anterior resection or abdominoperineal resection (Figure 2), there was a higher rate of positive circumferential margins, although this did not impact local recurrence or survival[47]. Overall, male sexual and erectile function was worse in the laparoscopic group[46].

In rectal cancer, when using the minimally invasive approach, particularly for tumors in low rectum, a further challenge is represented by the anatomical conformation of the pelvis. Elements that can hinder the execution of an oncological adequate resection for rectal cancer laparoscopically are the size and location of the tumor. Additional clinical-anatomical factors such as narrow pelvis, obesity, large uterus and preoperative radiation effects are of particular importance. The inability to conduct demolition in accordance with oncological principles should lead to conversion to open surgery. Similar considerations must guide the choice of the type of colorectal anastomosis or the creation of a temporary or permanent stoma.

Complications of large bowel diseases account for 47% of gastrointestinal emergencies. Colorectal cancer presents as emergency in a wide range of patients (from 7% to 40% of the total). Large bowel obstruction represents almost 80% of the emergencies related to colorectal cancer, while perforation accounts for the remaining 20%. The most common location of bowel obstruction is the sigmoid colon, with 75% of the tumors located distal to the splenic flexure. Perforation occurs at the tumor site in almost 70% of cases and proximal to the tumor site in around 30% of cases[48]. The management of colon and rectal obstruction and perforation is challenging in terms of clinical severity, diagnostic and therapeutic options, and management of septic (Figure 3) and oncological issues. As a general rule, the principles of



Figure 1 Surgical specimen of anterior resection of the rectum with complete removal of the mesorectum (personal observations).

oncological resection should be followed. It should be emphasized that in these conditions it is important to consider the role of medical comorbidities, sarcopenia and local or systemic septic status. Even in these patients, the main objective is to optimize the postoperative course, avoiding and preventing complications, especially anastomotic leakage, to allow the completion of oncological staging and the start of integrated chemotherapy and/or radiotherapy treatments[48].

In case of colonic obstruction due to tumor of the right colon or proximal transverse colon, right hemicolectomy, classic or extended, with subsequent primary ileocolic anastomosis represents the most appropriate treatment. The general condition of the patient strongly affects the choice to perform an anastomosis. The patient's condition, including hemodynamic stability, the extent of abdominal distention, the resectability of the carcinoma and the surgeon's ability to perform a curative resection represent the elements that must be taken into consideration when choosing a possible laparoscopic approach in the presence of an occlusive colorectal carcinoma[49]. Although there have been some retrospective studies demonstrating feasibility of laparoscopic resection with benefits in short-term outcomes, a prospective randomized controlled trial has not yet been published[50-52].

In case of obstructing cancer of the left colon, a variety of options have been advocated[53]. Resection and primary anastomosis, with or without protective stoma, resection according to Hartmann, intraabdominal subtotal colectomy with ileostomy or ileorectal anastomosis are the most frequently used procedures. More recently, endoscopically placed colonic stents are used in selected patients. These endoscopic procedures, allowing the decompression of the colon and favoring the clinical stabilization of the patient, allow urgent surgery to be postponed and elective colectomies with primary anastomosis to be performed in a re-balanced patient. In this way, such an approach allows the decrease in colostomy creation rates in patients with occluding cancer of the left colon.

The use of laparoscopy in the emergency treatment of colorectal cancer cannot be recommended and should be reserved to selected favorable cases and in specialized centers[54]. Emergency presentation has been considered an absolute contraindication to laparoscopy, due to the profile of the patient at high septic risk and the level of technical operative difficulties due to the dilated and vulnerable intestine. However, with the spread of colorectal laparoscopy and the increase in experience, favorable results have been published[55], but no randomized trials.

Risk factors for conversion for different populations have been widely reported in the literature. A recent meta-analysis documented an average conversion rate of 17.9%. An evaluation of the factors that negatively influence the completion of the laparoscopic surgical procedure has shown that the factors that are most responsible for the conversion to open surgery are male sex, a tumor localized in the extraperitoneal rectum, the T3/T4 stage and the presence of metastases to locoregional lymph nodes[56]. With increasing laparoscopic hospital volume, conversion decreases below 10% with only

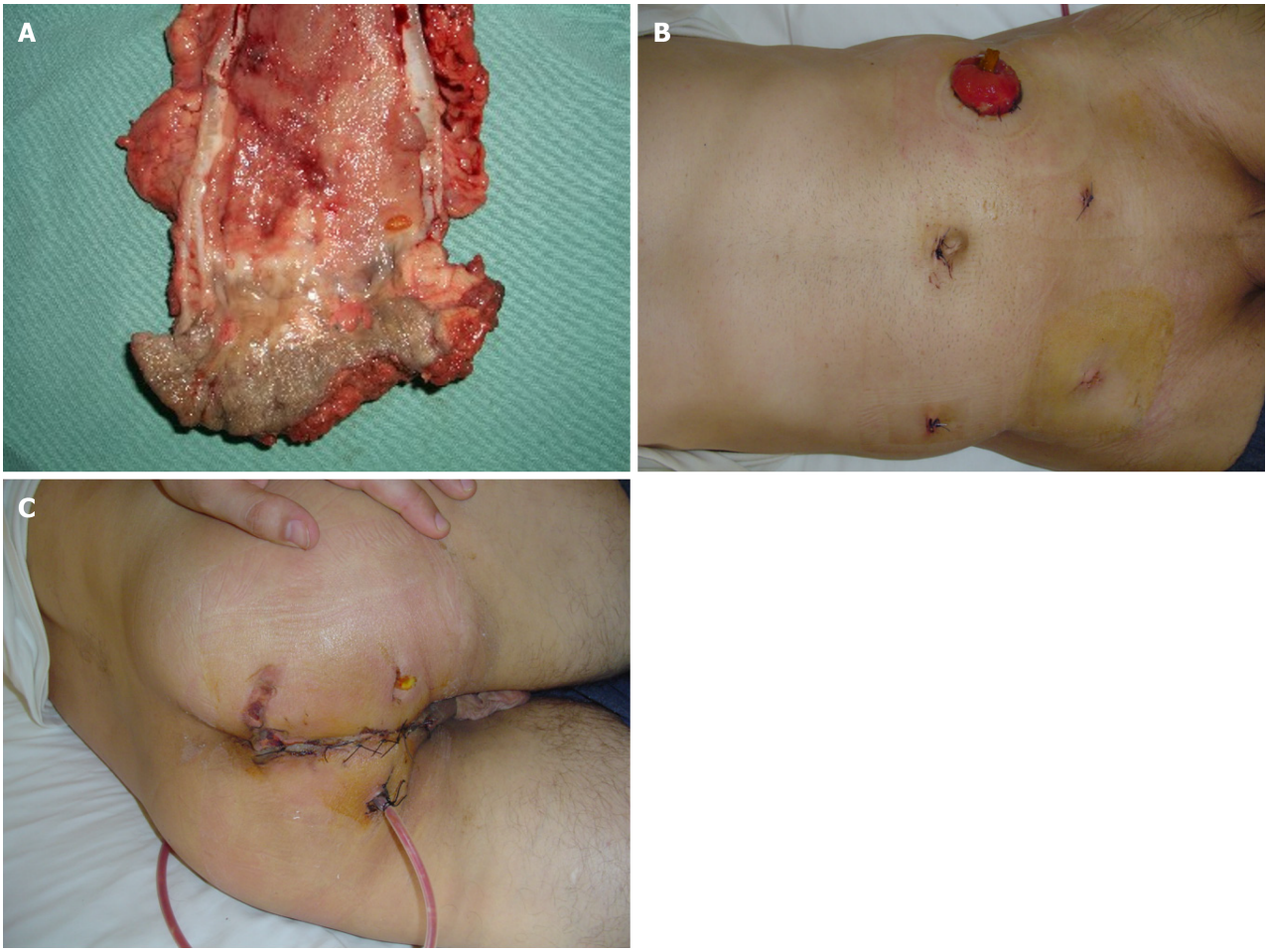


Figure 2 Clinical case of adenocarcinoma of the low rectum treated with laparoscopic abdominoperineal resection sec. Miles after neoadjuvant treatment. A: Surgical specimen of abdominoperineal resection; B: Photo of the abdomen; C: Perineal wound (personal observations).

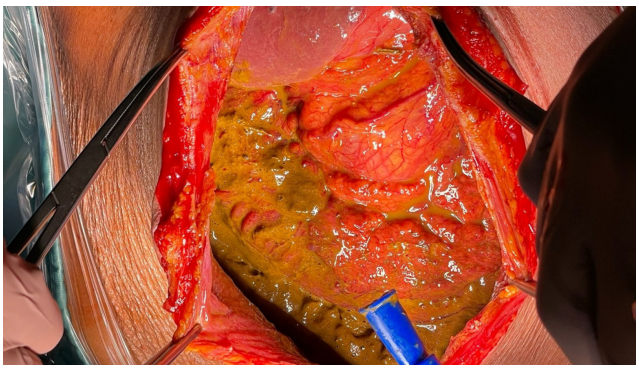


Figure 3 Intraoperative photo of diffuse fecal peritonitis due to perforation of the cecum in a patient with neoplastic stenosis of the sigmoid colon (personal observations).

minimal impact of conversion on short-term postoperative outcome. To perform an early conversion can be an appropriate decision, for which reason this type of conversion should not be considered a failure[57-59].

CONCLUSION

Laparoscopy is a safe and effective surgical technique for the treatment of colorectal cancer. Laparoscopy remains an acceptable minimally invasive option in well trained hands. Surgeon represents a significant prognostic factor: His operative volume and that of the team with which he works is linked to surgical mortality, peri-operative complications and prognosis. Locally advanced disease and emergency presentation are relative contraindications to the laparoscopic

approach. Highly predictive factors of conversion are the lower and left site of the tumor, obesity as well as previous major abdominal surgery.

Laparoscopic surgery for low rectal cancer, when performed by experienced surgeons, could produce pathological outcomes comparable to those of open surgery. In large surgical series and multicenter studies, no differences are observed regarding complete excision of the mesorectum and the appropriateness of the resection margins. In the population of patients undergoing laparoscopic demolition, a higher rate of sphincter preservation and a favorable postoperative recovery are documented. While no differences in short-term oncological outcomes have been observed, long-term oncological outcomes in homogeneous patient populations are currently being evaluated.

FOOTNOTES

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REFERENCES

1 **Morgan E**, Arnold M, Gini A, Lorenzoni V, Cabasag CJ, Laversanne M, Vignat J, Ferlay J, Murphy N, Bray F. Global burden of colorectal cancer in 2020 and 2040: incidence and mortality estimates from GLOBOCAN. *Gut* 2023; **72**: 338-344 [PMID: 36604116 DOI: 10.1136/gutjnl-2022-327736]

2 **AIOM**. I numeri del cancro in Italia 2023. Roma: Intermedia Editore, 2023

3 **Angenete E**. The importance of surgery in colorectal cancer treatment. *Lancet Oncol* 2019; **20**: 6-7 [PMID: 30545751 DOI: 10.1016/S1470-2045(18)30679-X]

4 **Sartori CA**, D'Annibale A, Cutini G, Senargiotto C, D'Antonio D, Dal Pozzo A, Fiorino M, Gagliardi G, Franzato B, Romano G. Laparoscopic surgery for colorectal cancer: clinical practice guidelines of the Italian Society of Colo-Rectal Surgery. *Tech Coloproctol* 2007; **11**: 97-104 [PMID: 17510740 DOI: 10.1007/s10151-007-0345-y]

5 **Green CJ**, Maxwell R, Verne J, Martin RM, Blazeby JM. The influence of NICE guidance on the uptake of laparoscopic surgery for colorectal cancer. *J Public Health (Oxf)* 2009; **31**: 541-545 [PMID: 19321518 DOI: 10.1093/pubmed/fdp027]

6 **Levine RA**, Chawla B, Bergeron S, Wasvary H. Multidisciplinary management of colorectal cancer enhances access to multimodal therapy and compliance with National Comprehensive Cancer Network (NCCN) guidelines. *Int J Colorectal Dis* 2012; **27**: 1531-1538 [PMID: 22645076 DOI: 10.1007/s00384-012-1501-z]

7 **You YN**, Hardiman KM, Bafford A, Poylin V, Francone TD, Davis K, Paquette IM, Steele SR, Feingold DL; On Behalf of the Clinical Practice Guidelines Committee of the American Society of Colon and Rectal Surgeons. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Rectal Cancer. *Dis Colon Rectum* 2020; **63**: 1191-1222 [PMID: 33216491 DOI: 10.1097/DCR.0000000000001762]

8 **Wood TF**, Saha S, Morton DL, Tsioulias GJ, Rangel D, Hutchinson W Jr, Foshag LJ, Bilchik AJ. Validation of lymphatic mapping in colorectal cancer: in vivo, ex vivo, and laparoscopic techniques. *Ann Surg Oncol* 2001; **8**: 150-157 [PMID: 11258780 DOI: 10.1007/s10434-001-0150-1]

9 **Bilchik AJ**, Trocha SD. Lymphatic mapping and sentinel node analysis to optimize laparoscopic resection and staging of colorectal cancer: an update. *Cancer Control* 2003; **10**: 219-223 [PMID: 12794620 DOI: 10.1177/107327480301000305]

10 **Wu Z**, Zhang S, Aung LH, Ouyang J, Wei L. Lymph node harvested in laparoscopic versus open colorectal cancer approaches: a meta-analysis. *Surg Laparosc Endosc Percutan Tech* 2012; **22**: 5-11 [PMID: 22318051 DOI: 10.1097/SLE.0b013e3182432b49]

11 **Yeung TM**, Wang LM, Colling R, Kraus R, Cahill R, Hompes R, Mortensen NJ. Intraoperative identification and analysis of lymph nodes at laparoscopic colorectal cancer surgery using fluorescence imaging combined with rapid OSNA pathological assessment. *Surg Endosc* 2018; **32**: 1073-1076 [PMID: 28643063 DOI: 10.1007/s00464-017-5644-4]

12 **Lykke J**, Jess P, Roikjær O; Danish Colorectal Cancer Group. A high lymph node yield in colon cancer is associated with age, tumour stage, tumour sub-site and priority of surgery. Results from a prospective national cohort study. *Int J Colorectal Dis* 2016; **31**: 1299-1305 [PMID: 27220610 DOI: 10.1007/s00384-016-2599-1]

13 **Liang Y**, Li G, Chen P, Yu J. Laparoscopic versus open colorectal resection for cancer: a meta-analysis of results of randomized controlled trials on recurrence. *Eur J Surg Oncol* 2008; **34**: 1217-1224 [PMID: 18155389 DOI: 10.1016/j.ejso.2007.11.004]

14 **Bonjer HJ**, Hop WC, Nelson H, Sargent DJ, Lacy AM, Castells A, Guillou PJ, Thorpe H, Brown J, Delgado S, Kuhrij E, Haglind E, Påhlman

L; Transatlantic Laparoscopically Assisted vs Open Colectomy Trials Study Group. Laparoscopically assisted vs open colectomy for colon cancer: a meta-analysis. *Arch Surg* 2007; **142**: 298-303 [PMID: 17372057 DOI: 10.1001/archsurg.142.3.298]

15 **Guillou PJ**, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM; MRC CLASICC trial group. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet* 2005; **365**: 1718-1726 [PMID: 15894098 DOI: 10.1016/S0140-6736(05)66545-2]

16 **Kang SB**, Park JW, Jeong SY, Nam BH, Choi HS, Kim DW, Lim SB, Lee TG, Kim DY, Kim JS, Chang HJ, Lee HS, Kim SY, Jung KH, Hong YS, Kim JH, Sohn DK, Kim DH, Oh JH. Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): short-term outcomes of an open-label randomised controlled trial. *Lancet Oncol* 2010; **11**: 637-645 [PMID: 20610322 DOI: 10.1016/S1470-2045(10)70131-5]

17 **van der Pas MH**, Haglind E, Cuesta MA, Fürst A, Lacy AM, Hop WC, Bonjer HJ; COlorectal cancer Laparoscopic or Open Resection II (COLOR II) Study Group. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. *Lancet Oncol* 2013; **14**: 210-218 [PMID: 23395398 DOI: 10.1016/S1470-2045(13)70016-0]

18 **Fleshman J**, Branda M, Sargent DJ, Boller AM, George V, Abbas M, Peters WR Jr, Maun D, Chang G, Herline A, Fichera A, Mutch M, Wexner S, Whiteford M, Marks J, Birnbaum E, Margolin D, Larson D, Marcello P, Posner M, Read T, Monson J, Wren SM, Pisters PW, Nelson H. Effect of Laparoscopic-Assisted Resection vs Open Resection of Stage II or III Rectal Cancer on Pathologic Outcomes: The ACOSOG Z6051 Randomized Clinical Trial. *JAMA* 2015; **314**: 1346-1355 [PMID: 26441179 DOI: 10.1001/jama.2015.10529]

19 **Stevenson AR**, Solomon MJ, Lumley JW, Hewett P, Clouston AD, Gebski VJ, Davies L, Wilson K, Hague W, Simes J; ALaCaRT Investigators. Effect of Laparoscopic-Assisted Resection vs Open Resection on Pathological Outcomes in Rectal Cancer: The ALaCaRT Randomized Clinical Trial. *JAMA* 2015; **314**: 1356-1363 [PMID: 26441180 DOI: 10.1001/jama.2015.12009]

20 **Jiang WZ**, Xu JM, Xing JD, Qiu HZ, Wang ZQ, Kang L, Deng HJ, Chen WP, Zhang QT, Du XH, Yang CK, Guo YC, Zhong M, Ye K, You J, Xu DB, Li XX, Xiong ZG, Tao KX, Ding KF, Zang WD, Feng Y, Pan ZZ, Wu AW, Huang F, Huang Y, Wei Y, Su XQ, Chi P; LASRE trial investigators. Short-term Outcomes of Laparoscopy-Assisted vs Open Surgery for Patients With Low Rectal Cancer: The LASRE Randomized Clinical Trial. *JAMA Oncol* 2022; **8**: 1607-1615 [PMID: 36107416 DOI: 10.1001/jamaoncol.2022.4079]

21 **Bonjer HJ**, Deijen CL, Abis GA, Cuesta MA, van der Pas MH, de Lange-de Klerk ES, Lacy AM, Bemelman WA, Andersson J, Angenete E, Rosenberg J, Fuerst A, Haglind E; COLOR II Study Group. A randomized trial of laparoscopic versus open surgery for rectal cancer. *N Engl J Med* 2015; **372**: 1324-1332 [PMID: 25830422 DOI: 10.1056/NEJMoa1414882]

22 **Lacy AM**, García-Valdecasas JC, Delgado S, Castells A, Taurá P, Piqué JM, Visa J. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. *Lancet* 2002; **359**: 2224-2229 [PMID: 12103285 DOI: 10.1016/S0140-6736(02)09290-5]

23 **Hewett PJ**, Allardyce RA, Bagshaw PF, Frampton CM, Frizelle FA, Rieger NA, Smith JS, Solomon MJ, Stephens JH, Stevenson AR. Short-term outcomes of the Australasian randomized clinical study comparing laparoscopic and conventional open surgical treatments for colon cancer: the ALCCaS trial. *Ann Surg* 2008; **248**: 728-738 [PMID: 18948799 DOI: 10.1097/SLA.0b013e31818b7595]

24 **Veldkamp R**, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, Haglind E, Påhlman L, Cuesta MA, Msika S, Morino M, Lacy AM; COlon cancer Laparoscopic or Open Resection Study Group (COLOR). Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. *Lancet Oncol* 2005; **6**: 477-484 [PMID: 15992696 DOI: 10.1016/S1470-2045(05)70221-7]

25 **Tjandra JJ**, Chan MK, Yeh CH. Laparoscopic- vs. hand-assisted ultralow anterior resection: a prospective study. *Dis Colon Rectum* 2008; **51**: 26-31 [PMID: 18085339 DOI: 10.1007/s10350-007-9107-1]

26 **Morino M**, Parini U, Giraudo G, Salval M, Brachet Contul R, Garrone C. Laparoscopic total mesorectal excision: a consecutive series of 100 patients. *Ann Surg* 2003; **237**: 335-342 [PMID: 12616116 DOI: 10.1097/01.SLA.0000055270.48242.D2]

27 **Cheung HY**, Chung CC, Wong JC, Yau KK, Li MK. Laparoscopic rectal cancer surgery with and without neoadjuvant chemo-irradiation: a comparative study. *Surg Endosc* 2009; **23**: 147-152 [PMID: 18802735 DOI: 10.1007/s00464-008-0081-z]

28 **Hasegawa H**, Ishii Y, Nishibori H, Endo T, Watanabe M, Kitajima M. Short- and midterm outcomes of laparoscopic surgery compared for 131 patients with rectal and rectosigmoid cancer. *Surg Endosc* 2007; **21**: 920-924 [PMID: 17285382 DOI: 10.1007/s00464-006-9132-5]

29 **Miyajima N**, Fukunaga M, Hasegawa H, Tanaka J, Okuda J, Watanabe M; Japan Society of Laparoscopic Colorectal Surgery. Results of a multicenter study of 1,057 cases of rectal cancer treated by laparoscopic surgery. *Surg Endosc* 2009; **23**: 113-118 [PMID: 18802736 DOI: 10.1007/s00464-008-0078-7]

30 **Franks PJ**, Bosanquet N, Thorpe H, Brown JM, Copeland J, Smith AM, Quirke P, Guillou PJ; CLASICC trial participants. Short-term costs of conventional vs laparoscopic assisted surgery in patients with colorectal cancer (MRC CLASICC trial). *Br J Cancer* 2006; **95**: 6-12 [PMID: 16755298 DOI: 10.1038/sj.bjc.6603203]

31 **Marusch F**, Gastinger I, Schneider C, Scheidbach H, Konradt J, Bruch HP, Köhler L, Bärlehner E, Köckerling F; Laparoscopic Colorectal Surgery Study Group (LCSSG). Experience as a factor influencing the indications for laparoscopic colorectal surgery and the results. *Surg Endosc* 2001; **15**: 116-120 [PMID: 11285950 DOI: 10.1007/s004640000340]

32 **Schlachta CM**, Mamazza J, Grégoire R, Burpee SE, Pace KT, Poulin EC. Predicting conversion in laparoscopic colorectal surgery. Fellowship training may be an advantage. *Surg Endosc* 2003; **17**: 1288-1291 [PMID: 12739116 DOI: 10.1007/s00464-002-8920-9]

33 **Schlachta CM**, Mamazza J, Seshadri PA, Cadeddu M, Gregoire R, Poulin EC. Defining a learning curve for laparoscopic colorectal resections. *Dis Colon Rectum* 2001; **44**: 217-222 [PMID: 11227938 DOI: 10.1007/BF02234296]

34 **Künzli BM**, Friess H, Shrikhande SV. Is laparoscopic colorectal cancer surgery equal to open surgery? An evidence based perspective. *World J Gastrointest Surg* 2010; **2**: 101-108 [PMID: 21160858 DOI: 10.4240/wjgs.v2.i4.101]

35 **Arteaga González I**, Díaz Luis H, Martín Malagón A, López-Tomassetti Fernández EM, Arranz Duran J, Carrillo Pallares A. A comparative clinical study of short-term results of laparoscopic surgery for rectal cancer during the learning curve. *Int J Colorectal Dis* 2006; **21**: 590-595 [PMID: 16292517 DOI: 10.1007/s00384-005-0057-6]

36 **Akiyoshi T**, Kuroyanagi H, Ueno M, Oya M, Fujimoto Y, Konishi T, Yamaguchi T. Learning curve for standardized laparoscopic surgery for colorectal cancer under supervision: a single-center experience. *Surg Endosc* 2011; **25**: 1409-1414 [PMID: 20953880 DOI: 10.1007/s00464-010-1404-4]

37 **Chen G**, Liu Z, Han P, Li JW, Cui BB. The learning curve for the laparoscopic approach for colorectal cancer: a single institution's experience. *J Laparoendosc Adv Surg Tech A* 2013; **23**: 17-21 [PMID: 23317439 DOI: 10.1089/lap.2011.0540]

38 **Berends FJ**, Kazemier G, Bonjer HJ, Lange JF. Subcutaneous metastases after laparoscopic colectomy. *Lancet* 1994; **344**: 58 [PMID: 7912321 DOI: 10.1016/s0140-6736(94)91079-0]

39 **Martel G**, Crawford A, Barkun JS, Boushey RP, Ramsay CR, Fergusson DA. Expert opinion on laparoscopic surgery for colorectal cancer

parallels evidence from a cumulative meta-analysis of randomized controlled trials. *PLoS One* 2012; **7**: e35292 [PMID: 22532846 DOI: 10.1371/journal.pone.0035292]

40 **Ng DC**, Co CS, Cheung HY, Chung CC, Li MK. The outcome of laparoscopic colorectal resection in T4 cancer. *Colorectal Dis* 2011; **13**: e349-e352 [PMID: 21689365 DOI: 10.1111/j.1463-1318.2011.02698.x]

41 **Bretagnol F**, Dedieu A, Zappa M, Guedj N, Ferron M, Panis Y. T4 colorectal cancer: is laparoscopic resection contraindicated? *Colorectal Dis* 2011; **13**: 138-143 [PMID: 20653697 DOI: 10.1111/j.1463-1318.2010.02380.x]

42 **Kim IY**, Kim BR, Kim HS, Kim YW. Differences in clinical features between laparoscopy and open resection for primary tumor in patients with stage IV colorectal cancer. *Onco Targets Ther* 2015; **8**: 3441-3448 [PMID: 26640384 DOI: 10.2147/OTT.S93420]

43 **Sugarbaker PH**. Revised guidelines for second-look surgery in patients with colon and rectal cancer. *Clin Transl Oncol* 2010; **12**: 621-628 [PMID: 20851803 DOI: 10.1007/s12094-010-0567-8]

44 **Turaga K**, Levine E, Barone R, Sticca R, Petrelli N, Lambert L, Nash G, Morse M, Adbel-Misih R, Alexander HR, Attiyeh F, Bartlett D, Bastidas A, Blazer T, Chu Q, Chung K, Dominguez-Parra L, Espat NJ, Foster J, Fournier K, Garcia R, Goodman M, Hanna N, Harrison L, Hoefer R, Holtzman M, Kane J, Labow D, Li B, Lowy A, Mansfield P, Ong E, Pameijer C, Pingpank J, Quinones M, Royal R, Salti G, Sardi A, Shen P, Skitzki J, Spellman J, Stewart J, Esquivel J. Consensus guidelines from The American Society of Peritoneal Surface Malignancies on standardizing the delivery of hyperthermic intraperitoneal chemotherapy (HIPEC) in colorectal cancer patients in the United States. *Ann Surg Oncol* 2014; **21**: 1501-1505 [PMID: 23793364 DOI: 10.1245/s10434-013-3061-z]

45 **Jayne DG**, Guillou PJ, Thorpe H, Quirke P, Copeland J, Smith AM, Heath RM, Brown JM; UK MRC CLASICC Trial Group. Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. *J Clin Oncol* 2007; **25**: 3061-3068 [PMID: 17634484 DOI: 10.1200/JCO.2006.09.7758]

46 **Jayne DG**, Thorpe HC, Copeland J, Quirke P, Brown JM, Guillou PJ. Five-year follow-up of the Medical Research Council CLASICC trial of laparoscopically assisted versus open surgery for colorectal cancer. *Br J Surg* 2010; **97**: 1638-1645 [PMID: 20629110 DOI: 10.1002/bjs.7160]

47 **Sawyer MA**, Sawyer EM. Controversies in laparoscopic surgery for colorectal cancer. *Curr Surg* 2004; **61**: 334-341 [PMID: 15276336 DOI: 10.1016/j.cursur.2004.01.013]

48 **Pisano M**, Zorcolo L, Merli C, Cimbanassi S, Poiasina E, Ceresoli M, Agresta F, Allievi N, Bellanova G, Coccolini F, Coy C, Fugazzola P, Martinez CA, Montori G, Paolillo C, Penachim TJ, Pereira B, Reis T, Restivo A, Rezende-Neto J, Sartelli M, Valentino M, Abu-Zidan FM, Ashkenazi I, Bala M, Chiara O, De' Angelis N, Deidda S, De Simone B, Di Saverio S, Finotti E, Kenji I, Moore E, Wexner S, Biffl W, Coimbra R, Guttadauro A, Leppäniemi A, Maier R, Magnone S, Mefire AC, Peitzmann A, Sakakushev B, Sugrue M, Viale P, Weber D, Kashuk J, Fraga GP, Kluger I, Catena F, Ansaloni L. 2017 WSES guidelines on colon and rectal cancer emergencies: obstruction and perforation. *World J Emerg Surg* 2018; **13**: 36 [PMID: 30123315 DOI: 10.1186/s13017-018-0192-3]

49 **Fleshman J**, Marcello P, Stamos MJ, Wexner SD; American Society of Colon and Rectal Surgeons (ASCRS); Society of American Gastrointestinal and Endoscopic Surgeons (SAGES). Focus Group on Laparoscopic Colectomy Education as endorsed by The American Society of Colon and Rectal Surgeons (ASCRS) and The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES). *Dis Colon Rectum* 2006; **49**: 945-949 [PMID: 16649114 DOI: 10.1007/s10350-006-0559-5]

50 **Kleespies A**, Füessl KE, Seeliger H, Eichhorn ME, Müller MH, Rentsch M, Thasler WE, Angele MK, Kreis ME, Jauch KW. Determinants of morbidity and survival after elective non-curative resection of stage IV colon and rectal cancer. *Int J Colorectal Dis* 2009; **24**: 1097-1109 [PMID: 19495779 DOI: 10.1007/s00384-009-0734-y]

51 **Tebala GD**. Colorectal surgery in a rural setting. *Updates Surg* 2015; **67**: 407-419 [PMID: 26545384 DOI: 10.1007/s13304-015-0331-2]

52 **Smyth R**, Darbyshire A, Mercer S, Khan J, Richardson J. Trends in emergency colorectal surgery: a 7-year retrospective single-centre cohort study. *Surg Endosc* 2023; **37**: 3911-3920 [PMID: 36729232 DOI: 10.1007/s00464-023-09876-0]

53 **Vallance AE**, Keller DS, Hill J, Braun M, Kuryba A, van der Meulen J, Walker K, Chand M. Role of Emergency Laparoscopic Colectomy for Colorectal Cancer: A Population-based Study in England. *Ann Surg* 2019; **270**: 172-179 [PMID: 29621034 DOI: 10.1097/SLA.0000000000002752]

54 **Marcello PW**, Milsom JW, Wong SK, Brady K, Goormastic M, Fazio VW. Laparoscopic total colectomy for acute colitis: a case-control study. *Dis Colon Rectum* 2001; **44**: 1441-1445 [PMID: 11598472 DOI: 10.1007/BF02234595]

55 **Gash K**, Chambers W, Ghosh A, Dixon AR. The role of laparoscopic surgery for the management of acute large bowel obstruction. *Colorectal Dis* 2011; **13**: 263-266 [PMID: 19906058 DOI: 10.1111/j.1463-1318.2009.02123.x]

56 **Clancy C**, O'Leary DP, Burke JP, Redmond HP, Coffey JC, Kerin MJ, Myers E. A meta-analysis to determine the oncological implications of conversion in laparoscopic colorectal cancer surgery. *Colorectal Dis* 2015; **17**: 482-490 [PMID: 25524157 DOI: 10.1111/codi.12875]

57 **Casillas S**, Delaney CP, Senagore AJ, Brady K, Fazio VW. Does conversion of a laparoscopic colectomy adversely affect patient outcome? *Dis Colon Rectum* 2004; **47**: 1680-1685 [PMID: 15540299 DOI: 10.1007/s10350-004-0692-4]

58 **White I**, Greenberg R, Itah R, Inbar R, Schneebaum S, Avital S. Impact of conversion on short and long-term outcome in laparoscopic resection of curable colorectal cancer. *JSLS* 2011; **15**: 182-187 [PMID: 21902972 DOI: 10.4293/108680811X13071180406439]

59 **de Neree Tot Babberich MPM**, van Groningen JT, Dekker E, Wiggers T, Wouters MWJM, Bemelman WA, Tanis PJ; Dutch Surgical Colorectal Audit. Laparoscopic conversion in colorectal cancer surgery; is there any improvement over time at a population level? *Surg Endosc* 2018; **32**: 3234-3246 [PMID: 29344789 DOI: 10.1007/s00464-018-6042-2]

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EDITORIAL

Intestinal Behçet's disease: A review of clinical diagnosis and treatment

Ying Liu, Feng Gao, Ding-Quan Yang, Yan Jiao

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Abstract

Behçet's disease (BD) is a chronic inflammatory disorder prone to frequent recurrences, with a high predilection for intestinal involvement. However, the efficacy and long-term effects of surgical treatment for intestinal BD are unknown. In the current issue of *World J Gastrointest Surg*, Park *et al* conducted a retrospective analysis of 31 patients with intestinal BD who received surgical treatment. They found that elevated C-reactive protein levels and emergency surgery were poor prognostic factors for postoperative recurrence, emphasizing the adverse impact of severe inflammation on the prognosis of patients with intestinal BD. This work has clinical significance for evaluating the postoperative condition of intestinal BD. The editorial attempts to summarize the clinical diagnosis and treatment of intestinal BD, focusing on the impact of adverse factors on surgical outcomes. We hope this review will facilitate more precise postoperative management of patients with intestinal BD by clinicians.

Key Words: Intestinal Behçet's disease; Diagnosis; Treatment; Surgery; Recurrence

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Core Tip: Intestinal Behçet's disease (BD) is the gastrointestinal manifestation of BD, characterized primarily by intestinal ulcerations. The differential diagnosis of intestinal BD is challenging, the disease course is prolonged, and surgical intervention is often necessary to achieve cure or remission. Despite surgical treatment, postoperative recurrence and reoperation rates remain high. Understanding the timing of surgery and factors associated with postoperative recurrence is critical for standardized surgical and follow-up management of patients with intestinal BD.

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INTRODUCTION

Behçet's disease (BD) is a chronically relapsing multisystem inflammatory disorder primarily characterized by vasculitis [1], with an etiology remaining elusive. Genetic polymorphisms, encompassing IL23R/IL12RB2, ERAP1, and HLA-B51, are postulated as significant contributors to the dysregulation of inflammatory responses in BD pathogenesis[2-5]. Additionally, microbial factors such as herpes simplex virus infection[2,6], increased colonization of Streptococcus mutans [7], and intestinal microbial dysbiosis[8] provide clues to its underlying pathomechanisms. BD can involve multiple organs or systems, including recurrent oral and genital ulcerations, intestinal involvement, arthritis, ocular manifestations, skin lesions, as well as vascular and neural involvement[1,9]. The distribution of BD in the population varies widely (0.64-420/100000)[10], with a predilection for countries along the "ancient Silk Road" route, stretching from the Mediterranean, Middle East, to East Asia[11]. Prevalence is lower in Nordic and North American regions[12]. Notably, the diversity of intestinal involvement in BD seems more common in East Asian countries, including South Korea and Japan[13].

Intestinal BD, a significant subtype of BD, exhibits two distinct forms of intestinal pathology. One manifests as mucosal inflammation and ulceration triggered by neutrophilic venulitis, while the other involves ischemic injury caused by vasculitis[14]. Characterized by diverse, fluctuating courses, repeated remissions and relapses[15], intestinal BD can affect any part of the gastrointestinal tract[16] and potentially involve extraintestinal organs such as the liver[17], pancreas[18], or spleen[19]. Notably, the onset of intestinal BD symptoms typically lags behind those of extragastrointestinal manifestations[20]. Approximately 5-10% of patients with systemic BD develop intestinal BD approximately 7.35 years after initial disease onset[13], and approximately 75% patients require hospitalization[21].

Due to unsatisfactory control of disease symptoms with empirical medication, intestinal BD can lead to complications, such as anemia[22], and even increased risk of hematologic malignancies[23]. Severe cases can cause intestinal perforation or massive gastrointestinal bleeding, necessitating intestinal resection. Notably, 30.5% of patients with intestinal BD are more likely to require emergency surgical intervention[24]. Postsurgical recurrence is common, with the possibility of requiring second or multiple surgeries. Park *et al*[25] argue in "Short- and long-term outcomes of surgical treatment in patients with intestinal Behcet's disease" that significant inflammation may be a key component in postsurgical recurrence of intestinal BD. Therefore, exploring the clinical course following abdominal surgery and identifying predictors of clinical outcomes are essential for deepening understanding of intestinal BD and individualizing treatment approaches.

DIAGNOSIS OF INTESTINAL BD

Intestinal BD is characterized by well-demarcated deep ulcers with smooth surrounding mucosa, most commonly affecting the ileocecal region[26]. Clinical symptoms include nausea, vomiting, abdominal pain, diarrhea, gastrointestinal bleeding, and perforation[27]. The systemic and intestinal symptoms and genetic origins of intestinal BD are remarkably similar to those of other inflammatory intestinal disorders, such as Crohn's disease (CD) and intestinal tuberculosis, making differential diagnosis difficult[28,29]. Approximately half of patients with intestinal BD are misdiagnosed as having CD[30].

Endoscopy[31,32] and capsule endoscopy[33] are the best and most widely used methods for diagnosing and assessing the progression of inflammatory intestinal diseases. These procedures allow for the observation of ulcer size and location [34], as well as mucosal healing[35], which aid in evaluating the severity and prognosis of intestinal BD. Additionally, endoscopy can facilitate the development of scoring systems to predict the clinical course after surgical resection of intestinal BD[36]. Endoscopic and histologic examinations are also effective in distinguishing intestinal BD from CD[29, 30]. Currently, colonoscopy is not an accurate predictor of the Disease Activity Index for Intestinal BD (DAIBD) scores. However, volcanic ulcers and ulcer counts obtained through colonoscopy are independent predictors of DAIBD[15]. Therefore, endoscopy remains crucial in diagnosing intestinal BD and assessing disease activity indices.

Computed tomography enterography is a valuable imaging modality that can enhance clinical differentiation between intestinal BD and CD by assessing the characteristics of intestinal images and analyzing body composition[37,38]. However, some studies raised concerns that computed tomography (CT) may expose intestinal BD to ionizing radiation, potentially causing damage and exacerbating inflammatory injury[39]. Therefore, a more cautious approach to CT examination management is necessary for patients with intestinal BD.

In clinical practice, assessing intestinal BD activity is critical for selecting appropriate treatment regimens. One widely used and relatively simple scoring system is the DAIBD[40]. The DAIBD incorporates eight parameters: Overall general health, fever, extraintestinal manifestations, abdominal pain, abdominal mass, abdominal tenderness, intestinal complications, and frequency of loose bowel movements within a week. The total score is calculated by adding the inactive (≤ 19), mild (20-39), moderate (40-74), and severe (≥ 75) categories[40]. However, additional markers or models, such as biodiversity indices[41] and endoscopic scoring systems[36], are needed to further evaluate and define intestinal BD activity.

Non-invasive tests are more amenable to screening and real-time assessment of diseases, facilitating their widespread application. Hou *et al*[42] discovered that interleukin-6 (> 7 pg/mL), hemoglobin (< 130 g/L), C-reactive protein (CRP) (> 10 mg/L) and erythrocyte sedimentation rate (ESR) (≥ 15 mm/H), suggest the presence of intestinal symptoms in patients with BD. Lee *et al*[43] also reported proteomic findings indicating that high serum amyloid A implies intestinal involvement in patients with BD. Elevated inflammatory markers can indicate the occurrence of intestinal BD[44]. Notably, CRP and ESR levels are significantly higher in patients with severe intestinal BD compared to those with mild disease [45], and serum procalcitonin levels have unique advantages in assessing the severity of intestinal BD infection[46]. In individuals with intestinal BD, albumin levels are also lowered due to increasing disease activity[45]. Additionally, the exploration of novel markers for intestinal BD exhibits tremendous potential, offering unique advantages in diagnosis. The soluble triggering receptor expressed on myeloid cells-1[47], fecal calprotectin[48,49], fecal lactoferrin[50], anti-alpha-enolase antibody[51], and lipoprotein-associated phospholipase A2[52] may emerge as diagnostic and activity monitoring markers for intestinal BD. Furthermore, anti-Saccharomyces cerevisiae antibody was higher in 44.3% of patients with intestinal BD, and positively correlated with surgical rates[53]. Moreover, the detection of heat shock protein family A member 6[54] and maltase-glucoamylase[55] can assist in distinguishing intestinal BD from CD.

MEDICAL TREATMENT OF INTESTINAL BD

Currently, the conventional treatment for intestinal BD remains empirical, with aminosalicylates recommended for mild cases[56]. However, a significant proportion of patients, particularly those who are young (< 35 years) or have high levels of CRP or a high intestinal BD score, exhibit poor response to these medications[57]. For moderate to severe cases, glucocorticoids and immunomodulators such as thalidomide, thiopurine, cyclophosphamide, and methotrexate, used alone or in combination, are necessary[2]. Nevertheless, there remains a risk of disease recurrence, exacerbation of gastrointestinal bleeding, venous thrombosis, and infection[58,59]. Tumour necrosis factor-α (TNF-α) inhibitors, such as infliximab and adalimumab, are often used to treat severe and refractory cases of intestinal BD[60,61]. Patients with intestinal BD localized outside the ileocecal region may also have a greater need for anti-TNF-α immunotherapy[56]. Those who respond poorly to anti-TNF-α therapy have a higher likelihood of undergoing surgical intervention[60], and combination therapy with thalidomide has been suggested[62]. The future holds promise for the discovery and development of additional biologic agents, such as baricitinib[63] and calcineurin inhibitors[64], as novel therapeutic options for severe and refractory intestinal BD[27].

SURGICAL TREATMENT OF INTESTINAL BD

Surgical intervention is often necessary in patients with intestinal BD who present with medically refractory disease, fistula or abscess formation, intestinal obstruction, or abdominal mass. Emergency surgery is required for intestinal perforation and severe gastrointestinal bleeding. The cumulative rate of surgical intervention in patients with intestinal BD is not low: 20% after one year, 27%-33% at five years, and 31%-46% at ten years following diagnosis[60]. Studies have shown that the progression of intestinal BD to more extensive ocular and ileal disease is an important indicator for needing surgery treatment[65]. Findings suggested history of appendectomy and high DAIBD score at diagnosis increase likelihood of intestinal surgery[21]. However, there is no difference in short-term outcomes between laparoscopic and open surgery for intestinal BD patients[66].

Postoperative complications, including anastomotic leak, abscess or fistula formation, wound infection, intestinal obstruction, bleeding, and perforation, can significantly impact recovery of patients with intestinal BD. Elevated CRP levels immediately postoperatively significantly increase risk of postoperative complications[67]. Combined use of glucocorticoids and immunosuppressants postoperatively can significantly reduce incidence of postoperative complications [68].

PROGNOSIS OF SURGICAL INTERVENTION

Postoperative recurrence is a substantial contributor to the ongoing non-healing of intestinal BD. Approximately 13%-75% of patients with intestinal BD experience postoperative recurrence, carrying high risk of disease recurrence (Table 1). Therefore, regular post-surgery follow-up is strongly recommended[36]. The endoscopic-intestinal BD scoring system, utilizing parameters such as number and size of ulcers, can aid disease recurrence assessment[36]. As shown in Table 1, various factors influence intestinal BD prognosis post-surgery. Among these, elevated CRP levels identified by Kang *et al* [67] and Jung *et al*[69], and emergency surgery identified by Park *et al*[70], are poor postoperative prognostic factors in intestinal BD. These findings are consistent with the results of the current study by Park *et al*[25].

Table 1 Surgical prognosis of intestinal Behçet's disease

Cases	Recurrence rate after surgery (%)	Factors associated with recurrence	Ref.
31	20.5	Preoperative increased CRP levels; Emergency surgery	Park *et al*[25]
54	68.5	Colonoscopy; Colonoscopic recurrence	Park *et al*[36]
8	75	Increased peripheral CD8+DR+ lymphocytes (%)	Naganuma *et al*[65]
90	57.8	Higher CRP level immediately after surgery	Kang *et al*[67]
72	58.3	Volcano-type ulcerations; Increased CRP levels; Intestinal perforations	Jung *et al*[69]
90	45.6	Initial emergency operation; Higher initial perioperative erythrocyte sedimentation rate	Park *et al*[70]
16 (Complete remission of intestinal lesions)	13	Incomplete remission of intestinal lesions; the history of intestinal perforation or fistula; did not take azathioprine	Choi *et al*[72]
27 (Incomplete remission of intestinal lesions)	43		
50 (5-ASA)	66.0	Thiopurine was not used postoperatively	Lee *et al*[73]
27 (Thiopurine)	37.0		
33 (Intestinal perforations)	42.4	NA	Moon *et al*[76]
40 (Early surgery)	35.0	Late surgery	Jung *et al*[77]
62 (Late surgery)	45.2		
9	55.6	Intraoperative endoscopy	Iida *et al*[78]
91	51.1	NA	Jung *et al*[79]
16	50.0	Volcano-type ulcerations	Kim *et al*[80]
91	35.2	Postoperative use of steroids; postoperative complications; high BMI	Baek *et al*[81]

CRP: C-reactive protein; 5-ASA: 5-aminosalicylic acid; BMI: Body mass index; NA: Not available.

In addition to identifying factors associated with postoperative recurrence, it is crucial to consider factors such as disease duration[45] to assess disease activity and severity. Postoperative systemic pharmacological treatment, particularly the use of immunosuppressants[71], is critical. Regular administration of azathioprine postoperatively also can result in partial or complete resolution of intestinal symptoms and, to some extent, reduce the recurrence rate of intestinal BD[72], outperforming the use of 5-aminosalicylic acid alone[73].

Especially in younger patients, greater attention should be paid to disease progression, as multiple clinical evidences suggested that they often exhibit more severe clinical symptoms and poorer prognoses[74-76]. Patients with severe courses tend to be younger than those with mild courses[45], resulting in higher demand for outpatient, inpatient treatment, and intestinal surgery[75]. They are also more prone to postoperative recurrence[76]. Therefore, it is essential to develop targeted treatment strategies for younger patients with intestinal BD, and to initiate immunosuppressant therapy early in the course of the disease[75].

The timing of surgery is worth discussing. Compared to patients with advanced BD undergoing surgery, those with intestinal BD receiving early intestinal surgery have better prognosis, with significantly reduced postoperative clinical recurrence and reoperation rates[77]. Anti-TNF-α medication can effectively treat refractory intestinal BD. If patients with intestinal BD get anti-TNF-α therapy and experience poor response (within one month), ESR > 42.5 mm/H, skin and joint symptoms, or geographic ulcers, surgical intervention may be required[60]. Therefore, it is crucial to individualize treatment plans based on risk factors, deciding whether to prioritize pharmacological therapy or early surgery as the primary treatment goal.

CONCLUSION

The pathogenesis of intestinal BD remains unclear, lacking radical treatment and often requiring surgical intervention[25, 76-81]. In a retrospective clinical analysis spanning nearly 11 years, Park *et al*[25]. found that the postoperative recurrence rate among patients with intestinal BD was 20.5%. Severe inflammatory variables, notably emergency surgery and increased CRP levels, were found as the main predictors of postoperative recurrence or reoperation. This work by Park *et al*[25] can assist clinicians in better assessing the surgical prognosis of intestinal BD and developing more precise, individualized treatment plans.

However, numerous areas require further improvement in future studies. Future research should examine age, inflammatory status, and drug treatment impacts on surgical outcomes, postoperative complications, and recurrence. Additionally, multicenter collaborations should further explore and refine prognostic risk factor assessment for intestinal BD through retrospective and prospective studies. Elevated CRP levels associate with surgical recurrence at various time points[67,69], so real-time CRP inflammatory marker monitoring before, during, and after surgery may aid real-time management of intestinal BD. These efforts could enable risk-stratified, tailored drug therapies and personalized patient monitoring.

FOOTNOTES

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REFERENCES

1 **Hatemi G**, Seyahi E, Fresko I, Talarico R, Uçar D, Hamuryudan V. Behçet's syndrome: one year in review 2022. *Clin Exp Rheumatol* 2022; **40**: 1461-1471 [PMID: 35894066 DOI: 10.55563/clinexprheumatol/h4dkrs]
2 **van der Houwen TB**, van Hagen PM, van Laar JAM. Immunopathogenesis of Behçet's disease and treatment modalities. *Semin Arthritis Rheum* 2022; **52**: 151956 [PMID: 35038644 DOI: 10.1016/j.semarthrit.2022.151956]
3 **Kang EH**, Kim S, Park MY, Choi JY, Choi IA, Kim MJ, Ha YJ, Lee EY, Lee YJ, Lee EB, Kang C, Song YW. Behçet's disease risk association fine-mapped on the IL23R-IL12RB2 intergenic region in Koreans. *Arthritis Res Ther* 2017; **19**: 227 [PMID: 29017598 DOI: 10.1186/s13075-017-1435-5]
4 **Cavers A**, Kugler MC, Ozguler Y, Al-Obeidi AF, Hatemi G, Ueberheide BM, Ucar D, Manches O, Nowatzky J. Behçet's disease risk-variant HLA-B51/ERAP1-Hap10 alters human CD8 T cell immunity. *Ann Rheum Dis* 2022; **81**: 1603-1611 [PMID: 35922122 DOI: 10.1136/ard-2022-222277]
5 **Yılmaz MA**, Türsen Ü. The Immunogenetics of Behcet's Disease. *Adv Exp Med Biol* 2022; **1367**: 335-347 [PMID: 35286701 DOI: 10.1007/978-3-030-92616-8_12]
6 **Evereklioglu C**. Current concepts in the etiology and treatment of Behçet disease. *Surv Ophthalmol* 2005; **50**: 297-350 [PMID: 15967189 DOI: 10.1016/j.survophthal.2005.04.009]
7 **Mumcu G**, Inanc N, Aydin SZ, Ergun T, Direskeneli H. Association of salivary S. mutans colonisation and mannose-binding lectin deficiency with gender in Behçet's disease. *Clin Exp Rheumatol* 2009; **27**: S32-S36 [PMID: 19796530]
8 **van der Houwen TB**, van Laar JAM, Kappen JH, van Hagen PM, de Zoete MR, van Muijlwijk GH, Berbers RM, Fluit AC, Rogers M, Groot J, Hazelbag CM, Consolandi C, Severgnini M, Peano C, D'Elios MM, Emmi G, Leavis HL. Behçet's Disease Under Microbiotic Surveillance? A Combined Analysis of Two Cohorts of Behçet's Disease Patients. *Front Immunol* 2020; **11**: 1192 [PMID: 32595645 DOI: 10.3389/fimmu.2020.01192]
9 **Kötter I**, Lötscher F. Behçet's Syndrome Apart From the Triple Symptom Complex: Vascular, Neurologic, Gastrointestinal, and Musculoskeletal Manifestations. A Mini Review. *Front Med (Lausanne)* 2021; **8**: 639758 [PMID: 33898481 DOI: 10.3389/fmed.2021.639758]
10 **Akbaba TH**, Ekici M, Çolpak Aİ, Brown KL, Karadağ Ö, Balci-Peynircioglu B. Behçet's syndrome: recent advances to aid diagnosis. *Clin Exp Med* 2023; **23**: 4079-4090 [PMID: 37897656 DOI: 10.1007/s10238-023-01226-7]
11 **Alpsoy E**, Leccese P, Ergun T. Editorial: Behçet's Disease: Epidemiology, Etiopathogenesis, Diagnosis and Treatment. *Front Med (Lausanne)* 2021; **8**: 794874 [PMID: 34805237 DOI: 10.3389/fmed.2021.794874]
12 **Mahr A**, Maldini C. [Epidemiology of Behçet's disease]. *Rev Med Interne* 2014; **35**: 81-89 [PMID: 24398415 DOI: 10.1016/j.revmed.2013.12.005]
13 **Han M**, Jung YS, Kim WH, Cheon JH, Park S. Incidence and clinical outcomes of intestinal Behçet's disease in Korea, 2011-2014: a nationwide population-based study. *J Gastroenterol* 2017; **52**: 920-928 [PMID: 28028610 DOI: 10.1007/s00535-016-1300-3]
14 **Vaiopoulos AG**, Sfikakis PP, Kanakis MA, Vaiopoulos G, Kaklamanis PG. Gastrointestinal manifestations of Behçet's disease: advances in evaluation and management. *Clin Exp Rheumatol* 2014; **32**: S140-S148 [PMID: 25268668]
15 **Lee HJ**, Kim YN, Jang HW, Jeon HH, Jung ES, Park SJ, Hong SP, Kim TI, Kim WH, Nam CM, Cheon JH. Correlations between endoscopic and clinical disease activity indices in intestinal Behcet's disease. *World J Gastroenterol* 2012; **18**: 5771-5778 [PMID: 23155319 DOI:

10.3748/wjg.v18.i40.5771]
16 **Manuelyan Z**, Butt E, Parupudi S. Gastrointestinal Behçet's disease: Manifestations, diagnosis, and management. *Dis Mon* 2024; **70**: 101674 [PMID: 38185603 DOI: 10.1016/j.disamonth.2023.101674]
17 **Erul E**, Uzun GS, Koksal D, Keskin O, Uysal S, Inkaya AC, Kalyoncu U. Behçet's Disease-related Budd-Chiari Syndrome Successfully Managed with anti-TNF Antibody: A Case Report and Review of the Literature. *Eur J Case Rep Intern Med* 2022; **9**: 003515 [PMID: 36093305 DOI: 10.12890/2022_003515]
18 **Mahmoud GA**, Mohamed SS, Abd El-Malek NS, Zayed HS. Acute necrotizing pancreatitis as a manifestation of Behcet's Disease: A case report and review of the literature. *Egyptian Rheumatologist* 2022; **44**: 165-169 [DOI: 10.1016/j.ejr.2021.11.003]
19 **Jazeer M**, Antony D, Pakkiyaretnam M. Aseptic Abscess of the Spleen as an Antecedent Manifestation of Behçet's Disease. *Cureus* 2023; **15**: e38375 [PMID: 37265896 DOI: 10.7759/cureus.38375]
20 **Wang WB**, Zhao YP, Cong L, Jing H, Liao Q, Zhang TP. Clinical characters of gastrointestinal lesions in intestinal Behcet's disease. *Chin Med Sci J* 2011; **26**: 168-171 [PMID: 22207926 DOI: 10.1016/s1001-9294(11)60043-6]
21 **Park J**, Park SJ, Park JJ, Kim TI, Cheon JH. Long-term clinical outcomes of intestinal Behçet's disease: A 30-year cohort study at a tertiary hospital in South Korea. *J Gastroenterol Hepatol* 2023; **38**: 386-392 [PMID: 36346041 DOI: 10.1111/jgh.16056]
22 **Ye JF**, Chen Y, Cai JF, Shen Y, Zou J, Guan JL. Incidence and risk factors for anemia among newly-diagnosed intestinal Behcet's disease patients. *J Natl Med Assoc* 2019; **111**: 407-412 [PMID: 30803717 DOI: 10.1016/j.jnma.2019.01.010]
23 **Han M**, Jung YS, Kim WH, Cheon JH, Park S. Cancer Risk in Patients with Intestinal Behçet's Disease: A Nationwide Population-Based Study. *Gut Liver* 2018; **12**: 433-439 [PMID: 29429154 DOI: 10.5009/gnl17324]
24 **Park J**, Cheon JH, Park Y, Park SJ, Kim TI, Kim WH. Risk Factors and Outcomes of Emergency Room Visits in Intestinal Behçet's Disease. *Digestion* 2017; **96**: 231-238 [PMID: 29131059 DOI: 10.1159/000484084]
25 **Park MY**, Yoon YS, Park JH, Lee JL, Yu CS. Short- and long-term outcomes of surgical treatment in patients with intestinal Behcet's disease. *World J Gastrointest Surg* 2024; **16**: 429-437 [PMID: 38463356 DOI: 10.4240/wjgs.v16.i2.429]
26 **Curtin BF**, Hill KL, Bhattacharya S, Powers A, Venkatesan A, Bagi P, Joyal E, Alimchandani M, Goldbach-Mansky R, Grayson P, Quezado M, Sibley C, Heller T. Clinical, Endoscopic, and Histopathologic Gastrointestinal Disease in an American Cohort With Behçet's Disease. *Clin Transl Gastroenterol* 2023; **14**: e00591 [PMID: 37114910 DOI: 10.14309/ctg.0000000000000591]
27 **He K**, Yan X, Wu D. Intestinal Behcet's Disease: A Review of the Immune Mechanism and Present and Potential Biological Agents. *Int J Mol Sci* 2023; **24** [PMID: 37175882 DOI: 10.3390/ijms24098176]
28 **Yoo JW**, Jo SI, Shin DW, Park JW, Kim SE, Lim H, Kang HS, Moon SH, Kim MK, Kim SY, Hwang SW, Soh JS. Clinical Usefulness of Immune Profiling for Differential Diagnosis between Crohn's Disease, Intestinal Tuberculosis, and Behcet's Disease. *Diagnostics (Basel)* 2023; **13** [PMID: 37761270 DOI: 10.3390/diagnostics13182904]
29 **Wu YC**, Fu YJ, Xia HJ, Zhu J, Huang Y, Jiang ZN. Ileocecal involvement in intestinal Behçet's disease and Crohn's disease: comparison of clinicopathological and immunophenotypic features. *J Dig Dis* 2023; **24**: 594-602 [PMID: 37864553 DOI: 10.1111/1751-2980.13236]
30 **Ye JF**, Guan JL. Differentiation between intestinal Behçet's disease and Crohn'sdisease based on endoscopy. *Turk J Med Sci* 2019; **49**: 42-49 [PMID: 30761850 DOI: 10.3906/sag-1807-67]
31 **Ye JF**, Hou CC, Bao HF, Guan JL. New insight into the features of Behçet's disease with gastrointestinal ulcer: a cross-sectional observational study. *Orphanet J Rare Dis* 2021; **16**: 444 [PMID: 34674734 DOI: 10.1186/s13023-021-02056-0]
32 **Cheon JH**, Kim WH. Recent advances of endoscopy in inflammatory bowel diseases. *Gut Liver* 2007; **1**: 118-125 [PMID: 20485627 DOI: 10.5009/gnl.2007.1.2.118]
33 **Arimoto J**, Endo H, Kato T, Umezawa S, Fuyuki A, Uchiyama S, Higurashi T, Ohkubo H, Nonaka T, Takeno M, Ishigatsubo Y, Sakai E, Matsuhashi N, Nakajima A. Clinical value of capsule endoscopy for detecting small bowel lesions in patients with intestinal Behçet's disease. *Dig Endosc* 2016; **28**: 179-185 [PMID: 26459917 DOI: 10.1111/den.12552]
34 **Zu X**, Xiong S, Lu Y, Zhang N, Xu S, Feng R, Chen B, Zeng Z, Chen M, He Y. Predicting Factors of Long-term Outcome of Gastrointestinal Behçet's Disease: A Chinese Retrospective Study. *Clin Ther* 2024; **46**: 201-207 [PMID: 38296718 DOI: 10.1016/j.clinthera.2023.12.012]
35 **Gong L**, Zhang YL, Sun LX, Chen GR, Wu D. Mucosal healing in intestinal Behçet's disease: A systematic review and meta-analysis. *J Dig Dis* 2021; **22**: 83-90 [PMID: 33314672 DOI: 10.1111/1751-2980.12965]
36 **Park JW**, Park Y, Park SJ, Kim TI, Kim WH, Cheon JH. Development of a Novel Endoscopic Scoring System to Predict Relapse after Surgery in Intestinal Behçet's Disease. *Gut Liver* 2018; **12**: 674-681 [PMID: 29938457 DOI: 10.5009/gnl17547]
37 **Li Y**, Xiong Z, Jiang Y, Shen Y, Hu X, Hu D, Li Z. Enhancing the Differentiation between Intestinal Behçet's Disease and Crohn's Disease through Quantitative Computed Tomography Analysis. *Bioengineering (Basel)* 2023; **10** [PMID: 37892941 DOI: 10.3390/bioengineering10101211]
38 **Yang H**, Zhang H, Liu W, Han W, Guo T, Lai Y, Tan B, Wang C, Chen M, Gao X, Ran Z, Liu Z, Wu K, Cao Q, Qian J. Computed tomography enterography increases the ability of endoscopy to differentiate Crohn's disease from intestinal Behçet's disease. *Front Med (Lausanne)* 2022; **9**: 900458 [PMID: 36059846 DOI: 10.3389/fmed.2022.900458]
39 **Jung YS**, Park DI, Moon CM, Park SJ, Hong SP, Kim TI, Kim WH, Cheon JH. Radiation exposure from abdominal imaging studies in patients with intestinal Behçet disease. *Gut Liver* 2014; **8**: 380-387 [PMID: 25071902 DOI: 10.5009/gnl.2014.8.4.380]
40 **Cheon JH**, Han DS, Park JY, Ye BD, Jung SA, Park YS, Kim YS, Kim JS, Nam CM, Kim YN, Yang SK, Kim WH; Korean IBD Study Group. Development, validation, and responsiveness of a novel disease activity index for intestinal Behçet's disease. *Inflamm Bowel Dis* 2011; **17**: 605-613 [PMID: 20848515 DOI: 10.1002/ibd.21313]
41 **International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD)**. The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. *J Eur Acad Dermatol Venereol* 2014; **28**: 338-347 [PMID: 23441863 DOI: 10.1111/jdv.12107]
42 **Hou CC**, Ye JF, Ma HF, Guan JL. Clinical characteristics and risk factors of intestinal involvement in Behçet's syndrome patients: a cross-sectional study from a single center. *Orphanet J Rare Dis* 2021; **16**: 132 [PMID: 33731182 DOI: 10.1186/s13023-021-01772-x]
43 **Lee HJ**, Kim JH, Kim SW, Joo HA, Lee HW, Kim YS, Park SJ, Hong SP, Kim TI, Kim WH, Kim YH, Cheon JH. Proteomic Analysis of Serum Amyloid A as a Potential Marker in Intestinal Behçet's Disease. *Dig Dis Sci* 2017; **62**: 1953-1962 [PMID: 28523576 DOI: 10.1007/s10620-017-4606-y]
44 **Hou CC**, Luo D, Bao HF, Ye JF, Ma HF, Shen Y, Zou J, Guan JL. Clinical heterogeneity of ocular Behçet's syndrome versus intestinal Behçet's syndrome: a cross-sectional study from Shanghai Behçet's syndrome database. *Arthritis Res Ther* 2022; **24**: 98 [PMID: 35488313

DOI: 10.1186/s13075-022-02782-1]
45 **Jung YS**, Cheon JH, Park SJ, Hong SP, Kim TI, Kim WH. Clinical course of intestinal Behcet's disease during the first five years. *Dig Dis Sci* 2013; **58**: 496-503 [PMID: 22899244 DOI: 10.1007/s10620-012-2351-9]
46 **Chung SH**, Lee HW, Kim SW, Park SJ, Hong SP, Kim TI, Kim WH, Cheon JH. Usefulness of Measuring Serum Procalcitonin Levels in Patients with Inflammatory Bowel Disease. *Gut Liver* 2016; **10**: 574-580 [PMID: 26780089 DOI: 10.5009/gnl15209]
47 **Jung YS**, Kim SW, Yoon JY, Lee JH, Jeon SM, Hong SP, Kim TI, Kim WH, Cheon JH. Expression of a soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) correlates with clinical disease activity in intestinal Behcet's disease. *Inflamm Bowel Dis* 2011; **17**: 2130-2137 [PMID: 21910175 DOI: 10.1002/ibd.21600]
48 **Kim DH**, Park Y, Kim B, Kim SW, Park SJ, Hong SP, Kim TI, Kim WH, Cheon JH. Fecal calprotectin as a non-invasive biomarker for intestinal involvement of Behçet's disease. *J Gastroenterol Hepatol* 2017; **32**: 595-601 [PMID: 27521492 DOI: 10.1111/jgh.13530]
49 **Esatoglu SN**, Hatemi I, Ozguler Y, Hatemi G, Uzun H, Celik AF, Yazici H. Faecal but not serum calprotectin levels look promising in predicting active disease in Behçet's syndrome patients with gastrointestinal involvement. *Clin Exp Rheumatol* 2018; **36**: 90-96 [PMID: 30582504]
50 **Hayashida M**, Miyoshi J, Mitsui T, Miura M, Saito D, Sakuraba A, Kawashima S, Ikegaya N, Fukuoka K, Karube M, Komagata Y, Kaname S, Okada AA, Fujimori S, Matsuura M, Hisamatsu T. Elevated fecal calprotectin and lactoferrin associated with small intestinal lesions in patients with Behçet disease. *J Gastroenterol Hepatol* 2020; **35**: 1340-1346 [PMID: 31999379 DOI: 10.1111/jgh.14995]
51 **Shin SJ**, Kim BC, Kim TI, Lee SK, Lee KH, Kim WH. Anti-alpha-enolase antibody as a serologic marker and its correlation with disease severity in intestinal Behçet's disease. *Dig Dis Sci* 2011; **56**: 812-818 [PMID: 20632102 DOI: 10.1007/s10620-010-1326-y]
52 **Örem A**, Yayli S, Arıca DA, Akcan B, Yücesan FB, Bahadir S. Lipoprotein-associated phospholipase A2 level in patients with Behçet's disease. *J Eur Acad Dermatol Venereol* 2013; **27**: e289-e293 [PMID: 22755553 DOI: 10.1111/j.1468-3083.2012.04631.x]
53 **Choi CH**, Kim TI, Kim BC, Shin SJ, Lee SK, Kim WH, Kim HS. Anti-Saccharomyces cerevisiae antibody in intestinal Behçet's disease patients: relation to clinical course. *Dis Colon Rectum* 2006; **49**: 1849-1859 [PMID: 17080284 DOI: 10.1007/s10350-006-0706-z]
54 **Feng R**, Chao K, Chen SL, Sun CH, Qiu Y, Chen BL, Mao R, He Y, Cao QH, Xue L, Zeng ZR, Zhang SH, Chen MH. Heat shock protein family A member 6 combined with clinical characteristics for the differential diagnosis of intestinal Behçet's disease. *J Dig Dis* 2018; **19**: 350-358 [PMID: 29851304 DOI: 10.1111/1751-2980.12613]
55 **Park J**, Jeong D, Chung YW, Han S, Kim DH, Yu J, Cheon JH, Ryu JH. Proteomic analysis-based discovery of a novel biomarker that differentiates intestinal Behçet's disease from Crohn's disease. *Sci Rep* 2021; **11**: 11019 [PMID: 34040049 DOI: 10.1038/s41598-021-90250-2]
56 **Kimura Y**, Asako K, Kikuchi H, Kono H. Characteristics of patients with intestinal Behçet's disease requiring treatment with immunosuppressants or anti-TNFα antibody. *Mod Rheumatol* 2016; **26**: 132-137 [PMID: 26025434 DOI: 10.3109/14397595.2015.1056956]
57 **Jung YS**, Hong SP, Kim TI, Kim WH, Cheon JH. Long-term clinical outcomes and factors predictive of relapse after 5-aminosalicylate or sulfasalazine therapy in patients with intestinal Behcet disease. *J Clin Gastroenterol* 2012; **46**: e38-e45 [PMID: 22298088 DOI: 10.1097/MCG.0b013e3182431d56]
58 **Park J**, Cheon JH, Park YE, Lee YJ, Lee HJ, Park SJ, Hong SP, Kim TI, Kim WH. Risk factors and outcomes of acute lower gastrointestinal bleeding in intestinal Behçet's disease. *Int J Colorectal Dis* 2017; **32**: 745-751 [PMID: 27924367 DOI: 10.1007/s00384-016-2728-x]
59 **Emmi G**, Bettiol A, Silvestri E, Di Scala G, Becatti M, Fiorillo C, Prisco D. Vascular Behçet's syndrome: an update. *Intern Emerg Med* 2019; **14**: 645-652 [PMID: 30499073 DOI: 10.1007/s11739-018-1991-y]
60 **Han SJ**, Kang EA, Park J, Park SJ, Park JJ, Kim TI, Kim WH, Cheon JH. Risk Factors for Surgery in Patients with Intestinal Behçet's Disease During Anti-Tumor Necrosis Factor-Alpha Therapy. *Yonsei Med J* 2023; **64**: 111-116 [PMID: 36719018 DOI: 10.3349/ymj.2022.0264]
61 **Zhang Q**, Ma C, Dong R, Xiang W, Li M, Ma Z, Yang Q. Efficacy and Safety of Anti-Tumor Necrosis Factor-Alpha Agents for Patients with Intestinal Behcet's Disease: A Systematic Review and Meta-Analysis. *Yonsei Med J* 2022; **63**: 148-157 [PMID: 35083900 DOI: 10.3349/ymj.2022.63.2.148]
62 **Bao HF**, Hou CC, Ye B, Zou J, Luo D, Cai JF, Shen Y, Guan JL. Predictors of infliximab refractory intestinal Behçet's syndrome: A retrospective cohort study from the Shanghai Behçet's syndrome database. *Mod Rheumatol* 2023; **33**: 207-216 [PMID: 34932796 DOI: 10.1093/mr/roab127]
63 **Liu J**, Yu X, Wang Z, Liu W, Liu X, Wang X, Zhang M, Zhao Y, Zhang F, Yang H, Zheng W. Baricitinib for the treatment of intestinal Behçet's disease: A pilot study. *Clin Immunol* 2023; **247**: 109241 [PMID: 36702180 DOI: 10.1016/j.clim.2023.109241]
64 **Kawaguchi T**, Fukata M, Omori T, Kiyohara H, Sugimoto S, Nanki K, Sujino T, Mikami Y, Kanai T. Efficacy of Calcineurin Inhibitors for Induction of Remission in Intestinal Behçet's Disease. *Crohns Colitis 360* 2022; **4**: otac017 [PMID: 36777415 DOI: 10.1093/crocol/otac017]
65 **Naganuma M**, Iwao Y, Inoue N, Hisamatsu T, Imaeda H, Ishii H, Kanai T, Watanabe M, Hibi T. Analysis of clinical course and long-term prognosis of surgical and nonsurgical patients with intestinal Behçet's disease. *Am J Gastroenterol* 2000; **95**: 2848-2851 [PMID: 11051358 DOI: 10.1111/j.1572-0241.2000.03198.x]
66 **Baek SJ**, Baik SH, Kim CW, Cho MS, Jang HA, Hur H, Min BS, Kim NK. Short- and long-term outcomes of laparoscopic surgery for intestinal Behcet's disease: a comparative study with open surgery. *Surg Endosc* 2016; **30**: 99-105 [PMID: 25801111 DOI: 10.1007/s00464-015-4166-1]
67 **Kang EA**, Park JW, Park Y, Park SJ, Kim TI, Kim WH, Cho MS, Cheon JH. C-reactive protein is associated with postoperative outcomes in patients with intestinal Behçet's disease. *BMC Gastroenterol* 2021; **21**: 362 [PMID: 34620099 DOI: 10.1186/s12876-021-01922-2]
68 **Park MC**, Hong BK, Kwon HM, Hong YS. Surgical outcomes and risk factors for postoperative complications in patients with Behcet's disease. *Clin Rheumatol* 2007; **26**: 1475-1480 [PMID: 17235654 DOI: 10.1007/s10067-006-0530-9]
69 **Jung YS**, Yoon JY, Lee JH, Jeon SM, Hong SP, Kim TI, Kim WH, Cheon JH. Prognostic factors and long-term clinical outcomes for surgical patients with intestinal Behcet's disease. *Inflamm Bowel Dis* 2011; **17**: 1594-1602 [PMID: 21674717 DOI: 10.1002/ibd.21517]
70 **Park YE**, Cheon JH, Park J, Lee JH, Lee HJ, Park SJ, Kim TI, Kim WH. The outcomes and risk factors of early reoperation after initial intestinal resective surgery in patients with intestinal Behçet's disease. *Int J Colorectal Dis* 2017; **32**: 591-594 [PMID: 28028614 DOI: 10.1007/s00384-016-2743-y]
71 **Hatemi I**, Esatoglu SN, Hatemi G, Erzin Y, Yazici H, Celik AF. Characteristics, Treatment, and Long-Term Outcome of Gastrointestinal Involvement in Behcet's Syndrome: A Strobe-Compliant Observational Study From a Dedicated Multidisciplinary Center. *Medicine (Baltimore)* 2016; **95**: e3348 [PMID: 27100417 DOI: 10.1097/MD.0000000000003348]
72 **Choi IJ**, Kim JS, Cha SD, Jung HC, Park JG, Song IS, Kim CY. Long-term clinical course and prognostic factors in intestinal Behçet's disease. *Dis Colon Rectum* 2000; **43**: 692-700 [PMID: 10826433 DOI: 10.1007/bf02235590]
73 **Lee HW**, Cheon JH, Lee HJ, Park SJ, Hong SP, Kim TI, Kim WH. Postoperative Effects of Thiopurines in Patients with Intestinal Behçet's

Disease. *Dig Dis Sci* 2015; **60**: 3721-3727 [PMID: 26199149 DOI: 10.1007/s10620-015-3799-1]

74 **Jung YS**, Yoon JY, Hong SP, Kim TI, Kim WH, Cheon JH. Influence of age at diagnosis and sex on clinical course and long-term prognosis of intestinal Behcet's disease. *Inflamm Bowel Dis* 2012; **18**: 1064-1071 [PMID: 21793128 DOI: 10.1002/ibd.21833]

75 **Chang JY**, Park SJ, Park JJ, Kim TI, Cheon JH, Park J. Impact of age at diagnosis on long-term prognosis in patients with intestinal Behçet's disease. *J Gastroenterol Hepatol* 2024; **39**: 519-526 [PMID: 38149352 DOI: 10.1111/jgh.16449]

76 **Moon CM**, Cheon JH, Shin JK, Jeon SM, Bok HJ, Lee JH, Park JJ, Hong SP, Kim TI, Kim NK, Kim WH. Prediction of free bowel perforation in patients with intestinal Behçet's disease using clinical and colonoscopic findings. *Dig Dis Sci* 2010; **55**: 2904-2911 [PMID: 20094787 DOI: 10.1007/s10620-009-1095-7]

77 **Jung YS**, Hong SP, Kim TI, Kim WH, Cheon JH. Early versus late surgery in patients with intestinal Behçet disease. *Dis Colon Rectum* 2012; **55**: 65-71 [PMID: 22156869 DOI: 10.1097/DCR.0b013e318238b57e]

78 **Iida M**, Kobayashi H, Matsumoto T, Okada M, Fuchigami T, Yao T, Fujishima M. Postoperative recurrence in patients with intestinal Behçet's disease. *Dis Colon Rectum* 1994; **37**: 16-21 [PMID: 8287741 DOI: 10.1007/bf02047208]

79 **Jung YS**, Cheon JH, Park SJ, Hong SP, Kim TI, Kim WH. Long-term clinical outcomes of Crohn's disease and intestinal Behcet's disease. *Inflamm Bowel Dis* 2013; **19**: 99-105 [PMID: 22508364 DOI: 10.1002/ibd.22991]

80 **Kim JS**, Lim SH, Choi IJ, Moon H, Jung HC, Song IS, Kim CY. Prediction of the clinical course of Behçet's colitis according to macroscopic classification by colonoscopy. *Endoscopy* 2000; **32**: 635-640 [PMID: 10935793 DOI: 10.1055/s-2000-9012]

81 **Baek SJ**, Kim CW, Cho MS, Jang HA, Baik SH, Hur H, Min BS, Kim NK. Surgical Treatment and Outcomes in Patients With Intestinal Behçet Disease: Long-term Experience of a Single Large-Volume Center. *Dis Colon Rectum* 2015; **58**: 575-581 [PMID: 25944429 DOI: 10.1097/DCR.0000000000000373]

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EDITORIAL

Non-operative management of rectal cancer: Highlighting the controversies

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Abstract

There remains much ambiguity on what non-operative management (NOM) of rectal cancer truly entails in terms of the methods to be adopted and the best algorithm to follow. This is clearly shown by the discordance between various national and international guidelines on NOM of rectal cancer. The main aim of the NOM strategy is organ preservation and avoiding unnecessary surgical intervention, which carries its own risk of morbidity. A highly specific and sensitive surveillance program must be devised to avoid patients undergoing unnecessary surgical interventions. In many studies, NOM, often interchangeably called the Watch and Wait strategy, has been shown as a promising treatment option when undertaken in the appropriate patient population, where a clinical complete response is achieved. However, there are no clear guidelines on patient selection for NOM along with the optimal method of surveillance.

Key Words: Non-operative; Management; Rectal cancer; Highlighting; Controversies

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Core Tip: Patients with locally advanced rectal cancers are ideally treated with neoadjuvant chemoradiation therapy followed by surgical resection. As neoadjuvant treatments evolved, an increasing number of patients showed a complete response to neoadjuvant therapy. The complete response of rectal cancers to neoadjuvant treatment inspired the concept of non-operative management (NOM). Following extensive multidisciplinary team meeting discussion, patients can be considered for NOM. Questions arose regarding patient selection for NOM and the best surveillance program to ensure no red flags for recurrent disease. Another consideration is how patients who develop recurrence be managed.

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INTRODUCTION

Rectal cancer is one of the challenging colorectal conditions and is responsible for a significant portion of cancer-related morbidity and mortality. The current gold standard treatment of rectal cancer is total mesorectal excision (TME) which aims at reducing the incidence of local recurrence[1]. Patients with locally advanced rectal cancers should be treated upfront with neoadjuvant chemoradiation therapy to help downstage the tumor and clear lateral lymph node involvement. As neoadjuvant treatments evolved to include the new concept of total neoadjuvant therapy (TNT)[2], an increasing number of patients were found to exhibit complete response to neoadjuvant therapy with no residual tumor cells in the rectum or the lymph nodes after radical resection, known as pathologic complete response. The complete response of rectal cancers to neoadjuvant treatment inspired one of the colorectal surgery leaders, Dr Angelita Habr-Gama, the concept of non-operative management (NOM) of rectal cancer in patients with a complete response to treatment. NOM simply entails that patients with a complete response may not undergo TME as previously planned, but rather be subject to strict surveillance to detect early recurrence of cancer, if occurred, known as the Watch & Wait strategy[3]. In this editorial, we highlight the main controversies on NOM of rectal cancer, with implications for future research directions.

'WHO' SHOULD RECEIVE NOM?

Patients eligible for NOM should be those with a clinical complete response after neoadjuvant radiation. However, even some patients with a clinical near-complete response may also be eligible for NOM as 15% of them have evidence of complete pathologic response after surgery[4]. Some authors suggest that the ideal candidates for NOM are patients with middle or low rectal cancers who would otherwise have a low colorectal/coloanal anastomosis or an abdominoperineal resection if were surgically treated as planned[5]. However, even patients with upper rectal cancers may opt for NOM to avoid the consequences of surgery, namely low anterior resection syndrome and autonomic nerve injury with subsequent genitourinary dysfunction.

Consistent with the current guidelines, imaging and endoscopy should be the standard tools for assessment of clinical response after neoadjuvant therapy, in comparison to the baseline before initiation of treatment[6]. Combined with digital rectal examination, these tools have a very high accuracy in excluding residual tumors and verifying a complete response [7]. The evaluation criteria for a clinical complete response of rectal cancer comprise a complete disappearance of all cancerous lesions in clinical examination as shown by the absence of residual ulceration, masses, or mucosal irregularity together with the absence of residual nodal disease on imaging with a reduction in short axis of pathologic lymph nodes to less than 1 cm[8,9].

The conclusions of follow-up imaging after treatment may not be very reliable. Gefen *et al*[10] showed that restaging magnetic resonance imaging (MRI) had a fair concordance with the pathology report for the T stage (kappa -0.316) and slight concordance for the N stage (kappa -0.11) and CRM status, (kappa = 0.089). The concordance was even lower when TNT was used. Some 73% of patients with pathologic N+ stage had no evidence of nodal involvement in the restaging MRI which calls for caution when interpreting the MRI assessment of nodal disease. Because of imaging inaccuracies, patients with a residual disease and false negative imaging may be treated with NOM, and patients who responded to treatment yet had false positive imaging be precluded from NOM and undergo surgery that can otherwise be unnecessary.

Another controversy regarding patient selection for NOM is patients with adverse baseline features such as involved mesorectal fascia, extramural venous invasion, and extensive lymph node involvement[11]. In addition, ulcerating and annular lesions may not be eligible for NOM since they may undergo extensive fibrosis after radiation therapy with subsequent luminal stenosis that may hinder endoscopic assessment and follow-up[9]. Furthermore, another hurdle related to the inaccurate assessment of clinical response is the potential of missing residual nodal disease even with a complete mucosal response. A large database analysis found that 8% of patients with complete mucosal response had positive lymph nodes on pathologic assessment after surgery[12]. These patients with residual nodal disease may not have been detected using imaging which has a low sensitivity in detecting nodal involvement in rectal cancer[13]. This calls for more novel tools for the assessment of complete response after neoadjuvant therapy, some of these tools, including dynamic contrast-enhanced MRI, ctDNA, and molecular biomarkers, are still under investigation[5].

Selection of patients for NOM should ideally be based on clinical complete response as evident by clinical and imaging tools. Recently, some prediction models have been developed to help predict complete response after neoadjuvant therapy. Shin and colleagues[14] analyzed data of 1089 patients with rectal cancer and constructed a prognostic model for complete response to neoadjuvant therapy that incorporated clinical N0 stage, small (< 4 cm) and well differentiated cancers. Artificial intelligence (AI) was also used to generate predictive models based on pretreatment MRI. A systematic review[15] of 21 AI studies based on MRI-predicted complete response to neoadjuvant therapy found AI to have an

exceptional accuracy with a pooled area under the curve of the models assessed of 0.91 and pooled sensitivity and specificity of 82% and 86%, respectively.

'WHEN' TO REASSESS THE RESPONSE OF RECTAL CANCER TO NEOADJUVANT TREATMENT?

Another controversy related to patient selection is when is the optimal time to assess the response to treatment. It has been shown that a too-early assessment may erroneously render a wrong judgment of an incomplete response. Generally, an interval >8 wk after neoadjuvant treatment is needed before reassessment to measure the maximal tumor regression. However, this interval has not been agreed upon in the literature and could range from four to 20 wk. Some investigators suggested an 8-wk interval while others thought a 12-wk interval would be ideal before reassessment[16,17]. The minimum cutoff of 8 wk was selected because a reassessment earlier than 8 wk may fail to detect complete regression of cancer that can be still ongoing, and thus could be misinterpreted as an incomplete response. Based on the same concept, an interval of > 8 wk before reassessment was proposed to allow for maximal tumor regression and thus more precise assessment of response. Nonetheless, this lack of consensus is considered another important controversy that needs more research to resolve.

'HOW' SHOULD PATIENTS UNDERGOING NOM BE FOLLOWED UP?

The standard methods used for surveillance after NOM include digital rectal examination, Pelvic MRI, and endoscopy. In addition, carcinoembryonic antigen (CEA)-level assessment and computed tomography (CT) scans of the chest, abdomen, and pelvis may be also used for surveillance. The protocol used for follow-up of patients undergoing NOM quite varies. The first protocol described by Habr-Gama *et al*[18] entailed follow-up with a digital rectal examination, proctoscopy, and CEA level measurement every 6-10 wk in the first two years then the follow-up is scheduled every three months in the third year and every 6 months afterward. Another follow-up protocol entailed digital rectal examination and MRI every six months in the first two years and endoscopic examination plus CT scan of the chest, abdomen, and pelvis in the first two years[17].

A standardized surveillance program for the NOM of rectal cancer has yet to be established. Each society guideline offers different recommendations regarding the methods and frequency of surveillance. This diversity in guidance is logical, given the varying nature of disease recurrence, which may necessitate different surveillance approaches that would involve physical examinations, blood markers such as CEA, imaging, and endoscopy.

While a comprehensive review[19], aggregating data from eight meta-analyses of RCTs, revealed a unanimous and significant benefit of surveillance strategies, the question of whether intensive or less intensive follow-up regimens confer superior outcomes is still open. According to ASCO guidelines[20], for patients with stage II or III disease, the initial 2-4 years after surgery should involve more rigorous testing, as approximately 80% of recurrences are detected within the first two years. Conversely, the NCCN[6] and ESMO[21] guidelines recommended a semi-annual to annual abdomen and chest CT scanning over 5 years, considering that up to 10% of recurrences occur after 3 years. ASCRS[22] guidelines closely align with these recommendations, emphasizing the potential survival benefits of follow-up for patients with stage I disease. Less intensive surveillance programs are suggested by ESMO and ACPGBI[23], consisting of a minimum of two CT scans of the chest, abdomen, and pelvis with a regular CEA-level assessment in the first three years.

Surveillance strategies may also vary based on the type of initial management received. For instance, the ASCRS[22] and NCCN[6] guidelines advocate for a more intensive approach for patients treated with transanal excision, while ASCO suggests an equally intensive approach for patients who did not receive radiotherapy. Overall, the NCCN guidelines[6] tend to recommend more frequent surveillance compared to other programs. A survey conducted by the ASCRS in 2000[24] assessed the methods and frequency of follow-up. Interestingly, the survey revealed a wide range of diagnostic modalities utilized in surveillance, with only 50% of surgeons adhering to the recommendations of ASCRS guidelines. This discrepancy could be attributed to the divergent guidelines, making it challenging for surgeons to determine the most effective surveillance method.

'WHAT' SHOULD BE DONE WHEN LOCAL RECURRENCE AFTER NOM IS DETECTED?

Disease recurrence after NOM is the most serious adverse effect of this treatment strategy. The 3-year cumulative risk of local recurrence after NOM in patients with clinical complete response is approximately 25%[25]. The pretreatment T stage is considered the most influential risk factor for local recurrence after NOM. The risk of local recurrence tends to increase by 10% for every transition in the T stage[26]. Early recognition of local recurrence in the setting of NOM is of paramount importance. Patients in whom local recurrence was detected early may have similar survival outcomes to patients with an incomplete response after neoadjuvant treatment[27]. However, other studies implied a negative impact of local recurrence on survival[28].

Management of local recurrence in the setting of NOM may represent a clinical challenge. Local recurrences may be managed by either a radical or local excisional surgery. While local excision preserves the rectum and obviates the risk of major surgery associated with proctectomy, it may be associated with considerably higher rates of positive resection margins, and thus disease recurrence. Most (> 90%) local recurrences of rectal cancer can be treated with salvage sph-

incter-sparing surgery[29]. Smith *et al*[30] reported an 83% R0 rate after treating six patients with local recurrence after NOM for rectal cancer. On the other hand, conflicting outcomes were reported after wide local excision of local recurrence after NOM. While Li *et al*[31] successfully treated two patients with local recurrence after NOM by local excision, another study that treated local recurrence after NOM by transanal endoscopic surgery reported positive surgical margins that warranted an abdominoperineal resection[32]. Despite that local recurrence after NOM may be adequately managed, there remains the risk of distant metastatic disease that can be as high as 8%-10%[33]. Figure 1 illustrates the main controversies about NOM of rectal cancer.

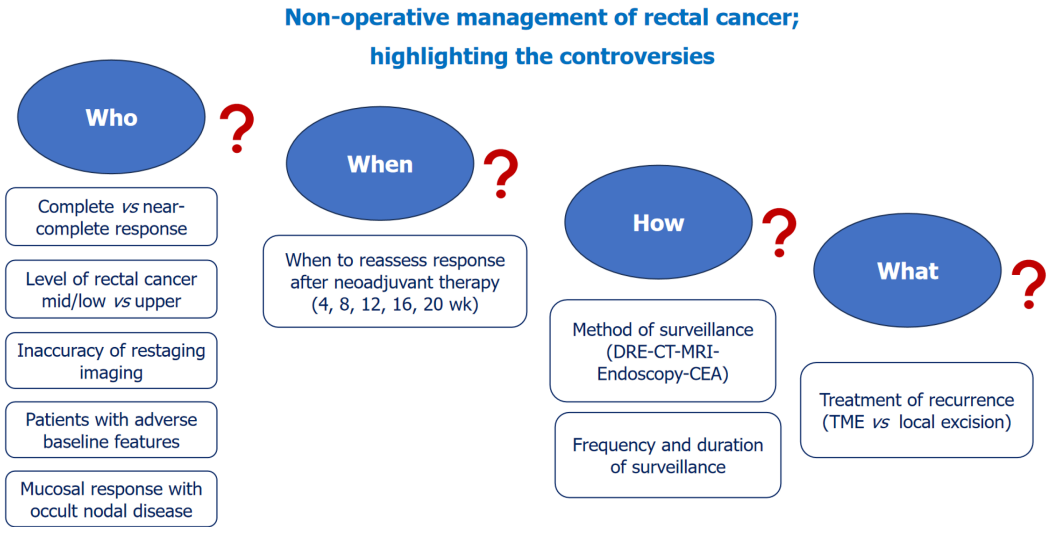


Figure 1 The main controversies about non-operative management of rectal cancer. CT: Computed tomography; MRI: Magnetic resonance imaging; DRE: Digital rectal examination; CEA: Carcinoembryonic antigen; TME: Total mesorectal excision.

CONCLUSION

NOM of rectal cancer that showed complete response to neoadjuvant therapy is a viable option in select patients. There are several controversies on the optimal method for and timing of assessment of complete response, surveillance strategies, and management of local recurrence. Hence, further studies are needed to help resolve these controversies to achieve the best outcomes of this novel management strategy.

FOOTNOTES

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REFERENCES

1 **Ridgway PF**, Darzi AW. The role of total mesorectal excision in the management of rectal cancer. *Cancer Control* 2003; **10**: 205-211 [PMID: 12794618 DOI: 10.1177/107327480301000303]

2 **Lin W**, Li C, Clement EA, Brown CJ, Raval MJ, Karimuddin AA, Ghuman A, Phang PT. Surgical Outcomes in Total Neoadjuvant Therapy for Rectal Cancer Versus Standard Long-course Chemoradiation: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Ann Surg* 2024; **279**: 620-630 [PMID: 38009646 DOI: 10.1097/SLA.0000000000006161]

3 **Habr-Gama A**, Perez RO. Non-operative management of rectal cancer after neoadjuvant chemoradiation. *Br J Surg* 2009; **96**: 125-127 [PMID: 19160360 DOI: 10.1002/bjs.6470]

4 **Habr-Gama A**, Perez RO, Nadalin W, Sabbaga J, Ribeiro U Jr, Silva e Sousa AH Jr, Campos FG, Kiss DR, Gama-Rodrigues J. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann Surg* 2004; **240**: 711-718 [PMID: 15383798 DOI: 10.1097/01.sla.0000141194.27992.32]

5 **Goffredo P**, Quezada-Diaz FF, Garcia-Aguilar J, Smith JJ. Non-Operative Management of Patients with Rectal Cancer: Lessons Learnt from the OPRA Trial. *Cancers (Basel)* 2022; **14** [PMID: 35804975 DOI: 10.3390/cancers14133204]

6 **Benson AB**, Venook AP, Al-Hawary MM, Azad N, Chen YJ, Ciombor KK, Cohen S, Cooper HS, Deming D, Garrido-Laguna I, Grem JL, Gunn A, Hecht JR, Hoffe S, Hubbard J, Hunt S, Jeck W, Johung KL, Kirilcuk N, Krishnamurthi S, Maratt JK, 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, Stotsky-Himelfarb E, Tavakkoli A, Willett CG, Gregory K, Gurski L. Rectal Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2022; 20: 1139-1167 [PMID: 36240850 DOI: 10.6004/jnccn.2022.0051]

7 **Maas M**, Lambregts DM, Nelemans PJ, Heijnen LA, Martens MH, Leijtens JW, Sosef M, Hulsewé KW, Hoff C, Breukink SO, Stassen L, Beets-Tan RG, Beets GL. Assessment of Clinical Complete Response After Chemoradiation for Rectal Cancer with Digital Rectal Examination, Endoscopy, and MRI: Selection for Organ-Saving Treatment. *Ann Surg Oncol* 2015; **22**: 3873-3880 [PMID: 26198074 DOI: 10.1245/s10434-015-4687-9]

8 **Eisenhauer EA**, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228-247 [PMID: 19097774 DOI: 10.1016/j.ejca.2008.10.026]

9 **Habr-Gama A**, Perez RO, Wynn G, Marks J, Kessler H, Gama-Rodrigues J. Complete clinical response after neoadjuvant chemoradiation therapy for distal rectal cancer: characterization of clinical and endoscopic findings for standardization. *Dis Colon Rectum* 2010; **53**: 1692-1698 [PMID: 21178866 DOI: 10.1007/DCR.0b013e3181f42b89]

10 **Gefen R**, Garoufalia Z, Horesh N, Freund MR, Emile SH, Parlade A, Berho M, Allende D, DaSilva G, Wexner SD. How reliable is restaging MRI after neoadjuvant therapy in rectal cancer? *Colorectal Dis* 2023; **25**: 1631-1637 [PMID: 37376824 DOI: 10.1111/codi.16641]

11 **Smith N**, Brown G. Preoperative staging of rectal cancer. *Acta Oncol* 2008; **47**: 20-31 [PMID: 17957502 DOI: 10.1080/02841860701697720]

12 **Emile SH**, Maron DJ, Horesh N, Garoufalia Z, Gefen R, Zhou P, Wexner SD. Predictors of Nodal Disease in Rectal Cancer Patients with Complete Mucosal Response to Neoadjuvant Therapy. *World J Surg* 2023; **47**: 2013-2022 [PMID: 37084107 DOI: 10.1007/s00268-023-07012-6]

13 **Emile SH**, Silva-Alvarenga E, Horesh N, Freund MR, Garoufalia Z, Wexner SD. Concordance between clinical and pathologic assessment of T and N stages of rectal adenocarcinoma patients who underwent surgery without neoadjuvant therapy: A National Cancer Database analysis. *Eur J Surg Oncol* 2023; **49**: 426-432 [PMID: 36257901 DOI: 10.1016/j.ejso.2022.09.014]

14 **Shin JK**, Huh JW, Lee WY, Yun SH, Kim HC, Cho YB, Park YA. Clinical prediction model of pathological response following neoadjuvant chemoradiotherapy for rectal cancer. *Sci Rep* 2022; **12**: 7145 [PMID: 35504888 DOI: 10.1038/s41598-022-10974-7]

15 **Jia LL**, Zheng QY, Tian JH, He DL, Zhao JX, Zhao LP, Huang G. Artificial intelligence with magnetic resonance imaging for prediction of pathological complete response to neoadjuvant chemoradiotherapy in rectal cancer: A systematic review and meta-analysis. *Front Oncol* 2022; **12**: 1026216 [PMID: 36313696 DOI: 10.3389/fonc.2022.1026216]

16 **Byun HK**, Koom WS. A practical review of watch-and-wait approach in rectal cancer. *Radiat Oncol J* 2023; **41**: 4-11 [PMID: 37013413 DOI: 10.3857/roj.2023.00038]

17 **Renehan AG**, Malcomson L, Emsley R, Gollins S, Maw A, Myint AS, Rooney PS, Susnerwala S, Blower A, Saunders MP, Wilson MS, Scott N, O'Dwyer ST. Watch-and-wait approach *vs* surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. *Lancet Oncol* 2016; **17**: 174-183 [PMID: 26705854 DOI: 10.1016/S1470-2045(15)00467-2]

18 **Habr-Gama A**, São Julião GP, Vailati BB, Sabbaga J, Aguilar PB, Fernandez LM, Araújo SEA, Perez RO. Organ Preservation in cT2N0 Rectal Cancer After Neoadjuvant Chemoradiation Therapy: The Impact of Radiation Therapy Dose-escalation and Consolidation Chemotherapy. *Ann Surg* 2019; **269**: 102-107 [PMID: 28742703 DOI: 10.1097/SLA.0000000000002447]

19 **Lauretta A**, Montori G, Guerrini GP. Surveillance strategies following curative resection and non-operative approach of rectal cancer: How and how long? Review of current recommendations. *World J Gastrointest Surg* 2023; **15**: 177-192 [PMID: 36896297 DOI: 10.4240/wjgs.v15.i2.177]

20 **Meyerhardt JA**, Mangu PB, Flynn PJ, Korde L, Loprinzi CL, Minsky BD, Petrelli NJ, Ryan K, Schrag DH, Wong SL, Benson AB 3rd; American Society of Clinical Oncology. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. *J Clin Oncol* 2013; **31**: 4465-4470 [PMID: 24220554 DOI: 10.1200/JCO.2013.50.7442]

21 **Glynne-Jones R**, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, Arnold D; ESMO Guidelines Committee. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; **28**: iv22-iv40 [PMID: 28881920 DOI: 10.1093/annonc/mdx224]

22 **Hardiman KM**, Felder SI, Friedman G, Migaly J, Paquette IM, Feingold DL; Prepared on behalf of the Clinical Practice Guidelines Committee of the American Society of Colon and Rectal Surgeons. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Surveillance and Survivorship Care of Patients After Curative Treatment of Colon and Rectal Cancer. *Dis Colon Rectum* 2021; **64**: 517-533 [PMID: 33591043 DOI: 10.1097/DCR.0000000000001984]

23 **Leong K**, Hartley J, Karandikar S. Association of Coloproctology of Great Britain & Ireland (ACPGBI): Guidelines for the Management of Cancer of the Colon, Rectum and Anus (2017) - Follow Up, Lifestyle and Survivorship. *Colorectal Dis* 2017; **19** Suppl 1: 67-70 [PMID: 28632315 DOI: 10.1111/codi.13706]

24 **Giordano P**, Efron J, Vernava AM 3rd, Weiss EG, Nogueras JJ, Wexner SD. Strategies of follow-up for colorectal cancer: a survey of the

American Society of Colon and Rectal Surgeons. *Tech Coloproctol* 2006; **10**: 199-207 [PMID: 16969616 DOI: 10.1007/s10151-006-0280-3]

25 **Dattani M**, Heald RJ, Goussous G, Broadhurst J, São Julião GP, Habr-Gama A, Perez RO, Moran BJ. Oncological and Survival Outcomes in Watch and Wait Patients With a Clinical Complete Response After Neoadjuvant Chemoradiotherapy for Rectal Cancer: A Systematic Review and Pooled Analysis. *Ann Surg* 2018; **268**: 955-967 [PMID: 29746338 DOI: 10.1097/SLA.0000000000002761]

26 **Chadi SA**, Malcomson L, Ensor J, Riley RD, Vaccaro CA, Rossi GL, Daniels IR, Smart NJ, Osborne ME, Beets GL, Maas M, Bitterman DS, Du K, Gollins S, Sun Myint A, Smith FM, Saunders MP, Scott N, O'Dwyer ST, de Castro Araujo RO, Valadao M, Lopes A, Hsiao CW, Lai CL, Smith RK, Paulson EC, Appelt A, Jakobsen A, Wexner SD, Habr-Gama A, Sao Julião G, Perez R, Renehan AG. Factors affecting local regrowth after watch and wait for patients with a clinical complete response following chemoradiotherapy in rectal cancer (InterCoRe consortium): an individual participant data meta-analysis. *Lancet Gastroenterol Hepatol* 2018; **3**: 825-836 [PMID: 30318451 DOI: 10.1016/S2468-1253(18)30301-7]

27 **Habr-Gama A**, Perez RO, Proscurshim I, Nunes Dos Santos RM, Kiss D, Gama-Rodrigues J, Cecconello I. Interval between surgery and neoadjuvant chemoradiation therapy for distal rectal cancer: does delayed surgery have an impact on outcome? *Int J Radiat Oncol Biol Phys* 2008; **71**: 1181-1188 [PMID: 18234443 DOI: 10.1016/j.ijrobp.2007.11.035]

28 **Smith JJ**, Strombom P, Chow OS, Roxburgh CS, Lynn P, Eaton A, Widmar M, Ganesh K, Yaeger R, Cercek A, Weiser MR, Nash GM, Guillem JG, Temple LKF, Chalasani SB, Fuqua JL, Petkovska I, Wu AJ, Reyngold M, Vakiani E, Shia J, Segal NH, Smith JD, Crane C, Gollub MJ, Gonen M, Saltz LB, Garcia-Aguilar J, Paty PB. Assessment of a Watch-and-Wait Strategy for Rectal Cancer in Patients With a Complete Response After Neoadjuvant Therapy. *JAMA Oncol* 2019; **5**: e185896 [PMID: 30629084 DOI: 10.1001/jamaoncol.2018.5896]

29 **Habr-Gama A**, Gama-Rodrigues J, São Julião GP, Proscurshim I, Sabbagh C, Lynn PB, Perez RO. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. *Int J Radiat Oncol Biol Phys* 2014; **88**: 822-828 [PMID: 24495589 DOI: 10.1016/j.ijrobp.2013.12.012]

30 **Smith JD**, Ruby JA, Goodman KA, Saltz LB, Guillem JG, Weiser MR, Temple LK, Nash GM, Paty PB. Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. *Ann Surg* 2012; **256**: 965-972 [PMID: 23154394 DOI: 10.1097/SLA.0b013e3182759f1c]

31 **Li J**, Li L, Yang L, Yuan J, Lv B, Yao Y, Xing S. Wait-and-see treatment strategies for rectal cancer patients with clinical complete response after neoadjuvant chemoradiotherapy: a systematic review and meta-analysis. *Oncotarget* 2016; **7**: 44857-44870 [PMID: 27070085 DOI: 10.18632/oncotarget.8622]

32 **Smith RK**, Fry RD, Mahmoud NN, Paulson EC. Surveillance after neoadjuvant therapy in advanced rectal cancer with complete clinical response can have comparable outcomes to total mesorectal excision. *Int J Colorectal Dis* 2015; **30**: 769-774 [PMID: 25787162 DOI: 10.1007/s00384-015-2165-2]

33 **van der Valk MJM**, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL, Habr-Gama A, Perez RO, Renehan AG, van de Velde CJH; IWWD Consortium. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. *Lancet* 2018; **391**: 2537-2545 [PMID: 29976470 DOI: 10.1016/S0140-6736(18)31078-X]

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EDITORIAL

Current considerations for the surgical management of gallbladder adenomas

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Abstract

Gallbladder adenomas are rare lesions (0.5%) associated with potential malignant transformation, particularly with gallbladder adenomas that are ≥ 1 cm in size. Early detection and management are crucial for preventing lethal carcinoma development. These polyps can often be distinguished from the more often nonneoplastic cholesterol pseudopolyps (5%-10%), which are benign. Ultrasonography is the first-line tool for initial diagnosis and follow-up when indicated. The question is whether cholecystectomy is always necessary for all adenomas. The management of gallbladder adenomas is determined according to the size of the tumor, the growth rate of the tumor, the patient's symptoms and whether risk factors for malignancy are present. Adenomas ≥ 1 cm in size, an age > 50 years and a familial history of gallbladder carcinoma are indications for immediate laparoscopic cholecystectomy. Otherwise, ultrasound follow-up is indicated. For adenomas 6-9 mm in size, the absence of ≥ 2 mm growth at 6 months, one year, and two years, as well as an adenoma sized < 5 mm without existing risk factors indicates that no further surveillance is required. However, it would be preferable to individualize the management in doubtful cases. Novel interventional modalities for preserving the gallbladder need further evaluation, especially to determine the long-term outcomes.

Key Words: Biliary diseases; True neoplastic polyps; Gallbladder adenomas; Benign biliary tumors; Gallbladder polyps; Extrahepatic biliary neoplasms

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Core Tip: Gallbladder adenomas are rare benign neoplastic lesions associated with malignant potential. Thus, early management is essential to prevent transformation. They are usually detected incidentally by imaging. Current imaging modalities can ensure a reliable diagnosis in vague cases. The management includes either laparoscopic cholecystectomy or ultrasound surveillance.

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INTRODUCTION

Gallbladder polyps affecting 5%-10% of the adult population, consist of nonneoplastic cholesterol pseudopolyps in the vast majority of cases and they are usually discovered incidentally[1]. Adenomas or true neoplastic polyps are rare benign lesions that represent 0.5% of gallbladder neoplasms and 3%-9% of gallbladder polyps[2-5]. However, they can have malignant potential according to their size, which leads to gallbladder cancer with poor prognosis (a 5-year overall survival of 5%-8%)[6]. The malignant transformation process follows the dysplasia-carcinoma in situ-invasive carcinoma sequence[7]. The transformation is related to the adenoma's size, and the transformation rate can be as high as 5% when the size of the adenoma is ≥ 10 mm and is up to 40% when the size of the adenoma is ≥ 20 mm[2,6,8]. The early-stage diagnosis of gallbladder cancer is important for optimizing therapeutic management[9,10]. It is obvious that timely cholecystectomy prevents the progression of any adenoma, but whether timely cholecystectomy is necessary in all patients or constitutes overtreatment in some patients remains unclear[11]. Indications for immediate laparoscopic cholecystectomy include an adenoma size ≥ 10 mm or the presence of specific imaging findings, an age > 50 years and a familial history of GB carcinoma[11-15]. Otherwise, ultrasound follow-up is indicated in patients under 50 years of age who have adenomas that are < 10 mm in size and who do not have any predisposing genetic factors[7,16-19]. A follow-up is not considered necessary for patients who have an adenoma that is < 5 mm in size and who do not have any significant family history[16-19].

The initial diagnostic approach is based on plain abdominal ultrasound. The distinction of adenomas from cholesterol pseudopolyps is a challenging task. The use of computed tomography (CT), magnetic resonance imaging (MRI), and current ultrasonic modalities, including simple endoscopic or enhanced contrast endoscopic, high resolution, and novel of three dimensions ultrasound, increase the diagnostic accuracy[6,15,18]. Various scoring system models can accurately predict true adenomas and should be developed[20-24].

The risk of malignant transformation of adenomas is correlated with age > 60 years; the presence of gallstones ≥ 3 cm for at least twenty years; a polyp size equal to or greater than 10 mm; patient origin from Asia, mainly India[25]; chronic infection by *Salmonella*[7] or *Helicobacter pylori* (*H. pylori*)[26]; a body mass index greater than 30 kg/m^2; a diagnosis of schistosomiasis[27]; a diagnosis of primary sclerosing cholangitis; a polyp with a broad basis; and a thickened gallbladder wall greater than 4 mm and/or the presence of an abnormal gallbladder wall layer[7,15,18,28]. *H. pylori* may not be associated with gallbladder adenoma or gallstone formation[29]. However, the most reliable risk factor for malignant transformation of gallbladder adenomas is size, regardless of the presence or absence of other factors[30].

Minimally invasive procedures for polypectomy alone, in which the gallbladder is preserved and is functional, have recently gained increasing interest[31]. These methods include: (1) Ultrasound-guided radiofrequency for adenoma ablation[32-34]; (2) endoscopic cholecystostomy under ultrasound guidance, which serves as a bridging procedure to endoscopic polypectomy through the gallbladder wall[35,36]; (3) laparoscopic-assisted transumbilical gastroscopy for gallbladder-preserving adenoma resection[37-39]; (4) peroral choledochoscopic gallbladder-preserving adenoma resection[40,41]; and (5) transgastric endoscopic gallbladder preserving surgery[42]. However, there are still no adequate data available, and these novel approaches require expertise and further evaluation, including further evaluation of the long-term outcomes. Additionally, some skepticism exists about the use of these methods in the current era of laparoscopic cholecystectomy, which is a minimally invasive procedure.

DIAGNOSIS

For gallbladder pathology assessment and differentiation of malignant from benign lesions, the most applicable diagnostic technique worldwide in clinical practice is ultrasound[43-45], and CT[46] and MRI are the second most applicable diagnostic techniques[6,47,48]. However, ultrasound alone is not accurate enough[49]. Further reliability can be obtained with additional CT scans, or better yet, MRI, and this highlights the misdiagnosis bias and can prevent unnecessary operations and thus overtreatment[50]. When a strong possibility of malignancy exists clinically, MRI should be the first-line imaging modality. Contrast-enhanced or endoscopic ultrasound (EUS) is valuable when the equipment is available [28]. High-frequency ultrasound in combination with color Doppler ultrasound constitutes a valuable diagnostic modality with high diagnostic accuracy for gallbladder adenomas (sensitivity of over 90% and specificity of 100%)[51]. High-resolution ultrasound is considered particularly reliable for the assessment of the gallbladder wall layering[49]. In sus-

picious cases, EUS provides high-resolution images, and the combination of EUS with fine needle aspiration ensures the safe diagnosis of malignant transformation of adenomas[52].

During the recommended ultrasound follow-up of small gallbladder adenomas, a growth rate ≥ 2 mm is considered a risk factor for malignant transformation, indicating that there should be no delay in pursuing cholecystectomy[53,54]. In general, a size of 10 mm is considered the limit for operative intervention, while a size of 7 mm is an indication for waiting and ultrasound follow-up[55].

The tumor markers CA19-9, CEA, CA125, and CA242 may be elevated in patients with gallbladder carcinoma, and measurements of these markers can contribute to the early diagnosis of gallbladder carcinoma[56]. In patients with an adenoma ≥ 11 mm in size, increased CA19-9, CEA, and CA72-4 levels constitute strong indications of malignant transformation[57].

SURGICAL MANAGEMENT

The therapeutic management of gallbladder adenomas remains somewhat debated. The European Association for Endoscopic Surgery and other Interventional Techniques, the European Society of Gastrointestinal Endoscopy, the International Society of Digestive Surgery - European Federation and the European Society of Gastrointestinal and Abdominal Radiology have set guidelines[58], and these guidelines have recently been updated[15]. The recommended management depends on whether symptoms are present and the size and the rate of adenoma growth[28]. However, due to the rarity of gallbladder adenomas, there are few large studies, and the current studies have provided low-quality data and thus somewhat unreliable recommendations. In addition, obtaining new knowledge and following the current guidelines are crucial for the correct treatment of gallbladder adenomas[28].

Cholecystectomy is strongly recom-mended for adenomas ≥ 10 mm in size, those that are associated with symptoms, regardless of size, and those with a growth rate of ≥ 2 mm within two years. Monitoring is recommended for patients with smaller lesions, regardless of whether the patient is or without risk factors[15,28,58]. The assessment and definition of risk factors is a multidisciplinary task[20,37,58].

For patients with adenomas 6-9 mm in size without growth or a small size increase ≤ 2 mm during the scheduled follow-up at 6 months, one year, and two years, follow-up should be terminated[8,15,28,58]. Cholecystectomy is recommended for patients who are fit for surgery if any risk factor for malignancy is found at the initial diagnosis of adenomas that are 6-9 mm in size, and surgery should be performed after patients are reassured and consent is obtained[6,15,28,58].

For patients with adenomas ≤ 5 mm in size without risk factors, no follow-up is necessary. Otherwise, follow-up lasting two years is recommended[11,15,19,58]. These small adenomas have a low risk of size increase, and there are no reports of malignant transformation in these types of tumors according to long-term (up to 10 years) ultrasound follow-up[59]. Subsequently, small adenoma surveillance has limited benefit and is not recommended[16]. However, when a risk factor coexists, ultrasound surveillance lasting at least 5 years is recommended, and for any 2 mm increase in the adenoma's size, imperative cholecystectomy is recommended[60].

Laparoscopic cholecystectomy is currently the gold standard for gallbladder adenomas that require interventional procedures[6,15,61]. However, if a gallbladder adenoma ≥ 20 mm in size exists, a surgical plan similar to that of gallbladder carcinoma will be drawn up, as long as there are not any preoperative evidence or even an indication of malignancy[62]. Laparoscopic cholecystectomy is not recommended for such patients since there is a strong possibility of malignant transformation[63]. Thus, an open surgery should preferably be carried out by a surgeon experienced in hepatobiliary surgery, who should keep in mind the following cancer management strategy.

For patients with adenomas 10-15 mm in size or with gallbladder wall thickening, it is recommended that an experienced general surgeon safely perform laparoscopic cholecystectomy, as long as there is not any preoperative evidence or even an indication of malignancy. It is of the utmost importance to avoid gallbladder perforation in any case to prevent the possible intraperitoneal spread of cancer cells in cases of initially hidden malignancy, which will eventually be discovered *via* specimen biopsy. This obligation may necessitate the conversion of laparoscopic surgery to open surgery without any hesitation due to the possible operative difficulties encountered[60,64].

In cases where a cholecystectomy specimen biopsy is used to diagnose gallbladder adenocarcinoma, the extent of subsequent surgical resection depends on the disease stage. An already performed simple cholecystectomy is an adequate treatment for stage T1a disease, and no further treatment is needed. Otherwise, for more advanced disease, an additional operation will be needed. Some of the additional operations include wide lymphadenectomy in every case, accompanied by complementary gallbladder bed hepatic resection, in patient with T1b stage; resection of the IV and V hepatic segments for patients with T2 stage; hepatic trisegmentectomy or major hepatectomy with Roux-Y hepaticojejunostomy and, if needed, adjacent organ resection for patients with T3 stage[9,65].

CONCLUSION

Gallbladder adenomas have a low incidence but have a risk of malignancy. These patients are usually asymptomatic, and these tumors are usually detected incidentally by imaging. The management policy must be planned according to whether symptoms are present as well as the size and the rate of adenoma growth. Gallbladder removal is needed for all patients with tumors sized ≥ 10 mm, those patients who have a tumor 6-9 mm in size with a coexisting malignancy risk factor, those who have symptoms, those who have gallstones, and those who have had an adenoma growth rate ≥ 2 mm during the regular two-year ultrasound follow-up. For small adenomas ≤ 5 mm in size without risk factors, no follow-up

is needed. The management of gallbladder adenomas should be individualized in ambiguous cases.

FOOTNOTES

Author contributions: Pavlidis TE designed research, contributed new analytic tools, analyzed data and review; Galanis IN analyzed data and review; Pavlidis ET performed research, analyzed data, review and wrote the article.

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REFERENCES

1 **Tian F**, Ma YX, Liu YF, Liu W, Hong T, He XD, Qu Q. Management Strategy for Gallbladder Polypoid Lesions: Results of a 5-Year Single-Center Cohort Study. *Dig Surg* 2022; **39**: 263-273 [PMID: 36696883 DOI: 10.1159/000529221]
2 **Inzunza M**, Irarrazaval MJ, Pozo P, Pimentel F, Crovari F, Ibañez L. Gallbladder polyps: correlation and agreement between ultrasonographic and histopathological findings in a population with high incidence of gallbladder cancer. *Arq Bras Cir Dig* 2023; **36**: e1732 [PMID: 37162074 DOI: 10.1590/0102-672020230002e1732]
3 **Alyanak A**, Aslan F. Gallbladder Polyp and Cancer Evaluation After Cholecystectomy: A Retrospective Observational Study. *Cureus* 2022; **14**: e28089 [PMID: 36127982 DOI: 10.7759/cureus.28089]
4 **Foley KG**, Riddell Z, Coles B, Roberts SA, Willis BH. Risk of developing gallbladder cancer in patients with gallbladder polyps detected on transabdominal ultrasound: a systematic review and meta-analysis. *Br J Radiol* 2022; **95**: 20220152 [PMID: 35819918 DOI: 10.1259/bjr.20220152]
5 **Li Y**, Tejirian T, Collins JC. Gallbladder Polyps: Real or Imagined? *Am Surg* 2018; **84**: 1670-1674 [PMID: 30747692]
6 **McCain RS**, Diamond A, Jones C, Coleman HG. Current practices and future prospects for the management of gallbladder polyps: A topical review. *World J Gastroenterol* 2018; **24**: 2844-2852 [PMID: 30018479 DOI: 10.3748/wjg.v24.i26.2844]
7 **Kjær MK**, Erritzøe LW, Helgestrand UF, Nolsøe CP. Follow-up programmes for gallbladder polyps. *Ugeskr Laeger* 2023; **185** [PMID: 37539809]
8 **Kalbi DP**, Bapatla A, Chaudhary AJ, Bashar S, Iqbal S. Surveillance of Gallbladder Polyps: A Literature Review. *Cureus* 2021; **13**: e16113 [PMID: 34350077 DOI: 10.7759/cureus.16113]
9 **Pavlidis ET**, Galanis IN, Pavlidis TE. New trends in diagnosis and management of gallbladder carcinoma. *World J Gastrointest Oncol* 2024; **16**: 13-29 [PMID: 38292841 DOI: 10.4251/wjgo.v16.i1.13]
10 **Szpakowski JL**, Tucker LY. Outcomes of Gallbladder Polyps and Their Association With Gallbladder Cancer in a 20-Year Cohort. *JAMA Netw Open* 2020; **3**: e205143 [PMID: 32421183 DOI: 10.1001/jamanetworkopen.2020.5143]
11 **Metman MJH**, Olthof PB, van der Wal JBC, van Gulik TM, Roos D, Dekker JWT. Clinical relevance of gallbladder polyps; is cholecystectomy always necessary? *HPB (Oxford)* 2020; **22**: 506-510 [PMID: 31481314 DOI: 10.1016/j.hpb.2019.08.006]
12 **Politano SA**, Hamiduzzaman N, Alhaqqan D. Diseases of the Gallbladder and Biliary Tree. *Prim Care* 2023; **50**: 377-390 [PMID: 37516509 DOI: 10.1016/j.pop.2023.03.004]
13 **Pickering O**, Pucher PH, Toale C, Hand F, Anand E, Cassidy S, McEntee G, Toh SKC. Prevalence and Sonographic Detection of Gallbladder Polyps in a Western European Population. *J Surg Res* 2020; **250**: 226-231 [PMID: 32106001 DOI: 10.1016/j.jss.2020.01.003]
14 **Konstantinoff KS**, Feister KF, Mellnick VM. RadioGraphics Update: New Follow-up and Management Recommendations for Polypoid Lesions of the Gallbladder. *Radiographics* 2023; **43**: e220189 [PMID: 36757883 DOI: 10.1148/rg.220189]
15 **Foley KG**, Lahaye MJ, Thoeni RF, Soltes M, Dewhurst C, Barbu ST, Vashist YK, Rafaelsen SR, Arvanitakis M, Perinel J, Wiles R, Roberts SA. Management and follow-up of gallbladder polyps: updated joint guidelines between the ESGAR, EAES, EFISDS and ESGE. *Eur Radiol* 2022; **32**: 3358-3368 [PMID: 34918177 DOI: 10.1007/s00330-021-08384-w]
16 **Seguin CL**, Davidi B, Peters MLB, Eckel A, Harisinghani MG, Goiffon RJ, Knudsen AB, Pandharipande PV. Ultrasound Surveillance of Small, Incidentally Detected Gallbladder Polyps: Projected Benefits by Sex, Age, and Comorbidity Level. *J Am Coll Radiol* 2023; **20**: 1031-1041 [PMID: 37406750 DOI: 10.1016/j.jacr.2023.05.015]
17 **Kang SK**. Weighing the Trade-Offs of a Revised Approach to Small Gallbladder Polyps. *J Am Coll Radiol* 2023; **20**: 1042-1043 [PMID: 37422160 DOI: 10.1016/j.jacr.2023.06.006]
18 **Son JH**. [Recent Updates on Management and Follow-up of Gallbladder Polyps]. *Korean J Gastroenterol* 2023; **81**: 197-202 [PMID: 37226819 DOI: 10.4166/kjg.2023.038]
19 **Babu BI**, Dennison AR, Garcea G. Management and diagnosis of gallbladder polyps: a systematic review. *Langenbecks Arch Surg* 2015; **400**:

455-462 [PMID: 25910600 DOI: 10.1007/s00423-015-1302-2]
20 **Zhang D**, Li Q, Zhang X, Jia P, Wang X, Geng X, Zhang Y, Li J, Yao C, Liu Y, Guo Z, Yang R, Lei D, Yang C, Hao Q, Yang W, Geng Z. Establishment of a nomogram prediction model for long diameter 10-15 mm gallbladder polyps with malignant tendency. *Surgery* 2021; **170**: 664-672 [PMID: 34090677 DOI: 10.1016/j.surg.2021.04.035]
21 **Fujiwara K**, Abe A, Masatsugu T, Hirano T, Sada M. Effect of gallbladder polyp size on the prediction and detection of gallbladder cancer. *Surg Endosc* 2021; **35**: 5179-5185 [PMID: 32974780 DOI: 10.1007/s00464-020-08010-8]
22 **Wang Y**, Peng J, Liu K, Sun P, Ma Y, Zeng J, Jiang Y, Tan B, Cao J, Hu W. Preoperative prediction model for non-neoplastic and benign neoplastic polyps of the gallbladder. *Eur J Surg Oncol* 2024; **50**: 107930 [PMID: 38159390 DOI: 10.1016/j.ejso.2023.107930]
23 **Tang C**, Geng Z, Wen J, Wang L, You Q, Jin Y, Wang W, Xu H, Yu Q, Yuan H. Risk stratification model for incidentally detected gallbladder polyps: A multicentre study. *Eur J Radiol* 2024; **170**: 111244 [PMID: 38043381 DOI: 10.1016/j.ejrad.2023.111244]
24 **Choi JH**, Lee J, Lee SH, Lee S, Moon AS, Cho SH, Kim JS, Cho IR, Paik WH, Ryu JK, Kim YT. Analysis of ultrasonographic images using a deep learning-based model as ancillary diagnostic tool for diagnosing gallbladder polyps. *Dig Liver Dis* 2023; **55**: 1705-1711 [PMID: 37407319 DOI: 10.1016/j.dld.2023.06.023]
25 **Chavan S**, Rathi P. Gallbladder Polyp: Review and Proposed Algorithm for Management. *J Assoc Physicians India* 2022; **70**: 11-12 [PMID: 35062812]
26 **Lim KPK**, Lee AJL, Jiang X, Teng TZJ, Shelat VG. The link between Helicobacter pylori infection and gallbladder and biliary tract diseases: A review. *Ann Hepatobiliary Pancreat Surg* 2023; **27**: 241-250 [PMID: 37357161 DOI: 10.14701/ahbps.22-056]
27 **Emara MH**, Mahros AM, Rasheda AMA, Radwan MI, Mohamed B, Abdelrazik O, Elazab M, Elbatae H. Schistosomal (bilharzial) polyps: Travel through the colon and beyond. *World J Gastroenterol* 2023; **29**: 4156-4165 [PMID: 37475844 DOI: 10.3748/wjg.v29.i26.4156]
28 **Aziz H**, Hewitt DB, Pawlik TM. Critical Analysis of the Updated Guidelines for Management of Gallbladder Polyps. *Ann Surg Oncol* 2022; **29**: 3363-3365 [PMID: 35419760 DOI: 10.1245/s10434-022-11701-2]
29 **Zhang J**, Zhang Y, Chen Y, Chen W, Xu H, Sun W. Helicobacter pylori is not a contributing factor in gallbladder polyps or gallstones: a case-control matching study of Chinese individuals. *J Int Med Res* 2020; **48**: 300060520959220 [PMID: 33045881 DOI: 10.1177/0300060520959220]
30 **Hajibandeh S**, Ashar S, Parry C, Ellis-Owen R, Kumar N. The risk and predictors of gallbladder cancer in patients with gallbladder polyps: A retrospective cohort study with an insight into confounding by indication. *J Gastroenterol Hepatol* 2023; **38**: 2247-2253 [PMID: 37926936 DOI: 10.1111/jgh.16399]
31 **Liu H**, Lu Y, Shen K, Zhou M, Mao X, Li R. Advances in the management of gallbladder polyps: establishment of predictive models and the rise of gallbladder-preserving polypectomy procedures. *BMC Gastroenterol* 2024; **24**: 7 [PMID: 38166603 DOI: 10.1186/s12876-023-03094-7]
32 **Yue W**, Dong G, Qing Y, Sun L, Li N. Safety and Efficacy of Ultrasound-Guided Radiofrequency Ablation in the Treatment of Gallbladder Polyps. *Acad Radiol* 2024 [PMID: 38290887 DOI: 10.1016/j.acra.2024.01.016]
33 **Zhao H**, Chen Y, Zhang Z, Shang M, Cai Y, Ge J, Min X, Wu X, Zhao S, Chen B. Ultrasound-guided percutaneous microwave ablation of gallbladder polyps: A case report. *Medicine (Baltimore)* 2023; **102**: e36622 [PMID: 38134113 DOI: 10.1097/MD.0000000000036622]
34 **Chen SA**, Feng ZN, Li S, Zhang YC, Sun XL, Liu ZH, Liu MN, Jin SZ. EUS-guided gallbladder polyp resection: A new method for treatment of gallbladder polyps. *Hepatobiliary Pancreat Dis Int* 2019; **18**: 296-297 [PMID: 30497886 DOI: 10.1016/j.hbpd.2018.11.004]
35 **Shen Y**, Cao J, Zhou X, Zhang S, Li J, Xu G, Zou X, Lu Y, Yao Y, Wang L. Endoscopic ultrasound-guided cholecystostomy for resection of gallbladder polyps with lumen-apposing metal stent. *Medicine (Baltimore)* 2020; **99**: e22903 [PMID: 33120842 DOI: 10.1097/MD.0000000000022903]
36 **Ge N**, Sun S, Sun S, Wang S, Liu X, Wang G. Endoscopic ultrasound-assisted transmural cholecystoduodenostomy or cholecystogastrostomy as a bridge for per-oral cholecystoscopy therapy using double-flanged fully covered metal stent. *BMC Gastroenterol* 2016; **16**: 9 [PMID: 26782105 DOI: 10.1186/s12876-016-0420-9]
37 **Zheng Q**, Zhang G, Yu XH, Zhao ZF, Lu L, Han J, Zhang JZ, Zhang JK, Xiong Y. Perfect pair, scopes unite - laparoscopic-assisted transumbilical gastroscopy for gall-bladder-preserving polypectomy: A case report. *World J Clin Cases* 2021; **9**: 9617-9622 [PMID: 34877298 DOI: 10.12998/wjcc.v9.i31.9617]
38 **Li M**, Wu H, Wei S. New-Style Laparoscope and Endoscope Cooperative Gallbladder-Preserving Surgery for Polyps. *J Coll Physicians Surg Pak* 2016; **26**: 91-95 [PMID: 26876392]
39 **He XJ**, Chen ZP, Zeng XP, Jiang CS, Liu G, Li DL, Li DZ, Wang W. Gallbladder-preserving polypectomy for gallbladder polyp by embryonic-natural orifice transumbilical endoscopic surgery with a gastric endoscopy. *BMC Gastroenterol* 2022; **22**: 216 [PMID: 35505286 DOI: 10.1186/s12876-022-02269-y]
40 **Tao L**, Wang H, Guo Q, Du Y. Gallbladder polyp removal by hot biopsy forceps under direct visualization using a novel peroral choledochoscope. *Gastrointest Endosc* 2023; **98**: 1030-1031 [PMID: 37394039 DOI: 10.1016/j.gie.2023.06.065]
41 **Tang BF**, Dang T, Wang QH, Chang ZH, Han WJ. Confocal laser endomicroscopy distinguishing benign and malignant gallbladder polyps during choledochoscopic gallbladder-preserving polypectomy: A case report. *World J Clin Cases* 2020; **8**: 6358-6363 [PMID: 33392318 DOI: 10.12998/wjcc.v8.i24.6358]
42 **Zhang Y**, Mao XL, Zhou XB, You NN, Xu SW, Zhu LH, Ye LP. Feasibility of transgastric endoscopic gallbladder-preserving surgery for benign gallbladder diseases (with video). *Surg Endosc* 2022; **36**: 2705-2711 [PMID: 35075524 DOI: 10.1007/s00464-021-08890-4]
43 **de Sio I**, D'Onofrio M, Mirk P, Bertolotto M, Priadko K, Schiavone C, Cantisani V, Iannetti G, Vallone G, Vidili G; SIUMB experts committee. SIUMB recommendations on the use of ultrasound in neoplastic lesions of the gallbladder and extrahepatic biliary tract. *J Ultrasound* 2023; **26**: 725-731 [PMID: 37147558 DOI: 10.1007/s40477-023-00788-2]
44 **Jenssen C**, Lorentzen T, Dietrich CF, Lee JY, Chaubal N, Choi BI, Rosenberg J, Gutt C, Nolsøe CP. Incidental Findings of Gallbladder and Bile Ducts-Management Strategies: General Aspects, Gallbladder Polyps and Gallbladder Wall Thickening-A World Federation of Ultrasound in Medicine and Biology (WFUMB) Position Paper. *Ultrasound Med Biol* 2022; **48**: 2355-2378 [PMID: 36058799 DOI: 10.1016/j.ultrasmedbio.2022.06.016]
45 **Riddell ZC**, Corallo C, Albazaz R, Foley KG. Gallbladder polyps and adenomyomatosis. *Br J Radiol* 2023; **96**: 20220115 [PMID: 35731858 DOI: 10.1259/bjr.20220115]
46 **Satoh T**, Kikuyama M, Sasaki K, Ishiwatari H, Kawaguchi S, Sato J, Kaneko J, Matsubayashi H. Detectability on Plain CT is an Effective Discriminator between Carcinoma and Benign Disorder for a Polyp >10 mm in the Gallbladder. *Diagnostics (Basel)* 2021; **11** [PMID: 33668755 DOI: 10.3390/diagnostics11030388]

47 **Wennmacker SZ**, de Savornin Lohman EAJ, de Reuver PR, Drenth JPH, van der Post RS, Nagtegaal ID, Hermans JJ, van Laarhoven CJHM; Collaborator Group. Imaging based flowchart for gallbladder polyp evaluation. *J Med Imaging Radiat Sci* 2021; **52**: 68-78 [PMID: 33422451 DOI: 10.1016/j.jmir.2020.12.003]

48 **Yu MH**, Kim YJ, Park HS, Jung SI. Benign gallbladder diseases: Imaging techniques and tips for differentiating with malignant gallbladder diseases. *World J Gastroenterol* 2020; **26**: 2967-2986 [PMID: 32587442 DOI: 10.3748/wjg.v26.i22.2967]

49 **Costa AG**, Guerrero VL, Monforte MNG, González NB, Monzonís AR, Maroto BC, Borobia FG. Is ultrasonography accurate for the diagnosis of gallbladder polyps? A review of cholecystectomy specimens from patients diagnosed with gallbladder polyps over a 14-years period. *Cir Esp (Engl Ed)* 2023; **101**: 701-707 [PMID: 37748643 DOI: 10.1016/j.cireng.2023.02.009]

50 **Sabour S**. Ultrasonography for diagnosis of gallbladder polyps: Methodological issues on accuracy and reliability. *Radiography (Lond)* 2020; **26**: 272-273 [PMID: 32402705 DOI: 10.1016/j.radi.2020.04.013]

51 **Li Y**, Wang Y, Chi M. The diagnostic value of high-frequency ultrasound combined with color Doppler ultrasound versus surgical pathology in gallbladder polyps. *Am J Transl Res* 2021; **13**: 7990-7996 [PMID: 34377280]

52 **Hashimoto S**, Nakaoka K, Kawabe N, Kuzuya T, Funasaka K, Nagasaka M, Nakagawa Y, Miyahara R, Shibata T, Hirooka Y. The Role of Endoscopic Ultrasound in the Diagnosis of Gallbladder Lesions. *Diagnostics (Basel)* 2021; **11** [PMID: 34679486 DOI: 10.3390/diagnostics11101789]

53 **Han JW**, Choi YH, Lee IS, Choi HJ, Hong TH, You YK. Gallbladder polyps growth rate is an independent risk factor for neoplastic polyps. *United European Gastroenterol J* 2022; **10**: 651-656 [PMID: 36087036 DOI: 10.1002/ueg2.12274]

54 **González-Gómez S**, Paez H, Karen CG. Risk Factors and Recommendations for Follow-Up of Gallbladder Polyps. *AJR Am J Roentgenol* 2022; **219**: 1005 [PMID: 36069723 DOI: 10.2214/AJR.22.27959]

55 **Middleton WD**, Fung C, Dahiya N, Szpakowski JL, Corwin MT, Fetzer DT, Gabriel H, Rodgers SK, Tublin ME, Walsh AJ, Kamaya A. Survey Study on the Experience, Practice Patterns, and Preferences of the Fellows of the Society of Radiologists in Ultrasound for Evaluation and Management of Gallbladder Polyps Detected With Ultrasound. *Ultrasound Q* 2022; **38**: 96-102 [PMID: 35221317 DOI: 10.1097/RUQ.0000000000000597]

56 **Sinha SR**, Prakash P, Singh RK, Sinha DK. Assessment of tumor markers CA 19-9, CEA, CA 125, and CA 242 for the early diagnosis and prognosis prediction of gallbladder cancer. *World J Gastrointest Surg* 2022; **14**: 1272-1284 [PMID: 36504513 DOI: 10.4240/wjgs.v14.i11.1272]

57 **Ozer N**, Sozutek A, Sahin A, Seker A, Genc IC, Yugruk A. The Role of Ca 19-9, Ca 72-4, Cea and Cholesterol Levels in Predicting Malignancy in Gallbladder Polyps. *J Coll Physicians Surg Pak* 2021; **31**: 1422-1427 [PMID: 34794281 DOI: 10.29271/jcpsp.2021.12.1422]

58 **Wiles R**, Thoeni RF, Barbu ST, Vashist YK, Rafaelsen SR, Dewhurst C, Arvanitakis M, Lahaye M, Soltes M, Perinel J, Roberts SA. Management and follow-up of gallbladder polyps : Joint guidelines between the European Society of Gastrointestinal and Abdominal Radiology (ESGAR), European Association for Endoscopic Surgery and other Interventional Techniques (EAES), International Society of Digestive Surgery - European Federation (EFISDS) and European Society of Gastrointestinal Endoscopy (ESGE). *Eur Radiol* 2017; **27**: 3856-3866 [PMID: 28185005 DOI: 10.1007/s00330-017-4742-y]

59 **Rafaelsen SR**, Otto PO, Pedersen MRV. Long-term ultrasound follow-up in patients with small gallbladder polyps. *Dan Med J* 2020; **67** [PMID: 33046206]

60 **Valibouze C**, El Amrani M, Truant S, Leroy C, Millet G, Pruvot FR, Zerbib P. The management of gallbladder polyps. *J Visc Surg* 2020; **157**: 410-417 [PMID: 32473822 DOI: 10.1016/j.jviscsurg.2020.04.008]

61 **Jang SI**, Cho JH, Lee DK. [Recent Updates on Diagnosis, Treatment, and Follow-up of Gallbladder Polyps]. *Korean J Gastroenterol* 2020; **76**: 102-107 [PMID: 32969359 DOI: 10.4166/kjg.2020.76.3.102]

62 **Akbulut S**, Sahin TT. Comment on gallbladder polyps: Correlation of size and clinicopathologic characteristics based on updated definitions. *Int J Surg Case Rep* 2021; **83**: 105947 [PMID: 34015684 DOI: 10.1016/j.ijscr.2021.105947]

63 **Pavlidis ET**, Pavlidis TE. The Role of Open Cholecystectomy in the Current Era of Laparoscopic Surgery and the Trainee Experience. *Am Surg* 2018; **84**: e106-e107 [PMID: 30454425]

64 **Björk D**, Bartholomä W, Hasselgren K, Edholm D, Björnsson B, Lundgren L. Malignancy in elective cholecystectomy due to gallbladder polyps or thickened gallbladder wall: a single-centre experience. *Scand J Gastroenterol* 2021; **56**: 458-462 [PMID: 33590795 DOI: 10.1080/00365521.2021.1884895]

65 **Kim BJ**, Newhook TE, Tzeng CD, Ikoma N, Chiang YJ, Chun YS, Vauthey JN, Tran Cao HS. Lymphadenectomy and margin-negative resection for biliary tract cancer surgery in the United States-Differential technical performance by approach. *J Surg Oncol* 2022; **126**: 658-666 [PMID: 35578764 DOI: 10.1002/jso.26924]

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EDITORIAL

Immunotherapy in gastric cancer with liver metastasis: Challenges and opportunities

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Abstract

In this editorial, we review the article by Liu *et al* published in the *World Journal of Gastrointestinal Surgery* investigating the efficacy and safety of immunotherapy in patients with gastric cancer (GC) and liver metastasis. GC, the fifth most commonly diagnosed malignancy worldwide, presents a significant challenge due to its multifactorial etiology and a grim prognosis for unresectable or recurrent cases. The advent of immune checkpoint inhibitors (ICIs) has revolutionized oncology; yet liver metastasis has been associated with reduced response rates, progression-free survival, and overall survival in various malignancies. The CheckMate-649 and KEYNOTE-859 trials demonstrated promising results with ICIs in advanced GC, particularly in patients with liver metastasis. However, a meta-analysis of liver metastatic solid tumors revealed worse outcomes with ICIs, highlighting the need for further investigation. While combined therapies, including ICIs with local treatments, show promise in improving outcomes, the nuanced landscape of ICIs in liver metastatic GC necessitates continued research for robust conclusions. The current contradictions in the literature underscore the importance of cautious interpretation and the exploration of tailored approaches to enhance clinical efficacy in this challenging patient population.

Key Words: Gastric cancer; Liver metastasis; Immunotherapy; Immune checkpoint inhibitors; Transarterial chemoembolization; Tumor microenvironment

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Core Tip: In the context of gastric cancer patients with liver metastases, the standard treatment often involves combinations of immunotherapy and chemotherapy, particularly in specific patient groups. However, considering the intricate dynamics of the tumor microenvironment, the effectiveness of immunotherapies may be limited in cases of liver metastatic disease. In this context, especially considering the potential benefits of locally targeted treatments to the liver, further research and clinical studies are necessary to expand effective therapeutic options.

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INTRODUCTION

Gastric cancer (GC) is the fifth most commonly diagnosed malignancy globally and ranks as the fourth leading cause of cancer-related deaths, making it a prominent digestive system malignancy[1]. The multifactorial nature of GC development involves *Helicobacter pylori* infection as a significant pathogenic factor, alongside other risk factors such as smoking, alcohol, poor nutrition, age, sex, and race[2,3]. Unfortunately, the prognosis for patients diagnosed with unresectable or recurrent GC is grim, with a median overall survival (OS) of approximately 12-15 months[4,5].

Immune checkpoint inhibitors (ICIs) have revolutionized oncology, showing success in various tumors. However, studies indicate that liver metastasis reduces response rates, progression-free survival (PFS), and OS in malignancies when ICIs are used[6-9]. Despite the accumulating clinical evidence, uncertainty about how liver metastasis modulates the systemic antitumor immune response persists, and the underlying pathophysiological reasons for ICI resistance in these patients remain unclear. Previous studies in melanoma patients revealed that the presence of liver metastases is associated with decreased expression of activation and functional markers of CD8+ tumor-infiltrating lymphocytes during pre-ICI treatment cutaneous tumor biopsies, suggesting that liver-specific tolerance mechanisms may suppress systemic antitumor T-cell immunity[10,11].

In patients with metastatic disease, nonregional lymph nodes are the most common sites of metastasis in GC, with the liver being the most common target organ for hematogenous metastasis[12]. Due to the high incidence of liver metastasis in advanced GC patients, the prognosis is poor, with a five-year survival rate of < 10%[13]. Previously, the first-line systemic treatment regimen for metastatic GC consisted of dual chemotherapy (platinum and fluoropyrimidine) with trastuzumab in cases of HER2 overexpression.

The CheckMate-649 trial, a phase III study, randomized treatment-naive patients with advanced or metastatic gastroesophageal adenocarcinoma to receive either nivolumab plus chemotherapy (n = 473) or chemotherapy alone (n = 482)[14]. The 3-year results indicated that in patients with a tumor PD-L1 combined positive score (CPS) ≥ 5, the combination of nivolumab and chemotherapy resulted in continued improvement in OS, PFS, and overall response rate compared to chemotherapy alone. This supports the ongoing use of nivolumab plus chemotherapy as the standard first-line treatment, providing significant long-term survival benefits. Subgroup analysis demonstrated a statistically significant improvement in median OS for patients with liver metastasis [hazard ratio (HR): 0.72, 95% confidence interval (95%CI): 0.60-0.85] and those without liver metastasis (HR: 0.84, 95%CI: 0.73-0.97). Similarly, the KEYNOTE-859 trial, a phase III study involving untreated patients with HER2-negative gastric or gastroesophageal junction adenocarcinoma, randomized participants to receive pembrolizumab plus chemotherapy (n = 790) or placebo plus chemotherapy (n = 789)[15]. The pembrolizumab plus chemotherapy group showed a significant improvement in OS with manageable toxicity, particularly in patients with liver metastasis (HR: 0.83, 95%CI: 0.70-0.99) and those without liver metastasis (HR: 0.73, 95%CI: 0.63-0.84).

A meta-analysis of 163 studies involving patients with liver metastatic solid tumors treated with ICIs revealed worse OS (HR: 1.82, 95%CI: 1.59-2.08) and PFS (HR: 1.68, 95%CI: 1.49-1.89) for individuals with liver metastasis compared to those without[16]. The impact of liver metastasis on ICI efficacy varied across tumor types, with the poorest prognosis observed in patients with urinary system tumors (HR: 2.47, 95%CI: 1.76-3.45; and HR: 2.37, 95%CI: 2.03-2.76, renal cell carcinoma and urothelial carcinoma, respectively), followed by melanoma (HR: 2.04, 95%CI: 1.68-2.49) and non-small cell lung cancer (HR: 1.81, 95%CI: 1.72-1.91). Digestive system tumors, including colorectal cancer (HR: 1.35, 95%CI: 1.07-1.71) and gastric/esophagogastric cancer (HR: 1.17, 95%CI: 0.90-1.52), were less affected. In a retrospective study by Liu *et al*[17], which is the focus of this editorial, 48 patients were included, 20 of whom had liver metastases. The objective response rates were 15.0% and 35.7% in the metastatic and nonmetastatic cohorts, respectively (P > 0.05). Similarly, disease control rates in these cohorts were 65.0% and 82.1%, respectively (P > 0.05). The median PFS was 5.0 months in the liver metastasis group compared to 11.2 months in the nonmetastatic group, and the median OS was 12.0 months in the liver metastasis group and 19.0 months in the nonmetastatic group. This study suggests that immunotherapy may be less effective in GC patients with liver metastases, but diverse results in the current literature emphasize the need for more extensive studies with homogeneous patient groups to draw definitive conclusions.

Targeted therapy and/or chemotherapy with immunotherapy, along with palliative radiotherapy, contribute to improved survival outcomes in patients with liver metastatic GC, with promising synergistic effects reported[18]. Following the development of new antitumor drugs, therapeutic efficacy against tumors has significantly increased. The stimulation of tumor angiogenesis accompanies tumor progression and metastasis. Antiangiogenesis therapy can inhibit tumor an-

giogenesis, reducing tumor growth and metastasis. Targeting angiogenesis by inhibiting vascular endothelial growth factors (VEGFs) has shown significant therapeutic effects in lung, hepatic, renal, gastric, and colon cancers[19,20]. Initiating an immune response requires antigen-presenting cells to acquire and process tumor antigens. Tumors such as hepatocellular carcinoma (HCC) lack sufficient lymphocyte infiltration in both the tumor and the surrounding microenvironment, making it challenging to generate an effective antitumor immune response. Local treatments, such as transarterial chemoembolization (TACE), induce tumor necrosis, exposing a large amount of tumor antigen and initiating the immune response cycle[21,22]. In a study involving patients diagnosed with unresectable HCC, the combination of lenvatinib (anti-VEGF) and PD-1 inhibitors after drug-eluting bead TACE (DEB-TACE) resulted in higher objective response rates and surgical conversion rates[23].

CLINICAL IMPLICATIONS

Due to conflicting data in the literature, a definitive conclusion regarding the effectiveness of ICIs in liver metastatic GC cannot be reached at present. The existing contradictions in the literature underscore the need for further investigation and a cautious interpretation of available data.

Considering the unfavorable prognosis associated with liver metastasis, the exploration of combined therapies becomes paramount. Strategies such as combining ICIs with local treatments can be pivotal in optimizing outcomes for these patients. By doing so, we may unlock avenues to overcome the potential limitations posed by liver metastasis and enhance the overall effectiveness of immunotherapeutic interventions in managing advanced GC. Developing tailored and integrated approaches is promising in improving clinical outcomes in this challenging patient population.

CONCLUSION

The effectiveness of ICIs in liver metastatic GC remains unclear, with conflicting data in the current literature. The challenging prognosis necessitates the exploration of combined therapies, like integrating ICIs with local treatments, to enhance outcomes for these patients. Research focusing on specific approaches is crucial to overcome the complexities of advanced GC with liver metastases and improve overall clinical efficacy.

FOOTNOTES

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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 **Yoon H**, Kim N. Diagnosis and management of high risk group for gastric cancer. *Gut Liver* 2015; **9**: 5-17 [PMID: 25547086 DOI: 10.5009/gnl14118]

3 **Joshi SS**, Badgwell BD. Current treatment and recent progress in gastric cancer. *CA Cancer J Clin* 2021; **71**: 264-279 [PMID: 33592120 DOI: 10.3322/caac.21657]

4 **Bang YJ**, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK; ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for

treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376**: 687-697 [PMID: 20728210 DOI: 10.1016/S0140-6736(10)61121-X]

5 **Cunningham D**, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR; Upper Gastrointestinal Clinical Studies Group of the National Cancer Research Institute of the United Kingdom. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008; **358**: 36-46 [PMID: 18172173 DOI: 10.1056/NEJMoa073149]

6 **Tumeh PC**, Hellmann MD, Hamid O, Tsai KK, Loo KL, Gubens MA, Rosenblum M, Harview CL, Taube JM, Handley N, Khurana N, Nosrati A, Krummel MF, Tucker A, Sosa EV, Sanchez PJ, Banayan N, Osorio JC, Nguyen-Kim DL, Chang J, Shintaku IP, Boasberg PD, Taylor EJ, Munster PN, Algazi AP, Chmielowski B, Dummer R, Grogan TR, Elashoff D, Hwang J, Goldinger SM, Garon EB, Pierce RH, Daud A. Liver Metastasis and Treatment Outcome with Anti-PD-1 Monoclonal Antibody in Patients with Melanoma and NSCLC. *Cancer Immunol Res* 2017; **5**: 417-424 [PMID: 28411193 DOI: 10.1158/2326-6066.CIR-16-0325]

7 **Pires da Silva I**, Lo S, Quek C, Gonzalez M, Carlino MS, Long GV, Menzies AM. Site-specific response patterns, pseudoprogression, and acquired resistance in patients with melanoma treated with ipilimumab combined with anti-PD-1 therapy. *Cancer* 2020; **126**: 86-97 [PMID: 31584722 DOI: 10.1002/cncr.32522]

8 **Schmid S**, Diem S, Li Q, Krapf M, Flatz L, Leschka S, Desbiolles L, Klingbiel D, Jochum W, Früh M. Organ-specific response to nivolumab in patients with non-small cell lung cancer (NSCLC). *Cancer Immunol Immunother* 2018; **67**: 1825-1832 [PMID: 30171269 DOI: 10.1007/s00262-018-2239-4]

9 **Bilen MA**, Shabto JM, Martini DJ, Liu Y, Lewis C, Collins H, Akce M, Kissick H, Carthon BC, Shaib WL, Alese OB, Steuer CE, Wu C, Lawson DH, Kudchadkar R, Master VA, El-Rayes B, Ramalingam SS, Owonikoko TK, Harvey RD. Sites of metastasis and association with clinical outcome in advanced stage cancer patients treated with immunotherapy. *BMC Cancer* 2019; **19**: 857 [PMID: 31464611 DOI: 10.1186/s12885-019-6073-7]

10 **Loo K**, Tsai KK, Mahuron K, Liu J, Pauli ML, Sandoval PM, Nosrati A, Lee J, Chen L, Hwang J, Levine LS, Krummel MF, Algazi AP, Pampaloni M, Alvarado MD, Rosenblum MD, Daud AI. Partially exhausted tumor-infiltrating lymphocytes predict response to combination immunotherapy. *JCI Insight* 2017; **2** [PMID: 28724802 DOI: 10.1172/jci.insight.93433]

11 **Daud AI**, Loo K, Pauli ML, Sanchez-Rodriguez R, Sandoval PM, Taravati K, Tsai K, Nosrati A, Nardo L, Alvarado MD, Algazi AP, Pampaloni MH, Lobach IV, Hwang J, Pierce RH, Gratz IK, Krummel MF, Rosenblum MD. Tumor immune profiling predicts response to anti-PD-1 therapy in human melanoma. *J Clin Invest* 2016; **126**: 3447-3452 [PMID: 27525433 DOI: 10.1172/JCI87324]

12 **Verstegen MH**, Harker M, van de Water C, van Dieren J, Hugen N, Nagtegaal ID, Rosman C, van der Post RS. Metastatic pattern in esophageal and gastric cancer: Influenced by site and histology. *World J Gastroenterol* 2020; **26**: 6037-6046 [PMID: 33132653 DOI: 10.3748/wjg.v26.i39.6037]

13 **Song JC**, Ding XL, Zhang Y, Zhang X, Sun XH. Prospective and prognostic factors for hepatic metastasis of gastric carcinoma: A retrospective analysis. *J Cancer Res Ther* 2019; **15**: 298-304 [PMID: 30964101 DOI: 10.4103/jcrt.JCRT_576_17]

14 **Janjigian YY**, Ajani JA, Moehler M, Shen L, Garrido M, Gallardo C, Wyrwicz L, Yamaguchi K, Cleary JM, Elimova E, Karamouzis M, Bruges R, Skoczylas T, Bragagnoli A, Liu T, Tehfe M, Zander T, Kowalyszyn R, Pazo-Cid R, Schenker M, Feeny K, Wang R, Lei M, Chen C, Nathani R, Shitara K. First-Line Nivolumab Plus Chemotherapy for Advanced Gastric, Gastroesophageal Junction, and Esophageal Adenocarcinoma: 3-Year Follow-Up of the Phase III CheckMate 649 Trial. *J Clin Oncol* 2024; JCO2301601 [PMID: 38382001 DOI: 10.1200/JCO.23.01601]

15 **Rha SY**, Oh DY, Yañez P, Bai Y, Ryu MH, Lee J, Rivera F, Alves GV, Garrido M, Shiu KK, Fernández MG, Li J, Lowery MA, Çil T, Cruz FM, Qin S, Luo S, Pan H, Wainberg ZA, Yin L, Bordia S, Bhagia P, Wyrwicz LS; KEYNOTE-859 investigators. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol* 2023; **24**: 1181-1195 [PMID: 37875143 DOI: 10.1016/S1470-2045(23)00515-6]

16 **Tian BW**, Han CL, Wang HC, Yan LJ, Ding ZN, Liu H, Mao XC, Tian JC, Xue JS, Yang LS, Tan SY, Dong ZR, Yan YC, Wang DX, Li T. Effect of liver metastasis on the efficacy of immune checkpoint inhibitors in cancer patients: a systemic review and meta-analysis. *Clin Exp Metastasis* 2023; **40**: 255-287 [PMID: 37308706 DOI: 10.1007/s10585-023-10217-7]

17 **Liu K**, Wu CX, Liang H, Wang T, Zhang JY, Wang XT. Analysis of the impact of immunotherapy efficacy and safety in patients with gastric cancer and liver metastasis. *World J Gastrointest Surg* 2024; **16**: 700-709 [PMID: 38577087 DOI: 10.4240/wjgs.v16.i3.700]

18 **Kong Y**, Zhao X, Xu M, Pan J, Ma Y, Zou L, Peng Q, Zhang J, Su C, Xu Z, Zhou W, Peng Y, Yang J, Zhou C, Li Y, Guo Q, Chen G, Wu H, Xing P, Zhang L. PD-1 Inhibitor Combined With Radiotherapy and GM-CSF (PRaG) in Patients With Metastatic Solid Tumors: An Open-Label Phase II Study. *Front Immunol* 2022; **13**: 952066 [PMID: 35874780 DOI: 10.3389/fimmu.2022.952066]

19 **Tanigawa N**, Amaya H, Matsumura M, Shimomatsuya T. Correlation between expression of vascular endothelial growth factor and tumor vascularity, and patient outcome in human gastric carcinoma. *J Clin Oncol* 1997; **15**: 826-832 [PMID: 9053510 DOI: 10.1200/JCO.1997.15.2.826]

20 **Folkman J**. Angiogenesis in cancer, vascular, rheumatoid and other disease. *Nat Med* 1995; **1**: 27-31 [PMID: 7584949 DOI: 10.1038/nm0195-27]

21 **Ochoa de Olza M**, Navarro Rodrigo B, Zimmermann S, Coukos G. Turning up the heat on non-immunoreactive tumours: opportunities for clinical development. *Lancet Oncol* 2020; **21**: e419-e430 [PMID: 32888471 DOI: 10.1016/S1470-2045(20)30234-5]

22 **Rizvi S**, Wang J, El-Khoueiry AB. Liver Cancer Immunity. *Hepatology* 2021; **73** Suppl 1: 86-103 [PMID: 32516437 DOI: 10.1002/hep.31416]

23 **Wu SJ**, Ruan DD, Wu QY, Tang Y, Zhang JH, Cai SL, Zhou YF, Luo JW, Fang ZT. Safety and Efficacy of Drug-Eluting Bead Transarterial Chemoembolization Combined with Lenvatinib and Anti-PD-1 Antibodies for Unresectable Hepatocellular Carcinoma: A Retrospective Analysis. *J Hepatocell Carcinoma* 2023; **10**: 807-820 [PMID: 37292114 DOI: 10.2147/JHC.S408819]

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EDITORIAL

From the mathematical model to the patient: The scientific and human aspects of artificial intelligence in gastrointestinal surgery

Javier Arredondo Montero

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Abstract

Recent medical literature shows that the application of artificial intelligence (AI) models in gastrointestinal pathology is an exponentially growing field, with promising models that show very high performances. Regarding inflammatory bowel disease (IBD), recent reviews demonstrate promising diagnostic and prognostic AI models. However, studies are generally at high risk of bias (especially in AI models that are image-based). The creation of specific AI models that improve diagnostic performance and allow the establishment of a general prognostic forecast in IBD is of great interest, as it may allow the stratification of patients into subgroups and, in turn, allow the creation of different diagnostic and therapeutic protocols for these patients. Regarding surgical models, predictive models of postoperative complications have shown great potential in large-scale studies. In this work, the authors present the development of a predictive algorithm for early post-surgical complications in Crohn's disease based on a Random Forest model with exceptional predictive ability for complications within the cohort. The present work, based on logical and reasoned, clinical, and applicable aspects, lays a solid foundation for future prospective work to further develop post-surgical prognostic tools for IBD. The next step is to develop in a prospective and multicenter way, a collaborative path to optimize this line of research and make it applicable to our patients.

Key Words: Survivor bias; Data analysis; Machine learning; Ethics; Critical thinking; Postsurgical; Complications; Inflammatory bowel disease; Gastrointestinal surgery

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Core Tip: Recent medical literature shows that the application of artificial intelligence models in gastrointestinal pathology is an exponentially growing field. In this work, the authors present the development of a predictive algorithm for early post-surgical complications in Crohn's disease based on a Random Forest model with exceptional predictive ability for complications within the cohort. The present work, based on logical and reasoned, clinical, and applicable aspects lays, a solid foundation for future prospective work to further develop post-surgical prognostic tools for inflammatory bowel disease.

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INTRODUCTION

These are times of change. Technological development has undergone exponential growth in recent decades, which has had direct repercussions on practically all aspects of our lives. And although healthcare moves at a different pace, marked by rigorous safety and ethical protocols, it has not escaped this change. The progressive computerization of our clinical records and the introduction of novel technology in the assistance of our patients, for example, are tangible realities. Although these changes in our clinical practice can undoubtedly be beneficial, they often constitute a challenge and require further research to optimize them[1].

As scientists, the basis of our work is data. A physician cannot work without data. And if there is a technological revolution these days that is pertinent to highlight, it is that of data. The computerization and digitalization that I mentioned previously, together with the appearance of multiple tools that make it possible to obtain more and more accurate data, mean that we are at a historic moment in which we can obtain the greatest amount of data, (as well as the most accurate data), from our patients. But data alone is of no value. Data acquire value at the expense of their correct interpretation. An illustrative example is the so-called survivor bias. This logical fallacy leads us to focus on people who pass a selection process while leaving out those who do not, which can lead to false conclusions. During World War II, for example, the United States government incurred this bias when analyzing aircraft returning from combat, recommending that damaged areas be reinforced. However, the interpretation was incorrect: It was the undamaged parts that should have been reinforced because the aircraft that suffered damage in those areas were those that did not return from combat. It was statistician Abraham Wald from the Statistical Research Group at Columbia University who analyzed the data in the right way and understood what was happening[2]. Therefore, Wald proposed that the Navy reinforce areas where the returning aircraft were unscathed. The data was there, it was just that it had not been interpreted correctly.

ARTIFICIAL INTELLIGENCE

And amid this information revolution, artificial intelligence (AI) emerges. But what is AI? According to Wikipedia, it is a discipline and a set of cognitive and intellectual capabilities expressed by computer systems or combinations of algorithms whose purpose is the creation of machines that mimic human intelligence to perform tasks, and that can improve as they gather information. And from this definition, I would like to highlight a few aspects: The first is that these computer capabilities mimic human intelligence. We can teach these tools to simulate our way of thinking, to “mimic” it, but never to replace it. The conception of original ideas in medical research, the "spark" inherent to our species that has led to unique and extraordinary discoveries is, in the opinion of the author of this text, inimitable. I think it is important that we encourage and safeguard critical thinking and the ability to produce original ideas, since one of the risks of the abuse of these models is precisely this, the loss of our "spark". The second is that these models improve as they accumulate and compile information. This is the basis of progress in science and medicine: Collaboration. I believe it is essential that strong international research groups are encouraged to develop these lines of research together to enhance their results and allow them to be extrapolated globally. Together we are more.

That said, I would like to turn my attention to the paper entitled "Predicting short-term major postoperative complications in intestinal resection for Crohn’s disease: A machine learning-based study”[3]. In this paper, the authors present the development of a predictive algorithm for early post-surgical complications in Crohn's disease based on a Random Forest model with exceptional predictive ability for complications within the cohort [area under the curve (AUC) = 0.965 in the training cohort, AUC = 0.924 in the validation cohort].

Concerning AI models and gastrointestinal pathology, recent medical literature shows that this is an exponentially growing field, which indirectly translates the existing interest in this area. We found promising models for different pathologies, such as gastric cancer, liver fibrosis and cirrhosis, gastrointestinal stromal tumors, and Barrett's esophagus, among others[4,5]. Overall, all these models (both diagnostic and prognostic) show very high performances that exceed the gold standards previously used. However, in most cases, they have been conceived for research purposes and their actual implementability in clinical practice is low or non-existent. Regarding AI models and inflammatory bowel disease (IBD), recent reviews demonstrate promising diagnostic and prognostic AI models. However, studies are generally at high risk of bias (especially in AI models that are image-based)[6]. The availability of specific AI models that improve

diagnostic performance and allow the establishment of a general prognostic forecast in IBD is of great interest, as it may allow the stratification of patients into subgroups and in turn, allow the creation of different diagnostic and therapeutic protocols for these patients. This goes hand in hand with the general trend in our profession towards so-called personalized medicine.

Surgery has always been a complex area in scientific terms due to multiple factors. First, the variability between surgeons in terms of surgical technique: Although the current tendency is to protocolize and standardize surgical practice, many variables are difficult to quantify (from the pressure exerted on the sutures to the amount of monopolar energy used). Second, the difficulty in reflecting as objective data many of the intraoperative aspects: We can quantify the surgical time, but it is difficult to quantify the degree of peritoneal involvement in a patient with peritonitis or the degree of intestinal involvement in a diverticular disease. Nevertheless, despite the conceptual aspects previously explained, predictive models of postoperative complications have shown great potential in large-scale studies[7]. In this case, the authors have opted for the creation of a model with variables that are simple to collect and reproducible, which, in addition to making it rigorous, allows for possible external validation in the future. The Crohn's disease activity index (CDAI), the serum preoperative albumin, and the surgical duration are parameters that any surgeon can easily collect on their patients. On the other hand, it is pertinent to note that all the elements included have a strong biological plausibility in terms of post-surgical complications: A patient with hypoproteinaemia, high CDAI, or prolonged surgery is logically more susceptible to complications than a patient in a more favorable situation. In this case, except for urgent surgery, there are two modifiable factors such as CDAI and hypoalbuminemia, and a factor that the surgeon can keep in mind during the procedure such as surgical time.

Although there is a significant lack of knowledge regarding AI models, most of them are based on mathematical algorithms that, through iterations, create predictive models. This is the same principle as that of other statistical models we are already familiar with, such as logistic regression. In this article, the authors opted for a Random Forest type model. This is a reasonable and justified decision, given that previous work has demonstrated the superiority of these models to other traditional models such as logistic regression[8]. However, there are nuances to this, given that in certain cases it may be preferable to opt for a model such as logistic regression (for example, in cases where the noise variables are scarce). Random forest models have important advantages such as they can handle missing values and outliers, they can deal with classification and regression problems, and they can handle large amounts of data efficiently. However, it can be difficult and time-consuming to train them.

As I said at the beginning, we live in times of change, of rapid, almost vertiginous change. The amount of data we handle daily has become practically unmanageable, we are becoming dependent on technology. I think this is a mistake. I think we need to reflect long and hard about the direction we are heading in and realize that speed, while important, is not paramount. We must protect our critical thinking. We must reflect on the why of things. We must use technology as a resource within our reach, but not become dependent on it. We must look at the data and analyze it, and it is our responsibility to interpret it properly, no matter how many tools we have to assist us. When an anesthesiologist sees a desaturation on his patient's pulse oximetry monitor, the first thing he does is not to open the oxygen flow, but to look at the patient's finger to see if the sensor is correctly positioned: That is what defines us, the ability to think and reason. Feynman, a renowned physicist who laid the foundations of quantum mechanics, once said, "Direction is more important than speed." I couldn't agree more. The present work lays a solid foundation for future prospective work to further develop post-surgical prognostic tools for IBD. And it does so because it is based on logical and reasoned, clinical and applicable aspects. This must be the way forward for AI. The next step, as I mentioned, is to develop a collaborative path to optimize this line of research in a prospective and multicenter way and make it applicable to our patients. We must not forget that we do not work with machines, we work with patients.

CONCLUSION

AI-based predictive models for gastrointestinal surgical pathology, such as the commented work, show promising results. However, larger-scale prospective studies are needed for validation. These models cannot supplant human reasoning and the human mind, so they should be conceived as complementary tools in research and not as integral automated elements.

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REFERENCES

1 **Berardi C**, Antonini M, Jordan Z, Wechtler H, Paolucci F, Hinwood M. Barriers and facilitators to the implementation of digital technologies in mental health systems: a qualitative systematic review to inform a policy framework. *BMC Health Serv Res* 2024; **24**: 243 [PMID: 38408938 DOI: 10.1186/s12913-023-10536-1]

2 **Wald A**. A Method of Estimating Plane Vulnerability Based on Damage of Survivors. Statistical Research Group, Columbia University. CRC 432- reprint from July 1980 Archived 2019-07-13 at the Wayback Machine. Center for Naval Analyses. 1943. Available from: https://apps.dtic.mil/sti/citations/ADA091073

3 **Wang FT**, Lin Y, Yuan XQ, Gao RY, Wu XC, Xu WW, Wu TQ, Xia K, Jiao YR, Yin L, Chen CQ. Predicting short-term major postoperative complications in intestinal resection for Crohn's disease: A machine learning-based study. *World J Gastrointest Surg* 2024; **16**: 717-730 [PMID: 38577067 DOI: 10.4240/wjgs.v16.i3.717]

4 **Shi Y**, Fan H, Li L, Hou Y, Qian F, Zhuang M, Miao B, Fei S. The value of machine learning approaches in the diagnosis of early gastric cancer: a systematic review and meta-analysis. *World J Surg Oncol* 2024; **22**: 40 [PMID: 38297303 DOI: 10.1186/s12957-024-03321-9]

5 **Tan JL**, Chinnaratha MA, Woodman R, Martin R, Chen HT, Carneiro G, Singh R. Diagnostic Accuracy of Artificial Intelligence (AI) to Detect Early Neoplasia in Barrett's Esophagus: A Non-comparative Systematic Review and Meta-Analysis. *Front Med (Lausanne)* 2022; **9**: 890720 [PMID: 35814747 DOI: 10.3389/fmed.2022.890720]

6 **Liu X**, Reigle J, Prasath VBS, Dhaliwal J. Artificial intelligence image-based prediction models in IBD exhibit high risk of bias: A systematic review. *Comput Biol Med* 2024; **171**: 108093 [PMID: 38354499 DOI: 10.1016/j.compbiomed.2024.108093]

7 **Xue B**, Li D, Lu C, King CR, Wildes T, Avidan MS, Kannampallil T, Abraham J. Use of Machine Learning to Develop and Evaluate Models Using Preoperative and Intraoperative Data to Identify Risks of Postoperative Complications. *JAMA Netw Open* 2021; **4**: e212240 [PMID: 33783520 DOI: 10.1001/jamanetworkopen.2021.2240]

8 **Couronné R**, Probst P, Boulesteix AL. Random forest versus logistic regression: a large-scale benchmark experiment. *BMC Bioinformatics* 2018; **19**: 270 [PMID: 30016950 DOI: 10.1186/s12859-018-2264-5]

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MINIREVIEWS

Laparoscopic right radical hemicolectomy: Central vascular ligation and complete mesocolon excision *vs* D3 lymphadenectomy - How I do it?

Kaushal Yadav

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Abstract

In colon cancer surgery, ensuring the complete removal of the primary tumor and draining lymph nodes is crucial. Lymphatic drainage in the colon follows the vascular supply, typically progressing from pericolic to paraaortic lymph nodes. While NCCN guidelines recommend the removal of 10-12 lymph nodes for adequate oncological resection, achieving complete oncological resection involves more than just meeting these numerical targets. Various techniques have been developed and studied over time to attain optimal oncological outcomes. A key technique central to this goal is identifying the ileocolic vessels at their origin from the superior mesenteric vessels. Complete excision of the visceral and parietal mesocolon ensures the intact removal of the specimen, while D3 lymphadenectomy targets all draining regional lymph nodes. Although these principles emphasize different aspects, they ultimately converge to achieve the same goal of complete oncological resection. This article aims to simplify the surgical steps that align with the principle of central vascular ligation and mesocolon mobilization while ensuring adequate D3 dissection.

Key Words: Carcinoma caecum; Carcinoma ascending colon; Right hemicolectomy; Extended right hemicolectomy; Central vascular ligation; Complete mesocolon excision; D3 lymphadenectomy; Laparoscopic right hemicolectomy; Minimally invasive hemicolectomy

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Core Tip: Despite many decades of research, there is no consensus on standard surgical techniques for right-side colon cancer. The complete oncological resection is much more than simple number of harvested lymph nodes. Identifying the ileocolic vessels at their origin from superior mesenteric vessels is the central technique to serve this purpose. Complete visceral and parietal mesocolon excision removes the intact specimen. D3 lymphadenectomy removes all draining regional lymph nodes. Both principles serve the same goal with different emphases. So addressing adequate lymphadenectomy with complete negative margin R0 resection is central to this article.

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INTRODUCTION

Radical right hemicolectomy remains the preferred treatment for right-sided colon cancers, with the removal of draining lymph nodes being a crucial step for long-term survival. Despite decades of research, controversies persist regarding which lymph node stations should be removed and the establishment of universal nomenclature. The Japanese classification for colon cancer categorizes regional lymph nodes into D1 (pericolic lymph nodes), D2 (pericolic and intermediate lymph nodes), and D3 (nodes at the origin of blood supply)[1]. In right hemicolectomy, D3 dissection entails removing lymph nodes along the ileocolic (ICL) artery, the right colic artery if present, and the right branch of the middle colic artery (MCA). Extended right hemicolectomy includes resection of lymph nodes along the MCA, including its left branch[2] (Figure 1). The JCOG0205 study, comparing oral with intravenous fluorouracil as adjuvant chemotherapy for stage III colorectal cancer, reported a 5-year overall survival rate of 87.5% in the D2/D3 dissection group[3].

An oncologically appropriate surgery with R0 resection and adequate lymphadenectomy significantly improves the survival of colon cancer patients[4,5]. Complete mesocolon excision (CME) with central vascular ligation (CVL) has been associated with a 15% better overall survival at 5 years, with this improvement reaching up to 27% in stage III cases[6]. The fundamental principle is to remove the cancer-bearing segment of the colon along with the intact fascia and lymphovascular drainage[5]. The Japanese Society recommends D2 dissection for early-stage and D3 dissection for higher stages, with a focus on retrieving more affected lymph nodes. European centers advocate for CME + CVL, with an emphasis on embryological planes of surgery. Both principles have been developed independently to achieve the best possible survival outcomes and are the result of constant efforts by dedicated cancer surgeons, evolving from simply ligating feeding vessels. In this paper, we describe our surgical technique involving CME + CVL while also addressing D3 lymph node removal.

SURGICAL TECHNIQUE

Preoperative preparation and patient position

Before surgery, patients undergo preoperative bowel preparation with a laxative, along with prophylactic intravenous third-generation cephalosporin and metronidazole administered 30 min prior. Patients are positioned in a low lithotomy position, with a body warmer blanket and belt applied over the chest. Shoulder supports are utilized, and the legs are secured in lithotomy poles along with deep vein thrombosis pumps. A 12-mm camera port is inserted just above the umbilicus, and two 5-mm ports are inserted along the midclavicular line in the epigastric and left iliac regions. An additional 5-mm port may be used in the right iliac region for retraction. The table is positioned in the Trendelenburg position with the right side upwards.

Exposure of superior mesenteric vessels

The mesentery of the ascending colon and terminal ileum is retracted upwards and laterally, creating tension on the ICL pedicle. This maneuver induces a stretch in the midline at the origin of the ICL pedicle from the superior mesenteric vessels, facilitating identification of the superior mesenteric vein (SMV). The mesentery is incised along an appropriate line over the SMV, below the third part of the duodenum and approximately opposite the falciform ligament. Fibrofatty and lymphatic tissue are reflected towards the right, exposing the right side of the SMV. The origin of the ICL pedicle is identified, and further dissection superiorly over the SMV reveals the MCA.

Ligation of ICL pedicle

The duodenum is identified, and the mesentery overlying it is reflected, revealing an avascular plane. Continued inferior dissection over the SMV allows for the skeletonization of the ICL pedicle origin. All lymphatic tissue is reflected towards the right, and the ICL pedicle is doubly ligated at its origin with hemoclip and then cut (Figure 2).

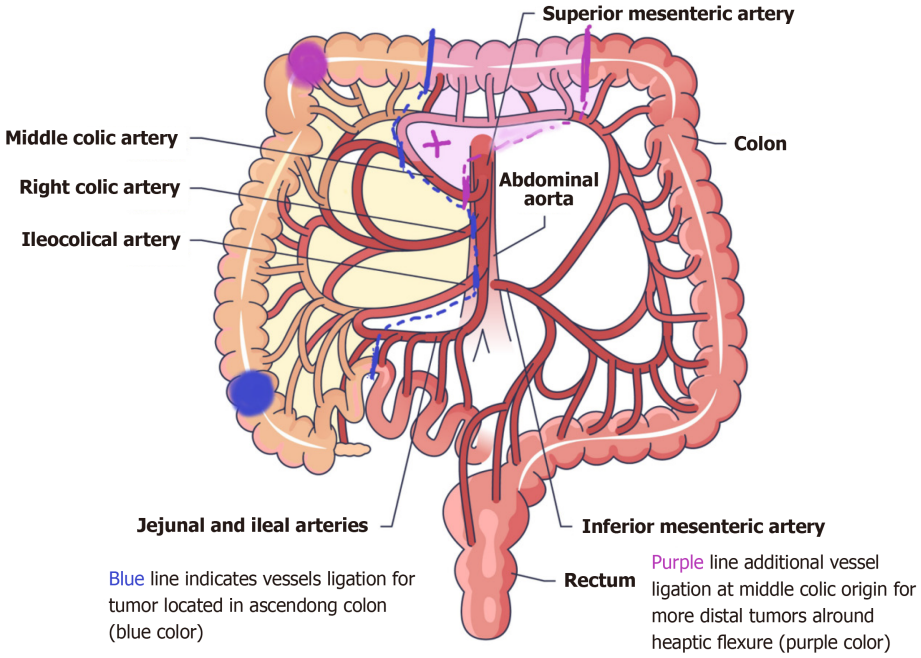


Figure 1 Line of resection for ascending colon/ caecum malignancy (blue line) & malignancy near hepatic flexure (purple line). Resection areas are shaded.

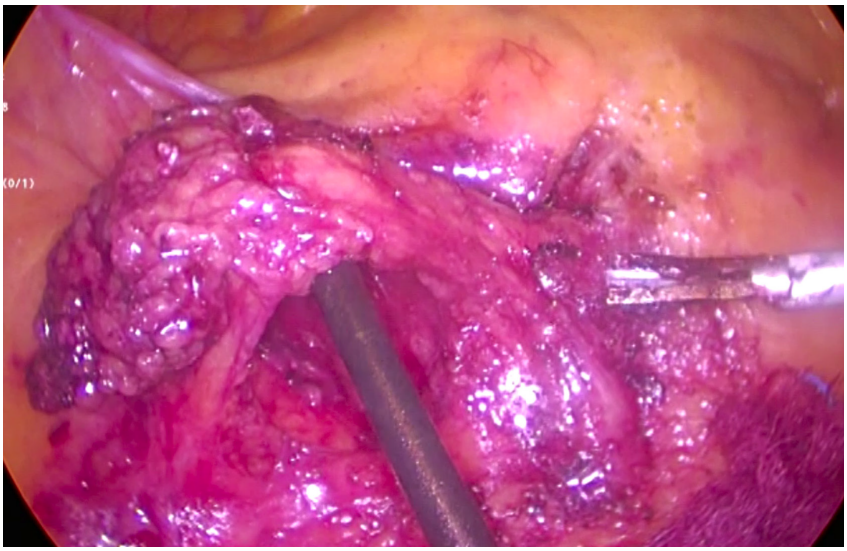


Figure 2 Ileocolic pedicle skeletonized and ligated at origin.

Ligation of the right branch of MCA or MCA at the origin

The MCA is identified through previous dissection, and the transverse colon is retracted upwards to expose both the right and left branches of the MCA. In cases where the primary tumor is located in the cecum or ascending colon, the right branch of the MCA is ligated and cut (Figure 3). Alternatively, in cases where the primary tumor is around the hepatic flexure, the MCA is ligated at its origin. These resection lines allow for the removal of all draining lymph nodes up to D3 stations (Figure 4).

Medial to lateral mobilization of mesocolon

The ligated ICL pedicle is lifted upwards, and dissection is performed along the fascia above the retroperitoneum, identifying Toldt's fascia, a thin white fascia between the ascending colon anteriorly and the retroperitoneum posteriorly[7]. By pushing the mesocolon above the duodenum upwards and the duodenum downwards, mobilization in an avascular plane is achieved. This embryological fascial plane that lines between the ascending colon anteriorly and the duodenum and pancreas posteriorly is Fredet's fascia[8]. This mobilization, starting at the origin of the vascular pedicle along the right border of the SMV, proceeds laterally to the abdominal wall. Thin white fascia is kept intact towards the mesocolon and lifted above from the retroperitoneum, duodenum, and pancreas posteriorly. A mesenteric cut is made along the ter-

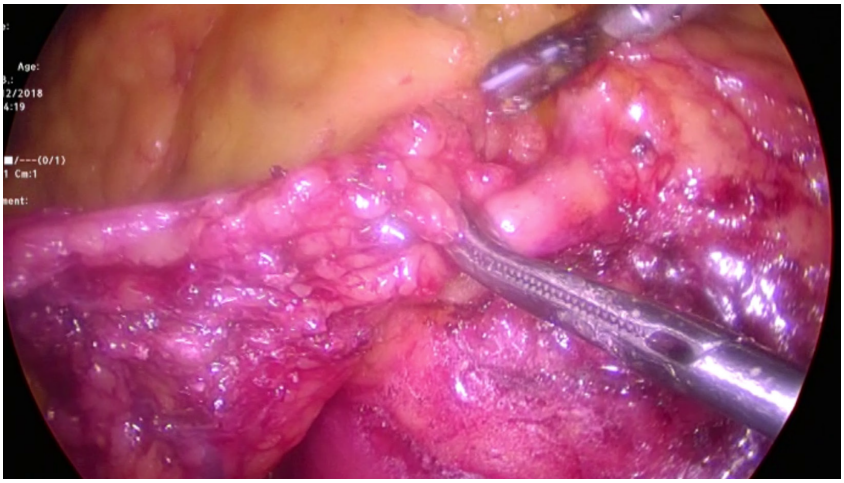


Figure 3 Right branch of middle colic artery ligated at division.

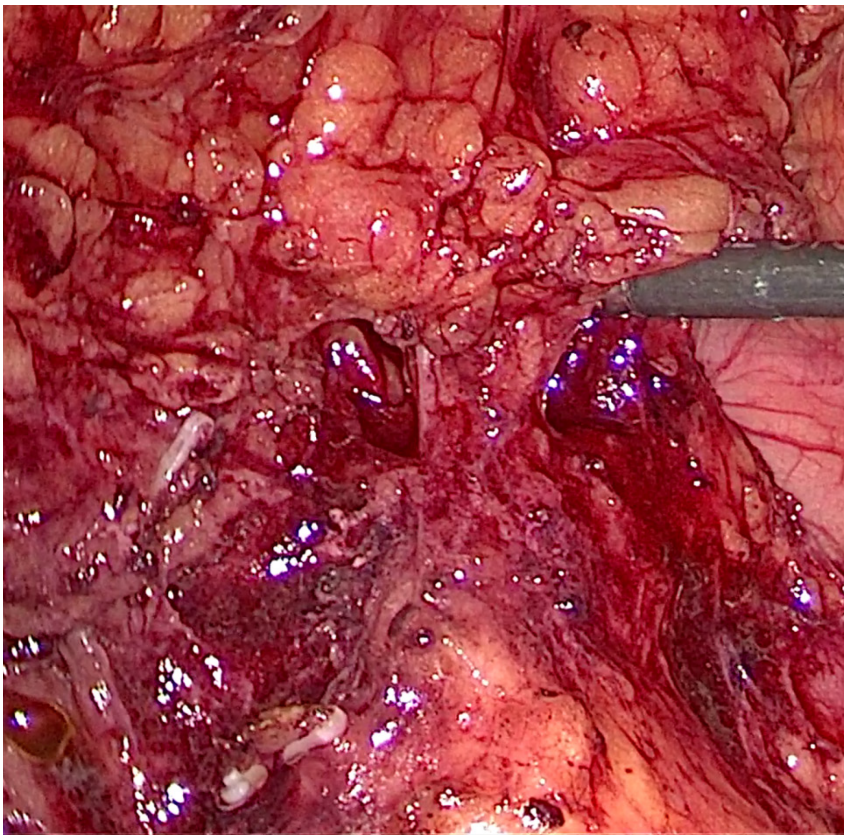


Figure 4 Middle colic artery origin from superior mesenteric artery.

minal ileum at 7-10 cm, depending on the location of the primary tumor and vascular supply. Mesocolon is cut along the MCA superiorly, and medial to lateral mobilization is completed above the duodenum and pancreas up to the hepatic flexure.

Supracolic and lateral dissection

The gastrocolic omentum is divided, entering the lesser sac and completing the mobilization of the hepatic flexure. Lateral dissection of the already mobilized ascending colon along Toldt's line is performed, completing the dissection (Video 1).

Anastomosis and specimen delivery

The umbilical port is enlarged by 2-3 cm, and a wound protector is applied. The mobilized colon is delivered out, mesenteric cuts are identified, and the ileum is positioned alongside the transverse colon. Enterotomy is made towards the ascending colon, and a linear cutter stapler is introduced into the ileum and transverse colon, performing side-to-side

anastomosis with the first fire. Subsequently, the linear cutter stapler is placed beyond the enterotomy towards the anastomosis, and anastomosis is completed with the second fire. The specimen is delivered out, and the ileotransverse anastomosis segment is positioned internally. This technique minimizes stapler usage and is cost-effective. Alternatively, intracorporeal anastomosis can be performed using Endo GIA staplers.

DISCUSSION

Studies on CME have demonstrated a survival advantage of > 10% with the adoption of this technique[9]. Similarly, research focusing on D3 lymphadenectomy has shown a relative risk reduction in mortality by 18%[10]. Despite originating from different understandings and evolving in various regions globally, both approaches ultimately aim for the same outcome of improved cure rates and follow similar surgical principles. CME emphasizes the complete excision of the mesocolon fascia on both sides, while D3 lymphadenectomy focuses on removing lymph nodes along major feeding blood vessels. However, both techniques ultimately dissect along embryological fusion planes. Surgeons have meticulously confirmed the existence of colonic mesentery along the full length of the colon, which can be separated from the retroperitoneum along an avascular areolar tissue[11,12]. Goligher described the separation of this mesocolon towards the midline starting from Toldt's line and along Toldt's fascia[13]. Despite these universally recognized embryological principles, there remains a lack of consensus on what constitutes radical optimal right hemicolectomy. CVL is the surgical principle that is widely accepted across studies[14-16]. The distinction between D3 Lymphadenectomy and CME primarily lies in the extent of longitudinal bowel length dissection.

Our study seeks to underscore the importance of modern surgical principles in right hemicolectomy for malignancy. In the contemporary era, all advancements should be integrated, and efforts should be made to standardize surgical techniques for colon cancer globally. These principles should be incorporated into the teaching curriculum of medical colleges. By incorporating crucial cure-defining steps into a consensus definition, there could be broader adoption of those surgical techniques. The incorporation of important surgical techniques has led to oncological benefits worldwide, such as total mesocolon excision for rectal cancer and D2 Lymphadenectomy for gastric cancer[14,17]. Recognizing these potential benefits, we propose that the nomenclature for standard right radical hemicolectomy surgery should reflect survival-improving steps. It is suggested to use "Central Vascular Ligation with Complete Mesocolon Excision (CVL + CME) with D3 lymphadenectomy" for right-sided colon cancer surgery. This emphasis on nomenclature may lead to better adoption of key surgical principles in this procedure, resulting in proven better overall survival rates globally.

CONCLUSION

Surgical techniques are refined based on embryology and tumor biology, with the adoption of these techniques resulting in better survival and cure rates in oncology. We advocate for the adoption of CME + CVL with D3 lymphadenectomy as the standard approach for carcinoma of the right side of the colon. Both open and minimally invasive approaches can be utilized when performing this surgery.

FOOTNOTES

Author contributions: Yadav K performed and depicts the surgical technique in the article.

Conflict-of-interest statement: Dr. Kaushal has nothing to disclose.

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REFERENCES

1 **Muro K**. Systemic chemotherapy for metastatic colorectal cancer -Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2016 for treatment of colorectal cancer. *Nihon Shokakibyo Gakkai Zasshi* 2017; **114**: 1217-1223 [PMID: 28679979 DOI: 10.11405/nisshoshi.114.1217]

2 **Kobayashi H**, West NP. CME versus D3 Dissection for Colon Cancer. *Clin Colon Rectal Surg* 2020; **33**: 344-348 [PMID: 33162838 DOI: 10.1055/s-0040-1714237]

3 **Shimada Y**, Hamaguchi T, Mizusawa J, Saito N, Kanemitsu Y, Takiguchi N, Ohue M, Kato T, Takii Y, Sato T, Tomita N, Yamaguchi S, Akaike M, Mishima H, Kubo Y, Nakamura K, Fukuda H, Moriya Y. Randomised phase III trial of adjuvant chemotherapy with oral uracil and tegafur plus leucovorin versus intravenous fluorouracil and levofolinate in patients with stage III colorectal cancer who have undergone Japanese D2/D3 lymph node dissection: final results of JCOG0205. *Eur J Cancer* 2014; **50**: 2231-2240 [PMID: 24958736 DOI: 10.1016/j.ejca.2014.05.025]

4 **Enker WE**, Laffer UT, Block GE. Enhanced survival of patients with colon and rectal cancer is based upon wide anatomic resection. *Ann Surg* 1979; **190**: 350-360 [PMID: 485609 DOI: 10.1097/00000658-197909000-00010]

5 **Bokey EL**, Chapuis PH, Dent OF, Mander BJ, Bissett IP, Newland RC. Surgical technique and survival in patients having a curative resection for colon cancer. *Dis Colon Rectum* 2003; **46**: 860-866 [PMID: 12847357 DOI: 10.1007/s10350-004-6673-3]

6 **West NP**, Morris EJ, Rotimi O, Cairns A, Finan PJ, Quirke P. Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study. *Lancet Oncol* 2008; **9**: 857-865 [PMID: 18667357 DOI: 10.1016/S1470-2045(08)70181-5]

7 **Mike M**, Kano N. Laparoscopic surgery for colon cancer: a review of the fascial composition of the abdominal cavity. *Surg Today* 2015; **45**: 129-139 [PMID: 24515451 DOI: 10.1007/s00595-014-0857-9]

8 **Garcia-Granero A**, Pellino G, Frasson M, Fletcher-Sanfeliu D, Bonilla F, Sánchez-Guillén L, Domenech Dolz A, Primo Romaguera V, Sabater Ortí L, Martinez-Soriano F, Garcia-Granero E, Valverde-Navarro AA. The fusion fascia of Fredet: an important embryological landmark for complete mesocolic excision and D3-lymphadenectomy in right colon cancer. *Surg Endosc* 2019; **33**: 3842-3850 [PMID: 31140004 DOI: 10.1007/s00464-019-06869-w]

9 **Anania G**, Davies RJ, Bagolini F, Vettoretto N, Randolph J, Cirocchi R, Donini A. Right hemicolectomy with complete mesocolic excision is safe, leads to an increased lymph node yield and to increased survival: results of a systematic review and meta-analysis. *Tech Coloproctol* 2021; **25**: 1099-1113 [PMID: 34120270 DOI: 10.1007/s10151-021-02471-2]

10 **Kotake K**, Mizuguchi T, Moritani K, Wada O, Ozawa H, Oki I, Sugihara K. Impact of D3 lymph node dissection on survival for patients with T3 and T4 colon cancer. *Int J Colorectal Dis* 2014; **29**: 847-852 [PMID: 24798631 DOI: 10.1007/s00384-014-1885-z]

11 **Toldt C**, Dalla Rosa A, Paul E, Toldt C. An atlas of human anatomy for students and physicians. New York: Rebman Company, 1919 [DOI: 10.5962/bhl.title.44195]

12 **Congdon ED**, Blumberg R, Henry W. Fasciae of fusion and elements of the fused enteric mesenteries in the human adult. *Am J Anat* 1942; **70**: 251-279 [DOI: 10.1002/aja.1000700204]

13 **Denman AM**. Principles of immunology. *J Med Microbiol* 1980; **13**: 485-485 [DOI: 10.1099/00222615-13-3-485]

14 **Hohenberger W**, Weber K, Matzel K, Papadopoulos T, Merkel S. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation--technical notes and outcome. *Colorectal Dis* 2009; **11**: 354-64; discussion 364 [PMID: 19016817 DOI: 10.1111/j.1463-1318.2008.01735.x]

15 **Siani LM**, Garulli G. Laparoscopic complete mesocolic excision with central vascular ligation in right colon cancer: A comprehensive review. *World J Gastrointest Surg* 2016; **8**: 106-114 [PMID: 26981184 DOI: 10.4240/wjgs.v8.i2.106]

16 **Sica GS**, Vinci D, Siragusa L, Sensi B, Guida AM, Bellato V, García-Granero Á, Pellino G. Definition and reporting of lymphadenectomy and complete mesocolic excision for radical right colectomy: a systematic review. *Surg Endosc* 2023; **37**: 846-861 [PMID: 36097099 DOI: 10.1007/s00464-022-09548-5]

17 **Hartgrink HH**, van de Velde CJ, Putter H, Bonenkamp JJ, Klein Kranenbarg E, Songun I, Welvaart K, van Krieken JH, Meijer S, Plukker JT, van Elk PJ, Obertop H, Gouma DJ, van Lanschot JJ, Taat CW, de Graaf PW, von Meyenfeldt MF, Tilanus H, Sasako M. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. *J Clin Oncol* 2004; **22**: 2069-2077 [PMID: 15082726 DOI: 10.1200/jco.2004.08.026]

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ORIGINAL ARTICLE

Case Control Study

Perioperative outcomes of transvaginal specimen extraction laparoscopic total gastrectomy and conventional laparoscopic-assisted total gastrectomy

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Abstract

BACKGROUND

Natural orifice specimen extraction surgery (NOSES) has emerged as a promising alternative compared to conventional laparoscopic-assisted total gastrectomy (LATG) for treating gastric cancer (GC). However, evidence regarding the efficacy and safety of NOSES for GC surgery is limited. This study aimed to compare the safety and feasibility, in addition to postoperative complications of NOSES and LATG.

AIM

To discuss the postoperative effects of two different surgical methods in patients with GC.

METHODS

Dual circular staplers were used in Roux-en-Y digestive tract reconstruction for transvaginal specimen extraction LATG, and its outcomes were compared with LATG in a cohort of 51 GC patients with tumor size ≤ 5 cm. The study was conducted from May 2018 to September 2020, and patients were categorized into the NOSES group (n = 22) and LATG group (n = 29). Perioperative parameters were compared and analyzed, including patient and tumor characteristics, postoperative outcomes, and anastomosis-related complications, postoperative hospital stay, the length of abdominal incision, difference in tumor type, postoperative complications, and postoperative survival.

RESULTS

Postoperative exhaust time, operation duration, mean postoperative hospital stay,

length of abdominal incision, number of specific staplers used, and Brief Illness Perception Questionnaire score were significant in both groups ($P < 0.01$). In the NOSES group, the postoperative time to first flatus, mean postoperative hospital stay, and length of abdominal incision were significantly shorter than those in the LATG group. Patients in the NOSES group had faster postoperative recovery, and achieved abdominal minimally invasive incision that met aesthetic requirements. There were no significant differences in gender, age, tumor type, postoperative complications, and postoperative survival between the two groups.

CONCLUSION

The application of dual circular staplers in Roux-en-Y digestive tract reconstruction combined with NOSES gastrectomy is safe and convenient. This approach offers better short-term outcomes compared to LATG, while long-term survival rates are comparable to those of conventional laparoscopic surgery.

Key Words: Gastric cancer; Circular stapler; Natural orifice specimen extraction surgery; Laparoscopic-assisted total gastrectomy

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Core Tip: Natural orifice specimen extraction surgery (NOSES) in laparoscopic-assisted total gastrectomy (LATG) has a reduced requirement for abdominal incision and associated complications, decreased pain and discomfort, and improved postoperative recovery. The combined use of dual circular staplers in Roux-en-Y digestive tract reconstruction in LATG has a lower incidence of postoperative stenosis complications. Postoperative exhaust time, operation duration, mean postoperative hospital stay, length of abdominal incision, number of specific staplers used, and Brief Illness Perception Questionnaire score were significant in both groups. NOSES has emerged as a promising alternative compared to conventional LATG for treating gastric cancer.

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INTRODUCTION

Gastric cancer (GC) remains a highly fatal disease with unfavorable overall survival rates worldwide. It ranks as the fourth most common cancer in men and the seventh most common in women[1,2]. Despite notable advances in science and technology, the survival rate for GC is still unsatisfactory. Conventional laparoscopic-assisted total gastrectomy (LATG) is a widely accepted approach for treatment of GC[3]. While it significantly minimizes surgical trauma, patients still experience physical and psychological distress due to the abdominal incision required for specimen extraction and digestive tract reconstruction. The prolonged duration of the operation and the postoperative recovery period not only cause psychological trauma on patients, but also pose additional emotional strains on their family. Natural orifice specimen extraction surgery (NOSES) is a novel, minimally invasive surgical technique that enables specimens to be extracted through natural orifices such as the anus or vagina, using conventional laparoscopic instruments, transanal endoscopic microsurgery, or soft endoscopy, without the need for additional incisions[4]. Compared to conventional abdominal surgery, NOSES is associated with reduced postoperative pain, fewer wound complications, earlier recovery of bowel function, and shorter hospital stays. Although there are limited reports on NOSES in GC, an increasing number of patients have benefited from this novel technique. At the same time, for patients with potentially curable GC (*i.e.*, nonmetastatic GC), NOSES may offer new prospects for achieving better clinical outcomes. Recent studies also suggested the feasibility of NOSES in advanced GC[5,6]. The benefits of NOSES over conventional LATG are gradually being accepted, including reduced surgical time and improved postoperative aesthetics. To address the aforementioned concerns, NOSES has emerged as an advanced laparoscopic technique that minimizes surgical injury, reduces the risk of wound complications, and alleviates postoperative pain by removing the specimen through natural orifices connected to the external environment, such as the vagina or anus. Several studies have reported that NOSES can reduce the use of postoperative analgesia, accelerate the recovery of intestinal function, and shorten the length of hospital stay for gastric surgery compared to conventional specimen extraction approaches[7,8].

There are two main choices for digestive tract reconstruction in total gastrectomy, the linear stapler and circular stapler, which are typically performed to restore continuity of the alimentary canal. Esophagojejunostomy using a linear stapler is associated with a higher likelihood of anastomotic leakage or stenosis in clinical practice[9,10]. In the era of open surgery and laparoscopic-assisted gastrectomy, surgeons preferred circular staplers. There are several advantages of using a circular stapler. First, it conforms to the natural physiological state of the digestive tract; second, it can avoid the

common opening made by a linear stapler; and third, the anastomosis created by a circular stapler is less prone to narrowing. One of the two circular staplers we used is OrVil™, which is inserted through the mouth to complete the esophagojejunostomy. OrVil is a device designed to make it easier to perform this procedure in a minimally invasive manner, thereby avoiding difficulties caused by a short esophageal stump and reducing the need for purse-string sutures [11]. Studies have indicated that the application of OrVil for gastrointestinal reconstruction procedures can be both safe and effective, with comparable outcomes to the traditional circular stapling techniques[12,13]. In this study, we introduced a dual circular stapler combined with NOSES for LATG for GC. At a distance of 40 cm from the gastroenterostomy of the esophagus, we performed an anastomosis of the jejunum using a circle stapler with a diameter of 21 mm, thus achieving Roux-en-Y digestive tract reconstruction following total gastrectomy.

MATERIALS AND METHODS

Patient eligibility

A total of 51 patients who were diagnosed with GC and underwent LATG with D2 regional lymph node dissection between May 2018 and September 2020 at the Department of General Surgery, Xinqiao Hospital were included in this study, and categorized into the NOSES group and LATG group. The patients in the NOSES group were selected based on the following criteria: (1) Female patients with stage II or II GC with the lesion located in the fundus or showing poorly differentiated adenocarcinoma, requiring total gastrectomy; (2) Patients who did not require fertility preservation and had no history of gynecological or obstetric diseases; and (3) Written informed consent was obtained. The remaining patients were assigned to the LATG group.

Two types of gastrointestinal reconstructive surgery were evaluated for their clinical outcomes. Patient data were collected from medical records, including age, sex, body mass index (BMI), extent of lymph node dissection, anastomosis method, anastomosis-related complications, number of stapler cartridges used, time required for anastomosis, operation time, estimated blood loss, days to first flatus, liquid diet time, length of postoperative hospital stay, and postoperative complications. The resected specimens were histologically assessed for the length of proximal and distal margins, number of harvested lymph nodes, and TNM stage, according to the 8th edition of the Union for International Cancer Control (UICC).

Patients were routinely followed up at outpatient clinics 2 weeks after discharge and at 3 and 6 months after the operation, and then every 3 months thereafter. The presence of postoperative symptoms was recorded for each patient during each follow-up visit, and included reflux, dyspepsia, dumping syndrome, postprandial discomfort, and diarrhea. The study was approved by the Institutional Review Board, and all patients provided written informed consent.

Preoperative treatment

Preoperative chemoradiotherapy was performed by radiation oncologists and medical oncologists based on the clinical stages and patients' preferences, which was not included in the protocol of this trial. For patients who received preoperative chemotherapy, the surgery was performed 6-8 weeks after the completion of chemotherapy. Before surgery, these patients were evaluated for eligibility, and assigned to treatment groups according to the trial protocol.

Surgical procedure

All surgeons were qualified and experienced. The surgeon stood on the left side of the patient, with the first assistant standing on the right side. During the operation, the surgeon and the first assistant switched positions as needed. The camera assistant stood between the patient's legs. Under general anesthesia, the abdomen, pelvis and vaginal canal were disinfected with diluted iodophor water. In the reverse Trendelenburg position with the legs apart, five trocars were inserted. During the operation, the greater curvature was mobilized along the transverse colon using a harmonic scalpel (Ethicon Endo-Surgery Inc., Cincinnati, OH, United States). The left gastric vessels were identified after opening the bursa omentalis. The greater curvature was mobilized until the splenic hilum for complete omentectomy. The infrapyloric lymph nodes were dissected toward the duodenum and the distal gastric vessels (right gastroepiploic and right gastric) were transected using the harmonic scalpel. The duodenum was then cut using a laparoscopic 60-mm stapler (EndoGIA, Covidien, Mansfield, MA, United States), and the roots of the left gastric vessels were exposed. The left gastric vein was divided using the harmonic scalpel and the intact left gastric artery was used to expose the other branches of the celiac trunk. Lymph node dissection was continued along the hepatic and splenic arteries. The left gastric artery was subsequently divided near its root after double clipping. Dissection was then extended to the esophagocardiac junction at the lesser curvature and these lymph nodes were included in the resection specimen. The stomach was divided at the esophagogastric junction using a 60-mm laparoscopic stapler, and the specimen was placed and sealed in a retrieval bag.

Following the dual circular staplers operating instructions, the anvil of OrVil™ (Covidien) was placed through the mouth. Under the laparoscopic monitoring, the head joint of the anvil was pulled out from the esophageal stump (Figure 1A). The jejunum and mesentery was cut at a distance of 30 cm from the flexor's ligament using an endoscopic linear cutter. The operating handle of the 25-mm diameter circular stapler was then placed into the abdominal cavity through the left upper abdominal puncture hole (Figure 1B), with posture adjustments made to avoid damage to the gut. A plastic specimen bag that was inserted from the left upper abdominal puncture hole was used to isolate the hole from the stapler. Under laparoscopic monitoring, the esophagojejunostomy of Roux-en-Y reconstruction was performed using the first circular stapler (Figure 1C). The jejunal stump was closed with a 60-mm linear stapler (Figure 1D). Subsequently, a 3-cm transverse transvaginal posterior colpotomy was performed under laparoscopic control, and the incision was enlarged bluntly using the fingers. Another anvil with a diameter of 21 mm was inserted through the vagina and into the

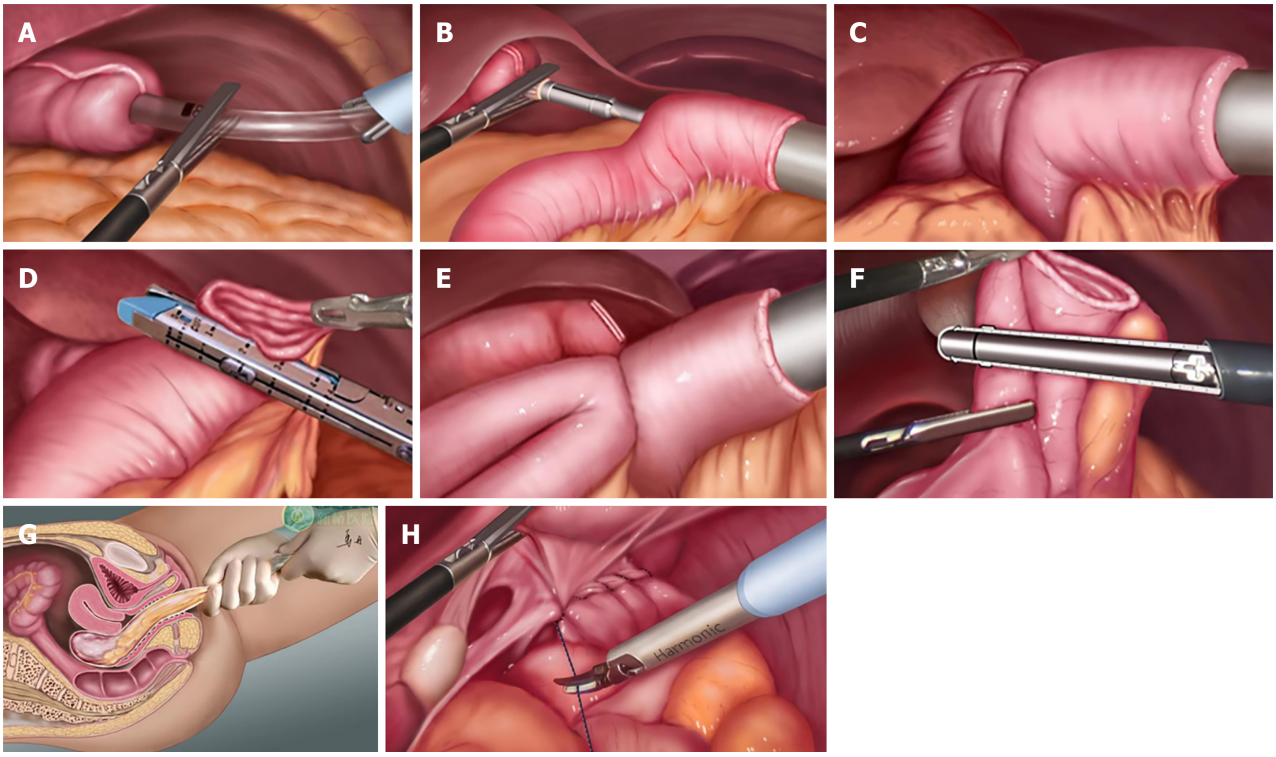


Figure 1 Surgical procedure. A: The anvil was pulled out from the esophageal stump; B: The operating handle was placed through the left upper abdominal puncture hole; C: The esophagojejunal anastomosis was performed by laparoscopic 25-mm circular stapler; D: The jejunal stump was closed with a linear stapler; E: The 21-mm anvil was fixed by purse-string suturing under laparoscopy; F: The jejunal stump was closed with linear stapler; G: The specimen was delivered through the vagina; H: The horizontal incision on the posterior wall of the vagina was closed with a running absorbable suture.

distal jejunum at 40 cm from the esophagojejunostomy. The anvil was secured with a purse-string suture under laparoscopy (Figure 1E). The handle of the stapler was inserted into the proximal jejunum *via* the left upper abdominal puncture hole too, with isolation from a plastic specimen bag. The end-to-side jejunostomy was fashioned using the second circular stapler and the stump was closed intracorporeally. The jejunal stump was closed with a 60-mm linear stapler (Figure 1F). The specimen was grasped with an ovary clamp through the vaginal incision and carefully pulled into the vagina (Figure 1G). The specimen was always contained within a retrieval bag, and there was no contact between the specimen and the abdominal cavity or the vagina throughout the procedure. Following removal of the specimen, the horizontal incision on the posterior wall of the vagina was closed using a running absorbable suture (Figure 1H), and an abdominal drain was used. Meticulous closure of the colpotomy and the use of an abdominal drain minimized the risk of postoperative complications.

Outcome measurement

The primary outcomes in this trial study were significantly different regarding postoperative abdominal incision length and postoperative exhaust time. Secondary outcomes included surgical quality, pathological outcomes, intraoperative blood loss, postoperative discharge time, and long-term tumor outcomes. Two distinct surgical procedures were used in this trial, and intraoperative hemorrhage was measured by subtracting the weight of the irrigation fluid from the suction blood and wet gauze. Pathology specimens were processed and assessed by the Department of Pathology, Xinqiao Hospital of Army Medical University in accordance with the Chinese Standardization Criteria for Tumor Pathology Diagnosis. The macroscopic completeness and quality of the specimen were assessed by pathologists according to previously reported criteria. The tumor stage was determined according to the 8th edition of the UICC TNM staging system. All enrolled patients were evaluated using the Brief Illness Perception Questionnaire (BIQ) and the Quality of Life Questionnaire (QLQ) scales. These questionnaires were distributed and collected by specialized staff, without the participation of the surgeons. All patients were asked to complete a questionnaire at the time of postoperative assessment. Follow-up principles were based on the Chinese standards of diagnosis and treatment of GC. Patients were asked to attend the hospital's outpatient department for documented visits and examinations. Specialized staff were arranged to collect follow-up data by making phone calls or sending emails if the patient did not come on time. An independent statistician monitored the data and focused on the safety markers. All data were recorded in the case report form by the trial investigators. Two different investigators checked the records for confirmation. Although no blinding to treatment allocation was incorporated in this trial, the outcomes were evaluated and recorded by two blinded assessors according to medical documents without knowledge of the grouping allocation.

Statistical analysis

All data were analyzed using GraphPad Prism 8.0 (La Jolla, CA, United States) and displayed as the mean ± SE.

Comparisons between two experimental groups were conducted using nonparametric tests, while differences among more than two groups were analyzed using one-way ANOVA followed by Dunnett's *post hoc* tests. The primary outcome measure was the 30-day postoperative complication rate (Clavien–Dindo Grade II or higher), which was compared using Fisher's exact test without adjustment for baseline characteristics. The difference and 95% confidence interval (CI) in postoperative complication rate were evaluated using unadjusted Miettinen–Nurminen scoring methods. Adjusted analysis for the primary outcome was conducted as per the predefined statistical analysis plan (Supporting Information: Trial Protocol), using multilevel logistic regression for the following factors: sex, age, ASA classification, BMI, abdominal surgery history, preoperative chemoradiotherapy, tumor size, pathological T stage, and pathological N stage. All *P* values were two-sided and considered significant when < 0.05.

RESULTS

Clinical characteristics

Between May 2018 and September 2020, 51 eligible patients with GC were randomized to receive either NOSES or LATG (Table 1). The surgeons were on the same team after grouping, and both groups were similar regarding age, BMI, extent of lymph node dissection, time to eat, and tumor stage with no significant differences in statistical analysis (Figure 2). The average total operating time was 284.23 min in the NOSES group and 221.15 min in the LATG group. Notably, the postoperative exhaust time was significantly shorter in the NOSES group (63.86 h) than in the LATG group (81.27 h). Nonetheless, there were no significant differences between the two groups (Figure 2). No patients were lost to follow-up after 2 years, four (7.8%) experienced recurrence (locoregional recurrence or distant metastases), one (1.9%) died, two (3.9%) had postoperative increase in carcinoembryonic antigen (CEA) increase, and two (3.9%) experienced postoperative hemorrhage.

Postoperative complications

During the 2-year follow-up period, one death occurred in the control group because of myocardial infarction. Two patients showed an increase in CEA levels and one patient developed bone metastasis in the experimental group. In the control group, one patient experienced postoperative abdominal metastasis or recurrence, one patient had liver metastasis, and one patient had pulmonary infection. Postoperative complications such as anastomotic leakage, abdominal infection, intestinal obstruction, incision-related complications, and deep vein thrombosis or pulmonary embolism were observed. However, there was no significant difference in the incidence of these complications between the two groups (Table 2).

Pathological characteristics

The postoperative pathological findings were compared between the two groups. There was no significant difference in the pathological TNM stage or other pathological characteristics (Figure 3).

Surgical outcomes

All operations in both groups were successfully completed. However, the NOSES group had a significantly longer mean operating time (NOSES 284.2 minutes *vs* LATG 221.5 minutes), and higher mean BIQ score (NOSES 41 *vs* LATG 31). Additionally, there was a significant difference between the two groups for the mean number of anvils used (LATG 3.5 *vs* NOSES 5). The mean abdominal incision length was longer in the LATG group (9.3 cm) than in the NOSES group (3.1 cm).

Postoperative short-term recovery

The NOSES group demonstrated significantly better postoperative gastrointestinal recovery, as evidence by a shorter mean time to first flatus emission (NOSES 63.8 hours *vs* LATG 81.3 hours), and a shorter mean time to consume a semifluid diet (NOSES 5.5 days *vs* LATG 6 days). Although there was a significant difference in the time to exhaust, no significant difference was found between the two groups for mean length of hospital stay (LATG 8.5 days *vs* NOSES 8.2 days).

DISCUSSION

Laparoscopic surgery for GC has several advantages of reduced surgical trauma, less gastrointestinal interference, minimal bleeding (no or less need for blood transfusion), decreased postoperative pain, shorter recovery time, smaller incision scars, and significantly lower rates of postoperative complications. As a result, laparoscopic surgery has become more popular for treatment of GC. In the early stage of laparoscopic surgery, abdominal incision was necessary for specimen collection and release. Over time, the introduction of NOSES technology has gradually shifted the concept of minimally invasive surgery. There are three potential natural orifices for abdominal specimen extraction in humans, transanal, transoral and transvaginal.

Reconstruction of the digestive tract after total gastrectomy is difficult and is a focus of debate and research[14,15]. The principles of gastrointestinal reconstruction in GC surgery include ensuring oncological safety, safe anastomosis, not increasing the risk of anastomotic complications, reducing functional damage, and ease of operation[16,17]. There are

Table 1 Baseline characteristics

	NOSES	LATG
Sex, *n* (%)		
Male	0 (0)	23 (79.3)
Female	22 (100)	6 (20.7)
Age (year), mean (SD)	56.59	56.86
ASA classification, *n* (%)		
I	14 (63.7)	19 (65.5)
II	8 (36.3)	10 (34.5)
Intraoperative blood loss (mL, SD)	218.18	211.72
Concomitant disease, *n* (%)		
Hypertension	7 (32)	8 (27.6)
Diabetes	2 (9)	4 (13.8)
Cardiac	10 (4.5)	10 (3.4)
Abdominal incision length (cm)	3.18	9.28
Postoperative exhaust time (h, SD)	63.86	81.28
Body mass index (kg/m^2), *n* (%)		
Underweight < 18.5	1 (4.5)	1 (3.4)
Normal 18.5-23.9	2 (9.1)	19 (65.5)
Overweight 24-27.9	16 (72.8)	8 (27.6)
Obese ≥ 28	3 (13.6)	1 (3.5)
With previous abdominal surgery, *n* (%)	3 (13.6)	3 (10.3)
Preoperative CEA (ng/mL), *n* (%)		
< 5	20 (91)	29 (100)
≥ 5	2 (9)	0 (0)
Clinical TNM stage, *n* (%)		
I	9 (40.9)	13 (44.8)
II	4 (18.1)	1 (3.5)
III	9 (41)	15 (51.7)
Mean operation time (minutes)	284.23	221.15
Undergo postoperative chemotherapy, *n* (%)	17 (77.3)	18 (62)
Postoperative complications, *n* (%)		
Postoperative bleeding	0 (0)	0 (0)
Postoperative liver metastasis	0 (0)	0 (0)
Bone metastasis	0 (0)	0 (0)
Pulmonary infection	0 (0)	0 (0)
Postoperative anastomotic leakage	0 (0)	0 (0)
Postoperative abdominal infection	0 (0)	0 (0)
Incision-related complications	0 (0)	0 (0)
Postoperative intestinal obstruction	0 (0)	0 (0)
Deep vein thrombosis or pulmonary embolism	0 (0)	0 (0)

NOSES: Natural orifice specimen extraction surgery; LATG: Laparoscopic-assisted total gastrectomy.

Table 2 Statistical analysis

	P value	Mean of LATG	Mean of NOSES	Difference	SE of difference
Operation time (minutes)	0.000215	225.0	284.2	-59.23	14.81
Postoperative exhaust time (hours)	0.001373	81.28	63.86	17.41	5.130
Abdominal incision length (cm)	< 0.000001	9.276	3.182	6.094	0.3357
Number of anvil used	< 0.000001	3.586	5.000	-1.414	0.2021
BIQ score	< 0.000001	31.10	41.45	-10.35	0.4849
Age	0.921270	56.86	56.59	0.2712	2.729
Weight (kg)	0.348282	60.37	57.09	3.283	3.466
BMI (kg/m^2)	0.368479	22.78	23.89	-1.106	1.218
Intraoperative blood loss (mL)	0.884527	211.7	218.2	-6.458	44.23
Lymph node dissection	0.431364	20.24	17.59	2.650	3.341
Postoperative hospital stay (days)	0.723817	8.448	8.227	0.2210	0.6218
Analgesic drug use	0.453535	0.5172	0.4091	0.1082	0.1431
History of abdominal operation	0.724385	0.1034	0.1364	-0.03292	0.09281
Eat a liquid diet (days)	0.079366	6.000	5.545	0.4545	0.2537
Postoperative adjuvant therapy	0.255226	0.6207	0.7727	-0.1520	0.1321

NOSES: Natural orifice specimen extraction surgery; LATG: Laparoscopic-assisted total gastrectomy.

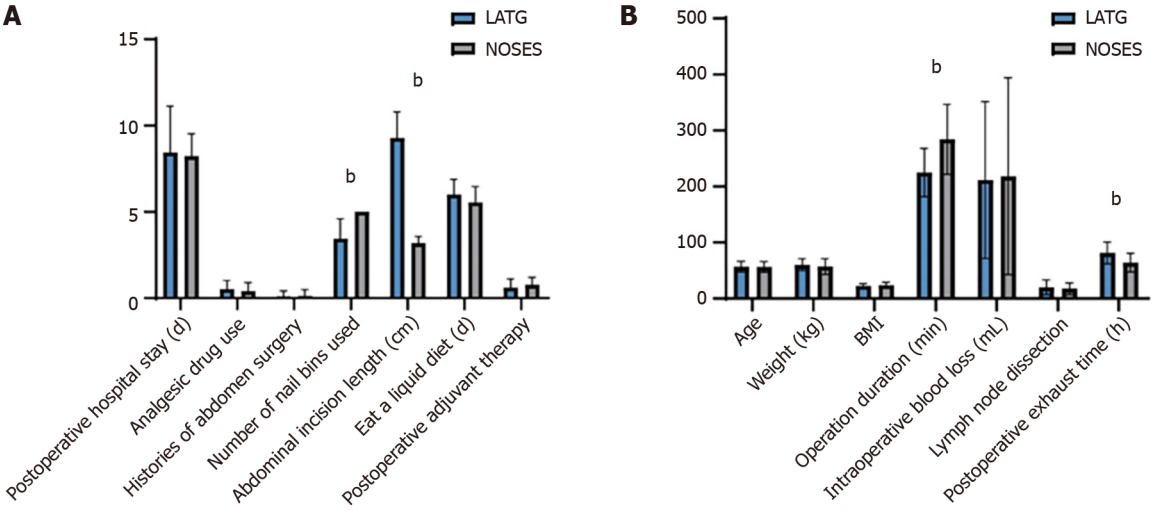


Figure 2 Clinical characteristics in the natural orifice specimen extraction surgery group and laparoscopic-assisted total gastrectomy group. NOSES: Natural orifice specimen extraction surgery; LATG: Laparoscopic-assisted total gastrectomy; BMI: Body mass index. $^bP < 0.01$.

several options for digestive tract reconstruction after total gastrectomy, including jejunal interposition, double channel method, storage bag, loop anastomosis. Roux-en-Y anastomosis has become the most commonly used method for digestive tract reconstruction. The choice of which method to implement for esophagojejunal anastomosis, whether to use a tubular stapler or a linear cutter, and determining which method is superior, are all urgent questions[18,19]. Where is the esophagojejunal anastomosis pathway for complete LATG? We believe that using a linear cutter to perform esophagojejunal lateral anastomosis and complete endoscopic total gastrectomy for digestive tract reconstruction may be the most common choice using the existing anastomotic instruments. However, there are still many problems with linear staplers, such as the need to preserve a longer segment of the lower esophagus. Therefore, it is necessary to clearly understand the appropriate indications. One of the advantages of circular staplers is that they eliminate the need for manual purse-string sutures, simplifying the surgical procedure. We believe that the breakthrough in research and development of a tubular stapler suitable for complete laparoscopic esophagojejunostomy means that the use of tubular staplers for complete endoscopic total gastrectomy and digestive tract reconstruction may become mainstream again.

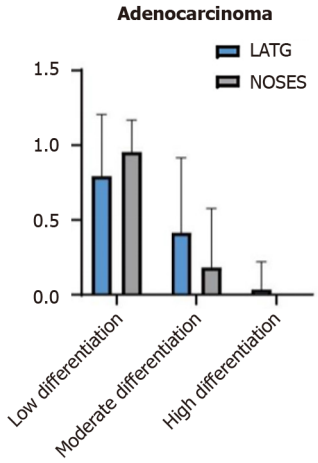


Figure 3 Adenocarcinoma. NOSES: Natural orifice specimen extraction surgery; LATG: Laparoscopic-assisted total gastrectomy.

With the progress of minimally invasive technology, an increasing number of people can accept the use of natural cavity specimen retrieval technology. To date, there are no studies reporting on NOSES compared to conventional LATG. Our study provides clinicians with valuable reference data related to both surgical options. Our findings indicated that the experimental group showed significant improvements in terms of gastrointestinal recovery time and abdominal incision length. Gastrojejunostomy may be difficult to perform through a small incision in obese patients due to poor visualization, and extracorporeal anastomosis has been associated with tissue traction, injury, and an increased risk of infection. In such cases, an extension of the laparotomy may be necessary to obtain a better view and ensure a secure anastomosis during gastrectomy for GC. Additionally, tumors located at the gastroesophageal junction may require a longer remaining healthy esophageal stump to ensure adequate negative margins, which may not be conducive to esophagojejunostomy. In terms of esophagojejunal anastomosis, the use of a linear cutting stapler requires a high level of technical skill. In recent years, many surgeons have proposed the use of linear staplers in LATG, such as the π anastomosis and overlap techniques[20,21]. One disadvantage is that a longer segment of the lower esophagus is needed, while ensuring sufficient safety of the incisional margin. It is generally easier to maintain a 4.5-6.0-cm length of the abdominal segment of the esophagus for patients with tumors located in the gastric body, while it is challenging for upper GC to meet this condition, particularly for tumors in the esophagogastric junction that invade the dentate line. Therefore, it is not suitable for patients with high esophageal resection lines, and its indications are strictly limited. Although it is ensured that the lower segment of the esophagus remains 4.5-6.0 cm when the esophagus is free and naked, in clinical practice, most of the broken ends retract into the esophageal hiatus after the esophagus is severed. To prevent retraction of the esophageal stump into the chest cavity, Lee *et al*[15] attempted to suture one needle on each side of the esophageal stump opening to assist pulling and inserting a linear cutter into the esophageal opening, thereby reducing the difficulty of anastomosis. However, completing the anastomosis without disconnecting the esophagus and verifying the incision margin for safety does not adhere to the principles of oncology. Moreover, traction during the anastomosis can reduce tension at the anastomotic site during the operation, but once the esophagus is severed, traction is no longer present, leading to inevitable tension-related issues.

Esophagojejunostomy using a circular stapler has become a standard technique in open total gastrectomy. Therefore, in LATG, esophagojejunostomy using a circular stapler has emerged as the preferred method. The method we used to reconstruct the digestive tract after total gastrectomy included a novel circular stapling technique that could be used to complete the esophagojejunostomy using a transorally inserted anvil (OrVil). This technique avoids the difficulties associated with a short esophageal stump, especially the purse-string suture, and can ensure a high-quality anastomosis, thereby preventing complications such as stenosis and anastomotic leaks. This surgical method does not require endoscopic purse string suture, nor does it require the surgeon to insert a stapler anvil into the abdominal cavity, which seems to simplify the surgical process. For GC at a higher position, a higher incision margin can be obtained than the suture purse string method, ensuring a sufficient safe esophageal incision margin. However, pulling out the anvil catheter through the abdominal cavity increases the risk of abdominal contamination and does not comply with the principle of sterility. In addition, OrVil is inserted through the mouth, which reduces the difficulty associated with the suture purse and insertion of the anvil *via* the abdominal cavity. However, it requires the assistance of an anesthesiologist, and it is difficult to pass the anvil through the esophageal stricture, which can cause esophageal injury. There can be accidents if the anvil becomes stuck in the esophagus and a digestive endoscope is needed for removal. In order to overcome the difficulties in purse-string suturing of the lower esophagus and insertion of the anvil head into the esophagus, a newly developed transoral device (OrVil™), equipped with an anvil, was designed by Covidien. This device was first reported in 2009 for application in complete LATG and digestive tract reconstruction[21].

With reference to the application of a circular stapler in esophagojejunal anastomosis, our team pioneered a technique using a smaller circular stapler (diameter 21 mm) for complete jejunojejunostomy. This approach makes the two anastomoses more reliable and convenient, resolving the problems associated with frequently used methods. Our study suggests that laparoscopic reconstruction of Roux-en-Y anastomosis with a dual circular stapler and NOSES is safer, more feasible and less invasive than other methods. Based on our results, when considering short-term efficacy and 3-year

follow-up, it is evident that a longer operating time contributes to increased anesthesia and cost; however, it will decrease as the surgical team gains experience and proficiency.

CONCLUSION

Our novel method (combined use of dual circular staplers in Roux-en-Y digestive tract reconstruction with NOSES in LATG) provides significant advantages over conventional LATG, including enhanced visibility during the anastomosis, reduced requirement for abdominal incision and associated complications, decreased pain and discomfort, improved postoperative recovery, and lower incidence of postoperative stenosis complications. However, further studies with larger populations and longer follow-up are necessary to obtain more comprehensive results.

FOOTNOTES

Author contributions: Zhang ZC and Ma D contributed to the conceptualization; Zhang ZC contributed to the data collation, statistics, surgery, and manuscript writing; Wang WS, Chen JH, Ma YH, and Ma D contributed to the formal analysis, and visualization; Wang WS, Chen JH, and Ma YH contributed to the follow-up visit data curation; Ma D contributed to the funding acquisition, project administration, supervision, and writing - review & editing; all authors have read and approved the final version to be published.

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REFERENCES

1 **Sylla P**, Rattner DW, Delgado S, Lacy AM. NOTES transanal rectal cancer resection using transanal endoscopic microsurgery and laparoscopic assistance. *Surg Endosc* 2010; **24**: 1205-1210 [PMID: 20186432 DOI: 10.1007/s00464-010-0965-6]
2 **Sumer F**, Kayaalp C, Ertugrul I, Yagci MA, Karagul S. Total laparoscopic subtotal gastrectomy with transvaginal specimen extraction is feasible in advanced gastric cancer. *Int J Surg Case Rep* 2015; **16**: 56-58 [PMID: 26413924 DOI: 10.1016/j.ijscr.2015.08.043]
3 **Sun P**, Wang XS, Liu Q, Luan YS, Tian YT. Natural orifice specimen extraction with laparoscopic radical gastrectomy for distal gastric cancer: A case report. *World J Clin Cases* 2019; **7**: 4314-4320 [PMID: 31911913 DOI: 10.12998/wjcc.v7.i24.4314]
4 **Nishimura A**, Kawahara M, Honda K, Ootani T, Kakuta T, Kitami C, Makino S, Kawachi Y, Nikkuni K. Totally laparoscopic anterior resection with transvaginal assistance and transvaginal specimen extraction: a technique for natural orifice surgery combined with reduced-port surgery. *Surg Endosc* 2013; **27**: 4734-4740 [PMID: 23949481 DOI: 10.1007/s00464-013-3120-3]
5 **Yagci MA**, Kayaalp C, Novruzov NH. Intracorporeal mesenteric division of the colon can make the specimen more suitable for natural orifice extraction. *J Laparoendosc Adv Surg Tech A* 2014; **24**: 484-486 [PMID: 24905885 DOI: 10.1089/lap.2014.0116]
6 **Jeong SH**, Lee YJ, Choi WJ, Paik WY, Jeong CY, Park ST, Choi SK, Hong SC, Jung EJ, Joo YT, Ha WS. Trans-vaginal specimen extraction following totally laparoscopic subtotal gastrectomy in early gastric cancer. *Gastric Cancer* 2011; **14**: 91-96 [PMID: 21264485 DOI: 10.1007/s10120-011-0006-8]
7 **Xiao Y**, Xu L, Zhang JJ, Xu PR. Transvaginal laparoscopic right colectomy for colon neoplasia. *Gastroenterol Rep (Oxf)* 2020; **8**: 76-78

[PMID: 32104587 DOI: 10.1093/gastro/goz059]

8 **Du J**, Xue H, Hua J, Zhao L, Zhang Z. Intracorporeal classic circular-stapled gastrojejunostomy and jejunojejunostomy during laparoscopic distal gastrectomy: A simple, safe "intraluminal poke technique" for anvil placement. *J Surg Oncol* 2019; **119**: 464-471 [PMID: 30582618 DOI: 10.1002/jso.25353]

9 **Wang Q**, Yang KL, Guo BY, Shang LF, Yan ZD, Yu J, Zhang D, Ji G. Safety of early oral feeding after total laparoscopic radical gastrectomy for gastric cancer (SOFTLY-1): a single-center randomized controlled trial. *Cancer Manag Res* 2019; **11**: 4839-4846 [PMID: 31239762 DOI: 10.2147/CMAR.S199552]

10 **Ojima T**, Nakamura M, Hayata K, Yamaue H. Laparoscopic Roux-en-Y reconstruction using conventional linear stapler in robotic total gastrectomy for gastric cancer. *Surg Oncol* 2020; **33**: 9-10 [PMID: 31885361 DOI: 10.1016/j.suronc.2019.12.003]

11 **He L**, Zhao Y. Is Roux-en-Y or Billroth-II reconstruction the preferred choice for gastric cancer patients undergoing distal gastrectomy when Billroth I reconstruction is not applicable? A meta-analysis. *Medicine (Baltimore)* 2019; **98**: e17093 [PMID: 31770192 DOI: 10.1097/MD.0000000000017093]

12 **Gong CS**, Kim BS, Kim HS. Comparison of totally laparoscopic total gastrectomy using an endoscopic linear stapler with laparoscopic-assisted total gastrectomy using a circular stapler in patients with gastric cancer: A single-center experience. *World J Gastroenterol* 2017; **23**: 8553-8561 [PMID: 29358863 DOI: 10.3748/wjg.v23.i48.8553]

13 **Zhang ZC**, Luo QF, Wang WS, Chen JH, Wang CY, Ma D. Development and future perspectives of natural orifice specimen extraction surgery for gastric cancer. *World J Gastrointest Surg* 2022; **14**: 1198-1203 [PMID: 36504515 DOI: 10.4240/wjgs.v14.i11.1198]

14 **López MJ**, Carbajal J, Alfaro AL, Saravia LG, Zanabria D, Araujo JM, Quispe L, Zevallos A, Buleje JL, Cho CE, Sarmiento M, Pinto JA, Fajardo W. Characteristics of gastric cancer around the world. *Crit Rev Oncol Hematol* 2023; **181**: 103841 [PMID: 36240980 DOI: 10.1016/j.critrevonc.2022.103841]

15 **Lee SR**, Kim HO, Son BH, Shin JH, Yoo CH. Laparoscopic-assisted total gastrectomy versus open total gastrectomy for upper and middle gastric cancer in short-term and long-term outcomes. *Surg Laparosc Endosc Percutan Tech* 2014; **24**: 277-282 [PMID: 24710235 DOI: 10.1097/SLE.0b013e3182901290]

16 **Guan X**, Liu Z, Parvaiz A, Longo A, Saklani A, Shafik AA, Cai JC, Ternent C, Chen L, Kayaalp C, Sumer F, Nogueira F, Gao F, Han FH, He QS, Chun HK, Huang CM, Huang HY, Huang R, Jiang ZW, Khan JS, da JM, Pereira C, Nunoo-Mensah JW, Son JT, Kang L, Uehara K, Lan P, Li LP, Liang H, Liu BR, Liu J, Ma D, Shen MY, Islam MR, Samalavicius NE, Pan K, Tsarkov P, Qin XY, Escalante R, Efetov S, Jeong SK, Lee SH, Sun DH, Sun L, Garmanova T, Tian YT, Wang GY, Wang GJ, Wang GR, Wang XQ, Chen WT, Yong Lee W, Yan S, Yang ZL, Yu G, Yu PW, Zhao D, Zhong YS, Wang JP, Wang XS. International consensus on natural orifice specimen extraction surgery (NOSES) for gastric cancer (2019). *Gastroenterol Rep (Oxf)* 2020; **8**: 5-10 [PMID: 32104581 DOI: 10.1093/gastro/goz067]

17 **Zhu Q**, Yu L, Zhu G, Jiao X, Li B, Qu J. Laparoscopic Subtotal Gastrectomy and Sigmoidectomy Combined With Natural Orifice Specimen Extraction Surgery (NOSES) for Synchronous Gastric Cancer and Sigmoid Colon Cancer: A Case Report. *Front Surg* 2022; **9**: 907288 [PMID: 35756479 DOI: 10.3389/fsurg.2022.907288]

18 **Salih AE**, Bass GA, D'Cruz Y, Brennan RP, Smolarek S, Arumugasamy M, Walsh TN. Extending the reach of stapled anastomosis with a prepared OrVil™ device in laparoscopic oesophageal and gastric cancer surgery. *Surg Endosc* 2015; **29**: 961-971 [PMID: 25159628 DOI: 10.1007/s00464-014-3768-3]

19 **Jung YJ**, Kim DJ, Lee JH, Kim W. Safety of intracorporeal circular stapling esophagojejunostomy using trans-orally inserted anvil (OrVil) following laparoscopic total or proximal gastrectomy - comparison with extracorporeal anastomosis. *World J Surg Oncol* 2013; **11**: 209 [PMID: 23972079 DOI: 10.1186/1477-7819-11-209]

20 **Thrift AP**, El-Serag HB. Burden of Gastric Cancer. *Clin Gastroenterol Hepatol* 2020; **18**: 534-542 [PMID: 31362118 DOI: 10.1016/j.cgh.2019.07.045]

21 **Jeong O**, Park YK. Intracorporeal circular stapling esophagojejunostomy using the transorally inserted anvil (OrVil) after laparoscopic total gastrectomy. *Surg Endosc* 2009; **23**: 2624-2630 [PMID: 19343421 DOI: 10.1007/s00464-009-0461-z]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Optimal extent of lymphadenectomy improves prognosis and guides adjuvant chemotherapy in esophageal cancer: A propensity score-matched analysis

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Abstract

BACKGROUND

The optimal extent of lymphadenectomy in esophageal squamous cell carcinoma (ESCC) patients remained debatable.

AIM

To explore the ideal number of cleared lymph nodes in ESCC patients undergoing upfront surgery.

METHODS

In this retrospective, propensity score-matched study, we included 1042 ESCC patients who underwent esophagectomy from November 2008 and October 2019. Patients who underwent neoadjuvant therapy were excluded. We collected patients' clinicopathological features and information regarding lymph nodes, including the total number of resected lymph nodes (NRLN), and pathologically diagnosed positive lymph nodes (RPLN). SPSS and R software were used for statistical analysis.

RESULTS

Among the included 1042 patients, two cohorts: ≤ 21 (n = 664) and > 21 NRLN (n = 378) were identified. The final prognostic model included four variables: T stage, N, venous thrombus, and the number of removed lymph nodes. Among them, NRLN > 21 was determined as an independent prognosticator after surgery for esophageal cancer (hazards regression = 0.66, 95% confidence interval: 0.50-0.87, P = 0.004). A nomogram was created based on the regression coefficients of the variables in the final model. In the training cohort, the predictive model dis-

played an uncorrected five-year overall survival C-index of 0.659, with a bootstrap-corrected C-index of 0.654. In the subgroup analysis, adjuvant chemotherapy was beneficial in the subgroup with NRLN > 21 and RPLN ≤ 0.16 and NRLN ≤ 21 and RPLN > 0.16.

CONCLUSION
NRLN > 21 was an independent prognostic factor after ESCC surgery. The combination of NRLN and RPLN may provide a reference for adjuvant chemotherapy use in potential beneficiaries.

Key Words: Esophageal squamous cell carcinoma; Lymphadenectomy; Adjuvant chemotherapy; Prognosis; Nomogram

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Core Tip: This study delineates the prognostic value of the number of lymph nodes removed during esophagectomy in esophageal squamous cell carcinoma (ESCC) patients, highlighting that a count greater than 21 significantly improves survival outcomes. It introduces a novel prognostic model, incorporating lymph node count with clinical variables, and proposes a nuanced approach to post-operative adjuvant chemotherapy based on lymph node ratio. These insights affirm the importance of extensive lymphadenectomy in ESCC and offer a refined strategy for tailoring adjuvant treatment, thereby enhancing personalized patient care.

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INTRODUCTION

Esophageal cancer (EC) is one of the deadliest cancers in the world[1], and most of the cases are esophageal squamous cell carcinoma (ESCC). Benefiting from multimodality treatment, the mortality rate of EC is decreasing year by year[2,3]. Neoadjuvant therapy followed by surgery is the current standard treatment option for patients with locally advanced ESCC[4]. Despite advances in clinical research, the significance of the number of lymph nodes removed in clinical practice is still unclear. On one hand, performing a more comprehensive lymphadenectomy could lead to more precise staging, which in turn may enhance postoperative treatment guidance and improve disease-specific survival rates[5], on the other hand, extensive lymphadenectomy is associated with more postoperative complications in the short term[6]. A study shows that removing more lymph nodes increases the risk of chylothorax, which makes it more difficult for thoracic surgeons to manage post-operative events[7]. The National Comprehensive Cancer Network currently recommends that at least 15 lymph nodes be resected during lymphadenectomy[8]. However, the proper upper limit of lymph node resection remains unclear for preventing complications of excessive surgery. Consequently, investigating the optimal number of lymph node resection is essential to strike a balance between survival benefits and potential complications. In the present study, we studied the appropriate number of lymph node resections for specific patients to ensure survival benefits and reduce postoperative complications. We tried to obtain the extent of lymph node resection for a better prognosis and provide a reference for the thoracic surgeon to perform lymphadenectomy.

MATERIALS AND METHODS

Patients and database

This multicenter database contains specific information on patients' clinicopathological features, information regarding lymph nodes including the total number of resected lymph nodes, and pathologically diagnosed positive lymph nodes. The naming of the lymph node stations was based on the 11th Japanese Classification of Esophageal Cancer[9].

Between November 2008 and October 2019, 1821 patients with EC who underwent esophagectomy at the First Affiliated Hospital of Shantou University Medical College and Guangdong Provincial People's Hospital were eligible for further selection. In this retrospective cohort study, the inclusion criteria included: (1) Pathologically confirmed diagnosis of ESCC; (2) Thoracic EC; (3) Underwent lymph nodes resection; and (4) No history of other cancers. 1470 patients met the inclusion criteria. Patients with a lack of lymph node information (n = 364), lack of follow-up information (n = 29), positive resection margins (n = 22), and death within one month after surgery (n = 13) were excluded. Eventually, a total of 1042 patients were enrolled in this study. All clinical characteristics and pathological data were retrieved from medical records.

Preoperative workup

The preoperative workup included upper gastrointestinal endoscopy to confirm the diagnosis of EC; chest computed tomography or positron emission tomography-computed tomography reveal tumor and lymph node features.

Surgical procedures and pathological stage

The patients underwent a right or left transthoracic esophagectomy with lymphadenectomy. Resection of lymph nodes was performed with standard lymphadenectomy, extended lymphadenectomy, and total lymphadenectomy. Standard 2-field lymphadenectomy is defined as an extent that covers the entire posterior mediastinum and includes the resection of lymph nodes in the abdomen, along the celiac trunk, common hepatic and splenic arteries, and those along the lesser curvature of the stomach and in the lesser omentum; extended 2-field lymphadenectomy includes all lymph nodes addressed in the standard 2-field, with additional clearance of the nodes in the right paratracheal gutter; total 2-field lymphadenectomy expands upon the extended 2-field resection by also removing the lymph nodes in the left paratracheal gutter. Among the included patients, 519 received standard 2-field lymphadenectomy, 335 received extended 2-field lymphadenectomy, and 188 received total 2-field lymphadenectomy. Pathological staging was assigned to each patient following the eighth edition of the tumor-node-metastasis (TNM) staging system released by the American Joint Committee on Cancer[10]. T staging was based on the depth of tumor invasion, and N staging was categorized by the number of regional positive lymph nodes.

Follow-up and outcomes

Patients were monitored every three months for the first two years post-esophagectomy and biannually for the subsequent three years. Follow-up continued until January 31, 2022, or until the patient's death, with a median follow-up duration of 53.0 months. The primary endpoints were overall survival (OS) and disease-free survival (DFS) which were defined as the survival time after surgery and the time with no evidence of local or distant disease recurrence, respectively.

Ethical approval

The ethics committee of the two hospitals approved our work (No. GDREC2019687H), and written consent was waived due to the retrospective nature of this study. The Declaration of Helsinki's rules and regulations were followed when carrying out the study protocol.

Statistical analysis

The Student's *t*-test was employed to analyze continuous variables, while the χ^2 test or Fisher's exact test was utilized for comparing categorical variables. The optimal cutoff values of the total lymph nodes number were determined by the "surv_cutpoint" function of the "survminer" R package (Supplementary Figure 1). We employed the Kaplan-Meier method and the log-rank test for univariate analysis, selecting variables with a *P* value less than 0.05 for inclusion in the multivariate analysis, which was performed using forward stepwise Cox proportional hazards regression. The prognostic model, developed from variables that were statistically significant in the multivariate analysis, was depicted using a nomogram. The performance of the predictive model was evaluated using operating characteristic curves (ROC) curve analysis and calibration curves, while decision curve analysis (DCA) was utilized to assess its clinical utility. Propensity score matching was used to compare the OS between the cohorts with different numbers of cleared lymph nodes. The variables age, sex, tumor stage, nodal stage, differentiation grade, venous thrombus, perineurial invasion, positive lymph node number, and positive lymph node ratio were matched. Using nearest neighbor-matching, a 1:1 match was conducted on the propensity score with a maximum caliper of 0.2 (Supplementary Table 1). All statistical analyses were performed by SPSS software (version 26.0; IBM Corp) and R software (version 4.0.0, R Foundation).

RESULTS

Clinicopathological characteristics of the investigated populations

In the enrolled cohort of 1042 patients, their median age was 60 (interquartile range: 54-66) years and most of the patients were male (78.7%). More than half of the patients were at the T3 stage (46.7%). Most of the patients had moderately differentiated pathologic outcomes. Most patients were negative for venous thrombus (14.9% positive) and perineurial invasion (25.0% positive) (Table 1). 12 patients died within 90 d, with a 90-d mortality rate of 1.15%. 130 patients died within 1 year, with a 1-year mortality rate of 12.18%. Based on the optimal cutoff values of the total number of removed lymph nodes number, the patients were divided into two cohorts: ≤ 21 cohorts (n = 664) and > 21 cohorts (n = 378). Patients in > 21 cohorts were more likely to achieve a longer survival time at the follow-up (P = 0.049; Figure 1A). In the final result, 203 patients were matched well. Patients in > 21 cohorts continued to have better survival outcomes (P = 0.035; Figure 1B).

Construction and evaluation of the predictive model

A univariate regression analysis was applied to the clinicopathological characteristics to determine which variables affected the prognosis (Table 2). There were statistically significant differences in G stage, N stage, T stage, venous thrombus [hazards regression (HR) = 2.1, 95% confidence interval (CI): 1.68-2.36, P < 0.001], perineurial Invasion (HR = 1.79, 95%CI: 1.41-2.29, P < 0.001), maximal tumor diameter (HR = 1.01, 95%CI: 1-1.01, P = 0.038), adjuvant chemotherapy

Table 1 Clinicopathological information of the study population

Variables	Level	Overall
Number		1042
Sex, *n* (%)	Male	820 (78.7)
	Female	222 (21.3)
Age (yr), median (IQR)		60 (54, 66)
T, *n* (%)	1	98 (9.4)
	2	219 (21.0)
	3	487 (46.7)
	4	238 (22.8)
N, *n* (%)	0	612 (58.7)
	1	234 (22.5)
	2	134 (12.9)
	3	62 (6.0)
G, *n* (%)	Well differentiated	124 (11.9)
	Moderate differentiated	740 (71.0)
	Poor differentiated	178 (17.1)
Venous thrombus, *n* (%)	Negative	887 (85.1)
	Positive	155 (14.9)
Perineurial invasion, *n* (%)	Negative	509 (75.0)
	Positive	170 (25.0)
NPLN, mean (SD)		1.17 (2.15)
RPLN, mean (SD)		0.06 (0.11)
NRLN, mean (SD)		19.67 (9.81)
Adjuvant chemotherapy, *n* (%)	No	599 (57.5)
	Yes	443 (42.5)

IQR: Interquartile range; NPLN: Number of positive lymph nodes; RPLN: Ratio of positive lymph nodes.

(HR = 1.27, 95%CI: 1.06-1.52, P = 0.009) and the number of removed lymph nodes (> 21 *vs* ≤ 21, HR = 0.83, 95%CI: 0.68-1, P = 0.049). The forward stepwise Cox regression model for multivariate analysis included a univariate analysis of variables with significant differences. By excluding the interaction between variables, the final prognostic model included four variables: T stage, N, venous thrombus, and the number of removed lymph nodes (Table 3). The number of lymph nodes > 21 was identified as an independent favorable prognostic factor following EC surgery (HR = 0.66, 95%CI: 0.50-0.87, P = 0.004). A nomogram was created based on the regression coefficients of the variables in the final model (Figure 2). The model in the training cohort had an uncorrected 5-year OS C-index of 0.659 and a bootstrap-corrected 5-year OS C-index of 0.654. To assess the discriminatory ability of the predictive models, the calibration curve of the nomogram predicting 3-year and 5-year OS (Figure 3A) and 3-year OS and 5-year OS ROC were plotted with area under the ROC curves (AUCs) of 0.676 and 0.647 (Figure 3B), respectively. The clinical utility of the models was assessed using DCA (Figure 3C).

Cross-validation of the prediction model

A 5-fold internal cross-validation was conducted 200 times to protect against the influence of the random splits (Figure 3D).

Stratified effect of number of resected lymph nodes and ratio of positive lymph nodes on adjuvant chemotherapy

We used the Kaplan-Meier analysis to draw survival curves to further explore the stratified effect of number of resected lymph nodes (NRLN) and ratio of positive lymph nodes (RPLN) on adjuvant chemotherapy. The results found that a combination of NRLN and RPLN could identify the patients who underwent adjuvant chemotherapy and could receive a better prognosis (Figure 4).

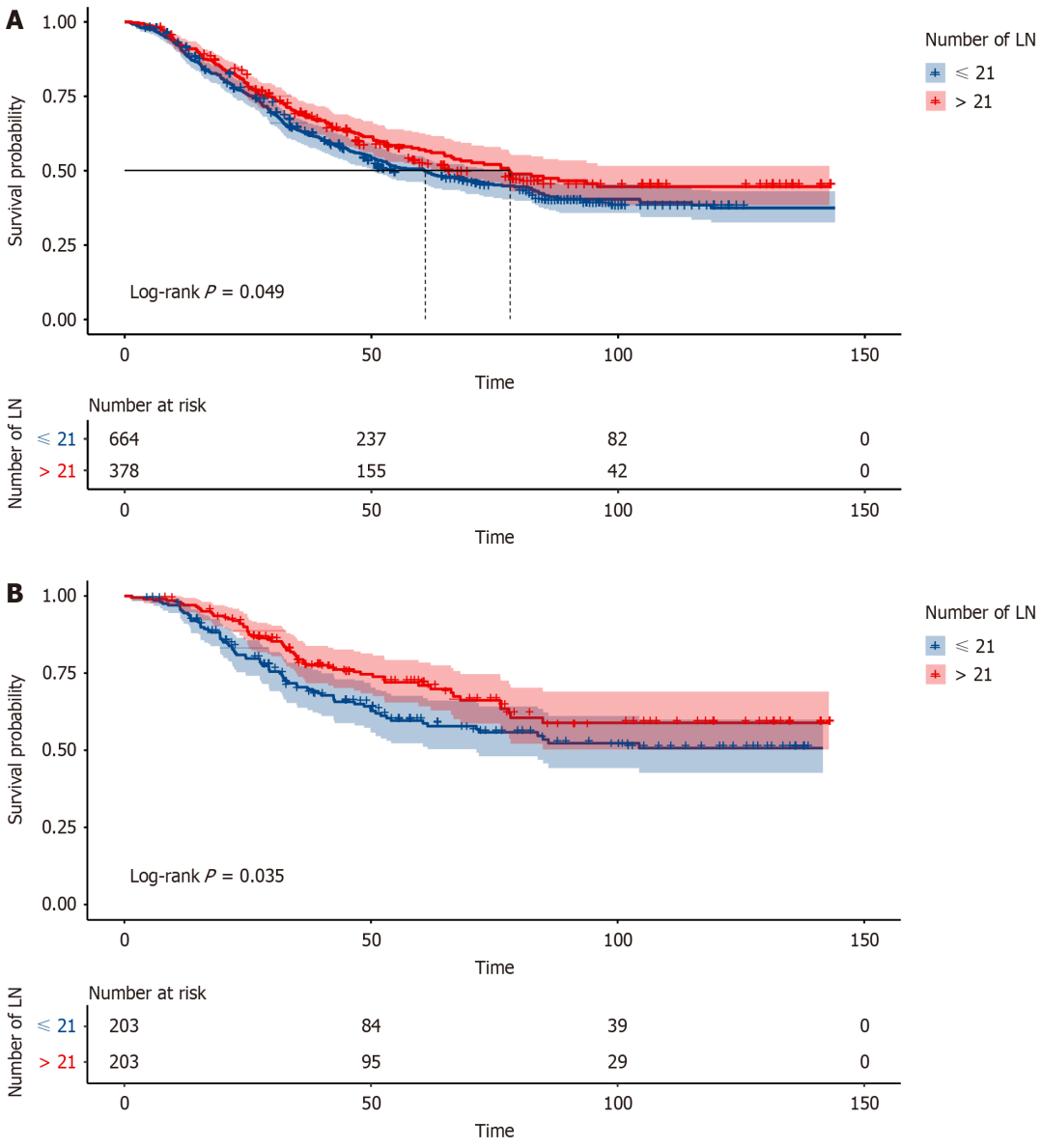


Figure 1 Kaplan-Meier curve for overall survival before and after propensity-scoring matching. A: Survival difference between the number of removed lymph node > 21 and ≤ 21 before propensity-scoring matching; B: Survival difference between two cohorts after propensity-scoring matching. LN: Lymph nodes.

DISCUSSION

Surgery is the foundation of the treatment of EC, and lymph node resection is an important part[11,12]. Nonetheless, the effect of the number of lymph nodes resected on survival remains uncertain. For years, researchers have argued whether adequate lymph node resection yields actual therapeutic benefit. The appropriate NRLN should be carefully selected to balance the potential survival benefit with lower postoperative morbidity. In this retrospective analysis, data from two thoracic surgical centers with radical esophagectomy were used to identify the role of NRLN in survival prognosis. Given the potential impact of neoadjuvant therapy on lymph node status, which could bias the results, patients with neoadjuvant therapy were excluded from this study.

Our results indicate that NRLN is an independent prognostic factor, with the survival of NRLN > 21 better than ≤ 21. By matching the propensity scores of clinicopathological information between the two groups, the differences remained. In this study, we observed a 90-d mortality rate of 1.15% and a 1-year mortality rate of 12.18%, reflecting the technical challenges and complexity of esophageal surgery. Specifically, patients with more than 21 lymph nodes removed exhibited improved survival metrics compared to the general cohort, suggesting that extensive lymphadenectomy might be associated with better medium-term survival outcomes despite its complexity. This comparison underscores the importance of surgical precision and comprehensive perioperative care in enhancing patient survival.

There is a rich longitudinal lymphatic network in the submucosa of the esophagus[13]. The extended lymph node resection removed potential micrometastases that were not detected by pathological examination[14]. Kamel *et al*[15] noted that patients with 20 or more lymph nodes removed experienced a 14% relative improvement in OS, and underwent esophagectomy following neoadjuvant chemoradiation. In contrast, this study was conducted on patients

Table 2 Univariate analysis for overall survival

Prognostic factors		*P* value	HR (95%CI)
Age		0.576	1 (0.99-1.01)
Maximal tumor diameter		0.038	1.01 (1-1.01)
NRLN		0.049	0.83 (0.68-1)
Sex (ref male)		0.634	0.95 (0.76-1.18)
Tumor location (ref upper)			
	Middle	0.065	0.71 (0.49-1.02)
	Lower	0.051	0.65 (0.43-1)
T (ref T1)			
	T2	0.028	1.78 (1.07-2.99)
	T3	< 0.001	2.8 (1.74-4.52)
	T4	< 0.001	2.71 (1.65-4.44)
N (ref N0)			
	N1	< 0.001	2.04 (1.64-2.53)
	N2	< 0.001	2.35 (1.82-3.02)
	M3	< 0.001	3.38 (2.45-4.65)
G (ref G1)			
	G2	0.006	1.57 (1.14-2.15)
	G3	0.002	1.81 (1.25-2.61)
Venous thrombus (ref negative)	Positive	< 0.001	2.1 (1.68-2.63)
Perineurial Invasion (ref negative)	Positive	< 0.001	1.79 (1.41-2.29)
Adjuvant chemotherapy (ref no)	Yes	0.009	1.27 (1.06-1.52)

NRLN: Number of removed lymph nodes; HR: Hazards regression; CI: Confidence interval.

who did not receive neoadjuvant therapy. However, the results of the exploration are similar. This indicates that the NRLN is an important factor in improving postoperative survival.

The TNM staging system is now the most frequently applied tool for assessing patient outcomes. However, considerable variations in survival have been reported among individuals with the same clinical stage[16]. As a result, a more accurate and effective prognostic model is urgently required. Nomograms have long been used in oncology to evaluate a patient's prognosis based on important clinical factors[17,18]. In this research, we constructed and internally verified a nomogram to predict postoperative survival time in patients with ESCC, and we discovered that our model had good performance in predictive accuracy. This tool was developed using independent prognostic factors for ESCC, including T stage, N stage, Venous Thrombus, and NRLN. The 3- and 5-year AUCs were 0.676 and 0.647, respectively. By combining several independent prognostic factors in a prognostic model, this nomogram scoring system is more accurate and convincing in predicting different patients, helping to identify different prognoses of ESCC patients and accurately predicting long-term survival. This scoring system is indicative of postoperative treatment strategy decisions for ESCC patients. The thoracic surgeon can easily predict OS rates based on the clinicopathological characteristics of a specific patient by visualization.

The effectiveness of adjuvant chemotherapy after ESCC has been hotly debated[19-24], and while some articles have reported on the survival benefits of adjuvant chemotherapy[25], there is still a lack of high-level evidence to identify specific groups of ESCC who would benefit from adjuvant chemotherapy, such as the phase III randomized controlled trials[8]. Our study stratified patients by the number of lymph nodes removed and the rate of positive lymph nodes and we were surprised to find that different subgroups responded differently to adjuvant chemotherapy. In the subgroup with positive postoperative pathological lymph nodes(pN+), adjuvant chemotherapy was beneficial in the subgroup with NRLN ≤ 21 and RPLN > 0.16. Similarly, adjuvant chemotherapy was beneficial in the subgroup with NRLN > 21 and RPLN ≤ 0.16. Consistent with our findings, Zheng *et al*[26] and Feng *et al*[27] suggested that postoperative adjuvant chemotherapy improves the OS of patients with resected ESCC with positive lymph nodes. However, our study also found that a subgroup of lymph node-positive patients with NRLN > 21 and RPLN > 0.16 did not benefit from adjuvant chemotherapy. A comprehensive treatment plan may be required for this group of patients.

Table 3 Multivariate analysis for overall survival

Prognostic factors		*P* value	HR (95%CI)
Maximal tumor diameter		0.667	1 (0.99-1.01)
T (ref T1)			
	T2	0.055	2.04 (0.99-4.20)
	T3	0.002	3.09 (1.51-6.31)
	T4	0.005	7.44 (1.82-30.35)
N (ref N0)			
	N1	0.077	1.35 (0.97-1.89)
	N2	0.075	1.46 (0.96-2.21)
	M3	0.002	1.99 (1.28-3.11)
G (ref G1)			
	G2	0.103	1.42 (0.93-2.16)
	G3	0.387	1.25 (0.76-2.05)
Venous thrombus (ref negative)	Positive	< 0.001	1.8 (1.34-2.42)
Perineurial invasion (ref negative)	Positive	0.088	1.29 (0.96-1.71)
Adjuvant chemotherapy (ref no)	Yes	0.738	0.95 (0.71-1.27)
NRLN (ref ≤ 21)	> 21	0.004	0.66 (0.50-0.87)

NRLN: Number of removed lymph nodes; HR: Hazards regression; CI: Confidence interval.

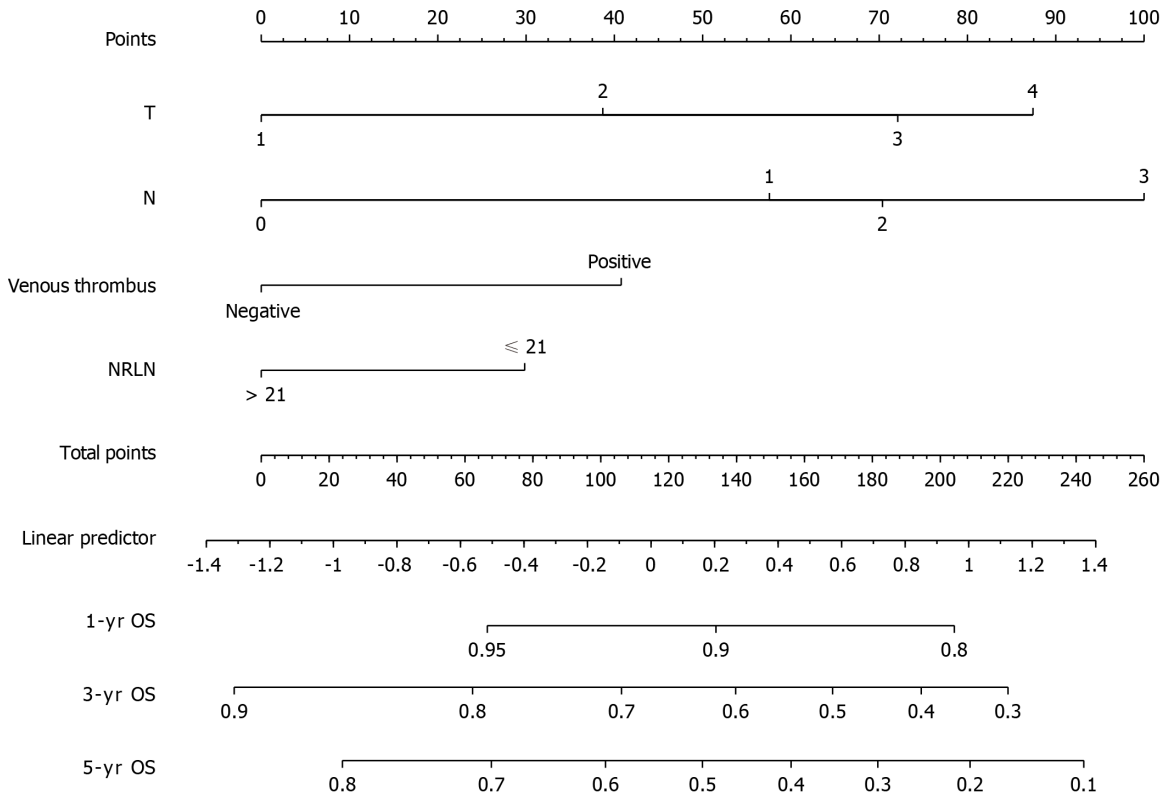


Figure 2 Nomogram integrating number of resected lymph nodes for overall survival in patients with esophageal squamous cell carcinoma. NRLN: Number of resected lymph nodes; OS: Overall survival.

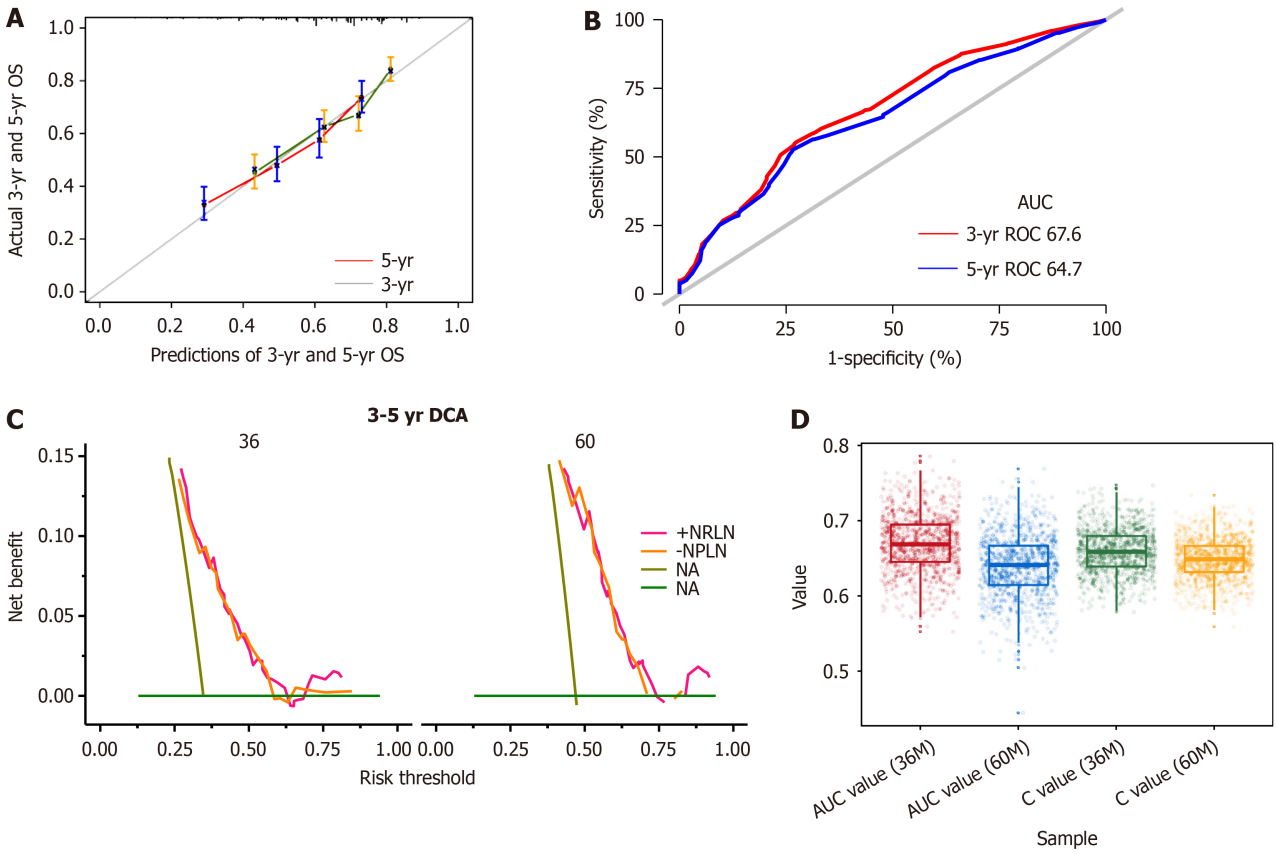


Figure 3 Indices assessing the prognostic ability of nomogram. A: Calibration curve predicting 3-year and 5-year overall survival (OS); B: 3-year OS and 5-year OS receiver operating characteristic curves curve; C: Decision curve analysis; D: 5-fold internal cross-validation. OS: Overall survival; DCA: Decision curve analysis; AUC: Area under the receiver operating characteristic curve; ROC: Receiver operating characteristic curve; NRLN: Number of resected lymph nodes; NA: Not applicable.

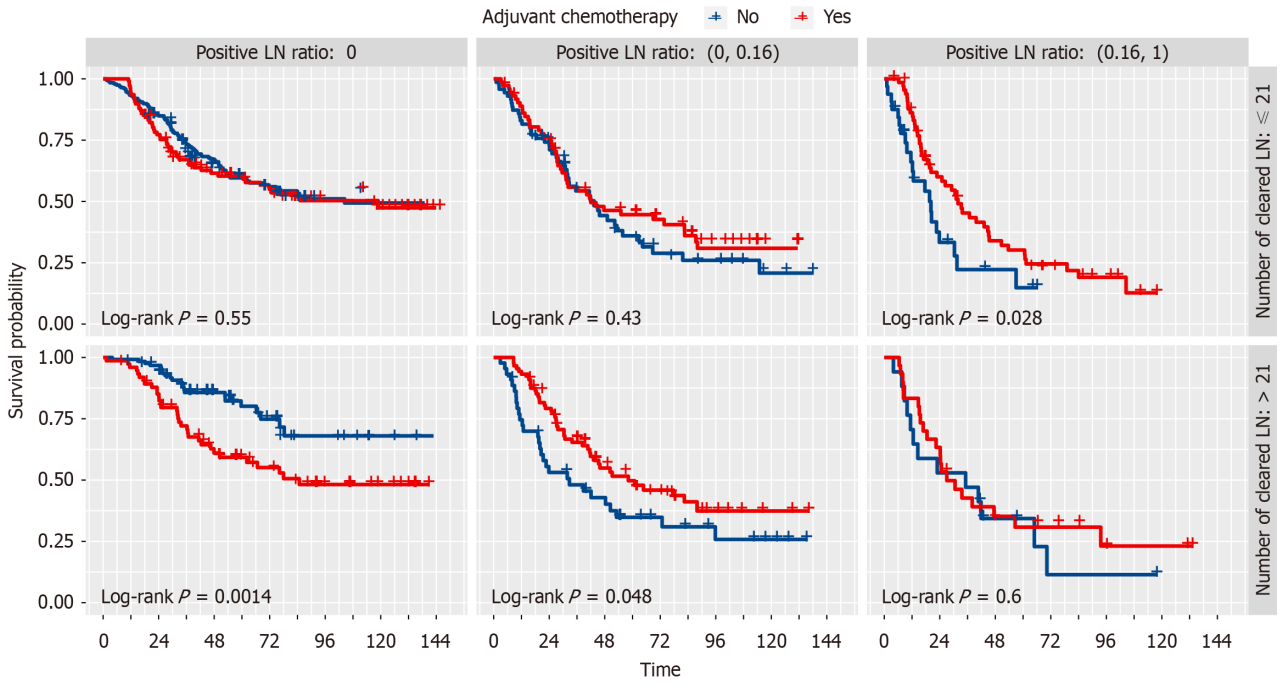


Figure 4 Survival differences between the adjuvant chemotherapy group and non-adjuvant chemotherapy group in different subgroup comparisons. LN: Lymph nodes.

Findings were also obtained in our analysis of subgroups with negative postoperative pathological lymph nodes (pN0). In the NRLN ≤ 21 subgroup, no significant differences in OS were found between the adjuvant-treated and non-adjuvant-treated groups. In the NRLN > 21 subgroup, patients treated with adjuvant chemotherapy obtained a worse prognosis. Adjuvant chemotherapy may do more harm than good to patients in this population. On the contrary, Deng *et al*[28] showed that adjuvant chemotherapy prolonged OS and DFS in ESCC patients with pN0 disease. Further research is needed to elucidate such differences.

Our study primarily investigates the prognostic value of the extent of lymphadenectomy in EC. While this focus is crucial, we also recognize the significant impact that perioperative care factors, such as advancements in anesthesia, pain management, and Enhanced Recovery After Surgery protocols, have on patient recovery and morbidity. The perioperative period in foregut cancer surgery is complex, with numerous elements influencing outcomes. In addition to these perioperative factors, nutritional status emerges as a critical component of patient management. The anatomical impacts of foregut cancers often lead to complications such as dysphagia or vomiting, directly impairing oral intake and contributing to malnutrition. This decline in nutritional status can profoundly affect treatment outcomes, including poorer responses to chemotherapy, increased susceptibility to postoperative complications, and a diminished capacity for tissue repair and immune function.

One of the limitations of our retrospective analysis is the unavailability of certain prognostic variables which could potentially influence the outcomes. Due to the retrospective nature of our study, variables such as albumin levels, nutritional status, and liver function, which could significantly impact patient outcomes, were not included in our analysis. Moreover, in assessing the predictive performance of our model, it is important to recognize that the AUC value obtained is below 0.70, indicating moderate discriminative ability. This level of discrimination reflects a certain degree of uncertainty in the model's predictive accuracy and presents a potential limitation to the robustness of our prognostic evaluations. Prospective validation with a more comprehensive dataset and potentially the integration of additional predictive variables may enhance the discriminative capacity of future models.

CONCLUSION

In conclusion, NRLN > 21 was an independent prognostic factor after ESCC surgery. We developed and validated a nomogram, which is useful for thoracic surgeons to assess the prognosis of different patients.

FOOTNOTES

Author contributions: Tang JM, Huang SJ, and Chen QB contributed to the conceptualization, data curation, and formal analysis of this study; Tang JM, Huang SJ, Chen QB, and Wu HS were involved in the investigation, methodology of this manuscript; Wu HS contributed to the software, validation, and visualization of this study; Tang JM, Huang SJ, Chen QB, Wu HS, and Qiao GB participated in the writing - original draft, review and editing; Qiao GB contributed to the project administration, resources, and supervision of this study.

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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 **Liang H**, Fan JH, Qiao YL. Epidemiology, etiology, and prevention of esophageal squamous cell carcinoma in China. *Cancer Biol Med* 2017; **14**: 33-41 [PMID: 28443201 DOI: 10.20892/j.issn.2095-3941.2016.0093]

3 **Zheng R**, Zhang S, Zeng H, Wang S, Sun K, Chen R, Li L, Wei W, He J. Cancer incidence and mortality in China, 2016. *JNCC* 2022; **2**: 1-9 [DOI: 10.1016/j.jncc.2022.02.002]

4 **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]

5 **Peyre CG**, Hagen JA, DeMeester SR, Altorki NK, Ancona E, Griffin SM, Hölscher A, Lerut T, Law S, Rice TW, Ruol A, van Lanschot JJ, Wong J, DeMeester TR. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. *Ann Surg* 2008; **248**: 549-556 [PMID: 18936567 DOI: 10.1097/SLA.0b013e318188c474]

6 **Koterazawa Y**, Oshikiri T, Takiguchi G, Hasegawa H, Yamamoto M, Kanaji S, Yamashita K, Matsuda T, Nakamura T, Fujino Y, Tominaga M, Suzuki S, Kakeji Y. Prophylactic Cervical Lymph Node Dissection in Thoracoscopic Esophagectomy for Esophageal Cancer Increases Postoperative Complications and Does Not Improve Survival. *Ann Surg Oncol* 2019; **26**: 2899-2904 [PMID: 31187365 DOI: 10.1245/s10434-019-07499-1]

7 **Sachdeva UM**, Axtell AL, Kroese TE, Chang DC, Mathisen DJ, Morse CR. Contributing factors to lymph node recovery with esophagectomy by thoracic surgeons: an analysis of the Society of Thoracic Surgeons General Thoracic Surgery Database. *Dis Esophagus* 2022; **35** [PMID: 35091737 DOI: 10.1093/dote/doab101]

8 **National Comprehensive Cancer Network**. Esophageal and Esophagogastric Junction Cancers (Version 3. 2024). [cited 25 April 2024]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf

9 **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]

10 **Rice TW**, Ishwaran H, Ferguson MK, Blackstone EH, Goldstraw P. Cancer of the Esophagus and Esophagogastric Junction: An Eighth Edition Staging Primer. *J Thorac Oncol* 2017; **12**: 36-42 [PMID: 27810391 DOI: 10.1016/j.jtho.2016.10.016]

11 **Lagergren J**, Mattsson F, Zylstra J, Chang F, Gossage J, Mason R, Lagergren P, Davies A. Extent of Lymphadenectomy and Prognosis After Esophageal Cancer Surgery. *JAMA Surg* 2016; **151**: 32-39 [PMID: 26331431 DOI: 10.1001/jamasurg.2015.2611]

12 **van der Schaaf M**, Johar A, Wijnhoven B, Lagergren P, Lagergren J. Extent of lymph node removal during esophageal cancer surgery and survival. *J Natl Cancer Inst* 2015; **107** [PMID: 25748792 DOI: 10.1093/jnci/djv043]

13 **Kumakura Y**, Yokobori T, Yoshida T, Hara K, Sakai M, Sohda M, Miyazaki T, Yokoo H, Handa T, Oyama T, Yorifuji H, Kuwano H. Elucidation of the Anatomical Mechanism of Nodal Skip Metastasis in Superficial Thoracic Esophageal Squamous Cell Carcinoma. *Ann Surg Oncol* 2018; **25**: 1221-1228 [PMID: 29476296 DOI: 10.1245/s10434-018-6390-0]

14 **Shigeno T**, Hoshino A, Matsunaga S, Shimano R, Ishibashi N, Shinohara H, Shiobara H, Tomii C, Saito K, Fujiwara N, Sato Y, Kawada K, Tokunaga M, Kinugasa Y. The impact of lymphadenectomy on lymph node recurrence after performing various treatments for esophageal squamous cell carcinoma. *BMC Surg* 2022; **22**: 171 [PMID: 35545769 DOI: 10.1186/s12893-022-01618-8]

15 **Kamel MK**, Harrison S, Lee B, Port JL, Stiles BM, Altorki NK. Extended Lymphadenectomy Improves Survival After Induction Chemoradiation for Esophageal Cancer: A Propensity-Matched Analysis of the National Cancer Database. *Ann Surg* 2023; **277**: e772-e776 [PMID: 34475320 DOI: 10.1097/SLA.0000000000005197]

16 **Wang H**, Chen Y, Pi G, Zhu Y, Yang S, Mei H, Lin Z, Zhang T. Validation and proposed modification of the 8th edition American Joint Committee on Cancer staging system for patients with esophageal neuroendocrine neoplasms: Evaluation of a revised lymph node classification. *Oncol Lett* 2020; **19**: 4122-4132 [PMID: 32382351 DOI: 10.3892/ol.2020.11480]

17 **Zhu J**, Han Y, Ni W, Chang X, Wu L, Wang Y, Jiang L, Tan Y, Xiao Z, Wang Q, Peng L. Nomogram-Based Survival Predictions and Treatment Recommendations for Locally Advanced Esophageal Squamous Cell Carcinoma Treated with Upfront Surgery. *Cancers (Basel)* 2022; **14** [PMID: 36428660 DOI: 10.3390/cancers14225567]

18 **Li X**, Xing J, Li P, Xie S, Lin Q, Zhang Q, Zhang S. A nomogram and risk classification system predicting esophageal stricture after endoscopic submucosal dissection of a large area for early esophageal cancer. *J Surg Oncol* 2023; **127**: 568-577 [PMID: 36537007 DOI: 10.1002/jso.27172]

19 **Zhou Z**, Huang S, Ben X, Zhuang W, Hong L, Xie Z, Zhang D, Xie L, Zhou H, Tang J, Chen G, Wu H, Qiao G. A novel prognostic model: which group of esophageal squamous cell carcinoma patients could benefit from adjuvant chemotherapy. *Ann Transl Med* 2022; **10**: 182 [PMID: 35280404 DOI: 10.21037/atm-22-46]

20 **Sohda M**, Saito H, Kuriyama K, Yoshida T, Kumakura Y, Honjyo H, Hara K, Ozawa D, Suzuki S, Tanaka N, Sakai M, Miyazaki T, Fukuchi M, Kuwano H. Post-esophagectomy Adjuvant Chemotherapy Benefits Esophageal Cancer Patients. *In Vivo* 2019; **33**: 501-506 [PMID: 30804133 DOI: 10.21873/invivo.11502]

21 **Pasquer A**, Gronnier C, Renaud F, Duhamel A, Théreaux J, Carrere N, Gagniere J, Meunier B, Collet D, Mariette C. Impact of Adjuvant Chemotherapy on Patients with Lymph Node-Positive Esophageal Cancer who are primarily Treated with Surgery. *Ann Surg Oncol* 2015; **22** Suppl 3: S1340-S1349 [PMID: 26065869 DOI: 10.1245/s10434-015-4658-1]

22 **Qin RQ**, Wen YS, Wang WP, Xi KX, Yu XY, Zhang LJ. The role of postoperative adjuvant chemotherapy for lymph node-positive esophageal squamous cell carcinoma: a propensity score matching analysis. *Med Oncol* 2016; **33**: 31 [PMID: 26922662 DOI: 10.1007/s12032-016-0746-8]

23 **Wong AT**, Shao M, Rineer J, Lee A, Schwartz D, Schreiber D. The Impact of Adjuvant Postoperative Radiation Therapy and Chemotherapy on Survival After Esophagectomy for Esophageal Carcinoma. *Ann Surg* 2017; **265**: 1146-1151 [PMID: 27280504 DOI: 10.1097/SLA.0000000000001825]

24 **Zhao P**, Yan W, Fu H, Lin Y, Chen KN. Efficacy of postoperative adjuvant chemotherapy for esophageal squamous cell carcinoma: A meta-analysis. *Thorac Cancer* 2018; **9**: 1048-1055 [PMID: 29927075 DOI: 10.1111/1759-7714.12787]

25 **Burt BM**, Groth SS, Sada YH, Farjah F, Cornwell L, Sugarbaker DJ, Massarweh NN. Utility of Adjuvant Chemotherapy After Neoadjuvant Chemoradiation and Esophagectomy for Esophageal Cancer. *Ann Surg* 2017; **266**: 297-304 [PMID: 27501170 DOI: 10.1097/SLA.0000000000001954]

26 **Zheng B**, Chen M, Chen C, Xiao J, Cai B, Zhang S, Liang M, Zeng T, Chen H, Wu W, Xu G, Zheng W, Zhu Y. Adjuvant chemoradiotherapy for patients with pathologic node-positive esophageal cancer following radical resection is associated with improved survival. *Ann Transl Med* 2020; **8**: 1633 [PMID: 33490145 DOI: 10.21037/atm-20-4893]

27 **Feng SK**, Liu XB, Xing WQ, Liu Y, Chen PN, Jiang D, Sun HB. Adjuvant Chemotherapy for Node-positive Esophageal Squamous Cell Carcinoma Improves Survival. *Ann Thorac Surg* 2022; **114**: 1205-1213 [PMID: 34626616 DOI: 10.1016/j.athoracsur.2021.08.068]

28 **Deng X**, He W, Jiang Y, Deng S, Mao T, Leng X, Luo Q, Zheng K, Han Y. The impact of adjuvant therapy on survival for node-negative esophageal squamous cell carcinoma: a propensity score-matched analysis. *Ann Transl Med* 2021; **9**: 998 [PMID: 34277798 DOI: 10.21037/atm-21-2539]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Efficacy of laparoscopic low anterior resection for colorectal cancer patients with 3D-vascular reconstruction for left coronary artery preservation

Ye Wang, Zhi-Sheng Liu, Zong-Bao Wang, Shawn Liu, Feng-Bo Sun

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Abstract

BACKGROUND

Laparoscopic low anterior resection (LLAR) has become a mainstream surgical method for the treatment of colorectal cancer, which has shown many advantages in the aspects of surgical trauma and postoperative rehabilitation. However, the effect of surgery on patients' left coronary artery and its vascular reconstruction have not been deeply discussed. With the development of medical imaging technology, 3D vascular reconstruction has become an effective means to evaluate the curative effect of surgery.

AIM

To investigate the clinical value of preoperative 3D vascular reconstruction in LLAR of rectal cancer with the left colic artery (LCA) preserved.

METHODS

A retrospective cohort study was performed to analyze the clinical data of 146 patients who underwent LLAR for rectal cancer with LCA preservation from January to December 2023 in our hospital. All patients underwent LLAR of rectal cancer with the LCA preserved, and the intraoperative and postoperative data were complete. The patients were divided into a reconstruction group (72 patients) and a nonreconstruction group (74 patients) according to whether 3D vascular reconstruction was performed before surgery. The clinical features, operation conditions, complications, pathological results and postoperative recovery of the two groups were collected and compared.

RESULTS

A total of 146 patients with rectal cancer were included in the study, including 72 patients in the reconstruction group and 74 patients in the nonreconstruction group. There were 47 males and 25 females in the reconstruction group, aged (59.75 ± 6.2) years, with a body mass index (BMI) (24.1 ± 2.2) kg/m^2, and 51 males and 23 females in the nonreconstruction group, aged (58.77 ± 6.1) years, with a BMI (23.6 ± 2.7) kg/m^2. There was no significant difference in the baseline data between the two groups ($P > 0.05$). In the submesenteric artery reconstruction group, 35 patients were type I, 25 patients were type II, 11 patients were type III, and 1 patient was type IV. There were 37 type I patients, 24 type II patients, 12 type III patients, and 1 type IV patient in the nonreconstruction group. There was no significant difference in arterial typing between the two groups ($P > 0.05$). The operation time of the reconstruction group was 162.2 ± 10.8 min, and that of the nonreconstruction group was 197.9 ± 19.1 min. Compared with that of the reconstruction group, the operation time of the two groups was shorter, and the difference was statistically significant ($t = 13.840$, $P < 0.05$). The amount of intraoperative blood loss was 30.4 ± 20.0 mL in the reconstruction group and 61.2 ± 26.4 mL in the nonreconstruction group. The amount of blood loss in the reconstruction group was less than that in the control group, and the difference was statistically significant ($t = -7.930$, $P < 0.05$). The rates of anastomotic leakage (1.4% *vs* 1.4%, $P = 0.984$), anastomotic hemorrhage (2.8% *vs* 4.1%, $P = 0.672$), and postoperative hospital stay (6.8 ± 0.7 d *vs* 7.0 ± 0.7 d, $P = 0.141$) were not significantly different between the two groups.

CONCLUSION

Preoperative 3D vascular reconstruction technology can shorten the operation time and reduce the amount of intraoperative blood loss. Preoperative 3D vascular reconstruction is recommended to provide an intraoperative reference for laparoscopic low anterior resection with LCA preservation.

Key Words: Laparoscopic low anterior resection; 3D vascular reconstruction; Coronary artery; Colorectal cancer; Retrospective cohort study

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Core Tip: Through the observation of left coronary artery three-dimensional vascular reconstruction in patients with colorectal cancer after laparoscopic low anterior resection, the effect of surgery on the vascular system and its curative effect were discussed. The preservation of the left coronary artery and its possible effects were evaluated by comparing preoperative and postoperative vascular remodeling. The results of this study will help to deeply understand the impact of laparoscopic surgery on the cardiovascular system of patients with colorectal cancer, and provide an important reference for postoperative management and clinical treatment, and improve the safety and effect of surgery.

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INTRODUCTION

Colorectal cancer is a malignant tumor of the digestive system with a high incidence worldwide, and surgical treatment has always been one of the main treatment methods[1-3]. In terms of surgical methods, low anterior resection is favored because of its lower trauma and faster recovery speed[4]. However, with improvements in surgical techniques, the need for preoperative evaluation is also increasing. As an accurate preoperative evaluation method, 3D vascular reconstruction imaging provides clearer anatomical information for the surgical process, especially for patients with left coronary artery preservation, which has unique value[5]. In recent years, with the continuous development of laparoscopic technology, colorectal cancer surgery has gradually evolved into a minimally invasive and individualized approach[6-8]. In this context, low anterior resection, a common surgical method, has attracted much attention. The purpose of this retrospective cohort study was to investigate the efficacy of laparoscopic low anterior resection (LLAR) for colorectal cancer and 3D vascular reconstruction imaging in patients with left coronary artery preservation and to further analyze the effects of surgical modalities and angiography on patient recovery and survival.

LLAR to preserve the left colic artery (LCA) is a surgical procedure for rectal cancer. Its advantages include a good blood supply for anastomosis and better protection of autonomic nerves, especially for elderly patients with diabetes, hypertension, and extensive arterial disease[9]. Although there is still controversy and debate about the preservation of the LCA, many surgeons have chosen to perform this procedure to dissect and preserve the LCA while thoroughly clearing the regional lymph nodes[10]. The enlarged field of view and fine anatomy provided by laparoscopic surgery make it relatively easier and more feasible to preserve the LCA than open surgery. Preoperative computed tomography

(CT) angiography and 3D reconstruction can provide 3D visual reconstruction of the inferior mesenteric artery (IMA) and its branches and provide the necessary reference for colorectal cancer surgery. However, the effect of preoperative 3D vascular reconstruction on LCA-preserving rectal surgery is inconclusive[11-13].

Therefore, we conducted this study to evaluate the clinical application of 3D vascular reconstruction technology in the surgical and postoperative outcomes of LLAR of rectal cancer patients with left colon preservation, to provide new ideas and evidence supporting the individualized treatment of colorectal cancer surgery and to promote the wider application of minimally invasive technology in clinical practice.

MATERIALS AND METHODS

General clinical data of the patients

A total of 146 patients with left colon-preserved LLAR who underwent gastrointestinal surgery at the National University Hospital of Singapore from January to December 2023 were included in this retrospective cohort study. The inclusion criteria for patients were as follows: (1) Had a diagnosis of colonoscopy-confirmed and pathological biopsy-confirmed colorectal adenocarcinoma; (2) Had a tumor location 7 cm–15 cm from the anal margin; (3) Underwent LLAR of rectal cancer with the LCA preserved; and (4) Had a pathological stage of I–III. The exclusion criteria were as follows: (1) Had a diagnosis of stage IV rectal cancer; (2) Had a previous history of abdominal surgery; (3) Had intestinal obstruction, bleeding, perforation, *etc*., or needed emergency surgery; and (4) Had incomplete relevant case data and data. The main indications include large tumors, high surgical difficulty, and a need to improve surgical feasibility. In the pretreatment evaluation, we paid attention to the joint decision-making of the medical team and comprehensively considered preoperative chemotherapy, radiotherapy, and other treatment methods according to individual conditions.

Enhanced CT and 3D vascular reconstruction

A Philips or GE 64-slice CT scanner was used for enhanced CT. The tube voltage was 120 kV, the tube current was automatic MA, the layer thickness was 1.25 mm, the interval was 0.8 mm, and the detector collimation was 320 mm × 0.5 mm. The samples were fasted for 4 h before the examination. The patient was supine and scanned from the apex of the diaphragm to the level of the ischial tubercle. After a normal scan, 85 mL of the enhancer (iodohydramol, iodiproamine, *etc*., at a concentration of 350-370 mg/mL) was applied. Intravenously, 2 to 5 mL/s. The delay time of arterial phase scanning was 30 s, and 3D vascular reconstruction was performed using a Philips or GE workstation.

Mode of operation

Patients in both groups were given general anesthesia with tracheal intubation, lithotomy at the head lower and foot higher, and 3D laparoscopic surgery. A 1 cm incision was made at the upper edge of the navel to establish a CO_2 pneumoperitoneum, and the pressure was maintained at 12 mmHg-14 mmHg (1 mmHg = 0.133 kPa). The five-hole method was used. The whole abdominal cavity, location and size of the tumor and whether there was distant metastasis were investigated. Through the middle approach, the sigmoid colon is traversed with an ultrasound knife or electrotome.

The serous membrane at the yellow-white junction of the mesangial root was opened to fully nip the IMA to avoid nerve injury. From the inside to the outside and from the head to the side, the IMA roots reach the Toldt space to skeletonize the IMA and protect the submesenteric plexus. The IMA branch was clearly dissected, and the lymph nodes and adipose tissue of Group 253 were completely cleared to the LCA branch. After completing the lymph node dissection in Group 253, the IMA branches were clearly dissected, ligation was performed below the bifurcation of the LCA, the LCA was retained, and the other branches were ligated and severed (Figure 1).

The Toldt space was fully extended, and the pelvic nerve plexus was fully protected. The submesenteric vein was separated to the left, and the surrounding fat and lymph nodes were removed. The mesosigmoid was trimmed along the LCA branch, preserving the marginal vascular arch. The intestinal tube was cut at a distance of more than 2 cm from the tumor, and all the specimens were removed from the lower abdomen in a sterile specimen bag. End-to-end anastomosis was performed to reconstruct the digestive tract. After the abdominal cavity was cleaned, the drainage tube was placed and fixed, and the operating hole was sutured.

Statistical analysis

SPSS software package 25.0 was used for the statistical analysis. Clinical and pathological data are presented as the mean ± SD, and statistical data are presented as the quantity and percentage. The *t* test was used for measurement data, and the chi-square test or Fisher's exact test was used for counting data. A *P* value (bilateral) < 0.05 was considered to indicate statistical significance.

RESULTS

Analysis of general data and basic patient information

Between January 2023 and December 2023, we enrolled 146 patients who underwent LLAR-preserving LCA based on the inclusion criteria. In our study, preoperative treatment included chemotherapy, radiotherapy, or other related treatments to reduce tumor volume, improve surgical feasibility, and improve patients' postoperative quality of life. In particular, we observed that a subset of patients in the retrospective cohort received radiation therapy, and this decision was based on a

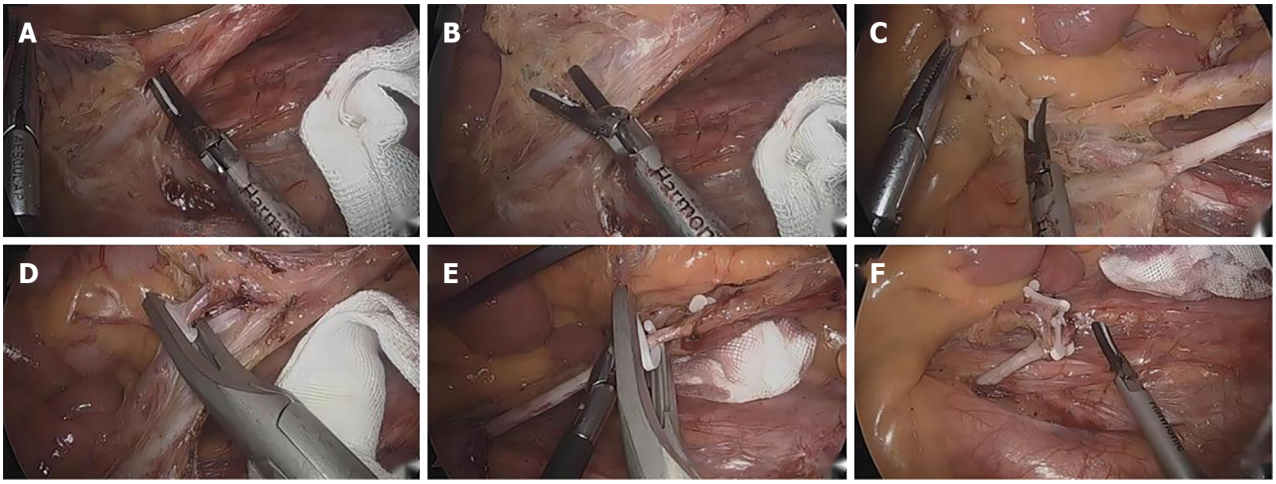


Figure 1 The left colic artery was preserved. A: Isolation of the main naked inferior mesenteric artery; B: Isolatedisolation of the naked left colic artery; C: Clearance of the lymph nodes in group 253; D: Ligation and dissection of the sigmoid artery; E: Ligation of the severed superior rectal artery; F: Operation.

comprehensive assessment of the individual's condition and the clinical team. Table 1 summarizes the basic information and clinical features of the patients in the reconstruction group (n = 72, 49.3%) and the nonreconstruction group (n = 74, 50.7%). There were 47 males and 25 females in the reconstruction group, aged (59.75 ± 6.2) years, with a body mass index (BMI) (24.1 ± 2.2) kg/m^2, and 51 males and 23 females in the nonreconstruction group, aged (58.77 ± 6.1) years, with a BMI (23.6 ± 2.7) kg/m^2. There was no significant difference in the baseline data between the two groups (P > 0.05). There were no statistically significant differences between the two groups in terms of sex, age, BMI, American Society of Anesthesiology (ASA) score, or neoadjuvant therapy.

Preoperative 3D vascular reconstruction and intraoperative vascular anatomy observation

Preoperative 3D vascular reconstruction or surgery was used to study the IMA and its branches in a total of 146 patients. Four IMA blood vessel types were identified in our study. The four blood vessel types are as follows: Type I (Figures 2A and 3A), the LCA alone from the IMA, the sigmoid artery (SA) and the superior rectal artery (SRA) together; Type II (Figures 2B and 3B), the LCA and the SA originate together from a single backbone, and the SRA originates independently from the IMA. In type III (Figures 2C and 3C), all three branches of the IMA emanated at the same level; in type IV and type IV (Figures 2D and 3D), there was no LCA, and only the LCA and SA branched out from the IMA. There was no significant difference in blood vessel types between the two groups (χ^2 = 0.092, P = 0.993) (Table 2).

In the reconstruction group, there were 35 cases of IMA type I, 25 cases of type II, 11 cases of type III, and 1 case of type IV. There were 37 type I patients, 24 type II patients, 12 type III patients, and 1 type IV patient in the nonreconstruction group. There was no significant difference in arterial typing between the two groups (χ^2 = 0.092, P = 0.993). In terms of branch type, both the reconstructed group and the nonreconstructed group were classified as type I (35 patients in the reconstructed group, 48.6% *vs* 37 patients (50.0%) in the nonreconstruction group and type II (25 patients (34.7%) in the reconstruction group *vs* 24 patients (32.4%) in the nonreconstruction group), followed by type III and type IV.

Surgery-related data and complication analysis

The surgical data and related surgical complications are shown in Tables 2 and 3. According to our results, the operation time for LLAR to retain the LCA was shorter in the reconstructive group (162.2 ± 10.8 min *vs* 197.9 ± 19.1 min, t = -13.840; P < 0.05). Intraoperative blood output was also significantly lower in the reconstruction group than in the nonreconstruction group (30.4 ± 20.0 *vs* 61.2 ± 26.4 mL, t = -7.930, P = 0.000). All procedures in both groups were performed by the same group of experienced surgeons specializing in colorectal cancer. There was no conversion to laparotomy in either group. There was no significant difference in postoperative complications, including anastomotic leakage (1 case, 1.4% *vs* 1 case, 1.4%, χ^2 = 0.000, P = 0.984) or anastomotic hemorrhage (2 cases, 2.8% *vs* 3 cases, 4.1%, χ^2 = 0.180, P = 0.672), between the two groups. All of these complications were successfully resolved. There was no significant difference in postoperative recovery between the reconstruction group (6.8 ± 0.7) and the nonreconstruction group (7.0 ± 0.7) (t = 1.480, P = 0.141).

Pathological analysis

The pathological results of the surgical patients are summarized in Table 4. The tumor size (3.1 ± 0.8 *vs* 2.9 ± 0.9 cm, t = 1.309, P = 0.193), differentiation degree (χ^2 = 0.085, P = 0.958) and TNM stage (χ^2 = 0.248, P = 0.958) of the two groups were evaluated. P = 0.883, and there was no significant difference (P > 0.05). In terms of lymph node dissection, the number of lymph nodes in the reconstruction group (18.3 ± 2.7) was slightly greater than that in the nonreconstruction group (17.6 ± 2.1), but the difference was not statistically significant (t = 1.720, P = 0.088).

Table 1 Baseline data of included patients [mean ± SD, *n* (%)]

Clinical features	3D vascular reconstruction group (*n* = 72)	Non-3D vascular reconstruction group (*n* = 74)	*t* value	*P* value
Gender			0.219	0.64
Male	47 (65.3)	51 (68.9)		
Female	25 (34.7)	23 (31.1)		
Age (year)	59.75 ± 6.2	58.77 ± 6.1	0.961	0.338
BMI (kg/m^2)	24.1 ± 2.2	23.6 ± 2.7	1.123	0.263
Neoadjuvant therapy	12 (16.7)	13 (17.6)	0.021	0.885
ASA score			0.174	0.917
ASA I	24 (33.3.0)	23 (31.3)		
ASA II	37 (51.4)	38 (51.4)		
ASA III	11 (15.3)	13 (17.6)		

BMI: Body mass index; ASA: American Society of Anesthesiology.

Table 2 Submesenteric artery branch types [*n* (%)]

Arterial classification	3D vascular reconstruction group (*n* = 72)	Non-3D vascular reconstruction group (*n* = 74)	X^2	*P* value
Branch type			0.092	0.993
Type I	35 (48.6)	37 (50.0)		
Type II	25 (34.7)	24 (32.4)		
Type III	11 (15.3)	12 (16.2)		
Type IV	1 (1.4)	1 (1.4)		

Table 3 Data analysis of surgery and complications (mean ± SD)

Intraoperative and postoperative indicators	3D vascular reconstruction group (*n* = 72)	Non-3D vascular reconstruction group (*n* = 74)	X^2	*P* value
Operation time (min)	162.2 ± 10.8	197.9 ± 19.1	-13.84	0.001
Conversion to laparotomy	0	0		
Intraoperative blood loss (mL)	30.4 ± 20.0	61.2 ± 26.4	-7.93	0.001
Anastomotic leak	1 (1.4%)	1 (1.4%)	0.001	0.984
Anastomotic hemorrhage	2 (2.8%)	3 (4.1%)	0.18	0.672
Postoperative hospital stay	6.8 ± 0.7	7.0 ± 0.7	1.48	0.141

DISCUSSION

Colorectal cancer is the third most commonly diagnosed cancer internationally, and laparoscopic colorectal cancer surgery has been widely accepted worldwide[14-16]. Preserving the LCA means that the IMA ligation is located far from the origin of the LCA, which is one of the surgical options for rectal cancer[17]. Our study showed that preoperative 3D vascular reconstruction can provide a preoperative reference for LCA-sparing rectal cancer surgery and can shorten the operation time and reduce the amount of intraoperative blood loss.

3D vascular reconstruction technology has been widely used in a variety of diseases, such as coronary artery disease, lower limb artery stenosis, aortic aneurysm, aortic dissection, and hepatic artery variation. Coronary CT and 3D reconstruction of blood vessels have become the gold standard noninvasive methods for detecting coronary artery disease in clinical practice[18-20]. Previous studies[21-24] have shown that 3D vascular reconstruction techniques are 100% accurate at identifying variations and stenoses in the arteries that supply the lower limbs and the liver, respectively.

With regard to submesenteric artery branch types, we identified four submesenteric artery types using 3D vascular reconstruction techniques and surgical dissection[25]. In our study, both the reconstructed and nonreconstructed groups included four types, of which types I and II were the most common, type III was the most common, and type IV was the

Table 4 Postoperative pathological results [mean ± SD, *n* (%)]

Pathological index	3D vascular reconstruction group (*n* = 72)	Non-3D vascular reconstruction group (*n* = 74)	χ^2	*P* value
Tumor size (cm)	3.1 ± 0.8	2.9 ± 0.9	1.309	0.193
Number of lymph nodes	18.3 ± 2.7	17.6 ± 2.1	1.72	0.088
Degree of differentiation			0.085	0.958
Low	20 (27.8)	19 (25.7)		
Middle	39 (54.2)	41 (55.4)		
High	13 (18.1)	14 (18.9)		
Pathological stage			0.248	0.883
Stage I	14 (19.4)	13 (17.6)		
Stage II	35 (48.6)	39 (52.7)		
Stage III	23 (31.9)	22 (29.7)		

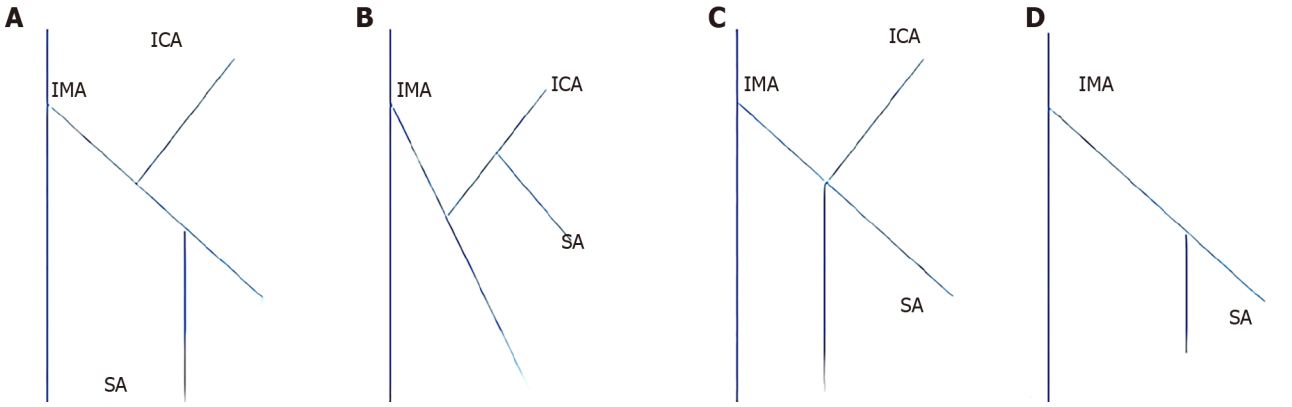


Figure 2 Submesenteric artery classification model. A: Type I; B: Type II; C: Type III; D: Type IV. IMA: Inferior mesenteric artery; LCA: Left colic artery; SA: Sigmoid artery.

least common. In type IV patients, the LCA could not be maintained, but it was impossible to determine whether the patients in the nonreconstruction group would not have the LCA ahead of time[26-28]. This could only be proven by separating the organs along the main IMA during surgery[29]. Therefore, for strict control between the two groups, type IV patients were included in the study. This type of study also highlights the important reference significance of preoperative 3D vascular reconstruction technology for surgical planning and design.

Our study showed that surgical time was shorter in the reconstruction group than in the nonreconstruction group. Although there are no studies that have compared the use of 3D vascular reconstruction in LCA-sparing rectal surgery, a study involving 112 patients who underwent right hemicolectomy, left hemicolectomy, or prerectal resection reported similar results and shortened the time required for surgery for colon and rectal cancer. One study showed that in colorectal cancer surgery, the surgery time in the reconstruction group was significantly shorter than that in the control group[30-32]. According to their experience, preoperative 3D vascular reconstruction may show significant advantages in identifying blood vessels, even in special cases of vascular anatomical variation or obesity[33]. Because less time is spent dissecting blood vessels and looking for aberrant or missing blood vessels, this approach can help surgeons shorten the operation time. Another study showed that in laparoscopic right hemicolectomy, the surgical time in the reconstruction group was shorter than that in the control group (154.7 ± 25.9 min and 177.6 ± 24.4 min, respectively).

In terms of operation time, according to our experience, the application of preoperative vascular reconstruction has shortened the operation time for the following reasons. First, 3D vascular reconstruction helps to accurately plan surgical strategies and programs before surgery. Similarly, many scholars have proposed similar effects of 3D reconstruction technology on surgical planning and design in stomach and liver operations[34]. Second, 3D reconstruction of blood vessels can help clinicians predict the type of blood vessels before surgery, find blood vessels during surgery, and correctly anatomize blood vessels. This is especially helpful for people who are very overweight, have experienced major changes in their anatomy, or have severe abdominal adhesions[35]. Third, 3D vascular reconstruction technology may help avoid some intraoperative complications, such as visceral damage, vascular damage, and bleeding, which are some of the main reasons for prolonged surgical time. Preoperative 3D vascular reconstruction can provide surgeons with basic information on arterial classification and variation before surgery, which is of great help and important reference significance for safe and effective colorectal cancer surgery[36-38]. Compared with digital subtraction angiography, 3D

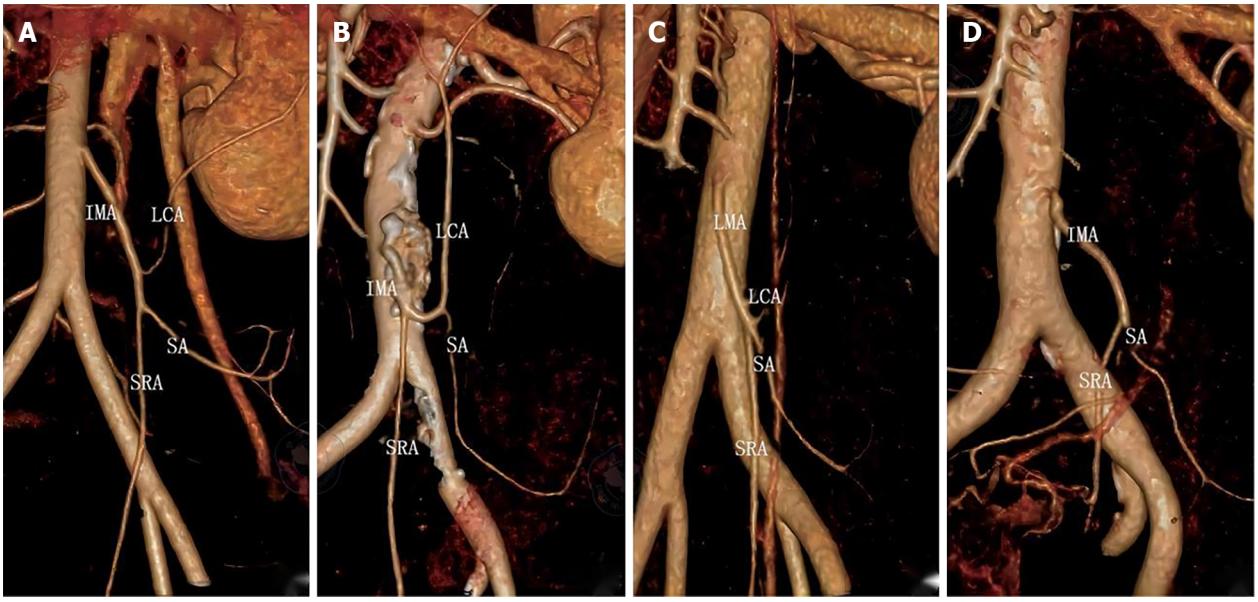


Figure 3 3D reconstruction of submesenteric artery typing. A: Type I; B: Type II; C: Type III; D: Type IV. IMA: Inferior mesenteric artery; LCA: Left colic artery; SA: Sigmoid artery; SRA: Superior rectal artery.

vascular reconstruction is a better way to quickly reconstruct IMA branching patterns with less damage[39]. Moreover, with the rapid development of CT technology, 3D reconstruction of blood vessels can now be performed more quickly and at a lower cost. In terms of postoperative pathology, there was no significant difference in tumor size, number of lymph nodes, degree of differentiation, or pathological stage between the reconstructed group and the nonreconstructed group. Some studies[40-42] have shown that vascular reconstruction technology may have a positive impact on the number of lymph nodes because vascular reconstruction can help surgeons better cut the blood vessels at the root and clean the lymph nodes at the root of the blood vessels to clear the local lymph nodes more thoroughly. Although the number of lymph nodes in the reconstructed group was slightly greater than that in the nonreconstructed group (18.3 ± 2.7 *vs* 17.6 ± 2.1), the difference was not statistically significant in our study. This may be related to the fact that we were the same group of surgeons who performed the operation, and the location of the vessel ligation and the scope of regional lymph node dissection were the same. Whether vascular reconstruction techniques have a positive effect on the number of lymph nodes obtained in colorectal cancer surgery is also a hot issue, and multicenter, prospective clinical studies may provide a greater amount of evidence[43-45].

Our study also has several limitations. First, the study design was retrospective in nature. Prospective studies may better confirm future results. Second, the study represents the experience of a single center, which may limit its external validation validity. Therefore, conducting large-scale, multicenter studies is the direction of further research to better verify the conclusions of this study.

CONCLUSION

Our study suggested that preoperative 3D vascular reconstruction can shorten the operative time and reduce intraoperative blood loss during LLAR of rectal cancer while preserving the LCA. Therefore, for LCA-sparing rectal cancer surgery, preoperative 3D vascular reconstruction is recommended.

FOOTNOTES

Author contributions: Wang Y wrote the manuscript; Liu ZS, Wang ZB, and Liu S collected the data; Sun FB guided the study. All authors reviewed, edited, and approved the final manuscript and revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Institutional review board statement: This study has been approved by the Clinical Medical Ethics Committee of National University Hospital of Singapore.

Informed consent statement: This study has obtained the informed consent of the patients and their families, and has signed the informed consent for relevant surgical treatment.

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

Data sharing statement: The technical appendix, statistical code, and dataset are available from the corresponding author at sunfengbo1983@163.com.

STROBE statement: This study has strictly complied with the STROBE statement and met the relevant conditions and requirements of the STROBE statement.

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REFERENCES

1 **Garcia-Granero A**, Jerí Mc-Farlane S, Gamundí Cuesta M, González-Argente FX. Application of 3D-reconstruction and artificial intelligence for complete mesocolic excision and D3 lymphadenectomy in colon cancer. *Cir Esp (Engl Ed)* 2023; **101**: 359-368 [PMID: 36709852 DOI: 10.1016/j.cireng.2023.01.006]

2 **Yotsov T**, Karamanliev M, Maslyankov S, Iliev S, Ramadanov N, Dimitrov D. Mesenteric Vascular Evaluation with Pre-operative Multidetector Computed Tomographic Angiography and Intraoperative Indocyanine Green Angiography to Reduce Anastomotic Leaks after Minimally Invasive Surgery for Colorectal Cancer. *JSLS* 2022; **26** [PMID: 35967960 DOI: 10.4293/JSLS.2022.00022]

3 **Andersen BT**, Stimec BV, Kazaryan AM, Rancinger P, Edwin B, Ignjatovic D. Re-interpreting mesenteric vascular anatomy on 3D virtual and/or physical models, part II: anatomy of relevance to surgeons operating splenic flexure cancer. *Surg Endosc* 2022; **36**: 9136-9145 [PMID: 35773607 DOI: 10.1007/s00464-022-09394-5]

4 **Fletcher J**, Ilangovan R, Hanna G, Miskovic D, Lung P. The impact of three-dimensional reconstruction and standardised CT interpretation (AMIGO) on the anatomical understanding of mesenteric vascular anatomy for planning complete mesocolic excision surgery: A randomised crossover study. *Colorectal Dis* 2022; **24**: 388-400 [PMID: 34989089 DOI: 10.1111/codi.16041]

5 **Cotsoglou C**, Granieri S, Bassetto S, Bagnardi V, Pugliese R, Grazi GL, Guglielmi A, Ruzzenente A, Aldrighetti L, Ratti F, De Carlis L, De Carlis R, Centonze L, De Angelis N, Memeo R, Delvecchio A, Felli E, Izzo F, Belli A, Patrone R, Ettorre GM, Berardi G, Di Benedetto F, Di Sandro S, Romano F, Garancini M, Scotti MA, Bianchi G, Germini A, Gjoni E, Bonomi A, Bruno F, Paleino S, Pugliese G. Dynamic surgical anatomy using 3D reconstruction technology in complex hepato-biliary surgery with vascular involvement. Results from an international multicentric survey. *HPB (Oxford)* 2024; **26**: 83-90 [PMID: 37838501 DOI: 10.1016/j.hpb.2023.10.003]

6 **Brown PJ**, Toh EW, Smith KJ, Jones P, Treanor D, Magee D, Burke D, Quirke P. New insights into the lymphovascular microanatomy of the colon and the risk of metastases in pT1 colorectal cancer obtained with quantitative methods and three-dimensional digital reconstruction. *Histopathology* 2015; **67**: 167-175 [PMID: 25557923 DOI: 10.1111/his.12639]

7 **Miyamoto R**, Nagai K, Kemmochi A, Inagawa S, Yamamoto M. Three-dimensional reconstruction of the vascular arrangement including the inferior mesenteric artery and left colic artery in laparoscope-assisted colorectal surgery. *Surg Endosc* 2016; **30**: 4400-4404 [PMID: 26850027 DOI: 10.1007/s00464-016-4758-4]

8 **Andersen BT**, Stimec BV, Edwin B, Kazaryan AM, Maziarz PJ, Ignjatovic D. Re-interpreting mesenteric vascular anatomy on 3D virtual and/or physical models: positioning the middle colic artery bifurcation and its relevance to surgeons operating colon cancer. *Surg Endosc* 2022; **36**: 100-108 [PMID: 33492511 DOI: 10.1007/s00464-020-08242-8]

9 **Giusti I**, Carnevali P, Bertoglio CL, Giani A, Achilli P, Grimaldi S, Origi M, Mazzola M, Magistro C, Ferrari G. Laparoscopic right hemicolectomy for hepatic flexure adenocarcinoma with complete mesocolic excision and 3D-CT vascular reconstruction. *Tech Coloproctol* 2022; **26**: 1003-1004 [PMID: 35749022 DOI: 10.1007/s10151-022-02639-4]

10 **Miyamoto R**, Tadano S, Sano N, Inagawa S, Yamamoto M. The Impact of Laparoscopic-assisted Colorectal Surgery Using 3-dimensional Reconstruction for Highly Obese Patients With Colorectal Cancer. *Surg Laparosc Endosc Percutan Tech* 2017; **27**: 175-178 [PMID: 28346287 DOI: 10.1097/SLE.0000000000000392]

11 **Kobayashi M**, Morishita S, Okabayashi T, Miyatake K, Okamoto K, Namikawa T, Ogawa Y, Araki K. Preoperative assessment of vascular anatomy of inferior mesenteric artery by volume-rendered 3D-CT for laparoscopic lymph node dissection with left colic artery preservation in lower sigmoid and rectal cancer. *World J Gastroenterol* 2006; **12**: 553-555 [PMID: 16489667 DOI: 10.3748/wjg.v12.i4.553]

12 **Forgione A**, Barberio M, Agnus V, Swanström L, Marescaux J, Diana M, Gallix B. Precision image-guided colonic surgery: proof of concept for enhanced preoperative and intraoperative vascular imaging. *Surg Endosc* 2021; **35**: 962-970 [PMID: 32997271 DOI: 10.1007/s00464-020-08000-w]

13 **Pérez-Corbal L**, Trujillo-Diaz JC, Alarcón I, Licardie E, Senent A, Morales-Conde S. Interactive 3D vascular reconstruction: A navigation tool to improve safety in laparoscopic D3 right colectomy - a video vignette. *Colorectal Dis* 2021; **23**: 3030-3032 [PMID: 34416059 DOI: 10.1111/codi.15881]

14 **Wu L**, Zheng Y, Liu J, Luo R, Wu D, Xu P, Li X. Comprehensive evaluation of the efficacy and safety of LPV/r drugs in the treatment of SARS and MERS to provide potential treatment options for COVID-19. *Aging (Albany NY)* 2021; **13**: 10833-10852 [PMID: 33879634 DOI: 10.18632/aging.202860]

15 **Bonomi AM**, Kersik A, Bracchetti G, Cotsoglou C. 3D reconstruction in complex parenchymal sparing liver surgery. *Heliyon* 2023; **9**: e13857

[PMID: 36879963 DOI: 10.1016/j.heliyon.2023.e13857]

16 **Wu L**, Li X, Qian X, Wang S, Liu J, Yan J. Lipid Nanoparticle (LNP) Delivery Carrier-Assisted Targeted Controlled Release mRNA Vaccines in Tumor Immunity. *Vaccines (Basel)* 2024; **12** [PMID: 38400169 DOI: 10.3390/vaccines12020186]

17 **Miyamoto R**, Tadano S, Sano N, Inagawa S, Adachi S, Yamamoto M. The impact of three-dimensional reconstruction on laparoscopic-assisted surgery for right-sided colon cancer. *Wideochir Inne Tech Maloinwazyjne* 2017; **12**: 251-256 [PMID: 29062445 DOI: 10.5114/wiitm.2017.67996]

18 **Bodensteiner C**, Darolti C, Schweikard A. Vascular tree reconstruction with discrete tomography: intensity based camera correction for 3D reconstruction. *Int J Comput Assist Radiol Surg* 2009; **4**: 189-202 [PMID: 20033619 DOI: 10.1007/s11548-009-0283-4]

19 **Groves LA**, VanBerlo B, Veinberg N, Alboog A, Peters TM, Chen ECS. Automatic segmentation of the carotid artery and internal jugular vein from 2D ultrasound images for 3D vascular reconstruction. *Int J Comput Assist Radiol Surg* 2020; **15**: 1835-1846 [PMID: 32839888 DOI: 10.1007/s11548-020-02248-2]

20 **Luzon JA**, Kumar RP, Stimec BV, Elle OJ, Bakka AO, Edwin B, Ignjatovic D. Semi-automated vs. manual 3D reconstruction of central mesenteric vascular models: the surgeon's verdict. *Surg Endosc* 2020; **34**: 4890-4900 [PMID: 31745632 DOI: 10.1007/s00464-019-07275-y]

21 **Toutouzas K**, Chatzizisis YS, Riga M, Giannopoulos A, Antoniadis AP, Tu S, Fujino Y, Mitsouras D, Doulaverakis C, Tsampoulatidis I, Koutkias VG, Bouki K, Li Y, Chouvarda I, Cheimariotis G, Maglaveras N, Kompatsiaris I, Nakamura S, Reiber JH, Rybicki F, Karvounis H, Stefanadis C, Tousoulis D, Giannoglou GD. Accurate and reproducible reconstruction of coronary arteries and endothelial shear stress calculation using 3D OCT: comparative study to 3D IVUS and 3D QCA. *Atherosclerosis* 2015; **240**: 510-519 [PMID: 25932791 DOI: 10.1016/j.atherosclerosis.2015.04.011]

22 **Wu L**, Zhong Y, Wu D, Xu P, Ruan X, Yan J, Liu J, Li X. Immunomodulatory Factor TIM3 of Cytolytic Active Genes Affected the Survival and Prognosis of Lung Adenocarcinoma Patients by Multi-Omics Analysis. *Biomedicines* 2022; **10** [PMID: 36140350 DOI: 10.3390/biomedicines10092248]

23 **Melville JC**, Manis CS, Shum JW, Alsuwied D. Single-Unit 3D-Printed Titanium Reconstruction Plate for Maxillary Reconstruction: The Evolution of Surgical Reconstruction for Maxillary Defects-A Case Report and Review of Current Techniques. *J Oral Maxillofac Surg* 2019; **77**: 874.e1-874.e13 [PMID: 30615849 DOI: 10.1016/j.joms.2018.11.030]

24 **Gao B**, Jing H, Gao M, Wang S, Fu W, Zhang X, He X, Zheng J. Long-segmental tracheal reconstruction in rabbits with pedicled Tissue-engineered trachea based on a 3D-printed scaffold. *Acta Biomater* 2019; **97**: 177-186 [PMID: 31352107 DOI: 10.1016/j.actbio.2019.07.043]

25 **Li F**, Chenoune Y, Ouenniche M, Blanc R, Petit E. Segmentation and reconstruction of cerebral vessels from 3D rotational angiography for AVM embolization planning. *Annu Int Conf IEEE Eng Med Biol Soc* 2014; **2014**: 5522-5525 [PMID: 25571245 DOI: 10.1109/EMBC.2014.6944877]

26 **Arkill KP**, Neal CR, Mantell JM, Michel CC, Qvortrup K, Rostgaard J, Bates DO, Knupp C, Squire JM. 3D reconstruction of the glycocalyx structure in mammalian capillaries using electron tomography. *Microcirculation* 2012; **19**: 343-351 [PMID: 22324320 DOI: 10.1111/j.1549-8719.2012.00168.x]

27 **Wu L**, Li H, Liu Y, Fan Z, Xu J, Li N, Qian X, Lin Z, Li X, Yan J. Research progress of 3D-bioprinted functional pancreas and in vitro tumor models. *Int J Bioprint* 2024; **10**: 1256 [DOI: 10.36922/ijb.1256]

28 **Waechter I**, Bredno J, Weese J, Barratt DC, Hawkes DJ. Using flow information to support 3D vessel reconstruction from rotational angiography. *Med Phys* 2008; **35**: 3302-3316 [PMID: 18697555 DOI: 10.1118/1.2938729]

29 **Wu L**, Liu Q, Ruan X, Luan X, Zhong Y, Liu J, Yan J, Li X. Multiple Omics Analysis of the Role of RBM10 Gene Instability in Immune Regulation and Drug Sensitivity in Patients with Lung Adenocarcinoma (LUAD). *Biomedicines* 2023; **11** [PMID: 37509501 DOI: 10.3390/biomedicines11071861]

30 **Lu TW**, Chen WT, Ji T. Accuracy of Mandibular Reconstruction with a Vascularised Iliac Flap Using 3D Templates: a Systematic Review. *Chin J Dent Res* 2022; **25**: 37-43 [PMID: 35293709 DOI: 10.3290/j.cjdr.b2752689]

31 **Kresakova L**, Danko J, Andrejcakova Z, Petrovova E, Vdoviakova K, Cizkova D, Maloveska M, Toth T, Tomco M, Vrzgula A, Teleky J, Supuka P. 3D Reconstruction and Evaluation of Accessory Hepatic Veins in Right Hemilivers in Laboratory Animals by Metrotomography: Implications for Surgery. *Med Sci Monit* 2019; **25**: 920-927 [PMID: 30707686 DOI: 10.12659/MSM.911726]

32 **Wu L**, Zheng Y, Ruan X, Wu D, Xu P, Liu J, Li X. Long-chain noncoding ribonucleic acids affect the survival and prognosis of patients with esophageal adenocarcinoma through the autophagy pathway: construction of a prognostic model. *Anticancer Drugs* 2022; **33**: e590-e603 [PMID: 34338240 DOI: 10.1097/CAD.0000000000001189]

33 **Coste E**, Vasseur C, Rousseau J. 3D reconstruction of the cerebral arterial network from stereotactic DSA. *Med Phys* 1999; **26**: 1783-1793 [PMID: 10505865 DOI: 10.1118/1.598682]

34 **Qiu MG**, Zhang SX, Liu ZJ, Tan LW, Wang YS, Deng JH, Tang ZS. Plastination and computerized 3D reconstruction of the temporal bone. *Clin Anat* 2003; **16**: 300-303 [PMID: 12794912 DOI: 10.1002/ca.10076]

35 **Miyashita Y**, Ikeda T, Shinto E, Okano S, Korehisa S, Shimazaki H, Oki E, Ueno H, Oda Y, Mori M. Three-dimensional imaging of intramural perineural invasion in colorectal cancer: Three-dimensional reconstruction approach with multiple immunohistochemically stained sections. *Pathol Int* 2022; **72**: 293-299 [PMID: 35352858 DOI: 10.1111/pin.13222]

36 **Misri H**, Pöckler-Schöniger C, Gaa J, Georgi M, Sturm J, Ihle V. [Ultrafast contrast-enhanced 3D MR angiography in the preoperative diagnosis of liver tumors]. *Rofo* 1998; **169**: 278-283 [PMID: 9779068 DOI: 10.1055/s-2007-1015090]

37 **Adam DR**, Burstein P. Vascular imaging by ultrasound: 3D reconstruction of flow velocity fields for endothelial shear stress calculation. *Adv Exp Med Biol* 1997; **430**: 177-185 [PMID: 9330728 DOI: 10.1007/978-1-4615-5959-7_15]

38 **Wu L**, Chen X, Zeng Q, Lai Z, Fan Z, Ruan X, Li X, Yan J. NR5A2 gene affects the overall survival of LUAD patients by regulating the activity of CSCs through SNP pathway by OCLR algorithm and immune score. *Heliyon* 2024; **10**: e28282 [PMID: 38601554 DOI: 10.1016/j.heliyon.2024.e28282]

39 **DeFazio MV**, Arribas EM, Ahmad FI, Le-Petross HT, Liu J, Chu CK, Santiago L, Clemens MW. Application of Three-Dimensional Printed Vascular Modeling as a Perioperative Guide to Perforator Mapping and Pedicle Dissection during Abdominal Flap Harvest for Breast Reconstruction. *J Reconstr Microsurg* 2020; **36**: 325-338 [PMID: 32000277 DOI: 10.1055/s-0039-1700991]

40 **Romano G**, Di Buono G, Galia M, Agnello F, Anania G, Guerrieri M, Milone M, Silecchia G, Buscemi S, Agrusa A. Role of preoperative CT angiography with multimodality imaging reconstruction to perform laparoscopic Complete Mesocolic Excision (CME) and Central Vascular Ligation (CVL) in right-sided colon cancer: Is it really useful? A prospective clinical study. *Eur J Surg Oncol* 2023; **49**: 209-216 [PMID: 36002353 DOI: 10.1016/j.ejso.2022.08.007]

41 **Yano M**, Okazaki S, Kawamura I, Ito S, Nozu S, Ashitomi Y, Suzuki T, Kamio Y, Hachiya O. A three-dimensional computed tomography

angiography study of the anatomy of the accessory middle colic artery and implications for colorectal cancer surgery. *Surg Radiol Anat* 2020; **42**: 1509-1515 [PMID: 32500228 DOI: 10.1007/s00276-020-02511-w]

42 **Ueda T**, Morita K, Koyama F, Teramura Y, Nakagawa T, Nakamura S, Matsumoto Y, Inoue T, Nakamoto T, Sasaki Y, Kuge H, Takeda M, Ohbayashi C, Fujii H, Sho M. A detailed comparison between the endoscopic images using blue laser imaging and three-dimensional reconstructed pathological images of colonic lesions. *PLoS One* 2020; **15**: e0235279 [PMID: 32598341 DOI: 10.1371/journal.pone.0235279]

43 **Wu L**, Zhong Y, Yu X, Wu D, Xu P, Lv L, Ruan X, Liu Q, Feng Y, Liu J, Li X. Selective poly adenylation predicts the efficacy of immunotherapy in patients with lung adenocarcinoma by multiple omics research. *Anticancer Drugs* 2022; **33**: 943-959 [PMID: 35946526 DOI: 10.1097/CAD.0000000000001319]

44 **Ke J**, Cai J, Wen X, Wu X, He Z, Zou Y, Qiu J, He X, Lian L, Zhou Z, Lan P. Anatomic variations of inferior mesenteric artery and left colic artery evaluated by 3-dimensional CT angiography: Insights into rectal cancer surgery - A retrospective observational study. *Int J Surg* 2017; **41**: 106-111 [PMID: 28323157 DOI: 10.1016/j.ijsu.2017.03.012]

45 **Griffini P**, Smorenburg SM, Verbeek FJ, van Noorden CJ. Three-dimensional reconstruction of colon carcinoma metastases in liver. *J Microsc* 1997; **187**: 12-21 [PMID: 9263437 DOI: 10.1046/j.1365-2818.1997.2140770.x]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Robotic-assisted low anterior resection for rectal cancer shows similar clinical efficacy to laparoscopic surgery: A propensity score matched study

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Abstract

BACKGROUND

Rectal cancer ranks as the second leading cause of cancer-related mortality worldwide, necessitating surgical resection as the sole treatment option. Over the years, there has been a growing adoption of minimally invasive surgical techniques such as robotic and laparoscopic approaches. Robotic surgery represents an innovative modality that effectively addresses the limitations associated with traditional laparoscopic techniques. While previous studies have reported favorable perioperative outcomes for robot-assisted radical resection in rectal cancer patients, further evidence regarding its oncological safety is still warranted.

AIM

To conduct a comparative analysis of perioperative and oncological outcomes between robot-assisted and laparoscopic-assisted low anterior resection (LALAR) procedures.

METHODS
The clinical data of 125 patients who underwent robot-assisted low anterior resection (RALAR) and 279 patients who underwent LALAR resection at Shandong Provincial Hospital Affiliated to Shandong First Medical University from December 2019 to November 2022 were retrospectively analyzed. After performing a 1:1 propensity score matching, the patients were divided into two groups: The RALAR group and the LALAR group (111 cases in each group). Subsequently, a comparison was made between the short-term outcomes within 30 d after surgery and the 3-year survival outcomes of these two groups.

RESULTS
Compared to the LALAR group, the RALAR group exhibited a significantly earlier time to first flatus [2 (2-2) d *vs* 3 (3-3) d, $P = 0.000$], as well as a shorter time to first fluid diet [4 (3-4) d *vs* 5 (4-6) d, $P = 0.001$]. Additionally, the RALAR group demonstrated reduced postoperative indwelling catheter time [2 (1-3) d *vs* 4 (3-5) d, $P = 0.000$] and decreased length of hospital stay after surgery [5 (5-7) d *vs* 7(6-8) d, $P = 0.009$]. Moreover, there was an observed increase in total cost of hospitalization for the RALAR group compared to the LALAR group [10777 (10780-11850) dollars *vs* 10550 (8766-11715) dollars, $P = 0.012$]. No significant differences were found in terms of conversion rate to laparotomy or incidence of postoperative complications between both groups. Furthermore, no significant disparities were noted regarding the 3-year overall survival rate and 3-year disease-free survival rate between both groups.

CONCLUSION
Robotic surgery offers potential advantages in terms of accelerated recovery of gastrointestinal and urologic function compared to LALAR resection, while maintaining similar perioperative and 3-year oncological outcomes.

Key Words: Rectal cancer; Robotic surgical procedures; Laparoscopy; Low anterior resection; Clinical efficacy

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Core Tip: Robotic surgery is increasingly utilized in the management of rectal cancer. However, only retrospective studies and small-scale clinical trials have reported its perioperative outcomes. In this study, propensity score matching was employed to balance baseline data, thereby enhancing the credibility of the conclusions compared to general retrospective studies. Moreover, it is encouraging that the perioperative results and 3-year oncological outcomes of robotic surgery are similar to those of traditional laparoscopic surgery.

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INTRODUCTION

Rectal cancer ranks as the second leading cause of cancer-related fatalities worldwide[1]. Remarkable advancements have been achieved in the treatment of rectal cancer over recent decades. Since the 1980s, total mesorectal excision (TME) technique has served as the fundamental principle for surgical management of rectal cancer. Initially introduced through open surgery[2], the TME technique has subsequently benefited from laparoscopic techniques and instruments development. Multiple randomized controlled trials have demonstrated that laparoscopic-assisted TME not only matches the quality of tumor resection[3-5], but also yields comparable long-term oncological outcomes[6,7] to traditional open surgery. Nevertheless, surgeons continue to encounter challenges when performing rectal cancer surgery using conventional laparoscopic platforms due to inherent limitations such as reduced instrument flexibility and unstable exposure of the surgical field within a narrow pelvis. Furthermore, establishing noninferiority of laparoscopic-assisted TME compared with open surgery for successful resection remains unresolved[8,9].

In rectal cancer surgery, the robotic digital platform offers distinct technical advantages. It enhances surgical precision through a three-dimensional high-definition field of view, a multi-joint robotic arm, rotatable wrist surgical instruments, tremor filtering, and fluorescence imaging[10,11]. These theoretical benefits suggest that robot-assisted TME may yield superior clinical outcomes compared to laparoscopic-assisted TME.

The objective of this study was to assess the safety and efficacy of robot-assisted low anterior resection (RALAR), with a focus on reporting perioperative and 3-year oncological outcomes for both robotic and laparoscopic surgery.

MATERIALS AND METHODS

Patients

This retrospective cohort study was conducted at the Department of Gastrointestinal Surgery, Shandong Provincial Hospital Affiliated to Shandong First Medical University, and included clinical data from patients who underwent low anterior resection for rectal cancer between December 2019 and November 2022. The inclusion criteria were as follows: (1) Diagnosis of rectal adenocarcinoma; (2) robotic or laparoscopic surgery; (3) low anterior resection; (4) distance from the lower edge of the tumor to the anal edge ≤ 15 cm; and (5) the postoperative pathological TNM stage was I-III. The exclusion criteria were as follows: (1) Preoperative detection of distant metastasis; (2) tumor invasion of adjacent organs; (3) previous history of any other malignant tumors; (4) combined with other organ resections; and (5) preoperative neoadjuvant therapy. The third generation Da Vinci robotic surgical system was utilized in the robotic group.

Data collection

The baseline characteristics encompass the following variables: Gender, age, preoperative hemoglobin level, preoperative albumin level, presence of preoperative intestinal obstruction, comorbidity (including cardiovascular diseases, cerebrovascular disorders, diabetes mellitus, lung diseases, and liver diseases), previous abdominal surgery, history of smoking, height of tumor from anal verge, preventive stoma status, American Society of Anesthesiologists score, classification of New York Heart Association heart function, body mass index (BMI), differentiation grade, maximum tumor diameter, pathological T stage and N stage as well as TNM staging based on AJCC 8th edition criteria for cancer staging purposes, and surgical approach.

The perioperative outcomes encompass the following parameters: Complications within 30 d after surgery and Clavien-Dindo classification[12-14] (All postoperative complications were assessed and classified based on the patient's clinical manifestations, laboratory findings, radiographic results, and treatment modalities), the rate of conversion to laparotomy (Conversion is defined as the transition from robot-assisted or laparoscopic-assisted surgery to open abdominal surgery), approximate intraoperative blood loss, rate of intraoperative blood transfusion, positive rate of distal resection margin, harvested lymph nodes, harvested positive lymph nodes, duration of surgery, intraoperative dose of sufentanil, time to first flatus, time to first fluid diet, postoperative indwelling catheter time, total cost of hospitalization (treatment costs arising from readmission due to complications were not included), postoperative hospital stay, readmission rate within 30 d after surgery(Readmission for adjuvant therapy was not included), and reoperation rate within 30 d after surgery.

Survival outcomes were assessed based on the 3-year overall survival (OS) and 3-year disease-free survival (DFS) rates following surgical intervention. OS was defined as the duration from the date of surgery until the last follow-up visit or death from any cause. DFS referred to the period between surgery and either first recurrence, last follow-up visit, or death from any cause. Local recurrence was determined by radiological or histologic evidence indicating tumor reappearance at the primary site. Distant metastasis denoted the presence of metastatic lesions in organs other than the primary site. Data collection involved telephone interviews and outpatient follow-up visits, with surgery serving as the starting point and death, recurrence, or metastasis as endpoints. Examinations encompassed digital rectal examination, serum tumor markers assessment, colonoscopy, and contrast-enhanced CT scans of chest, abdomen, and pelvis.

Clinical management

The preoperative examination includes routine blood tests, chest and abdominal computed tomography (CT), pelvic magnetic resonance imaging, and colonoscopy. TME is the standard surgical method for rectal cancer, and the surgical technique is carried out as described in previous reports[15,16]. Similar perioperative management was performed as recommended by the Enhanced Recovery After Surgery guidelines[17]. Postoperative oral nutritional supplementation is provided as early as possible, and a liquid diet is resumed early based on the patient's abdominal signs and flatulence. Typically, urinary catheterization is routinely performed 1-3 d after rectal cancer surgery, and the duration should also be individualized based on risk factors (such as male gender, epidural analgesia, and pelvic surgery).

Statistical analysis

The data were analyzed using SPSS 26.0 software. For measurement data conforming to a normal distribution, an independent sample *t*-test was employed; for measurement data and hierarchical data not conforming to a normal distribution, the Mann-Whitney *U* test was utilized; and for count data, either the χ^2 test or Fisher's exact test was applied. A logistic regression model with a caliper value set at 0.02 was used to calculate the propensity score for each patient. The baseline characteristics were utilized as covariates to achieve a 1:1 matching ratio between the RALAR group and the laparoscopic-assisted low anterior resection (LALAR) group. After propensity score matching, paired sample *t*-tests were conducted for measurement data conforming to a normal distribution, McNemar tests were performed for count data, and Wilcoxon tests were employed for measurement data and hierarchical data not conforming to a normal distribution. Univariate logistic regression analysis followed by multivariate logistic regression analysis was conducted to identify risk factors associated with anastomotic leakage. Kaplan-Meier method was used to plot survival curves depicting the 3-year OS rate and 3-year DFS rate after surgery, with between-group differences compared using Log-rank test. A significance level of $P < 0.05$ has been reached, indicating a statistically meaningful difference. mean ± SD values were reported for measurement data conforming to a normal distribution; median and quartile values were provided for measurement data not conforming to a normal distribution; while number and percentage values represented count data.

RESULTS

Patient characteristics

A total of 404 patients were enrolled in this study, with 125 (31%) undergoing RALAR and 279 (69%) undergoing LALAR. Significant differences existed between the two groups prior to matching in terms of patients presenting preoperative intestinal obstruction, liver diseases, height of tumor from anal verge, preventive stoma, and pathological N stage. Propensity score matching was employed to mitigate selection bias and achieve balanced baseline characteristics for both groups (111 patients per group). Table 1 shows the clinical characteristics of the patient.

Perioperative clinical outcomes

The RALAR group exhibited earlier time to first flatus [2 (2-2) d *vs* 3 (3-3) d, $P = 0.000$] and time to first fluid diet [4 (3-4) d *vs* 5 (4-6) d, $P = 0.001$], shorter postoperative indwelling catheter time [2 (1-3) d *vs* 4 (3-5) d, $P = 0.000$] and length of hospital stay after surgery [5 (5-7) d *vs* 7 (6-8) d, $P = 0.009$], as well as higher total cost of hospitalization [10777 (10780-11850) dollars *vs* 10550 (8766-11715) dollars, $P = 0.012$] compared to the LALAR group. The rate of conversion to laparotomy did not differ significantly between the RALAR group and the LALAR group (0% *vs* 1.8%, $P = 0.498$). There were no significant differences observed in the remaining perioperative outcomes between the two groups. Table 2 shows the perioperative results.

Postoperative complications

The overall incidence of postoperative complications was 13.5% in the RALAR group and 12.6% in the LALAR group ($P = 1.000$). Moreover, the incidence of severe complications (Clavien-Dindo grade ≥ III) was 0.9% in the RALAR group and 3.6% in the LALAR group ($P = 0.375$). The incidence of each complication and each Clavien-Dindo grade ≥ III complication did not exhibit any significant differences between the two groups. Table 3 shows the postoperative complications.

Subgroup analysis of anastomotic leakage

Univariate logistic regression analysis revealed that BMI ≥ 25 (kg/m^2) and maximum tumor diameter ≥ 6 cm were identified as risk factors for postoperative anastomotic leakage. Subsequently, multivariate logistic regression analysis was conducted on the variables with significant statistical associations in the univariate logistic regression analysis. The results demonstrated that BMI ≥ 25 (kg/m^2) [odds ratio (OR): 2.85; 95% confidence interval (95%CI): 1.23-6.59; $P = 0.015$] and maximum tumor diameter ≥ 6 cm (OR: 2.81; 95%CI: 1.10-7.15; $P = 0.030$) independently contributed to the risk of postoperative anastomotic leakage occurrence. Figure 1 depict the risk factor analysis of postoperative anastomotic leakage, while subgroup analyses were performed based on the independent risk factors for this complication. Among patients with BMI ≥ 25 (kg/m^2), there was a respective incidence of anastomotic leakage of 17.8% in the RALAR group and 12.0% in the LALAR group ($P = 0.428$). In patients with maximum tumor diameter ≥ 6 cm, the incidence of anastomotic leakage was observed to be 28.6% in the RALAR group compared to only 8.3% in the LALAR group ($P = 0.330$). In summary, although slightly higher incidences of anastomotic leakage were noted in the RALAR group during subgroup analyses, these differences did not reach statistical significance. Table 4 presents detailed findings from subgroup analyses regarding anastomotic leakage.

3-year oncological outcomes

After matching, a total of 10 patients (5 in the RALAR group and 5 in the LALAR group) were lost to follow-up, resulting in a loss rate of 4.5%. However, there was no statistically significant difference observed between the two groups. The median duration of follow-up was 33 months. The 3-year OS rate was 96.4% in the RALAR group and 95.6% in the LALAR group ($P = 0.909$), indicating no statistically significant difference between the two groups. According to TNM staging, the 3-year OS rate in the RALAR group was 100% in stage I, 100% in stage II, and 91.8% in stage III, while the 3-year OS rate in the LALAR group was 100.0% in stage I, 92.2% in stage II, and 95.0% in stage III. There was no statistically significant difference in the 3-year OS rate at each stage between the RALAR group and the LALAR group. The 3-year OS rate of the two groups was compared in Figure 2A-D. The 3-year DFS rate was 87.7% in the RALAR group and 91.2% in the LALAR group ($P = 0.738$), with no statistically significant difference between the two groups. According to TNM staging, the 3-year DFS rate in the RALAR group was 96.8% in stage I, 89.6% in stage II, and 78.3% in stage III, while the 3-year DFS rate in the LALAR group was 92.8% in stage I, 92.7% in stage II, and 88.8% in stage III. There was no statistically significant difference in the 3-year DFS rate at each stage between the RALAR group and the LALAR group. The 3-year DFS rate of the two groups was compared in Figure 2E-H.

DISCUSSION

This retrospective cohort study aimed to compare the clinical outcomes of robotic-assisted and LALAR for rectal cancer. Only patients undergoing low anterior resection for rectal cancer were included during the study period. Surgeons' expectations regarding advanced technology may lead to selective application of robotic surgery in more complex cases, such as advanced tumors or abdominoperineal resection for rectal cancer, potentially exacerbating selection bias in the retrospective analysis. To address baseline data imbalance, we performed propensity score matching analysis based on patient clinical characteristics and tumor pathological characteristics after excluding cases of abdominoperineal resection.

Table 1 Baseline characteristics, *n* (%)

Item	Before matching		*P* value	After matching		*P* value
	RALAR, *n* = 125	LALAR, *n* = 279		RALAR, *n* = 111	LALAR, *n* = 111	
Gender			0.871			0.896[1]
Male	76 (60.8)	172 (61.6)		67 (60.4)	65 (58.6)	
Female	49 (39.2)	107 (38.4)		44 (39.6)	46 (41.4)	
Age (yr)	62 (55-68)	63 (54-68)	0.957	62 (55-66)	61 (53-68)	0.761
Preoperative hemoglobin (g/L)	135.0 (123.5-143.5)	134.0 (123.0-145.0)	0.593	131.7 ± 15.7	133.1 ± 17.5	0.510
Preoperative albumin (g/L)	39.5 ± 3.0	39.1 ± 3.2	0.246	39.4 ± 3.0	39.8 ± 3.3	0.430
Preoperative intestinal obstruction	8 (6.4)	44 (15.8)	0.009	8 (7.2)	7 (6.3)	1.000[1]
Comorbidity						
Cardiovascular diseases	48 (38.4)	106 (38.0)	0.938	44 (39.6)	38 (34.2)	0.441[1]
Cerebrovascular disorders	11 (8.8)	38 (13.6)	0.170	10 (9.0)	10 (9.0)	1.000[1]
Diabetes mellitus	16 (12.8)	41 (14.7)	0.613	13 (11.7)	12 (10.8)	1.000[1]
Lung diseases	43 (34.4)	96 (34.4)	0.999	36 (32.4)	38 (34.2)	0.885[1]
Liver diseases	9 (7.2)	8 (2.9)	0.045	4 (3.6)	5 (4.5)	1.000[1]
Previous abdominal surgery	12 (9.6)	33 (11.8)	0.511	11 (9.9)	15 (13.5)	0.523[1]
History of smoking	47 (37.6)	81 (29.0)	0.087	39 (35.1)	36 (32.4)	0.761[1]
Height of tumor from anal verge (cm)	10 (8.0-13.5)	10 (6.0-10.0)	0.005	10 (8.0-12.0)	10 (8.0-12.0)	0.754
Preventive stoma	23 (18.4)	111 (39.8)	0.000	22 (19.8)	23 (20.7)	1.000[1]
ASA score			0.340			0.602
I	0	1 (0.4)		0	0	
II	102 (81.6)	214 (76.7)		90 (81.1)	93 (83.8)	
III	23 (18.4)	64 (22.9)		21 (18.9)	18 (16.2)	
Classification of NYHA heart function			0.837			0.893
I	77 (61.6)	170 (60.9)		67 (60.4)	68 (61.3)	
II	48 (38.4)	106 (38.0)		44 (39.6)	43 (38.7)	
III	0	3 (1.1)		0	0	
BMI (kg/m^2)	24.2 (22.8-25.9)	24.2 (22.1-26.7)	0.780	24.5 ± 2.8	24.6 ± 3.5	0.795
Differentiation			0.053			0.317
Low	3 (2.4)	37 (13.3)		3 (2.7)	4 (3.6)	
Medium	114 (91.2)	218 (78.1)		102 (91.9)	95 (85.6)	
High	8 (6.4)	24 (8.6)		6 (5.4)	12 (10.8)	
Maximum tumor diameter (cm)	4 (3.0-5.0)	4 (3.5-5.0)	0.128	4 (3.0-5.0)	4 (3.0-5.0)	0.693
Pathological T stage			0.693			0.925
Tis	0	2 (0.7)		0	2 (1.8)	
1	10 (8.0)	15 (5.4)		9 (8.1)	7 (6.3)	
2	34 (27.2)	70 (25.1)		32 (28.8)	26 (23.4)	
3	74 (59.2)	185 (66.3)		64 (57.7)	74 (66.7)	
4a	7 (5.6)	7 (2.5)		6 (5.4)	2 (1.8)	
Pathological N stage			0.046			0.534

0	80 (64.0)	154 (55.2)		69 (62.2)	72 (64.9)
1a	19 (15.2)	38 (13.6)		18 (16.2)	17 (15.3)
1b	13 (10.4)	38 (13.6)		12 (10.8)	12 (10.8)
1c	0	7 (2.5)		0	2 (1.8)
2a	8 (6.4)	19 (6.8)		8 (7.2)	6 (5.4)
2b	5 (4.0)	23 (8.2)		4 (3.6)	2 (1.8)
Pathological TNM stage			0.140		0.712
0	0	2 (0.7)		0	2 (1.8)
I	34 (27.2)	69 (24.7)		31 (27.9)	28 (25.2)
IIA	43 (34.4)	81 (29.0)		36 (32.4)	41 (36.9)
IIB	3 (2.4)	2 (0.7)		2 (1.8)	1 (0.9)
IIIA	9 (7.2)	15 (5.4)		9 (8.1)	5 (4.5)
IIIB	30 (24.0)	85 (30.5)		28 (25.2)	31 (27.9)
IIIC	6 (4.8)	25 (9.0)		5 (4.5)	3 (2.7)

[1]McNemar's test.
RALAR: Robot-assisted low anterior resection; LALAR: Laparoscopic-assisted low anterior resection; ASA: American Society of Anesthesiologists; NYHA: New York Heart Association; BMI: Body mass index.

Table 2 Perioperative outcomes, *n* (%) or median (interquartile range)

	RALAR, *n* = 111	LALAR, *n* = 111	*P* value
Conversion to laparotomy	0	2 (1.8)	0.498[2]
Approximate intraoperative blood loss (mL)	50 (20-50)	50 (30-50)	0.276
Intraoperative blood transfusion	4 (3.6)	3 (2.7)	1.000[1]
Distal resection margin			1.000[2]
Involved	0	1 (0.9)	
Harvested lymph nodes	14 (11-16)	13 (11-17)	0.627
Harvested positive lymph nodes	0 (0-1)	0 (0-1)	0.317
Duration of surgery (min)	187 (160-215)	185 (155-230)	0.977
Intraoperative dose of sufentanil (μg/kg/min)	0.0050 (0.0040-0.0062)	0.0048 (0.0040-0.0064)	0.948
Time to first flatus (d)	2(2-2)	3 (3-3)	0.000
Time to first fluid diet (d)	4 (3-4)	5 (4-6)	0.001
Postoperative indwelling catheter time (d)	2 (1-3)	4 (3-5)	0.000
Total cost of hospitalization (dollars)	10777 (10780-11850)	10550 (8766-11715)	0.012
Length of hospital stay after surgery (d)	5 (5-7)	7 (6-8)	0.009
Readmission within 30 d after operation	1 (0.9)	1 (0.9)	1.000[1]
Reoperation within 30 d after operation	0	1 (0.9)	1.000[2]

[1]McNemar's test.
[2]Fisher's exact test.
RALAR: Robot-assisted low anterior resection; LALAR: Laparoscopic-assisted low anterior resection.

The findings of this study demonstrated that among patients undergoing low anterior resection for rectal cancer, both the RALAR group and the LALAR group exhibited comparable perioperative and 3-year oncological outcomes.

The rate of conversion to laparotomy is a crucial parameter for evaluating the benefits of robotic-assisted radical resection for rectal cancer, as it is believed that the technical advantages of robotics can effectively overcome challenging pelvic anatomy[18] and minimize the need for conversion to laparotomy[19]. Previous studies have demonstrated that

Table 3 Complications within 30 d after surgery, *n* (%)

	RALAR (*n* = 111)					LALAR (*n* = 111)					*P* value	*P* value
	I	II	IIIa	IIIb	Overall	I	II	IIIa	IIIb	Overall	Overall	≥ III
Overall	0	14	1	0	15 (13.5)	3	7	2	2	14 (12.6)	1.000[1]	0.375[1]
Anastomotic leakage	0	12	1	0	13 (11.7)	1	6	0	2	9 (8.1)	0.481[1]	1.000[1]
Anastomotic stenosis	0	0	0	0	0	2	0	0	0	2 (1.8)	0.498[2]	
Intestinal obstruction	0	1	0	0	1 (0.9)	0	2	1	0	3 (2.7)	0.625[1]	1.000[2]
Intraabdominal infection	0	2	0	0	2 (1.8)	0	2	0	1	3 (2.7)	1.000[1]	1.000[2]
Hemoperitoneum	0	0	0	0	0	0	0	1	0	1 (0.9)	1.000[2]	1.000[2]
Pneumonia	0	0	0	0	0	0	2	0	0	2 (1.8)	0.498[2]	
Pulmonary atelectasis	0	0	0	0	0	4	0	0	0	4 (3.6)	0.122[2]	
Venous thrombosis	0	1	0	0	1 (0.9)	0	0	0	0	0	1.000[2]	

[1]McNemar's test.
[2]Fisher's exact test.
RALAR: Robot-assisted low anterior resection; LALAR: Laparoscopic-assisted low anterior resection.

Table 4 Subgroup analysis of anastomotic leakage, *n* (%)

	Anastomotic leakage	*P* value
BMI ≥ 25 (kg/m^2)		0.428
RALAR (*n* = 45)	8 (17.8)	
LALAR (*n* = 50)	6 (12.0)	
Maximum tumor diameter ≥ 6 cm		0.330[1]
RALAR (*n* = 14)	4 (28.6)	
LALAR (*n* = 12)	1 (8.3)	

[1]Fisher's exact test.
RALAR: Robot-assisted low anterior resection; LALAR: Laparoscopic-assisted low anterior resection; BMI: Body mass index.

conversion to laparotomy is associated with inferior long-term oncological outcomes in rectal cancer surgery[20]. Furthermore, conversion to laparotomy leads to increased utilization of intraoperative analgesics[21]. A randomized, unblinded, multicenter study conducted in Denmark revealed that patients undergoing rectal cancer resection using robotic technology required fewer analgesics during surgery and experienced a lower rate of conversion to laparotomy compared to those undergoing traditional laparoscopic surgery[21]. The ROLARR multicenter randomized controlled trial designated the primary endpoint as the conversion rate to laparotomy[22]. In line with our findings, no significant disparity was observed in the rate of conversion to laparotomy between robotic-assisted and laparoscopic-assisted radical resection for rectal cancer in the ROLARR trial. However, subgroup analysis of the ROLARR trial revealed that robotic surgery exhibited a lower incidence of conversion to laparotomy among male patients. Furthermore, two multicenter retrospective cohort studies[23,24] reported that robotic-assisted radical resection for rectal cancer did not significantly mitigate the risk of conversion to laparotomy, which is consistent with our results. In this study, two patients in the LALAR group opted for conversion to laparotomy due to severe abdominal adhesions, while no patient in the RALAR group required conversion to laparotomy. The rate of converting to laparotomy did not exhibit a statistically significant difference between the two groups, thereby failing to demonstrate any advantage of robotic surgery over laparoscopy in terms of conversion rates.

Urogenital dysfunction is considered a significant complication that adversely affects the quality of life in patients following rectal cancer surgery. A prospective controlled study evaluated the urogenital function of patients by International Prostate Symptom Score, International Index of Erectile Function text, Female Sexual Function Index and urodynamic examination, and found that robotic technology was conducive to the early recovery of postoperative urogenital function, which was related to the superiority of robotic surgical technology in identifying and preserving autonomic nerves[25]. Moreover, consistent findings from prospective cohort studies[26] and meta-analyses[27] have shown that male patients undergoing robotic surgery experience improved micturition and erectile function compared to those undergoing traditional laparoscopic rectal cancer surgery. Similarly, our study revealed an earlier removal of catheter in the RALAR group than in the LALAR group, further supporting faster recovery of postoperative urogenital

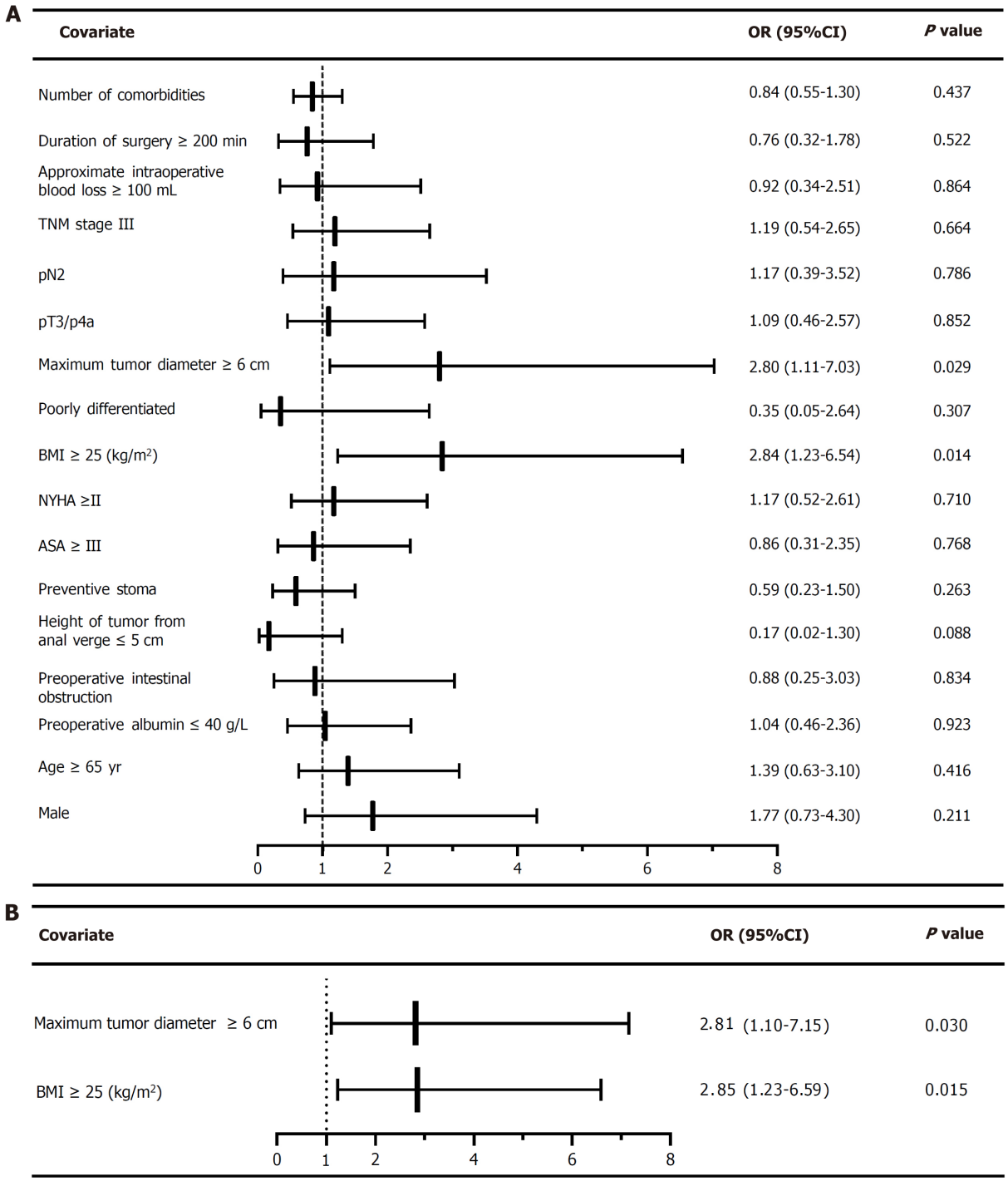


Figure 1 Univariate and multivariate analysis of anastomotic leakage (Clavien-Dindo grade ≥ II). A: Univariate analysis; B: Multivariate analysis. BMI: Body mass index; ASA: American Society of Anesthesiologists. NYHA: New York Heart Association; 95%CI: 95% confidence interval; OR: Odds ratio.

function with robotic surgical technology. However, it is important to note that this study did not include long-term follow-up or evaluation of patients' urogenital function; therefore, these clinically significant results should be interpreted cautiously and confirmed by other high-level evidence.

The faster recovery of gastrointestinal function is a significant advantage of robot-assisted radical resection for rectal cancer[28], as also supported by the findings of this study. However, it is important to address the cost issue, which poses a major barrier to the widespread adoption of robotic technology. Previous studies have highlighted the increased costs associated with robotic surgery[29]. In our preliminary analysis of hospitalization costs, we observed that the total hospitalization costs for patients in the RALAR group were significantly higher compared to those in the LALAR group, primarily due to elevated direct operation expenses. Nevertheless, as robotic surgery becomes more popular and its utilization increases rapidly, there is potential for a decrease in equipment and consumable costs. Furthermore, given that robotic surgery promotes accelerated recovery of gastrointestinal function[28], and reduces postoperative hospital stays [19,29,30], it can help control postoperative expenses and potentially lead to an overall reduction in costs at an acceptable

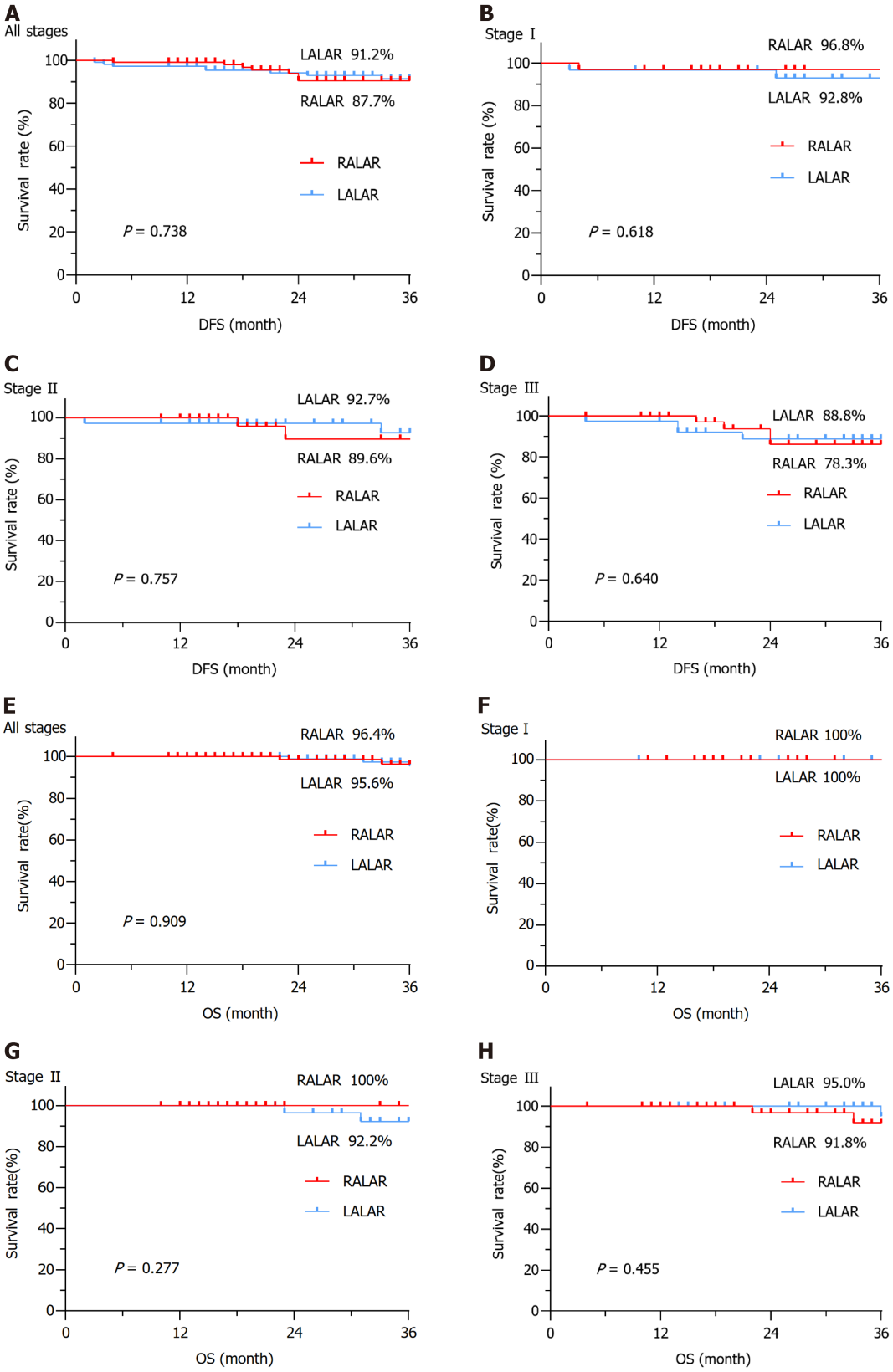


Figure 2 The 3-year overall survival and disease-free survival rate between robotic and laparoscopic surgical procedures. A: Overall survival (OS) rate for all stages in both groups; B: OS rate for stage I in both groups. In stage I, the Log-rank test could not calculate a meaningful statistic or *P* value; C: OS rate for stage II in both groups; D: OS rate for stage III in both groups; E: Disease-free survival (DFS) rate for all stages in both groups; F: DFS rate for stage I in both groups; G: DFS rate for stage II in both groups; H: DFS rate for stage III in both groups. RALAR: Robot-assisted low anterior resection; LALAR: Laparoscopic-assisted low anterior resection; OS: Overall survival.

level.

The incidence of postoperative complications was comparable between the RALAR group and the LALAR group, with no significant difference observed in the occurrence of severe complications. These findings align with previous studies demonstrating similar short-term outcomes for robot-assisted and laparoscopic-assisted radical resection for rectal cancer [19,23,24,30,31]. Anastomotic leakage is a common complication of low anterior resection for rectal cancer. Preventive stoma is considered to be effective in preventing anastomotic leakage[32]. The LASRE trial, a multicenter noninferiority randomized clinical trial for low rectal cancer, demonstrated that the rates of preventive stoma and anastomotic leakage following laparoscopic-assisted radical resection for rectal cancer were 78.8% and 2.5%[5], 81.0% and 3.0% in the ALaCaRT trial[8], 97.6% and 2.1% in the ACOSOG Z6051 trial (a multicenter noninferiority randomized clinical trial for rectal cancer after stage II and III neoadjuvant therapy)[9], and 35% and 13% in the COLOR II trial[3]. Considering the incidence of anastomotic leakage, the risk of reoperation, and patient preference, our hospital's laparoscopic team favors performing preventive stoma during surgery rather than resorting to stoma rerouting post-occurrence. In this study, a statistically significant difference was observed in the rate of preventive stoma between the RALAR group and the LALAR group (18.4% *vs* 39.8%, $P = 0.000$). Following propensity score matching, both the RALAR group (19.8%) and the LALAR group (20.7%) exhibited similar rates of preventive stoma, indicating balanced and comparable baseline data. Furthermore, after matching, there was no significant difference in the incidence of anastomotic leakage between the two groups with rates of 11.7% in the RALAR group and 8.1% in the LALAR group. Due to the theoretical advantages of robotic technology, surgeons are able to have better visualization of the surgical field and operate with increased flexibility in the pelvic cavity, potentially reducing accidental trauma to the intestinal wall. The aforementioned perspective is consistent with a multi-center randomized controlled trial that reported improved macroscopic completeness of specimens in the robotic surgery[28]. Therefore, this study also conducted a subgroup analysis on patients with risk factors for anastomotic leakage (BMI ≥ 25 kg/m^2 and maximum tumor diameter ≥ 6 cm); however, no significant difference in the incidence of anastomotic leakage was observed between the RALAR group and the LALAR group.

In terms of oncology, this study demonstrated comparable 3-year oncological outcomes between robot-assisted and LALAR procedures. Subgroup analysis based on TNM staging revealed no significant differences between the two groups. We compared these findings with previous studies investigating the oncological outcomes of robotic or laparoscopic rectal cancer surgery. Feroci *et al*[30], utilizing data from 2 centers, reported a 3-year OS rate of 90.2% and a 3-year DFS rate of 79.2% for patients undergoing robotic surgery for rectal cancer, while patients undergoing laparoscopic surgery achieved rates of 90.0% and 83.4%, respectively. A multicenter retrospective study conducted by Burghgraef *et al* [33] also reported similar 3-year oncological outcomes. The results of Park *et al*[29] were not inferior to these aforementioned findings, as they observed a 5-year OS rate of 92.8% and a 5-year DFS rate of 81.9% following RALAR. Furthermore, a subgroup analysis of a retrospective study demonstrated that in patients with ypT3-4 tumors who underwent preoperative chemoradiotherapy, the 5-year distant recurrence rate was 44.8% in the laparoscopic group and 9.8% in the robotic group, suggesting potential benefits of robotic surgery for advanced rectal cancer patients with poor response to neoadjuvant chemoradiotherapy[34]. However, considering that distant metastasis is primarily influenced by biological behavior and tumor staging[35], which may not be directly associated with surgical procedure, more robust evidence is still required to substantiate this conclusion.

The retrospective nature of this study was its most significant limitation; therefore, propensity score matching was employed to mitigate confounding from baseline data. Additionally, the evaluation of robotic technique quality should consider the achievement of a radical resection, specifically complete removal of the mesorectum, as circumferential resection margin involvement is a crucial predictor for local recurrence[36] and distant metastasis[37]. Several multicenter retrospective studies have demonstrated comparable specimen quality and circumferential resection margin involvement between robotic-assisted TME and laparoscopic-assisted TME[23,24,30]. However, comprehensive pathological results encompassing circumferential resection margin involvement and integrity of the mesorectum specimen were not available in this study.

In conclusion, this study demonstrated that both techniques yielded satisfactory perioperative and 3-year oncological outcomes. Moreover, robotic techniques exhibited certain advantages in rectal cancer surgery, which warrant further validation through subsequent investigations.

CONCLUSION

The robotic-assisted low anterior resection is a secure surgical technique that not only expedites the recovery of gastrointestinal and urinary function but also demonstrates promising perioperative and 3-year oncological outcomes.

FOOTNOTES

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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 **Martling AL**, Holm T, Rutqvist LE, Moran BJ, Heald RJ, Cedemark B. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Stockholm Colorectal Cancer Study Group, Basingstoke Bowel Cancer Research Project. *Lancet* 2000; **356**: 93-96 [PMID: 10963244 DOI: 10.1016/s0140-6736(00)02469-7]

3 **van der Pas MH**, Haglind E, Cuesta MA, Fürst A, Lacy AM, Hop WC, Bonjer HJ; COlorectal cancer Laparoscopic or Open Resection II (COLOR II) Study Group. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. *Lancet Oncol* 2013; **14**: 210-218 [PMID: 23395398 DOI: 10.1016/S1470-2045(13)70016-0]

4 **Kang SB**, Park JW, Jeong SY, Nam BH, Choi HS, Kim DW, Lim SB, Lee TG, Kim DY, Kim JS, Chang HJ, Lee HS, Kim SY, Jung KH, Hong YS, Kim JH, Sohn DK, Kim DH, Oh JH. Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): short-term outcomes of an open-label randomised controlled trial. *Lancet Oncol* 2010; **11**: 637-645 [PMID: 20610322 DOI: 10.1016/S1470-2045(10)70131-5]

5 **Jiang WZ**, Xu JM, Xing JD, Qiu HZ, Wang ZQ, Kang L, Deng HJ, Chen WP, Zhang QT, Du XH, Yang CK, Guo YC, Zhong M, Ye K, You J, Xu DB, Li XX, Xiong ZG, Tao KX, Ding KF, Zang WD, Feng Y, Pan ZZ, Wu AW, Huang F, Huang Y, Wei Y, Su XQ, Chi P; LASRE trial investigators. Short-term Outcomes of Laparoscopy-Assisted vs Open Surgery for Patients With Low Rectal Cancer: The LASRE Randomized Clinical Trial. *JAMA Oncol* 2022; **8**: 1607-1615 [PMID: 36107416 DOI: 10.1001/jamaoncol.2022.4079]

6 **Bonjer HJ**, Deijen CL, Abis GA, Cuesta MA, van der Pas MH, de Lange-de Klerk ES, Lacy AM, Bemelman WA, Andersson J, Angenete E, Rosenberg J, Fuerst A, Haglind E; COLOR II Study Group. A randomized trial of laparoscopic versus open surgery for rectal cancer. *N Engl J Med* 2015; **372**: 1324-1332 [PMID: 25830422 DOI: 10.1056/NEJMoa1414882]

7 **Park JW**, Kang SB, Hao J, Lim SB, Choi HS, Kim DW, Chang HJ, Kim DY, Jung KH, Kim TY, Kang GH, Chie EK, Kim SY, Sohn DK, Kim JS, Lee HS, Kim JH, Jeong SY, Oh JH. Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): 10-year follow-up of an open-label, non-inferiority, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2021; **6**: 569-577 [PMID: 33894918 DOI: 10.1016/S2468-1253(21)00094-7]

8 **Stevenson AR**, Solomon MJ, Lumley JW, Hewett P, Clouston AD, Gebski VJ, Davies L, Wilson K, Hague W, Simes J; ALaCaRT Investigators. Effect of Laparoscopic-Assisted Resection vs Open Resection on Pathological Outcomes in Rectal Cancer: The ALaCaRT Randomized Clinical Trial. *JAMA* 2015; **314**: 1356-1363 [PMID: 26441180 DOI: 10.1001/jama.2015.12009]

9 **Fleshman J**, Branda M, Sargent DJ, Boller AM, George V, Abbas M, Peters WR Jr, Maun D, Chang G, Herline A, Fichera A, Mutch M, Wexner S, Whiteford M, Marks J, Birnbaum E, Margolin D, Larson D, Marcello P, Posner M, Read T, Monson J, Wren SM, Pisters PW, Nelson H. Effect of Laparoscopic-Assisted Resection vs Open Resection of Stage II or III Rectal Cancer on Pathologic Outcomes: The ACOSOG Z6051 Randomized Clinical Trial. *JAMA* 2015; **314**: 1346-1355 [PMID: 26441179 DOI: 10.1001/jama.2015.10529]

10 **Stefanidis D**, Wang F, Korndorffer JR Jr, Dunne JB, Scott DJ. Robotic assistance improves intracorporeal suturing performance and safety in the operating room while decreasing operator workload. *Surg Endosc* 2010; **24**: 377-382 [PMID: 19536599 DOI: 10.1007/s00464-009-0578-0]

11 **Stefanidis D**, Hope WW, Scott DJ. Robotic suturing on the FLS model possesses construct validity, is less physically demanding, and is

favored by more surgeons compared with laparoscopy. *Surg Endosc* 2011; **25**: 2141-2146 [PMID: 21184110 DOI: 10.1007/s00464-010-1512-1]

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 **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]

14 **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]

15 **Feroci F**, Kröning KC, Lenzi E, Moraldi L, Cantafio S, Scatizzi M. Laparoscopy within a fast-track program enhances the short-term results after elective surgery for resectable colorectal cancer. *Surg Endosc* 2011; **25**: 2919-2925 [PMID: 21789649 DOI: 10.1007/s00464-011-1643-z]

16 **Bianchi PP**, Ceriani C, Locatelli A, Spinoglio G, Zampino MG, Sonzogni A, Crosta C, Andreoni B. Robotic versus laparoscopic total mesorectal excision for rectal cancer: a comparative analysis of oncological safety and short-term outcomes. *Surg Endosc* 2010; **24**: 2888-2894 [PMID: 20526623 DOI: 10.1007/s00464-010-1134-7]

17 **Gustafsson UO**, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, Rockall TA, Young-Fadok TM, Hill AG, Soop M, de Boer HD, Urman RD, Chang GJ, Fichera A, Kessler H, Grass F, Whang EE, Fawcett WJ, Carli F, Lobo DN, Rollins KE, Balfour A, Baldini G, Riedel B, Ljungqvist O. Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS(®)) Society Recommendations: 2018. *World J Surg* 2019; **43**: 659-695 [PMID: 30426190 DOI: 10.1007/s00268-018-4844-y]

18 **Baek SJ**, Kim CH, Cho MS, Bae SU, Hur H, Min BS, Baik SH, Lee KY, Kim NK. Robotic surgery for rectal cancer can overcome difficulties associated with pelvic anatomy. *Surg Endosc* 2015; **29**: 1419-1424 [PMID: 25159651 DOI: 10.1007/s00464-014-3818-x]

19 **Matsuyama T**, Endo H, Yamamoto H, Takemasa I, Uehara K, Hanai T, Miyata H, Kimura T, Hasegawa H, Kakeji Y, Inomata M, Kitagawa Y, Kinugasa Y. Outcomes of robot-assisted versus conventional laparoscopic low anterior resection in patients with rectal cancer: propensity-matched analysis of the National Clinical Database in Japan. *BJS Open* 2021; **5** [PMID: 34553225 DOI: 10.1093/bjsopen/zrab083]

20 **Jayne DG**, Thorpe HC, Copeland J, Quirke P, Brown JM, Guillou PJ. Five-year follow-up of the Medical Research Council CLASICC trial of laparoscopically assisted versus open surgery for colorectal cancer. *Br J Surg* 2010; **97**: 1638-1645 [PMID: 20629110 DOI: 10.1002/bjs.7160]

21 **Tolstrup R**, Funder JA, Lundbech L, Thomassen N, Iversen LH. Perioperative pain after robot-assisted versus laparoscopic rectal resection. *Int J Colorectal Dis* 2018; **33**: 285-289 [PMID: 29242972 DOI: 10.1007/s00384-017-2943-0]

22 **Jayne D**, Pigazzi A, Marshall H, Croft J, Corrigan N, Copeland J, Quirke P, West N, Rautio T, Thomassen N, Tilney H, Gudgeon M, Bianchi PP, Edlin R, Hulme C, Brown J. Effect of Robotic-Assisted vs Conventional Laparoscopic Surgery on Risk of Conversion to Open Laparotomy Among Patients Undergoing Resection for Rectal Cancer: The ROLARR Randomized Clinical Trial. *JAMA* 2017; **318**: 1569-1580 [PMID: 29067426 DOI: 10.1001/jama.2017.7219]

23 **Hol JC**, Burghgraef TA, Rutgers MLW, Crolla RMPH, van Geloven NAW, Hompes R, Leijtens JWA, Polat F, Pronk A, Smits AB, Tuynman JB, Verdaasdonk EGG, Consten ECJ, Sietses C. Comparison of laparoscopic versus robot-assisted versus transanal total mesorectal excision surgery for rectal cancer: a retrospective propensity score-matched cohort study of short-term outcomes. *Br J Surg* 2021; **108**: 1380-1387 [PMID: 34370834 DOI: 10.1093/bjs/znab233]

24 **Burghgraef TA**, Crolla RMPH, Verheijen PM, Fahim M, van Geloven A, Leijtens JWA, Pronk A, Smits AB, Verdaasdonk EGG, Consten ECJ. Robot-Assisted Total Mesorectal Excision Versus Laparoscopic Total Mesorectal Excision: A Retrospective Propensity Score-Matched Cohort Analysis in Experienced Centers. *Dis Colon Rectum* 2022; **65**: 218-227 [PMID: 34459449 DOI: 10.1097/DCR.0000000000002031]

25 **Liu Y**, Liu M, Lei Y, Zhang H, Xie J, Zhu S, Jiang J, Li J, Yi B. Evaluation of effect of robotic versus laparoscopic surgical technology on genitourinary function after total mesorectal excision for rectal cancer. *Int J Surg* 2022; **104**: 106800 [PMID: 35934282 DOI: 10.1016/j.ijsu.2022.106800]

26 **Tang B**, Gao G, Ye S, Liu D, Jiang Q, Ai J, Lei X, Shi J, Li T. Male urogenital function after robot-assisted and laparoscopic total mesorectal excision for rectal cancer: a prospective cohort study. *BMC Surg* 2022; **22**: 185 [PMID: 35568823 DOI: 10.1186/s12893-022-01592-1]

27 **Fleming CA**, Cullinane C, Lynch N, Killeen S, Coffey JC, Peirce CB. Urogenital function following robotic and laparoscopic rectal cancer surgery: meta-analysis. *Br J Surg* 2021; **108**: 128-137 [PMID: 33711141 DOI: 10.1093/bjs/znaa067]

28 **Feng Q**, Yuan W, Li T, Tang B, Jia B, Zhou Y, Zhang W, Zhao R, Zhang C, Cheng L, Zhang X, Liang F, He G, Wei Y, Xu J; REAL Study Group. Robotic versus laparoscopic surgery for middle and low rectal cancer (REAL): short-term outcomes of a multicentre randomised controlled trial. *Lancet Gastroenterol Hepatol* 2022; **7**: 991-1004 [PMID: 36087608 DOI: 10.1016/S2468-1253(22)00248-5]

29 **Park EJ**, Cho MS, Baek SJ, Hur H, Min BS, Baik SH, Lee KY, Kim NK. Long-term oncologic outcomes of robotic low anterior resection for rectal cancer: a comparative study with laparoscopic surgery. *Ann Surg* 2015; **261**: 129-137 [PMID: 24662411 DOI: 10.1097/SLA.0000000000000613]

30 **Feroci F**, Vannucchi A, Bianchi PP, Cantafio S, Garzi A, Formisano G, Scatizzi M. Total mesorectal excision for mid and low rectal cancer: Laparoscopic vs robotic surgery. *World J Gastroenterol* 2016; **22**: 3602-3610 [PMID: 27053852 DOI: 10.3748/wjg.v22.i13.3602]

31 **Ose I**, Perdawood SK. A nationwide comparison of short-term outcomes after transanal, open, laparoscopic, and robot-assisted total mesorectal excision. *Colorectal Dis* 2021; **23**: 2671-2680 [PMID: 34273239 DOI: 10.1111/codi.15809]

32 **Xu J**, Tang B, Li T, Jia B, Yao H, Zhao R, Yuan W, Zhong M, Chi P, Zhou Y, Yang X, Cheng L, He Y, Li Y, Tong W, Sun X, Jiang Z, Wang K, Li X, Wang X, Wei Y, Chen Z, Zhang X, Ye Y, Han F, Tao K, Kong D, Wang Z, Zhang C, He G, Feng Q. Robotic colorectal cancer surgery in China: a nationwide retrospective observational study. *Surg Endosc* 2021; **35**: 6591-6603 [PMID: 33237468 DOI: 10.1007/s00464-020-08157-4]

33 **Burghgraef TA**, Hol JC, Rutgers ML, Crolla RMPH, van Geloven AAW, Hompes R, Leijtens JWA, Polat F, Pronk A, Smits AB, Tuynman JB, Verdaasdonk EGG, Verheijen PM, Sietses C, Consten ECJ. Laparoscopic Versus Robot-Assisted Versus Transanal Low Anterior Resection: 3-Year Oncologic Results for a Population-Based Cohort in Experienced Centers. *Ann Surg Oncol* 2022; **29**: 1910-1920 [PMID: 34608557 DOI: 10.1245/s10434-021-10805-5]

34 **Park SY**, Lee SM, Park JS, Kim HJ, Choi GS. Robot Surgery Shows Similar Long-term Oncologic Outcomes as Laparoscopic Surgery for Mid/Lower Rectal Cancer but Is Beneficial to ypT3/4 After Preoperative Chemoradiation. *Dis Colon Rectum* 2021; **64**: 812-821 [PMID: 33833141 DOI: 10.1097/DCR.0000000000001978]

35 **Valentini V**, van Stiphout RG, Lammering G, Gambacorta MA, Barba MC, Bebenek M, Bonnetain F, Bosset JF, Bujko K, Cionini L, Gerard JP, Rödel C, Sainato A, Sauer R, Minsky BD, Collette L, Lambin P. Nomograms for predicting local recurrence, distant metastases, and overall

survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. *J Clin Oncol* 2011; **29**: 3163-3172 [PMID: 21747092 DOI: 10.1200/JCO.2010.33.1595]

36 **Agger EA**, Jörgren FH, Lydrup MA, Buchwald PL. Risk of local recurrence of rectal cancer and circumferential resection margin: population-based cohort study. *Br J Surg* 2020; **107**: 580-585 [PMID: 32133651 DOI: 10.1002/bjs.11478]

37 **Agger E**, Jörgren F, Lydrup ML, Buchwald P. Circumferential Resection Margin is Associated With Distant Metastasis After Rectal Cancer Surgery: A Nation-wide Population-based Study Cohort. *Ann Surg* 2023; **277**: e346-e352 [PMID: 34793342 DOI: 10.1097/SLA.0000000000005302]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Machine learning prediction model for gray-level co-occurrence matrix features of synchronous liver metastasis in colorectal cancer

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Abstract

BACKGROUND

Synchronous liver metastasis (SLM) is a significant contributor to morbidity in colorectal cancer (CRC). There are no effective predictive device integration algorithms to predict adverse SLM events during the diagnosis of CRC.

AIM

To explore the risk factors for SLM in CRC and construct a visual prediction model based on gray-level co-occurrence matrix (GLCM) features collected from magnetic resonance imaging (MRI).

METHODS

Our study retrospectively enrolled 392 patients with CRC from Yichang Central People's Hospital from January 2015 to May 2023. Patients were randomly divided into a training and validation group (3:7). The clinical parameters and GLCM features extracted from MRI were included as candidate variables. The prediction model was constructed using a generalized linear regression model, random forest model (RFM), and artificial neural network model. Receiver operating characteristic curves and decision curves were used to evaluate the prediction model.

RESULTS

Among the 392 patients, 48 had SLM (12.24%). We obtained fourteen GLCM imaging data for variable screening of SLM prediction models. Inverse difference, mean sum, sum entropy, sum variance, sum of squares, energy, and difference variance were listed as candidate variables, and the prediction efficiency (area under the curve) of the subsequent RFM in the training set and internal validation

set was 0.917 [95% confidence interval (95%CI): 0.866-0.968] and 0.09 (95%CI: 0.858-0.960), respectively.

CONCLUSION
A predictive model combining GLCM image features with machine learning can predict SLM in CRC. This model can assist clinicians in making timely and personalized clinical decisions.

Key Words: Colorectal cancer; Synchronous liver metastasis; Gray-level co-occurrence matrix; Machine learning algorithm; Prediction model

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Core Tip: Our predictive model for synchronous liver metastasis (SLM) in colorectal cancer (CRC) patients can screen reliable predictive variables based on clinical features. This is crucial for predicting SLM in CRC and improving patient prognosis. Imaging omics is a discipline that has developed in recent years. Based on advanced deep learning algorithms, extracting imaging features will have practical clinical value for constructing prediction models for SLM in CRC. This study combines imaging and deep learning to construct an early warning prediction model, to provide necessary auxiliary predictions for the occurrence of SLM and guide clinical decision-making.

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INTRODUCTION

Colorectal cancer (CRC), the third most common malignant tumor worldwide, has a high incidence and mortality rate[1]. Approximately 25%-30% of patients with CRC experience synchronous liver metastasis (SLM), and SLM is one of the most common causes of death in this disease[2,3]. However, despite advancements in surgical interventions, only about 25% of patients are suitable for resection surgery, which is considered a major curative treatment for SLM in CRC[4-6]. As such, early detection of SLM from CRC is important for diagnosis, treatment, and improvement of patient prognosis.

Deep learning algorithms use reliable algorithm development that integrates computing, storage, networking, and other technologies. Machine learning (ML) is a branch of artificial intelligence that focuses on predicting patterns in data through the use of mathematical algorithms. These algorithms are popular for accurately calculating and predicting cancer risk events by combining potential risk factors of tumor development[7]. Existing research has focused on the deep learning applications and integration of different data types to develop decision support tools. However, the lack of alternative candidate parameters for predicting disease urgently needs to be addressed. Imaging is a major component of cancer screening, staging, monitoring, and the evaluation of the aforementioned[8]. In this study, we extracted grayscale features from magnetic resonance imaging (MRI) images from patients with CRC and constructed a gray-level co-occurrence matrix (GLCM) to quantitatively measure texture characteristics.

We utilized GLCM features to capture texture information and image texture specificity to screen candidate variables and to establish a prediction model for SLM that helps clinicians make decisions and provides guidance for early clinical diagnosis and treatment decisions.

MATERIALS AND METHODS

Study population

We retrospectively selected 392 patients with CRC from the Gastrointestinal Surgery Department of Yichang Central People's Hospital from January 2015 to May 2023. The inclusion criteria were as follows: (1) Patients diagnosed with CRC and undergoing surgery; (2) patients aged ≥ 18 years old; (3) patients with complete postoperative pathological information; (4) CRC is the only primary malignant tumor; and (5) patients undergoing preoperative MRI. The exclusion criteria included: (1) Patients who received neoadjuvant radiotherapy and chemotherapy before surgery; (2) patients with incomplete recorded baseline and pathological data; and (3) patients with positive surgical margins and distant metastasis other than SLM after tumor surgery. This retrospective study was approved by the Ethics Committee of Yichang Central People's Hospital, and the research protocol conforms to the accuracy of artificial intelligence model training while ensuring the confidentiality of personal privacy of all patients included in the study. The study received an informed consent exemption from the Ethics Committee. The process of incorporating patients and building prediction models is shown in Figure 1 and Supplementary Figure 1.

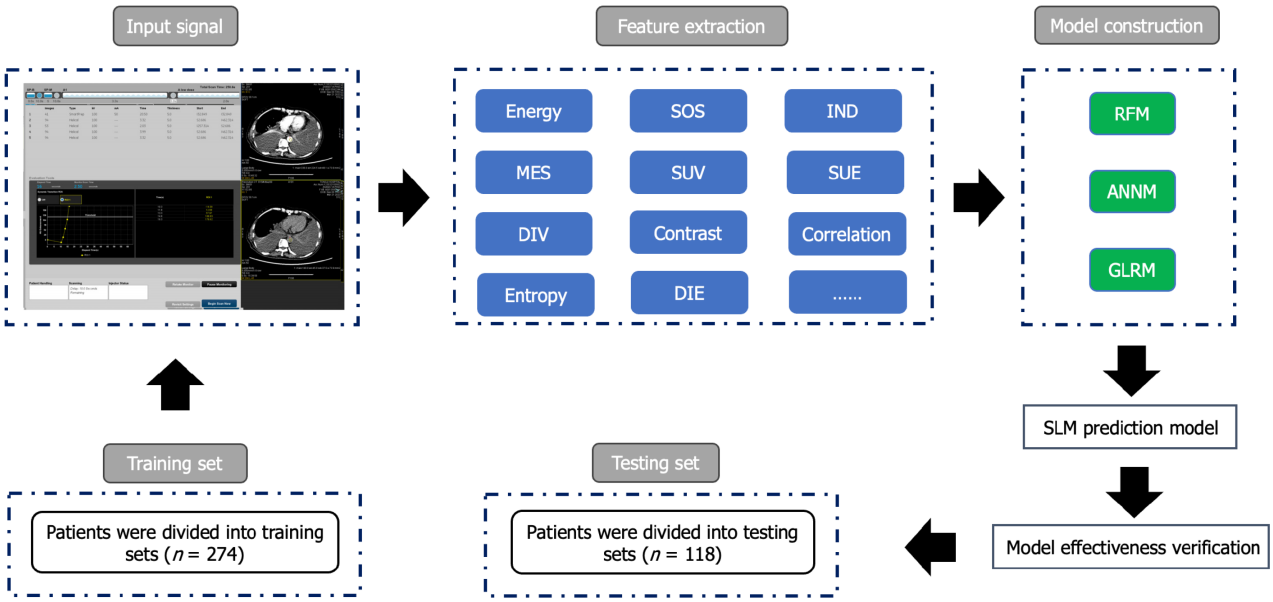


Figure 1 The flow chart of patient selection and data process. SOS: Sum of squares; IND: Inverse difference; MES: Mean sum; SUV: Sum variance; SUE: Sum entropy; DIV: Difference variance; DIE: Difference entropy; RFM: Random forest model; ANNM: Artificial neural network model; GLRM: Generalized linear regression model; SLM: Synchronous liver metastasis.

Diagnostic criteria of SLM

Synchronous detection of liver metastasis was defined as SLM detected before or during the resection of the primary tumor, and in the case of unresectable patients, it was defined as SLM detected before or simultaneously with the primary tumor.

Acquisition of MRI-based radiomic parameters

We used Skyra 3.0T or Avanto 1.5T MRI instruments (provided by Siemens) to perform abdominal imaging examinations. The parameter settings were as follows: T2W1, TR 2500 ms, TE 83 ms, layer spacing 1.8 mm, layer thickness 6.0 mm, matrix 352 × 352, FOV 36 cm × 36 cm; The *b* values of DWI were set to 50 and 800, respectively. A vibe sequence was used for enhanced scanning, with TR 3.97 ms, TE 1.29 ms, and FOV 36 cm × 36 cm. Glucosamine gadolinium pentobate (*i.e.*, Magentavir, 0.2 mL/kg) was injected through the elbow vein at a rate of 2.0 mL/s, followed by 20.0 mL of physiological saline. We used an independent blind method to analyze the MRI images, including the maximum diameter of colorectal liver metastases (CRLM) before enhancement, the maximum diameter of CRLM during arterial phase, the edge of CRLM after enhancement, edge enhancement, and peripheral parenchymal enhancement.

Data entry and quality control analysis

To ensure the accuracy of data input, we used the following strategies. Firstly, the clinical baseline data and imaging data of patients were independently entered by two people, and the final analysis was proofread. Secondly, both imaging data and review were completed by two senior radiologists (with more than 7 years of experience). If there was a disagreement between the two during the film review, a third party made a ruling. Finally, all records included in this study had less than 5% missing data. Candidate variables exceeding this threshold were imputed using missing values (*i.e.*, median or mean imputation). If the missing value was greater than 10%, it was discarded immediately.

Training and verification of the segmentation model

We automatically extracted imageomics features (*i.e.*, T2W1 and VP images) from the VOIs of each patient's enhanced venous phase MRI image, including first-order features, morphological features, texture features, and filter-based higher-order features. These features were obtained by analyzing the original image and applying multiple filters to the derived images, including exponential filters, square filters, square root filters, logarithmic filters, and wavelet decomposition. Image texture features (*i.e.*, exponent, square, square root, logarithm, and wavelet transform) were divided into three subgroups: GLCM, including the sum of squares (SOS), mean sum (MES), the inverse difference (IND), sum entropy (SUE), correlation, sum variance (SUV), difference entropy (DIE), difference variance (DIV), energy, entropy, entropy, and contrast, grayscale length matrix, and grayscale shape matrix. In addition, wavelet decomposition included three-dimensional wavelet transform with low-pass filtering and high-pass filtering to quantitatively capture MRI image features.

We adopted a random grouping method (70% and 30% were included in the training and internal validation sets, respectively). In addition, we use lasso regression (*i.e.*, with minimum penalty coefficient and Pearson correlation coefficient) to select candidate predictive variables to use to construct SLM prediction models. We used three popular ML algorithms, namely the generalized linear regression model (GLRM), random forest model (RFM), and artificial neural

network model (ANNM), to construct a visual prediction model for SLM[9-12]. We chose the minimum absolute shrinkage and selection operator algorithm and then constructed an SLM prediction model based on MRI features[13]. We used decision curve analysis (DCA)[14], receiver operating characteristic (ROC), and clinical impact curves (CIC) to evaluate the predictive performance of each predictive model[15].

Statistical analysis

The categorical variables and continuous variables involved in this statistical analysis were tested using the chi-square test, Wilcoxon rank sum test, or *T*-test, respectively. As for the correlation analysis between two continuous variables, we used the Pearson correlation coefficient evaluation[16]. We used R studio software for data visualization and statistical analysis. A *P* value less than 0.05 was considered statistically significant.

RESULTS

Comparison of clinical characteristics between SLM and non-SLM groups

In the study, a total of 392 patients with CRC were included for SLM prediction model construction. Among them, 48 and 344 patients were assigned to the SLM group and non-SLM group, respectively. The incidence of SLM in the training and validation sets was 13.87% (38/274) and 8.47% (10/118), respectively. The baseline data of the two groups of patients with CRC are summarized in Table 1 and Supplementary Table 1.

Selection of candidate variables for constructing SLM prediction models

Considering that the candidate variables have biases and non-normal distributions, we performed loss function correction (*i.e.*, added penalty coefficients) to facilitate the selection of the optimal variables. By setting penalty coefficients, we ensured that the coefficients of features with smaller impacts will be infinitely close to zero [*i.e.*, least absolute shrinkage and selection operator (LASSO) regression coefficient screening] to ensure that important features are retained. In the subsequent prediction model construction, we selected candidate variables from 21 variables based on the LASSO coefficient curve to construct independent variables for predicting the risk of SLM. The independent variables were tumor type, vascular invasion, energy, SOS, IND, MES, SUV, SUE, and DIV (Figure 2).

Construction of SLM nomogram prediction model

We conducted a logistic regression analysis on all candidate variables (Supplementary Table 2) and ultimately established 9 variables as independent risk predictors for SLM. Based on the Akaike information criterion, we then established a prediction model for SLM and drew a nomogram (Figure 3; Supplementary Table 2). Finally, with the help of nomogram visualization analysis, we evaluated the specific risk coefficient of SLM in patients based on the corresponding risk scale values of the total score. In addition, the C-index value, validated internally by the bootstrap method, was 0.739, indicating that the predictive model had good clinical robustness.

Construction of the ML-based SLM prediction model

RFM and ANNM are the most commonly used algorithms in ML[9]. In this study, we established SLM prediction models based on four ML algorithms. As shown in Supplementary Table 3, in the RFM prediction model, IND, MES, SUE, DIV, SOS energy, and SUV were the top-ranking weight values, indicating that these variables are potential candidate variables for RFM prediction of SLM (Figure 4). Meanwhile, ANNM, IND, MES, SUE, DIV, SOS energy, and SUV were candidate variables to predict SLM, and their weight proportions in the three different algorithm prediction models did not match, highlighting the different prediction weights of candidate variables (Figure 5; Supplementary Table 4).

Performance of SLM prediction models

The ROC curve showed that the predictive efficacy of RFM in predicting SLM in the training and validation sets was area under the curve (AUC): 0.917 [95% confidence interval (95%CI): 0.866-0.680] and AUC: 0.09 (95%CI: 0.858-0.960), respectively. The ROC curve of ANNM in predicting SLM in the training and validation sets was AUC: 0.796 (95%CI: 0.745-0.847) and AUC: 0.806 (95%CI: 0.755-0.857), respectively, indicating that the predictive efficacy was not as good as RFM. Table 2 and Supplementary Figure 2 show the predictive performance of preoperative GLCM-based radiomics for SLM. Overall, the predictive efficiency of the SLM models based on ML algorithms for patients with CRC is significantly better than GLRM.

In Figure 6, the horizontal and vertical axes of DCA represent the threshold probability and net benefit, respectively. The black horizontal line indicated that when all patients had no SLM status, the net benefit rate was zero. Conversely, the gray diagonal line indicated the gap between all SLM patients receiving treatment and their ideal state. The DCA curve can assist in guiding the clinical performance of predictive models, thereby evaluating the superiority or inferiority of these models.

Performance evaluation of SLM prediction model based on ML

To further evaluate the discriminative efficiency of the RFM prediction models, we used CIC. As shown in Supplementary Figure 3, RFM can distinguish SLM patients and was highly consistent with the postoperative pathological examination results. Our research indicates that RFM, as a predictive tool for evaluating SLM in patients with CRC, has high predictive reliability and may be used as a clinical decision aid. This also shows that RFM is more suitable for

Table 1 Clinicopathological characteristics of patients with colorectal cancer, *n* (%)

Variables	Overall (*n* = 392)
Age, yr	
≥ 60	215 (54.8)
< 60	177 (45.2)
Sex	
Male	194 (49.5)
Female	198 (50.5)
BMI, kg/m^2	
≤ 18.5	101 (25.8)
18.5-23.9	89 (22.7)
24.0-27.9	104 (26.5)
≥ 28.0	98 (25.0)
Smoking	
Yes	201 (51.3)
No	191 (48.7)
Drinking	
Yes	222 (56.6)
No	170 (43.4)
Intestinal polyp	
Yes	180 (45.9)
No	212 (54.1)
AST, U/L	
< 40	203 (51.8)
≥ 40	189 (48.2)
ALT, U/L	
< 50	179 (45.7)
≥ 50	213 (54.3)
Hypertension	
Yes	180 (45.9)
No	212 (54.1)
Diabetes	
Yes	183 (46.7)
No	209 (53.3)
CEA, ng/mL	
Normal	216 (55.1)
Abnormal	176 (44.9)
CA199, U/mL	
Normal	194 (49.5)
Abnormal	198 (50.5)
AFP, ng/mL	
≤ 100	191 (48.7)
> 100	201 (51.3)

HbsAg	
Yes	203 (51.8)
No	189 (48.2)
Tumor type	
Adenocarcinoma	211 (53.8)
Mucinous adenocarcinoma	181 (46.2)
Tumor size, cm	
< 5	204 (52.0)
≥ 5	188 (48.0)
NI	
Yes	180 (45.9)
No	212 (54.1)
VI	
Yes	134 (34.2)
No	258 (65.8)
Energy, median [IQR]	3.91 [2.55, 5.62]
SOS, median [IQR]	0.88 [0.69, 1.05]
IND, median [IQR]	1.46 [1.17, 1.80]
MES, median [IQR]	2.84 [1.94, 3.36]
SUV, median [IQR]	20.90 [16.28, 25.33]
SUE, median [IQR]	22.20 [17.10, 27.10]
DIV, median [IQR]	87.50 [67.00, 107.00]
Contrast, median [IQR]	291.00 [275.00, 308.00]
Correlation, median [IQR]	16.13 [12.00, 19.22]
Entropy, median [IQR]	2.17 [1.62, 2.64]
DIE, median [IQR]	230.00 [188.00, 276.00]

IQR: Inter-quartile range; BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen199; AFP: Alpha-fetoprotein; NI: Neural infiltration; VI: Vascular invasion; SOS: Sum of squares; IND: Inverse difference; MES: Mean sum; SUV: Sum variance; SUE: Sum entropy; DIV: Difference variance; DIE: Difference entropy; HbsAg: Hepatitis B surface antigen.

Table 2 Comparison of predictive efficacy of pulmonary infection prediction models *via* receiver operating characteristic curves

Model	Training set			Internal validation set		
	AUC mean	AUC 95%CI	Variables[1]	AUC mean	AUC 95%CI	Variables[1]
RFM	0.917	0.866-0.968	7	0.909	0.858-0.960	7
ANNM	0.796	0.745-0.847	7	0.806	0.755-0.857	7
GLRM	0.783	0.732-0.834	6	0.739	0.688-0.790	6

[1]Variables included in the model.
RFM: Random forest model; GLRM: Generalized linear regression model; AUC: Area under the curve; 95%CI: 95% confidence interval; ANNM: Artificial neural network model.

preoperative risk assessment in SLM.

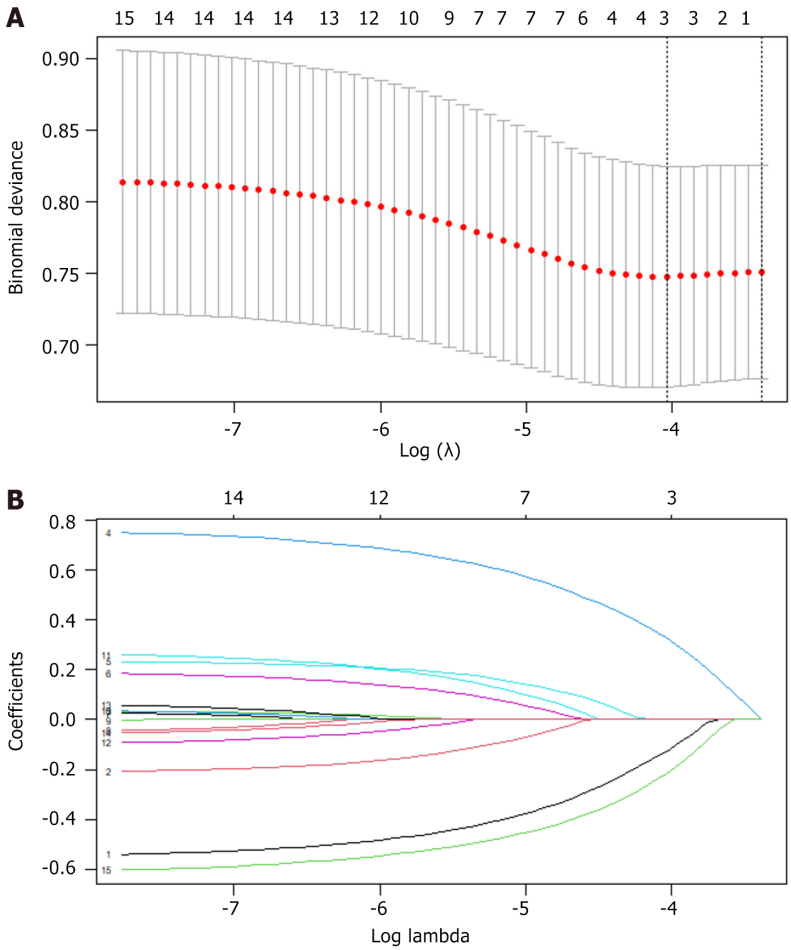


Figure 2 Predictor variable selection based on the least absolute shrinkage and selection operator regression method. A: Optimal parameter (lambda) selection in the least absolute shrinkage and selection operator (LASSO) model; B: LASSO coefficient profiles of the candidate features.

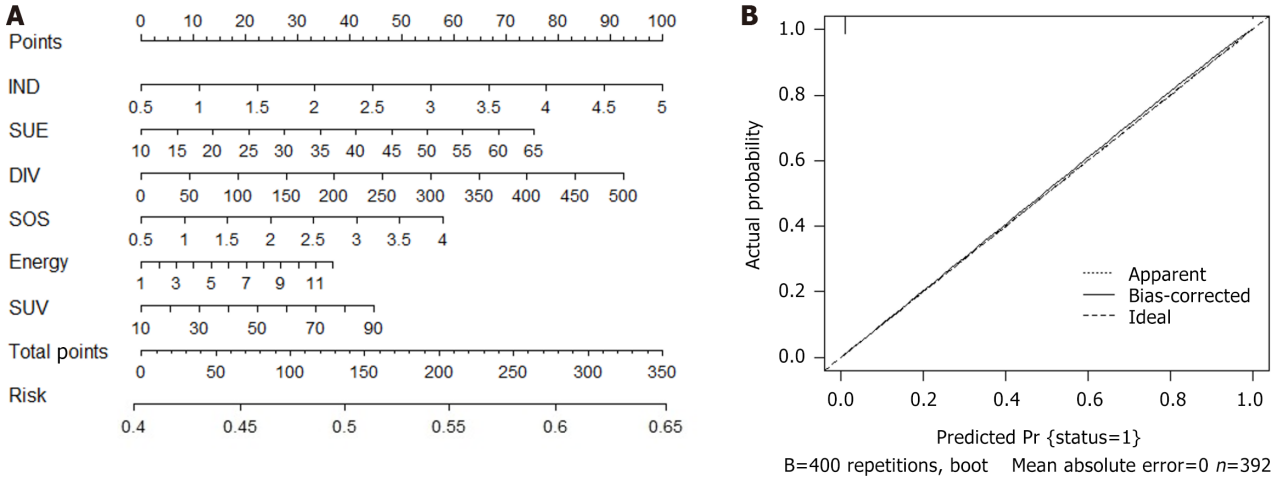


Figure 3 Nomogram prediction model for predicting synchronous liver metastasis in patients with colorectal cancer. A: Nomogram predicts risk of synchronous liver metastasis; B: The calibration curves for the nomogram. IND: Inverse difference; SUE: Sum entropy; DIV: Difference variance; SOS: Sum of squares; SUV: Sum variance.

DISCUSSION

CRC is one of the main contributors to global cancer incidence and mortality. Distant metastasis is the predominant reason for poor patient prognosis and the liver is the most common metastatic organ[17,18]. Previous studies have shown that the survival rate of patients with regional or distal CRC is low, and if there is no metastasis, the prognosis is better[2, 19]. Over 25% of patients with CRC have SLM detected at the first diagnosis, and up to 25% have SLM detected after

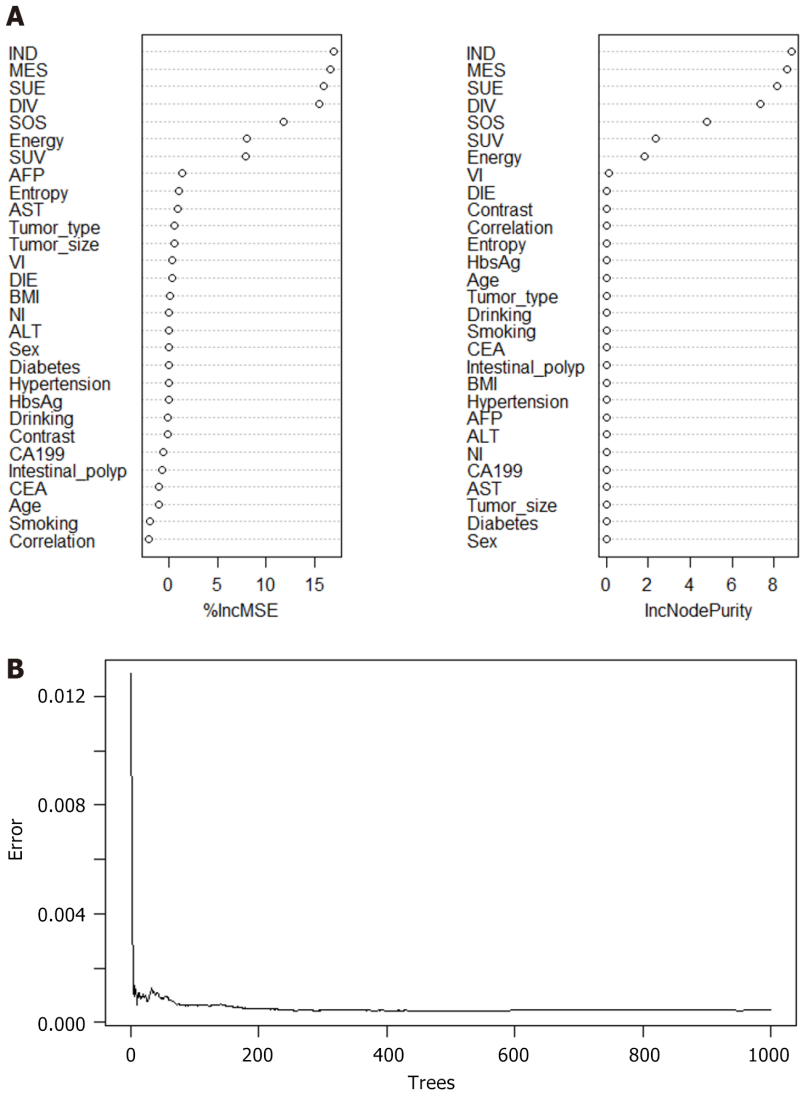


Figure 4 Construction of synchronous liver metastasis prediction model *via* random forest model. A: The application prediction model formula of random forest model (RFM) is as follows: C = argmax (∑ (Ci)), where "Ci" represents the type of in prediction for the i-th tree, "C" is the final classification result, and "I" is the number of trees; B: The gravel plot indicates the robustness of the RFM prediction model. IND: Inverse difference; MES: Mean sum; SUV: Sum variance; SUE: Sum entropy; DIV: Difference variance; DIE: Difference entropy; RFM: Random forest model; ANNM: Artificial neural network model; GLRM: Generalized linear regression model; SLM: Synchronous liver metastasis; BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen 199; AFP: Alpha-fetoprotein; NI: Neural infiltration; VI: Vascular invasion; HbsAg: Hepatitis B surface antigen.

primary tumor resection[20-22]. More than one-third of patients with CRC already have cancer development into all liver tissues when SLM is diagnosed[23]. Early detection can lead to early treatment and reduce mortality. Thus, effective SLM biomarkers may contribute to early treatment management. In this study, we constructed a GLCM composed of MRI, which has the potential to evaluate SLM in CRC patients based on feature-based risk scoring. We found that indicates that preoperative MRI examination and texture analysis using sequence images in CRC have significant application prospects in the risk stratification of SLM.

Although radiomic models have been increasingly used in computer-aided diagnosis and imaging biomarkers, their application in computed tomography or MRI is limited by the variability of image characteristics generated by different scanners, imaging protocols, patient anatomies, and increasingly diverse reconstruction and post-processing software[24, 25]. While these effects can be mitigated through careful data management and protocol standardization, these measures are impractical for applying to different sources of image data. In this study, we adopted a generalized traditional end-to-end imaging system model, using radiomic calculations as an explicit stage[26]. This model not only predicts unexpected variability in radiomics but also forms an estimation of the true potential of radiomics. This framework has the potential to standardize radiomics under imaging conditions, making radiomics more widely applicable. We added candidate variables with predicted values to the ML-based algorithm model, and the results showed that the GLCM-based prediction efficiency reaches the highest of 0.917 without distinguishing the predicted variables.

ML can handle complex phenomena through data-driven analysis[27]. Compared with traditional methods, ML significantly reduces the prediction error of trajectories[28,29]. Consistent with previous studies, this study also indicates that due to the continuous updating of predictive model algorithms, ML models typically provide better predictive

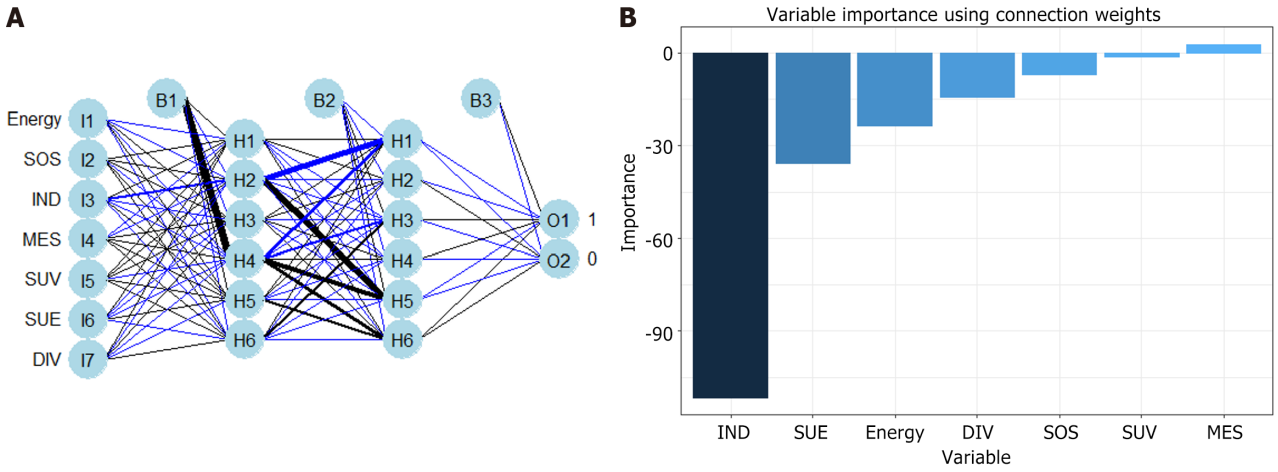


Figure 5 Construction of pulmonary infection prediction model *via* artificial neural network model. A: The formula of artificial neural network model is as follows: θ = θ-η × ∇ (θ).J (θ). Among them "η" is the learning rate, "so (θ).J (θ)" represents the gradient change of the loss function [*i.e.*, J(θ)]; B: Variable importance using connection weights for the artificial neural network model. IND: Inverse difference; SUV: Sum variance; SUE: Sum entropy; DIV: Difference variance; SOS: Sum of squares; MES: Mean sum.

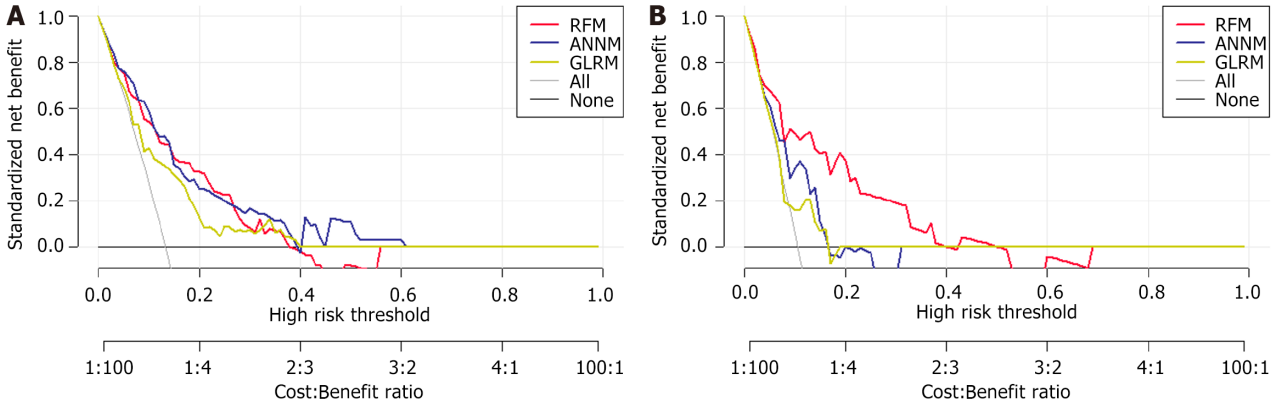


Figure 6 Prediction performance of synchronous liver metastasis risk based on different supervised algorithm. A: Decision curve analysis (DCA) for three prediction models in the training set; B: DCA for three prediction models in the testing set. RFM: Random forest model; ANNM: Artificial neural network model; GLRM: Generalized linear regression model.

performance than traditional linear models[30]. These models can effectively utilize limited data and improve the robustness of prediction models by transferring existing similar models or training them repeatedly. For example, the best prediction model trained in this study, RFM, had superior robustness and prediction accuracy compared to traditional linear regression models. These results further confirm the generalizability and clinical applicability of deep learning in combining radiomics to predict synchronous SLM.

This study has some limitations. Firstly, due to the standard requirements of the acquisition of MRI parameters and equipment, the sample size included in this study is relatively small and comes from a single center. Future prospective cohort studies encompassing multiple centers and large samples should be conducted. Secondly, as a retrospective study, there is inevitably selection bias in the inclusion of research subjects, as well as potential bias caused by personal experience or non-objective factors. Thirdly, this study obtained GLCM-related parameters based on MRI but did not include features such as high-order textures in the analysis. Therefore, it is necessary to optimize and expand the filtering of high-order texture parameters in subsequent research, to obtain more candidate variables with potential predictive value to construct better SLM prediction models.

CONCLUSION

Combining ML-based algorithms with readily available GLCM radiomic features can quickly and accurately assess the risk of SLM in patients with CRC before surgery. In particular, algorithms based on RFM can help clinicians identify high-risk patients with SLM promptly, and make robust surgical decisions.

FOOTNOTES

Author contributions: Zheng YB is responsible for the conceptualization and design of this project; Yang KF and Zheng YB are responsible for manuscript writing and monitoring the progress of the project; Li SJ and Xu J are responsible for data collection, analysis, and visualization; and all authors shall verify and submit the manuscript.

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REFERENCES

1 **Dekker E**, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. *Lancet* 2019; **394**: 1467-1480 [PMID: 31631858 DOI: 10.1016/S0140-6736(19)32319-0]
2 **Engstrand J**, Nilsson H, Strömberg C, Jonas E, Freedman J. Colorectal cancer liver metastases - a population-based study on incidence, management and survival. *BMC Cancer* 2018; **18**: 78 [PMID: 29334918 DOI: 10.1186/s12885-017-3925-x]
3 **Adam R**, De Gramont A, Figueras J, Guthrie A, Kokudo N, Kunstlinger F, Loyer E, Poston G, Rougier P, Rubbia-Brandt L, Sobrero A, Tabernero J, Teh C, Van Cutsem E; Jean-Nicolas Vauthey of the EGOSLIM (Expert Group on OncoSurgery management of LIver Metastases) group. The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. *Oncologist* 2012; **17**: 1225-1239 [PMID: 22962059 DOI: 10.1634/theoncologist.2012-0121]
4 **Hackl C**, Neumann P, Gerken M, Loss M, Klinkhammer-Schalke M, Schlitt HJ. Treatment of colorectal liver metastases in Germany: a ten-year population-based analysis of 5772 cases of primary colorectal adenocarcinoma. *BMC Cancer* 2014; **14**: 810 [PMID: 25369977 DOI: 10.1186/1471-2407-14-810]
5 **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]
6 **House MG**, Ito H, Gönen M, Fong Y, Allen PJ, DeMatteo RP, Brennan MF, Blumgart LH, Jarnagin WR, D'Angelica MI. Survival after hepatic resection for metastatic colorectal cancer: trends in outcomes for 1,600 patients during two decades at a single institution. *J Am Coll Surg* 2010; **210**: 744-752, 752 [PMID: 20421043 DOI: 10.1016/j.jamcollsurg.2009.12.040]
7 **Tran KA**, Kondrashova O, Bradley A, Williams ED, Pearson JV, Waddell N. Deep learning in cancer diagnosis, prognosis and treatment selection. *Genome Med* 2021; **13**: 152 [PMID: 34579788 DOI: 10.1186/s13073-021-00968-x]
8 **Kijima S**, Sasaki T, Nagata K, Utano K, Lefor AT, Sugimoto H. Preoperative evaluation of colorectal cancer using CT colonography, MRI, and PET/CT. *World J Gastroenterol* 2014; **20**: 16964-16975 [PMID: 25493009 DOI: 10.3748/wjg.v20.i45.16964]
9 **Uddin S**, Khan A, Hossain ME, Moni MA. Comparing different supervised machine learning algorithms for disease prediction. *BMC Med Inform Decis Mak* 2019; **19**: 281 [PMID: 31864346 DOI: 10.1186/s12911-019-1004-8]
10 **Choi RY**, Coyner AS, Kalpathy-Cramer J, Chiang MF, Campbell JP. Introduction to Machine Learning, Neural Networks, and Deep Learning. *Transl Vis Sci Technol* 2020; **9**: 14 [PMID: 32704420 DOI: 10.1167/tvst.9.2.14]
11 **Ghiasi MM**, Zendehboudi S, Mohsenipour AA. Decision tree-based diagnosis of coronary artery disease: CART model. *Comput Methods Programs Biomed* 2020; **192**: 105400 [PMID: 32179311 DOI: 10.1016/j.cmpb.2020.105400]
12 **Huang S**, Cai N, Pacheco PP, Narrandes S, Wang Y, Xu W. Applications of Support Vector Machine (SVM) Learning in Cancer Genomics. *Cancer Genomics Proteomics* 2018; **15**: 41-51 [PMID: 29275361 DOI: 10.21873/cgp.20063]

13 **Alhamzawi R**, Ali HTM. The Bayesian adaptive lasso regression. *Math Biosci* 2018; **303**: 75-82 [PMID: 29920251 DOI: 10.1016/j.mbs.2018.06.004]

14 **Van Calster B**, Wynants L, Verbeek JFM, Verbakel JY, Christodoulou E, Vickers AJ, Roobol MJ, Steyerberg EW. Reporting and Interpreting Decision Curve Analysis: A Guide for Investigators. *Eur Urol* 2018; **74**: 796-804 [PMID: 30241973 DOI: 10.1016/j.eururo.2018.08.038]

15 **Hou N**, Li M, He L, Xie B, Wang L, Zhang R, Yu Y, Sun X, Pan Z, Wang K. Predicting 30-days mortality for MIMIC-III patients with sepsis-3: a machine learning approach using XGboost. *J Transl Med* 2020; **18**: 462 [PMID: 33287854 DOI: 10.1186/s12967-020-02620-5]

16 **Fay MP**, Malinovsky Y. Confidence intervals of the Mann-Whitney parameter that are compatible with the Wilcoxon-Mann-Whitney test. *Stat Med* 2018; **37**: 3991-4006 [PMID: 29984411 DOI: 10.1002/sim.7890]

17 **Siegel RL**, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2020. *CA Cancer J Clin* 2020; **70**: 145-164 [PMID: 32133645 DOI: 10.3322/caac.21601]

18 **van der Geest LG**, Lam-Boer J, Koopman M, Verhoef C, Elferink MA, de Wilt JH. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. *Clin Exp Metastasis* 2015; **32**: 457-465 [PMID: 25899064 DOI: 10.1007/s10585-015-9719-0]

19 **Willem H**, Jooste V, Boussari O, Romain G, Bouvier AM. Impact of absence of consensual cutoff time distinguishing between synchronous and metachronous metastases: illustration with colorectal cancer. *Eur J Cancer Prev* 2019; **28**: 167-172 [PMID: 29738323 DOI: 10.1097/CEJ.0000000000000450]

20 **Al Bandar MH**, Kim NK. Current status and future perspectives on treatment of liver metastasis in colorectal cancer (Review). *Oncol Rep* 2017; **37**: 2553-2564 [PMID: 28350137 DOI: 10.3892/or.2017.5531]

21 **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]

22 **Robinson JR**, Newcomb PA, Hardikar S, Cohen SA, Phipps AI. Stage IV colorectal cancer primary site and patterns of distant metastasis. *Cancer Epidemiol* 2017; **48**: 92-95 [PMID: 28437692 DOI: 10.1016/j.canep.2017.04.003]

23 **Wang SH**, Song L, Tang JY, Sun WP, Li Z. Safety and long-term prognosis of simultaneous versus staged resection in synchronous colorectal cancer with liver metastasis: a systematic review and meta-analysis. *Eur J Med Res* 2022; **27**: 297 [PMID: 36529740 DOI: 10.1186/s40001-022-00937-z]

24 **Gang GJ**, Deshpande R, Stayman JW. End-to-end Modeling for Predicting and Estimating Radiomics: Application to Gray Level Co-occurrence Matrices in CT. *Proc SPIE Int Soc Opt Eng* 2021; **11595** [PMID: 34621102 DOI: 10.1117/12.2582150]

25 **Larue RT**, Defraene G, De Ruysscher D, Lambin P, van Elmpt W. Quantitative radiomics studies for tissue characterization: a review of technology and methodological procedures. *Br J Radiol* 2017; **90**: 20160665 [PMID: 27936886 DOI: 10.1259/bjr.20160665]

26 **Mackin D**, Fave X, Zhang L, Fried D, Yang J, Taylor B, Rodriguez-Rivera E, Dodge C, Jones AK, Court L. Measuring Computed Tomography Scanner Variability of Radiomics Features. *Invest Radiol* 2015; **50**: 757-765 [PMID: 26115366 DOI: 10.1097/RLI.0000000000000180]

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

28 **Sultan AS**, Elgharib MA, Tavares T, Jessri M, Basile JR. The use of artificial intelligence, machine learning and deep learning in oncologic histopathology. *J Oral Pathol Med* 2020; **49**: 849-856 [PMID: 32449232 DOI: 10.1111/jop.13042]

29 **Rauschert S**, Raubenheimer K, Melton PE, Huang RC. Machine learning and clinical epigenetics: a review of challenges for diagnosis and classification. *Clin Epigenetics* 2020; **12**: 51 [PMID: 32245523 DOI: 10.1186/s13148-020-00842-4]

30 **Zhou H**, Tang J, Zheng H. Machine learning for medical applications. *ScientificWorldJournal* 2015; **2015**: 825267 [PMID: 25692180 DOI: 10.1155/2015/825267]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Risk factors associated with intraoperative persistent hypotension in pancreaticoduodenectomy

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Abstract

BACKGROUND

Intraoperative persistent hypotension (IPH) during pancreaticoduodenectomy (PD) is linked to adverse postoperative outcomes, yet its risk factors remain unclear.

AIM

To clarify the risk factors associated with IPH during PD, ensuring patient safety in the perioperative period.

METHODS

A retrospective analysis of patient records from January 2018 to December 2022 at the First Affiliated Hospital of Nanjing Medical University identified factors associated with IPH in PD. These factors included age, gender, body mass index, American Society of Anesthesiologists classification, comorbidities, medication history, operation duration, fluid balance, blood loss, urine output, and blood gas parameters. IPH was defined as sustained mean arterial pressure < 65 mmHg, requiring prolonged deoxyepinephrine infusion for > 30 min despite additional deoxyepinephrine and fluid treatments.

RESULTS

Among 1596 PD patients, 661 (41.42%) experienced IPH. Multivariate logistic regression identified key risk factors: increased age [odds ratio (OR): 1.20 per decade, 95% confidence interval (CI): 1.08-1.33] (P < 0.001), longer surgery duration (OR: 1.15 per additional hour, 95%CI: 1.05-1.26) (P < 0.01), and greater blood loss (OR: 1.18 per 250-mL increment, 95%CI: 1.06-1.32) (P < 0.01). A novel finding was the association of arterial blood Ca^{2+} < 1.05 mmol/L with IPH (OR:

2.03, 95%CI: 1.65-2.50) ($P < 0.001$).

CONCLUSION
IPH during PD is independently associated with older age, prolonged surgery, increased blood loss, and lower plasma Ca^{2+}.

Key Words: Risk factors; Pancreaticoduodenectomy; Perioperative period; Intraoperative persistent hypotension; Retrospective cohort study

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Core Tip: This study examines risk factors for intraoperative persistent hypotension (IPH) in pancreaticoduodenectomy. Key risk factors include patient age, prolonged surgery duration, greater blood loss, and lower calcium levels. Prompt recognition and early intervention can effectively mitigate IPH in these operations.

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INTRODUCTION

Intraoperative hypotension, even brief episodes lasting 1-5 min, is closely associated with postoperative adverse outcomes[1]. Intraoperative persistent hypotension (IPH), generally requiring a continuous administration of vasopressors, can lead to severe complications and poor prognoses during and after extensive surgical procedures[2-4]. Such phenomena may arise from impaired blood pressure regulation resulting from the vasodilatory effects of anesthetics, surgery-related inflammation or insufficient circulating blood volume[5].

Pancreaticoduodenectomy (PD) as a complex and challenging abdominal operation has been reported to have a high incidence with IPH following long surgical procedures of extensive digestive tract reconstruction and multiple anastomoses[6]. IPH during PD is suggested to be related to the vascular paralysis seen in cardiac surgery; primarily characterized by a reduction in peripheral vascular resistance[7-9]. The small arteries located anterior to the capillaries predominantly determine peripheral vascular resistance, which is influenced by the autonomic nervous system, self-regulation, endothelial-cell-derived molecules and inflammatory factors[10]. The increased inflammatory markers, such as C-reactive protein, can increase the risk for severe hypotension and vasopressor dependency during postoperative day 1 after PD[11]. A more positive fluid balance commonly seen in PD implicates inadequate circulating blood volume in the risk of IPH. However, the underlying risk factors for PD-related IPH are still not clear. Identifying such risk factors is crucial for early detection and treatment of IPH, thereby reducing severe postoperative complications.

Given the limited research on IPH in PD, we conducted a comprehensive retrospective data analysis to investigate its associated risk factors. We found that these risk factors for the IPH during PD were linked to older patients, longer surgical procedures, more blood loss and decreased plasma Ca^{2+} concentration.

MATERIALS AND METHODS

Study population

We retrospectively analyzed 2432 patients who underwent open PD at the First Affiliated Hospital of Nanjing Medical University between January 2018 and December 2022. We included 1596 patients based on the inclusion and exclusion criteria. Among them, 661 patients were assigned to the IPH group, and the remaining 935 patients who did not experience persistent hypotension were assigned to the non-IPH group.

Inclusion and exclusion criteria

Inclusion criteria: Patients who underwent open PD under general anesthesia; American Society of Anesthesiologists (ASA) class I-III; aged 18-80 years.

Exclusion criteria: Patients diagnosed with distant metastasis; patients undergoing local or palliative pancreatic surgery; ASA class IV or higher; patients exhibiting cancerous changes in organs other than the metastasis site; patients undergoing neoadjuvant chemotherapy prior to surgery; age < 18 years or > 80 years; and pregnant women.

Clinical data and indices

The digitized anesthesia records were automatically reviewed to identify patients meeting the inclusion criteria. Only data from eligible patients were included in subsequent analyses. To minimize the impact of missing data, we conducted a comprehensive manual review and collected supplementary information from medical records. Key medical indicators, such as age, gender, body mass index (BMI), ASA classification, pre-existing comorbidities, long-term medication, surgery duration, total intake, excess intake, blood loss, urine output, and blood gas analysis (including pH, $PaCO_2$, HCO_3^-, hemoglobin, lactic acid, Ca^{2+}, mean blood glucose concentration, and glucose variability), were extracted. Supplementary data encompassing preoperative surgery and anesthesia-related details, along with hemodynamic measurements, were compiled for evaluation.

IPH

The definition of perioperative hypotension remains undecided. However, the majority of studies adopt mean arterial pressure (MAP) < 65 mmHg as a benchmark for defining preoperative hypotension[12-15]. In our study, IPH was characterized by hemodynamic instability with MAP < 65 mmHg, necessitating continuous deoxyepinephrine administration for > 30 min, even after repeated bolus administration of deoxyepinephrine and fluid therapy.

Outcome measures

The primary outcomes involved factors associated with IPH, comprising age, ASA classification, preoperative hypertension, preoperative albumin concentration, surgical duration, arterial blood Ca^{2+} concentration, total intake, excess intake, blood loss, lactic acid concentration, mean blood glucose, and glucose variability. The secondary outcome focused on the incidence of IPH during PD.

Statistical analysis

Patient baseline characteristics were compared between the IPH and non-IPH groups for the normality of continuous data using the Kolmogorov-Smirnov test. Results were presented as mean ± SD for normally distributed data and as median (interquartile range) for non-normally distributed continuous data. The independent samples *t*-test and Mann-Whitney *U* test were utilized to compare mean and median data, respectively, between the groups. The categorical variables were analyzed using the χ^2 or Fisher's exact test, with results presented as percentages. For ordered categorical variables, such as the ASA classification, comparison was conducted using the Mann-Whitney *U* test, and outcomes were likewise expressed in terms of percentages. Univariate logistic regression analyses were used to assess the relationship of various factors with IPH during PD. Significant variables ($P < 0.05$) were incorporated into a backward elimination multivariate logistic regression model to identify independent risk factors associated with IPH. Statistical analysis was conducted using R 4.3.1 software (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). The study was reviewed by our biostatistics expert (Nana Li).

RESULTS

Baseline characteristics

Our study included 1596 patients, among whom 661 (41.42%) experienced IPH (Figure 1). There were no observed significant differences in gender, BMI, preoperative blood gas analysis, and biochemical indicators between the two groups. However, significant differences were noted in age, ASA classification, and preoperative history of hypertension, diabetes mellitus ($P < 0.001$) and albumin level ($P < 0.01$) (Table 1). Notably, patients aged > 60 years showed a higher propensity for IPH. Patients experiencing IPH were older, had higher ASA classification, and had a documented history of hypertension and diabetes mellitus, in addition to lower preoperative albumin levels, in comparison to those without IPH.

Intraoperative comparative analysis

The patients in the IPH group underwent longer surgical procedures (4.75 h *vs* 4.45 h, $P < 0.001$) and received higher volumes of intraoperative fluids (3100 mL *vs* 2760 mL, $P < 0.001$), comprising crystalloids, colloids and blood transfusion (Table 2). Additionally, this group experienced more blood loss (350 mL *vs* 300 mL, $P < 0.001$), with a higher proportion exhibiting 500-1000 mL of bleeding. In terms of blood gas analysis conducted 3 h after surgery, the IPH group showed lower pH and HCO_3^-, along with higher lactic acid, increased blood glucose concentrations and the coefficient of variation of blood glucose. Arterial blood Ca^{2+} concentrations significantly decreased in the IPH group compared with the non-IPH group (1.05 mmol/L *vs* 1.07 mmol/L, $P < 0.001$). Since the difference of arterial blood Ca^{2+} concentration between these two groups was marginal, we further divided these patients into two subgroups using arterial blood Ca^{2+} 1.05 mmol/L as a cutoff. The proportion of patients in the IPH group with arterial $Ca^{2+} \leq 1.05$ mmol/L was higher than in the non-IPH group (56.73 % *vs* 38.50%, $P < 0.001$).

Risk factor analysis

We categorized preoperative and intraoperative factors that could potentially affect blood pressure, encompassing age, ASA level, pre-existing conditions, preoperative albumin level, surgery duration, blood loss, arterial blood glucose, and Ca^{2+} concentrations. Multivariate logistic regression analysis further indicated that older age, extended surgery duration, increased blood loss, and reduced intraoperative arterial Ca^{2+} levels constituted independent risk factors for IPH during

Table 1 Baseline characteristics, *n* (%)

	Total (*n* = 1596)	Intraoperative persistent hypotension (*n* = 661)	Non-intraoperative persistent hypotension (*n* = 935)	*P* value
Age, yr, median (IQR)	64.0 (56.0-70.0)	65.0 (57.0-70.0)	63.0 (55.0-69.5)	0.001
Age, yr				0.030
≤ 40	50 (3.13)	16 (2.42)	34 (3.63)	
41-50	135 (8.45)	51 (7.71)	84 (8.98)	
51-60	422 (26.44)	152 (23.0)	270 (28.87)	
61-70	631 (39.53)	283 (42.81)	348 (37.21)	
> 70	358 (22.43)	159 (24.05)	199 (21.28)	
Sex				0.620
Male	957 (59.96)	401 (60.66)	556 (59.46)	
Female	639 (40.03)	260 (39.33)	379 (40.53)	
Body mass index, kg/m^2, median (IQR)	22.83 (20.89-24.77)	22.86 (20.81-24.91)	22.80 (20.97-24.64)	0.830
ASA physical status				0.001
I	43 (2.69)	14 (2.11)	29 (31.00)	
II	1255 (78.63)	500 (75.64)	755 (80.75)	
III	298 (18.67)	147 (22.23)	151 (16.15)	
Basic diseases				
Hypertension	539 (33.77)	242 (36.61)	297 (31.76)	< 0.001
Diabetes	312 (19.55)	134 (20.27)	178 (19.04)	< 0.001
Preoperative albumin level, g/L (IQR)	37.60 (35.50-40.80)	37.60 (35.10-40.30)	38.00 (35.90-41.20)	< 0.010
Preoperative blood gas analysis, median (IQR)				
pH	7.45 (7.44-7.47)	7.46 (7.44-7.47)	7.45 (7.43-7.47)	0.100
$PaCO_2$ (mmHg)	38 (36-41)	39 (36-41)	39 (36-41)	0.270
HCO_3^- (mmol/L)	27.10 (25.90-28.40)	27.00 (25.80-28.20)	27.20 (25.90-28.50)	0.090
Hb (mmol/L)	12.50 (11.20-13.60)	12.50 (11.00-13.60)	12.50 (11.20-13.60)	0.250
Lac (mmol/L)	0.90 (0.70-1.10)	0.90 (0.70-1.20)	0.90 (0.70-1.10)	0.360
Ca^{2+} (mmol/L)	1.11 (1.06-1.15)	1.11 (1.07-1.14)	1.11 (1.06-1.15)	0.470
Glu (mmol/L)	6.20 (5.40-7.60)	6.20 (5.40-7.70)	6.10 (5.30-7.50)	0.270

IQR: Interquartile range; pH: Arterial plasma pH; $PaCO_2$: Arterial carbon dioxide partial pressure; HCO_3: Plasma bicarbonate ions; Hb: Arterial hemoglobin; Lac: Arterial plasma lactate; Ca^{2+}: Arterial plasma calcium ions; Glu: Arterial blood glucose concentration; ASA: American Society of Anesthesiologists.

PD. The relative risk increased by 1.20-fold for each additional decade of age [odds ratio (OR): 1.20; 95% confidence interval (CI): 1.08-1.33] ($P < 0.001$); 1.15-fold (OR: 1.15; 95%CI: 1.05-1.26) ($P < 0.01$) for an additional hour of surgery; 1.18-fold (OR: 1.18; 95%CI: 1.06-1.32) ($P < 0.01$) for every 250 mL increase in blood loss; and 2.03-fold (OR: 2.03; 95%CI: 1.65-2.50) ($P < 0.001$) for the arterial blood $Ca^{2+} < 1.05$ mmol/L (Figure 2).

DISCUSSION

In the present retrospective cohort study, we found that the risk factors associated with IPH during PD were age, prolonged surgical procedures, more blood loss, and even more notably, decreased arterial Ca^{2+} concentration. The incidence of IPH during PD was 41.42; similar to the report by Pitter and colleagues[11]. Our study confirms findings from previous studies, which indicated a close relationship of prolonged surgery and increased blood loss to intraop-

Table 2 Comparison of general conditions between two groups during surgery

	Total (*n* = 1596)	Intraoperative persistent hypotension (*n* = 661)	Non-intraoperative persistent hypotension (*n* = 935)	*P* value
Surgery time, h (IQR)	4.58 (3.87-5.48)	4.75 (4.07-5.83)	4.45 (3.78-4.49)	< 0.001
Total infusion, mL (IQR)	2800 (2300-3500)	3100 (2595-3700)	2760 (2300-3277)	< 0.001
Crystal liquid, mL (IQR)	1600 (1500-2100)	1600 (1500-2100)	1600 (1500-2000)	< 0.001
Colloidal liquid, mL (IQR)	1000 (700-1200)	1000 (700-1200)	1000 (700-1200)	0.015
Red blood cell infusion, mL (IQR)	0 (0-260)	0 (0-390)	0 (0-0)	< 0.001
Grading of red blood cell infusion, *n* (%)				< 0.001
1-259 mL	26 (1.62)	10 (1.51)	16 (1.71)	
260-519 mL	218 (13.66)	115 (17.40)	103 (11.00)	
520-779 mL	172 (10.78)	89 (13.46)	83 (8.88)	
780-1039 mL	50 (3.13)	30 (4.54)	20 (2.13)	
≥ 1040 mL	10 (0.63)	10 (1.51)	0 (0)	
Plasma, mL (IQR)	0 (0-325)	0 (0-375)	0 (0-370)	< 0.001
Total output, mL (IQR)	800 (550-1200)	850 (550-1300)	750 (500-1150)	< 0.001
Blood loss, mL (IQR)	300 (200-500)	350 (200-600)	300 (200-400)	< 0.001
Grading of blood loss, *n* (%)				< 0.001
< 250 mL	639 (40.04)	200 (30.26)	439 (46.95)	
250-499 mL	510 (31.95)	215 (32.53)	295 (31.55)	
500-749 mL	258 (16.17)	139 (21.03)	119 (12.73)	
750-999 mL	107 (6.70)	52 (7.87)	55 (5.88)	
≥ 1000 mL	82 (5.14)	55 (8.32)	27 (2.89)	
Intraoperative urine output, mL (IQR)	400 (300-650)	400 (300-700)	400 (250-350)	0.054
Intraoperative blood gas analysis, median (IQR)				
pH	7.38 (7.35-7.42)	7.38 (7.35-7.41)	7.38 (7.36-7.42)	< 0.001
$PaCO_2$ (mmHg)	41 (38-44)	41 (38-44)	42 (39-44)	0.270
HCO_3 (mmol/L)	25.00 (23.70-25.90)	24.60 (23.40-25.80)	25.00 (24.00-25.90)	< 0.001
Hb (mmol/L)	11.00 (10.20-11.90)	11.00 (9.90-11.90)	11.00 (10.20-11.90)	0.190
Lac (mmol/L)	1.00 (0.80-1.20)	1.00 (0.80-1.30)	1.00 (0.80-1.10)	< 0.001
Ca^{2+} (mmol/L)	1.06 (1.02-1.10)	1.05 (1.01-1.09)	1.07 (1.03-1.11)	< 0.001
Glu (mmol/L)	8.90 (7.70-10.00)	9.35 (7.90-10.4)	8.90 (7.50-9.80)	< 0.001
Glu_{mean} (mmol/L)	7.18 (6.46-8.30)	7.26 (6.54-8.45)	7.13 (6.41-8.17)	0.023
Glu_{cv} (%)	28 (20-36)	29 (21-36)	27 (19-35)	0.002
Ca^{2+} level, *n* (%)				< 0.001
Ca^{2+} ≤ 1.05 mmol/L	735 (46.05)	375 (56.73)	360 (38.50)	
Ca^{2+} > 1.05 mmol/L	861 (53.95)	286 (43.27)	575 (61.50)	

Glu_{mean}: The patient's blood glucose at the time of hospital admission, preoperative blood glucose level, and blood glucose level recorded 3 h into the surgical procedure; Glu_{cv}: The coefficient of variation of blood glucose.

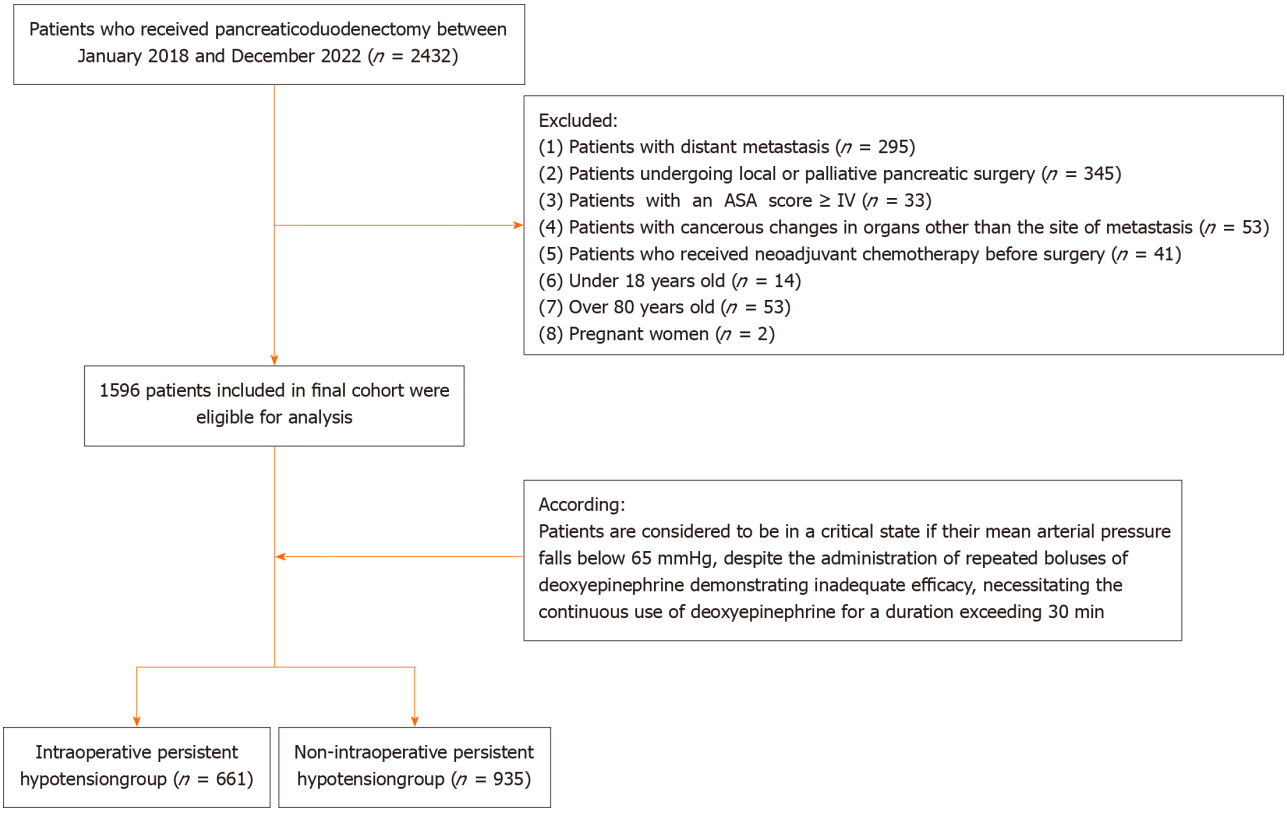


Figure 1 Patient selection flow chart. ASA: American Society of Anesthesiologists.

erative hypotension[4,16,17]. The risk of intraoperative hypotension escalates with age, especially in older patients, likely attributable to diminished cardiac function, reduced vascular elasticity from atherosclerosis, and decreased sympathetic nerve sensitivity, which impair blood pressure regulation[18-20]. Extended surgery and significant blood loss are indicative of substantial surgical trauma, resulting in prolonged anesthesia exposure and alterations in internal homeostasis[21]. These changes may impair sympathetic nervous system function, leading to reduced myocardial contractility and vascular smooth muscle function, ultimately resulting in hypotension[22,23]. Therefore, IPH during PD seems to be associated with imbalances in internal homeostasis that potentially disrupt blood pressure regulation, especially in older patients with extended surgical stress.

A novel finding of our study concerns the close association between decreased arterial blood Ca^{2+} concentration and the occurrence of IPH during PD. Our observations indicate that the risk of hypotension escalated when arterial Ca^{2+} concentration fell below 1.05 mmol/L, which led us to establish this level as a threshold to analyze the potential role of Ca^{2+} concentration in IPH during PD. It is known that Ca^{2+} ions perform a pivotal role in numerous physiological processes, such as blood coagulation, muscle function, neural signal transmission, and cellular signaling[24]. Arterial Ca^{2+}, comprising primarily free ions, constitute approximately 50% of venous Ca^{2+} levels[25]. Reduced arterial Ca^{2+} during PD might adversely affect the myocardium, vascular smooth muscle, sympathetic nervous system and hormone secretion; all of which act as critical components in modulating intraoperative blood pressure[26].

Hyperglycemia, oxidative stress and inflammatory reaction are known to enhance intracellular Ca^{2+} concentration by increasing Ca^{2+} release from intracellular stores and Ca^{2+} influx through store-dependent and store-independent channels [27]. Stress response in the endoplasmic reticulum and mitochondria can be induced by the stimulation of surgical stress and inflammatory reaction, which is characterized by the widespread transfer of Ca^{2+} from the endoplasmic reticulum to the mitochondria[28]. The massive shift of intracellular Ca^{2+} may lead to membrane-associated calcium channels open, including transient receptor potential channels and Ca^{2+} release-activated Ca^{2+} channel protein 1, resulting in an influx of extracellular Ca^{2+} into the cells[29]. We observed lower plasma Ca^{2+} along with higher blood glucose and prolonged surgical procedures in patients with IPH, raising the possibility that reduced plasma Ca^{2+} might result from the extensive surgical-induced release of inflammatory factors and stress-related hyperglycemia during PD[30]. These operative responses might disrupt the balance of intracellular-extracellular Ca^{2+} transport by remarkable Ca^{2+} influx into the endothelial cells, leading to a relatively quick drop of plasma Ca^{2+}. Abnormal Ca^{2+} metabolism or distribution including intracellular Ca^{2+} overload or insufficient elevation may cause endothelial leakage and severely compromise cardiovascular homeostasis[31]. This can be seen in conditions of acute and chronic hyperglycemia that potentially affect Ca^{2+} distribution, such as intracellular Ca^{2+} overload, and subsequently cause aberrant vascular function and endothelial permeability[32,33]. The massive blood transfusions, normally defined as infusion of > 10 units at a time, may result in hypocalcemia[34,35]. However, in our study, the proportion of patients who received blood transfusions > 1040 mL was 1.51% (10 cases in the IPH group). Even after excluding these patients, the group with IPH still exhibited a significant reduction in arterial blood Ca^{2+} concentration. Therefore, this excluded the possibility of decreased Ca^{2+} induced by a

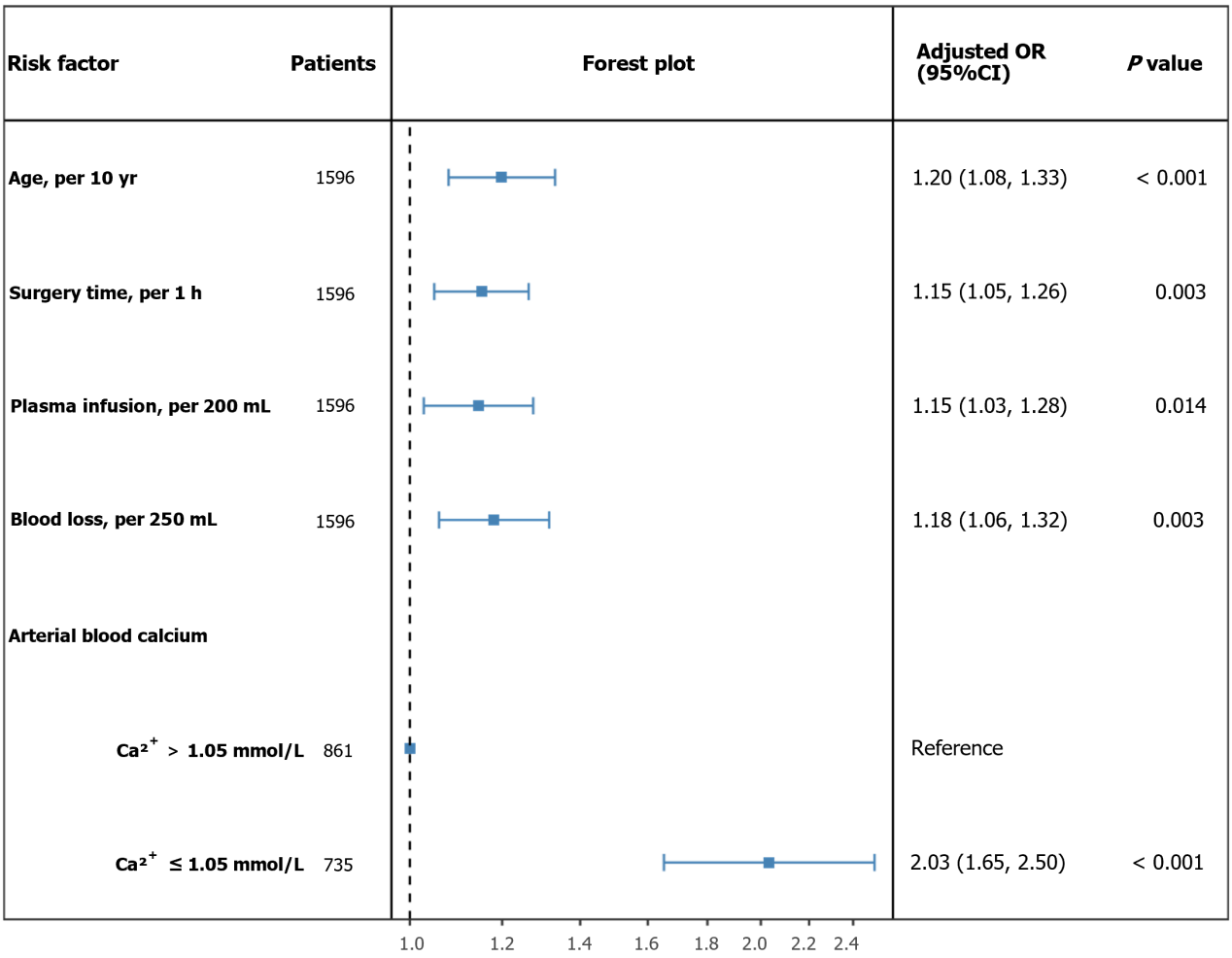


Figure 2 Forest plot illustrating risk factors associated with intraoperative persistent hypotension during pancreaticoduodenectomy. OR: Odd ratio.

greater number of blood transfusions contributing to IPH during PD. The surgical stress-inflammation-endocrine response induced decrease in plasma Ca^{2+} might disrupt endothelial function, reduce peripheral vascular resistance, and then hamper cardiovascular regulation during PD. Arterial Ca^{2+} levels emerge as a valuable predictor of intraoperative hypotension. Considering the identified risk factors—increased age, prolonged surgical duration, and substantial blood loss—it is plausible that these factors may collectively reduce arterial Ca^{2+} concentration.

Hypotension is recognized as an independent predictor of myocardial infarction, particularly when intraoperative MAP drops below 40% of preinduction levels for > 30 min, markedly elevating the risk of postoperative myocardial injury. The severity and duration of intraoperative hypotension are related to postoperative acute renal failure[36]. Numerous meta-analyses recommend classifying intraoperative hypotension as an independent predictor of adverse postoperative outcomes[37-39]. Early identification and effective intervention in high-risk patients are imperative to mitigate intraoperative hypotension and expedite patient recovery. Therefore, based on our findings on the risk factors for the IPH, preoperative assessment should include patient's age, anticipated surgery duration, and potential blood loss.

This study had some limitations. We investigated the relationship between preoperative ASA scores and intraoperative hypotension. While initial univariate analysis suggested higher ASA scores in the IPH group, subsequent analysis with post-adjustment for confounders indicated that ASA score was not an independent risk factor for IPH, possibly owing to the small sample size and stringent selection criteria. The smaller proportion of patients with ASA grade III suggests that some patients may have missed optimal surgical opportunities due to underlying conditions. Moreover, the present study analyzes the impact of preoperative hypertension and history of diabetes on intraoperative hypotension. Although initial analysis revealed differences between groups, these disparities were rendered insignificant after adjusting for other factors. This inconsistency may be attributed to inadequate preoperative knowledge about hypertension and diabetes, resulting in inadequate information being provided during preoperative consultations.

CONCLUSION

The independent risk factors for IPH during PD are patient age, prolonged surgery duration, more blood loss and reduced Ca^{2+} level. The early identification of these factors and the implementation of appropriate preemptive

interventions can significantly aid in preventing IPH in PD.

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FOOTNOTES

Author contributions: Wang XJ, Sun ZC, and Hu YL contributed to study conception and design; Wang XJ, Xuan XC, Shen S, Yu F, Chu XC, and Yin H contributed to data collection; Wang XJ, Sun ZC, and Li NN contributed to data analysis and interpretation; Wang XJ and Hu YL drafted the manuscript; and all authors have reviewed and approved the final manuscript version.

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Informed consent statement: This research is a retrospective analysis utilizing anonymized patient data from the hospital system, posing no risk of harm to patients. An exemption from patient informed consent has been requested from the hospital's ethics committee.

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REFERENCES

1 **Monk TG**, Bronsert MR, Henderson WG, Mangione MP, Sum-Ping ST, Bentt DR, Nguyen JD, Richman JS, Meguid RA, Hammermeister KE. Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. *Anesthesiology* 2015; **123**: 307-319 [PMID: 26083768 DOI: 10.1097/ALN.0000000000000756]

2 **Südfeld S**, Brechnitz S, Wagner JY, Reese PC, Pinnschmidt HO, Reuter DA, Saugel B. Post-induction hypotension and early intraoperative hypotension associated with general anaesthesia. *Br J Anaesth* 2017; **119**: 57-64 [PMID: 28974066 DOI: 10.1093/bja/aex127]

3 **Sessler DI**, Khanna AK. Perioperative myocardial injury and the contribution of hypotension. *Intensive Care Med* 2018; **44**: 811-822 [PMID: 29868971 DOI: 10.1007/s00134-018-5224-7]

4 **Wijnberge M**, Geerts BF, Hol L, Lemmers N, Mulder MP, Berge P, Schenk J, Terwindt LE, Hollmann MW, Vlaar AP, Veelo DP. Effect of a Machine Learning-Derived Early Warning System for Intraoperative Hypotension *vs* Standard Care on Depth and Duration of Intraoperative Hypotension During Elective Noncardiac Surgery: The HYPE Randomized Clinical Trial. *JAMA* 2020; **323**: 1052-1060 [PMID: 32065827 DOI: 10.1001/jama.2020.0592]

5 **Awad H**, Alcodray G, Raza A, Boulos R, Essandoh M, Bhandary S, Dalton R. Intraoperative Hypotension-Physiologic Basis and Future Directions. *J Cardiothorac Vasc Anesth* 2022; **36**: 2154-2163 [PMID: 34218998 DOI: 10.1053/j.jvca.2021.05.057]

6 **Wang M**, Li D, Chen R, Huang X, Li J, Liu Y, Liu J, Cheng W, Chen X, Zhao W, Tan Z, Huang H, Zhu F, Qin T, Ma J, Yu G, Zhou B, Zheng S, Tang Y, Han W, Meng L, Ke J, Feng F, Chen B, Yin X, Chen W, Ma H, Xu J, Lin R, Dong Y, Yu Y, Zhang H, Qin R; Minimally Invasive Treatment Group in the Pancreatic Disease Branch of China's International Exchange and Promotion Association for Medicine and Healthcare (MITG-P-CPAM). Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours: a multicentre, open-label, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2021; **6**: 438-447 [PMID: 33915091 DOI: 10.1016/S2468-1253]

7 **Liu H**, Yu L, Yang L, Green MS. Vasoplegic syndrome: An update on perioperative considerations. *J Clin Anesth* 2017; **40**: 63-71 [PMID: 28625450 DOI: 10.1016/j.jclinane.2017.04.017]

8 **van Vessem ME**, Palmen M, Couperus LE, Mertens B, Berendsen RR, Tops LF, Verwey HF, de Jonge E, Klautz RJ, Schalij MJ, Beeres SL. Incidence and predictors of vasoplegia after heart failure surgery. *Eur J Cardiothorac Surg* 2017; **51**: 532-538 [PMID: 28364440 DOI:

10.1093/ejcts/ezw316]
9 **Tsiouris A**, Wilson L, Haddadin AS, Yun JJ, Mangi AA. Risk assessment and outcomes of vasoplegia after cardiac surgery. *Gen Thorac Cardiovasc Surg* 2017; **65**: 557-565 [PMID: 28612323 DOI: 10.1007/s11748-017-0789-6]
10 **Boutouyrie P**, Chowienczyk P, Humphrey JD, Mitchell GF. Arterial Stiffness and Cardiovascular Risk in Hypertension. *Circ Res* 2021; **128**: 864-886 [PMID: 33793325 DOI: 10.1161/CIRCRESAHA.121.318061]
11 **Pitter SET**, Kehlet H, Hansen CP, Bundgaard-Nielsen M, Storkholm J, Aasvang EK. Persistent severe post-operative hypotension after pancreaticoduodenectomy is related to increased inflammatory response. *Acta Anaesthesiol Scand* 2020; **64**: 455-463 [PMID: 31828772 DOI: 10.1111/aas.13522]
12 **Sessler DI**, Bloomstone JA, Aronson S, Berry C, Gan TJ, Kellum JA, Plumb J, Mythen MG, Grocott MPW, Edwards MR, Miller TE; Perioperative Quality Initiative-3 workgroup; POQI chairs, Miller TE, Mythen MG, Grocott MP, Edwards MR; Physiology group; Preoperative blood pressure group; Intraoperative blood pressure group; Postoperative blood pressure group. Perioperative Quality Initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. *Br J Anaesth* 2019; **122**: 563-574 [PMID: 30916004 DOI: 10.1016/j.bja.2019.01.013]
13 **Salmasi V**, Maheshwari K, Yang D, Mascha EJ, Singh A, Sessler DI, Kurz A. Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery: A Retrospective Cohort Analysis. *Anesthesiology* 2017; **126**: 47-65 [PMID: 27792044 DOI: 10.1097/ALN.0000000000001432]
14 **Futier E**, Lefrant JY, Guinot PG, Godet T, Lorne E, Cuvillon P, Bertran S, Leone M, Pastene B, Piriou V, Molliex S, Albanese J, Julia JM, Tavernier B, Imhoff E, Bazin JE, Constantin JM, Pereira B, Jaber S; INPRESS Study Group. Effect of Individualized *vs* Standard Blood Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk Patients Undergoing Major Surgery: A Randomized Clinical Trial. *JAMA* 2017; **318**: 1346-1357 [PMID: 28973220 DOI: 10.1001/jama.2017.14172]
15 **Wesselink EM**, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. *Br J Anaesth* 2018; **121**: 706-721 [PMID: 30236233 DOI: 10.1016/j.bja.2018.04.036]
16 **Liang X**, Chen X, Wang G, Wang Y, Shi D, Zhao M, Zheng H, Cui X. Intraoperative hypotension, oliguria and operation time are associated with pulmonary embolism after radical resection of head and neck cancers: a case control study. *BMC Anesthesiol* 2021; **21**: 304 [PMID: 34856931 DOI: 10.1186/s12871-021-01521-4]
17 **Hallqvist L**, Granath F, Fored M, Bell M. Intraoperative Hypotension and Myocardial Infarction Development Among High-Risk Patients Undergoing Noncardiac Surgery: A Nested Case-Control Study. *Anesth Analg* 2021; **133**: 6-15 [PMID: 33555690 DOI: 10.1213/ANE.0000000000005391]
18 **Chiang TY**, Wang YK, Huang WC, Huang SS, Chu YC. Intraoperative hypotension in non-emergency decompression surgery for cervical spondylosis: The role of chronic arterial hypertension. *Front Med (Lausanne)* 2022; **9**: 943596 [PMID: 36330062 DOI: 10.3389/fmed.2022.943596]
19 **Hoppe P**, Burfeindt C, Reese PC, Briesenick L, Flick M, Kouz K, Pinnschmidt H, Hapfelmeier A, Sessler DI, Saugel B. Chronic arterial hypertension and nocturnal non-dipping predict postinduction and intraoperative hypotension: A secondary analysis of a prospective study. *J Clin Anesth* 2022; **79**: 110715 [PMID: 35306353 DOI: 10.1016/j.jclinane.2022.110715]
20 **Czajka S**, Putowski Z, Krzych ŁJ. Post-induction hypotension and intraoperative hypotension as potential separate risk factors for the adverse outcome: a cohort study. *J Anesth* 2023; **37**: 442-450 [PMID: 37083989 DOI: 10.1007/s00540-023-03191-7]
21 **Curry NS**, Davenport R. Transfusion strategies for major haemorrhage in trauma. *Br J Haematol* 2019; **184**: 508-523 [PMID: 30592036 DOI: 10.1111/bjh.15737]
22 **Saugel B**, Sessler DI. Perioperative Blood Pressure Management. *Anesthesiology* 2021; **134**: 250-261 [PMID: 33206118 DOI: 10.1097/ALN.0000000000003610]
23 **Mancia G**, Grassi G. The autonomic nervous system and hypertension. *Circ Res* 2014; **114**: 1804-1814 [PMID: 24855203 DOI: 10.1161/CIRCRESAHA.114.302524]
24 **Eisner D**, Neher E, Taschenberger H, Smith G. Physiology of intracellular calcium buffering. *Physiol Rev* 2023; **103**: 2767-2845 [PMID: 37326298 DOI: 10.1152/physrev.00042.2022]
25 **Martin CM**, Priestap F. Agreement between venous and arterial blood gas analysis of acid-base status in critical care and ward patients: a retrospective cohort study. *Can J Anaesth* 2017; **64**: 1138-1143 [PMID: 28836153 DOI: 10.1007/s12630-017-0951-8]
26 **Dalal PJ**, Muller WA, Sullivan DP. Endothelial Cell Calcium Signaling during Barrier Function and Inflammation. *Am J Pathol* 2020; **190**: 535-542 [PMID: 31866349 DOI: 10.1016/j.ajpath.2019.11.004]
27 **Giorgi C**, Danese A, Missiroli S, Patergnani S, Pinton P. Calcium Dynamics as a Machine for Decoding Signals. *Trends Cell Biol* 2018; **28**: 258-273 [PMID: 29409699 DOI: 10.1016/j.tcb.2018.01.002]
28 **Kwon J**, Kim J, Kim KI. Crosstalk between endoplasmic reticulum stress response and autophagy in human diseases. *Anim Cells Syst (Seoul)* 2023; **27**: 29-37 [PMID: 36860271 DOI: 10.1080/19768354.2023.2181217]
29 **Giorgi C**, Marchi S, Pinton P. The machineries, regulation and cellular functions of mitochondrial calcium. *Nat Rev Mol Cell Biol* 2018; **19**: 713-730 [PMID: 30143745 DOI: 10.1038/s41580-018-0052-8]
30 **Matikainen N**, Pekkarinen T, Ryhänen EM, Schalin-Jäntti C. Physiology of Calcium Homeostasis: An Overview. *Endocrinol Metab Clin North Am* 2021; **50**: 575-590 [PMID: 34774235 DOI: 10.1016/j.ecl.2021.07.005]
31 **Pizzo P**. Cell calcium: Mitochondria: function and disease. *Cell Calcium* 2021; **96**: 102370 [PMID: 33674068 DOI: 10.1016/j.ceca.2021.102370]
32 **Navedo MF**, Takeda Y, Nieves-Cintrón M, Molkentin JD, Santana LF. Elevated Ca2+ sparklet activity during acute hyperglycemia and diabetes in cerebral arterial smooth muscle cells. *Am J Physiol Cell Physiol* 2010; **298**: C211-C220 [PMID: 19846755 DOI: 10.1152/ajpcell.00267.2009]
33 **Nieves-Cintrón M**, Flores-Tamez VA, Le T, Baudel MM, Navedo MF. Cellular and molecular effects of hyperglycemia on ion channels in vascular smooth muscle. *Cell Mol Life Sci* 2021; **78**: 31-61 [PMID: 32594191 DOI: 10.1007/s00018-020-03582-z]
34 **Giancarelli A**, Birrer KL, Alban RF, Hobbs BP, Liu-DeRyke X. Hypocalcemia in trauma patients receiving massive transfusion. *J Surg Res* 2016; **202**: 182-187 [PMID: 27083965 DOI: 10.1016/j.jss.2015.12.036]
35 **Sihler KC**, Napolitano LM. Complications of massive transfusion. *Chest* 2010; **137**: 209-220 [PMID: 20051407 DOI: 10.1378/chest.09-0252]
36 **Rangasamy V**, de Guerre L, Xu X, Schermerhorn ML, Novack V, Subramaniam B. Association Between Intraoperative Hypotension and Postoperative Adverse Outcomes in Patients Undergoing Vascular Surgery - A Retrospective Observational Study. *J Cardiothorac Vasc Anesth* 2021; **35**: 1431-1438 [PMID: 33293215 DOI: 10.1053/j.jvca.2020.11.005]

37 **Gu WJ**, Hou BL, Kwong JSW, Tian X, Qian Y, Cui Y, Hao J, Li JC, Ma ZL, Gu XP. Association between intraoperative hypotension and 30-day mortality, major adverse cardiac events, and acute kidney injury after non-cardiac surgery: A meta-analysis of cohort studies. *Int J Cardiol* 2018; **258**: 68-73 [PMID: 29429638 DOI: 10.1016/j.ijcard.2018.01.137]

38 **Cai J**, Tang M, Wu H, Yuan J, Liang H, Wu X, Xing S, Yang X, Duan XD. Association of intraoperative hypotension and severe postoperative complications during non-cardiac surgery in adult patients: A systematic review and meta-analysis. *Heliyon* 2023; **9**: e15997 [PMID: 37223701 DOI: 10.1016/j.heliyon.2023.e15997]

39 **D'Amico F**, Fominskiy EV, Turi S, Pruna A, Fresilli S, Triulzi M, Zangrillo A, Landoni G. Intraoperative hypotension and postoperative outcomes: a meta-analysis of randomised trials. *Br J Anaesth* 2023; **131**: 823-831 [PMID: 37739903 DOI: 10.1016/j.bja.2023.08.026]

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ORIGINAL ARTICLE

Retrospective Study

Endoscopic ultrasound-guided biliary drainage *vs* percutaneous transhepatic bile duct drainage in the management of malignant obstructive jaundice

Qin-Qin Zhu, Bing-Fang Chen, Yue Yang, Xue-Yong Zuo, Wen-Hui Liu, Ting-Ting Wang, Yin Zhang

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Abstract

BACKGROUND

Malignant obstructive jaundice (MOJ) is a condition characterized by varying degrees of bile duct stenosis and obstruction, accompanied by the progressive development of malignant tumors, leading to high morbidity and mortality rates. Currently, the two most commonly employed methods for its management are percutaneous transhepatic bile duct drainage (PTBD) and endoscopic ultrasound-guided biliary drainage (EUS-BD). While both methods have demonstrated favorable outcomes, additional research needs to be performed to determine their relative efficacy.

AIM

To compare the therapeutic effectiveness of EUS-BD and PTBD in treating MOJ.

METHODS

This retrospective analysis, conducted between September 2015 and April 2023 at The Third Affiliated Hospital of Soochow University (The First People's Hospital of Changzhou), involved 68 patients with MOJ. The patients were divided into two groups on the basis of surgical procedure received: EUS-BD subgroup (n = 33) and PTBD subgroup (n = 35). Variables such as general data, preoperative and postoperative indices, blood routine, liver function indices, myocardial function indices, operative success rate, clinical effectiveness, and complication rate were analyzed and compared between the subgroups.

RESULTS
In the EUS-BD subgroup, hospital stay duration, bile drainage volume, effective catheter time, and clinical effectiveness rate were superior to those in the PTBD subgroup, although the differences were not statistically significant ($P > 0.05$). The puncture time for the EUS-BD subgroup was shorter than that for the PTBD subgroup ($P < 0.05$). Postoperative blood routine, liver function index, and myocardial function index in the EUS-BD subgroup were significantly lower than those in the PTBD subgroup ($P < 0.05$). Additionally, the complication rate in the EUS-BD subgroup was lower than in the PTBD subgroup ($P < 0.05$).

CONCLUSION
EUS-BD may reduce the number of punctures, improve liver and myocardial functions, alleviate traumatic stress, and decrease complication rates in MOJ treatment.

Key Words: Percutaneous hepatic biliary drainage; Endoscopic ultrasound-guided biliary drainage; Malignant obstructive jaundice; Clinical effect; Liver function; Postoperative complications

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Core Tip: Malignant obstructive jaundice (MOJ) primarily manifests in advanced tumors, posing significant risks to patient survival and necessitating prompt treatment. The principal treatment methods for MOJ are endoscopic ultrasound-guided biliary drainage and percutaneous transhepatic bile duct drainage. However, the efficacy of these two procedures varies, and their clinical value and postoperative effects require further analysis. This study, involving 68 patients, compares the therapeutic outcomes of these two surgical treatments for MOJ, aiming to identify the optimal treatment strategy.

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INTRODUCTION

Malignant obstructive jaundice (MOJ) is a type of jaundice disease arising from hepatic duct occlusion, which leads to impaired bile excretion and abnormal elevation of serum bilirubin[1]. MOJ commonly results in biliary tract infection or suppurative cholangitis. Without timely treatment, it can progress to abnormal coagulation function, impaired immune function, liver failure, and even death[2]. Currently, endoscopic retrograde cholangiopancreatography (ERCP) combined with biliary stent implantation is the primary standard treatment in clinical practice. However, intubation may pose a challenge in certain patients, with a failure rate reaching as high as 7%. Consequently, traditional percutaneous transhepatic biliary drainage (PTBD) is often employed for these patients, boasting a success rate of 87% to 100%. Yet, it is associated with risks such as bile duct injury, biliary fistula, drainage tube obstruction, dislocation, and other complications. Moreover, long-term external drainage can lead to bile loss, electrolyte disturbances, and infection, significantly impacting patients' quality of life and their functional recovery[3,4]. Endoscopic ultrasound-guided biliary drainage (EUS-BD), a newer internal drainage technique, is an alternative when ERCP treatment fails. It has a technical success rate of over 90% and an adverse event rate of less than 15%[5]. EUS-BD has shown promise in treating MOJ, particularly in terms of postoperative complications[6]. Therefore, this study aims to compare the effects of EUS-BD and PTBD in treating MOJ using a multi-variable and multi-sample approach. The specifics of this study are outlined below.

MATERIALS AND METHODS

Patient characteristics

This retrospective analysis included 68 patients with MOJ who were admitted to The Third Affiliated Hospital of Soochow University (The First People's Hospital of Changzhou) between September 2015 and April 2023. On the basis of the treatment methods employed, these patients were divided into two groups: the EUS-BD subgroup ($n = 33$) and the PTBD subgroup ($n = 35$).

Inclusion criteria: MOJ diagnosis was confirmed through B-ultrasound, computed tomography (CT), or Magnetic resonance cholangiopancreatography prior to surgery; patients for whom conventional ERCP procedures had failed or were deemed unsuitable by endoscopists; availability of complete clinical data; absence of distant metastasis; normal coagulation function.

Exclusion criteria: Patients who had undergone radiotherapy or chemotherapy; those with hemophilia or other significant coagulation disorders; and patients suffering from severe infections.

Preoperative preparation

Prior to surgery, patients underwent routine blood tests, coagulation function assessment, liver function tests, and general blood biochemistry analysis. They were required to fast for 4 to 6 hours before the procedure. Additionally, medications that affect platelet aggregation and anticoagulation, such as clopidogrel, warfarin, aspirin, and low-molecular-weight heparin, were discontinued. Imaging data from the planned puncture site (abdominal CT or magnetic resonance imaging) were carefully reviewed to ascertain the presence of any large vessels crossing or adjacent to the site. The procedure was performed under general anesthesia or intravenous sedation, with assistance from an anesthesiologist.

Surgical methods

EUS-BD Subgroup: Using linear array endoscopic ultrasonography (UCT-260, Olympus Medical Systems, Tokyo, Japan), the appropriate puncture site was selected under guidance. Color Doppler was used to avoid blood flow signals in the puncture path. A 19G needle (ECHO-19, Cook Ireland Ltd, Limerick, Ireland) was inserted through the digestive tract into the intrahepatic bile duct. After confirming the aspiration fluid as bile, a contrast agent was injected to delineate the biliary system under X-ray guidance. A 0.035-inch guidewire was then introduced into the biliary system, exiting from the puncture needle. A cystotome along the guidewire was used to dilate the sinus tract, followed by the insertion of a nasobiliary tube or stent into the tract.

PTBD Subgroup: Under B-mode ultrasound guidance, bile duct dilatation was identified. The local skin was disinfected, and local infiltration anesthesia (2% lidocaine) was administered. To avoid blood vessels and intestinal structures, a 16G puncture needle was percutaneously inserted into the corresponding bile duct. Bile was withdrawn to confirm the needle's placement within the bile duct. A guidewire was then placed through the puncture needle, the puncture site expanded, and the tube inserted. Finally, an external drainage bag was connected, and the drainage device secured.

Observational indicators

General clinical data: This includes age, sex, body mass index (BMI), smoking history, cancer type, duration of the disease, duration of surgery, and length of hospital stay.

Surgery-related indicators: These encompass operation time, hospital stay duration, number of punctures, bile drainage flow rate, and effective duration of tube maintenance.

Blood routine before and 7 d after surgery: Measurements of red blood cells (RBC), white blood cells (WBC), and platelets (PLT).

Liver function indices before and 7 d after surgery: Levels of total protein (TP), albumin (ALB), serum alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT), total bilirubin (TBIL), direct bilirubin (DBIL), and total bile acid are determined, along with hypersensitive C-reactive protein (hs-CRP), using an automatic biochemical analyzer (DNM-9602, Beijing Pulang New Technology Co., Ltd).

Myocardial function before and 7 d after surgery: Assessments of lactate dehydrogenase (LDH), creatine kinase (CK), and creatine kinase isoenzyme (CK-MB).

Surgical success rate and clinical efficiency: Successful surgery is defined as the correct placement of the stent or drain in the desired position. The clinical effectiveness rate is determined on the basis of the reduction in TBIL levels before and 7 d after surgery, as well as the absence of stent blockage or displacement one month post-surgery. A significant effective rate is characterized by a decrease in TBIL of > 30% post-surgery, with no stent blockage or displacement within one month. Effectiveness is defined as a 10%-30% decrease in TBIL post-surgery, without stent blockage or displacement within one month. Ineffectiveness is indicated by a less than 10% decrease in postoperative TBIL and stent blockage or displacement within one month.

Postoperative complications: These include biliary fistula, cholangitis, bile duct bleeding, pneumoperitoneum, stent blockage, stent displacement, and mucosal laceration.

Statistical analysis

The measurement data, such as age, BMI, disease course, operation-related indicators, liver function indicators, and myocardial function indicators, are expressed as mean ± SD, and the *t*-test was used to analyze these data. Count data, such as sex, smoking history, cancer type, surgical success rate, clinical effective rate, and postoperative complications, are expressed as rates and were analyzed using the chi-square test. SPSS 27.0 software (IBM Corp.) was used to process the data. $P < 0.05$ was considered statistically significant.

RESULTS

General data comparison

The subgroups EUS-BD and PTBD were comparable in terms of age, sex, BMI, smoking history, cancer type, and duration of illness. No significant differences were observed between these groups ($P > 0.05$), as detailed in Table 1.

Comparison of surgery-related indicators

The EUS-BD subgroup exhibited shorter operative times and reduced lengths of hospital stay compared with the PTBD subgroup. Additionally, the EUS-BD subgroup demonstrated higher bile drainage volumes and longer effective tube times than the PTBD subgroup, though these differences were not statistically significant ($P > 0.05$). Notably, the number of punctures in the EUS-BD subgroup was fewer than in the PTBD subgroup ($P < 0.05$), as illustrated in Figure 1A.

Blood routine comparison

Prior to surgery, the blood routine parameters of the two subgroups EUS-BD and PTBD showed no significant differences ($P > 0.05$). However, 7 d post-surgery, the levels of RBC, WBC, and PLT in the EUS-BD subgroup were significantly lower than those in the PTBD subgroup ($P < 0.05$), as illustrated in Figure 1B.

Liver function comparison

Prior to surgery, the serum indices of both groups EUS-BD and PTBD were similar ($P > 0.05$). Postoperatively, the levels of TP, ALP, adenosine triphosphate, ALT, AST, GGT, TBIL, DBIL, and hs-CRP in the EUS-BD subgroup were lower than those in the PTBD subgroup ($P < 0.05$), as shown in Table 2.

Comparison of myocardial function indices

Postoperative myocardial function indices in the EUS-BD subgroup were significantly lower than those in the PTBD subgroup ($P < 0.05$), as illustrated in Figure 1C.

Comparing surgical success rate and clinical response rate

In the EUS-BD subgroup, 31 patients experienced successful biliary drainage, resulting in a success rate of 93.94%, which surpassed the 85.71% success rate observed in the PTBD subgroup. Among the EUS-BD subgroup, 16 patients (48.49%) demonstrated a postoperative decrease in TBIL of > 30%, a value of > 40.00% was observed in the PTBD subgroup. The proportion of patients whose TBIL decreased by 10%-30% post-surgery was 42.42% in the EUS-BD subgroup, comparable to that in the PTBD subgroup. Only 9.09% of the EUS-BD subgroup showed a TBIL decrease of < 10%, which was lower than the 17.14% in the PTBD subgroup. However, the differences in efficacy and clinical response between the two subgroups were not statistically significant ($P > 0.05$), as shown in Table 3.

Comparative analysis of postoperative complications

In the EUS-BD subgroup, complications were observed in 3 patients (9.09%), comprising 1 case of biliary fistula, 1 of stent blockage, and 1 of mucosal laceration. All these patients showed improvement following treatment. In the PTBD subgroup, 10 patients (28.57%) experienced complications, including 2 biliary fistulas, 2 instances of cholangitis, 1 bile duct hemorrhage, 1 pneumoperitoneum, 3 stent blockages, and 1 stent displacement, with all patients improving post-treatment. The EUS-BD subgroup had a significantly lower complication rate than the PTBD subgroup ($P < 0.05$), as shown in Table 4.

DISCUSSION

MOJ is a common surgical condition characterized by symptoms of bile duct obstruction, including yellowing of the skin, sclera, and other tissues. The pathogenesis of the disease mainly consists of compromised bile excretion and subsequent sepsis, causing infiltration of cytokines, oxidative stress, and disruption of physiological functions, resulting in hepatic cell injury and apoptosis[7-9]. The predominant clinical approach to MOJ is surgical intervention, yet the efficacy of various surgical techniques varies. ERCP is frequently used but can be technically challenging and carries a risk of postoperative biliary tract infection, thus affecting the surgical success rate. Recently, PTBD and EUS-BD have gained prominence in MOJ treatment owing to their minimal invasiveness. While both methods have shown effective outcomes and serve as alternatives for ERCP failures, determining which procedure holds greater clinical value remains a subject of ongoing exploration[10,11]. This study aims to compare and analyze the clinical effects of PTBD and EUS-BD in treating MOJ by examining surgery-related metrics, blood routine, liver and myocardial function indices, surgical success rate, clinical effectiveness, and complication rate, to identify a superior treatment approach.

PTBD and EUS-BD are comparable in terms of operation duration, hospital stay, bile flow, and effective drainage time. However, EUS-BD is characterized by a lower puncture frequency compared with PTBD. This may be attributed to the shorter puncture path in EUS-BD, its traversal through fewer organs, and its relatively higher accuracy. Additionally, EUS-BD offers a broader range of puncture sites. The stent can be positioned in the common bile duct under X-ray guidance, and its design often includes multiple side holes or a nasal cyst, enhancing the drainage effectiveness. In contrast, PTBD is more susceptible to complications like secondary biliary peritonitis and is limited by the extent of intrahepatic bile duct dilation, which can result in a lower puncture success rate[12,13].

Table 1 Comparison of general data between the two subgroups

	EUS-BD (*n* = 33)	PTBD (*n* = 35)	t/χ^2	*P* value
Age (mean SD, yr)	66.13 ± 10.04	64.36 ± 9.28	0.755	0.453
Sex, *n* (%)			0.391	0.532
Male	24 (72.73)	23 (65.71)		
Female	9 (27.27)	12 (34.29)		
BMI (mean SD, kg/m^2)	23.10 ± 3.18	23.25 ± 3.23	0.195	0.846
History of smoking, *n* (%)			0.000	0.994
Yes	17 (51.52)	18 (51.43)		
No	16 (48.48)	17 (48.57)		
Cancer type, *n* (%)			0.066	0.967
Carcinoma of head of pancreas	15 (45.46)	17 (48.57)		
Cholangiocarcinoma	10 (30.30)	10 (28.57)		
Other	8 (24.24)	8 (22.86)		
Disease course (mean SD, months)	6.30 ± 3.04	6.31 ± 3.17	0.015	0.988

BMI: Body mass index; EUS-BD: Endoscopic ultrasound-guided biliary drainage; PTBD: Percutaneous transhepatic puncture biliary drainage.

In the context of blood routine, liver function, and myocardial function indices, the postoperative metrics for these parameters in the EUS-BD subgroup were lower than those in the PTBD subgroup. This suggests that EUS-BD causes less trauma to the body, can effectively improve serum levels, liver function, and myocardial function in patients, and inflicts minimal damage to the liver. Firstly, routine blood tests are fundamental in clinical diagnostics, encompassing a range of commonly used sensitive indicators that are responsive to various bodily disease changes and assist in disease assessment. WBCs are a crucial type of blood cell, capable of phagocytizing foreign bodies and producing antibodies. RBCs play a role in clearing immune complexes and participating in immune regulation. PLTs are indicators reflecting the formation and reduction of platelets; changes in PLT levels can indicate alterations or damage within the blood system[14-16].

Secondly, MOJ frequently leads to abnormal coagulation function, as well as impairment of liver and kidney functions, often resulting in secondary infections. TBIL serves as a crucial liver function marker and a primary indicator for diagnosing jaundice. Elevated TBIL levels, particularly high DBIL, suggest potential liver lesions or bile duct obstruction. In this study, preoperative TBIL levels in patients with MOJ were high, but post-treatment levels significantly decreased, with a more pronounced reduction observed in the EUS-BD group. This suggests that EUS-BD treatment for MOJ can alleviate biliary obstruction, lower biliary pressure, reduce infection rates, and consequently enhance liver function in patients[17,18]. Additionally, some patients with MOJ experience abnormal metabolism, potentially affecting the energy metabolism of cardiomyocytes and leading to myocardial damage. Commonly assessed myocardial damage markers include LDH, CK, and CK-MB[19,20]. LDH and CK are enzymes widely distributed in body tissues such as the heart, liver, and kidneys, and are closely linked to myocardial function. CK-MB is predominantly found in the myocardium, and an increase in its blood levels, due to increased cell permeability following myocardial injury, is indicative of such damage[21,22].

This and other studies indicate that the success rate and clinical effectiveness of the EUS-BD subgroup were lower than those of the PTBD subgroup, although the difference was not statistically significant[23,24]. Regarding complication rates, the PTBD subgroup exhibited a higher incidence compared with the EUS-BD subgroup. While the PTBD procedure is straightforward with a high success rate, it often leads to complications, resulting in a poorer prognosis for some patients. In this study, the complication rate for patients with PTBD was as high as 28.57%, with common issues including cholangitis, stent blockage, and biliary fistula. In contrast, the complication rate in the EUS-BD subgroup was 9.09%, which could be managed with conservative treatment, effectively reducing patient discomfort[8,25]. Complications typically arise due to the following: (1) Mucosal tear and injury to peripheral blood vessels during endoscopic procedures; (2) Bile retrograding into blood, leading to infection; (3) Cholestasis causing biliary sludge formation, either from longitudinal tissue development or tumor growth causing stent obstruction; and (4) Injury to the pancreas, gallbladder, and bile duct during surgery. EUS-BD, conducted under endoscopic ultrasound and X-ray guidance, can enhance operational accuracy and reduce postoperative complications like infection and bleeding.

This study has the following limitations: (1) This study employed a retrospective research design, which retrospectively examined past data to determine present outcomes. The collected data may be subject to interference from various factors, potentially affecting the results; (2) Owing to the limited number of patients meeting the inclusion criteria at our hospital, only 68 patients were included, leading to potential bias and compromising the accuracy of our study's conclusions; and (3) Given the restricted sample size, this study did not assess the advantages and disadvantages of different types of stents and malignant tumors in relation to both treatment methods; thus, further research is needed to

Table 2 Comparison of preoperative and postoperative serum indices between the two subgroups, mean ± SD

Index	Time	EUS-BD (*n* = 33)	PTBD (*n* = 35)	*t*	*P* value
TP (g/L)	Before surgery	61.85 ± 7.14	59.25 ± 7.12	-1.498	0.139
	7 d after surgery	41.75 ± 5.80[a,b]	55.13±6.82[a]	8.687	< 0.001
ALB (g/L)	Before surgery	44.04 ± 6.98	40.97 ± 6.70	-1.846	0.069
	7 d after surgery	31.20 ± 4.45[a,b]	39.55 ± 6.07[a]	6.439	< 0.001
ALP (U/L)	Before surgery	529.68 ± 182.52	505.45 ± 176.87	-0.559	0.578
	7 d after surgery	285.39 ± 97.22[a,b]	360.65 ± 150.02[a]	2.439	0.017
ALT (U/L)	Before surgery	148.76 ± 52.55	146.58 ± 53.35	-0.169	0.866
	7 d after surgery	51.33 ± 6.61[a,b]	73.58 ± 7.03[a]	13.424	< 0.001
AST (U/L)	Before surgery	121.29 ± 37.58	107.62 ± 28.98	-1.685	0.097
	7 d after surgery	42.02 ± 13.95[a,b]	75.03 ± 16.25[a]	8.969	< 0.001
GGT (U/L)	Before surgery	612.05 ± 179.24	575.13 ± 174.30	-0.861	0.391
	7 d after surgery	213.67 ± 61.37[a,b]	299.65 ± 65.12[a]	5.595	< 0.001
TBIL (mmol/L)	Before surgery	228.02 ± 66.39	205.23 ± 76.28	-1.311	0.194
	7 d after surgery	107.93 ± 52.43[a,b]	144.79 ± 59.10[a]	2.714	0.008
DBIL (mmol/L)	Before surgery	204.18 ± 52.86	192.13 ± 49.66	-0.969	0.336
	7 d after surgery	70.19 ± 17.16[a,b]	84.48 ± 19.41[a]	3.208	0.002
TBA (mmol/L)	Before surgery	228.62 ± 55.45	208.90 ± 63.35	-1.362	0.178
	7 d after surgery	66.31 ± 18.61[a,b]	90.55 ± 20.11[a]	5.152	< 0.001
hs-CRP (mg/L)	Before surgery	13.22 ± 3.29	11.60 ± 3.90	-1.843	0.070
	7 d after surgery	4.58 ± 1.33[a,b]	7.66 ± 2.36[a]	6.576	< 0.001

[a]$P < 0.05$, compared to the preoperative subgroup.
[b]$P < 0.05$ compared to the percutaneous transhepatic puncture biliary drainage subgroup.
TP: Total protein; ALB: Albumin; ALP: Serum alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate transaminase; GGT: Gamma-glutamyl transferase; TBIL: Total bilirubin; DBIL: Direct bilirubin; TBA: Total bile acid; hs-CRP: Hypersensitive C-reactive protein; EUS-BD: Endoscopic ultrasound-guided biliary drainage; PTBD: Percutaneous transhepatic puncture biliary drainage.

Table 3 Comparison of surgical success rates and clinical response rates between the two subgroups, *n* (%)

	EUS-BD (*n* = 33)	PTBD (*n* = 35)	χ^2	*P* value
Successful operation	31 (93.94)	30 (85.71)	1.244	0.265
Excellent	16 (48.49)	14 (40.00)		
Effective	14 (42.42)	15 (42.86)		
Ineffective	3 (9.09)	6 (17.14)		
Total effective	30 (90.91)	29 (82.86)	0.959	0.327

EUS-BD: Endoscopic ultrasound-guided biliary drainage; PTBD: Percutaneous transhepatic puncture biliary drainage.

strengthen our findings. In future clinical practice, we aim to expand our sample size, conduct prospective controlled studies, and incorporate multiple influencing factors to enhance the clinical application of EUS-BD.

CONCLUSIONS

When comparing the EUS-BD subgroup with the PTBD subgroup, the differences in surgical success rates and clinical efficiency were not significant. However, the EUS-BD subgroup showed superiority in several aspects, including the number of punctures, blood routine, liver function, myocardial function, and complications, when compared with the

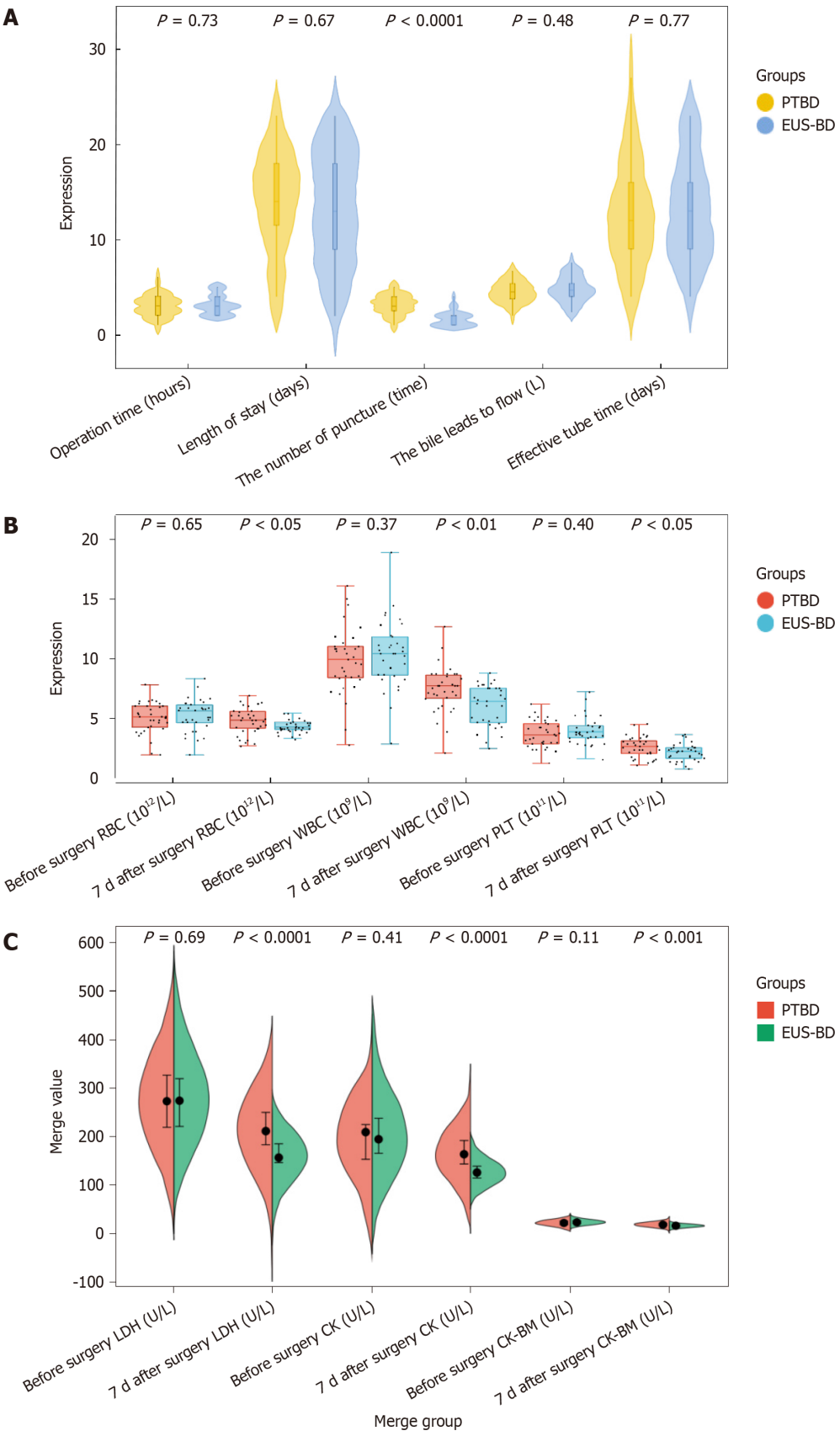


Figure 1 Comparison of procedure-related measures, routine blood parameters, and myocardial function measures between the endoscopic ultrasound-guided biliary drainage and percutaneous transhepatic puncture biliary drainage groups. A: Comparison of procedure-related measures between the endoscopic ultrasound-guided biliary drainage (EUS-BD) and percutaneous transhepatic puncture biliary drainage (PTBD) groups; B: Comparison of routine blood parameters between the EUS-BD and PTDB groups; C: Comparison of myocardial function measures between the EUS-BD and PTDB groups. EUS-BD: Endoscopic ultrasound-guided biliary drainage; PTBD: Percutaneous transhepatic puncture biliary drainage; RBC: Red blood cells; WBC: White blood cells; PLT: Platelets; LDH: Lactate dehydrogenase; CK: Creatine kinase; CK-MB: Creatine kinase isoenzyme.

Table 4 Comparison of postoperative complications between the two subgroups, *n* (%)

Complication	EUS-BD (*n* = 33)	PTBD (*n* = 35)	χ^2	*P* value
Biliary fistula	1 (3.03)	2 (5.71)		
Cholangitis	0 (0.00)	2 (5.71)		
Bile tube bleeding	0 (0.00)	1 (2.86)		
Pneumoperitoneum	0 (0.00)	1 (2.86)		
Stent blockage	1 (3.03)	3 (8.57)		
Stent displacement	0 (0.00)	1 (2.86)		
Mucosal laceration	1 (3.03)	0 (0.00)		
Total	3 (9.09)	10 (28.57)	4.169	0.041

EUS-BD: Endoscopic ultrasound-guided biliary drainage; PTBD: Percutaneous transhepatic puncture biliary drainage.

PTBD subgroup. Consequently, it can be concluded that EUS-BD offers an effective therapeutic approach for patients with MOJ. Compared with PTBD, EUS-BD presents advantages such as reduced puncture frequency, improved liver and myocardial functions, alleviated traumatic stress, and fewer complications.

FOOTNOTES

Author contributions: Zhu QQ conceptualized and conducted the research, authored the manuscript, and performed data analysis; Chen BF and Yang Y conducted literature review and provided research guidance; Zuo XY and Liu WH were responsible for data collection; Wang TT contributed to formal analysis and data visualization; Zhang Y offered research advice and oversaw the report preparation.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of The Third Affiliated Hospital of Soochow University (The First People's Hospital of Changzhou).

Informed consent statement: An exemption from informed consent was requested and obtained from the Ethics Committee.

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REFERENCES

1 **Zerem E**, Imširović B, Kunosić S, Zerem D, Zerem O. Percutaneous biliary drainage for obstructive jaundice in patients with inoperable, malignant biliary obstruction. *Clin Exp Hepatol* 2022; **8**: 70-77 [PMID: 35415254 DOI: 10.5114/ceh.2022.114190]
2 **Wang T**, Liu S, Zheng YB, Song XP, Sun BL, Jiang WJ, Wang LG. Clinical Study on Using (125)I Seeds Articles Combined with Biliary Stent Implantation in the Treatment of Malignant Obstructive Jaundice. *Anticancer Res* 2017; **37**: 4649-4653 [PMID: 28739766 DOI: 10.21873/anticanres.11867]
3 **Shao JH**, Fang HX, Li GW, He JS, Wang BQ, Sun JH. Percutaneous transhepatic biliary drainage and stenting for malignant obstructive jaundice: A report of two cases. *Exp Ther Med* 2015; **10**: 1503-1506 [PMID: 26622515 DOI: 10.3892/etm.2015.2701]
4 **Wang HB**, Peng F, Wang M, Qin RY, Zhu F. Impact of Percutaneous Transhepatic Biliary Drainage on Clinical Outcomes of Patients with Malignant Obstructive Jaundice Undergoing Laparoscopic Pancreaticoduodenectomy. *Curr Med Sci* 2021; **41**: 375-380 [PMID: 33877556

DOI: 10.1007/s11596-021-2357-7]

5 **Hayat U**, Bakker C, Dirweesh A, Khan MY, Adler DG, Okut H, Leul N, Bilal M, Siddiqui AA. EUS-guided *versus* percutaneous transhepatic cholangiography biliary drainage for obstructed distal malignant biliary strictures in patients who have failed endoscopic retrograde cholangiopancreatography: A systematic review and meta-analysis. *Endosc Ultrasound* 2022; **11**: 4-16 [PMID: 35083977 DOI: 10.4103/EUS-D-21-00009]

6 **Makar M**, Zhao E, Tyberg A. Personalized Approach to the Role of Endoscopic Ultrasound in the Diagnosis and Management of Pancreaticobiliary Malignancies. *J Pers Med* 2021; **11** [PMID: 33806458 DOI: 10.3390/jpm11030180]

7 **Zhao B**, Cheng Q, Cao H, Zhou X, Li T, Dong L, Wang W. Dynamic change of serum CA19-9 levels in benign and malignant patients with obstructive jaundice after biliary drainage and new correction formulas. *BMC Cancer* 2021; **21**: 517 [PMID: 33962560 DOI: 10.1186/s12885-021-08204-w]

8 **Duan F**, Cui L, Bai Y, Li X, Yan J, Liu X. Comparison of efficacy and complications of endoscopic and percutaneous biliary drainage in malignant obstructive jaundice: a systematic review and meta-analysis. *Cancer Imaging* 2017; **17**: 27 [PMID: 29037223 DOI: 10.1186/s40644-017-0129-1]

9 **Li J**, Zhuo S, Chen B, Liu Y, Wu H. Clinical efficacy of laparoscopic modified loop cholecystojejunostomy for the treatment of malignant obstructive jaundice. *J Int Med Res* 2020; **48**: 300060519866285 [PMID: 31547725 DOI: 10.1177/0300060519866285]

10 **Rizzo A**, Ricci AD, Frega G, Palloni A, DE Lorenzo S, Abbati F, Mollica V, Tavolari S, DI Marco M, Brandi G. How to Choose Between Percutaneous Transhepatic and Endoscopic Biliary Drainage in Malignant Obstructive Jaundice: An Updated Systematic Review and Meta-analysis. *In Vivo* 2020; **34**: 1701-1714 [PMID: 32606139 DOI: 10.21873/invivo.11964]

11 **Morita S**, Sugawara S, Suda T, Hoshi T, Abe S, Yagi K, Terai S. Conversion of percutaneous transhepatic biliary drainage to endoscopic ultrasound-guided biliary drainage. *DEN Open* 2021; **1**: e6 [PMID: 35310153 DOI: 10.1002/deo2.6]

12 **Liu JG**, Wu J, Wang J, Shu GM, Wang YJ, Lou C, Zhang J, Du Z. Endoscopic Biliary Drainage Versus Percutaneous Transhepatic Biliary Drainage in Patients with Resectable Hilar Cholangiocarcinoma: A Systematic Review and Meta-Analysis. *J Laparoendosc Adv Surg Tech A* 2018; **28**: 1053-1060 [PMID: 29641365 DOI: 10.1089/lap.2017.0744]

13 **Pedersoli F**, Schröder A, Zimmermann M, Schulze-Hagen M, Keil S, Ulmer TF, Neumann UP, Kuhl CK, Bruners P, Isfort P. Percutaneous transhepatic biliary drainage (PTBD) in patients with dilated vs. nondilated bile ducts: technical considerations and complications. *Eur Radiol* 2021; **31**: 3035-3041 [PMID: 33051733 DOI: 10.1007/s00330-020-07368-6]

14 **Jin H**, Pang Q, Liu H, Li Z, Wang Y, Lu Y, Zhou L, Pan H, Huang W. Prognostic value of inflammation-based markers in patients with recurrent malignant obstructive jaundice treated by reimplantation of biliary metal stents: A retrospective observational study. *Medicine (Baltimore)* 2017; **96**: e5895 [PMID: 28099348 DOI: 10.1097/MD.0000000000005895]

15 **Vinnik YS**, Pakhomova RA, Kochetova LV, Voronova EA, Kozlov VV, Kirichenko AK. [Predictors of hepatic insufficiency in obstructive jaundice]. *Khirurgiia (Mosk)* 2018; 37-41 [PMID: 29560957 DOI: 10.17116/hirurgia2018337-41]

16 **Sahinli H**, Özet A. Prognostic and predictive factors in cancer patients with obstructive jaundice treated by percutaneous transhepatic biliary drainage: A single-center experience. *J Cancer Res Ther* 2020; **16**: S99-S103 [PMID: 33380661 DOI: 10.4103/jcrt.JCRT_521_19]

17 **Liu W**, Liu Q, Wang W, Wang P, Chen J, Hong T, Zhang N, Li B, Qu Q, He X. Differential diagnostic roles of the serum CA19-9, total bilirubin (TBIL) and the ratio of CA19-9 to TBIL for benign and malignant. *J Cancer* 2018; **9**: 1804-1812 [PMID: 29805707 DOI: 10.7150/jca.25093]

18 **Chen WY**, Kong CL, Meng MM, Chen WQ, Zheng LY, Mao JT, Fang SJ, Chen L, Shu GF, Yang Y, Weng QY, Chen MJ, Xu M, Ji JS. Percutaneous biliary stent combined with brachytherapy using ^{125}I seeds for treatment of unresectable malignant obstructive jaundice: A meta-analysis. *World J Clin Cases* 2021; **9**: 10979-10993 [PMID: 35047608 DOI: 10.12998/wjcc.v9.i35.10979]

19 **Stupin V**, Abramov I, Gahramanov T, Kovalenko A, Manturova N, Litvitskiy P, Balkizov Z, Silina E. Comparative Study of the Results of Operations in Patients with Tumor and Non-Tumor Obstructive Jaundice Who Received and Did Not Receive Antioxidant Therapy for the Correction of Endotoxemia, Glycolysis, and Oxidative Stress. *Antioxidants (Basel)* 2022; **11** [PMID: 35740100 DOI: 10.3390/antiox11061203]

20 **Ng TG**, Damiris K, Trivedi U, George JC. Obstructive jaundice, a rare presentation of lung cancer: A case report. *Respir Med Case Rep* 2021; **33**: 101425 [PMID: 34401271 DOI: 10.1016/j.rmcr.2021.101425]

21 **Segaran N**, Sandrasegaran K, Devine C, Wang MX, Shah C, Ganeshan D. Features of primary pancreatic lymphoma: A bi-institutional review with an emphasis on typical and atypical imaging features. *World J Clin Oncol* 2021; **12**: 823-832 [PMID: 34631445 DOI: 10.5306/wjco.v12.i9.823]

22 **Nakamura Y**, Ito K, Takemura N, Inagaki F, Mihara F, Kokudo N. Elevation in creatine kinase isoenzyme-MM associated with hepatocellular carcinoma: a case report and review of literature. *Clin J Gastroenterol* 2022; **15**: 460-466 [PMID: 35199319 DOI: 10.1007/s12328-022-01612-w]

23 **Pang L**, Wu S, Kong J. Comparison of Efficacy and Safety between Endoscopic Retrograde Cholangiopancreatography and Percutaneous Transhepatic Cholangial Drainage for the Treatment of Malignant Obstructive Jaundice: A Systematic Review and Meta-Analysis. *Digestion* 2023; **104**: 85-96 [PMID: 36617409 DOI: 10.1159/000528020]

24 **Hasimu A**, Gu JP, Ji WZ, Zhang HX, Zhu DW, Ren WX. Comparative Study of Percutaneous Transhepatic Biliary Stent Placement with or without Iodine-125 Seeds for Treating Patients with Malignant Biliary Obstruction. *J Vasc Interv Radiol* 2017; **28**: 583-593 [PMID: 28162906 DOI: 10.1016/j.jvir.2016.11.038]

25 **Turan AS**, Jenniskens S, Martens JM, Rutten MJCM, Yo LSF, van Strijen MJL, Drenth JPH, Siersema PD, van Geenen EJM. Complications of percutaneous transhepatic cholangiography and biliary drainage, a multicenter observational study. *Abdom Radiol (NY)* 2022; **47**: 3338-3344 [PMID: 34357434 DOI: 10.1007/s00261-021-03207-4]

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ORIGINAL ARTICLE

Retrospective Study

Clinical efficacy of Gamma Knife® combined with transarterial chemoembolization and immunotherapy in the treatment of primary liver cancer

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Abstract

BACKGROUND

This study was designed to investigate the clinical efficacy and safety of Gamma Knife® combined with transarterial chemoembolization (TACE) and immunotherapy in the treatment of primary liver cancer.

AIM

To investigate the clinical efficacy and safety of Gamma Knife® combined with TACE and immune-targeted therapy in the treatment of primary liver cancer.

METHODS

Clinical data from 51 patients with primary liver cancer admitted to our hospital between May 2018 and October 2022 were retrospectively collected. All patients underwent Gamma Knife® treatment combined with TACE and immunotherapy. The clinical efficacy, changes in liver function, overall survival (OS), and progression-free survival (PFS) of patients with different treatment responses were evaluated, and adverse reactions were recorded.

RESULTS

The last follow-up for this study was conducted on October 31, 2023. Clinical evaluation of the 51 patients with primary liver cancer revealed a partial response (PR) in 27 patients, accounting for 52.94% (27/51); stable disease (SD) in 16 patients, accounting for 31.37% (16/51); and progressive disease (PD) in 8 patients, accounting for 15.69% (8/51). The objective response rate was 52.94%, and the disease control rate was 84.31%. Alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, and alpha-fetoprotein isoform levels

decreased after treatment compared with pretreatment (all P = 0.000). The median OS was 26 months [95% confidence interval (95%CI): 19.946-32.054] in the PR group and 19 months (95%CI: 14.156-23.125) in the SD + PD group, with a statistically significant difference (P = 0.015). The median PFS was 20 months (95%CI: 18.441-34.559) in the PR group and 12 months (95%CI: 8.745-13.425) in the SD + PD group, with a statistically significant difference (P = 0.002). Common adverse reactions during treatment included nausea and vomiting (39.22%), thrombocytopenia (27.45%), and leukopenia (25.49%), with no treatment-related deaths reported.

CONCLUSION

Gamma Knife® combined with TACE and immune-targeted therapy is safe and effective in the treatment of primary liver cancer and has a good effect on improving the clinical benefit rate and liver function of patients.

Key Words: Gamma Knife®; Transarterial chemoembolization; Immunotherapy; Primary liver cancer; Liver function

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Core Tip: Most patients with primary liver cancer are diagnosed in the middle and late stage, and lose the best opportunity for surgical treatment. Transcatheter arterial chemoembolization (TACE), immune targeted therapy and gamma knife technology are all important methods for clinical treatment of liver cancer. This study mainly discusses the clinical efficacy of gamma knife combined with TACE and immune targeted therapy for primary liver cancer, and provides reference for clinical treatment.

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INTRODUCTION

Primary liver cancer is the fourth leading cause of cancer-related deaths worldwide, and China is considered a region with a high incidence of primary liver cancer, ranking second among malignant tumors in the country[1]. Due to its insidious onset and lack of obvious clinical symptoms in the early stages, more than 80% of patients are diagnosed at an advanced stage[2], resulting in missed opportunities for optimal surgical treatment and considerable resistance to conventional chemotherapy and radiation therapy. Transarterial chemoembolization (TACE) is a commonly used and effective method for patients with unresectable or advanced liver cancer, and multiple studies have shown favorable outcomes with TACE in the treatment of primary liver cancer[3]. However, some studies have indicated that the local tumor necrosis rate after TACE is only 10% to 20%[4]. It has been suggested that TACE treatment can induce partial ischemia and shrinkage of intrahepatic tumors, reducing tumor burden. At this stage, combination immunotherapy can achieve better clinical results[5]. Immunotherapy utilizes the body's own immune system to attack and destroy cancer cells, inhibiting tumor growth and improving patient survival. One commonly used method of immunotherapy is the use of checkpoint inhibitors, such as programmed cell death ligand 1 (PD-1) monoclonal antibodies, which block the interaction between PD-1 and its ligands PD-L1 and PD-L2, thus relieving immune suppression, activating T-cell function, generating tumor immune responses, and exerting antitumor effects. They have been widely used in immunotherapy[6]. With the development of stereotactic radiosurgery, Gamma Knife® has been extensively used to treat neurosurgical and somatic tumor diseases, improving treatment precision based on precise tumor localization[7]. In this study, we primarily aimed to explore the clinical efficacy of Gamma Knife® combined with TACE and immunotherapy in the treatment of primary liver cancer, providing a reference for clinical treatment.

MATERIALS AND METHODS

Subject selection

This retrospective study was conducted in accordance with the principles of the Helsinki Declaration. The clinical data of 51 patients with primary liver cancer admitted to Yangzhou Friendship Hospital Affiliated with the Medical College of Yangzhou University from May 2018 to October 2022 were retrospectively collected. The inclusion criteria were as follows: Histopathologically or radiologically confirmed primary liver cancer; barcelona clinic liver cancer (BCLC) stage B to C, with an expected survival period of more than 3 months; Child–Pugh class A or B; treatment plan involving Gamma Knife® combined with TACE and immunotherapy; and availability of complete clinical data. This study was approved by the Ethics Committee of Yangzhou Friendship Hospital Affiliated with the Medical College of Yangzhou University, and informed consent was waived.

The exclusion criteria included contraindications for TACE, the presence of other malignant tumors, coagulation disorders, or immune dysfunction, a pathological diagnosis of metastatic liver cancer, poor medication compliance, incomplete case data, and loss to follow-up.

Treatment protocol

TACE: After local infiltration anesthesia with 2% lidocaine injection, the Seldinger technique was used for percutaneous puncture of the femoral artery. A 5F catheter was inserted into the hepatic artery for angiography to identify the tumor-feeding arteries. Chemotherapeutic drugs, including floxuridine powder (30 mg) and gemcitabine powder (1000 mg/m^2), were infused through the catheter, and ethiodized oil was used as the embolic agent. The endpoint for embolization was the absence of tumor staining during angiography. After the procedure, patients underwent repeat TACE treatment every 3 to 4 wk based on the deposition of iodized oil, liver function, alpha-fetoprotein levels, and other laboratory indicators.

Gamma Knife® procedure: Gamma Knife® treatment was typically scheduled between two interventions or after the second intervention. Before treatment began, physicians utilized imaging techniques such as magnetic resonance imaging or computed tomography to determine the location and size of the tumors within the liver. A treatment plan was then formulated, specifying the direction, dosage, and treatment area for the radiation. The specific procedure involved the patient assuming a supine position and being immobilized using a vacuum body mold. The Gamma Knife®, a stereotactic radiosurgery system, was employed to deliver focused radiation in a 360-degree rotational manner, ensuring that the 50% isodose curve acutely covered the target volume. The tumor region was delineated through a dose-volume histogram, aiding in the development of the treatment strategy. The peripheral dose around the tumor ranged from 3 Gy to 5 Gy per session, with a total peripheral dose ranging from 36 Gy to 40 Gy over 2 wk to 3 wk. The shape of the radiation field was meticulously designed based on the visualization of the radiation beams, ensuring that the target tumor area was well within the treatment range while minimizing direct exposure to vital organs and tissues. Routine liver protection therapy was administered throughout the treatment period.

Targeted therapy: (1) For patients with a body weight < 60 kg, oral administration of lenvatinib mesylate capsules was at a dosage of 8 mg once daily. For patients with a body weight ≥ 60 kg, the dosage was 2 mg once daily; (2) oral administration of sorafenib tosylate tablets was at a dosage of 0.4 g twice daily; (3) the oral administration apatinib mesylate tablets dosage was 750 mg once daily. The aforementioned three medications were taken until progressive disease (PD) or the occurrence of intolerable adverse reactions; and (4) the oral administration dosage of regorafenib tablets was 160 mg once daily for 28 d, constituting one cycle. The medication was taken from day 1 to day 2 of each cycle.

Immunosuppressive therapy: (1) Dilly's regimen: 200 mg, given intravenously on day 1 of each cycle, every 3 wk; and (2) regarding bevacizumab biosimilar (Davotin, both referring to bevacizumab injection), the dosage was 7.5 mg/kg, administered *via* intravenous infusion once every 3 wk, starting on the first day of each cycle.

Observation indicators

(1) Treatment efficacy: The evaluation criteria for treatment efficacy followed the Response Evaluation Criteria in Solid Tumors (RECIST)[8], which categorizes the response as complete response (CR), partial response (PR), stable disease (SD), or PD. The objective response rate was calculated as (number of CRs + number of SD patients) divided by the total number of patients, multiplied by 100%. The disease control rate was calculated as (number of CRs + number of PRs + number of SD patients) divided by the total number of patients, multiplied by 100%; (2) liver function: Liver function changes before and after treatment were assessed; (3) adverse reaction evaluation: Adverse reactions during the treatment period were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE 5.0), which classifies adverse reactions into grades 1 to 5, with grades 3 to 5 indicating severe adverse events; and (4) survival outcomes: Analysis of overall survival (OS) and progression-free survival (PFS) among patients with different treatment efficacies. The final follow-up for this study was conducted until October 31, 2023. OS was defined as the time from diagnosis to either patient death or the last follow-up. PFS was defined as the time from diagnosis to PD or the last follow-up, with PD defined as abnormal serum tumor markers or imaging findings indicating an increase in preexisting lesions or the appearance of new lesions.

Statistical analysis

Data analysis was performed using SPSS 23.0 software. Normally distributed continuous data are presented as the mean ± SD, and the *t* test was used for group comparisons. Categorical data are presented as *n* (%) and were compared using the Chi-square test. K-M survival curves were used to analyze the OS and PFS of patients with different treatment outcomes. A level of $P < 0.05$ was considered indicative of statistical significance.

RESULTS

Baseline characteristics of 51 patients with primary liver cancer

Among the 51 patients with primary liver cancer, there were 42 males and 9 females. Seven patients were younger than 60 years, while 44 patients were 60 years old or older. Eleven patients had no viral infection, 34 patients had hepatitis B infection, 4 patients had hepatitis C infection, and 2 patients had coinfection of hepatitis B and hepatitis C. Forty-five

patients were classified as Child-Pugh grade A, and six patients were classified as grade B. Among the patients, 11 were in BCLC stage B, and 40 were in stage C. Twenty patients had a single tumor, while 31 had two or more tumors. Nineteen patients had a tumor diameter less than 5 cm, while 32 had a diameter of 5 cm or larger. The baseline characteristics are presented in Table 1.

Clinical efficacy evaluation

The last follow-up in this study was conducted until October 31, 2023. The clinical efficacy evaluation of 51 patients with primary liver cancer revealed a PR in 27 patients, accounting for 52.94% (27/51) of the total patients; SD in 16 patients, accounting for 31.37% (16/51); and PD in 8 patients, accounting for 15.69% (8/51). The objective response rate was 52.94%, and the disease control rate was 84.31% (Table 2).

Liver function index evaluation

After treatment, the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), alpha-fetoprotein isoform (AFP-L3) in the patients decreased significantly compared to those before treatment ($P < 0.001$). Table 3 shows the changes in liver function indices before and after treatment.

Survival outcome evaluation

The median OS times for patients in the PR group and the SD + PD group were 26 months [95% confidence interval (95%CI): 19.946-32.054] and 19 months (95%CI: 14.156-23.125), respectively, which were significantly different ($P = 0.015$). Figure 1A shows a comparison of OS curves between the PR group and the SD + PD group. The median PFS times for patients in the PR group and the SD + PD group were 20 months (95%CI: 18.441-34.559) and 12 months (95%CI: 8.745-13.425), respectively, which were significantly different ($P = 0.002$). Figure 1B shows a comparison of PFS curves between the PR group and the SD + PD group.

Incidence of adverse events

During the treatment of the 51 patients with primary liver cancer, there were no treatment-related deaths. The common types of adverse reactions included nausea and vomiting (39.22%), platelet reduction (27.45%), and leukocyte reduction (25.49%). The most common adverse reactions were hypertension (7.84%), leukocyte reduction (5.88%), and platelet reduction (3.92%). All adverse reactions in the patients improved with corresponding symptomatic treatment and adjustment of the targeted drug dosage. Table 4 shows the details of the occurrence of adverse events.

DISCUSSION

The pathogenesis of primary liver cancer is complex, and early-stage cases often lack obvious symptoms. By the time symptoms such as liver pain, fatigue, weight loss, and decreased appetite manifest, the disease is usually in the advanced stage, and the optimal treatment window is often missed[8]. TACE is the main treatment method for advanced primary liver cancer. Although TACE has shown substantial efficacy in recent years, long-term outcomes are inevitably affected by the development of collateral vessels or revascularization, increasing the risk of tumor recurrence and distant metastasis and thus limiting the effectiveness of TACE as a standalone treatment for advanced primary liver cancer[9,10]. Therefore, it is highly important to explore other safer and more effective methods to improve the long-term prognosis of patients with advanced primary liver cancer, especially in combination with TACE.

Gamma Knife® technology is a stereotactic radiotherapy technique that uses high-dose focused radiation to treat tumors and protect normal tissue by irradiating the tumor tissue locally. In recent years, a large number of studies have indicated[11,12] that the combination of Gamma Knife® and TACE can further improve treatment outcomes for patients with primary liver cancer and promote disease improvement. Reports in the literature[13] indicate that compared to TACE alone, the combination of Gamma Knife® therapy and TACE for primary liver cancer treatment can enhance short-term treatment efficacy without increasing adverse reactions in patients and prolong survival time. The mechanism of TACE in treating primary liver cancer involves the direct killing of tumor cells and interruption of the tumor blood supply by delivering antitumor drugs and embolic agents into the hepatic artery. Additionally, TACE treatment can increase the expression of hypoxia-inducible factors, thereby upregulating the expression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor receptor (PDGFR), promoting tumor angiogenesis, and hindering antitumor effects[14,15]. In recent years, studies have indicated[16] that tyrosine kinase receptor inhibitors such as lenvatinib and sorafenib can inhibit the expression of VEGFR and PDGFR, further enhancing the therapeutic effect of TACE. Therefore, the combination of TACE and targeted drugs can to some extent compensate for the limitations of TACE.

Currently, various immune checkpoint inhibitors have been successfully used in clinical treatment. Among them, PD-1 monoclonal antibodies, which are widely used, can block the binding of PD-1 to its ligands PD-L1 and PD-L2, relieving immune suppression, activating T-cell function, eliciting tumor immune responses, and exerting antitumor effects[17]. Immune drug combinations with targeted therapy have become the standard first-line treatment for advanced primary liver cancer. In recent years, phase I/II studies of immune checkpoint inhibitors combined with targeted drugs such as lenvatinib combined with regorafenib and anlotinib combined with apatinib have shown promising results[18]. The results of the IMbrave150 trial showed that compared to sorafenib alone, the combination of atezolizumab and bevacizumab significantly prolonged the median PFS and OS of liver cancer patients[19]. Due to the unique and complex immune microenvironment of hepatocellular carcinoma, which is characterized mainly by immune suppression,

Table 1 Baseline characteristics of 51 patients with primary liver cancer, *n* (%)

Item	Case
Gender	
Male	42 (82.35)
Female	9 (17.65)
Age	
< 60	7 (13.73)
≥ 60	44 (86.27)
Viral infection	
No	11 (21.57)
HBV	34 (66.67)
HCV	4 (7.84)
HBV + HCV	2 (3.92)
Child-Pugh grade	
A	45 (88.24)
B	6 (11.76)
BCLC	
B	11 (21.57)
C	40 (78.43)
Tumor number	
1	20 (39.22)
≥ 2	31 (60.78)
Tumor diameter	
< 5 cm	19 (37.25)
≥ 5 cm	32 (62.75)

HBV: Hepatitis B virus; HCV: Hepatitis C virus; BCLC: Barcelona clinic liver cancer.

Table 2 Clinical efficacy evaluation of 51 patients with primary liver cancer, *n* (%)

Item	Case
CR	0 (0)
PR	27 (52.94)
SD	16 (31.37)
PD	8 (15.69)
Objective response rate	27 (52.94)
Disease control rate	43 (84.31)

CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease.

monotherapy with immune checkpoint inhibitors has limited efficacy. Therefore, we predict that combining immune therapy with Gamma Knife® therapy, TACE, and targeted drugs may be effective. Studies[20] have shown that compared with TACE alone in the treatment of patients with liver cancer, targeted therapy and immunotherapy used in conjunction with TACE can further prolong the survival time of patients and is safe and effective.

The results of this study showed that among 51 patients with primary liver cancer who received Gamma Knife® therapy combined with TACE and immune-targeted therapy, liver function indicators significantly improved. The clinical evaluation revealed a PR rate of 52.94%, an SD1 rate of 31.37%, a PD rate of 15.69%, an objective response rate of

Table 3 Changes in liver function indices before and after treatment (mean ± SD)

	Before (n = 51)	After (n = 51)	t	P value
ALT (U/L)	75.11 ± 4.62	60.62 ± 4.09	16.771	0
AST (U/L)	119.47 ± 11.69	41.57 ± 6.88	41.013	0
LDH (U/L)	439.15 ± 20.62	236.73 ± 18.15	52.623	0
AFP-13 (%)	18.52 ± 5.37	11.31 ± 2.65	8.598	0

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase; AFP-L3: Alpha-fetoprotein isoform.

Table 4 Incidence of adverse events, n (%)

	Incidence	Grade 3-5
Hypertension	10 (19.61)	4 (7.84)
Platelet reduction	14 (27.45)	2 (3.92)
ALT elevation	7 (13.73)	1 (1.96)
Leukocyte reduction	13 (25.49)	3 (5.88)
Nausea and vomiting	20 (39.22)	1 (1.96)
Fever	3 (5.88)	0 (0.00)
Hypothyroidism	2 (3.92)	0 (0.00)
Abdominal pain	4 (7.84)	0 (0.00)
Hyperbilirubinemia	6 (11.76)	0 (0.00)
Ascites	3 (5.88)	0 (0.00)
Hypokalemia	2 (3.92)	0 (0.00)

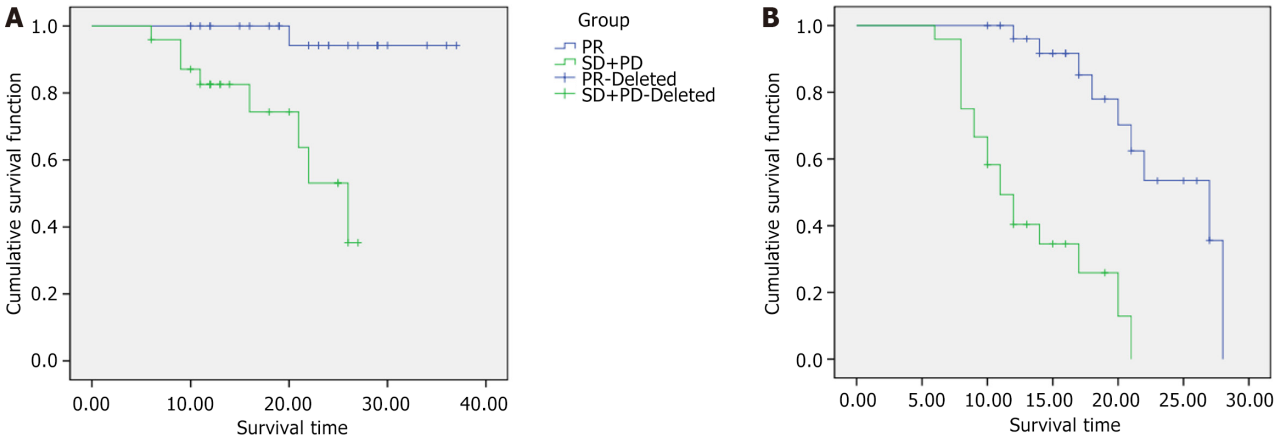


Figure 1 Comparison of overall survival and progression-free survival curves between the partial response group and the stable disease + progressive disease group. A: Overall survival; B: Progression-free survival. PR: Partial response; SD: Stable disease; PD: Progressive disease.

52.94%, and a disease control rate of 84.31%, similar to previous reports[21], indicating good efficacy of Gamma Knife® combined with TACE and immune-targeted therapy for primary liver cancer. From the comparison of OS and PFS between the PR group and the SD + PD group, the PR group was shown to exhibit significantly greater OS and PFS than the SD + PD group; this result suggests that Gamma Knife® combined with TACE and immune targeted therapy may increase the possibility of achieving curative resection in the conversion treatment of initially unresectable advanced primary liver cancer, potentially improving OS and recurrence-free survival. It is speculated that the reason may be that Gamma Knife® combined with TACE and immune-targeted therapy for primary liver cancer. TACE plays an antitumor role by directly killing and cutting off vascular nutrients. Immunotherapy can play a good antitumor role by generating a tumor immune response, while Gamma Knife® enables the delivery of higher doses of radiotherapy for smaller target lesions. The combination of the three in the treatment of patients with liver cancer can further improve the clinical benefit

rate and prolong the survival time of patients[11]. At the same time, in the present study, the common types of adverse reactions during the treatment of patients were nausea and vomiting (39.22%), thrombocytopenia (27.45%), leukopenia (25.49%), *etc*., and there were no treatment-related death events, confirming the safety of Gamma Knife® combined with TACE and immune-targeted therapy.

CONCLUSION

Gamma Knife® combined with TACE and immune-targeted therapy is safe and effective for treating primary liver cancer, improving clinical benefits and enhancing liver function in patients. This study has certain limitations, such as its small sample size and single-center retrospective nature. In the future, expanding the sample size and conducting multicenter clinical trials will be important for further validation of the research findings.

FOOTNOTES

Author contributions: Wang GF and Shu CX contributed equally to this work and are co-first authors, including design of the study, acquiring and analyzing data from experiments, and writing of the actual manuscript; Wang GF, Shu CX, and Jia YQ designed the experiment and conducted clinical data collection; Cai XD and Wang HB performed postoperative follow-up and recorded data; Wang GF, Shu CX, Xu JH, and Jia YQ conducted a number of collation and statistical analysis; and all the authors have read and approved the final manuscript.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Yangzhou Friendship Hospital Affiliated to Medical College of Yangzhou University.

Informed consent statement: The ethics committee agrees to waive informed consent.

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Data sharing statement: All data generated or analyzed during this study are included in this published article.

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REFERENCES

1 **Cao W**, Chen HD, Yu YW, Li N, Chen WQ. Changing profiles of cancer burden worldwide and in China: a secondary analysis of the global cancer statistics 2020. *Chin Med J (Engl)* 2021; **134**: 783-791 [PMID: 33734139 DOI: 10.1097/CM9.0000000000001474]
2 **Anwanwan D**, Singh SK, Singh S, Saikam V, Singh R. Challenges in liver cancer and possible treatment approaches. *Biochim Biophys Acta Rev Cancer* 2020; **1873**: 188314 [PMID: 31682895 DOI: 10.1016/j.bbcan.2019.188314]
3 **Wu JY**, Yin ZY, Bai YN, Chen YF, Zhou SQ, Wang SJ, Zhou JY, Li YN, Qiu FN, Li B, Yan ML. Lenvatinib Combined with Anti-PD-1 Antibodies Plus Transcatheter Arterial Chemoembolization for Unresectable Hepatocellular Carcinoma: A Multicenter Retrospective Study. *J Hepatocell Carcinoma* 2021; **8**: 1233-1240 [PMID: 34676181 DOI: 10.2147/JHC.S332420]
4 **Zhang C**, Dai YH, Lian SF, Liu L, Zhao T, Wen JY. Efficacy of transcatheter arterial chemoembolization using pirarubicin-loaded microspheres combined with lobaplatin for primary liver cancer. *World J Clin Cases* 2022; **10**: 9650-9656 [PMID: 36186198 DOI: 10.12998/wjcc.v10.i27.9650]
5 **Greten TF**, Mauda-Havakuk M, Heinrich B, Korangy F, Wood BJ. Combined locoregional-immunotherapy for liver cancer. *J Hepatol* 2019; **70**: 999-1007 [PMID: 30738077 DOI: 10.1016/j.jhep.2019.01.027]
6 **Zheng Y**, Wang S, Cai J, Ke A, Fan J. The progress of immune checkpoint therapy in primary liver cancer. *Biochim Biophys Acta Rev Cancer* 2021; **1876**: 188638 [PMID: 34688805 DOI: 10.1016/j.bbcan.2021.188638]
7 **Cai Y**, Chang Q, Xiao E, Shang QL, Chen Z. Transcatheter arterial chemoembolization (TACE) combined with γ-knife compared to TACE or γ-knife alone for hepatocellular carcinoma. *Medicine (Baltimore)* 2018; **97**: e10890 [PMID: 29851811 DOI: 10.1097/MD.0000000000010890]
8 **Chang Y**, Jeong SW, Young Jang J, Jae Kim Y. Recent Updates of Transarterial Chemoembololization in Hepatocellular Carcinoma. *Int J Mol Sci* 2020; **21** [PMID: 33142892 DOI: 10.3390/ijms21218165]
9 **Raoul JL**, Forner A, Bolondi L, Cheung TT, Kloeckner R, de Baere T. Updated use of TACE for hepatocellular carcinoma treatment: How and

when to use it based on clinical evidence. *Cancer Treat Rev* 2019; **72**: 28-36 [PMID: 30447470 DOI: 10.1016/j.ctrv.2018.11.002]

10 **Zhang H**, Wang J, Li W, Liu S, Li Z, Hu X. Microwave ablation combined with I125 seed implantation for treatment of residual lesions of liver cancer after TACE. *J Cancer Res Ther* 2022; **18**: 1392-1396 [PMID: 36204888 DOI: 10.4103/jcrt.jcrt_1252_21]

11 **Llovet JM**, De Baere T, Kulik L, Haber PK, Greten TF, Meyer T, Lencioni R. Locoregional therapies in the era of molecular and immune treatments for hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol* 2021; **18**: 293-313 [PMID: 33510460 DOI: 10.1038/s41575-020-00395-0]

12 **Wang J**, Luo J, Yin X, Huang W, Cao H, Wang G, Wang J, Zhou J. Jiedu Granule Combined with Transcatheter Arterial Chemoembolization and Gamma Knife Radiosurgery in Treating Hepatocellular Carcinoma with Portal Vein Tumor Thrombus. *Biomed Res Int* 2019; **2019**: 4696843 [PMID: 31341898 DOI: 10.1155/2019/4696843]

13 **Honda Y**, Kimura T, Aikata H, Kobayashi T, Fukuhara T, Masaki K, Nakahara T, Naeshiro N, Ono A, Miyaki D, Nagaoki Y, Kawaoka T, Takaki S, Hiramatsu A, Ishikawa M, Kakizawa H, Kenjo M, Takahashi S, Awai K, Nagata Y, Chayama K. Stereotactic body radiation therapy combined with transcatheter arterial chemoembolization for small hepatocellular carcinoma. *J Gastroenterol Hepatol* 2013; **28**: 530-536 [PMID: 23216217 DOI: 10.1111/jgh.12087]

14 **Peng Z**, Fan W, Zhu B, Wang G, Sun J, Xiao C, Huang F, Tang R, Cheng Y, Huang Z, Liang Y, Fan H, Qiao L, Li F, Zhuang W, Peng B, Wang J, Li J, Kuang M. Lenvatinib Combined With Transarterial Chemoembolization as First-Line Treatment for Advanced Hepatocellular Carcinoma: A Phase III, Randomized Clinical Trial (LAUNCH). *J Clin Oncol* 2023; **41**: 117-127 [PMID: 35921605 DOI: 10.1200/JCO.22.00392]

15 **Xiang Z**, Li G, Mu L, Wang H, Zhou C, Yan H, Huang M. TACE Combined with Lenvatinib and Camrelizumab for Unresectable Multiple Nodular and Large Hepatocellular Carcinoma (>5 cm). *Technol Cancer Res Treat* 2023; **22**: 15330338231200320 [PMID: 37723998 DOI: 10.1177/15330338231200320]

16 **Shimose S**, Iwamoto H, Niizeki T, Tanaka M, Shirono T, Moriyama E, Noda Y, Nakano M, Suga H, Kuromatsu R, Torimura T, Koga H, Kawaguchi T. Efficacy of Lenvatinib Combined with Transcatheter Intra-Arterial Therapies for Patients with Advanced-Stage of Hepatocellular Carcinoma: A Propensity Score Matching. *Int J Mol Sci* 2023; **24** [PMID: 37762018 DOI: 10.3390/ijms241813715]

17 **Cai M**, Huang W, Huang J, Shi W, Guo Y, Liang L, Zhou J, Lin L, Cao B, Chen Y, Zhu K. Transarterial Chemoembolization Combined With Lenvatinib Plus PD-1 Inhibitor for Advanced Hepatocellular Carcinoma: A Retrospective Cohort Study. *Front Immunol* 2022; **13**: 848387 [PMID: 35300325 DOI: 10.3389/fimmu.2022.848387]

18 **Wu JY**, Wu JY, Li YN, Qiu FN, Zhou SQ, Yin ZY, Chen YF, Li B, Zhou JY, Yan ML. Lenvatinib combined with anti-PD-1 antibodies plus transcatheter arterial chemoembolization for neoadjuvant treatment of resectable hepatocellular carcinoma with high risk of recurrence: A multicenter retrospective study. *Front Oncol* 2022; **12**: 985380 [PMID: 36212494 DOI: 10.3389/fonc.2022.985380]

19 **Finn RS**, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med* 2020; **382**: 1894-1905 [PMID: 32402160 DOI: 10.1056/NEJMoa1915745]

20 **Yuan Y**, He W, Yang Z, Qiu J, Huang Z, Shi Y, Lin Z, Zheng Y, Chen M, Lau WY, Li B, Yuan Y. TACE-HAIC combined with targeted therapy and immunotherapy versus TACE alone for hepatocellular carcinoma with portal vein tumour thrombus: a propensity score matching study. *Int J Surg* 2023; **109**: 1222-1230 [PMID: 37026861 DOI: 10.1097/JS9.0000000000000256]

21 **Kondo Y**, Morosawa T, Minami S, Tanaka Y. DEB-TACE combined with hepatic artery infusion chemotherapy might be an affordable treatment option for advanced stage of HCC. *Sci Rep* 2022; **12**: 16868 [PMID: 36207618 DOI: 10.1038/s41598-022-21472-1]

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ORIGINAL ARTICLE

Retrospective Study

Identifying the risk factors for pancreatic fistula after laparoscopic pancreaticoduodenectomy in patients with pancreatic cancer

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Abstract

BACKGROUND

Laparoscopic pancreaticoduodenectomy (LPD) is a surgical procedure for treating pancreatic cancer; however, the risk of complications remains high owing to the wide range of organs involved during the surgery and the difficulty of anastomosis. Pancreatic fistula (PF) is a major complication that not only increases the risk of postoperative infection and abdominal hemorrhage but may also cause multi-organ failure, which is a serious threat to the patient's life. This study hypothesized the risk factors for PF after LPD.

AIM

To identify the risk factors for PF after laparoscopic pancreatoduodenectomy in patients with pancreatic cancer.

METHODS

We retrospectively analyzed the data of 201 patients admitted to the Fudan University Shanghai Cancer Center between August 2022 and August 2023 who underwent LPD for pancreatic cancer. On the basis of the PF's incidence (grades B and C), patients were categorized into the PF (n = 15) and non-PF groups (n = 186). Differences in general data, preoperative laboratory indicators, and surgery-related factors between the two groups were compared and analyzed using multifactorial logistic regression and receiver-operating characteristic (ROC) curve analyses.

RESULTS

The proportions of males, combined hypertension, soft pancreatic texture, and pancreatic duct diameter ≤ 3 mm; surgery time; body mass index (BMI); and amylase (Am) level in the drainage fluid on the first postoperative day (Am >

1069 U/L) were greater in the PF group than in the non-PF group ($P < 0.05$), whereas the preoperative monocyte count in the PF group was lower than that in the non-PF group (all $P < 0.05$). The logistic regression analysis revealed that BMI > 24.91 kg/m² [odds ratio (OR) =13.978, 95% confidence interval (CI): 1.886-103.581], hypertension (OR = 8.484, 95%CI: 1.22-58.994), soft pancreatic texture (OR = 42.015, 95%CI: 5.698-309.782), and operation time > 414 min (OR = 15.41, 95%CI: 1.63-145.674) were risk factors for the development of PF after LPD for pancreatic cancer (all $P < 0.05$). The areas under the ROC curve for BMI, hypertension, soft pancreatic texture, and time prediction of PF surgery were 0.655, 0.661, 0.873, and 0.758, respectively.

CONCLUSION

BMI (> 24.91 kg/m²), hypertension, soft pancreatic texture, and operation time (> 414 min) are considered to be the risk factors for postoperative PF.

Key Words: Pancreatic cancer; Laparoscopy; Pancreaticoduodenectomy; Pancreatic fistula; Risk factors; Receiver-operating characteristic curve

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Core Tip: Controlling the highly correlated risk factors of pancreatic fistula (PF) following laparoscopic pancreaticoduodenectomy (LPD) can decrease PF incidence. Although existing studies have confirmed that the occurrence of PF after LPD is influenced by various factors, including self-development and surgery-related factors, few studies have examined the factors influencing the development of PF after LPD in pancreatic cancer. Here, we analyzed the factors associated with the development of PF after LPD for pancreatic cancer and found that body mass index (> 24.91 kg/m²), hypertension, soft pancreatic texture, and operation time (> 414 min) were risk factors.

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INTRODUCTION

Pancreatic cancer is characterized by rapid progression, high malignancy, and poor prognosis. Pancreatic cancer is not sensitive to chemotherapy; therefore, surgical removal is the only effective treatment for patients to achieve long-term survival[1]. Pancreaticoduodenectomy (PD) is frequently used in the treatment of pancreatic cancer, and it is the most complex clinical surgery involving the viscera and anatomical structures[2]. Following the advancements in minimally invasive technology, laparoscopic surgeries have been increasingly used in clinical PD, with significantly improved safety and reduced mortality[3]. However, owing to the wide range of organs involved in the operation and the difficulty of anastomosis, the risk of complications remains high. Pancreatic fistula (PF) is one of the main complications of laparoscopic PD (LPD). The flow of pancreatic fluid into the abdominal cavity can corrode abdominal organs, provide conditions for bacterial proliferation, and increase the probability of postoperative infection, bleeding, and secondary sepsis, leading to death[4]. Controlling the highly correlated risk factors of PF after LPD and implementing targeted measures can reduce the probability of PF and alleviate its symptoms. Although current studies have confirmed that the occurrence of PF after LPD is influenced by various factors, including developmental, environmental, and surgical-related factors[5-7], few studies have focused on the factors influencing PF after LPD in patients with pancreatic cancer. Therefore, this study aimed to analyze PF's risk factors after LPD in patients with pancreatic cancer and serve as a basis for clinical prevention and treatment.

MATERIALS AND METHODS

Data sources

The case data of 201 patients with pancreatic cancer, who underwent LPD at Fudan University Shanghai Cancer Center between August 2022 and August 2023, were retrospectively analyzed. The entry criteria were as follows: (1) Diagnosis confirmed by physical examination, ultrasound examination, and pathological examination in accordance with the diagnostic standards for pancreatic cancer in the National Comprehensive Cancer Network guidelines[8]; (2) Line of LPD surgery without LPD contraindication; and (3) Complete clinical information. The exclusion criteria were: (1) Abnormal coagulation function; (2) Combined cardiopulmonary liver and kidney dysfunction; (3) Transfer to the open abdomen during surgery for various reasons; (4) Immunosuppressive diseases; and (5) Distant metastasis.

Surgical methods

All surgeries were performed in our department by surgeons with senior professional titles. Preoperative blood clotting and liver and kidney function tests were the routine biochemical examinations. After general anesthesia was achieved, the internal jugular vein catheter was inserted. After the pneumoperitoneum was established, a laparoscope was first placed in it. A 12-mm incision was made below the patient's navel and a 12-mm tubular channel (trocar) was inserted. Further, the incisions were located 2 cm above the junction of the right mid-clavicular line and the level of the navel and 1 cm beneath the junction of the right anterior armpit line and the lower edge of the ribs. Trocars measuring 10 and 12 mm were placed. The abdominal cavity was laparoscopically examined and the superior mesenteric vein was exposed; the associated ligaments were detached; the jejunum was cut; and the distal stomach, pancreas, gallbladder, hepatic duct, and gallbladder were removed. During the process, it is important to pay attention to ligation of the common hepatic artery and other vessels, clean the lymph nodes, irrigate the abdominal cavity after excision, and re-establish pneumoperitoneum for routine gastrointestinal (GI) reconstruction. Next, the drainage tube was placed behind the biliary-intestinal anastomosis and in front of the pancreato-intestinal anastomosis and the fixed. After the laparoscope and other equipment were withdrawn, the abdominal cavity was closed layer by layer to complete the operation.

Diagnostic criteria and grouping of postoperative PF

Diagnostic criteria for PF: The definition of PF per the diagnostic criteria of the International Study Group on Pancreatic Fistula[9] includes fluid drainage from anastomosis or pancreatic stump (> 10 mL/d) on or after postoperative day 3 and drainage fluid amylase (Am) level exceeding more than three times the maximum normal value of plasma Am for > 3 d consecutively. It also includes the presence of clinical signs such as fever, fluid accumulation surrounding the anastomosis on ultrasound or computed tomography imaging examination, and puncture biopsy-proven Am levels in fluid three times higher than the normal maximum for plasma Am. According to the different clinical manifestations of the classification standard of PF, grade A (no clinical significance) was observed in PF, which does not have any adverse clinical consequences; it is defined as an Am level in the drainage fluid 3 days or more after surgery that is 3 times higher than the upper limit of the normal serum Am concentration, but does not require any clinical treatment or only minimal treatment (*e.g.*, only drainage tube placement). Grade B was clinically significant and curable PF, which will affect the patient's postoperative rehabilitation process and require symptomatic treatment and adequate drainage, with a relatively increased length of hospital stay; it is usually accompanied by a certain degree of signs of infection, such as an elevated white blood cell count and low fever, and it may require antimicrobial therapy. Grade C PF was a severe life-threatening condition leading to abdominal cavity infection, sepsis, and multiple organ failure requiring intensive care, percutaneous puncture catheter, and adequate drainage of peripancreatic fluid. The risk of serious complications occurs. Recently, the field of pancreatic surgery has redefined grade A postoperative PF as a biochemical fistula and no longer as a genuine postoperative PF because of no important clinical significance. Grade B and C PFs indicated the clinical significance of PF. Grouping: Enrolled patients with pancreatic cancer were classified into PF and non-PF groups on the basis of the presence or absence of PF (grades B and C) after LPD.

Indicators of observation

General data included sex; age; body mass index (BMI; kg/m^2); history of smoking, hypertension, and diabetes; and American Society of Anesthesiologists' classification. Preoperative laboratory indicators included values of preoperative hemoglobin (g/L), preoperative platelet count (× 10^9/L), preoperative neutrophil count (× 10^9/L), preoperative monocyte count (× 10^9/L), preoperative lymphocyte count (× 10^9/L), preoperative albumin (g/L), preoperative total bilirubin (mmol/L), preoperative carbohydrate antigen 199 (CA199) (U/mL), preoperative carbohydrate antigen-CA125 (U/mL), preoperative alpha-fetoprotein (ng/mL), and preoperative carcinoembryonic antigen (ng/mL). Intraoperative and postoperative indices included intraoperative blood loss (mL), operative time (min), pancreatic texture, pancreatic duct diameter (mm), and Am levels in the drainage fluid on the first postoperative day (Am, U/L).

Statistical analysis

Data were analyzed and processed using SPSS software (version 23.0; IBM Corp.). Quantitative data with a normal distribution are expressed as, and the *t*-test was used to compare the data between the groups. Normal distribution of the measurement data was not fitted to the median (first quartile, third quartile) or M (P25, P75) using a nonparametric test between the groups. Count data are expressed as (%), and the χ^2 test was used to compare the data between the groups. Multivariate logistic regression analysis was used analyze the factors influencing PF after LPD in patients with pancreatic cancer. The receiver-operating characteristic (ROC) curve was used to assess the risk factors for pancreatic cancer and the predictive value of LPD for postoperative PF. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Postoperative PF occurred

Among the 201 patients with pancreatic cancer enrolled in this study, 123 had grade A PF, 14 had grade B PF, and one had grade C PF. Fifteen patients with grades B and C PF, with a probability of 7.46%, were enrolled in the PF group. A total of 186 patients with and without grade A PF were included in the non-PF group.

Comparison of the general data of the two patient groups

The proportions of male and hypertension and BMI were higher in the PF group than in the non-PF group ($P < 0.05$) (Table 1).

The preoperative laboratory indices of the two groups were compared

The preoperative monocyte count were significantly different between patients in the PF group and those in the non-PF group ($P < 0.05$). Comparison of other preoperative laboratory parameters showed no significant differences ($P > 0.05$) (Table 2).

Comparison of surgery-related indicators in the PF group and the non-PF group

The proportions of soft pancreatic texture, diameter of pancreatic duct ≤ 3 mm, and Am > 1069 U/L were greater in the PF group than in the non-PF group (all $P < 0.05$). Moreover, the operation time was longer in the PF group than in the non-PF group ($P < 0.05$) (Table 3).

Influencing factors of PF after LPD in patients with pancreatic cancer

Considering the occurrence of PF after LPD for patients with pancreatic cancer as the dependent variable and the related indicators that may affect the occurrence of PF after LPD for pancreatic cancer patients as the independent variables, the eight factors with meaningful differences in Tables 1-3, including sex, BMI, hypertension, preoperative monocyte count, soft pancreatic texture, pancreatic duct diameter, operation time, and Am, were analyzed using a logistic regression model. The variable assignment is shown in Table 4, in which BMI, preoperative monocyte count, and operation time were assigned on the basis of the best cut-off value determined by the corresponding ROC curve drawn using MedCalc software. Logistic regression analysis showed that BMI (> 24.91 kg/m$^{2)}$, hypertension, soft pancreatic texture, and surgery time (> 414 min) were the associated risk factors for postoperative PF in patients with pancreatic cancer after LPD ($P < 0.05$) (Table 5).

The predictive efficacy of indicators for postoperative PF

The results analyzed by the ROC curve indicated that the areas under the curve (AUCs) of BMI, hypertension, soft pancreatic texture, and operation time were 0.655, 0.661, 0.873, and 0.758, respectively, which had a certain predictive efficacy ($P < 0.05$) (Table 6 and Figure 1).

DISCUSSION

With the increasing development and maturity of laparoscopic technology, LPD has gradually replaced PD as the first-choice treatment for pancreatic cancer[10]. Compared with PD, LPD has the benefits of less trauma, less bleeding, quicker recovery, shorter hospitalization period, and fewer postoperative complications; however, both PD and LPD have a high postoperative mortality. PF is also a major cause of postoperative death[11]. Therefore, the general data of patients with pancreatic cancer and the perioperative factor index, which is used to assess their risk of postoperative PF after LPD, intervene, and decrease the rate of patients with postoperative PF, have important clinical significance.

Many studies have suggested that an excessive BMI is associated with postoperative PF[12-15]. This study's findings also confirmed a higher BMI in the PF group than in the non-PF group ($P < 0.05$). Further logistic regression analysis revealed that a BMI > 24.91 kg/m² was a risk factor for PF after LPD in patients with pancreatic cancer. This may be associated with the high difficulty of surgery in patients with high BMIs; the position of the pancreas in patients with a high BMI is deeper than that in people with a healthy BMI, which makes it difficult to perform pancreatojejunostomy. Concurrently, high visceral fat leads to a softer texture of the pancreas and more abundant adipose tissue under the capsule, which is not conducive for anastomotic suturing and prolongs the healing time[16,17]. Our results also showed that soft pancreatic texture increases the probability of PF risk after LPD. The soft texture of the pancreas has better exocrine function and can secrete more trypsinogen than the normal pancreatic texture[18]. The soft pancreas in matches is easy to tear and suture, causing pancreatic leakage and corrosion of surrounding tissue and blood vessels, inducing and aggravating postoperative PFs[19,20]. However, the hardness of the pancreas can only be subjectively evaluated by observing its morphology under laparoscopy because of the lack of direct contact with the pancreas during LPD; therefore, its texture accuracy needs to be investigated owing to the lack of standardized criteria for assessing the softness and hardness of the pancreas.

This study showed that a long surgery time can lead to an increased risk of PF after LPD for pancreatic cancer treatment. Notably, a long surgery time is related to factors such as instability of the surgical team, limitations of surgical instruments, and failure to overcome the learning curve of LPD (mainly the small number of activities in the early stages of LPD)[21,22]. Gouma *et al*[23] found that the rate of postoperative complications and mortality in LPD were related to the level of surgeons and the scale of hospitals, whereas the scale of hospitals was mainly related to the number of surgeries performed. The aforementioned conclusions may explain the relationship between the surgery time and postoperative PF. In addition, this study found that comorbid hypertension was significantly associated with the development of PF after LPD. Analysis of its possible causes is that patients with hypertension are generally accompanied by vascular stiffness and hemodynamic weakening, leading to thrombosis, which is not conducive to postoperative anastomosis. This promotes the formation or aggravation of PFs[24,25].

Table 1 Comparison of general data between the two groups [mean ± SD, *n* (%)]

Profile	PF group (*n* = 15)	Non-PF group (*n* = 186)	$t/\chi^2/z$ value	*P* value
Sex			5.227	0.022
Male	13 (86.67)	105 (56.45)		
Female	2 (13.33)	81 (43.55)		
Age (yr)	66.00 ± 8.64	62.35 ± 9.19	1.486	0.139
BMI (kg/m^2)	24.17 ± 2.96	22.58 ± 2.43	2.404	0.017
Smoking history			0.408	0.523
Yes	3 (20.00)	26 (13.98)		
No	12 (80.00)	160 (86.02)		
Hypertension			6.209	0.013
Yes	10 (66.67)	64 (34.41)		
No	5 (33.33)	122 (65.59)		
Combined diabetes			0.053	0.818
Yes	3 (20.00)	42 (22.58)		
No	12 (80.00)	144 (77.42)		
ASA classification			0.849	0.654
Level 1	0	7 (3.76)		
Level 2	15 (100)	176 (94.62)		
Level 3	0	3 (1.62)		

BMI: Body mass index; PF: Pancreatic fistula; ASA: American Society of Anesthesiologists.

Table 2 Comparison of preoperative laboratory indicators between the two groups [mean ± SD, M (P25, P75), *n* (%)]

Laboratory index	PF group (*n* = 15)	Non-PF group (*n* = 186)	$t/\chi^2/z$ value	*P* value
Hemoglobin (g/L)	129.93 ± 19.42	127.24 ± 16.18	0.610	0.542
PLT (× 10^9/L)	229.00 (197.00, 293.00)	233.00 (194.75, 289.00)	-0.113	0.910
NEUT (× 10^9/L)	4.70 (2.40, 5.60)	4.10 (2.90, 5.30)	-0.552	0.581
Monocyte count (× 10^9/L)	0.50 (0.40, 0.70)	0.50 (0.40, 0.53)	-2.020	0.043
Lymphocyte count (× 10^9/L)	1.60 (1.10, 1.70)	1.50 (1.20, 1.90)	-0.125	0.901
ALB (g/L)	41.57 ± 3.95	43.29 ± 4.08	-1.579	0.116
TBIL (μmol/L)	14.10 (7.90, 87.20)	27.50 (11.20, 103.15)	-1.199	0.231
Carbohydrate antigen (CA199)			2.197	0.138
≥ 35 U/mL	14 (93.33)	143 (76.88)		
< 35 U/mL	1 (6.67)	43 (23.12)		
Carbohydrate antigen (CA125, U/mL)	17.30 (11.50, 24.40)	15.80 (10.80, 24.20)	-0.198	0.843
AFP (ng/mL)	3.38 (2.23, 3.79)	2.87 (2.16, 3.83)	-0.443	0.658
CEA (ng/mL)	2.28 (2.01, 3.83)	3.26 (2.03, 5.32)	-1.317	0.188

PLT: Platelet count; NEUT: Neutrophil count; ALB: Albumin; TBIL: Total bilirubin; AFP: Alpha-fetoprotein; CEA: Carcinoembryonic antigen; PF: Pancreatic fistula.

Table 3 Comparison of operation-related indicators between the two groups [mean ± SD, M (P25, P75), *n* (%)]

Operation-related index	PF group (*n* = 15)	Non-PF group (*n* = 186)	*t*/χ^2/*z* value	*P* value
Pancreatic texture			64.728	< 0.001
Soft	11 (93.33)	11 (5.91)		
Hard	4 (6.67)	175 (94.09)		
Pancreatic duct diameter			7.807	0.005
> 3 mm	5 (33.33)	128 (68.82)		
≤ 3 mm	10 (66.67)	58 (31.18)		
Intraoperative blood loss (mL)	200.00 (200.00, 300.00)	200.00 (100.00, 300.00)	-1.939	0.052
Operation time (min)	439.87 ± 51.184	382.94 ± 61.74	3.474	0.001
Am			17.323	< 0.001
> 1069 U/L	12 (80.00)	52 (27.96)		
≤ 1069 U/L	3 (20.00)	134 (72.04)		

Am: Amylase; PF: Pancreatic fistula.

Table 4 Variable assignment

Variable	Variable name	Assignment description
Pancreatic fistula in patients with pancreatic cancer after LPD	Y	Yes = 1
		No = 0
Sex	X1	Male = 1
		Female = 0
BMI	X2	> 24.91 kg/m² = 1
		≤ 24.91 kg/m² = 0
Hypertension	X3	Yes = 1
		No = 0
Monocyte count	X4	> 0.4 × 10^9/L = 1
		≤ 0.4 × 10^9/L = 0
Pancreatic texture	X5	Soft = 1
		Hard = 0
Pancreatic duct diameter	X6	> 3 mm = 1
		≤ 3mm = 0
Operation time	X7	> 414 min = 1
		≤ 414 min = 0
Am		> 1069 U/L = 1
		≤ 1069 U/L = 0

BMI: Body mass index; Am: Amylase.

ROC curve analysis showed that BMI, hypertension, soft pancreatic texture, and surgery time were valuable predictors of PF after LPD in patients with pancreatic cancer, with AUCs of 0.655, 0.661, 0.873, and 0.758, respectively. Our study limitations were that we used a small sample size from a single center, only considered clinical factors, and failed to comprehensively analyze patients' lifestyles and genetic factors. In the future, it is still necessary to study a larger sample size, adopt a multicenter study design, and consider patients' lifestyles and genetic backgrounds to further analyze factors relating to the development of PF after LPD treatment for pancreatic cancer.

Table 5 Results of logistic regression analysis of multiple factors influencing pancreatic fistula in patients with pancreatic cancer after laparoscopic pancreaticoduodenectomy

Variable	*B* value	*SE* value	Wald value	*P* value	OR	95%CI
Sex	1.086	1.039	1.091	0.296	2.961	0.386-22.71
BMI (kg/m²)	2.637	1.022	6.661	0.010	13.978	1.886-103.581
Hypertension	2.138	0.989	4.67	0.031	8.484	1.22-58.994
monocyte count (× 10^9/L)	1.591	1.135	1.966	0.161	4.909	0.531-45.372
Pancreatic texture	3.738	1.019	13.448	< 0.001	42.015	5.698-309.782
Pancreatic duct diameter	-0.755	1.122	0.452	0.501	0.470	0.052-4.244
Operation time (min)	2.735	1.146	5.694	0.017	15.41	1.63-145.674
Am (U/L)	1.662	1.056	2.476	0.116	5.268	0.665-41.734

BMI: Body mass index; Am: Amylase.

Table 6 Receiver operating characteristic curve analysis of influencing factors predicting pancreatic fistula after laparoscopic pancreaticoduodenectomy in patients with pancreatic cancer

Factor	AUC	Sensitivity	Specificity	95%CI	*P* value
BMI (kg/m²)	0.655	0.467	0.844	0.496-0.815	0.045
Hypertension	0.661	0.667	0.656	0.518-0.805	0.038
Pancreatic texture	0.837	0.733	0.941	0.702-0.972	< 0.001
Operation time (min)	0.758	0.800	0.715	0.634-0.881	0.001

AUC: Area under the curve; BMI: Body mass index; CI: Confidence interval.

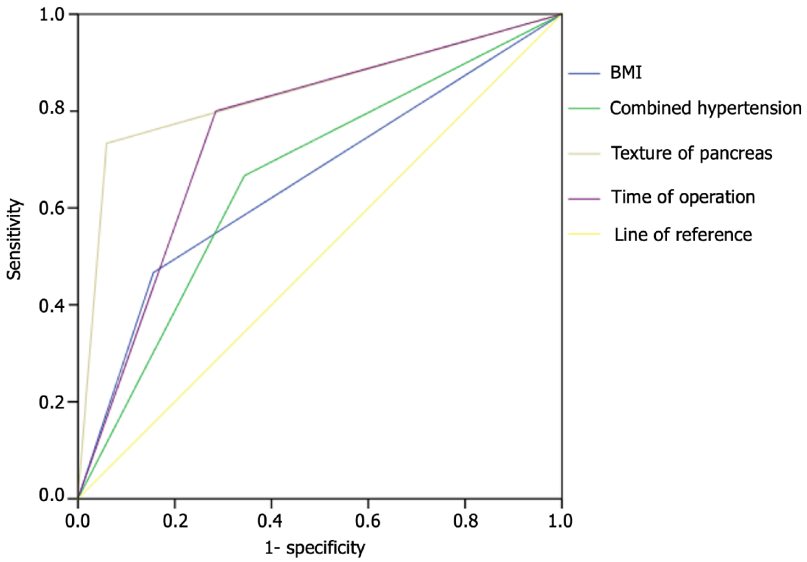


Figure 1 Receiver-operating characteristic analysis of influencing factors predicting pancreatic fistula after laparoscopic pancreaticoduodenectomy in pancreatic cancer patients. BMI: Body mass index.

CONCLUSION

In summary, high BMI, soft pancreatic texture, long surgery time, and hypertension are all risk factors for PF after LPD in patients with pancreatic cancer. For patients with a high BMI (> 24.91 kg/m²), their weights should be controlled by strengthening diet management combined with appropriate exercise measures. Patients with high blood pressure should undergo corresponding antihypertensive therapy preoperatively. If the patient's pancreas is found to have a soft texture

during the operation, the surgeon should be as cautious as possible, manage the anastomosis carefully, and control the operation time by continuously improving surgical skills and teamwork.

FOOTNOTES

Author contributions: Xu H performed the research; Hua J contributed to the analysis; Wand W and Meng QC supervised the report.

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REFERENCES

1 **Karunakaran M**, Barreto SG. Surgery for pancreatic cancer: current controversies and challenges. *Future Oncol* 2021; **17**: 5135-5162 [PMID: 34747183 DOI: 10.2217/fon-2021-0533]
2 **Shen Y**, Jin W. Early enteral nutrition after pancreatoduodenectomy: a meta-analysis of randomized controlled trials. *Langenbecks Arch Surg* 2013; **398**: 817-823 [PMID: 23695769 DOI: 10.1007/s00423-013-1089-y]
3 **Russell TB**, Aroori S. Procedure-specific morbidity of pancreatoduodenectomy: a systematic review of incidence and risk factors. *ANZ J Surg* 2022; **92**: 1347-1355 [PMID: 35088514 DOI: 10.1111/ans.17473]
4 **Niu CY**, Ji B, Dai XL, Guan QC, Liu YH. [Use of alternative pancreatic fistula risk score system for patients with clinical relevant postoperative pancreatic fistula after laparoscopic pancreaticoduodenectomy]. *Zhonghua Wai Ke Za Zhi* 2021; **59**: 631-635 [PMID: 34256465 DOI: 10.3760/cma.j.cn112139-20201026-00766]
5 **Sert OZ**, Berkesoglu M, Canbaz H, Olmez A, Tasdelen B, Dirlik MM. The factors of pancreatic fistula development in patients who underwent classical pancreaticoduodenectomy. *Ann Ital Chir* 2021; **92**: 35-40 [PMID: 32529981]
6 **Ramavath K**, Subbiah Nagaraj S, Kumar M, Raypattanaik NM, Dahiya D, Savlania A, Tandup C, Kalra N, Behera A, Kaman L. Visceral Obesity as a Predictor of Postoperative Complications After Pancreaticoduodenectomy. *Cureus* 2023; **15**: e35815 [PMID: 37033590 DOI: 10.7759/cureus.35815]
7 **Martin AN**, Narayanan S, Turrentine FE, Bauer TW, Adams RB, Zaydfudim VM. Pancreatic duct size and gland texture are associated with pancreatic fistula after pancreaticoduodenectomy but not after distal pancreatectomy. *PLoS One* 2018; **13**: e0203841 [PMID: 30212577 DOI: 10.1371/journal.pone.0203841]
8 **Tempero MA**. NCCN Guidelines Updates: Pancreatic Cancer. *J Natl Compr Canc Netw* 2019; **17**: 603-605 [PMID: 31117041 DOI: 10.6004/jnccn.2019.5007]
9 **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]
10 **Yin TY**, Zhang H, Wang M, Qin RY. [The value and controversy of laparoscopic pancreaticoduodenectomy in the treatment of pancreatic cancer]. *Zhonghua Wai Ke Za Zhi* 2022; **60**: 894-899 [PMID: 36207977 DOI: 10.3760/cma.j.cn112139-20220410-00154]
11 **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]
12 **Costa Santos M**, Cunha C, Velho S, Ferreira AO, Costa F, Ferreira R, Loureiro R, Santos AA, Maio R, Cravo M. Preoperative biliary drainage in patients performing pancreaticoduodenectomy : guidelines and real-life practice. *Acta Gastroenterol Belg* 2019; **82**: 389-395 [PMID:

31566326]

13 **Utsumi M**, Aoki H, Nagahisa S, Nishimura S, Une Y, Kimura Y, Watanabe M, Taniguchi F, Arata T, Katsuda K, Tanakaya K. Preoperative predictive factors of pancreatic fistula after pancreaticoduodenectomy: usefulness of the CONUT score. *Ann Surg Treat Res* 2020; **99**: 18-25 [PMID: 32676478 DOI: 10.4174/astr.2020.99.1.18]

14 **Nong K**, Zhang Y, Liu S, Yang Y, Sun D, Chen X. Analysis of pancreatic fistula risk in patients with laparoscopic pancreatoduodenectomy: what matters. *J Int Med Res* 2020; **48**: 300060520943422 [PMID: 33106067 DOI: 10.1177/0300060520943422]

15 **Kiełbowski K**, Bakinowska E, Uciński R. Preoperative and intraoperative risk factors of postoperative pancreatic fistula after pancreaticoduodenectomy - systematic review and meta-analysis. *Pol Przegl Chir* 2021; **93**: 1-10 [PMID: 36169536 DOI: 10.5604/01.3001.0014.9659]

16 **He C**, Zhang Y, Li L, Zhao M, Wang C, Tang Y. Risk factor analysis and prediction of postoperative clinically relevant pancreatic fistula after distal pancreatectomy. *BMC Surg* 2023; **23**: 5 [PMID: 36631791 DOI: 10.1186/s12893-023-01907-w]

17 **Zarzavadjian Le Bian A**, Fuks D, Montali F, Cesaretti M, Costi R, Wind P, Smadja C, Gayet B. Predicting the Severity of Pancreatic Fistula after Pancreaticoduodenectomy: Overweight and Blood Loss as Independent Risk Factors: Retrospective Analysis of 277 Patients. *Surg Infect (Larchmt)* 2019; **20**: 486-491 [PMID: 31063046 DOI: 10.1089/sur.2019.027]

18 **Schuh F**, Mihaljevic AL, Probst P, Trudeau MT, Müller PC, Marchegiani G, Besselink MG, Uzunoglu F, Izbicki JR, Falconi M, Castillo CF, Adham M, Z'graggen K, Friess H, Werner J, Weitz J, Strobel O, Hackert T, Radenkovic D, Kelemen D, Wolfgang C, Miao YI, Shrikhande SV, Lillemoe KD, Dervenis C, Bassi C, Neoptolemos JP, Diener MK, Vollmer CM Jr, Büchler MW. A Simple Classification of Pancreatic Duct Size and Texture Predicts Postoperative Pancreatic Fistula: A classification of the International Study Group of Pancreatic Surgery. *Ann Surg* 2023; **277**: e597-e608 [PMID: 33914473 DOI: 10.1097/SLA.0000000000004855]

19 **Chen CB**, McCall NS, Pucci MJ, Leiby B, Dabbish N, Winter JM, Yeo CJ, Lavu H. The Combination of Pancreas Texture and Postoperative Serum Amylase in Predicting Pancreatic Fistula Risk. *Am Surg* 2018; **84**: 889-896 [PMID: 29981620]

20 **Imam A**, Khalayleh H, Brakha M, Benson AA, Lev-Cohain N, Zamir G, Khalaileh A. The effect of atrophied pancreas as shown in the preoperative imaging on the leakage rate after pancreaticoduodenectomy. *Ann Hepatobiliary Pancreat Surg* 2022; **26**: 184-189 [PMID: 35370142 DOI: 10.14701/ahbps.21-145]

21 **Azzi AJ**, Shah K, Seely A, Villeneuve JP, Sundaresan SR, Shamji FM, Maziak DE, Gilbert S. Surgical team turnover and operative time: An evaluation of operating room efficiency during pulmonary resection. *J Thorac Cardiovasc Surg* 2016; **151**: 1391-1395 [PMID: 26874599 DOI: 10.1016/j.jtcvs.2015.12.040]

22 **Rothstein DH**, Raval MV. Operating room efficiency. *Semin Pediatr Surg* 2018; **27**: 79-85 [PMID: 29548356 DOI: 10.1053/j.sempedsurg.2018.02.004]

23 **Gouma DJ**, van Geenen RC, van Gulik TM, de Haan RJ, de Wit LT, Busch OR, Obertop H. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. *Ann Surg* 2000; **232**: 786-795 [PMID: 11088073 DOI: 10.1097/00000658-200012000-00007]

24 **Zhang JY**, Huang J, Zhao SY, Liu X, Xiong ZC, Yang ZY. Risk Factors and a New Prediction Model for Pancreatic Fistula After Pancreaticoduodenectomy. *Risk Manag Healthc Policy* 2021; **14**: 1897-1906 [PMID: 34007227 DOI: 10.2147/RMHP.S305332]

25 **Ke Z**, Cui J, Hu N, Yang Z, Chen H, Hu J, Wang C, Wu H, Nie X, Xiong J. Risk factors for postoperative pancreatic fistula: Analysis of 170 consecutive cases of pancreaticoduodenectomy based on the updated ISGPS classification and grading system. *Medicine (Baltimore)* 2018; **97**: e12151 [PMID: 30170457 DOI: 10.1097/MD.0000000000012151]

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ORIGINAL ARTICLE

Retrospective Study

Correlation between postoperative chemotherapy regimen and survival in patients with resectable gastric adenocarcinoma accompanied with vascular cancer thrombus

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Abstract

BACKGROUND

Patients with resectable gastric adenocarcinoma accompanied by vascular cancer thrombus (RGAVCT) have a poor prognosis, with a 5-year survival rate ranging from 18.42%-53.57%. These patients need a reasonable postoperative treatment plan to improve their prognosis.

AIM

To determine the most effective postoperative chemotherapy regimen for patients with RGAVCT.

METHODS

We retrospectively collected the clinicopathological data of 530 patients who underwent radical resection for gastric cancer between January 2017 and January

2022 and who were pathologically diagnosed with gastric adenocarcinoma with a choroidal cancer embolus. Furthermore, we identified the high-risk variables that can influence the prognosis of patients with RGAVCT by assessing the clinical and pathological features of the patients who met the inclusion criteria. We also assessed the significance of survival outcomes using Mantel-Cox univariate and multivariate analyses. The subgroups of patients with stages I, II, and III disease who received single-, dual-, or triple-drug regimens following surgery were analyzed using SPSS 25.0 and the ggplot2 package in R 4.3.0.

RESULTS

In all, 530 eligible individuals with RGAVCT were enrolled in this study. The median overall survival (OS) of patients with RGAVCT was 24 months, and the survival rates were 80.2%, 62.5%, and 42.3% at 12, 24, and 59 months, respectively. Preoperative complications, tumor size, T stage, and postoperative chemotherapy were identified as independent factors that influenced OS in patients with RGAVCT according to the Cox multivariate analysis model. A Kaplan-Meier analysis revealed that chemotherapy had no effect on OS of patients with stage I or II RGAVCT; however, chemotherapy did have an effect on OS of stage III patients. Stage III patients who were treated with chemotherapy consisting of dual- or triple-agent regimens had better survival than those treated with single-agent regimens, and no significant difference was observed in the survival of patients treated with chemotherapy consisting of dual- or triple-agent regimens.

CONCLUSION

For patients with stage III RGAVCT, a dual-agent regimen of postoperative chemotherapy should be recommended rather than a triple-agent treatment, as the latter is associated with increased frequency of adverse events.

Key Words: Vascular cancer embolism; Postoperative chemotherapy regimen; Gastric adenocarcinoma; Risk factors; Survival

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Core Tip: In patients with resectable gastric adenocarcinoma accompanied by vascular cancer thrombus (RGAVCT), postoperative chemotherapy has an independent effect on overall survival and may even improve survival. Patients with stage I and II RGAVCT should not receive postoperative chemotherapy, and low-toxicity single-agent therapy is advised even in the presence of high-risk variables. For patients with stage III RGAVCT, a dual-agent regimen of postoperative chemotherapy should be recommended rather than a triple-agent treatment, as the latter is associated with increased risks.

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INTRODUCTION

According to the 2020 Tumor Report[1], gastric cancer (GC) ranked fourth among all cancers according to the number of new cases, with approximately 1.1 million cases per year. GC ranked third in terms of mortality rate, with approximately 760000 deaths per year. GC is an important life-threatening disease and one of the most common malignant tumors worldwide. China ranks second and third in terms of new cases and deaths related to GC, respectively[2]. Studies by Zhang[3] and the Asian Cancer Research Group[4] marked significant advancements in the molecular typing of GC, thereby leading to enhanced medical treatment strategies. For stage III GC, the 5-year survival rate following surgery is 34.8%-54.6%[5], and radical surgical resection remains the preferred course of treatment. When tumor cells infiltrate the interior of lymphatic or vascular vessels, which are composed of endothelial cells, the condition is referred to as lymphatic and blood vessel invasion (LBVI)[6]. The literature indicates a 5-year survival rate of 18.42%-53.57% for patients with postoperatively resectable stomach cancer and pathologically identified vascular thrombus, which indicates a poor prognosis[7]. Consequently, the presence of vascular thrombus plays a significant role in the poor prognosis of patients with stomach cancer. Currently, few exploratory investigations on vascular tumor thrombus in gastric adenocarcinoma have been published, and thus the clinicopathological characteristics of this condition remain unknown. To identify alternative therapies to increase the survival of patients with resectable gastric adenocarcinoma accompanied by vascular cancer thrombus (RGAVCT), we retrospectively examined the clinical and pathological features of 530 patients with RGAVCT and conducted pertinent survival analyses. This manuscript was written according to the STROBE checklist.

MATERIALS AND METHODS

Clinical information

Clinicopathological data were retrospectively collected from 530 patients (107 women and 423 men) who underwent radical surgery for GC at Shanxi Cancer Hospital between January 2017 and January 2022 and who were pathologically diagnosed with stomach adenocarcinoma with a vascular cancer embolus. Patient ages ranged from 28-83 years (median, 63 years). This study was approved by the Clinical Research Ethics Committee of Shanxi Cancer Hospital (approval number: KY2023010). During their first visit to the hospital, all patients provided written informed consent for the collection and release of their medical information.

Inclusion and exclusion criteria: The inclusion criteria were as follows: (1) Radical resection of GC at Shanxi Cancer Hospital; (2) postoperative pathological confirmation of gastric adenocarcinoma or adenocarcinoma of the gastroesophageal junction; (3) postoperative pathological evidence of vascular cancer thrombus; (4) clinical stage I, II, or III disease; and (5) availability of complete clinicopathological data. The exclusion criteria were as follows: (1) Presence of other tumors; (2) nonradical resection, such as surgery with positive margins or palliative surgery; and (3) incomplete or unavailable pathological data.

Staging and Ki-67 positivity: Pathological and histological staging was performed according to the 2019 version of the World Health Organization Classification of Tumors of the Digestive System. Ki-67 positivity < 30% was considered low expression, while Ki-67 positivity ≥ 30% was considered high expression.

Follow-up: Regular gastroenterology outpatient reviews, hospitalization, and telephone interviews were used for patient survival follow-up. The deadline for follow-up was March 2023. Overall survival (OS) was defined as the time from the date of surgery to the date of death or the end of follow-up.

Information collection

Clinical information: Patient information, including sex, age at the time of surgery, medical history, family history, preoperative complications, surgical procedures, and postoperative chemotherapy, was collected.

Pathological information: The pathology report included information regarding the location and size of the tumor, the degree of tumor differentiation, the Lauren classification, LBVI, neural invasion, the depth of invasion, the total number of cleared lymph nodes, and immunohistochemistry findings.

Research participants and chemotherapy regimens: To ensure the authenticity and reliability of our results, we collected information on patients who received postoperative adjuvant chemotherapy at our hospital.

Statistical analysis

SPSS (version 25.0; IBM, Armonk, NY) and R 4.3.0 (R Foundation, Vienna, Austria) were used for the statistical analysis. The rank-sum test was used to evaluate the skewed distributions, which are expressed as the mean and standard deviation of the quantitative data. Mantel-Cox univariate regression analysis was used to identify possible prognostic factors. The clinicopathological variables that affected survival time were then analyzed using a multivariate Cox regression model to identify significant factors that might affect the prognosis of patients with RGAVCT. The Kaplan-Meier method was used to calculate the survival rates, and the log-rank test was used for intergroup comparisons of the survival curves. The survival curves were compared between groups using R 4.3.0. In R 4.3.0, the forest plot of the factors that influenced the survival of patients with RGAVCT was plotted using the "survival" and "forest plot" packages; the Kaplan-Meier survival curves for patients with RGAVCT were drawn using the "ggplot2" and "survminer" programs. Statistical significance was established at $P < 0.05$. The statistical methods used in this study were reviewed by Professor Yu HM from the Department of Health Statistics, Shanxi Medical University.

RESULTS

Clinicopathologic features of patients with RGAVCT

The 530 patients with RGAVCT who met the inclusion criteria ranged in age from 28–83 (median, 63) years (Table 1). A 4:1 male-to-female ratio was noted, with 423 men and 107 women. A total of 9.2% of patients had a family history of tumors, and 86.4% of patients had no preoperative complications. For those patients who did experience preoperative complications, 7.7%, 1.9%, 1.1%, and 2.8% experienced gastrointestinal obstruction, gastrointestinal hemorrhage, other complications (such as perforation, gastric retention, and anemia), and multiple complications, respectively. Open surgery was performed in 61.9% of patients, laparoscopic surgery in 33.8%, and combined thoracic and abdominal surgery in 4.3%. Postoperative chemotherapy was administered to approximately 74.3% of patients.

According to the Union for International Cancer Control TNM staging system (8th edition), 10 patients (1.9%) were categorized as stage IB, 43 (8.1%) as stage IIA, 80 (15.1%) as stage IIB, 132 (24.9%) as stage IIIA, 171 (32.3%) as stage IIIB, and 94 (17.7%) as stage IIIC. The RGAVCT tumor sites were mainly distributed in the proximal (54%), distal (27.2%), and gastric bodies (18.9%). Tumors were predominantly poorly differentiated (54.3%), intermediate-poorly differentiated (35.5%), and moderately differentiated (10.2%); none were well differentiated.

Table 1 Univariate analysis of the demographic, clinical, and pathological risk variables in 530 patients with resectable gastric adenocarcinoma accompanied by vascular cancer thrombus

Characteristic	*n* (%)	χ^2	*P* value
Age, yr			
< 60	211 (39.8)	5.943	0.015
≥ 60	319 (60.2)		
Sex			
Male	423 (79.8)	7.533	0.006
Female	107 (20.2)		
Past history			
No	289 (54.5)	3.76	0.052
Yes	241 (45.5)		
Family history			
No	479 (90.4)	4.711	0.030
Yes	51 (9.6)		
Preoperative complications			
No	458 (86.4)	1.982	0.037
Digestive tract obstruction	41 (7.7)		
Alimentary tract hemorrhage	10 (1.9)		
Others[1]	6 (1.1)		
≥ 2 complications	15 (2.8)		
Surgical method			
Open abdominal	328 (61.9)	1.853	0.396
Laparoscopy	179 (33.8)		
Joint thoracoabdominal	23 (4.3)		
Chemotherapy			
No	136 (25.7)	63.834	<0.001
Yes	394 (74.3)		
Tumor site			
Proximal	286 (54)	2.217	0.330
Distal	144 (27.2)		
Body	100 (18.9)		
Differentiation			
Moderate	54 (10.2)	5.742	0.057
Moderate-poor	188 (35.5)		
Poor	288 (54.3)		
Lauren classification			
Diffused type	182 (34.3)	11.859	0.008
Intestinal type	62 (11.7)		
Mixed type	252 (47.5)		
NA	34 (6.4)		
Neural invasion			
Absence	247 (46.6)	5.899	0.015

Presence	283 (53.4)		
Tumor size, cm			
< 5	231 (43.6)	8.976	0.003
≥ 5	299 (56.4)		
HER2 expression			
Negative	458 (86.4)	0.495	0.482
Positive	72 (13.6)		
MMR status			
dMMR	14 (2.6)	0.229	0.633
pMMR	516 (97.4)		
Ki-67 expression			
Low	8 (1.5)	6.019	0.014
High	522 (98.5)		
T stage			
2	44 (8.5)	25.459	< 0.001
3	374 (70.6)		
4a	93 (17.5)		
4b	18 (3.4)		
N stage			
0	37 (7)	42.8	< 0.001
1	104 (19.6)		
2	137 (25.8)		
3a	158 (29.8)		
3b	94 (17.7)		
Stage			
IB	10 (1.9)	62.765	< 0.001
IIA	43 (8.1)		
IIB	80 (15.1)		
IIIA	132 (24.9)		
IIIB	171 (32.3)		
IIIC	94 (17.7)		

[1]Others includes perforation, gastric retention and anemia.
dMMR: Defective mismatch repair; pMMR: Proficient mismatch repair.

The Lauren classification was predominantly mixed (47.5%) or diffused (34.3%), while the intestinal type was less frequent (11.7%). Neural invasion was observed in 53.4% of the patients. Tumors > 5 cm were found in 56.4% of the patients. Immunohistochemistry indicated Her-2 positivity (3+ or 2+ fluorescent in situ hybridization positivity) in approximately 13.6% of the patients. Moreover, mismatch repair proteins (MLH1, PMS2, MSH2, and MSH6) were absent in 2.6% and were expressed in 97.4% of the patients. Ki-67 was highly expressed in 98.5% of the patients.

Survival analysis of patients with RGAVCT

The median OS (mOS) of patients with RGAVCT was 24 months, with survival rates of 80.2%, 62.5%, 54.8%, and 42.3% at 12, 24, 37, and 59 months, respectively. The postoperative chemotherapy group had an mOS of 25 months, and the survival rates were 86.8%, 71.3%, 64.2%, and 52.8% at 12, 24, 37, and 53 months, respectively. The mOS was 15 months in the group that did not receive chemotherapy, and the survival rates were 61%, 38.1%, 28.5%, and 19% at 12, 24, 34, and 59 months, respectively. Patients with stage I and II cancer had an mOS of 27 months, with survival rates of 89.5%, 80%, 74.6%, and 52.2% at 12, 24, 34, and 59 months, respectively (Figure 1A). The mOS of patients with stage III cancer was 23 months, with survival rates of 77.8%, 57.8%, 49.5%, and 40.1% at 12, 24, 37, and 53 months, respectively. The best survival

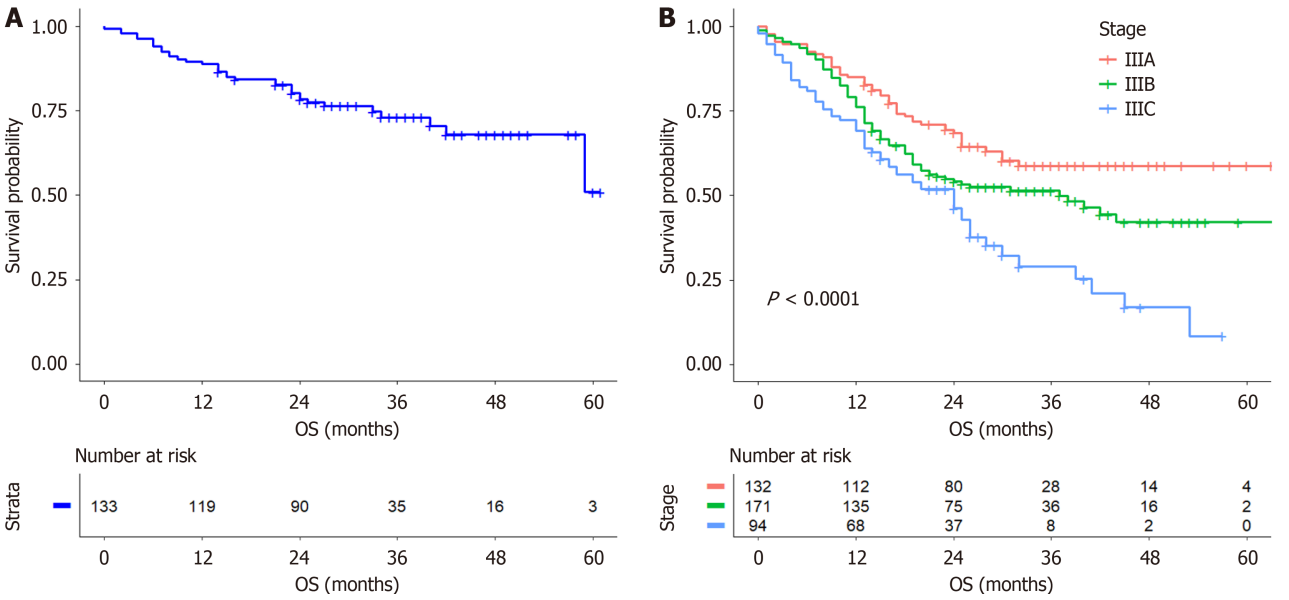


Figure 1 Survival curve of resectable gastric adenocarcinoma accompanied by vascular cancer thrombus patients. A: Stage I and II; B: Stage III. OS: Overall survival.

rate was observed in patients with stage IIIA cancer, followed by those with stage IIIB cancer, while the worst survival rate was observed in patients with stage IIIC cancer (Figure 1B).

Analysis of the factors influencing survival of patients with RGAVCT

The univariate analysis by Mantel-Cox regression revealed significant differences ($P < 0.05$) in age, sex, family history, preoperative complications, postoperative chemotherapy, Lauren classification, neural invasion status, tumor size, Ki-67 expression, T and N stage, and clinical stage, and these factors were significantly correlated with the OS of patients with RGAVCT. A multivariate Cox analysis of the significant influencing factors revealed that preoperative complications ($P = 0.035$), postoperative chemotherapy [$P < 0.001$; hazard ratio (HR) = 0.35; 95% confidence interval (CI) = 0.26-0.46], tumor size ($P = 0.035$; HR = 1.36; 95%CI = 1.02-1.80), and T stage ($P = 0.005$) were independent factors that affected OS (Figure 2).

RGAVCT postoperative chemotherapy regimen and survival correlation analysis

Of the 394 patients with RGAVCT who were administered postoperative adjuvant chemotherapy, 323 received chemotherapy at our institution (23 received a single-agent regimen, 272 received a dual-agent regimen, and 28 received a triple-agent regimen), and 71 received chemotherapy outside our hospital.

The univariate analysis revealed no significant difference between postoperative chemotherapy and survival in patients with stage I and II RGAVCT ($P = 0.527$). Preoperative complications, postoperative pathological neural invasion, and Ki-67 expression were factors that were found to influence the survival of patients with stage I and II RGAVCT ($P < 0.05$).

The Cox multivariate analysis revealed that preoperative complications ($P = 0.021$), neural invasion ($P = 0.02$; HR = 2.47; 95%CI = 1.16-5.28), and Ki-67 expression ($P = 0.007$; HR = 0.05; 95%CI = 0.01-0.44) were independent factors found to influence the survival of patients with stage I and II RGAVCT (Table 2). However, postoperative chemotherapy did not affect the OS of high-risk patients with stage I and II RGAVCT ($P = 0.653$).

The Kaplan-Meier analysis revealed that postoperative chemotherapy affected the OS of patients with stage III RGAVCT ($P < 0.001$) (Figure 3A). Furthermore, compared with patients treated with a single-agent regimen, individuals who were treated with chemotherapy consisting of dual- or triple-agent regimens had higher survival rates ($P = 0.047$ and $P = 0.034$) (Figure 3B and C), and no significant difference was observed between the survival of patients treated with dual-agent regimens and that of those treated with triple-agent regimens ($P = 0.646$) (Figure 3D).

DISCUSSION

The aim of this study was to determine the most effective postoperative chemotherapy regimen for patients with RGAVCT. According to the analysis, no significant survival difference was observed between patients with stage III RGAVCT treated with double-drug regimens and those treated with triple-drug regimens, but their survival rates were better than those who received single-drug regimens. For patients with stage III RGAVCT, a dual-agent regimen of postoperative chemotherapy should be recommended rather than a triple-agent treatment, as the latter is associated with increased adverse events.

Table 2 Univariate and multivariate analyses of 133 patients with stage I and stage II resectable gastric adenocarcinoma accompanied by vascular cancer thrombus to determine which clinicopathological characteristics are risk factors

Characteristic	N	Univariate analysis		Multivariate analysis	
		χ^2	*P* value	HR (95%CI)	*P* value
Preoperative complications					
No	115	27.724	< 0.001	1	0.021
Digestive tract obstruction	4			2.15 (0.50-9.32)	0.304
Alimentary tract hemorrhage	1			2.90 (0.38-22.41)	0.307
Others[1]	3			7.07 (1.91-26.15)	0.003
Neural invasion					
Absence	73	10.014	0.002	1	
Presence	50			2.47 (1.16-5.28)	0.02
Ki-67 expression					
Low	1	5.58	0.018	1	
High	122			0.05 (0.01-0.44)	0.007

[1]Others includes perforation, gastric retention and anemia.
HR: Hazard ratio; CI: Confidence interval.

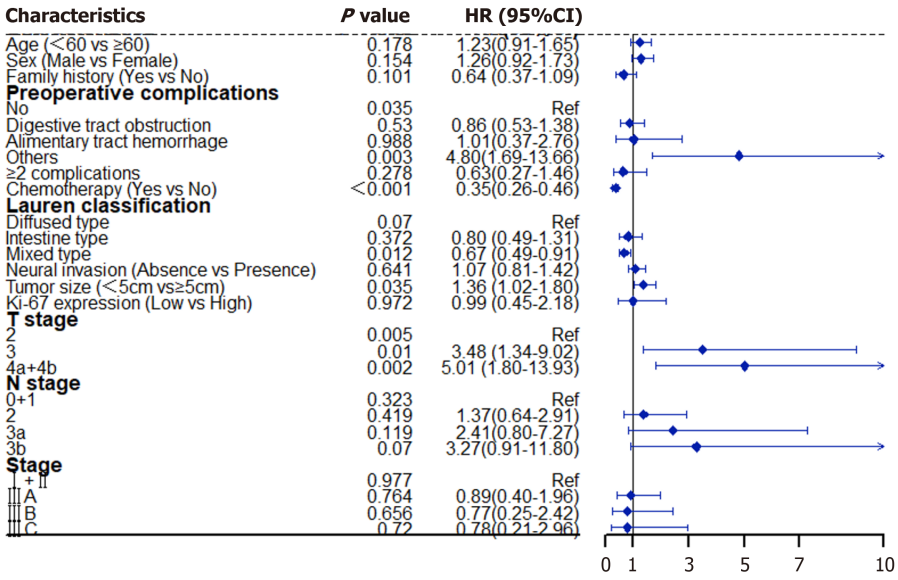


Figure 2 Multivariate analysis of risk factors in 530 patients with resectable gastric adenocarcinoma accompanied by vascular cancer thrombus.

GC is a life-threatening disease and is one of the primary causes of cancer-related death worldwide. The introduction of novel anticancer medications, neoadjuvant radiation, adjuvant chemotherapy, and late-stage palliative care are among the numerous advancements in the systemic treatment of GC. These measures have significantly increased the survival rates of patients with GC. However, high postoperative recurrence and metastasis rates adversely affect the survival of patients with GC. The postoperative clinicopathological features of GC are also the primary prognostic factors associated with this disease. In a study by Chen *et al*[8], the depth of tumor infiltration, extent of lymph node metastasis, extent of distant metastasis, and pathological score were used to predict the prognosis and OS of patients with GC. The impact of vascular cancer embolism on the prognosis of malignant tumors has received considerable attention because of detailed research on tumor prognostic variables and the concept of micrometastasis[9,10]. Vascular cancer emboli are tumor cells that form aggregates with fibrin clots, coexist with erythrocytes, infiltrate the endothelial cell space arrangement of the surrounding tissue in the absence of erythrocytes, or invade the smooth muscle cell space arrangement[11,12].

Torre *et al*[13] reported a 2:1 male-to-female ratio in the global incidence of GC in 2012, while Sung *et al*[1] reported that the global incidence of GC in 2020 was approximately 7.2% for men and 4.4% for women. These studies show that the

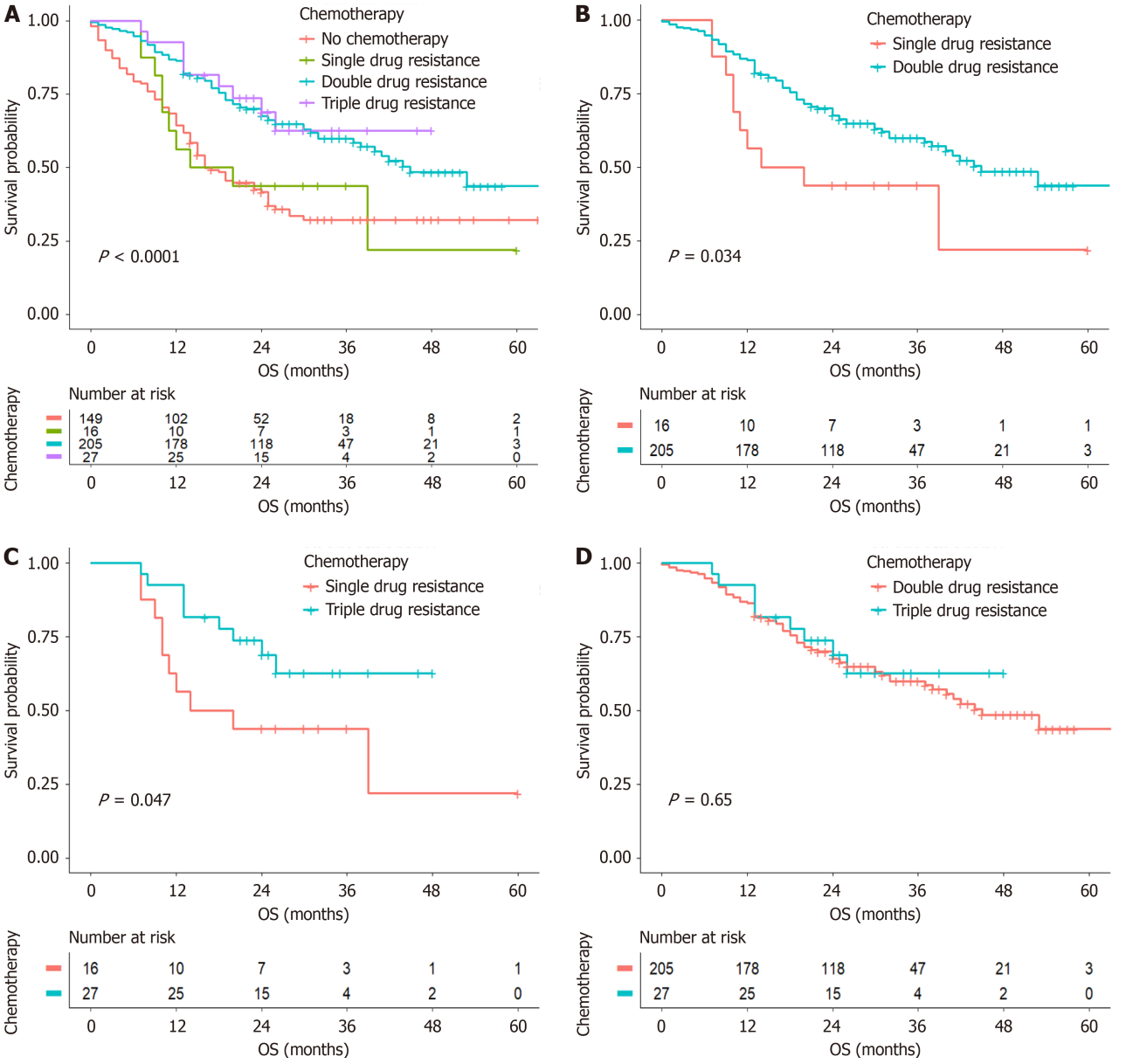


Figure 3 Comparison of chemotherapy schemes in 323 patients with stage Ⅲ resectable gastric adenocarcinoma accompanied by vascular cancer thrombus. A: Comparison of chemotherapy schemes for Stage Ⅲ patients; B: Comparison of single drug and double drug resistances; C: Comparison of single drug and triple drug resistances; D: Comparison of double drug and triple drug resistances. OS: Overall survival.

number of men with GC is greater than that of women. The male-to-female ratio of patients with RGAVCT in this study was 4:1, which was much higher than the global male-to-female ratio of GC patients. Consequently, vascular cancer emboli are more likely to occur in males with GC.

Regarding the baseline characteristics of patients with RGAVCT, our study revealed that the type of surgery (open, laparoscopic, or combined thoracoabdominal) had no effect on OS. Moreover, we found that surgeons involved in clinical assessments selected the appropriate surgical approach based on the specific conditions of the patients. In more than half (53.4%) of the patients with RGAVCT and concomitant neural invasion, we found that vascular cancer embolus and neural invasion were likely to occur simultaneously. Among the patients with RGAVCT who were analyzed, 10 had stage IB RGAVCT, 123 had stage II RGAVCT, and 397 had stage III RGAVCT, which accounted for 74.9% of all patients. This indicates that vascular cancer embolisms occurred more often in patients with advanced GC. The median survival time (mOS = 23 months) and survival rates at 12 months (77.8%), 24 months (57.8%), 34 months (49.5%), and 53 months (40.1%) of patients with stage III RGAVCT were significantly lower than those of patients with stages I and II RGAVCT (mOS = 27 months; 12 months, 89.5%; 59 months, 52.2%).

The risk factors for GC include many immutable variables, such as age[14], sex, and race/ethnicity. Additionally, some modifiable risk factors, such as *Helicobacter pylori* infection[15], smoking[16], and high nitrate and nitrite diets, have also been identified. Several known hereditary cancer syndromes are associated with GC, including hereditary diffuse GC (CDH1) syndrome, the most strongly associated syndrome, which occurs in approximately 80% of patients[17]. The multivariate analysis identified preoperative complications, postoperative chemotherapy, tumor size, and T stage as independent factors that affect the OS of patients with RGAVCT, with postoperative chemotherapy as the intervening factor.

In addition, a previous study[18] showed that lymph node metastasis in early GC can be predicted using nomograms, decision trees, and deep learning models. To better understand the prognostic factors of patients with RGAVCT, the derived prognostic elements can be utilized to construct a deep learning model. This model can then be applied to validate these factors using external databases.

In this study, the mOS was 25 months in the chemotherapy group, which was greater than that in the nonchemotherapy group (15 months), which indicates that chemotherapy could prolong the survival of patients with RGAVCT. Several studies[19-21] have suggested that postoperative chemotherapy can improve the prognosis of patients with GC. However, postoperative chemotherapy is the only intervening factor among the independent factors that affect the OS of patients with RGAVCT, and a rational postoperative chemotherapy regimen can further improve the prognosis of these patients. A clinical consensus[22] has been established that postoperative adjuvant therapy should be recommended for patients who undergo D2 radical surgery and who do not receive preoperative treatment for postoperative pathological stage II and III progressive GC. In this study, 530 patients were evaluated based on clinical stage, and we found that postoperative chemotherapy did not affect the OS of patients with stage I and II RGAVCT. We further investigated whether postoperative chemotherapy influenced the survival of high-risk patients with stage I and II RGAVCT. We found that preoperative complications, postoperative pathological neural invasion, and Ki-67 expression were independent factors that affected the survival of patients with stages I and II RGAVCT according to the univariate and multivariate analyses. However, the OS of patients with stage I and II RGAVCT who had a combination of high-risk factors was not affected by postoperative chemotherapy.

We explored the effect of postoperative chemotherapy on the OS of patients with stage III RGAVCT ($P < 0.001$) and discovered a substantial difference in survival between patients who received postoperative chemotherapy and those who did not. The recent JACCRO GC-07 study[23], which investigated chemotherapy regimens and clinical outcomes, showed that the continuation of an oral S-1 monotherapy regimen (DS sequential S-1) after six cycles of postoperative docetaxel combined with S-1 improved the survival of patients with stage III GC compared with S-1 alone (3-year recurrence-free survival: S-1/docetaxel group, 65.9% *vs* S-1 group, 49.6%; $P = 0.0007$). Moreover, combination therapy inhibited hematologic, lymphatic, and peritoneal recurrence. An analysis of the effects of dosing regimens on the survival of patients with stage III RGAVCT who received postoperative adjuvant chemotherapy at our institution showed that postoperative chemotherapy prolonged survival, that dual- and triple-agent regimens resulted in an equal survival benefit, and that both were better than a single-agent regimen. The CLASSIC study[24] used capecitabine combined with oxaliplatin in a dual-agent adjuvant chemotherapy regimen for advanced GC. The 5-year disease-free survival rate (68%) and 5-year OS rate (78%) with this regimen were better than those in the observation group (53% and 69%, for the 5-year disease-free survival and the 5-year OS, respectively). Therefore, postoperative chemotherapy for advanced GC should involve a dual-agent regimen of capecitabine and oxaliplatin. Another study[25] showed that the XELOX double-agent regimen was as effective as both regimens in the first-line treatment of advanced GC, unlike the EOX triple-agent regimen. This study, for the first time, established the optimal two-drug chemotherapy strategy for patients with stage III RGAVCT and identified the clinical features of patients with RGAVCT. However, our chemotherapeutic program design was not standardized, and the sample size was small, which limits the accuracy of the data in this study. A deep learning model using external databases for predicting variables will be created in the future to confirm the predictions for patients with RGAVCT. Long-term, randomized, controlled clinical research is also necessary to investigate the effect of chemotherapy regimens on the survival of patients with RGAVCT.

CONCLUSION

Postoperative chemotherapy has an independent effect on OS in patients with RGAVCT and can increase survival. However, chemotherapy administered after surgery had little effect on the OS of patients with stage I and II RGAVCT. Moreover, triple-agent treatment is associated with more adverse events than other forms of treatment. Therefore, we recommend that patients with stage II RGAVCT receive dual-agent chemotherapy. The clinical implications and future scope are clear.

FOOTNOTES

Author contributions: Wang YS, Yu HM and Yang ZF designed the research study; Yang ZF prepared the materials; Yang ZF, Dong ZX, Dai CJ, Fu LZ collected the data; Wang YS, Yu HM and Yang ZF analyzed the data; Yang ZF wrote the manuscript and edited it; Wang YS contributed to the writing review; Wang YS and Yang ZF completed the writing–final draft; Wang YS contributed fund support.

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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 **Cao W**, Chen HD, Yu YW, Li N, Chen WQ. Changing profiles of cancer burden worldwide and in China: a secondary analysis of the global cancer statistics 2020. *Chin Med J (Engl)* 2021; **134**: 783-791 [PMID: 33734139 DOI: 10.1097/CM9.0000000000001474]

3 **Zhang W**. TCGA divides gastric cancer into four molecular subtypes: implications for individualized therapeutics. *Chin J Cancer* 2014; **33**: 469-470 [PMID: 25223913 DOI: 10.5732/cjc.014.10117]

4 **Cristescu R**, Lee J, Nebozhyn M, Kim KM, Ting JC, Wong SS, Liu J, Yue YG, Wang J, Yu K, Ye XS, Do IG, Liu S, Gong L, Fu J, Jin JG, Choi MG, Sohn TS, Lee JH, Bae JM, Kim ST, Park SH, Sohn I, Jung SH, Tan P, Chen R, Hardwick J, Kang WK, Ayers M, Hongyue D, Reinhard C, Loboda A, Kim S, Aggarwal A. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. *Nat Med* 2015; **21**: 449-456 [PMID: 25894828 DOI: 10.1038/nm.3850]

5 **Katai H**, Ishikawa T, Akazawa K, Isobe Y, Miyashiro I, Oda I, Tsujitani S, Ono H, Tanabe S, Fukagawa T, Nunobe S, Kakeji Y, Nashimoto A; Registration Committee of the Japanese Gastric Cancer Association. Five-year survival analysis of surgically resected gastric cancer cases in Japan: a retrospective analysis of more than 100,000 patients from the nationwide registry of the Japanese Gastric Cancer Association (2001-2007). *Gastric Cancer* 2018; **21**: 144-154 [PMID: 28417260 DOI: 10.1007/s10120-017-0716-7]

6 **Zhao Y**, Wang X, Huang Y, Zhou X, Zhang D. Conversion of immunohistochemical markers and breast density are associated with pathological response and prognosis in very young breast cancer patients who fail to achieve a pathological complete response after neoadjuvant chemotherapy. *Cancer Manag Res* 2019; **11**: 5677-5690 [PMID: 31417311 DOI: 10.2147/CMAR.S198844]

7 **Kooby DA**, Suriawinata A, Klimstra DS, Brennan MF, Karpeh MS. Biologic predictors of survival in node-negative gastric cancer. *Ann Surg* 2003; **237**: 828-35; discussion 835 [PMID: 12796579 DOI: 10.1097/01.Sla.0000072260.77776.39]

8 **Chen D**, Fu M, Chi L, Lin L, Cheng J, Xue W, Long C, Jiang W, Dong X, Sui J, Lin D, Lu J, Zhuo S, Liu S, Li G, Chen G, Yan J. Prognostic and predictive value of a pathomics signature in gastric cancer. *Nat Commun* 2022; **13**: 6903 [PMID: 36371443 DOI: 10.1038/s41467-022-34703-w]

9 **Huang Q**, Fang C, Shi J, Sun Q, Wu H, Gold JS, Weber HC, Guan W, Zhang Y, Yu C, Zou X, Mashimo H. Differences in Clinicopathology of Early Gastric Carcinoma between Proximal and Distal Location in 438 Chinese Patients. *Sci Rep* 2015; **5**: 13439 [PMID: 26310451 DOI: 10.1038/srep13439]

10 **Skancke M**, Arnott SM, Amdur RL, Siegel RS, Obias VJ, Umapathi BA. Lymphovascular Invasion and Perineural Invasion Negatively Impact Overall Survival for Stage II Adenocarcinoma of the Colon. *Dis Colon Rectum* 2019; **62**: 181-188 [PMID: 30640833 DOI: 10.1097/DCR.0000000000001258]

11 **del Casar JM**, Corte MD, Alvarez A, García I, Bongera M, González LO, García-Muñiz JL, Allende MT, Astudillo A, Vizoso FJ. Lymphatic and/or blood vessel invasion in gastric cancer: relationship with clinicopathological parameters, biological factors and prognostic significance. *J Cancer Res Clin Oncol* 2008; **134**: 153-161 [PMID: 17628829 DOI: 10.1007/s00432-007-0264-3]

12 **Hyung WJ**, Lee JH, Choi SH, Min JS, Noh SH. Prognostic impact of lymphatic and/or blood vessel invasion in patients with node-negative advanced gastric cancer. *Ann Surg Oncol* 2002; **9**: 562-567 [PMID: 12095972 DOI: 10.1007/bf02573892]

13 **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]

14 **Camorlinga-Ponce M**, Flores-Luna L, Lazcano-Ponce E, Herrero R, Bernal-Sahagún F, Abdo-Francis JM, Aguirre-García J, Muñoz N, Torres J. Age and severity of mucosal lesions influence the performance of serologic markers in Helicobacter pylori-associated gastroduodenal pathologies. *Cancer Epidemiol Biomarkers Prev* 2008; **17**: 2498-2504 [PMID: 18768521 DOI: 10.1158/1055-9965.EPI-08-0289]

15 **Song H**, Ekheden IG, Zheng Z, Ericsson J, Nyrén O, Ye W. Incidence of gastric cancer among patients with gastric precancerous lesions: observational cohort study in a low risk Western population. *BMJ* 2015; **351**: h3867 [PMID: 26215280 DOI: 10.1136/bmj.h3867]

16 **González CA**, Pera G, Agudo A, Palli D, Krogh V, Vineis P, Tumino R, Panico S, Berglund G, Simán H, Nyrén O, Agren A, Martinez C, Dorronsoro M, Barricarte A, Tormo MJ, Quiros JR, Allen N, Bingham S, Day N, Miller A, Nagel G, Boeing H, Overvad K, Tjonneland A, Bueno-De-Mesquita HB, Boshuizen HC, Peeters P, Numans M, Clavel-Chapelon F, Helen I, Agapitos E, Lund E, Fahey M, Saracci R, Kaaks R, Riboli E. Smoking and the risk of gastric cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *Int J Cancer* 2003; **107**: 629-634 [PMID: 14520702 DOI: 10.1002/ijc.11426]

17 **Hansford S**, Kaurah P, Li-Chang H, Woo M, Senz J, Pinheiro H, Schrader KA, Schaeffer DF, Shumansky K, Zogopoulos G, Santos TA, Claro I, Carvalho J, Nielsen C, Padilla S, Lum A, Talhouk A, Baker-Lange K, Richardson S, Lewis I, Lindor NM, Pennell E, MacMillan A, Fernandez B, Keller G, Lynch H, Shah SP, Guilford P, Gallinger S, Corso G, Roviello F, Caldas C, Oliveira C, Pharoah PD, Huntsman DG. Hereditary Diffuse Gastric Cancer Syndrome: CDH1 Mutations and Beyond. *JAMA Oncol* 2015; **1**: 23-32 [PMID: 26182300 DOI: 10.1001/jamaoncol.2014.168]

18 **Zhao L**, Han W, Niu P, Lu Y, Zhang F, Jiao F, Zhou X, Wang W, Luan X, He M, Guan Q, Li Y, Nie Y, Wu K, Zhao D, Chen Y. Using nomogram, decision tree, and deep learning models to predict lymph node metastasis in patients with early gastric cancer: a multi-cohort study. *Am J Cancer Res* 2023; **13**: 204-215 [PMID: 36777507]

19 **Ajani JA**, D'Amico TA, Bentrem DJ, Chao J, Cooke D, Corvera C, Das P, Enzinger PC, Enzler T, Fanta P, Farjah F, Gerdes H, Gibson MK, Hochwald S, Hofstetter WL, Ilson DH, Keswani RN, Kim S, Kleinberg LR, Klempner SJ, Lacy J, Ly QP, Matkowskyj KA, McNamara M, Mulcahy MF, Outlaw D, Park H, Perry KA, Pimiento J, Poultsides GA, Reznik S, Roses RE, Strong VE, Su S, Wang HL, Wiesner G, Willett CG, Yakoub D, Yoon H, McMillian N, Pluchino LA. Gastric Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2022; **20**: 167-192 [PMID: 35130500 DOI: 10.6004/jnccn.2022.0008]

20 **Yoshida K**, Kodera Y, Kochi M, Ichikawa W, Kakeji Y, Sano T, Nagao N, Takahashi M, Takagane A, Watanabe T, Kaji M, Okitsu H, Nomura T, Matsui T, Yoshikawa T, Matsuyama J, Yamada M, Ito S, Takeuchi M, Fujii M. Addition of Docetaxel to Oral Fluoropyrimidine Improves Efficacy in Patients With Stage III Gastric Cancer: Interim Analysis of JACCRO GC-07, a Randomized Controlled Trial. *J Clin Oncol* 2019; **37**: 1296-1304 [PMID: 30925125 DOI: 10.1200/JCO.18.01138]

21 **Joshi SS**, Badgwell BD. Current treatment and recent progress in gastric cancer. *CA Cancer J Clin* 2021; **71**: 264-279 [PMID: 33592120 DOI: 10.3322/caac.21657]

22 **Wang FH**, Zhang XT, Li YF, Tang L, Qu XJ, Ying JE, Zhang J, Sun LY, Lin RB, Qiu H, Wang C, Qiu MZ, Cai MY, Wu Q, Liu H, Guan WL, Zhou AP, Zhang YJ, Liu TS, Bi F, Yuan XL, Rao SX, Xin Y, Sheng WQ, Xu HM, Li GX, Ji JF, Zhou ZW, Liang H, Zhang YQ, Jin J, Shen L, Li J, Xu RH. The Chinese Society of Clinical Oncology (CSCO): Clinical guidelines for the diagnosis and treatment of gastric cancer, 2021. *Cancer Commun (Lond)* 2021; **41**: 747-795 [PMID: 34197702 DOI: 10.1002/cac2.12193]

23 **Lee J**, Lim DH, Kim S, Park SH, Park JO, Park YS, Lim HY, Choi MG, Sohn TS, Noh JH, Bae JM, Ahn YC, Sohn I, Jung SH, Park CK, Kim KM, Kang WK. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. *J Clin Oncol* 2012; **30**: 268-273 [PMID: 22184384 DOI: 10.1200/JCO.2011.39.1953]

24 **Noh SH**, Park SR, Yang HK, Chung HC, Chung IJ, Kim SW, Kim HH, Choi JH, Kim HK, Yu W, Lee JI, Shin DB, Ji J, Chen JS, Lim Y, Ha S, Bang YJ; CLASSIC trial investigators. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; **15**: 1389-1396 [PMID: 25439693 DOI: 10.1016/S1470-2045(14)70473-5]

25 **Zhu XD**, Huang MZ, Wang YS, Feng WJ, Chen ZY, He YF, Zhang XW, Liu X, Wang CC, Zhang W, Ying JE, Wu J, Yang L, Qin YR, Luo JF, Zhao XY, Li WH, Zhang Z, Qiu LX, Geng QR, Zou JL, Zhang JY, Zheng H, Song XF, Wu SS, Zhang CY, Gong Z, Liu QQ, Wang XF, Xu Q, Wang Q, Ji JM, Zhao J, Guo WJ. XELOX doublet regimen versus EOX triplet regimen as first-line treatment for advanced gastric cancer: An open-labeled, multicenter, randomized, prospective phase III trial (EXELOX). *Cancer Commun (Lond)* 2022; **42**: 314-326 [PMID: 35212487 DOI: 10.1002/cac2.12278]

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ORIGINAL ARTICLE

Retrospective Study

Gastroesophageal signet ring cell carcinoma morbidity and mortality: A retrospective review

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Abstract

BACKGROUND

Upper gastrointestinal (GI) signet ring cell carcinomas (SRCC) confer a poor prognosis. The benefit of operative intervention for this patient group is controversial in terms of overall survival.

AIM

To investigate factors relating to survival in patients with upper GI SRCC.

METHODS

A retrospective, tertiary, single-centre review of patients who were diagnosed with oesophageal, gastroesophageal junction and gastric SRCC was performed. The primary outcome was to compare mortality of patients who underwent operative management with those who had nonoperative management. Secondary outcomes included assessing the relationship between demographic and histopathological factors, and survival.

RESULTS

One hundred and thirty-one patients were included. The one-year survival for the operative group was 81% and for the nonoperative group was 19.1%. The five-year survival in the operative group was 28.6% *vs* 1.5% in the nonoperative group. The difference in overall survival between groups was statistically significant (HR 0.19, 95%CI (0.13-0.30), $P < 0.001$). There was no difference in survival when adjusting for age, smoking status or gender. On multivariate analysis, patients who underwent surgical management, those with a lower stage of disease, and those with a lower Charlson Comorbidity Index (CCI) had significantly improved survival.

CONCLUSION

Well-selected patients with upper GI SRCC appear to have reasonable medium-term survival following surgery. Offering surgery to a carefully selected patient group may improve the outcome for this disease.

Key Words: Signet ring cell carcinoma; Gastric cancer; Oesophageal cancer; Poorly cohesive gastric cancer; Diffuse gastric cancer

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Core Tip: This retrospective review confirms that in a select group of patients, surgical management for upper gastrointestinal signet ring cell carcinoma may provide a survival benefit and should be considered. Demographic factors such as age, smoking status and gender do not have a relationship with survival. Patients who had surgical management, those with a lower Charlson Comorbidity Index, and those with a lower stage of disease had significantly improved survival.

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INTRODUCTION

Signet ring cell carcinomas (SRCC) are a rare and aggressive subtype of adenocarcinoma, found most frequently in the stomach. SRCC has specific oncogenesis and phenotypic and treatment resistance heterogeneity. The 2019 WHO classification defines poorly cohesive SRCC as a histological subtype of malignant gastric epithelial tumours[1]. It is characterised by prominent cytoplasmic mucin within the cells and an eccentrically placed crescent-shaped nucleus. The Lauren classification morphologically categorises gastric tumours as 'intestinal' or 'diffuse'[2]. Intestinal tumours tend to be more organised, and arrange themselves into tubular or glandular structures. Diffuse tumours include SRCC, and are less differentiated and more infiltrative. The loss of expression of adhesion molecules such as E-cadherin allows a more invasive and diffuse growth pattern[3].

Oesophageal SRCC is less common than gastric SRCC, ranging from 0.6%-9% of all oesophageal adenocarcinomas[3]. Oesophageal SRCC is an aggressive disease with poor chemoradiation response and diminished survival. The incidence of gastric SRCC has increased by more than 400% in the United States since the 1970s[4]. SRCC is estimated to account for 33%-71% of gastric adenocarcinomas[5,6].

Operative management for patients with SRCC of the oesophagus and stomach is generally viewed as the standard of care. However, survival is low and response to chemotherapy is typically poor in this subgroup of patients. Given its historical associations as a negative predictive factor in terms of mortality, the primary outcome was to identify whether operative management improves the prognosis of patients with oesophageal, gastroesophageal junction (GOJ) and gastric SRCC. Secondary outcomes were to identify exact characteristics that determine patient prognosis.

MATERIALS AND METHODS

Study design

All patients diagnosed with histologically confirmed oesophageal, GOJ or gastric SRCC between January 2010 and December 2020 were included for review from a single, tertiary surgical unit. The study was approved by the New Zealand Health and Disability Ethics Committee. Patient consent was not required due to the retrospective nature of the study. Electronic records were reviewed to obtain information on patient demographics including age, gender, ethnicity, comorbidities, histology, clinical and pathological staging, management, recurrence, and survival. Overall survival was obtained by reviewing the patient's date of death on the clinical database. If the patient was still alive, the last known date of patient contact was recorded.

Staging, neoadjuvant therapy and operative management

Clinical and pathological staging were performed in accordance to the American Joint Committee on Cancer Staging Manual and Handbook (Seventh Edition)[7]. Patient management was determined after discussion at a multidisciplinary meeting with a panel of experts. Appropriate patients with locally advanced cancer were treated with neoadjuvant chemotherapy, determined by local best practice guidelines, prior to operative intervention. The most common regime used was fluorouracil, leucovorin, oxaliplatin and docetaxel, given to 21 patients. The next most common regime was epirubicin, cisplatin and capecitabine, given to nine patients. Two patients had neoadjuvant radiation therapy included in their treatment protocol.

The initial clinical stage was compared with the final pathologic stage to determine response to induction therapy. Histopathological response to chemotherapy was evaluated in the final surgical specimen by using tumour regression grade. Operative management depended on tumour location. 45 patients underwent a partial or total gastrectomy, 14 patients had an Ivor-Lewis oesophagectomy, three patients had a palliative operation such as a bypass procedure, and one patient had an endoscopic resection. Palliative bypass patients were included in the operative group.

Statistical analysis

Patients were analysed on an intention-to-treat basis. *T*-test and chi-square tests were used to determine differences in baseline characteristics between the operative and nonoperative groups. Survival analysis using the log-rank test for univariate comparisons and Cox regression for multivariate analysis was used to determine differences in overall survival between those that underwent surgery and those that did not. Survival statistics were calculated using the Kaplan-Meier method. Survival was measured from the date of histological diagnosis to the date of death or follow-up as of 31st August 2023.

RESULTS

Patient characteristics

One hundred and thirty-one patients were identified in the 10-year period with oesophageal, GOJ or gastric SRCC. The majority of these were gastric (67.2%), followed by oesophageal (21.4%) and GOJ (12.2%) cancers. Patient demographics are summarised in Table 1. 52 patients were women and 79 were men. The mean patient age was 63.3 years. 63 (48%) patients underwent operative intervention. The average intensive care unit and total length of stay were 2.6 d and 16.1 d. Of the 68 patients who did not undergo resection, 47 (69.1%) were due to inoperable disease, 11 (16.2%) were deemed unfit for surgery due to comorbidities, seven (10.3%) patients declined operative management, two (2.9%) patients had an acute deterioration and died while waiting for an operation, and one (1.5%) reason was unknown. The Charlson Comorbidity Index (CCI) was significantly higher in the nonoperative group (7.7 ± 2.5 *vs* 6.5 ± 2.1, $P < 0.001$). The number of patients with stage IV disease in the nonoperative group compared with the operative group was significant when compared with other stages on univariate analysis ($P < 0.001$).

Survival analysis

Factors were analysed to identify if they contributed to patient survival. This is summarised in Table 2. The mean overall survival for all patients from the date of diagnosis was 2.1 years, and the median survival was 10.5 months. In the operative group, the mean survival was 3.2 years and the median survival was 2.5 years. In the nonoperative group, the mean survival was 22.4 months and the median survival was 3.3 months. 26/63 (41.3%) patients were reported to have a recurrence. The mean time from the date of operation to the date of recurrence was 18.1 months. The mean length of survival from date of recurrence was 7.6 months. Only 3/63 (4.8%) patients who had a documented recurrence survived within the time period of follow-up.

Late outcomes

The one-year survival for the operative group was 81% *vs* 19.1% in the nonoperative group. The five-year survival in the operative group was 28.6% *vs* 1.5% in the nonoperative group. The difference in overall survival between groups was statistically significant [HR 0.19, 95%CI (0.13, 0.30), $P < 0.001$]. This is represented by Figures 1 and 2.

On univariate analysis, there was no statistically significant difference in survival when adjusting for age, smoking status or gender. Asian patients appeared to have improved survival when compared with other ethnicities [HR 0.45, 95%CI (0.24-0.84), $P = 0.013$]. There were no other statistically significant survival differences within other ethnic groups.

Survival of patients who received neoadjuvant chemotherapy prior to surgery was directly compared with those who did not. The survival effect of neoadjuvant chemotherapy in operative patients did not reach statistical significance [HR 1.87, 95%CI (0.93-3.76), $P = 0.080$]. The small number of patients limited further analysis.

Surgical samples were analysed to determine histological response to chemotherapy. The histopathological analysis of the 31 patients showed 13 specimens with more than 50% of residual tumour (grade 3), 12 specimens with 10%-50% residual tumour (grade 2), four with less than 10% residual tumour (grade 1), and in two patients the response was not recorded. Neoadjuvant chemotherapy was therefore only partially or completely effective in 51.6% of selected operative candidates.

On multivariate analysis, patients who underwent surgical management, those with a lower stage of disease, and those with a lower CCI had significantly improved survival when accounting for other confounding factors.

Multivariate analysis was performed comparing operative with nonoperative groups, adjusting for the presence of stage IV disease as well as CCI. This found that even when adjusting for stage IV disease, the operative group had improved survival ($P = 0.031$). This would suggest that surgery may confer benefit, even after the confounding effect of stage, metastatic disease and patient comorbidities is considered.

Asian ethnicity was no longer significant after multivariate analysis. This may suggest that Asian patients presented with an earlier stage of disease, that they were more likely to have operative management, or that they benefited more from surgery than other ethnicities.

Table 1 Patient demographics and comorbidities

Variables	Operative group (*N* = 63)	Nonoperative group (*N* = 68)	*P* value
Demographics			
Age	63.3	66.7	
Age > 50 yr, *n* (%)	57 (90.5)	53 (78.0)	
Male sex, *n* (%)	37 (58.7)	42 (61.8)	
Ethnicity			
European	33	44	
Asian	15	4	0.013
Pacific Peoples	6	8	
Māori	7	10	
MELAA	0	2	0.004
Unknown	2	0	
Tumour location			
Oesophageal	9	19	
Gastro-oesophageal	10	6	
Gastric	44	43	
Pathological stage			
I	18	11	
II	10	6	
III	30	5	
IV	5	46	< 0.001
Current smoker	9	11	
Charlson Comorbidity Index	6.5 ± 2.1	7.7 ± 2.5	0.0073

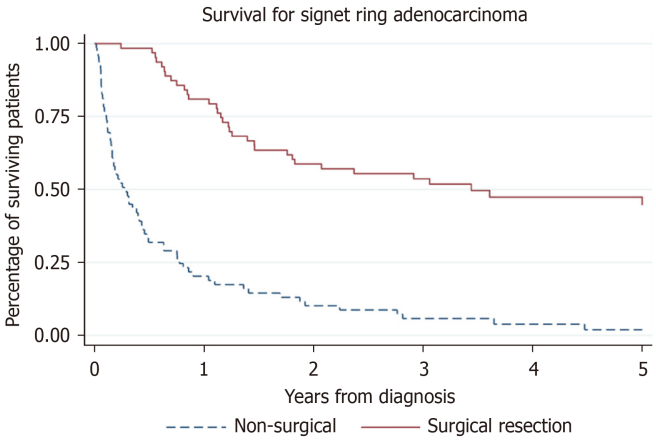


Figure 1 Survival for signet ring adenocarcinoma in operative *vs* nonoperative groups.

DISCUSSION

This study found that operative management of gastric, oesophageal and GOJ SRCCs appeared to be beneficial in a select group of patients. Patients with upper GI SRCC appear to benefit from surgical intervention, regardless of whether the tumour arises from the oesophagus or stomach. Analysing oesophageal, gastric and GOJ SRCCs separately may give more information about tumour-specific prognosis. However, dividing these patients further into subgroups limits meaningful analysis and results would be underpowered due to small numbers. In this study there was no significant difference in survival depending on location of the tumour. This suggests that the current paradigm of primary operative

Table 2 Demographic factors and their relationship with survival

Univariate analysis - factors associated with survival		
Demographic factors	**Hazard ratio**	***P* value**
Age	1.003 (0.99-1.02)	
Male	0.93 (0.63-1.38)	
Smoker	1.12 (0.63-1.98)	
European	1.24 (0.84-1.84)	
Asian	0.45 (0.24-0.84)	0.013
Pacific Peoples	0.92 (0.50-1.69)	
Māori	1.35 (0.78-2.34)	
MELAA	11.3 (2.62-48.64)	0.001
Unknown	0.66 (0.16-2.76)	
Surgery	0.20 (0.13-0.30)	< 0.001
Stage IV	5.13 (3.35-7.87)	< 0.001
Stage (overall)	2.23 (1.78-2.79)	< 0.001
Charlson Comorbidity Index	1.27 (1.18-1.38)	< 0.001
Proportion of signet ring cells	1.07 (0.72-1.58)	
Neoadjuvant chemotherapy	1.87 (0.93-3.76)	
Multivariate analysis - factors associated with survival		
Stage	1.62 (1.30-2.01)	< 0.001
Surgery	0.27 (0.17-0.42)	< 0.001
Charlson Comorbidity Index	1.19 (1.08-1.30)	< 0.001
Asian ethnicity	0.75 (0.39-1.43)	

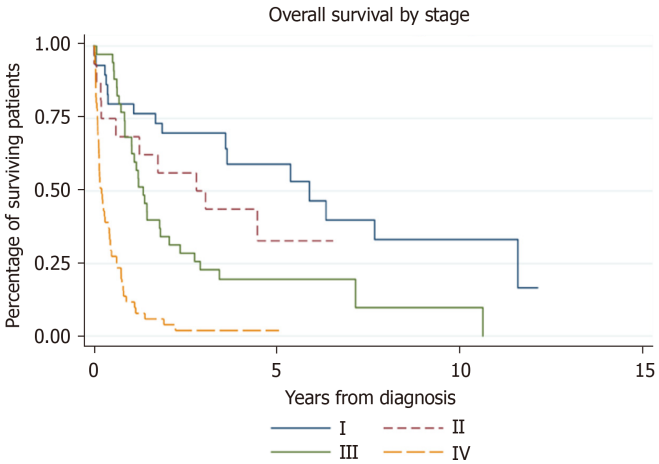


Figure 2 Overall survival of signet ring adenocarcinoma by stage I-V.

management in this group of patients is appropriate both in gastric and oesophageal tumours.

SRCC overview

SRCC is a rare pathological entity that is increasing in frequency worldwide. SRCC histology is an independent predictor of poor prognosis when compared with adenocarcinoma not otherwise specified (NOS) of the GI tract. Patients diagnosed with SRCC are typically younger and present with more advanced disease. Surgery and systemic therapy are understood to improve survival, although this is less successful than in NOS patients[8].

There is a paucity of literature directly comparing oesophageal and gastric SRCC. Piessen *et al*[9] found that gastric SRCCs were more likely to have metastasised to peritoneal tissues at the time of diagnosis, but are associated with a better prognosis than oesophageal SRCCs.

Gastric SRCC

Gastric SRCCs are aggressive tumours with a poor prognosis. Studies have found that gastric SRCCs are more infiltrative, diagnosed at a more advanced stage, have a greater incidence of lymph node metastases and peritoneal spread, and are more chemoresistant when compared with gastric adenocarcinoma NOS[5,6,9,10].

A recent study found that signet ring histology was an independent predictor for poor survival, and that perioperative chemotherapy for gastric SRCC provided no survival benefit[6]. Neoadjuvant chemotherapy also appeared to have a limited effect on patients in our study, although the study was not powered to analyse this outcome, and therefore the results must be interpreted with caution.

Despite these findings, there is ongoing controversy in the literature about whether SRCC is consistently a negative prognostic factor. Research is often restricted to noncomparative retrospective reviews, which can limit meaningful interpretation. A meta-analysis by Nie *et al*[11] found that SRCC may behave differently in early *vs* advanced gastric cancer, portending a better prognosis in early disease and a worse prognosis in advanced disease.

Multiple reports in Asian countries have found that SRCC features in gastric cancer were not found to be predictive of poor prognosis, and may even be associated with a better survival[12,13]. This finding is seen specifically in early gastric cancer, and may be because of lead time bias, or younger age at presentation[14].

A large database study in the United States of 10246 patients with gastric cancer found that patients with SRCC were more likely to present at stage 3-4, have lymph node spread and distant metastases, but did not have a worse prognosis [15]. The study also noted that Asian ethnicity appeared to confer a survival advantage. This was also seen in our cohort in the univariate, but not multivariate analysis. These results may suggest molecular or genetic factors that confer a survival benefit, rather than environmental factors such as screening programs and improved access to endoscopy.

Oesophageal SRCC

Oesophageal SRCC is less well studied than gastric SRCC due to its rarity. Multiple studies support the finding that oesophageal SRCC carries a worse prognosis when compared with adenocarcinoma NOS, regardless of stage at presentation[16,17]. Enlow *et al*[18] found that patients with oesophageal and GOJ SRCC cancers were less chemoresponsive, more likely to have disseminated disease, and had a worse prognosis when compared with adenocarcinoma NOS patients.

Limitations

This study is limited by its retrospective nature and the fact that it was carried out at a single institution. Known confounders such as age, smoking status and comorbidities were adjusted for in our statistical analysis but, as a retrospective, non-randomised study, there are likely to be unknown confounders that may have influenced the outcome. These may include subjective fitness for surgery, and patient wishes that are difficult to quantify in a formal statistical analysis beyond what has been adjusted for already.

Improved survival was seen even after accounting for stage, metastatic disease and CCI. This would suggest that there is a true possible survival benefit of surgery independent of patient factors, however selection bias may account for this.

Another limitation of this study is its record of patient deaths. This is dependent on the accuracy of the institutional regional electronic records used to access patient information. If a patient had moved to a different location, their death may not have been captured. However, this limitation applied equally to both operative and nonoperative groups, which reduces potential bias.

Despite these limitations, this study is one of the few in Australasia to analyse the outcomes of patients with this rare disease. This is one of the largest cohorts described for this illness in Aotearoa New Zealand. This adds to the sparse body of existing surgical literature on upper GI SRCC. The results of this study aim to improve evidence-based local clinical practice.

CONCLUSION

This study supports the decision to pursue operative management in a well-selected group of patients with upper GI SRCC. Operative intervention appeared to result in an improved survival for these patients. The survival advantage extended to at least five years. Age, smoking status and gender had no correlation with survival. Earlier tumour stage, and a lower CCI were other significant factors associated with improved survival. Despite the aggressive nature, high recurrence rate and subsequent mortality of SRCC, operative management should be considered as the first line strategy in appropriate patients with upper GI SRCC. Long term survival is possible in appropriately selected patients.

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FOOTNOTES

Author contributions: Grinlinton M, Furkert C and Booth M conceptualised and designed the research; Grinlinton M and Angelo N acquired the demographic and clinical data; Furkert C and Grinlinton M collected the clinical data; Maurice A performed data analysis; Grinlinton M wrote the paper; Grinlinton M and Maurice A have played important roles in the data interpretation and manuscript preparation as the authors; Maurice A was instrumental and responsible for data analysis and interpretation; Grinlinton M was responsible for literature search, preparation and submission of the current version of the manuscript. All authors have read and approve the final manuscript.

Institutional review board statement: This study was reviewed and approved by the New Zealand Health and Disability Ethics Committee (No. 15291).

Informed consent statement: Informed consent was not required due to the retrospective and anonymous nature of this study.

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

Data sharing statement: No additional data are available.

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REFERENCES

1 **Nagtegaal ID**, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, Washington KM, Carneiro F, Cree IA; WHO Classification of Tumours Editorial Board. The 2019 WHO classification of tumours of the digestive system. *Histopathology* 2020; **76**: 182-188 [PMID: 31433515 DOI: 10.1111/his.13975]
2 **LAUREN P**. THE TWO HISTOLOGICAL MAIN TYPES OF GASTRIC CARCINOMA: DIFFUSE AND SO-CALLED INTESTINAL-TYPE CARCINOMA. AN ATTEMPT AT A HISTO-CLINICAL CLASSIFICATION. *Acta Pathol Microbiol Scand* 1965; **64**: 31-49 [PMID: 14320675 DOI: 10.1111/apm.1965.64.1.31]
3 **Bleaney CW**, Barrow M, Hayes S, Ang Y. The relevance and implications of signet-ring cell adenocarcinoma of the oesophagus. *J Clin Pathol* 2018; **71**: 201-206 [PMID: 29212656 DOI: 10.1136/jclinpath-2017-204863]
4 **Henson DE**, Dittus C, Younes M, Nguyen H, Albores-Saavedra J. Differential trends in the intestinal and diffuse types of gastric carcinoma in the United States, 1973-2000: increase in the signet ring cell type. *Arch Pathol Lab Med* 2004; **128**: 765-770 [PMID: 15214826 DOI: 10.5858/2004-128-765-DTITIA]
5 **Piessen G**, Messager M, Leteurtre E, Jean-Pierre T, Mariette C. Signet ring cell histology is an independent predictor of poor prognosis in gastric adenocarcinoma regardless of tumoral clinical presentation. *Ann Surg* 2009; **250**: 878-887 [PMID: 19855261 DOI: 10.1097/SLA.0b013e3181b21c7b]
6 **Messager M**, Lefevre JH, Pichot-Delahaye V, Souadka A, Piessen G, Mariette C; FREGAT working group - FRENCH. The impact of perioperative chemotherapy on survival in patients with gastric signet ring cell adenocarcinoma: a multicenter comparative study. *Ann Surg* 2011; **254**: 684-93; discussion 693 [PMID: 22005144 DOI: 10.1097/SLA.0b013e3182352647]
7 **Frederick LG**, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, Morrow M. AJCC cancer staging manual. Springer Science & Business Media; 2002. Available from: https://www.facs.org/media/j30havyf/ajcc_7thed_cancer_staging_manual.pdf
8 **Franko J**, Le VH, Tee MC, Lin M, Sedinkin J, Raman S, Frankova D. Signet ring cell carcinoma of the gastrointestinal tract: National trends on treatment effects and prognostic outcomes. *Cancer Treat Res Commun* 2021; **29**: 100475 [PMID: 34655861 DOI: 10.1016/j.ctarc.2021.100475]
9 **Piessen G**, Messager M, Lefevre JH, Goéré D, Mabrut JY, Meunier B, Brigand C, Hamy A, Glehen O, Mariette C; FREGAT Working Group – FRENCH. Signet ring cell adenocarcinomas: different clinical-pathological characteristics of oesophageal and gastric locations. *Eur J Surg Oncol* 2014; **40**: 1746-1755 [PMID: 25012732 DOI: 10.1016/j.ejso.2014.04.019]
10 **Liu X**, Cai H, Sheng W, Yu L, Long Z, Shi Y, Wang Y. Clinicopathological Characteristics and Survival Outcomes of Primary Signet Ring Cell Carcinoma in the Stomach: Retrospective Analysis of Single Center Database. *PLoS One* 2015; **10**: e0144420 [PMID: 26642199 DOI: 10.1371/journal.pone.0144420]
11 **Nie RC**, Yuan SQ, Li YF, Chen YM, Chen XJ, Zhu BY, Xu LP, Zhou ZW, Chen S, Chen YB. Clinicopathological Characteristics and Prognostic Value of Signet Ring Cells in Gastric Carcinoma: A Meta-Analysis. *J Cancer* 2017; **8**: 3396-3404 [PMID: 29151922 DOI: 10.7150/jca.21017]
12 **Kao YC**, Fang WL, Wang RF, Li AF, Yang MH, Wu CW, Shyr YM, Huang KH. Clinicopathological differences in signet ring cell adenocarcinoma between early and advanced gastric cancer. *Gastric Cancer* 2019; **22**: 255-263 [PMID: 30069742 DOI: 10.1007/s10120-018-0860-8]

13 **Gronnier C**, Messager M, Robb WB, Thiebot T, Louis D, Luc G, Piessen G, Mariette C; FREGAT working group-FRENCH. Is the negative prognostic impact of signet ring cell histology maintained in early gastric adenocarcinoma? *Surgery* 2013; **154**: 1093-1099 [PMID: 24075273 DOI: 10.1016/j.surg.2013.05.020]

14 **Pernot S**, Voron T, Perkins G, Lagorce-Pages C, Berger A, Taieb J. Signet-ring cell carcinoma of the stomach: Impact on prognosis and specific therapeutic challenge. *World J Gastroenterol* 2015; **21**: 11428-11438 [PMID: 26523107 DOI: 10.3748/wjg.v21.i40.11428]

15 **Taghavi S**, Jayarajan SN, Davey A, Willis AI. Prognostic significance of signet ring gastric cancer. *J Clin Oncol* 2012; **30**: 3493-3498 [PMID: 22927530 DOI: 10.1200/JCO.2012.42.6635]

16 **Yendamuri S**, Huang M, Malhotra U, Warren GW, Bogner PN, Nwogu CE, Groman A, Demmy TL. Prognostic implications of signet ring cell histology in esophageal adenocarcinoma. *Cancer* 2013; **119**: 3156-3161 [PMID: 23719932 DOI: 10.1002/cncr.28099]

17 **Nafteux PR**, Lerut TE, Villeneuve PJ, Dhaenens JM, De Hertogh G, Moons J, Coosemans WJ, Van Veer HG, De Leyn PR. Signet ring cells in esophageal and gastroesophageal junction carcinomas have a more aggressive biological behavior. *Ann Surg* 2014; **260**: 1023-1029 [PMID: 24836142 DOI: 10.1097/SLA.0000000000000689]

18 **Enlow JM**, Denlinger CE, Stroud MR, Ralston JS, Reed CE. Adenocarcinoma of the esophagus with signet ring cell features portends a poor prognosis. *Ann Thorac Surg* 2013; **96**: 1927-1932 [PMID: 23987898 DOI: 10.1016/j.athoracsur.2013.06.047]

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ORIGINAL ARTICLE

Retrospective Study

Analysis of lymph node metastasis and survival prognosis in early gastric cancer patients: A retrospective study

Dong-Yuan Liu, Jin-Jin Hu, Yong-Quan Zhou, Ai-Rong Tan

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Abstract

BACKGROUND

Early gastric cancer (EGC) is a common malignant tumor of the digestive system, and its lymph node metastasis and survival prognosis have been concerning. By retrospectively analyzing the clinical data of EGC patients, we can better understand the status of lymph node metastasis and its impact on survival and prognosis.

AIM

To evaluate the prognosis of EGC patients and the factors that affect lymph node metastasis.

METHODS

The clinicopathological data of 1011 patients with EGC admitted to our hospital between January 2015 and December 2023 were collected in a retrospective cohort study. There were 561 males and 450 females. The mean age was 58 ± 11 years. The patient underwent radical gastrectomy. The status of lymph node metastasis in each group was determined according to the pathological examination results of surgical specimens. The outcomes were as follows: (1) Lymph node metastasis in EGC patients; (2) Analysis of influencing factors of lymph node metastasis in EGC; and (3) Analysis of prognostic factors in patients with EGC. Normally distributed measurement data are expressed as mean ± SD, and a *t* test was used

for comparisons between groups. The data are expressed as absolute numbers or percentages, and the chi-square test was used for comparisons between groups. Rank data were compared using a nonparametric rank sum test. A log-rank test and a logistic regression model were used for univariate analysis. A logistic stepwise regression model and a Cox stepwise regression model were used for multivariate analysis. The Kaplan-Meier method was used to calculate the survival rate and construct survival curves. A log-rank test was used for survival analysis.

RESULTS

Analysis of influencing factors of lymph node metastasis in EGC. The results of the multifactor analysis showed that tumor length and diameter, tumor site, tumor invasion depth, vascular thrombus, and tumor differentiation degree were independent influencing factors for lymph node metastasis in patients with EGC (odds ratios = 1.80, 1.49, 2.65, 5.76, and 0.60; 95%CI: 1.29–2.50, 1.11–2.00, 1.81–3.88, 3.87-8.59, and 0.48-0.76, respectively; $P < 0.05$). Analysis of prognostic factors in patients with EGC. All 1011 patients with EGC were followed up for 43 (0–13) months. The 3-year overall survival rate was 97.32%. Multivariate analysis revealed that age > 60 years and lymph node metastasis were independent risk factors for prognosis in patients with EGC (hazard ratio = 9.50, 2.20; 95%CI: 3.31-27.29, 1.00-4.87; $P < 0.05$). Further analysis revealed that the 3-year overall survival rates of gastric cancer patients aged > 60 years and ≤ 60 years were 99.37% and 94.66%, respectively, and the difference was statistically significant ($P < 0.05$). The 3-year overall survival rates of patients with and without lymph node metastasis were 95.42% and 97.92%, respectively, and the difference was statistically significant ($P < 0.05$).

CONCLUSION

The lymph node metastasis rate of EGC patients was 23.64%. Tumor length, tumor site, tumor infiltration depth, vascular cancer thrombin, and tumor differentiation degree were found to be independent factors affecting lymph node metastasis in EGC patients. Age > 60 years and lymph node metastasis are independent risk factors for EGC prognosis.

Key Words: Gastric neoplasms; Lymph node metastasis; Prognosis; Influencing factor; Retrospective study

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Core Tip: The clinical data of patients with early gastric cancer (EGC) were retrospectively analyzed to investigate the lymph node metastasis and its influence on survival and prognosis. We will focus on the incidence of lymph node metastasis in patients with EGC and the correlation between the number of metastatic lymph nodes and the survival of patients. The results of this study are helpful to further understand the pathological characteristics of EGC patients and their impact on prognosis, and provide scientific basis for developing personalized treatment and improving the quality of life of patients.

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INTRODUCTION

Early gastric cancer (EGC) is an adenocarcinoma that is limited to the gastric mucosa or submucosa, regardless of tumor size and lymph node metastasis[1-3]. In recent years, with the continuous improvement in the diagnosis and treatment of gastric cancer in our country, the detection rate of early-stage gastric cancer has been continuously increasing, and the 5-year survival rate is > 90%. Although the prognosis of EGC patients is good, the 5-year survival rate of EGC patients with lymph node metastasis is significantly lower than that of patients without lymph node metastasis[4]. The status of lymph node metastasis determines the treatment of EGC and affects the prognosis.

EGC research revealed that a large number of poorly differentiated cases involved the lower part of the stomach. This observation sparked our interest in a retrospective analysis of lymph node metastasis and survival outcomes in EGC patients. In clinical practice, low-differentiated cases typically show more aggressive characteristics, and their tendency to appear in the lower part of the stomach has attracted our attention[5]. There are several possible reasons. First, the lower part of the stomach has a more complex anatomical structure due to its anatomical location, close to the pylorus and gastric antrum, which may complicate the growth and spread of tumors in the lower part of the stomach. Additionally, the lower part of the stomach has more mucosal structure than the upper part. The submucosal tissue is also less dense, which may make it easier for tumor cells to enter lymphatic and blood vessels[6]. In addition, disease factors specific to the lower stomach, such as atrophic gastritis and *Helicobacter pylori* infection, may also be associated with low differentiation in gastric cancer and lymph node metastasis.

Early stomach cancer is the early stage of cancer, when the cancer cells are mostly confined to the stomach wall and have not yet spread to the lymph nodes or beyond[7]. Lymph node metastasis is an important sign of gastric cancer progression, which means that cancer cells enter lymphatic vessels from the primary site, reach lymph nodes, and continue to grow and spread. The occurrence and degree of lymph node metastasis have important influences on the prognosis of gastric cancer patients[8-10]. With the progress of medical technology, the diagnosis rate of EGC has improved, but lymph node metastasis is still a key factor affecting the prognosis of patients[11]. The presence of lymph node metastases in EGC can provide valuable information about the patient's prognosis and help physicians develop a more precise treatment plan. Studying the relationship between lymph node metastasis and the prognosis of EGC patients is helpful for further understanding the development of gastric cancer and providing clinicians with more targeted treatment recommendations to improve the survival rate and quality of life of patients[12-14]. Moreover, for patients with EGC with lymph node metastasis, effective treatments, such as surgery, chemotherapy, and radiotherapy, should be actively adopted to curb the spread of cancer cells and improve the cure rate[15].

Both anatomical pathways and tumor biology can help us understand the basic principle of lymph node metastasis, which is more concentrated in the first station. Anatomically, the lymphatic system forms specific channels in the body that direct tissue fluid and cellular waste from tissues to lymph nodes. When cancer cells invade lymphatic vessels and penetrate their walls, they usually first travel along an anatomical path to the nearest lymph node, the "first stop" of lymphatic metastasis. Tumor biology also influences this pattern; for example, tumor cells within lymphatic vessels may be influenced by specific factors that make them more inclined to stay and grow in specific lymph nodes along the anatomical path.

This study retrospectively analyzed the clinicopathological data of 1011 patients with EGC admitted to our department between January 2015 and December 2023 to explore the factors affecting lymph node metastasis and the prognosis of EGC patients.

MATERIALS AND METHODS

General clinical data analysis

The clinicopathological data of 1011 patients with EGC were collected in a prospective cohort study. There were 561 males and 450 females. The mean age was 58 ± 11 years. Among the 1011 patients, 577 had a tumor length ≤ 2 cm, and 434 had a length > 2 cm. The tumors were highly differentiated in 214 patients, moderately differentiated in 296 patients, and poorly differentiated in 501 patients. The tumors were located in the upper part of the stomach in 90 patients, the middle part of the stomach in 193 patients, and the lower part of the stomach in 728 patients. The depth of tumor invasion was mucosa (stage T1a) in 446 patients and submucosa (stage T1b) in 565 patients.

This study was approved by our hospital, and patients and their families signed informed consent forms.

Inclusion criteria: (1) A postoperative pathological examination confirmed EGC; (2) A radical gastrectomy was performed; (3) No antitumor therapy was administered before surgery; and (4) Complete clinicopathological data were available.

Exclusion criteria: (1) A postoperative pathological examination confirmed advanced gastric cancer; (2) Patients with a preoperative history of neoadjuvant therapy; (3) Other malignant tumors; (4) Gastric stump cancer; (5) Recurrent cancer; (6) Special types of gastric tumors, such as lymphoma, neuroendocrine tumors, and stromal tumors; and (7) Clinicopathological data were missing.

Research methods

The patient underwent radical gastrectomy. According to the pathological examination results of surgical specimens, lymph node metastasis in each group was determined according to the statistics of the 13th edition of the gastric cancer treatment protocol.

Observation indicators and evaluation criteria

Observation indicators: (1) Lymph node metastasis in EGC includes the lymph node metastasis rate, lymph node metastasis rate in different T stages, lymph node metastasis in different groups, and lymph node metastasis in different locations; (2) Analysis of influencing factors of lymph node metastasis in EGC: Sex, age, body mass index (BMI), family history of gastric cancer, smoking history, drinking history, tumor length, tumor site, tumor invasion depth, vascular cancer thrombus, nerve invasion, and tumor differentiation degree; and (3) Analysis of factors influencing the prognosis of patients with EGC: Number of patients with follow-up, follow-up time, and survival of patients. The clinicopathologic factors included sex, age, BMI, family history of gastric cancer, smoking history, drinking history, tumor length, tumor site, depth of tumor invasion, vascular cancer thrombus, nerve invasion, degree of tumor differentiation, and lymph node metastasis.

Evaluation criteria: The T and N stages were determined according to the American Joint Commission on Cancer (AJCC) 8th edition tumor-node-metastasis (TNM) staging criteria. The system classifies patients into different stages based on the primary tumor, lymph node metastasis, and distant metastasis status. Specifically, the T stage reflects the size and aggressiveness of the primary tumor in the stomach, the N stage reflects the presence of lymph node metastasis, and the M stage reflects the presence of distant metastasis. We retrospectively analyzed the patients' clinical data, classified them

according to the AJCC-TNM staging system, and recorded the number of patients, clinical features, and lymph node metastasis in each stage group.

Follow-up visit

Follow-up was conducted by outpatient visits or telephone to determine the survival of patients, and the follow-up time was up to May 2023.

Statistical analysis

SPSS 25.0 statistical software was used for the analysis. Normally distributed measurement data are expressed as mean ± SD, and a *t* test was used for comparisons between groups. The data are expressed as absolute numbers or percentages, and the chi-square test was used for comparisons between groups. Rank data were compared using a nonparametric rank sum test. A log-rank test and a logistic regression model were used for univariate analysis. A logistic stepwise regression model and a Cox stepwise regression model were used for multivariate analysis. The Kaplan-Meier method was used to calculate the survival rate and construct survival curves. A log-rank test was used for survival analysis. $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Lymph node metastasis in EGC

In 1011 patients with early-stage gastric cancer, the rate of lymph node metastasis was 23.64% (239/1011), among which the rate of lymph node metastasis was 11.88% (53/446) in patients with stage T1a disease and 32.92% (186/565) in patients with stage T1b disease. In 239 patients with lymph node metastasis, lymph node metastasis was mainly concentrated in the first-station lymph node, and in groups 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10, lymph node metastasis was 7, 11, 135, 59, 39, 91, 6, 8, 8, 8, and 6, respectively. The same patient may have multiple lymph node metastases. Lymph node metastasis at different tumor sites: 4, 2, and 1 patients were included in the 2nd, 3rd, and 5th groups of upper gastric tumors, respectively. There were 3, 7, 36, 15, 3, and 5 patients with lymph node metastasis in groups 1, 2, 3, 3, 6, 4, 4, and 6, respectively. There were 4, 97, 44, 35, and 86 patients with lymph node metastasis in groups 1, 3, 4, 5, and 6, respectively.

Analysis of influencing factors of lymph node metastasis in EGC

One-way analysis revealed that the factors that affected lymph node metastasis in EGC patients were tumor differentiation, tumor length, tumor location, tumor invasion depth, vascular thrombus, and tumor differentiation. Sex, age, BMI, family history of gastric cancer, smoking history, and drinking history were not correlated with lymph node metastasis in patients with EGC ($P > 0.05$; Table 1).

The results of the multifactor analysis showed that tumor length, tumor location, tumor invasion depth, vascular cancer thrombus, and tumor differentiation degree were independent factors affecting lymph node metastasis in EGC patients ($P < 0.05$; Table 2).

Analysis of factors influencing the prognosis of patients with EGC

All 1011 patients with EGC were followed up for 43 (0–13) months. The 3-year overall survival rate was 97.32%. Univariate analysis revealed that age, vascular thrombus, and lymph node metastasis were factors related to the prognosis of EGC patients ($P < 0.05$). Sex, BMI, family history of gastric cancer, smoking history, drinking history, tumor length, tumor site, depth of tumor invasion, nerve invasion, and degree of tumor differentiation were not correlated with the prognosis of EGC patients ($P > 0.05$; Table 3).

The results of multivariate analysis showed that age > 60 years and lymph node metastasis were independent risk factors for the prognosis of EGC patients ($P < 0.05$; Table 4). Further analysis revealed that the 3-year overall survival rates of gastric cancer patients aged > 60 years and ≤ 60 years were 99.37% and 94.66%, respectively, and the difference was statistically significant ($\chi^2 = 25.33$, $P < 0.001$; Figure 1A). The 3-year overall survival rates of patients with and without lymph node metastasis were 95.42% and 97.92%, respectively, and the difference was statistically significant ($\chi^2 = 5.69$, $P = 0.017$; Figure 1B).

DISCUSSION

The main treatment methods for EGC include simple surgery and endoscopic resection[16]. Compared with surgical resection, endoscopic resection has the advantages of less trauma and a greater postoperative quality of life and is the preferred treatment for EGC[17]. However, the risk of tumor recurrence after endoscopic resection is greater than that after surgical resection because the lymph nodes cannot be removed. Therefore, for EGC patients with lymph node metastasis, surgical operations are still needed to achieve radical resection of the tumor[18-20]. Lymph node metastasis is also a key factor affecting the prognosis of patients with EGC. The results of this study showed that the 3-year overall survival rate of patients with lymph node metastasis was significantly lower than that of patients without lymph node metastasis[21]. Therefore, accurately predicting the risk of lymph node metastasis in EGC and understanding the law of lymph node metastasis in EGC are conducive to selecting appropriate surgical methods and improving therapeutic

Table 1 Univariate analysis of lymph node metastasis in 1011 patients with early gastric cancer

Clinicopathological factors	Assignment	Lymph node metastasis (*n* = 239)	No lymph node metastasis (*n* = 772)	χ^2	*P* value
Sex					
Male	1	131	430	0.06	0.809
Female	0	108	342		
Age					
≤ 60 yr old	0	131	432	0.10	0.755
> 60 yr old	1	108	340		
BMI					
≤ 24 kg/m²	1	162	539	0.56	0.511
> 24 kg/m²	0	77	233		
Family history of gastric cancer					
Yes	1	92	284	0.23	0.633
No	0	147	488		
Smoking history					
Yes	1	84	266	0.04	0.845
No	0	155	506		
Drinking history					
Yes	1	67	191	1.04	0.308
No	0	172	581		
Tumor size					
≤ 2 cm	0	99	478	31.29	< 0.001
> 2 cm	1	140	294		
Tumor location					
Upper part of the stomach	1	6	84	15.82	< 0.001
Mid-stomach	2	50	143		
Lower part of the stomach	3	183	545		
Tumor invasion depth					
Mucosal lining	0	53	393	61.11	< 0.001
Submucosa	1	186	379		
Vasculatogenic cancer thrombus					
No	0	102	64	157.26	< 0.001
Yes	1	137	708		
Nerve invasion					
No	0	21	24	13.83	< 0.001
Yes	1	218	748		
Degree of tumor differentiation					
Low differentiation	1	125	376	*Z* = -2.45	0.014
Medium differentiation	2	88	208		
High differentiation	3	26	188		

BMI: Body mass index.

Table 2 Multivariate analysis of lymph node metastasis in 1011 patients with early gastric cancer

Clinicopathological factors	Regression coefficients	SE	Wald	OR	95%CI	*P* value
Tumor diameter	0.59	0.17	12.15	1.80	1.29-2.50	< 0.001
Tumor site	0.40	0.15	7.10	1.49	1.11-1.00	0.008
Depth of tumor invasion	0.97	0.20	24.84	2.65	1.81-3.88	< 0.001
Vasculatogenic cancer thrombus	1.75	0.20	73.99	5.76	3.87-8.59	< 0.001
Degree of tumor differentiation	-0.50	0.12	18.68	0.60	0.48-0.76	< 0.001

OR: Odds ratio.

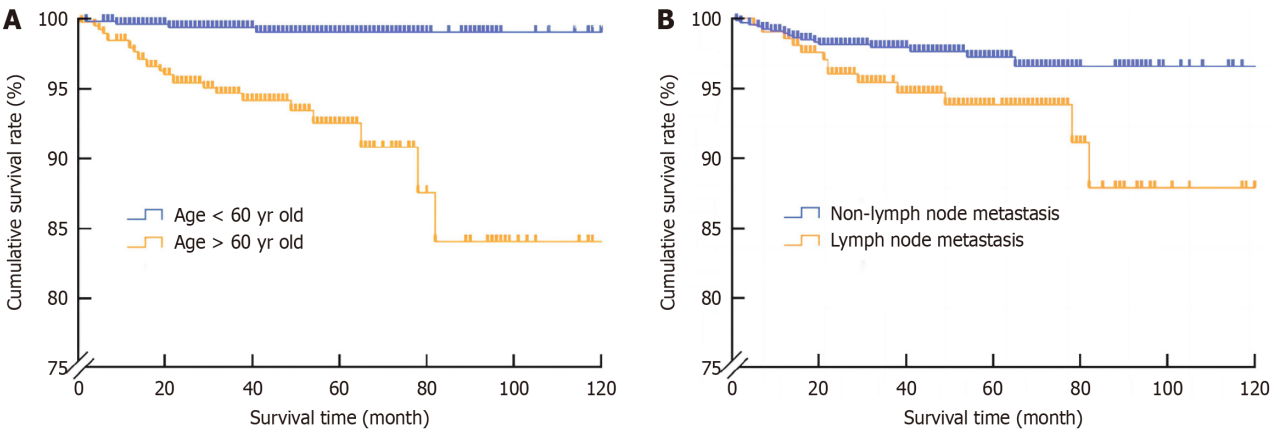


Figure 1 Overall survival curves of patients. A: Postoperative overall survival curves of patients aged < 60 years and > 60 years with early gastric cancer; B: Overall survival curve of patients with early gastric cancer without lymph node metastasis and with lymph node metastasis.

efficacy.

The results of this study showed that the lymph node metastasis rate of EGC patients was 23.64% (239/1011), which was similar to the findings of other studies[22]. There are many factors affecting lymph node metastasis in EGC, among which vascular invasion, depth of tumor invasion, and tumor size are recognized as influencing factors[23]. Multifactor analysis in this study showed that the length of the tumor, its location, its invasion depth, the presence of a vascular cancer thrombus, and its degree of differentiation were all separate factors that affected lymph node metastasis in EGC patients[24]. Among the many factors related to lymph node metastasis in EGC, the indicators that can be used for preoperative evaluation include tumor length, tumor site, and tumor invasion depth[25-27]. Preoperative operators can use endoscopic ultrasound and gastroscopy to accurately evaluate EGC and guide the selection of appropriate treatment [28].

The results of this study showed that lymph node metastasis in EGC patients was mainly concentrated in the first station lymph node[29]. The rate of lymph node metastasis differed among different tumor sites, and the rate of lymph node metastasis differed among groups[30]. Although the patterns of lymph node metastasis differed among the different sites of EGC, Group 3 lymph node metastasis was detected in all of the patients, which should be the focus of further studies. One study examined the clinical and pathological information of 33 people with EGC who had lymph node metastasis. Group 3 had the most lymph node metastasis, followed by Group 4. This is consistent with the results of this study. D2 lymph node dissection has become the standard surgical procedure for advanced gastric cancer[31-33].

The results showed that lymph node metastasis in gastric cancer was affected by the degree of tumor differentiation, the depth of invasion, and the extent of lymphatic vessel invasion. In particular, patients with low differentiation, deep invasion, and obvious lymphatic vessel invasion were more likely to have lymph node metastasis. In addition, the patient's age, sex, comorbidities, and other factors may also affect the incidence and prognosis of lymph node metastasis.

Lymph node metastasis in EGC is mainly concentrated in the first-station lymph node, and most patients with EGC may have excessive lymph node dissection[34]. In summary, this study revealed that we need to determine whether a patient has lymph node metastasis before surgery for early-stage gastric cancer, to ensure that the right lymph node dissection is performed to the greatest extent possible after radical treatment, and to improve the overall survival of patients[35]. The results of this study showed that age > 60 years and lymph node metastasis were independent risk factors affecting the prognosis of patients with EGC[36]. Further analysis revealed statistically significant differences in 3-year overall survival rates between patients aged > 60 years and those aged ≤ 60 years with and without lymph node metastasis[37]. Another study showed that vascular thrombus is an independent risk factor affecting the prognosis of patients with EGC and can be used as a reference index for postoperative adjuvant treatment. Age is an important predictor of the prognosis of gastric cancer patients, and there are significant differences in clinicopathological features

Table 3 Univariate analysis of prognosis in 1011 patients with early gastric cancer

Clinicopathological factors	Assignment	Cases	3-year overall survival rate (%)	χ^2	*P* value
Sex					
Male	1	561	96.6	1.89	0.169
Female	0	450	98.0		
Age					
≤ 60 yr old	0	563	98.9	5.95	0.015
> 60 yr old	1	448	97.3		
BMI					
≤ 24 kg/m²	0	701	97.4	0.76	0.384
> 24 kg/m²	1	310	96.9		
Family history of gastric cancer					
Yes	1	376	96.6	1.69	0.193
No	0	635	99.3		
Smoking history					
Yes	1	350	97.9	1.42	0.233
No	0	661	98.8		
Drinking history					
Yes	1	258	98.8	1.09	0.297
No	0	753	98.4		
Tumor length					
≤ 2 cm	0	577	97.5	0.14	0.708
> 2 cm	1	434	96.9		
Tumor location					
Upper part of the stomach	1	90	97.4	0.57	0.752
Mid-stomach	2	193	98.1		
Lower part of the stomach	3	728	98.2		
Tumor invasion depth					
Mucosal lining	0	446	98.0	3.39	0.066
Submucosa	1	565	96.6		
Vasculatogenic cancer thrombus					
No	0	166	97.8	5.26	0.022
Yes	1	845	94.4		
Nerve invasion					
No	0	45	98.8	0.30	0.587
Yes	1	966	95.1		
Degree of tumor differentiation					
Low differentiation	1	501	97.7	4.21	0.122
Medium differentiation	2	296	97.6		
High differentiation	3	214	95.6		
Lymph node metastases					
No	0	772	97.9	7.11	0.008
Yes	1	239	95.0		

BMI: Body mass index.

Table 4 Multivariate analysis of prognosis in 1011 patients with early gastric cancer

Clinicopathological factors	Regression coefficients	SE	Wald	RR	95%CI	*P* value
Age > 60 yr	2.25	0.54	17.47	9.5	3.31-27.29	< 0.001
Lymph node metastases	0.79	0.40	3.81	2.2	1.00-4.87	0.049

RR: Risk ratio.

and prognostic factors among different age groups[38]. Lymph node metastasis is an independent risk factor for the postoperative prognosis of gastric cancer patients and can better guide the diagnosis and treatment of postoperative patients[39-41]. This study revealed that people over 60 years old who have EGC and who undergo postoperative pathological examination that revealed lymph node metastasis should receive additional chemotherapy or radiotherapy after surgery to help them live longer.

CONCLUSION

In summary, the rate of lymph node metastasis in EGC patients was 23.64%. Tumor length, tumor site, tumor invasion depth, vascular cancer thrombin, and tumor differentiation degree were found to be independent factors affecting lymph node metastasis in EGC patients. Age > 60 years and lymph node metastasis are independent risk factors for EGC patients.

FOOTNOTES

Author contributions: Liu DY wrote the manuscript; Hu JJ and Zhou YQ collected the data; Tan AR guided the study; All authors reviewed, edited, and approved the final manuscript and revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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Informed consent statement: This study has obtained the consent and signed informed consent of the patients and their families.

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REFERENCES

1 **Dong D**, Fang MJ, Tang L, Shan XH, Gao JB, Giganti F, Wang RP, Chen X, Wang XX, Palumbo D, Fu J, Li WC, Li J, Zhong LZ, De Cobelli F, Ji JF, Liu ZY, Tian J. Deep learning radiomic nomogram can predict the number of lymph node metastasis in locally advanced gastric cancer: an international multicenter study. *Ann Oncol* 2020; **31**: 912-920 [PMID: 32304748 DOI: 10.1016/j.annonc.2020.04.003]

2 **Li GZ**, Doherty GM, Wang J. Surgical Management of Gastric Cancer: A Review. *JAMA Surg* 2022; **157**: 446-454 [PMID: 35319717 DOI: 10.1001/jamasurg.2022.0182]

3 **Liu Y**, Zhai E, Chen J, Qian Y, Zhao R, Ma Y, Liu J, Huang Z, Cai S. m(6) A-mediated regulation of PBX1-GCH1 axis promotes gastric cancer proliferation and metastasis by elevating tetrahydrobiopterin levels. *Cancer Commun (Lond)* 2022; **42**: 327-344 [PMID: 35261206 DOI: 10.1002/cac2.12281]

4 **Zhang G**, Gao Z, Guo X, Ma R, Wang X, Zhou P, Li C, Tang Z, Zhao R, Gao P. CAP2 promotes gastric cancer metastasis by mediating the interaction between tumor cells and tumor-associated macrophages. *J Clin Invest* 2023; **133** [PMID: 37707957 DOI: 10.1172/JCI166224]

5 **Wu L**, Zheng Y, Liu J, Luo R, Wu D, Xu P, Li X. Comprehensive evaluation of the efficacy and safety of LPV/r drugs in the treatment of SARS and MERS to provide potential treatment options for COVID-19. *Aging (Albany NY)* 2021; **13**: 10833-10852 [PMID: 33879634 DOI: 10.18632/aging.202860]

6 **Li Y**, Liu C, Zhang X, Huang X, Liang S, Xing F, Tian H. CCT5 induces epithelial-mesenchymal transition to promote gastric cancer lymph node metastasis by activating the Wnt/β-catenin signalling pathway. *Br J Cancer* 2022; **126**: 1684-1694 [PMID: 35194191 DOI: 10.1038/s41416-022-01747-0]

7 **Qian Y**, Zhai E, Chen S, Liu Y, Ma Y, Chen J, Liu J, Qin C, Cao Q, Cai S. Single-cell RNA-seq dissecting heterogeneity of tumor cells and comprehensive dynamics in tumor microenvironment during lymph nodes metastasis in gastric cancer. *Int J Cancer* 2022; **151**: 1367-1381 [PMID: 35716132 DOI: 10.1002/ijc.34172]

8 **Huang Y**, Pan M, Deng Z, Ji Y, Chen B. How useful is sentinel lymph node biopsy for the status of lymph node metastasis in cT1N0M0 gastric cancer? A systematic review and meta-analysis. *Updates Surg* 2021; **73**: 1275-1284 [PMID: 33723712 DOI: 10.1007/s13304-021-01026-2]

9 **Wu L**, Zhong Y, Wu D, Xu P, Ruan X, Yan J, Liu J, Li X. Immunomodulatory Factor TIM3 of Cytolytic Active Genes Affected the Survival and Prognosis of Lung Adenocarcinoma Patients by Multi-Omics Analysis. *Biomedicines* 2022; **10** [PMID: 36140350 DOI: 10.3390/biomedicines10092248]

10 **Chen X**, Chen Y, Li T, Liang W, Huang H, Su H, Sui C, Hu Y, Chen H, Lin T, Chen T, Zhao L, Liu H, Li G, Yu J. Diabetes mellitus promoted lymph node metastasis in gastric cancer: a 15-year single-institution experience. *Chin Med J (Engl)* 2022; **135**: 950-961 [PMID: 34711717 DOI: 10.1097/CM9.0000000000001795]

11 **Guo X**, Gu J, Xue A, Song S, Liu B, Gao X, Chang L, Ruan Y. Loss of GNE Predicts Lymph Node Metastasis in Early Gastric Cancer. *Cells* 2022; **11** [PMID: 36429052 DOI: 10.3390/cells11223624]

12 **Li X**, Zhai J, Shen Y, Zhang T, Wang Y, He Y, You Q, Shen L. Tumor-derived IL-8 facilitates lymph node metastasis of gastric cancer *via* PD-1 up-regulation in CD8(+) T cells. *Cancer Immunol Immunother* 2022; **71**: 3057-3070 [PMID: 35633411 DOI: 10.1007/s00262-022-03223-3]

13 **Xiao J**, Shen K, Liu K, Wang Y, Fan H, Cheng Q, Zhou X, Hu L, Wang G, Xu Z, Yang L. Obesity promotes lipid accumulation in lymph node metastasis of gastric cancer: a retrospective case-control study. *Lipids Health Dis* 2022; **21**: 123 [PMID: 36397145 DOI: 10.1186/s12944-022-01734-7]

14 **Cai F**, Dong Y, Wang P, Zhang L, Yang Y, Liu Y, Wang X, Zhang R, Liang H, Sun Y, Deng J. Risk assessment of lymph node metastasis in early gastric cancer: Establishment and validation of a Seven-point scoring model. *Surgery* 2022; **171**: 1273-1280 [PMID: 34865863 DOI: 10.1016/j.surg.2021.10.049]

15 **Wu L**, Liu Q, Ruan X, Luan X, Zhong Y, Liu J, Yan J, Li X. Multiple Omics Analysis of the Role of RBM10 Gene Instability in Immune Regulation and Drug Sensitivity in Patients with Lung Adenocarcinoma (LUAD). *Biomedicines* 2023; **11** [PMID: 37509501 DOI: 10.3390/biomedicines11071861]

16 **Díaz Del Arco C**, Ortega Medina L, Estrada Muñoz L, García Gómez de Las Heras S, Fernández Aceñero MJ. Pathologic Lymph Node Staging of Gastric Cancer. *Am J Clin Pathol* 2021; **156**: 749-765 [PMID: 34273159 DOI: 10.1093/ajcp/aqab031]

17 **Ma D**, Zhang Y, Shao X, Wu C, Wu J. PET/CT for Predicting Occult Lymph Node Metastasis in Gastric Cancer. *Curr Oncol* 2022; **29**: 6523-6539 [PMID: 36135082 DOI: 10.3390/curroncol29090513]

18 **Wu L**, Zhong Y, Yu X, Wu D, Xu P, Lv L, Ruan X, Liu Q, Feng Y, Liu J, Li X. Selective poly adenylation predicts the efficacy of immunotherapy in patients with lung adenocarcinoma by multiple omics research. *Anticancer Drugs* 2022; **33**: 943-959 [PMID: 35946526 DOI: 10.1097/CAD.0000000000001319]

19 **Yang Q**, Feng S, Liu H, Zhang X, Cao J, Zhu Y, Zheng H, Song H. Clinicopathological features and lymph node metastasis risk in early gastric cancer with WHO criteria in China: 304 cases analysis. *Ann Diagn Pathol* 2021; **50**: 151652 [PMID: 33157382 DOI: 10.1016/j.anndiagpath.2020.151652]

20 **Yao J**, Zhang Y, Xia Y, Zhu C, Wen X, Liu T, Da M. PRRX1 promotes lymph node metastasis of gastric cancer by regulating epithelial-mesenchymal transition. *Medicine (Baltimore)* 2021; **100**: e24674 [PMID: 33578599 DOI: 10.1097/MD.0000000000024674]

21 **Kotecha K**, Singla A, Townend P, Merrett N. Association between neutrophil-lymphocyte ratio and lymph node metastasis in gastric cancer: A meta-analysis. *Medicine (Baltimore)* 2022; **101**: e29300 [PMID: 35758361 DOI: 10.1097/MD.0000000000029300]

22 **Wang X**, Chen Y, Gao Y, Zhang H, Guan Z, Dong Z, Zheng Y, Jiang J, Yang H, Wang L, Huang X, Ai L, Yu W, Li H, Dong C, Zhou Z, Liu X, Yu G. Predicting gastric cancer outcome from resected lymph node histopathology images using deep learning. *Nat Commun* 2021; **12**: 1637 [PMID: 33712598 DOI: 10.1038/s41467-021-21674-7]

23 **Yang J**, Wu Q, Xu L, Wang Z, Su K, Liu R, Yen EA, Liu S, Qin J, Rong Y, Lu Y, Niu T. Integrating tumor and nodal radiomics to predict lymph node metastasis in gastric cancer. *Radiother Oncol* 2020; **150**: 89-96 [PMID: 32531334 DOI: 10.1016/j.radonc.2020.06.004]

24 **Wang B**, Zhang Y, Qing T, Xing K, Li J, Zhen T, Zhu S, Zhan X. Comprehensive analysis of metastatic gastric cancer tumour cells using single-cell RNA-seq. *Sci Rep* 2021; **11**: 1141 [PMID: 33441952 DOI: 10.1038/s41598-020-80881-2]

25 **Zhou CM**, Wang Y, Ye HT, Yan S, Ji M, Liu P, Yang JJ. Machine learning predicts lymph node metastasis of poorly differentiated-type intramucosal gastric cancer. *Sci Rep* 2021; **11**: 1300 [PMID: 33446730 DOI: 10.1038/s41598-020-80582-w]

26 **Wu L**, Zheng Y, Ruan X, Wu D, Xu P, Liu J, Li X. Long-chain noncoding ribonucleic acids affect the survival and prognosis of patients with esophageal adenocarcinoma through the autophagy pathway: construction of a prognostic model. *Anticancer Drugs* 2022; **33**: e590-e603 [PMID: 34338240 DOI: 10.1097/CAD.0000000000001189]

27 **Milhomem LM**, Milhomem-Cardoso DM, da Mota OM, Mota ED, Kagan A, Filho JBS. Risk of lymph node metastasis in early gastric cancer and indications for endoscopic resection: is it worth applying the east rules to the west? *Surg Endosc* 2021; **35**: 4380-4388 [PMID: 32880748 DOI: 10.1007/s00464-020-07932-7]

28 **Zhao B**, Huang R, Lu H, Mei D, Bao S, Xu H, Huang B. Risk of lymph node metastasis and prognostic outcome in early gastric cancer patients with mixed histologic type. *Curr Probl Cancer* 2020; **44**: 100579 [PMID: 32451068 DOI: 10.1016/j.currproblcancer.2020.100579]

29 **Watanabe A**, McKendry GJ, Yip L, Donnellan F, Hamilton TD. Risk of lymph node metastasis in early gastric cancer for a Western population. *J Surg Oncol* 2023; **127**: 791-797 [PMID: 36583664 DOI: 10.1002/jso.27192]

30 **Wu L**, Li X, Qian X, Wang S, Liu J, Yan J. Lipid Nanoparticle (LNP) Delivery Carrier-Assisted Targeted Controlled Release mRNA Vaccines in Tumor Immunity. *Vaccines (Basel)* 2024; **12** [PMID: 38400169 DOI: 10.3390/vaccines12020186]

31 **Khalayleh H**, Kim YW, Yoon HM, Ryu KW. Assessment of Lymph Node Metastasis in Patients With Gastric Cancer to Identify Those Suitable for Middle Segmental Gastrectomy. *JAMA Netw Open* 2021; **4**: e211840 [PMID: 33729506 DOI: 10.1001/jamanetworkopen.2021.1840]

32 **Zhu H**, Wang G, Zheng J, Zhu H, Huang J, Luo E, Hu X, Wei Y, Wang C, Xu A, He X. Preoperative prediction for lymph node metastasis in early gastric cancer by interpretable machine learning models: A multicenter study. *Surgery* 2022; **171**: 1543-1551 [PMID: 35131110 DOI: 10.1016/j.surg.2021.12.015]

33 **Ren MH**, Qi XS, Chu YN, Yu YN, Chen YQ, Zhang P, Mao T, Tian ZB. Risk of Lymph Node Metastasis and Feasibility of Endoscopic Treatment in Ulcerative Early Gastric Cancer. *Ann Surg Oncol* 2021; **28**: 2407-2417 [PMID: 32975685 DOI: 10.1245/s10434-020-09153-7]

34 **Yang J**, Wang L, Qin J, Du J, Ding M, Niu T, Li R. Multi-view learning for lymph node metastasis prediction using tumor and nodal radiomics in gastric cancer. *Phys Med Biol* 2022; **67** [PMID: 35108700 DOI: 10.1088/1361-6560/ac515b]

35 **Wu L**, Li H, Liu Y, Fan Z, Xu J, Li N, Qian X, Lin Z, Li X, Yan J. Research progress of 3D-bioprinted functional pancreas and in vitro tumor models. *Int J Bioprinting* 2024; **10**: 1256 [DOI: 10.36922/ijb.1256]

36 **Chen J**, Zhao G, Wang Y. Analysis of lymph node metastasis in early gastric cancer: a single institutional experience from China. *World J Surg Oncol* 2020; **18**: 57 [PMID: 32197625 DOI: 10.1186/s12957-020-01834-7]

37 **Li S**, Zhao Z, Yang H, Wang D, Sun W, Li S, Zhang Z, Fu W. Construction and Validation of a Nomogram for the Preoperative Prediction of Lymph Node Metastasis in Gastric Cancer. *Cancer Control* 2021; **28**: 10732748211027160 [PMID: 34155937 DOI: 10.1177/10732748211027160]

38 **Wu L**, Chen X, Zeng Q, Lai Z, Fan Z, Ruan X, Li X, Yan J. NR5A2 gene affects the overall survival of LUAD patients by regulating the activity of CSCs through SNP pathway by OCLR algorithm and immune score. *Heliyon* 2024; **10**: e28282 [PMID: 38601554 DOI: 10.1016/j.heliyon.2024.e28282]

39 **Lu H**, Zhao B, Huang R, Sun Y, Zhu Z, Xu H, Huang B. Central lymph node metastasis is predictive of survival in advanced gastric cancer patients treated with D2 lymphadenectomy. *BMC Gastroenterol* 2021; **21**: 15 [PMID: 33407177 DOI: 10.1186/s12876-020-01578-4]

40 **de Jongh C**, Triemstra L, van der Veen A, Brosens LAA, Luyer MDP, Stoot JHMB, Ruurda JP, van Hillegersberg R; LOGICA Study Group. Pattern of lymph node metastases in gastric cancer: a side-study of the multicenter LOGICA-trial. *Gastric Cancer* 2022; **25**: 1060-1072 [PMID: 36103060 DOI: 10.1007/s10120-022-01329-2]

41 **Zhang M**, Ding C, Xu L, Feng S, Ling Y, Guo J, Liang Y, Zhou Z, Chen Y, Qiu H. A nomogram to predict risk of lymph node metastasis in early gastric cancer. *Sci Rep* 2021; **11**: 22873 [PMID: 34819570 DOI: 10.1038/s41598-021-02305-z]

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ORIGINAL ARTICLE

Retrospective Study

Clinical study of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in hypertriglyceridemia-induced acute pancreatitis and acute biliary pancreatitis with persistent organ failure

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Abstract

BACKGROUND

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are novel inflammatory indicators that can be used to predict the severity and prognosis of various diseases. We categorize acute pancreatitis by etiology into acute biliary pancreatitis (ABP) and hypertriglyceridemia-induced acute pancreatitis (HTGP).

AIM

To investigate the clinical significance of NLR and PLR in assessing persistent organ failure (POF) in HTGP and ABP.

METHODS

A total of 1450 patients diagnosed with acute pancreatitis (AP) for the first time at Shanxi Bethune Hospital between January 2012 and January 2023 were enrolled. The patients were categorized into two groups according to the etiology of AP: ABP in 530 patients and HTGP in 241 patients. We collected and compared the clinical data of the patients, including NLR, PLR, and AP prognostic scoring systems, within 48 h of hospital admission.

RESULTS

The NLR (9.1 *vs* 6.9, $P < 0.001$) and PLR (203.1 *vs* 160.5, $P < 0.001$) were significantly higher in the ABP group than in the HTGP group. In the HTGP group, both NLR and PLR were significantly increased in patients with severe AP and

those with a SOFA score ≥ 3. Likewise, in the ABP group, NLR and PLR were significantly elevated in patients with severe AP, modified computed tomography severity index score ≥ 4, Japanese Severity Score ≥ 3, and modified Marshall score ≥ 2. Moreover, NLR and PLR showed predictive value for the development of POF in both the ABP and HTGP groups.

CONCLUSION

NLR and PLR vary between ABP and HTGP, are strongly associated with AP prognostic scoring systems, and have predictive potential for the occurrence of POF in both ABP and HTGP.

Key Words: Acute pancreatitis; Gallstone; Hypertriglyceridemia; Neutrophil-to-lymphocyte ratio; Platelet-to-lymphocyte ratio; Persistent organ failure

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Core Tip: The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are novel inflammatory indicators that can effectively predict disease severity and prognosis. In this study, starting from the two common causes of acute pancreatitis (AP), the difference between the NLR and PLR in hypertriglyceridemia-induced acute pancreatitis (HTGP) and acute biliary pancreatitis (ABP) was explored retrospectively, and the predictive value of the NLR and PLR for persistent organ failure in HTGP and ABP were determined. To help clinicians maintain a high degree of vigilance in the early stages of AP, timely treatment interventions are needed to reduce the mortality of AP.

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INTRODUCTION

Acute pancreatitis (AP) is a common exocrine inflammatory disorder[1] characterized by the activation of cytokine cascades, leading to systemic inflammation[2], severe abdominal pain, and multiorgan dysfunction[3]. Approximately one-third of patients may progress to severe pancreatitis[4], ultimately leading to pancreatic necrosis and persistent organ failure (POF), with a mortality rate of 1%-5%.

In European and North American countries, the main etiological factors of AP are gallstones (50%) and alcohol consumption (25%)[5], with hypertriglyceridemia (HTG) being the third leading cause, accounting for 10% of all pancreatitis episodes. However, epidemiological studies in China have shown that gallstones account for 63.0% of AP cases, hyperlipidemia for 8.5%, and alcohol-induced cases 7.4%[6]. With changes in the dietary habits of the human population, the proportion of hyperlipidemia-related cases is continuously increasing. Approximately, 15%-20% of patients with severe HTG (> 11.0 mmol/L) are estimated to develop AP, leading to persistent multiorgan failure[7]. The inflammatory mechanisms underlying AP remain unclear[8], and there is significant clinical heterogeneity. Currently, no specific drugs are available to alter the disease[9]. Although many patients with AP may appear relatively stable upon admission, their ultimate prognosis often falls short of expectations as the disease progresses. Therefore, a reliable and objective assessment method is required to assist in the clinical prognostic evaluation of AP.

Several AP scoring systems are currently available to assist clinicians in predicting the prognosis of AP patients. Common scores include the Bedside Index for Severity in Acute Pancreatitis (BISAP) score, modified computed tomography severity index (MCTSI), Modified Marshall score, Sequential Organ Failure Assessment (SOFA) score, and Japanese Severity Score (JSS). However, these scoring systems are time consuming and require extensive clinical data in combination with imaging[10]. In situations with limited resources, it may not be feasible to obtain all the parameters of these scoring systems promptly, leading to difficulties in the early assessment of AP severity and impacting patient management and prognosis. Therefore, there has been an ongoing search for a simple, practical, quantifiable, easily collectible, and readily available indicator for predicting AP severity[11]. Serum biomarkers such as white blood cell count, neutrophil count, lymphocyte count, platelet count, and C-reactive protein[12] have been identified as having good value in predicting the prognosis and severity of AP[13].

Recently, novel serum biomarkers such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have shown high value in predicting the severity of various diseases, including inflammation and tumors[14]. Studies have demonstrated that an elevated NLR within 48 h of admission is significantly associated with severe AP (SAP) and serves as an independent prognostic indicator for AP[15]; PLR has also been identified as an auxiliary marker for predicting the severity of AP[11]. Although these studies have explored the prognostic value of NLR and PLR in AP, there is a lack of comparative analyses regarding their prognostic significance in patients with AP of different etiologies. In this study, we aimed to evaluate and compare the prognostic values of NLR and PLR in HTG-induced acute pancre-

atitis (HTGP) and acute biliary pancreatitis (ABP) in terms of the development of POF. Additionally, we compared their effectiveness and practicality with those of the existing scoring systems.

MATERIALS AND METHODS

Patient characteristics

We retrospectively analyzed 1450 patients diagnosed with AP for the first time at Shanxi Bethune Hospital between January 2012 and January 2023. After strict selection, 771 patients were included. This study was retrospective, and all data were derived from the Hospital Information System (HIS). Informed consent was obtained from each patient upon admission, with informed consent forms stored in the HIS. This study strictly adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Shanxi Bethune Hospital (ethics approval No: YXLL-2023-237).

The diagnosis of AP requires two of the following three criteria: (1) Typical abdominal pain; (2) Serum amylase or lipase elevation ≥ 3 times the upper limit of normal; and (3) Characteristic findings of AP on contrast-enhanced computed tomography (CT), magnetic resonance imaging, or abdominal ultrasonography[16].

The diagnostic criteria for ABP are based on the diagnosis of AP, where imaging can confirm impaired emptying of the bile and pancreatic ducts at the ampulla of Vater because of causes such as gallbladder stones, common bile duct stones, and biliary tract infections[17]. The diagnostic criteria for HTGP are as follows: in the presence of an AP diagnosis, if the serum triglyceride (TG) level is ≥ 11.3 mmol/L, or when the TG level is between 5.65 and 11.3 mmol/L, if other causes of AP are excluded, a high suspicion of HTGP should be considered[18].

Patients were stratified based on disease severity using the revised Atlanta classification (RAC) as follows: (1) Mild acute pancreatitis (MAP), no organ failure or local or systemic complications; (2) Moderate to severe acute pancreatitis, transient organ failure (resolution within 48 h) or local complications; and (3) SAP: POF (lasting > 48 h)[2]. The diagnosis of organ failure (OF) was based on the Modified Marshall Scoring System, with any organ score ≥ 2 defining the presence of OF. OF lasting more than 48 h was defined as POF[19]. During the study period, 1450 patients were diagnosed with AP (Figure 1). Patients with etiologies other than gallstone or HTG were excluded. All patients were followed-up until discharge or death.

Inclusion criteria: (1) Meet the diagnostic criteria for AP, HTGP, and ABP; (2) Age ≥ 18 years; (3) Hospitalized within 48 h after onset of symptoms; (4) Patients admitted to Shanxi Bethune Hospital for the first time with a diagnosis of AP; and (5) Complete clinical data.

Exclusion criteria: (1) Incomplete clinical data or missing medical records; (2) Chronic pancreatitis, pancreatitis of other types such as alcohol-induced, trauma-induced, or pregnancy-related; (3) Patients with history of tumors, infections, immune system disorders, or hematological diseases; and (4) Use of antibiotics or corticosteroids within the past week.

Data collection

General Information: sex, age, height (cm), weight (kg), body mass index (BMI), underlying diseases (hypertension, diabetes, *etc.*), and presence or absence of POF. Laboratory and imaging indicators within 24 h of admission included liver and kidney function, complete blood count, coagulation function, arterial blood gas analysis, and abdominal CT.

Statistical analysis

The statistical software SPSS (version 26.0) was used for the data analysis. Normally distributed continuous variables are expressed as mean ± SD. The median (interquartile range, 25^{th}-75^{th} percentile) was used for variables that did not follow a normal distribution. Differences between the two groups were analyzed using Student's *t*-test. Binary logistic regression analysis was used to identify risk factors. The diagnostic performance of the indicators was evaluated using receiver operating characteristic curves, with a significance level of $P < 0.05$ indicating statistically significant differences.

RESULTS

Patient characteristics

Comparison of the baseline characteristics of patients: 466 male and 305 female patients with AP. In total, 128 patients had diabetes, 190 had hypertension, and 188 had hyperlipidemia. According to the Modified Marshall Scoring criteria, among patients with AP, 234 had POF and 537 did not have POF. The ABP group had a higher average age, lower BMI, lower male-to-female ratio, and lower proportion of smokers. The HTGP group had higher white blood cell, lymphocyte, and platelet counts. However, NLR (9.1 *vs* 6.9, $P < 0.001$) and PLR (203.1 *vs* 160.5, $P < 0.001$) were significantly higher in the ABP group than in the HTGP group. In terms of liver function indicators, the HTGP group had higher levels of cholesterol and TGs, whereas the other indicators were lower than those in the ABP group. The ABP group also had a higher proportion of patients with hypertension. The average length of hospital stay was shorter in the HTGP group than in the ABP group; however, the SAP incidence rate was higher in the HTGP group than in the ABP group. There were no significant differences between the two groups in terms of intensive care unit (ICU) admission rate, systemic inflammatory response syndrome (SIRS), POF incidence rate, and mortality rate. In the AP scoring system, there were no significant differences in the SOFA scores. The MCTSI score and JSS were higher in the HTGP group than in the ABP

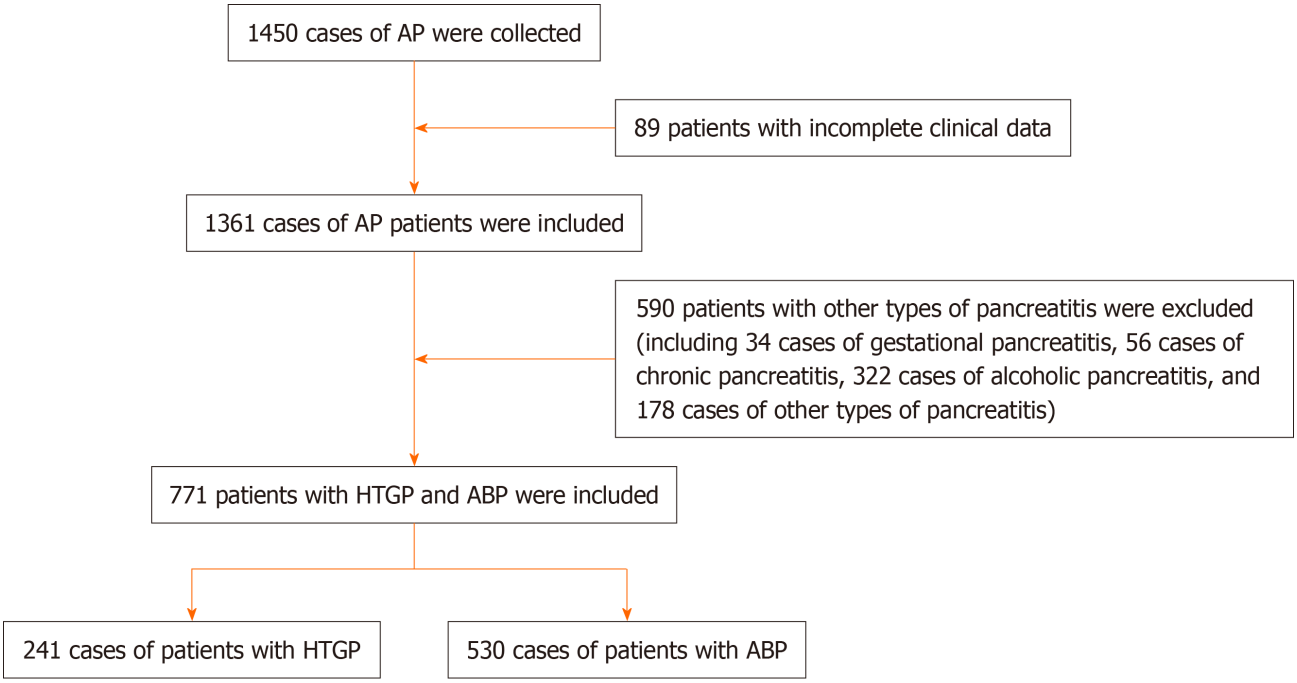


Figure 1 Flow chart of patient enrollment. AP: Acute pancreatitis; HTGP: Hypertriglyceridemia-induced acute pancreatitis; ABP: Acute biliary pancreatitis.

group, whereas the Modified Marshall and BISAP scores were significantly higher in the ABP group (Table 1).

Group analysis of NLR and PLR about the previous AP scoring system

We conducted a group analysis based on the etiology of AP. Regarding HTGP, patients with severe pancreatitis (defined according to the RAC) and a SOFA score ≥ 3 ($P < 0.05$) exhibited significantly higher PLR and NLR (Table 2).

The relationship between NLR, PLR, and the AP scoring system was more pronounced in ABP. In ABP, patients with severe pancreatitis (defined according to the RAC), MCTSI score ≥ 4, JSS ≥ 3, and Modified Marshall score ≥ 2 exhibited significantly higher PLR and NLR. However, when the BISAP score was ≥ 3 (15.6, $P = 0.002$) and SOFA score ≥ 3 (12.4, $P < 0.001$), only NLR showed a significant increase, whereas PLR did not show statistical significance (Table 3).

Comparison of the predictive value of NLR, PLR, and the AP scoring system for POF in HTGP

We calculated the area under the curve (AUC) of the NLR and PLR to predict the occurrence of POF in HTGP patients and compared them with the previous AP scoring system (Figure 2A). In HTGP patients, neither NLR nor PLR showed a significant advantage in predicting POF (NLR-AUC 0.619, 95%CI: 0.55-0.69; PLR-AUC 0.622, 95%CI: 0.55-0.70). In contrast, the SOFA and Modified Marshall scores had higher predictive values, with AUCs of 0.827 and 0.772, sensitivities of 71.3% and 66.3%, and specificities of 82.0% and 79.5%, respectively (Table 4).

Comparison of the predictive value of NLR, PLR, and the AP scoring system for POF in ABP

Similarly, we calculated the AUC of NLR and PLR to predict the occurrence of POF in ABP patients and compared them with the previous AP scoring system (Figure 2B). In ABP patients, NLR and PLR also did not demonstrate significant advantages in predictive value (NLR-AUC 0.668, 95%CI: 0.62-0.72; PLR-AUC 0.569, 95%CI: 0.52-0.62). However, the Modified Marshall score and JSS showed higher predictive values for biliary AP, with AUCs of 0.761 and 0.760, sensitivities of 67.5% and 59.1%, and specificities of 70.5% and 78.2%, respectively (Table 5).

DISCUSSION

AP is characterized by the activation of innate and adaptive immune responses, resulting in inflammation. AP manifests as an acute abdomen, primarily characterized by local pancreatic inflammation caused by the abnormal activation of pancreatic enzymes, leading to digestive effects on the pancreas and surrounding organs. An excessive inflammatory response can result in the transfer of a large number of inflammatory factors to the pancreas, causing pancreatic damage, and ultimately affecting multiple organs and systems throughout the body, leading to SAP[20]. The mortality rate of SAP is as high as 15%-30%, while that of MAP is only 0-1%. Furthermore, the clinical presentation of AP is unreliable and lacks specificity, with a sensitivity of less than 40% for predicting adverse outcomes[21].

Therefore, early identification, accurate staging, and timely treatment of SAP are crucial for reducing the incidence and mortality rates of AP[22]. Existing research has demonstrated that early prediction of AP severity allows for effective intervention, thereby improving patient outcomes[23].

Table 1 Baseline characteristics

Characteristics		Overall (771)	HTGP (241)	ABP (530)	*P* value
Age (yr)		49 (37.0; 63.0)	37 (26.0; 53.8)	56 (30.0; 84.0)	< 0.001
Sex, *n* (%)					< 0.001
	Male	466 (60.4)	184 (76.3)	282 (53.2)	
	Female	305 (39.6)	57 (23.7)	248 (46.8)	
BMI (kg/m^2)		26 (23.4; 28.7)	27.8 (22.0; 35.3)	25.4 (19.0; 33.7)	< 0.001
Smoking, *n* (%)					< 0.001
	N	515 (66.8)	131 (54.4)	384 (72.5)	
	Y	256 (33.2)	110 (45.6)	146 (27.5)	
Drinking, *n* (%)					< 0.001
	N	550 (71.3)	147 (61)	403 (76)	
	Y	221 (28.7)	94 (39)	127 (24)	
Diabetes, *n* (%)					< 0.001
	N	643 (83.4)	173 (71.8)	470 (88.7)	
	Y	128 (16.6)	68 (28.2)	60 (11.3)	
Hypertension, *n* (%)					< 0.001
	N	581 (75.4)	202 (83.8)	379 (71.5)	
	Y	190 (24.6)	39 (16.2)	151 (28.5)	
Hyperlipidemia, *n* (%)					< 0.001
	N	583 (75.6)	88 (36.5)	495 (93.4)	
	Y	188 (24.4)	153 (63.5)	35 (6.6)	
Laboratory data					
	ALT	63.6 (26.0; 181.3)	31.9 (9.7; 111.7)	108.8 (13; 616.8)	< 0.001
	AST	46.2 (24.4; 130.2)	28.8 (13.0; 114.1)	70.1 (16.1; 638.0)	< 0.001
	ALP	108.9 (79.1; 108.9)	101.1 (41.9; 118.1)	108.9 (55.3; 258.5)	< 0.001
	γ-GT	219.5 (119.7; 219.5)	219.5 (17.6; 318.2)	219.5 (31.0; 696.6)	< 0.001
	ALB	36.4 (31.8; 41.4)	37.0 (21.6; 48.6)	36.3 (18.3; 48.3)	0.018
	TBIL	23.7 (14.4; 36.7)	19.9 (3.0; 44.4)	27.1 (5.1; 106.1)	< 0.001
	DBIL	8.8 (3.8; 13.4)	4.0 (0.6; 15.1)	11.2 (2.5; 67.2)	< 0.001
	TC	4.8 (3.4; 5.4)	6.8 (3.3; 17.7)	4.0 (1.0; 5.5)	< 0.001
	TG	1.9 (0.9; 3.9)	7.4 (1.0; 38.8)	1.1 (0.3; 3.9)	< 0.001
	SCr	75.9 (62.9; 86.9)	79.0 (43.4; 157.4)	75.0 (48.4; 127.3)	0.174
	AMY	256.0 (82.6; 729.5)	191.6 (30.0; 927.5)	343.1 (38.4; 2053.5)	< 0.001
	LPS	344.3 (97.7; 878.8)	323.2 (47.5; 1312.0)	391.9 (28.4; 1709.6)	0.15
	PT-S	12.8 (11.9; 13.3)	12.2 (10.7; 14.4)	12.9 (11.1; 16.0)	< 0.001
	FIB	4.4 (3.3; 5.2)	5.2 (2.6; 9.0)	4.1 (2.4; 6.9)	< 0.001
	WBC	11.1 (7.7; 14.5)	11.8 (5.8; 21.0)	10.6 (4.6; 20.2)	< 0.001
	Lym	1.1 (0.7; 1.5)	1.3 (0.7; 3.1)	1.0 (0.4; 2.1)	< 0.001
	RBC	4.6 (4.1; 5.1)	5.0 (4.0; 6.1)	4.4 (3.4; 5.7)	< 0.001
	RDW	13.3 (12.5; 14.1)	13.2 (9.8; 14.4)	13.5 (9.9; 16.2)	0.003
	PLT	203.0 (164.0; 254.0)	223.0 (134.1; 391.0)	197.0 (103.6; 339.4)	< 0.001
	PDW	16.8 (16.3; 17.4)	17.3 (12.8; 19.1)	16.6 (11.8; 18.1)	< 0.001

NLR		8.3 (4.5; 14.2)	6.9 (1.6; 18.9)	9.1 (2.1; 33.1)	< 0.001
PLR		184.3 (131.6; 273.6)	160.5 (70.3; 379.0)	203.1 (83.4; 518.6)	< 0.001
Atlanta classification, *n* (%)					0.001
	MAP	437 (56.7)	125 (51.9)	312 (58.9)	
	MSAP	156 (20.2)	40 (16.6)	116 (21.9)	
	SAP	178 (23.1)	76 (31.5)	102 (19.2)	
Scoring systems					
	MCTSI	4.0 (2.0; 6.0)	4.0 (2.0; 8.0)	4.0 (2.0; 8.0)	0.005
	JSS	1.0 (0; 2.0)	1.0 (0; 4.0)	1.0 (0; 4.0)	0.029
	BISAP	1.0 (0; 1.0)	0 (0; 2.0)	1.0 (0; 2.0)	< 0.001
	Modified Marshall	2.0 (1.0; 4.0)	2.0(0; 5.9)	2.0 (0; 7.0)	0.049
	SOFA	1.0 (0; 3.0)	1.0 (0; 4.0)	1.0 (0; 5.0)	0.163
POF, *n* (%)					0.247
	N	537 (69.6)	161 (66.8)	376 (70.9)	
	Y	234 (30.4)	80 (33.2)	154 (29.1)	
SIRS, *n* (%)					0.956
	N	465 (60.3)	145 (60.2)	320 (60.4)	
	Y	306 (39.7)	96 (39.8)	210 (39.6)	
Hospital stay (d)		13.5 (9.4; 19.2)	12.0 (5.2; 29.3)	14.3 (5.4; 36.1)	< 0.001
Mortality, *n* (%)					0.556
	N	762 (98.8)	239 (99.2)	523 (98.7)	
	Y	9 (1.2)	2 (0.8)	7 (1.3)	

N: No; Y: Yes; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; γ-GT: Gamma-glutamyl transferase; ALB: Albumin; TBIL: Total bilirubin; DBIL: Direct bilirubin; TC: Total cholesterol; TG: Triglycerides; SCr: Serum creatinine; AMY: Serum amylase; LPS: Lipase; PT-S: Prothrombin time; FIB: Fibrinogen; WBC: White blood cell; Lym: Lymphocyte; RBC: Red blood cell; RDW: Red blood cell distribution width; PLT: Platelet; PDW: Platelet distribution width; MCTSI: Modified computed tomography severity index score; JSS: Japanese Severity Score; BISAP: Bedside Index of Severity in Acute Pancreatitis; Modified Marshall: Modified Organ Dysfunction Score; SOFA: Sequential Organ Failure Assessment Score; SIRS: Systemic Inflammatory Response Syndrome; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; HTGP: Hypertriglyceridemia-induced acute pancreatitis; ABP: Acute biliary pancreatitis.

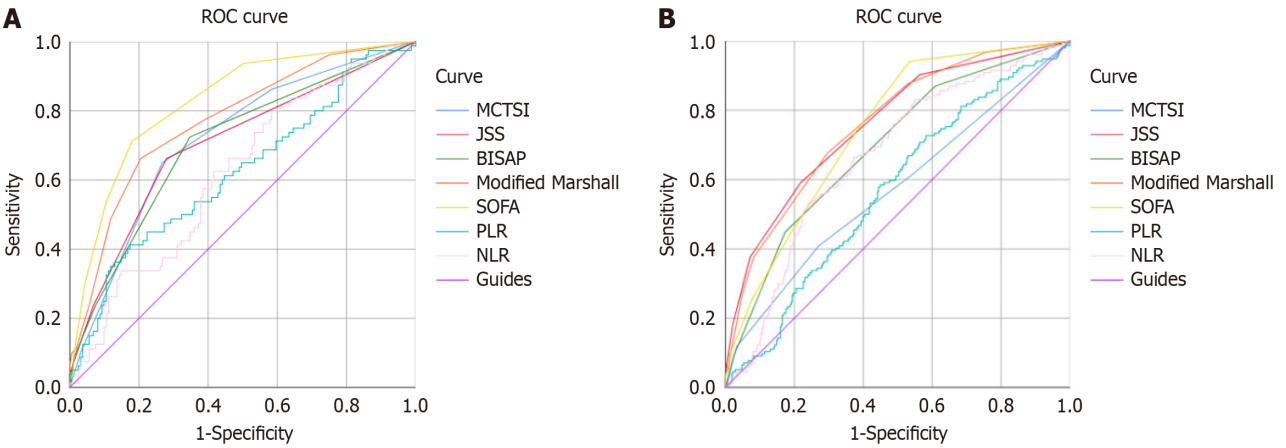


Figure 2 Receiver operating characteristic curve. A: Receiver operating characteristic (ROC) curve for the prediction of persistent organ failure (POF) in hypertriglyceridemia-induced acute pancreatitis by neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and the acute pancreatitis (AP) Scoring System; B: ROC curve for the prediction of POF in acute biliary pancreatitis by NLR, PLR, and the AP Scoring System. ROC: Receiver operating characteristic; MCTSI: Modified computed tomography severity index; JSS: Japanese Severity Score; BISAP: Bedside Index for Severity in Acute Pancreatitis; SOFA: Sequential Organ Failure Assessment; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

Table 2 Correlation analysis of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio with the acute pancreatitis Scoring System in hypertriglyceridemia-induced acute pancreatitis

Parameters	PLR	*P* value	NLR	*P* value
Atlanta classification		0.000		0.005
Mild/moderate	152.1 (110.8; 198.0)		6.3 (3.5; 10.2)	
Severe	188.2 (137.9; 265.6)		7.9 (5.5; 12.6)	
MCTSI		0.087		0.235
< 4	150.6 (113.4; 197.4)		6.1 (3.4; 10.1)	
≥ 4	161.7 (119.1; 240.6)		7.0 (4.4; 11.2)	
JSS		0.754		0.815
< 3	159.0 (119.9; 228.0)		6.9 (3.9; 11.2)	
≥ 3	161.2 (108.2; 257.6)		7.0 (5.0; 10.2)	
BISAP		0.384		0.395
< 3	159.1 (119.0; 228.4)		6.9 (4.0; 10.9)	
≥ 3	171.6 (136.7; 244.4)		9.1 (5.8; 12.9)	
Modified Marshall		0.167		0.813
< 2	156.2 (113.4; 214.1)		6.8 (3.8; 11.6)	
≥ 2	165.1 (132.0; 239.1)		7.0 (4.9; 10.3)	
SOFA		0.011		0.005
< 3	155.6 (113.2; 214.9)		6.4 (3.6; 10.1)	
≥ 3	175.0 (136.0; 259.6)		8.0 (5.9; 12.8)	

MCTSI: Modified computed tomography severity index score; JSS: Japanese Severity Score; BISAP: Bedside Index of Severity in Acute Pancreatitis; Modified Marshall: Modified Organ Dysfunction Score; SOFA: Sequential Organ Failure Assessment Score; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

Among the etiological factors of AP, gallstones and alcohol consumption are the predominant causes[24], and the incidence of HTG has been increasing annually. Currently, HTG is the second most common etiology of AP in Chinese patients[25]. Compared to AP caused by other etiologies, HTGP is characterized by a tendency to develop severe disease and frequent recurrence, which presents unique challenges in its diagnosis and treatment. The exact mechanisms underlying the development of HTGP are not yet fully understood; however, the prevailing theory suggests that chylomicrons play a central role. Chylomicrons are lipid-protein particles rich in TGs synthesized from dietary lipids within intestinal cells. They consist of a TG-rich core and carry esterified cholesterol and phospholipids[26]. When serum TG levels exceed 10 mmol/L, chylomicrons appear in the bloodstream[27], which can impede circulation in the capillary bed, leading to ischemia. In addition, chylomicrons increase plasma viscosity, causing capillary blockage, ischemia, and cellular acidosis. Moreover, chylomicrons undergo hydrolysis within the pancreatic vascular bed, releasing free fatty acids (FFA) that exceed the binding capacity of plasma albumin. The unbound FFA self-aggregate into micellar structures with detergent-like properties[28]. These toxic structures can damage the platelets, endothelial cells, and acinar cells, leading to pancreatic cell ischemia and acidosis. Acidosis, in turn, enhances the toxicity of FFA by activating pancreatic proteases, ultimately triggering AP[29]. A prospective study conducted by Nawaz *et al*[30] demonstrated that HTGP is an independent risk factor for POF. Compared with AP caused by other etiologies, HTGP has been shown to have a higher severity and incidence of complications[31,32]. This is in line with the conclusions of this study, which demonstrated that HTGP was more severe than ABP, but there was no significant difference in the rates of SIRS or POF between the two groups.

ABP is caused by various factors such as gallbladder stones, common bile duct stones, biliary tract infection, abnormal sphincter of Oddi spasm, and stenosis, which impair the emptying of the biliary and pancreatic ducts and cause abnormal biliary pressure. This results in bile reflux into the pancreatic duct, obstruction of pancreatic fluid drainage, and abnormal activation of pancreatic enzymes[33]. The mechanisms underlying the development of HTGP and ABP are completely different. However, both eventually lead to pancreatic cell injury and release of inflammatory mediators. Therefore, the use of inflammatory markers to assess the prognosis of pancreatitis caused by various mechanisms is particularly important.

Currently, there is increasing evidence supporting a close association between inflammatory mediators and the pathogenesis of AP[34], Inflammatory signals released by pancreatic acinar cells can mediate the recruitment and activation of circulating inflammatory cells[35]. Ultimately, excessive activation of inflammatory mediators can trigger a

Table 3 Correlation Analysis of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio with the acute pancreatitis Scoring System in acute biliary pancreatitis

Parameters	PLR	*P* value	NLR	*P* value
Atlanta classification		0.002		0.000
Mild/moderate	194.0 (136.2; 286.2)		8.1 (4.3; 13.8)	
Severe	239.1 (171.0; 358.9)		16.0 (8.9; 21.8)	
MCTSI		0.021		0.000
< 4	190.8 (135.4; 268.6)		7.4 (4.0; 12.8)	
≥ 4	212.7 (145.3; 322.9)		11.2 (6.0; 17.6)	
JSS		0.006		0.000
< 3	194.5 (139.2; 287.6)		8.2 (4.3; 14.2)	
≥ 3	250.6 (150.7; 359.1)		16.5 (8.7; 22.9)	
BISAP		0.921		0.002
< 3	203.8 (141.9; 295.9)		8.9 (4.5; 15.7)	
≥ 3	192.9 (130.4; 329.9)		15.6 (11.2; 20.4)	
Modified Marshall		0.015		0.000
< 2	181.2 (134.0; 272.3)		6.0 (3.5; 12.0)	
≥ 2	217.2 (145.2; 314.6)		11.3 (6.2; 18.3)	
SOFA		0.555		0.000
< 3	198.5 (140.4; 296.4)		8.2 (4.1; 14.5)	
≥ 3	212.2 (142.1; 311.3)		12.4 (7.3; 19.3)	

MCTSI: Modified computed tomography severity index score; JSS: Japanese Severity Score; BISAP: Bedside Index of Severity in Acute Pancreatitis; Modified Marshall: Modified Organ Dysfunction Score; SOFA: Sequential Organ Failure Assessment Score; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

Table 4 Predictive performance of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and the acute pancreatitis Scoring System for the occurrence of persistent organ failure in hypertriglyceridemia-induced acute pancreatitis

Parameters	AUC	95%CI		Sensitivity	Specificity	*P* value
		Lower	Upper			
MCTSI	0.718	0.649	0.786	0.650	0.733	< 0.001
JSS	0.703	0.631	0.775	0.663	0.720	< 0.001
BISAP	0.705	0.634	0.775	0.725	0.652	< 0.001
Modified Marshall	0.772	0.708	0.835	0.663	0.795	< 0.001
SOFA	0.827	0.772	0.882	0.713	0.820	< 0.001
PLR	0.622	0.546	0.699	0.413	0.826	0.002
NLR	0.619	0.546	0.693	0.800	0.720	0.003

CI: Confidence interval; AUC: Area under the curve; MCTSI: Modified computed tomography severity index score; JSS: Japanese Severity Score; BISAP: Bedside Index of Severity in Acute Pancreatitis; Modified Marshall: Modified Organ Dysfunction Score; SOFA: Sequential Organ Failure Assessment Score; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

systemic inflammatory response, leading to SAP.

NLR is a systemic inflammation marker based on the complete blood cell count and was initially proposed as a means of evaluating systemic inflammation and stress response in critically ill patients[36]. Generally, the neutrophil count in blood increases with the progression of inflammatory diseases. However, in certain conditions, such as cachexia, "false-negative" results may occur. The lymphocyte count also reflects the patient's immune status, which tends to decrease with

Table 5 Predictive performance of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and the acute pancreatitis Scoring System for the occurrence of persistent organ failure in acute biliary pancreatitis

Parameters	AUC	95%CI		Sensitivity	Specificity	*P* value
		Lower	Upper			
MCTSI	0.573	0.517	0.629	0.409	0.729	0.008
JSS	0.760	0.715	0.805	0.591	0.782	< 0.001
BISAP	0.694	0.645	0.743	0.448	0.827	< 0.001
Modified Marshall	0.761	0.717	0.804	0.675	0.705	< 0.001
SOFA	0.746	0.703	0.789	0.942	0.465	< 0.001
PLR	0.569	0.516	0.621	0.727	0.418	0.013
NLR	0.668	0.618	0.717	0.532	0.761	< 0.001

CI: Confidence interval; AUC: Area under the curve; MCTSI: Modified computed tomography severity index score; JSS: Japanese Severity Score; BISAP: Bedside Index of Severity in Acute Pancreatitis; Modified Marshall: Modified Organ Dysfunction Score; SOFA: Sequential Organ Failure Assessment Score; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

the progression of inflammatory diseases. However, lymphocyte count often decreases significantly only in the later stages of the disease, making it inadequate to reflect disease progression[37]. Therefore, NLR is considered more reliable than either neutrophil or lymphocyte count alone in predicting patient prognosis and survival rates[38]. Generally, NLR increases with the occurrence of systemic inflammatory diseases and severity of inflammation, which is consistent with the development of certain diseases[39]. Additionally, the measurement of NLR and PLR is simple, rapid, and cost-effective and does not cause discomfort to patients because it only requires a peripheral blood sample. Numerous studies have demonstrated that a high NLR can serve as an independent prognostic factor for various diseases, including liver cirrhosis[40], acute respiratory distress syndrome[41], and others.

The PLR has also been recognized as an inflammatory marker that can better predict clinical outcomes in patients with systemic inflammation than individual platelet or lymphocyte counts. Platelets play a crucial role in the interactions between inflammation and microvascular dysfunction. Under high levels of pro-inflammatory cytokines and in the presence of cellular debris and viral proteins, platelets can be directly activated, leading to increased aggregation, clotting, or degradation. This can result in a decreased platelet counts[42]. Therefore, PLR tends to decrease during the early stages of disease progression. However, in patients with severe conditions, the PLR significantly increases, which is associated with a substantial decrease in the lymphocyte count[43]. Changes in the PLR were positively correlated with other markers of systemic inflammation, especially the NLR. In the past decade, the PLR has emerged as a laboratory marker for predicting various conditions such as tumors, thrombosis, and metabolic diseases. These include peripheral arterial occlusive disease[44], colorectal tumors[45], acute coronary syndrome[46], acute pulmonary embolism[47], and others.

Azab *et al*[48] was the first to apply the NLR in patients with AP. They found that NLR was a better predictor of ICU admission rates and prolonged hospital stays in AP patients. However, this study did not assess the impact of NLR on organ failure. Suppiah *et al*[15] found a significant correlation between increased NLR within the first 48 h of hospitalization and SAP. They identified NLR as an independent prognostic indicator for SAP. However, the study had a small sample size (n = 146), with only 22 patients diagnosed with SAP. Zhang *et al*[14] indicated that an elevated NLR in the Chinese population was associated with POF, prolonged ICU stay, and increased in-hospital mortality. However, few studies have compared AP according to etiology. Silva-Vaz *et al*[49] found that the NLR had the best predictive value for severity in the ABP group. Huang *et al*[50] found that the NLR was only predictive of SAP in the HTGP group; however, this study had a small sample size of 23 patients in the HTGP group with SAP. Therefore, in this study, we excluded pancreatitis caused by factors other than biliary or HTG etiology. After grouping AP based on etiology, our findings were similar to those of Silva-Vaz *et al*[49], with higher values of NLR and PLR observed in the ABP group. NLR and PLR were both independent predictors of POF in ABP and HTGP. However, NLR and PLR did not demonstrate significant differences between these two types of pancreatitis, suggesting that although ABP and HTGP have different pathogenic mechanisms, the changes in routine blood tests have a similar effect on the progression of AP complicated by POF. In our study findings, compared to the HTGP group, patients in the ABP group exhibited higher levels of liver function indicators such as aspartate aminotransferase, alanine aminotransferase, and total bilirubin. This can be attributed to the presence of biliary obstruction, which leads to increased biliary pressure in the ABP, resulting in the accumulation of bilirubin and bile acids in the liver. The toxic effects of these substances can cause metabolic disturbances and even hepatocellular degeneration and necrosis. The average length of hospital stay was shorter in the HTGP group than in the ABP group. This is because patients in the ABP group often require surgical intervention to relieve biliary obstruction, in addition to general supportive and medical treatments, which, to some extent, prolong their hospital stay[51]. In this study, the incidence of SAP was higher in the HTGP group than in the ABP group. This finding is consistent with that of Anderson *et al*[31]. Furthermore, animal studies have shown that experimental mouse models of HTGP exhibit higher levels of pancreatic lipase activity and greater histological damage to the pancreatic tissue, making them more prone to progressing to SAP[52].

However, there were no significant differences between the two groups in terms of ICU admission rates, SIRS, POF incidence, and mortality rates. This may be attributed to the early and timely assessment, standardized treatment, and combined interventions implemented in our hospital, which prevented the further progression of AP to some extent. These findings highlight the crucial role of early assessment in guiding AP progression and intervention.

Additionally, the patients in the HTGP group had a younger average age, were predominantly male, and had a higher BMI than those in the ABP group. This is consistent with the clinical characteristics evaluated in international prospective cohorts that assessed HTGP[53]. No significant differences in the SOFA scores between the HTGP and ABP groups in the AP scoring system was observed. The MCTSI scores and JSS were higher in the HTGP group than in the ABP group. This can be attributed to the fact that both the MCTSI score and JSS involve assessment of the extent of pancreatic morphological changes, and studies have indicated a close relationship between pancreatic adipocytes and TGs. Pancreatic adipocytes are specialized cells found within pancreatic tissue and are primarily responsible for synthesizing and storing TGs to regulate pancreatic lipid metabolism. Under normal conditions, TGs are stored within pancreatic adipocytes and released when needed for energy and other biological processes. However, under certain circumstances, such as pancreatitis or pancreatic dysfunction, pancreatic adipocytes may be affected, leading to abnormal TG synthesis and metabolism. Therefore, when AP is caused by TGs, there is an increase in the volume of pancreatic adipocytes, which contributes to extensive pancreatic tissue necrosis[54]. Modified Marshall scores were higher in the ABP group than in the HTGP group. Currently, no literature explicitly indicates a higher incidence of organ failure in patients with ABP. However, recent studies have shown that in the HTGP group, there is a significant increase in the risk of organ failure only in males (excluding females), which to some extent lowers the overall incidence of organ failure in the HTGP group[55]. BISAP scores were significantly higher in the ABP group than in the HTGP group. This may be attributed to the fact that one of the scoring criteria in the BISAP is age > 60 years. In this study, there were 225 patients in the ABP group aged > 60 years, accounting for 42.5% of the total, whereas in the HTGP group, there was only one patient aged > 60 years, accounting for 0.4% of the total.

An *et al*[56] confirmed that inflammatory cytokines play a major role in the early stages of HTGP, which is consistent with the results of this study. The data collected in this group were laboratory test results within 48 h of admission, representing the early stage of AP progression. The HTGP group of inflammatory markers (white blood cell, lymphocyte, and platelet counts) were higher in the HTGP group than in the ABP group. Previous studies have indicated a positive correlation between the NLR and PLR and the severity of AP[57,58]. This finding was confirmed only in the ABP group regarding NLR. This inconsistency with previous studies may be attributed to the lack of etiological stratification of AP, as the pathophysiological mechanisms of AP may differ according to the underlying causes.

However, this study had several limitations. First, this was a single-center study, and further validation in multiple large-scale pancreatitis centers is required. Second, because of the different clinical manifestations of AP patients upon admission, most patients were not tested for C-reactive protein, procalcitonin, and cytokines after admission. Therefore, we did not compare NLR and PLR with other biomarkers such as C-reactive protein, procalcitonin, and cytokines. Third, because our dataset lacked sufficient information to assess all the potential confounding factors, we included only one clinical outcome (POF) in the analysis. Moreover, we did not report changes in NLR or PLR during the treatment course, which could potentially provide a better prognostic assessment of AP.

Despite these limitations, this study has several merits. We collected cases of AP from our hospital over the past decade, starting from the etiological grouping of AP, performed an etiological grouping of AP, and explored the differences in NLR and PLR between the two subgroups (ABP and HTGP). Furthermore, all laboratory parameters were derived from blood samples obtained before treatment initiation, minimizing the possible influence of fluid resuscitation and medication on white blood cell, lymphocyte, and platelet counts.

CONCLUSION

The NLR and PLR differed between ABP and HTGP. In patients with ABP, both the NLR and PLR values were higher than those in patients with HTGP. NLR and PLR had predictive value for POF in both ABP and HTGP.

FOOTNOTES

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REFERENCES

1 **Szatmary P**, Grammatikopoulos T, Cai W, Huang W, Mukherjee R, Halloran C, Beyer G, Sutton R. Acute Pancreatitis: Diagnosis and Treatment. *Drugs* 2022; **82**: 1251-1276 [PMID: 36074322 DOI: 10.1007/s40265-022-01766-4]
2 **Banks PA**, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; **62**: 102-111 [PMID: 23100216 DOI: 10.1136/gutjnl-2012-302779]
3 **Petrov MS**, Yadav D. Global epidemiology and holistic prevention of pancreatitis. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 175-184 [PMID: 30482911 DOI: 10.1038/s41575-018-0087-5]
4 **Garcea G**, Gouda M, Hebbes C, Ong SL, Neal CP, Dennison AR, Berry DP. Predictors of severity and survival in acute pancreatitis: validation of the efficacy of early warning scores. *Pancreas* 2008; **37**: e54-e61 [PMID: 18815539 DOI: 10.1097/MPA.0b013e3181771451]
5 **Johnson CD**, Besselink MG, Carter R. Acute pancreatitis. *BMJ* 2014; **349**: g4859 [PMID: 25116169 DOI: 10.1136/bmj.g4859]
6 **Huang SW**, Mao EQ, Wang HS, Zhao B, Chen Y, Qu HP, Chen EZ. Clinical characteristics of 5375 cases of acute pancreatitis from a single Chinese center, 1996-2015. *Chin Med J (Engl)* 2019; **132**: 1233-1236 [PMID: 31140993 DOI: 10.1097/CM9.0000000000000208]
7 **Adiamah A**, Psaltis E, Crook M, Lobo DN. A systematic review of the epidemiology, pathophysiology and current management of hyperlipidaemic pancreatitis. *Clin Nutr* 2018; **37**: 1810-1822 [PMID: 29056284 DOI: 10.1016/j.clnu.2017.09.028]
8 **Habtezion A**, Gukovskaya AS, Pandol SJ. Acute Pancreatitis: A Multifaceted Set of Organelle and Cellular Interactions. *Gastroenterology* 2019; **156**: 1941-1950 [PMID: 30660726 DOI: 10.1053/j.gastro.2018.11.082]
9 **Vege SS**, DiMagno MJ, Forsmark CE, Martel M, Barkun AN. Initial Medical Treatment of Acute Pancreatitis: American Gastroenterological Association Institute Technical Review. *Gastroenterology* 2018; **154**: 1103-1139 [PMID: 29421596 DOI: 10.1053/j.gastro.2018.01.031]
10 **Pavlidis TE**, Pavlidis ET, Sakantamis AK. Advances in prognostic factors in acute pancreatitis: a mini-review. *Hepatobiliary Pancreat Dis Int* 2010; **9**: 482-486 [PMID: 20943456]
11 **Junare PR**, Debnath P, Nair S, Chandnani S, Udgirkar S, Thange R, Jain S, Deshmukh R, Rathi P, Contractor Q, Deshpande A. Complete hemogram: simple and cost-effective in staging and predicting outcome in acute pancreatitis. *Wien Klin Wochenschr* 2021; **133**: 661-668 [PMID: 33620577 DOI: 10.1007/s00508-021-01821-2]
12 **Kaplan M**, Ates I, Oztas E, Yuksel M, Akpinar MY, Coskun O, Kayacetin E. A New Marker to Determine Prognosis of Acute Pancreatitis: PLR and NLR Combination. *J Med Biochem* 2018; **37**: 21-30 [PMID: 30581338 DOI: 10.1515/jomb-2017-0039]
13 **Cho SK**, Jung S, Lee KJ, Kim JW. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio can predict the severity of gallstone pancreatitis. *BMC Gastroenterol* 2018; **18**: 18 [PMID: 29370777 DOI: 10.1186/s12876-018-0748-4]
14 **Zhang Y**, Wu W, Dong L, Yang C, Fan P, Wu H. Neutrophil to lymphocyte ratio predicts persistent organ failure and in-hospital mortality in an Asian Chinese population of acute pancreatitis. *Medicine (Baltimore)* 2016; **95**: e4746 [PMID: 27631223 DOI: 10.1097/MD.0000000000004746]
15 **Suppiah A**, Malde D, Arab T, Hamed M, Allgar V, Smith AM, Morris-Stiff G. The prognostic value of the neutrophil-lymphocyte ratio (NLR) in acute pancreatitis: identification of an optimal NLR. *J Gastrointest Surg* 2013; **17**: 675-681 [PMID: 23371356 DOI: 10.1007/s11605-012-2121-1]
16 **Mederos MA**, Reber HA, Girgis MD. Acute Pancreatitis: A Review. *JAMA* 2021; **325**: 382-390 [PMID: 33496779 DOI: 10.1001/jama.2020.20317]
17 **Zver T**, Calame P, Koch S, Aubry S, Vuitton L, Delabrousse E. Early Prediction of Acute Biliary Pancreatitis Using Clinical and Abdominal CT Features. *Radiology* 2022; **302**: 118-126 [PMID: 34636635 DOI: 10.1148/radiol.2021210607]
18 **Yang AL**, McNabb-Baltar J. Hypertriglyceridemia and acute pancreatitis. *Pancreatology* 2020; **20**: 795-800 [PMID: 32571534 DOI: 10.1016/j.pan.2020.06.005]
19 **Siregar GA**, Siregar GP. Management of Severe Acute Pancreatitis. *Open Access Maced J Med Sci* 2019; **7**: 3319-3323 [PMID: 31949538 DOI: 10.3889/oamjms.2019.720]
20 **van den Berg FF**, Boermeester MA. Update on the management of acute pancreatitis. *Curr Opin Crit Care* 2023; **29**: 145-151 [PMID: 36727757 DOI: 10.1097/MCC.0000000000001017]
21 **Steinberg WM**. Predictors of severity of acute pancreatitis. *Gastroenterol Clin North Am* 1990; **19**: 849-861 [PMID: 2269521 DOI: 10.1016/S0889-8553(21)00517-3]
22 **Karakayali FY**. Surgical and interventional management of complications caused by acute pancreatitis. *World J Gastroenterol* 2014; **20**: 13412-13423 [PMID: 25309073 DOI: 10.3748/wjg.v20.i37.13412]
23 **Bülbüller N**, Doğru O, Ayten R, Akbulut H, Ilhan YS, Cetinkaya Z. Procalcitonin is a predictive marker for severe acute pancreatitis. *Ulus*

Travma Acil Cerrahi Derg 2006; **12**: 115-120 [PMID: 16676250]
24 **Zerem E**, Kurtcehajic A, Kunosić S, Zerem Malkočević D, Zerem O. Current trends in acute pancreatitis: Diagnostic and therapeutic challenges. *World J Gastroenterol* 2023; **29**: 2747-2763 [PMID: 37274068 DOI: 10.3748/wjg.v29.i18.2747]
25 **Mukherjee R**, Nunes Q, Huang W, Sutton R. Precision medicine for acute pancreatitis: current status and future opportunities. *Precis Clin Med* 2019; **2**: 81-86 [PMID: 35692449 DOI: 10.1093/pcmedi/pbz010]
26 **Rahmany S**, Jialal I. Biochemistry, Chylomicron. 2023 Jul 17. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan- [PMID: 31424741]
27 **Gan SI**, Edwards AL, Symonds CJ, Beck PL. Hypertriglyceridemia-induced pancreatitis: A case-based review. *World J Gastroenterol* 2006; **12**: 7197-7202 [PMID: 17131487 DOI: 10.3748/wjg.v12.i44.7197]
28 **Valdivielso P**, Ramírez-Bueno A, Ewald N. Current knowledge of hypertriglyceridemic pancreatitis. *Eur J Intern Med* 2014; **25**: 689-694 [PMID: 25269432 DOI: 10.1016/j.ejim.2014.08.008]
29 **de Pretis N**, Amodio A, Frulloni L. Hypertriglyceridemic pancreatitis: Epidemiology, pathophysiology and clinical management. *United European Gastroenterol J* 2018; **6**: 649-655 [PMID: 30083325 DOI: 10.1177/2050640618755002]
30 **Nawaz H**, Koutroumpakis E, Easler J, Slivka A, Whitcomb DC, Singh VP, Yadav D, Papachristou GI. Elevated serum triglycerides are independently associated with persistent organ failure in acute pancreatitis. *Am J Gastroenterol* 2015; **110**: 1497-1503 [PMID: 26323188 DOI: 10.1038/ajg.2015.261]
31 **Anderson F**, Thomson SR, Clarke DL, Buccimazza I. Dyslipidaemic pancreatitis clinical assessment and analysis of disease severity and outcomes. *Pancreatology* 2009; **9**: 252-257 [PMID: 19407479 DOI: 10.1159/000212091]
32 **Tsuang W**, Navaneethan U, Ruiz L, Palascak JB, Gelrud A. Hypertriglyceridemic pancreatitis: presentation and management. *Am J Gastroenterol* 2009; **104**: 984-991 [PMID: 19293788 DOI: 10.1038/ajg.2009.27]
33 **Oppenlander KE**, Chadwick C, Carman K. Acute Pancreatitis: Rapid Evidence Review. *Am Fam Physician* 2022; **106**: 44-50 [PMID: 35839366]
34 **Yang ZW**, Meng XX, Xu P. Central role of neutrophil in the pathogenesis of severe acute pancreatitis. *J Cell Mol Med* 2015; **19**: 2513-2520 [PMID: 26249268 DOI: 10.1111/jcmm.12639]
35 **Noel P**, Patel K, Durgampudi C, Trivedi RN, de Oliveira C, Crowell MD, Pannala R, Lee K, Brand R, Chennat J, Slivka A, Papachristou GI, Khalid A, Whitcomb DC, DeLany JP, Cline RA, Acharya C, Jaligama D, Murad FM, Yadav D, Navina S, Singh VP. Peripancreatic fat necrosis worsens acute pancreatitis independent of pancreatic necrosis *via* unsaturated fatty acids increased in human pancreatic necrosis collections. *Gut* 2016; **65**: 100-111 [PMID: 25500204 DOI: 10.1136/gutjnl-2014-308043]
36 **Huang Z**, Fu Z, Huang W, Huang K. Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: A meta-analysis. *Am J Emerg Med* 2020; **38**: 641-647 [PMID: 31785981 DOI: 10.1016/j.ajem.2019.10.023]
37 **Vidal AC**, Howard LE, de Hoedt A, Cooperberg MR, Kane CJ, Aronson WJ, Terris MK, Amling CL, Taioli E, Fowke JH, Freedland SJ. Neutrophil, lymphocyte and platelet counts, and risk of prostate cancer outcomes in white and black men: results from the SEARCH database. *Cancer Causes Control* 2018; **29**: 581-588 [PMID: 29663110 DOI: 10.1007/s10552-018-1031-2]
38 **Kumarasamy C**, Sabarimurugan S, Madurantakam RM, Lakhotiya K, Samiappan S, Baxi S, Nachimuthu R, Gothandam KM, Jayaraj R. Prognostic significance of blood inflammatory biomarkers NLR, PLR, and LMR in cancer-A protocol for systematic review and meta-analysis. *Medicine (Baltimore)* 2019; **98**: e14834 [PMID: 31192906 DOI: 10.1097/MD.0000000000014834]
39 **Jiang J**, Liu R, Yu X, Yang R, Xu H, Mao Z, Wang Y. The neutrophil-lymphocyte count ratio as a diagnostic marker for bacteraemia: A systematic review and meta-analysis. *Am J Emerg Med* 2019; **37**: 1482-1489 [PMID: 30413366 DOI: 10.1016/j.ajem.2018.10.057]
40 **Peng Y**, Li Y, He Y, Wei Q, Xie Q, Zhang L, Xia Y, Zhou X, Feng X, Chen K, Chen S, Chen W, Long Q, Chai J. The role of neutrophil to lymphocyte ratio for the assessment of liver fibrosis and cirrhosis: a systematic review. *Expert Rev Gastroenterol Hepatol* 2018; **12**: 503-513 [PMID: 29629626 DOI: 10.1080/17474124.2018.1463158]
41 **Wang Y**, Ju M, Chen C, Yang D, Hou D, Tang X, Zhu X, Zhang D, Wang L, Ji S, Jiang J, Song Y. Neutrophil-to-lymphocyte ratio as a prognostic marker in acute respiratory distress syndrome patients: a retrospective study. *J Thorac Dis* 2018; **10**: 273-282 [PMID: 29600057 DOI: 10.21037/jtd.2017.12.131]
42 **Sarkar S**, Kannan S, Khanna P, Singh AK. Role of platelet-to-lymphocyte count ratio (PLR), as a prognostic indicator in COVID-19: A systematic review and meta-analysis. *J Med Virol* 2022; **94**: 211-221 [PMID: 34436785 DOI: 10.1002/jmv.27297]
43 **Kosidło JW**, Wolszczak-Biedrzycka B, Matowicka-Karna J, Dymicka-Piekarska V, Dorf J. Clinical Significance and Diagnostic Utility of NLR, LMR, PLR and SII in the Course of COVID-19: A Literature Review. *J Inflamm Res* 2023; **16**: 539-562 [PMID: 36818192 DOI: 10.2147/JIR.S395331]
44 **Gary T**, Pichler M, Belaj K, Hafner F, Gerger A, Froehlich H, Eller P, Rief P, Hackl G, Pilger E, Brodmann M. Platelet-to-lymphocyte ratio: a novel marker for critical limb ischemia in peripheral arterial occlusive disease patients. *PLoS One* 2013; **8**: e67688 [PMID: 23844064 DOI: 10.1371/journal.pone.0067688]
45 **Tan D**, Fu Y, Su Q, Wang H. Prognostic role of platelet-lymphocyte ratio in colorectal cancer: A systematic review and meta-analysis. *Medicine (Baltimore)* 2016; **95**: e3837 [PMID: 27310960 DOI: 10.1097/MD.0000000000003837]
46 **Li W**, Liu Q, Tang Y. Platelet to lymphocyte ratio in the prediction of adverse outcomes after acute coronary syndrome: a meta-analysis. *Sci Rep* 2017; **7**: 40426 [PMID: 28071752 DOI: 10.1038/srep40426]
47 **Wang Q**, Ma J, Jiang Z, Ming L. Prognostic value of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in acute pulmonary embolism: a systematic review and meta-analysis. *Int Angiol* 2018; **37**: 4-11 [PMID: 28541022 DOI: 10.23736/S0392-9590.17.03848-2]
48 **Azab B**, Jaglall N, Atallah JP, Lamet A, Raja-Surya V, Farah B, Lesser M, Widmann WD. Neutrophil-lymphocyte ratio as a predictor of adverse outcomes of acute pancreatitis. *Pancreatology* 2011; **11**: 445-452 [PMID: 21968329 DOI: 10.1159/000331494]
49 **Silva-Vaz P**, Abrantes AM, Morgado-Nunes S, Castelo-Branco M, Gouveia A, Botelho MF, Tralhão JG. Evaluation of Prognostic Factors of Severity in Acute Biliary Pancreatitis. *Int J Mol Sci* 2020; **21** [PMID: 32560276 DOI: 10.3390/ijms21124300]
50 **Huang L**, Chen C, Yang L, Wan R, Hu G. Neutrophil-to-lymphocyte ratio can specifically predict the severity of hypertriglyceridemia-induced acute pancreatitis compared with white blood cell. *J Clin Lab Anal* 2019; **33**: e22839 [PMID: 30737845 DOI: 10.1002/jcla.22839]
51 **Bougard M**, Barbier L, Godart B, Le Bayon-Bréard AG, Marques F, Salamé E. Management of biliary acute pancreatitis. *J Visc Surg* 2019; **156**: 113-125 [PMID: 30385271 DOI: 10.1016/j.jviscsurg.2018.08.002]
52 **Hofbauer B**, Friess H, Weber A, Baczako K, Kisling P, Schilling M, Uhl W, Dervenis C, Büchler MW. Hyperlipaemia intensifies the course of acute oedematous and acute necrotising pancreatitis in the rat. *Gut* 1996; **38**: 753-758 [PMID: 8707124 DOI: 10.1136/gut.38.5.753]

53 **Pothoulakis I**, Paragomi P, Archibugi L, Tuft M, Talukdar R, Kochhar R, Goenka MK, Gulla A, Singh VK, Gonzalez JA, Ferreira M, Barbu ST, Stevens T, Nawaz H, Gutierrez SC, Zarnescu NO, Easler J, Triantafyllou K, Pelaez-Luna M, Thakkar S, Ocampo C, de-Madaria E, Wu BU, Cote GA, Tang G, Papachristou GI, Capurso G. Clinical features of hypertriglyceridemia-induced acute pancreatitis in an international, multicenter, prospective cohort (APPRENTICE consortium). *Pancreatology* 2020; **20**: 325-330 [PMID: 32107193 DOI: 10.1016/j.pan.2020.02.010]

54 **Navina S**, Acharya C, DeLany JP, Orlichenko LS, Baty CJ, Shiva SS, Durgampudi C, Karlsson JM, Lee K, Bae KT, Furlan A, Behari J, Liu S, McHale T, Nichols L, Papachristou GI, Yadav D, Singh VP. Lipotoxicity causes multisystem organ failure and exacerbates acute pancreatitis in obesity. *Sci Transl Med* 2011; **3**: 107ra110 [PMID: 22049070 DOI: 10.1126/scitranslmed.3002573]

55 **Lee PJ**, Lahooti A, Culp S, Boutsicaris A, Holovach P, Wozniak K, Lahooti I, Paragomi P, Hinton A, Pothoulakis I, Talukdar R, Kochhar R, Goenka MK, Gulla A, Gonzalez JA, Singh V, Bogado MF, Stevens T, Babu ST, Nawaz H, Gutierrez SC, Zarnescu N, Capurso G, Easler J, Triantafyllou K, Peláez Luna M, Thakkar S, Ocampo C, de-Madaria E, Cote GA, Wu BU, Hart PA, Krishna SG, Lara L, Han S, Papachristou GI. Obesity and alcoholic etiology as risk factors for multisystem organ failure in acute pancreatitis: Multinational study. *United European Gastroenterol J* 2023; **11**: 383-391 [PMID: 37096304 DOI: 10.1002/ueg2.12390]

56 **An F**, Zhan Q, Xia M, Jiang L, Lu G, Huang M, Guo J, Liu S. From moderately severe to severe hypertriglyceridemia induced acute pancreatitis: circulating miRNAs play role as potential biomarkers. *PLoS One* 2014; **9**: e111058 [PMID: 25365448 DOI: 10.1371/journal.pone.0111058]

57 **Abaylı B**, Gençdal G, Değirmencioğlu Ş. Correlation between neutrophil/lymphocyte ratio and Ranson score in acute pancreatitis. *J Clin Lab Anal* 2018; **32**: e22437 [PMID: 29575044 DOI: 10.1002/jcla.22437]

58 **Li Y**, Zhao Y, Feng L, Guo R. Comparison of the prognostic values of inflammation markers in patients with acute pancreatitis: a retrospective cohort study. *BMJ Open* 2017; **7**: e013206 [PMID: 28348184 DOI: 10.1136/bmjopen-2016-013206]

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ORIGINAL ARTICLE

Retrospective Study

Tumor recurrence and survival prognosis in patients with advanced gastric cancer after radical resection with radiotherapy and chemotherapy

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Abstract

BACKGROUND

Advanced gastric cancer is a common malignancy that is often diagnosed at an advanced stage and is still at risk of recurrence after radical surgical treatment. Chemoradiotherapy, as one of the important treatment methods for gastric cancer, is of great significance for improving the survival rate of patients. However, the tumor recurrence and survival prognosis of gastric cancer patients after radiotherapy and chemotherapy are still uncertain.

AIM

To analyze the tumor recurrence after radical radiotherapy and chemotherapy for advanced gastric cancer and provide more in-depth guidance for clinicians.

METHODS

A retrospective analysis was performed on 171 patients with gastric cancer who received postoperative adjuvant radiotherapy and chemotherapy in our hospital from 2021 to 2023. The Kaplan-Meier method was used to calculate the recurrence rate and survival rate; the log-rank method was used to analyze the single-factor prognosis; and the Cox model was used to analyze the prognosis associated with multiple factors.

RESULTS

The median follow-up time of the whole group was 63 months, and the follow-up rate was 93.6%. Stage II and III patients accounted for 31.0% and 66.7%, respectively. The incidences of Grade 3 and above acute gastrointestinal reactions and

hematological adverse reactions were 8.8% and 9.9%, respectively. A total of 166 patients completed the entire chemoradiotherapy regimen, during which no adverse reaction-related deaths occurred. In terms of the recurrence pattern, 17 patients had local recurrence, 29 patients had distant metastasis, and 12 patients had peritoneal implantation metastasis. The 1-year, 3-year, and 5-year overall survival (OS) rates were 83.7%, 66.3%, and 60.0%, respectively. The 1-year, 3-year, and 5-year disease-free survival rates were 75.5%, 62.7%, and 56.5%, respectively. Multivariate analysis revealed that T stage, peripheral nerve invasion, and the lymph node metastasis rate (LNR) were independent prognostic factors for OS.

CONCLUSION

Postoperative intensity-modulated radiotherapy combined with chemotherapy for gastric cancer treatment is well tolerated and has acceptable adverse effects, which is beneficial for local tumor control and can improve the long-term survival of patients. The LNR was an independent prognostic factor for OS. For patients with a high risk of local recurrence, postoperative adjuvant chemoradiation should be considered.

Key Words: Tumor recurrence; Survival prognosis; Advanced gastric cancer; Radical resection; Retrospective study

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Core Tip: This study analyzed the tumor recurrence and survival prognosis of patients with advanced gastric cancer after radical radiotherapy and chemotherapy, and explored the related influencing factors. By collecting clinical data of patients for analysis, we will reveal the actual situation of postoperative recurrence rate and survival rate, and further explore the possible influencing factors, so as to provide scientific basis for clinical practice. The innovation of this study lies in the in-depth analysis of the recurrence pattern and prognostic factors of gastric cancer patients after radical radiotherapy and chemotherapy, which provides a new idea for the formulation of individualized treatment plan, and is expected to provide an important reference for the management and prognosis assessment of patients with advanced gastric cancer.

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INTRODUCTION

Globally, the incidence and mortality of gastric cancer rank fifth and third, respectively, among all tumor diseases[1-3]. Between 2013 and 2023, the overall survival (OS) of gastric cancer patients in China significantly improved[4]. However, the prognosis of patients who have received radical gastrectomy and postoperative adjuvant chemotherapy is still not ideal, especially within 2 years after surgery, when more than 60% of patients relapse[5]. Although the clinical significance of adjuvant chemoradiation (CRT) after D0 or D1 Lymph node dissection has not been confirmed by large randomized clinical trials, with the release of the INT-0116 study results, postoperative adjuvant CRT is still the standard treatment for these gastric cancer patients[6]. At present, there is no global consensus on the optimal treatment for locally advanced gastric cancer[7-10].

Current guidelines in China recommend D2 radical surgery as the standard procedure for locally advanced gastric cancer. However, even in some of the best gastric cancer diagnosis and treatment centers in China, nearly half of the patients with advanced gastric cancer do not receive a standard D2 radical operation[11]. In other hospitals, especially primary hospitals, the proportion of patients receiving standard D2 radical surgery may be lower. Radiotherapy is an effective local treatment and can be used as a supplement to surgical treatment, so adjuvant chemoradiotherapy is crucial for the treatment of gastric cancer[12]. At present, the clinical evidence of adjuvant CRT after D2 radical surgery, especially for patients with different relapse patterns, is insufficient.

Therefore, this study reviewed and analyzed the recurrence pattern and related influencing factors of patients with locally advanced gastric cancer in our hospital, providing a new clinical basis for the choice of treatment for these patients.

MATERIALS AND METHODS

Entry criteria

(1) Gastric cancer patients who received postoperative CRT treatment in Zhongshan Hospital Affiliated to Fudan University from September 2021 to September 2023; (2) Receiving R0 resection of gastric cancer and > D 1 lymph node dissection (according to the definition of lymph node dissection in the 3rd edition of Japanese gastric cancer stage); (3) No

distant metastasis or peritoneal implantation metastasis; (4) Regular follow-up after treatment; and (5) Complete clinical data.

Treatment plan

All patients underwent radical resection. A total of 44.4% (76 patients) underwent distal subtotal gastrectomy, 15.2% (26 patients) underwent proximal subtotal gastrectomy, 33.9% (58 patients) underwent total gastrectomy, and 6.5% (11 patients) underwent combined organ resection. Patients received intensity-modulated radiotherapy (IMRT) at a median dose of 45 Gy (41.1–50.4 Gy) or 1.8 Gy/time once a day. The range of irradiation included the tumor bed, anastomosis, duodenal stump, and a specific lymph node drainage area. Radiation was not considered in the tumor bed area of patients with PT-1 and PT-2M0 gastric cancer. The delineation range of the lymph node drainage area (including residual and perigastric lymph nodes, peritruncus lymph nodes, hilar splenic lymph nodes, hepatoduodenal lymph nodes or hilar hepatic lymph nodes, pancreaticoduodenal lymph nodes, and paraaortic lymph nodes) depends on the tumor site. The median duration of radiotherapy was 35 days (30–45 d).

All enrolled patients received adjuvant chemotherapy before and after radiotherapy. The chemotherapy regimens used were as follows: capecitabine + oxaliplatin (81 patients, 47.4%), Ticeo + oxaliplatin (29 patients, 17.0%), epirubicin + oxaliplatin + fluorouracil (14 patients, 8.2%), oxaliplatin + fluorouracil + calcium folinate (15 patients, 8.8%), and other regimens. Adjuvant chemotherapy was administered from 3 to 8 wk after surgery, and simultaneous chemoradiotherapy was administered from 8 to 18 wk after surgery.

Follow-up information

The median follow-up period was 63 months (3–144 months) as of September 30, 2023. The first patient underwent radical gastrectomy in July 2021, and the last patient was treated in April 2023. During follow-up, 11 of 171 patients (6.4%) were lost to follow-up. All patients who completed adjuvant CRT therapy were regularly followed up, including medical history, physical examination, routine blood, biochemical and electrolyte tests, tumor marker analysis, chest, abdominal, and pelvic computed tomography (positron emission tomography-computed tomography if necessary), and endoscopy. All patients were followed up every 3 months for the first 2 years after completion of treatment, every 6 months for patients 2 to 5 years old, and annually for patients over 5 years old.

Recurrence pattern definition

Local recurrence refers to the recurrence of anastomosis, duodenal stump, tumor bed, or stomach stump. Regional recurrence refers to recurrence in areas such as the perigastric, hilar, peripancreatic, and paraaortic lymph node drainages. Peritoneal metastasis refers to peritoneal, colorectal, and ovarian metastases. Distant metastasis refers to metastasis to distant organs such as the liver, bone, or lungs or to lymph nodes other than regional lymph nodes.

All patients' medical records were retrospectively analyzed, and all relapses or metastases were recorded. If two or more sites recurred or metastasized at the same time, they were counted separately. The OS period was defined as the time from surgery to death, including tumor-specific death or death from any other cause. Disease-free survival (DFS) was defined as the time from surgery to initial progression or death. Local relapse-free survival (LFFS), regional relapse-free survival (RFFS), peritoneal metastasis-free survival (PFFS), and distant metastasis-free survival (DFFS) refer to the time from surgery to local recurrence, regional recurrence, peritoneal metastasis, and distant metastasis, respectively.

Statistical analysis

The Kaplan-Meier method in SPSS 25.0 software was used to calculate the OS rate, DFS rate, LFFS rate, RFFS rate, PFFS rate, DFFS rate, and locoregional failure-free survival (LRFFS) rate curves. Factors including age, sex, hospital of surgery, mode of surgery, primary tumor location, pathological type, Lauren classification, number of lymph nodes dissected, lymph node metastasis rate (LNR), postoperative T stage, postoperative N stage, postoperative TNM stage, lymphatic vessel invasion (LVI), peripheral nerve invasion (PNI), and concurrent chemical and adjuvant chemotherapy were analyzed. The Kaplan-Meier method was used to analyze the relationships between the prognosis and survival curves of different LNR subgroups, and a log-rank test was performed to compare the differences between groups. Multivariate prognosis analysis was performed by the Cox regression model, and $P < 0.05$ was considered to indicate statistical significance.

RESULTS

General clinical data analysis

A total of 171 patients were enrolled, including 124 males and 47 females aged 27–76 years (median 60 years). The primary lesions were located in the upper 1/3 of the stomach, the middle 1/3 of the stomach, the lower 1/3 of the stomach, and the whole stomach in 43 patients (25.2%), 37 patients (21.6%), 76 patients (44.4%), and 15 patients (8.8%), respectively. Nearly half (42.7%) of the enrolled patients had N stage N3 disease, 5-56 lymph nodes (median 19), and 0-47 positive lymph nodes (median 5). Patients with stages IIA, IIB, IIIA, IIIB, and IIIc accounted for 17.5%, 13.5%, 24.6%, 26.3%, and 15.8%, respectively, of the patients, as shown in Table 1.

Survival and prognosis analysis

As of September 2020, 60 patients (35.1%) had died, and 47 patients (27.5%) experienced recurrence or metastasis. As

Table 1 Clinical data of 171 gastric cancer patients

Project	*n* (%)	Project	*n* (%)
Age (yr)		T staging	
≤ 40	6 (3.5)	T1	8 (4.7)
41-65	126 (73.7)	T2	21 (12.3)
≥ 66	39 (22.8)	T3	86 (50.3)
Gender		T4a	31 (18.1)
Male	124 (72.5)	T4b	25 (14.6)
Female	47 (27.5)	N stages	
Surgical hospital		N0	24 (14.0)
Court	102 (59.6)	N1	33 (19.3)
Outer courtyard	69 (40.4)	N2	41 (24.0)
Operation		N3a	58 (33.9)
Subtotal proximal gastrectomy	26 (15.2)	N3b	15 (8.8)
Subtotal distal gastrectomy	76 (44.4)	Clinical stages	
Total gastrectomy	58 (33.9)	IB	4 (2.3)
Gastrectomy and other organ	11 (6.5)	IIA	30 (17.5)
Primary lesion site		IIB	23 (13.5)
1/3 upper stomach	37 (21.6)	IIIA	42 (24.6)
1/3 stomach	76 (44.4)	IIIB	45 (26.3)
1/3 subgastric	15 (8.8)	IIIC	27 (15.8)
Whole stomach	15 (8.8)	Lymphatic invasion	
Pathological type		Negative	82 (48.0)
Medium to high differentiation	58 (33.9)	Positive	89 (52.0)
Poorly differentiated	91 (53.2)	Peripheral nerve invasion	
Mucinous adenocarcinoma	9 (5.3)	Negative	91 (53.2)
Signet-ring cell carcinoma	12 (7.0)	Positive	80 (46.8)
Neuroendocrine degeneration	1 (0.6)	Synchronous chemotherapy	
Lauren typing		Capecitabine	95 (55.6)
Intestinal	69 (40.4)	Tegafur	25 (14.6)
Diffuse	95 (55.5)	Other	51 (29.8)
Mixed unclassified	7 (4.1)	Adjuvant chemotherapy regimen	
Number of lymph nodes cleaned		XELOX	81 (47.4)
< 15	57 (33.3)	SOX	29 (17.0)
≥ 15	114 (66.7)	FOLFOX	15 (8.8)
Positive lymph nodes		EOF	14 (8.2)
LNR ≤ 0.3	89 (52.0)	FLOT	5 (2.9)
0.3 < LNR ≤ 0.7	58 (33.9)	other	27 (15.7)
LNR > 0.7	24 (14.1)		
Age [yr, median (range)]			60 (27-76)
Number of lymph nodes cleaned [*n*, median (Range)]			19 (5-56)
Number of positive lymph nodes [*n*, median (Range)]			5 (0-47)

LNR: Lymph node metastasis rate.

shown in Figure 1A, the 1-year, 3-year, and 5-year OS rates and 1-year, 3-year, and 5-year DFS rates of the enrolled patients were 83.7%, 66.3%, 60.0%, 75.5%, 62.7%, and 56.5%, respectively. Single-factor analysis revealed that the Lauren classification, LNR, PNI, T stage, and N stage were factors affecting OS. The LNR, T stage, and N stage are factors affecting DFS. Multifactor analysis revealed that T stage, the LNR, and the PNI were independent prognostic factors affecting OS (Table 2). As shown in Figure 1B, the 5-year survival rates of the different LNR subgroups were 75.6%, 54.8%, and 26.2%, respectively. T stage was an independent prognostic factor for DFS (Table 3).

Analysis of recurrence

During follow-up, 47 patients (27.5%) had a total of 60 recurrences and metastases. Local recurrence, regional recurrence, abdominal metastasis, and distant metastasis accounted for 2.9%, 8.2%, 7.0%, and 17.0%, respectively. In terms of the recurrence mode (Table 4), 34 patients (72.3%) had a single recurrence mode, and 13 patients (27.7%) had a double recurrence mode. Distant metastases were the most common single-recurrence-mode metastases. In contrast, abdominal metastasis, regional recurrence, and local recurrence were less common. Four patients developed regional recurrence plus distant metastasis, a combination that was most common in the dual recurrence pattern group. As shown in Tables 5 and 6, in patients with recurrence and metastasis, the proportions of liver, bone, lung, brain, spleen, and adrenal gland metastases were 29.8%, 23.4%, 21.3%, 8.5%, 2.1%, and 2.1%, respectively.

Survival analysis of each recurrence mode

As shown in Figure 1C, the 3-year LFFS rate, PFFS rate, RFFS rate, LRFFS rate, and DFFS rate were 95.3%, 91.2%, 90.7%, 87.7%, and 82.0%, respectively. The 3-year survival of patients with each recurrence mode was as follows: 2 of 5 patients with local recurrence died; of the 14 patients with regional recurrence, 6 died. Of the 12 patients with abdominal metastasis, nine died. Of the 29 patients with distant metastasis, 23 died. Univariate analysis revealed that N stage was the most influential factor for all failure modes except abdominal metastasis, while T stage only affected LRFFS. LVI is the factor that affects PFFS, while the LNR is the factor that affects DFFS. Multifactor analysis revealed that T stage was an independent prognostic factor for LRFFS (P = 0.006) and PFFS (P = 0.003), as shown in Tables 7 and 8. No independent prognostic factors for DFFS were found in this study.

Adverse reaction analysis

Of all the patients, only five did not complete radiotherapy. All patients received concurrent chemotherapy, and 26 of them experienced dose reduction or a longer interval between treatments. The incidences of Grade 3 and above acute gastrointestinal reactions and hematological adverse reactions were 8.8% and 9.9%, respectively.

DISCUSSION

Although the incidence and mortality of gastric cancer have decreased in recent decades, the number of new cases per year is still very high due to population aging[13]. There are few specific clinical manifestations in patients with early gastric cancer, and with the exception of South Korea and Japan, gastric cancer screening is not routinely performed in other countries worldwide, fewer than half of patients receive D2 radical surgery, even in several good gastric cancer diagnosis and treatment centers[14-16]. Multiple studies have shown that even if the standard R0/D2 radical surgery requirements are met, the local recurrence rate after surgery can still reach 20% to 40%[17]. Radiotherapy is an effective local treatment that can compensate for incomplete surgical lymph node dissection to a certain extent. Therefore, adjuvant radiotherapy for gastric cancer is highly important for improving the local control rate of tumors and the long-term survival rate of patients.

The American INT-0116 study used adjuvant CRT as the standard treatment for high-risk gastric cancer patients undergoing radical resection[6]. However, there are some difficulties and challenges in adopting this scheme in China. One of the greatest problems we had was incomplete lymph node dissection; only 10% of patients met the criteria for D2 dissection. Another factor was the high rate of adverse reactions; 17% of patients in the INT-0116 study stopped treatment because of adverse reactions to adjuvant therapy. Since 2010, the guidelines for the diagnosis and treatment of gastric cancer issued by the National Health Commission have been updated to the third edition, which emphasizes the need for adjuvant radiotherapy and chemotherapy for high-risk locally advanced gastric cancer patients with one of the following conditions: patients who underwent R1 or R2 resection; patients who underwent D0 or D1 resection with pathological stage T 3-4 and/or N+ without distant metastasis; and patients who underwent R0 or D2 resection with pathological stage T 3-4 or more regional lymph node metastases. Because standard D2 radical surgery is uncommon in Chinese patients with stomach cancer, the goal of this retrospective study was to determine how well and how badly adjuvant CRT works after surgery, how often treatment fails, and how often clinical data related to recurrence patterns are available for patients who underwent > D1 resection and adjuvant CRT. At the same time, patients enrolled in this study were treated from 2008 to 2020, with a span of 12 years. To avoid heterogeneity caused by improvements in the scope and number of lymph nodes removed by radical gastrectomy and advancements in radiotherapy technology, patients who underwent gastric cancer D1 resection, conventional radiotherapy, or 3D-CRT were excluded from this study. Patients with gastric cancer > D1 who underwent IMRT after resection were selected for analysis. First, the 3-year OS and DFS

Table 2 Multivariate analysis of prognostic factors related to overall survival rate

Factors	Univariate analysis	Multivariate analysis		
		Hazard ratio	95%CI	*P* value
Age	0.092	1.659	0.977-2.815	0.061
Pathological type	0.063	0.826	0.263-2.593	0.743
Lauren typing	0.037	0.488	0.054-4.449	0.525
LNR	< 0.001	2.174	1.115-3.862	0.015
T stage	0.005	1.636	1.108-2.415	0.013
N stage	< 0.001	1.135	0.774-1.665	0.516
PNI	0.008	1.719	1.006-2.937	0.047

PNI: Peripheral nerve invasion; LNR: Lymph node metastasis rate.

Table 3 Multivariate analysis of prognostic factors related to disease-free survival rate

Factors	Univariate analysis	Multivariate analysis		
		Hazard ratio	95%CI	*P* value
Pathological type	0.096	0.850	0.276-2.618	0.778
Lauren typing	0.053	0.521	0.058-4.705	0.561
LNR	< 0.001	1.182	0.792-1.763	0.413
T stage	0.002	1.573	1.102-2.245	0.013
N stage	< 0.001	1.310	0.918-1.869	0.136
PNI	0.054	1.395	0.853-2.282	0.185

PNI: Peripheral nerve invasion; LNR: Lymph node metastasis rate.

Table 4 The proportion of different recurrence patterns in 47 recurrent gastric cancer patients out of 171 cases

Recurrence pattern	Cases	Proportion (%)	Recurrence pattern	Cases	Proportion (%)
Single mode	34	72.3	Dual mode	13	27.7
Local recurrence	1	2.1	Local recurrence + abdominal metastasis	2	4.3
Regional recurrence	5	10.6	Local recurrence + regional recurrence	2	4.3
Abdominal metastasis	5	10.6	Regional recurrence + abdominal metastasis	3	6.4
Distant metastasis	23	48.9	Regional recurrence + distant metastasis	4	8.5
Multi mode	0	0	Abdominal metastasis + distant metastasis	2	4.3

rates of this study were 66.3% and 62.7%, respectively, and the 5-year OS and DFS rates were 60.0% and 56.5%, respectively, which were more favorable than the results of the INT-0116 study. However, this approach is slightly inferior to that used by artists[6,9,18]. This may be due to the earlier stage of tumors in the Korean ARTIST study and more aggressive lymph node dissection. In the ARTIST study, only 40% of patients with stage III disease were enrolled, while in this study, the proportion of patients with stage III disease was as high as 66.7%, which may be related to the lack of large-scale gastric cancer screening programs in China. Second, the study revealed that both local (2.9%) and regional (8.1%) recurrence rates were low. These rates were much lower than those found in previous clinical studies from Western countries and were similar to those found in South Korea. This finding showed that chemoradiotherapy after surgery may help control tumors locally and regionally. In this study, distant metastasis was the most common failure mode. In addition, the local recurrence rate in China is 32.4%, and previous studies have shown that the incidence of local recurrence in patients after adjuvant chemotherapy is 7.8%-29.3%[5,18,19].

Traditional postoperative adjuvant chemotherapy and perioperative chemotherapy for gastric cancer have a high adverse reaction rate and a low completion rate. The previous Korean CLASSIC study, Japanese ACTS GC study,

Table 5 Recurrence patterns in 47 out of 171 gastric cancer patients with relapses of proportion a

Recurrence pattern	Cases	Proportion a (%)	Recurrence pattern	Cases	Proportion a (%)
Local recurrence	5	10.6	Distant metastasis	29	61.7
Gastric stump	1	2.1	Liver	14	29.8
Anastomotic opening	4	8.5	Bone	11	23.4
Regional recurrence	14	29.8	Lungs	10	21.3
Abdominal metastasis	12	25.5	Brain	4	8.5
Peritoneum	9	19.1	Spleen	1	2.1
Ovary	2	4.3	Adrenal gland	1	2.1
Colorectal	1	2.1	Non regional Lymph nodes	1	2.1

Table 6 Recurrence patterns in 47 out of 171 gastric cancer patients with relapses of proportion b

Recurrence pattern	Cases	Proportion b (%)	Recurrence pattern	Cases	Proportion b (%)
Local recurrence	5	2.9	Abdominal metastasis	12	7.0
Regional recurrence	14	8.2	Distant metastasis	29	17.0

Table 7 Analysis of prognostic factors related to local recurrence

Factors	Univariate analysis	Multivariate analysis		
		Hazard ratio	95%CI	*P* value
Gender	0.210	0.961	0.561-1.648	0.886
Pathological type	0.109	0.547	0.216-1.387	0.204
LNR	0.079	1.253	0.850-1.846	0.255
T stage	0.040	1.643	1.155-2.337	0.006
N stage	0.020	1.271	0.902-1.790	0.171
LVI	0.060	1.211	0.742-1.975	0.443

LVI: Lymphatic vessel invasion; LNR: Lymph node metastasis rate.

Table 8 Analysis of prognostic factors related to abdominal metastasis

Factors	Univariate analysis	Multivariate analysis		
		Hazard ratio	95%CI	*P* value
Pathological type	0.149	0.462	0.189-1.132	0.091
Cleaning lymph nodes	0.161	0.923	0.550-1.551	0.763
T stage	0.195	1.700	1.199-2.410	0.003
LVI	0.012	1.221	0.745-2.002	0.428

LVI: Lymphatic vessel invasion.

European FNCLCC/FFCD study, and MAGIC study had grade 3–4 adverse reaction rates as high as 56.0%, 20.7%, 40.0%, and 38.0%, respectively. However, the completion rates were only 67.0%, 65.8%, 49.5%, and 23.0%, respectively[20-23]. At present, a number of studies on adjuvant therapy for gastric cancer have shown that combining chemotherapy with radiotherapy can reduce the number of cycles of chemotherapy and the total dose of chemotherapy drugs to a certain extent and alleviate related adverse reactions, thus improving the completion rate of postoperative adjuvant therapy[24]. In the ARTIST study, patients with gastric cancer after radical surgery were randomly assigned to the chemotherapy

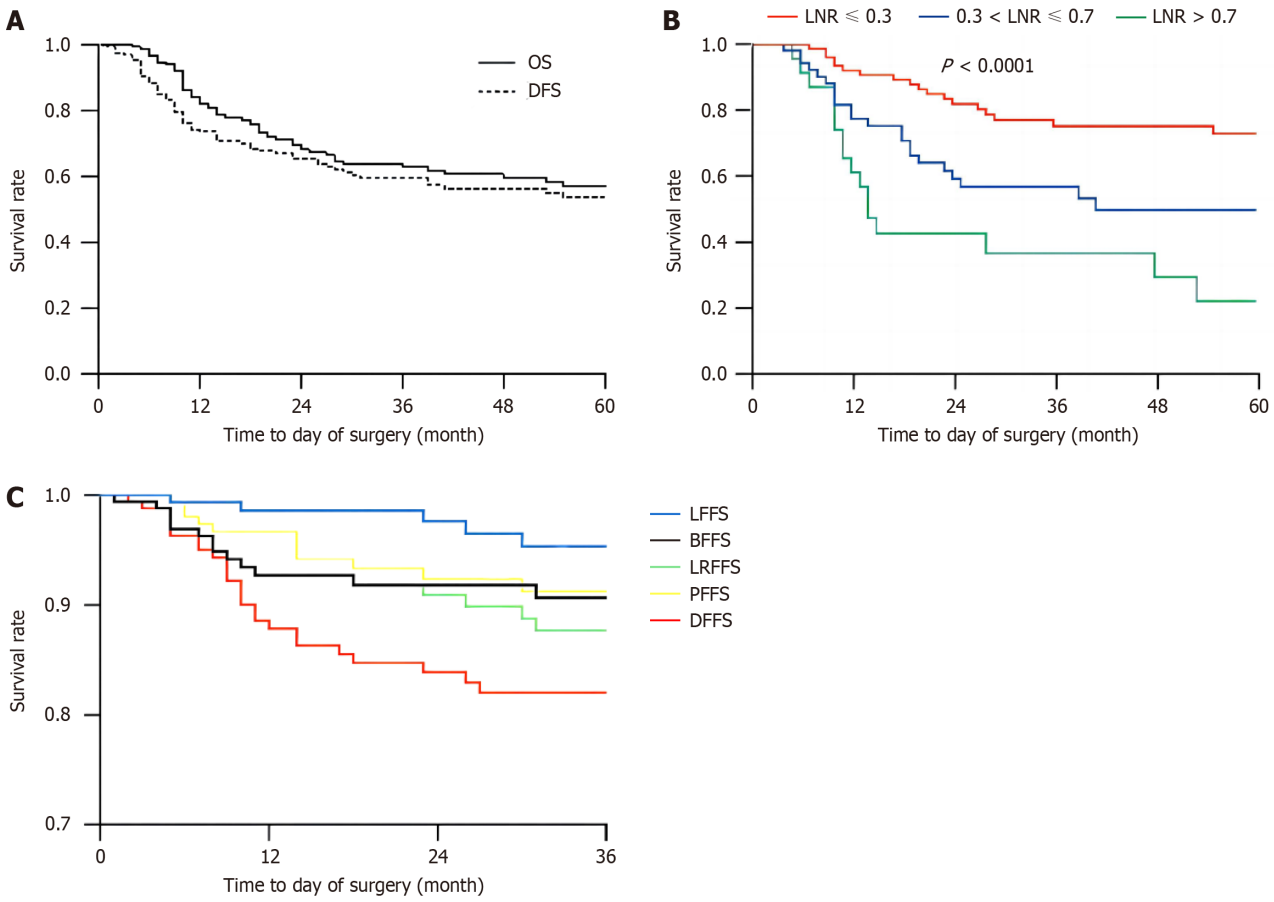


Figure 1 Kaplan-Meier curves in patients with gastric cancer. A: Overall survival (OS) and disease-free survival; B: OS between different lymph node metastasis rate subgroups; C: Local relapse-free survival, regional relapse-free survival, locoregional failure-free survival, peritoneal metastasis-free survival and distant metastasis-free survival. OS: Overall survival; DFS: Disease-free survival; LNR: Lymph node metastasis rate; LFFS: Local relapse-free survival; RFFS: Regional relapse-free survival; LRFFS: Locoregional failure-free survival; PFFS: Peritoneal metastasis-free survival; DFFS: Distant metastasis-free survival.

alone group or the combined chemoradiotherapy group. The results showed that the completion rate of the combined chemoradiotherapy group reached 81.7%, which was greater than that of the chemotherapy alone group (75.4%). At the same time, the adverse reaction rate of the combined group was lower. Compared with the INT-0116 study and the ARTIST study, this study revealed a lower incidence of grade 3–4 gastrointestinal adverse reactions, which may be partly related to the application of IMRT[25]. Studies have confirmed that IMRT is superior to 2D or 3D radiotherapy because it provides a more accurate dose distribution for the planned target area and reduces the risk of radiation-related adverse reactions[26-28]. Using IMRT technology, under the premise of effectively controlling the tumor, the dose of exposure to the surrounding normal tissue can also be reduced.

CONCLUSION

Postoperative IMRT and chemotherapy given at the same time are well tolerated and have acceptable side effects in the Chinese population. This approach helps control local tumors and improves long-term survival for people with locally advanced gastric cancer > D1 after resection. The LNR can be used as an important prognostic indicator for patients with gastric cancer > D1 undergoing adjuvant chemoradiotherapy after resection.

FOOTNOTES

Author contributions: Nie SF wrote the manuscript; Wang CY, Li L, Yang C and Zhu ZM collected the data; and Fei JD guided the study. All authors reviewed, edited, and approved the final manuscript and revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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REFERENCES

1 **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]

2 **Rha SY**, Oh DY, Yañez P, Bai Y, Ryu MH, Lee J, Rivera F, Alves GV, Garrido M, Shiu KK, Fernández MG, Li J, Lowery MA, Çil T, Cruz FM, Qin S, Luo S, Pan H, Wainberg ZA, Yin L, Bordia S, Bhagia P, Wyrwicz LS; KEYNOTE-859 investigators. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol* 2023; **24**: 1181-1195 [PMID: 37875143 DOI: 10.1016/S1470-2045(23)00515-6]

3 **Park SH**, Lim DH, Sohn TS, Lee J, Zang DY, Kim ST, Kang JH, Oh SY, Hwang IG, Ji JH, Shin DB, Yu JI, Kim KM, An JY, Choi MG, Lee JH, Kim S, Hong JY, Park JO, Park YS, Lim HY, Bae JM, Kang WK; ARTIST 2 investigators. A randomized phase III trial comparing adjuvant single-agent S1, S-1 with oxaliplatin, and postoperative chemoradiation with S-1 and oxaliplatin in patients with node-positive gastric cancer after D2 resection: the ARTIST 2 trial(☆). *Ann Oncol* 2021; **32**: 368-374 [PMID: 33278599 DOI: 10.1016/j.annonc.2020.11.017]

4 **Anderson PM**, Lalla RV. Glutamine for Amelioration of Radiation and Chemotherapy Associated Mucositis during Cancer Therapy. *Nutrients* 2020; **12** [PMID: 32512833 DOI: 10.3390/nu12061675]

5 **Plotti F**, Terranova C, Luvero D, Bartolone M, Messina G, Feole L, Cianci S, Scaletta G, Marchetti C, Di Donato V, Fagotti A, Scambia G, Benedetti Panici P, Angioli R. Diet and Chemotherapy: The Effects of Fasting and Ketogenic Diet on Cancer Treatment. *Chemotherapy* 2020; **65**: 77-84 [PMID: 33197913 DOI: 10.1159/000510839]

6 **Wu L**, Zheng Y, Liu J, Luo R, Wu D, Xu P, Li X. Comprehensive evaluation of the efficacy and safety of LPV/r drugs in the treatment of SARS and MERS to provide potential treatment options for COVID-19. *Aging (Albany NY)* 2021; **13**: 10833-10852 [PMID: 33879634 DOI: 10.18632/aging.202860]

7 **Shah MA**, Shitara K, Ajani JA, Bang YJ, Enzinger P, Ilson D, Lordick F, Van Cutsem E, Gallego Plazas J, Huang J, Shen L, Oh SC, Sunpaweravong P, Soo Hoo HF, Turk HM, Oh M, Park JW, Moran D, Bhattacharya P, Arozullah A, Xu RH. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. *Nat Med* 2023; **29**: 2133-2141 [PMID: 37524953 DOI: 10.1038/s41591-023-02465-7]

8 **Wang MQ**, Chen YR, Xu HW, Zhan JR, Suo DQ, Wang JJ, Ma YZ, Guan XY, Li Y, Zhu SL. HKDC1 upregulation promotes glycolysis and disease progression, and confers chemoresistance onto gastric cancer. *Cancer Sci* 2023; **114**: 1365-1377 [PMID: 36519789 DOI: 10.1111/cas.15692]

9 **Fang X**, Xu J, Jin K, Qian J. Combining of immunotherapeutic approaches with chemotherapy for treatment of gastric cancer: Achievements and limitations. *Int Immunopharmacol* 2023; **118**: 110062 [PMID: 36965367 DOI: 10.1016/j.intimp.2023.110062]

10 **Zeng L**, Liao Q, Zeng X, Ye J, Yang X, Zhu S, Tang H, Liu G, Cui W, Ma S, Cui S. Noncoding RNAs and hyperthermic intraperitoneal chemotherapy in advanced gastric cancer. *Bioengineered* 2022; **13**: 2623-2638 [PMID: 35089117 DOI: 10.1080/21655979.2021.2021348]

11 **Liang X**, Zhu J, Li Y, Xu Y, Chen K, Lv L, Mao W. Treatment strategies for metastatic gastric cancer: chemotherapy, palliative surgery or radiotherapy? *Future Oncol* 2020; **16**: 91-102 [PMID: 31868545 DOI: 10.2217/fon-2019-0495]

12 **Wu L**, Liu Q, Ruan X, Luan X, Zhong Y, Liu J, Yan J, Li X. Multiple Omics Analysis of the Role of RBM10 Gene Instability in Immune Regulation and Drug Sensitivity in Patients with Lung Adenocarcinoma (LUAD). *Biomedicines* 2023; **11** [PMID: 37509501 DOI: 10.3390/biomedicines11071861]

13 **Wu L**, Li H, Liu Y, Fan Z, Xu J, Li N, Qian X, Lin Z, Li X, Yan J. Research progress of 3D-bioprinted functional pancreas and *in vitro* tumor models. *IJB* 2024; **10**: 1256 [DOI: 10.36922/ijb.1256]

14 **Li J**, Qin S, Wen L, Wang J, Deng W, Guo W, Jia T, Jiang D, Zhang G, He Y, Ba Y, Zhong H, Wang L, Lin X, Yang J, Zhao J, Bai Y, Wu X, Gao F, Sun G, Wu Y, Ye F, Wang Q, Xie Z, Yi T, Huang Y, Yu G, Lu L, Yuan Y, Li W, Liu L, Sun Y, Yin L, Hou Z. Safety and efficacy of apatinib in patients with advanced gastric or gastroesophageal junction adenocarcinoma after the failure of two or more lines of chemotherapy (AHEAD): a prospective, single-arm, multicenter, phase IV study. *BMC Med* 2023; **21**: 173 [PMID: 37147645 DOI: 10.1186/s12916-023-02841-7]

15 **Kroese TE**, van Laarhoven HWM, Nilsson M, Lordick F, Guckenberger M, Ruurda JP, D'Ugo D, Haustermans K, van Cutsem E, van Hillegersberg R, van Rossum PSN. Definition of oligometastatic esophagogastric cancer and impact of local oligometastasis-directed treatment: A systematic review and meta-analysis. *Eur J Cancer* 2022; **166**: 254-269 [PMID: 35339868 DOI: 10.1016/j.ejca.2022.02.018]

16 **Lavacchi D**, Fancelli S, Buttitta E, Vannini G, Guidolin A, Winchler C, Caliman E, Vannini A, Giommoni E, Brugia M, Cianchi F, Pillozzi S, Roviello G, Antonuzzo L. Perioperative Tailored Treatments for Gastric Cancer: Times Are Changing. *Int J Mol Sci* 2023; **24** [PMID: 36902306 DOI: 10.3390/ijms24054877]

17 **Wu L**, Li X, Qian X, Wang S, Liu J, Yan J. Lipid Nanoparticle (LNP) Delivery Carrier-Assisted Targeted Controlled Release mRNA Vaccines in Tumor Immunity. *Vaccines (Basel)* 2024; **12** [PMID: 38400169 DOI: 10.3390/vaccines12020186]

18 **Wu L**, Zhong Y, Wu D, Xu P, Ruan X, Yan J, Liu J, Li X. Immunomodulatory Factor TIM3 of Cytolytic Active Genes Affected the Survival and Prognosis of Lung Adenocarcinoma Patients by Multi-Omics Analysis. *Biomedicines* 2022; **10** [PMID: 36140350 DOI: 10.3390/biomedicines10092248]

19 **Bazarbashi S**, Badran A, Gad AM, Aljubran A, Alzahrani A, Alshibani A, Alrakaf R, Elhassan T, Alsuhaibani A, Elshenawy MA. Combined Prophylactic Hyperthermic Intraperitoneal Chemotherapy and Intraoperative Radiotherapy for Localized Gastroesophageal Junction and Gastric Cancer: A Comparative Nonrandomized Study. *Ann Surg Oncol* 2023; **30**: 426-432 [PMID: 36042103 DOI: 10.1245/s10434-022-12467-3]

20 **Wu L**, Zhong Y, Yu X, Wu D, Xu P, Lv L, Ruan X, Liu Q, Feng Y, Liu J, Li X. Selective poly adenylation predicts the efficacy of immunotherapy in patients with lung adenocarcinoma by multiple omics research. *Anticancer Drugs* 2022; **33**: 943-959 [PMID: 35946526 DOI: 10.1097/CAD.0000000000001319]

21 **Cai L**, Ouyang G, Wang X, Li Z, Shen Y. Radiotherapy Combined with Chemotherapy for Regional Lymph Node Recurrence in Gastric Cancer. *Cancer Manag Res* 2020; **12**: 13339-13346 [PMID: 33380839 DOI: 10.2147/CMAR.S280225]

22 **Wei L**, Lv F, Luo C, Fang Y. Study on sentinel symptoms and influencing factors of postoperative chemotherapy in patients with gastric cancer. *Eur J Oncol Nurs* 2023; **64**: 102318 [PMID: 37167842 DOI: 10.1016/j.ejon.2023.102318]

23 **Wu L**, Chen X, Zeng Q, Lai Z, Fan Z, Ruan X, Li X, Yan J. NR5A2 gene affects the overall survival of LUAD patients by regulating the activity of CSCs through SNP pathway by OCLR algorithm and immune score. *Heliyon* 2024; **10**: e28282 [PMID: 38601554 DOI: 10.1016/j.heliyon.2024.e28282]

24 **Lee KW**, Van Cutsem E, Bang YJ, Fuchs CS, Kudaba I, Garrido M, Chung HC, Lee J, Castro HR, Chao J, Wainberg ZA, Cao ZA, Aurora-Garg D, Kobie J, Cristescu R, Bhagia P, Shah S, Tabernero J, Shitara K, Wyrwicz L. Association of Tumor Mutational Burden with Efficacy of Pembrolizumab±Chemotherapy as First-Line Therapy for Gastric Cancer in the Phase III KEYNOTE-062 Study. *Clin Cancer Res* 2022; **28**: 3489-3498 [PMID: 35657979 DOI: 10.1158/1078-0432.CCR-22-0121]

25 **Ren X**, Huang T, Tang X, Ma Q, Zheng Y, Hu Z, Wang Y, Zhou Y. Development and validation of nomogram models to predict radiotherapy or chemotherapy benefit in stage III/IV gastric adenocarcinoma with surgery. *Front Oncol* 2023; **13**: 1223857 [PMID: 37655111 DOI: 10.3389/fonc.2023.1223857]

26 **Wu L**, Zheng Y, Ruan X, Wu D, Xu P, Liu J, Li X. Long-chain noncoding ribonucleic acids affect the survival and prognosis of patients with esophageal adenocarcinoma through the autophagy pathway: construction of a prognostic model. *Anticancer Drugs* 2022; **33**: e590-e603 [PMID: 34338240 DOI: 10.1097/CAD.0000000000001189]

27 **Lumish MA**, Ku GY. Approach to Resectable Gastric Cancer: Evolving Paradigm of Neoadjuvant and Adjuvant Treatment. *Curr Treat Options Oncol* 2022; **23**: 1044-1058 [PMID: 35524838 DOI: 10.1007/s11864-021-00917-1]

28 **Ekheden I**, Ebrahim F, Ólafsdóttir H, Raaschou P, Wettermark B, Henriksson R, Ye W. Survival of esophageal and gastric cancer patients with adjuvant and palliative chemotherapy-a retrospective analysis of a register-based patient cohort. *Eur J Clin Pharmacol* 2020; **76**: 1029-1041 [PMID: 32372150 DOI: 10.1007/s00228-020-02883-3]

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ORIGINAL ARTICLE

Retrospective Study

Prediction and analysis of albumin-bilirubin score combined with liver function index and carcinoembryonic antigen on liver metastasis of colorectal cancer

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Abstract

BACKGROUND

Colorectal cancer (CRC) is a common malignant tumor, and liver metastasis is one of the main recurrence and metastasis modes that seriously affect patients' survival rate and quality of life. Indicators such as albumin bilirubin (ALBI) score, liver function index, and carcinoembryonic antigen (CEA) have shown some potential in the prediction of liver metastasis but have not been fully explored.

AIM

To evaluate its predictive value for liver metastasis of CRC by conducting the combined analysis of ALBI, liver function index, and CEA, and to provide a more accurate liver metastasis risk assessment tool for clinical treatment guidance.

METHODS

This study retrospectively analyzed the clinical data of patients with CRC who received surgical treatment in our hospital from January 2018 to July 2023 and were followed up for 24 months. According to the follow-up results, the enrolled patients were divided into a liver metastasis group and a nonliver metastasis group and randomly divided into a modeling group and a verification group at a ratio of 2:1. The risk factors for liver metastasis in patients with CRC were

analyzed, a prediction model was constructed by least absolute shrinkage and selection operator (LASSO) logistic regression, internal validation was performed by the bootstrap method, the reliability of the prediction model was evaluated by subject-work characteristic curves, calibration curves, and clinical decision curves, and a column graph was drawn to show the prediction results.

RESULTS

Of 130 patients were enrolled in the modeling group and 65 patients were enrolled in the verification group out of the 195 patients with CRC who fulfilled the inclusion and exclusion criteria. Through LASSO regression variable screening and logistic regression analysis. The ALBI score, alanine aminotransferase (ALT), and CEA were found to be independent predictors of liver metastases in CRC patients [odds ratio (OR) = 8.062, 95% confidence interval (CI): 2.545-25.540], (OR = 1.037, 95%CI: 1.004-1.071) and (OR = 1.025, 95%CI: 1.008-1.043). The area under the receiver operating characteristic curve (AUC) for the combined prediction of CRLM in the modeling group was 0.921, with a sensitivity of 78.0% and a specificity of 95.0%. The H-index was 0.921, and the H-L fit curve had $\chi 2$ = 0.851, a *P* value of 0.654, and a slope of the calibration curve approaching 1. This indicates that the model is extremely accurate, and the clinical decision curve demonstrates that it can be applied effectively in the real world. We conducted internal verification of one thousand resamplings of the modeling group data using the bootstrap method. The AUC was 0.913, while the accuracy was 0.869 and the kappa consistency was 0.709. The combination prediction of liver metastasis in patients with CRC in the verification group had an AUC of 0.918, sensitivity of 85.0%, specificity of 95.6%, C-index of 0.918, and an H-L fitting curve with χ^2 = 0.586, *P* = 0.746.

CONCLUSION

The ALBI score, ALT level, and CEA level have a certain value in predicting liver metastasis in patients with CRC. These three criteria exhibit a high level of efficacy in forecasting liver metastases in patients diagnosed with CRC. The risk prediction model developed in this work shows great potential for practical application.

Key Words: Albumin-bilirubin; Carcinoembryonic antigen; Colorectal cancer; Tumor metastasis; Prediction model

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Core Tip: This study investigated the application of the albumin bilirubin (ALBI) and liver function indices (aspartate aminotransferase, alanine aminotransferase, total bilirubin, *etc.*) combined with carcinoembryonic antigen (CEA) for the prediction of liver metastasis in patients with colorectal cancer (CRC). Through retrospective analysis of clinical data, we explored the associations of the ALBI and CEA level with liver metastasis in patients with CRC and established predictive models. The results of this study will provide clinicians with a simple and effective way to assess the risk of liver metastasis in patients with CRC and guide the development of treatment options that can help improve patient prognosis and survival.

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INTRODUCTION

According to the statistics of National Cancer Center of China in 2023, there are approximately 4.08 million newly diagnosed colorectal cancer (CRC) patients and 196000 deaths in China each year, ranking second and fourth in malignant tumors, respectively[1-4]. The main reason for the poor prognosis of CRC patients is liver metastasis, which occurs in approximately 50% of CRC patients at the initial visit or immediately after surgery. The median survival time of patients who underwent radical resection of liver metastases was 35 months, and the 5-year survival rate was 30%-57% [5]. The median survival time of patients without radical resection of liver metastases was less than 7 months, and the 5-year survival rate was only 5%. Therefore, early detection of liver metastasis can significantly improve the long-term prognosis and reduce the mortality of CRC patients[6-8].

At present, imaging is the main method for detecting liver metastasis in CRC patients, but it has high equipment requirements, is strongly affected by the professional level of imaging doctors, and has high examination costs[9]. Therefore, a simple, economical, and objective detection method is urgently needed. Clinical studies have shown that abnormal changes in liver function indexes occur when malignant tumors develop liver metastases[10-12], so routine liver function index detection is expected to detect liver metastases early[13]. A new model for evaluating liver function, the albumin bilirubin (ALBI) score, which is composed of bilirubin and serum albumin (ALB) levels, has been proposed [14]. The liver function was divided into 3 levels: The higher the level was, the worse the liver function was. Recent studies have shown that ALBI scores correlate with the prognosis of a variety of cancers, including CRC with liver

metastases, resectable gastric cancer, and resectable pancreatic cancer[15]. Carcinoembryonic antigen (CEA) is a widely recognized broad-spectrum tumor marker[16]. The detection of serum CEA levels before and after surgery can predict hepatic and occult metastasis of CRC. Several studies have shown that patients with a serum CEA concentration ≥ 15 μg/L after CRC surgery are at increased risk of distant metastasis[17-19].

Currently, there are no studies that have integrated the ALBI score with traditional liver function markers and CEA to predict CRC hepatic metastases. This study aimed to investigate the predictive value of a certain factor for CRC liver metastasis and to offer novel insights for the clinical identification and prediction of such metastasis.

MATERIALS AND METHODS

Study subjects and categorization

This retrospective analysis involved CRC patients who underwent surgery in our hospital between January 2018 and July 2023. The inclusion criteria for patients were as follows: (1) Had CRC confirmed through surgical pathology; (2) Had complete laboratory blood routine examination and tumor marker detection data; and (3) Had no prior treatment with chemoradiotherapy or hormone therapy before admission.

The exclusion criteria were as follows: (1) Had a follow-up duration of less than 24 months; (2) Had liver lesions in patients with liver metastasis confirmed as noncolorectal metastatic carcinoma by pathology or history combined with imaging; (3) Had a history of other malignant tumors or blood system diseases; and (4) Had primary malignant tumors at other sites.

According to the incidence of liver metastasis within 24 months after discharge, CRC patients were divided into a liver metastasis group and a nonliver metastasis group and randomly divided into a modeling group and a verification group at a ratio of 2:1. This research was approved by the Ethics Committee of Xiangya Hospital of Central South University (Approval number: 2023A-402), and patients who provided informed consent were excluded.

Data collection

The basic information of the patients, including age, sex, body mass index, primary tumor location, past history, prehospital treatment, preoperative laboratory examination, imaging results, and postoperative pathological diagnosis, was obtained through the electronic medical records system. The laboratory test results included aspartate aminotransferase/alanine aminotransferase transferase (AST/ALT), total protein (TP), ALB, globulin (GLO), ALB/GLO (A/G), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), alpha-fetoprotein (AFP), CEA, carbohydrate antigen 125 (CA125), and CA19-9 levels. The ALBI score was calculated based on the results of laboratory tests. Follow-up information was obtained *via* electronic medical records or telephone consultations.

Sample size estimation

The sample size was estimated according to the formula: $n = Z^2 \times P \times (1\text{-}P)/d^2$. Previous studies reported that the incidence of postoperative liver metastasis in CRC patients was 15%-25%, that is, $P = 15\%$, $Z = 1.96$, $d = 0.05$, and the minimum sample size of CRC patients was calculated to be 196.

Bias control analysis

The research subjects were selected strictly according to the inclusion and exclusion criteria. Data were entered and checked by two people to minimize subjective bias.

Statistical analysis

SPSS 26.0 (IBM Corp., Armonk, NY, United States) and R 4.2.2 software were used for the statistical analysis. The Wilcoxon rank sum test was used for comparisons between groups. Counting data are expressed as a percentage of cases, and a χ^2 test was used for comparisons between groups. In the modeling group, with the occurrence of liver metastasis as the dependent variable, least absolute shrinkage and selection operator (LASSO) regression variables were screened using the "glmnet" package, and the best λ value was selected through 10-fold cross-validation. The LASSO logistic regression model was constructed using the forward LR method, the receiver operating characteristic (ROC) curve was plotted, the area under the ROC curve (AUC) was calculated, its differentiation was evaluated, and the calibration curve and clinical decision curve were used to analyze its calibration and clinical benefit. At the same time, the bootstrap method was used to verify the modeling group internally. For the bilateral test, $P < 0.05$ indicated a statistically significant difference.

RESULTS

General patient data collection and analysis

Finally, 195 CRC patients who met the inclusion and exclusion criteria were enrolled in this study, and the enrollment process is shown in Figure 1. There were 113 males and 82 females. The average age was 60.05 ± 12.3 years, ranging from 26 to 90 years. The differences between the two groups in the primary tumor location, total bilirubin, direct bilirubin, ALT, AST, ALT/AST, TP, ALB, A/G, GGT, ALP, CEA, CA125, CA19-9, and ALBI scores were statistically significant ($P < 0.05$) (Table 1).

Table 1 Baseline data between liver metastasis group and non-liver metastasis group (*n* = 195)

Index	Liver metastases group (*n* = 70)	Non-liver metastases group (*n* = 125)	*P* value
Age (mean ± SD, yr)	58.3 ± 12.5	61.7 ± 12.0	0.067
Gender, *n* (%)			0.865
Man	40 (57.1)	73 (58.4)	
Female	30 (42.9)	52 (41.6)	
Primary tumor location, *n* (%)			0.042
Colon	38 (54.3)	49 (39.2)	
Rectum	32 (45.7)	76 (60.8)	
BMI, M (P_{25}, P_{75}), kg/m^2	22.5 (21.4, 24.7)	22.1 (20.2, 25.0)	0.28
TBIL, M (P_{25}, P_{75}), μmol/L	14.9 (11.6, 24.7)	12.8 (9.4, 16.9)	0.001
DBIL, M (P_{25}, P_{75}), μmol/L	7.2 (4.3, 10.6)	3.3 (2.3, 5.4)	< 0.001
IBIL, M (P_{25}, P_{75}), μmol/L	9.3 (5.2, 14.3)	8.8 (6.0, 12.1)	0.642
ALT, M (P_{25}, P_{75}), U/L	31.5 (16.0, 54.8)	17.0 (10.0, 25.0)	< 0.001
AST, M (P_{25}, P_{75}), U/L	40.0 (27.8, 87.3)	20.0 (16.0, 25.5)	< 0.001
AST/ALT, M (P_{25}, P_{75})	1.6 (1.1, 2.2)	1.4 (0.9, 1.7)	0.005
TP, M (P_{25}, P_{75}), g/L	65.1 (58.9, 70.6)	69.4 (64.3, 73.4)	0.001
ALB, M (P_{25}, P_{75}), g/L	36.3 (29.5, 40.2)	41.4 (38.3, 44.1)	< 0.001
GLO, M (P_{25}, P_{75}), g/L	29.3 (24.7, 33.5)	28.3 (24.0, 31.0)	0.124
A/G (mean ± SD)	1.2 ± 0.4	1.5 ± 0.3	< 0.001
GGT, M (P_{25}, P_{75}), U/L	59.0 (25.8, 148.0)	18.0 (13.0, 25.5)	< 0.001
ALP, M (P_{25}, P_{75}), U/L	122.5 (77.5, 211.0)	76.0 (63.0, 90.5)	< 0.001
AFP, M (P_{25}, P_{75}), μg/L	2.6 (1.6, 3.4)	2.5 (1.8, 3.2)	0.845
CEA, M (P_{25}, P_{75}), μg/L	79.5 (12.5, 476.0)	2.9 (1.8, 5.9)	< 0.001
CA125, M (P_{25}, P_{75}), U/mL	21.3 (11.0, 54.7)	11.1 (7.9, 16.7)	< 0.001
CA19-9, M (P_{25}, P_{75}), U/mL	85.5 (17.3, 801.7)	10.9 (7.5, 17.0)	< 0.001
ALBI score, M (P_{25}, P_{75})	-2.3 (-2.7, -1.6)	-2.8 (-3.0, -2.6)	< 0.001

BMI: Body mass index; TBIL: Total bilirubin; DBIL: Direct bilirubin; IBIL: Indirect bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TP: Total protein; ALB: Albumin; GLO: Globulin; A/G: Albumin/globulin; GGT: Gamma-glutamyltransferase; ALP: Alkaline phosphatase; AFP: Alpha-fetoprotein; CEA: Carcinoembryonic antigen; CA125: Carbohydrate antigen 125; ALBI: Albumin bilirubin.

The patients were randomly divided into a modeling group (130 patients) and a verification group (65 patients) at a ratio of 2:1. In the modeling group, there were 50 patients with liver metastasis and 80 patients without liver metastasis. In the verification group, there were 20 patients with liver metastasis and 45 patients without liver metastasis. There was no significant difference in the basic data between the two groups (all $P > 0.05$), as shown in Table 2.

Construction of the LASSO logistic regression prediction model

In the modeling group, variable screening was performed using LASSO regression with whether patients developed liver metastases as the dependent variable, and the optimal λ value was selected through 10-fold cross-validation (Figure 2). In this study, λmin was selected as the best λ value, LASSO regression and the forward LR method were applied for logistic analysis (Table 3). Based on the results of the statistical regression analysis, three variables, ALBI, ALT, and CEA, were included in the statistical regression prediction model.

Internal evaluation and internal verification of the prediction models

In the modeling group, the AUC of the ALBI score and the combination of ALT and CEA for the prediction of liver metastasis in patients with CRC was 0.921 (Figure 3), the sensitivity was 78.0%, the specificity was 95.0% (Table 4). For the data of the modeling group, the internal verification of 1000 samples was carried out by the bootstrap method (Figures 4 and 5). The accuracy was 0.869, the kappa consistency was 0.709, and the AUC was 0.913. When the ALT, CEA, and ALBI scores were used to diagnose CRC liver metastases alone, the bottom of the curve of CEA was the largest (AUC = 0.897),

Table 2 Baseline data between modeling group and validation group (*n* = 195)

Index	Modeling group (*n* = 130)	Validation group (*n* = 65)	*P* value
Age (mean ± SD, yr)	60.3 ± 11.8	60.8 ± 31.2	0.772
Gender, *n* (%)			0.473
Man	73 (56.2)	40 (61.5)	
Female	57 (43.8)	25 (38.5)	
Primary tumor location, *n* (%)			0.222
Colon	62 (47.7)	25 (38.5)	
Rectum	68 (52.3)	40 (61.5)	
BMI, M (P_{25}, P_{75}), kg/m^2	22.3 (20.3, 24.9)	22.0 (20.6, 25.0)	0.992
TBIL, M (P_{25}, P_{75}), μmol/L	13.3 (10.2, 18.0)	14.0 (9.6, 18.7)	0.825
DBIL, M (P_{25}, P_{75}), μmol/L	4.7 (2.8, 7.3)	3.9 (2.7, 7.1)	0.462
IBIL, M (P_{25}, P_{75}), μmol/L	8.7 (5.5, 11.9)	9.6 (5.6, 13.0)	0.412
ALT, M (P_{25}, P_{75}), U/L	17.5 (11.0, 31.0)	20.0 (11.0, 33.0)	0.518
AST, M (P_{25}, P_{75}), U/L	24.5 (17.0, 36.0)	24.0 (17.5, 38.0)	0.846
AST/ALT, M (P_{25}, P_{75})	1.4 (0.9, 1.8)	1.4 (0.9, 1.9)	0.715
TP, M (P_{25}, P_{75}), g/L	68.3 (63.8, 72.9)	67.1 (61.8, 73.0)	0.348
ALB, M (P_{25}, P_{75}), g/L	40.1 (35.8, 43.5)	39.1 (36.8, 42.7)	0.666
GLO, M (P_{25}, P_{75}), g/L	28.7 (24.4, 32.4)	28.4 (24.0, 31.4)	0.556
A/G (mean ± SD)	1.4 ± 0.4	1.4 ± 0.3	0.991
GGT, M (P_{25}, P_{75}), U/L	22.5 (14.0, 52.3)	22.0 (14.5, 40.5)	0.828
ALP, M (P_{25}, P_{75}), U/L	80.0 (63.8, 111.0)	86.0 (67.0, 110.0)	0.606
AFP, M (P_{25}, P_{75}), μg/L	2.5 (1.7, 3.3)	2.7 (1.6,3.2)	0.607
CEA, M (P_{25}, P_{75}), μg/L	4.7 (2.0, 33.3)	5.3 (2.5, 35.3)	0.514
CA125, M (P_{25}, P_{75}), U/mL	12.6 (8.6, 23.2)	31.2 (9.1, 22.7)	0.792
CA19-9, M (P_{25}, P_{75}), U/mL	13.9 (8.1, 52.6)	15.2 (8.2, 52.4)	0.697
ALBI score, M (P_{25}, P_{75})	-2.7 (-2.9, -2.3)	-2.7 (-2.9, -2.4)	0.522

BMI: Body mass index; TBIL: Total bilirubin; DBIL: Direct bilirubin; IBIL: Indirect bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TP: Total protein; ALB: Albumin; GLO: Globulin; A/G: Albumin/globulin; GGT: Gamma-glutamyltransferase; ALP: Alkaline phosphatase; AFP: Alpha-fetoprotein; CEA: Carcinoembryonic antigen; CA125: Carbohydrate antigen 125; ALBI: Albumin bilirubin.

Table 3 Multivariate Logistic regression analysis of factors influence liver metastasis of colorectal cancer

Variable	β	Error	Wald	Freedom	*P* value	OR	95%CI	
							Lower limit	Upper limit
ALT (U/L)	0.036	0.017	4.734	1	0.030	1.037	1.004	1.071
CEA (μg/L)	0.025	0.009	8.017	1	0.005	1.025	1.008	1.043
ALBI score	2.087	0.588	12.588	1	0.000	8.062	2.545	25.540
Constant term	3.047	1.555	3.839	1	0.050	21.058	-	

ALT: Alanine aminotransferase; CEA: Carcinoembryonic antigen; ALBI: Albumin bilirubin; OR: Odds ratio; CI: Confidence interval.

Table 4 Diagnostic efficacy between individual and combined detection of alanine aminotransferase, carcinoembryonic antigen, and albumin bilirubin score in modeling group

Testing index	AUC	Sensitivity (%)	Specificity (%)	*P* value
ALT	0.704	58.0	85.0	< 0.001
CEA	0.897	84.0	87.5	< 0.00
ALBI score	0.825	84.0	72.5	< 0.001
ALT combined with CEA	0.896	80.0	912	< 0.00
ALT combined with ALBI score	0.858	80.0	78.7	< 0.001
CEA combined with ALBI score	0. 91	82.0	86.3	< 0.001
Combination of the three	0.921	78.0	95.0	< 0.001

ALT: Alanine aminotransferase; CEA: Carcinoembryonic antigen; ALBI: Albumin bilirubin; AUC: Area under the receiver operating characteristic curve.

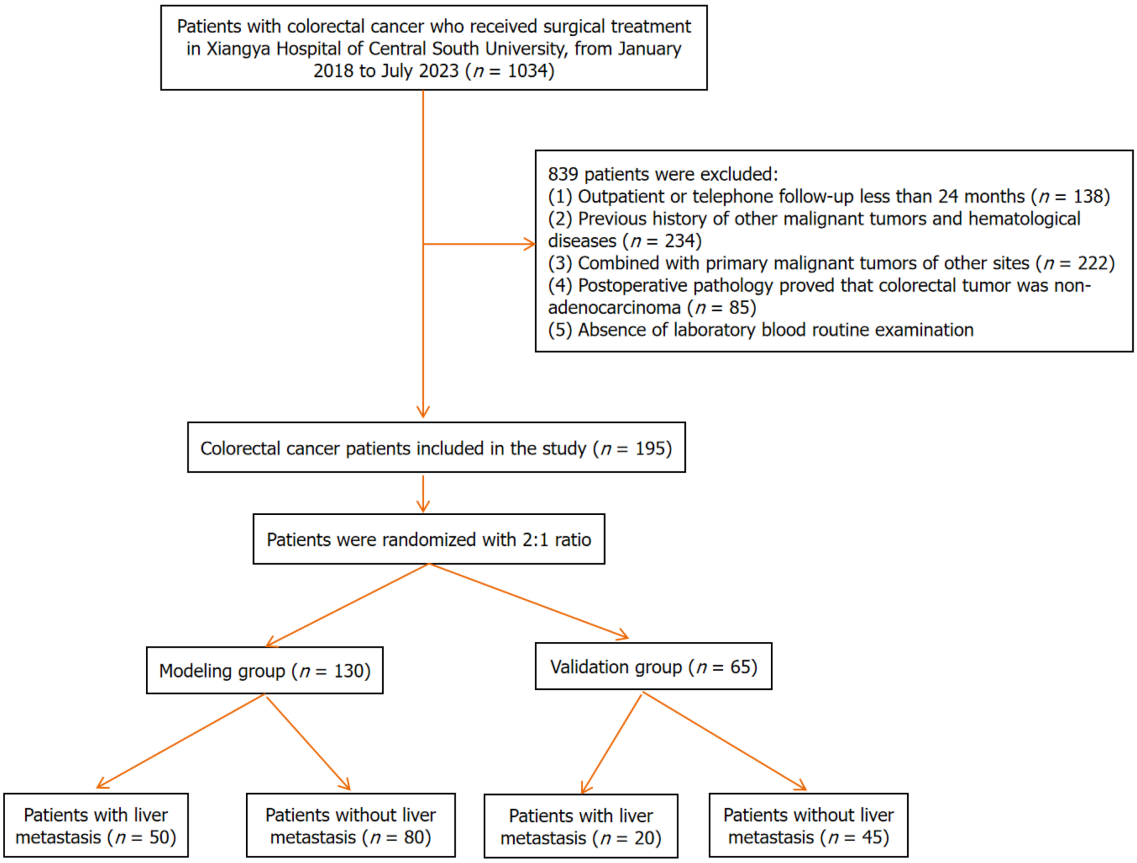


Figure 1 Patient inclusion and randomization flow charts.

and the combined performance of the three was the highest in diagnosing CRC liver metastases (Table 4). The combined prediction of the AUC of the verification group was 0.918 (Figure 3), the sensitivity of spirit was 85.0%, the specificity was 95.6% (Table 5), the C-index was 0.918, and the H-L fitting curve $\chi^2 = 0.586$, $P = 0.746$.

Visualization of risk prediction models

Based on the results of the statistical regression analysis, a column graph of liver metastasis in CRC was drawn, as shown in Figure 6. For example, if the ALBI score of a certain research object is -3.0, 100 μg/L CEA, and 50 U/L ALT are projected vertically to the scoring axis, and the obtained scores are added: 7 + 10 + 4 = 21. The corresponding position of 21 points on the total score axis was found, and the predicted risk value projected vertically down to the risk axis of CRC liver metastasis was approximately 0.70.

Table 5 Diagnostic efficacy between individual and combined detection of alanine aminotransferase, carcinoembryonic antigen, and albumin bilirubin score in verification group

Testing index	AUC	Sensitivity (%)	Specificity (%)	*P* value
ALT	0.774	75.0	73.3	< 0.001
CEA	0.864	75.0	88.9	< 0.001
ALBI score	0.659	45.0	97.8	0.042
ALT combined with CEA	0.916	85.0	95.6	< 0.001
ALT combined with ALBI score	0.784	60.0	91.1	< 0.001
CEA combined with ALBI score	0.834	70.0	100.0	< 0.001
Combination of the three	0.918	85.0	95.6	< 0.001

ALT: Alanine aminotransferase; CEA: Carcinoembryonic antigen; ALBI: Albumin bilirubin; AUC: Area under the receiver operating characteristic curve.

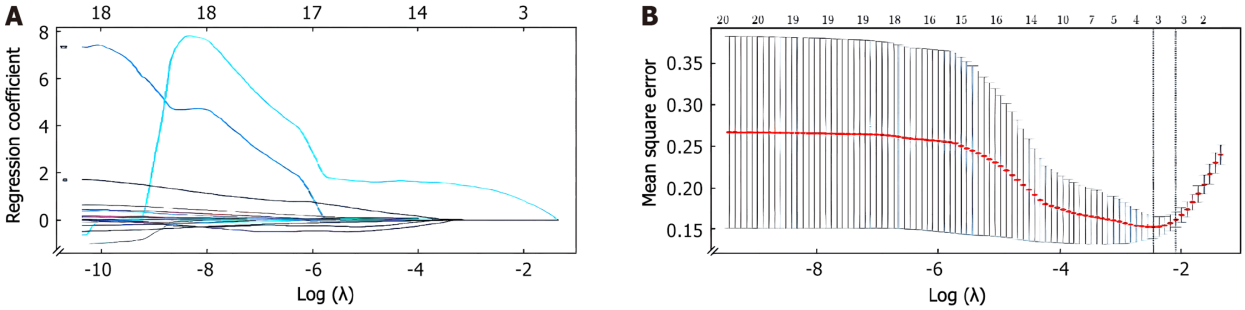


Figure 2 Feature variable selection based on least absolute shrinkage and selection operator regression. A: Tenfold cross-validation chart; B: Shrinkage coefficient chart.

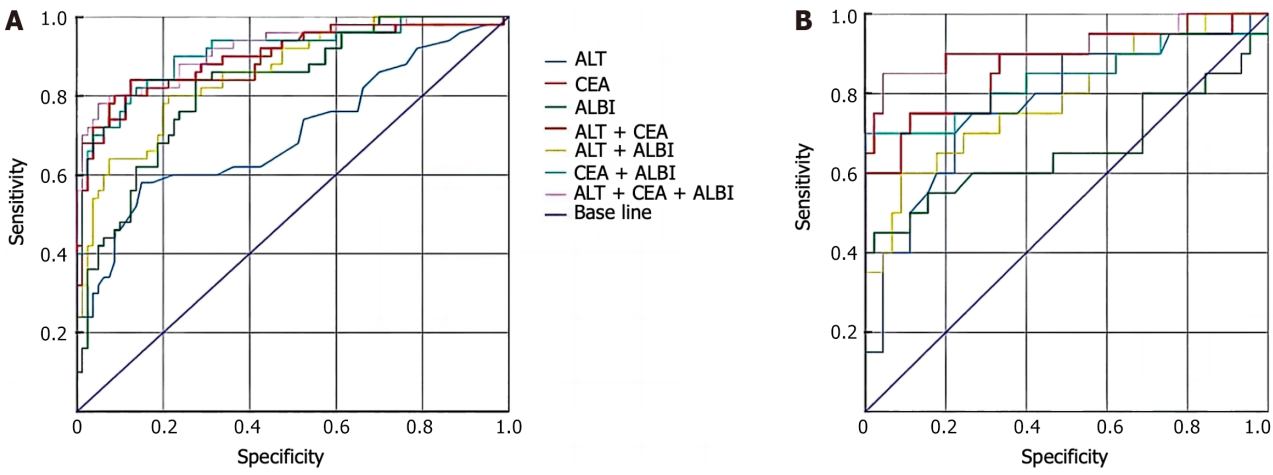


Figure 3 Receiver operating characteristic curve of the model for predicting liver metastasis in patients with colorectal cancer. A: Modeling group; B: Verification group. ALT: Alanine aminotransferase; CEA: Carcinoembryonic antigen; ALBI: Albumin-bilirubin.

DISCUSSION

Based on the analysis of the patient's ALBI score, conventional liver function indicators, tumor markers, *etc.*, this study concluded that the ALBI score, ALT level, and CEA level were independent predictors of the occurrence of liver metastases in CRC patients. The prediction model was then established by statistical logistic regression[20-22]. H-L fitting curve: χ^2 = 0.586, P = 0.746. These results indicate that the combined prediction of CRC liver metastasis is effective, and the risk prediction model constructed by the three methods has good clinical application prospects.

Due to the small number and low concentration of tumor cells in CRC liver metastases, routine imaging examinations (such as computed tomography, magnetic resonance imaging, *etc.*) cannot make an early diagnosis of CRC liver

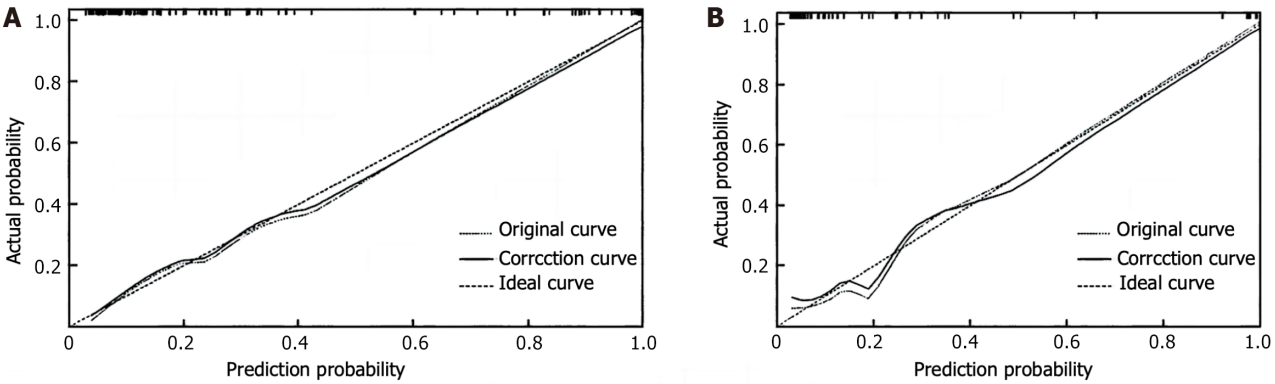


Figure 4 Calibration curves of the least absolute shrinkage and selection operator logistic regression model. A: Modeling group; B: Verification group.

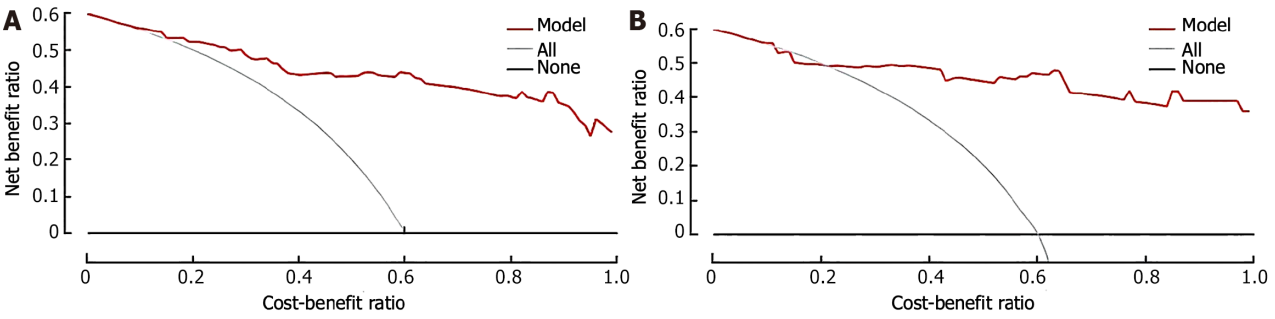


Figure 5 Decision curve analysis of the least absolute shrinkage and selection operator logistic regression model. A: Modeling group; B: Verification group.

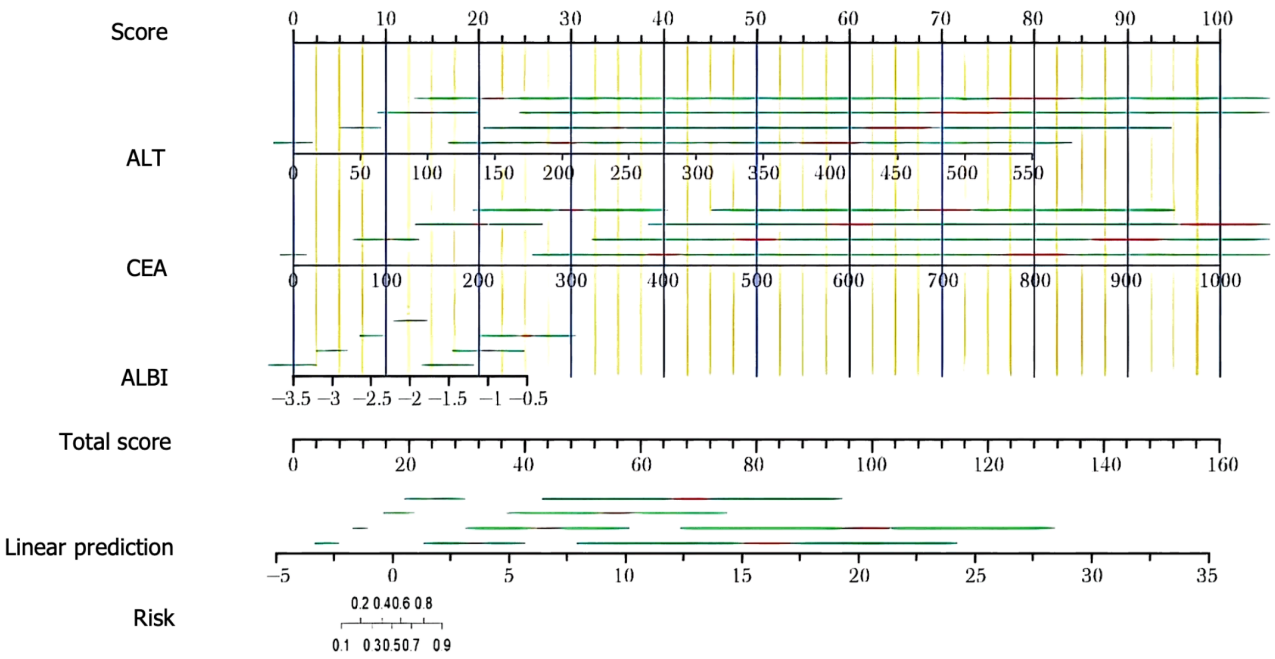


Figure 6 Nomogram prediction model for liver metastasis of colorectal cancer. ALT: Alanine aminotransferase; CEA: Carcinoembryonic antigen; ALBI: Albumin-bilirubin.

metastases[23]. Therefore, it is urgent to find a better method to accurately identify CRC liver metastases at an early stage [24-26]. CEA is present in malignant tumors of the gastrointestinal tract and pancreatic endoderm-derived epithelium, is overexpressed in CRC patients, and is distributed throughout the cell membrane. Previous studies have shown that high CEA expression is significantly correlated with CRC metastasis[27-29]. Serum CEA increases 6 months before imaging findings of liver metastases, and serum CEA, CA19-9, and AFP are significantly greater in CRC patients with liver metastases than in those without liver metastases[30]. The mechanism underlying the correlation between high CEA expression and CRC liver metastasis is as follows: CEA reduces the death of cancer cells in the blood by inhibiting apoptosis. CEA binds to the Kupffer cell receptor protein and changes the liver microenvironment, which is conducive to the survival of cancer cells. CEA upregulates cell adhesion molecules associated with metastasis. Recent studies have suggested that CEA reexamination every 2-3 months after CRC surgery is helpful for the early detection of liver metastasis[31-33]. Another study reported that the sensitivity of serum CEA in the diagnosis of CRC liver metastasis was only 36.5%[34], which made it difficult to meet the requirements of early detection of liver metastasis. The level of CEA in advanced CRC patients and other gastrointestinal malignancies is significantly increased, but early CEA detection alone may result in false-positive and false-negative results in the diagnosis of CRC liver metastases, and the diagnostic accuracy is low[35-37].

Following the introduction of the ALBI score, several studies have applied it to the prediction of CRC liver metastases, resectable gastric cancer, and resectable pancreatic cancer[38]. Compared with the Child-Pugh score, the most commonly used liver function evaluation index in clinical practice, the ALBI measures two subjective indicators of hepatic encephalopathy and ascites. In addition, data acquisition is more convenient[39]. However, the ALBI score contains only two indicators, there is no upper limit effect, and the ALBI score is biased if the patient has hypoproteinaemia or hyperbilirubinemia (such as obstructive jaundice)[40]. In addition, this score was originally proposed for liver cancer patients without considering the influence of other causes, and further studies are needed to confirm its practicality and accuracy for detecting liver function abnormalities caused by other causes. The above studies suggest that there are certain limitations in predicting CRC liver metastasis based only on tumor markers, liver function, and other single indicators, which may easily lead to misdiagnosis and missed diagnosis[41]. Therefore, in this study, the ALBI score was combined with conventional liver function indicators and CEA to detect CRC liver metastasis at an early stage.

The C-index of the CRC liver metastasis risk prediction model established in this study based on the ALBI score, ALT, and CEA was 0.921 and 0.918, respectively, in the modeling group and verification group, and the correlation between the two curves in the calibration chart was good and consistent[42]. The clinical decision curve also showed good clinical application value. According to the analysis, the AUCs of the ALBI score, ALT level, CEA level, and their combination for predicting CRC liver metastasis were 0.825, 0.704, 0.897, and 0.921, respectively. With the introduction of the ALBI score, several studies have applied it to the prediction of CRC liver metastasis, resectable gastric cancer, and resectable pancreatic cancer[43]. Compared with the Child-Pugh score, which is the most commonly used liver function indicator in clinical practice, the ALBI removes two subjective indicators, namely, hepatic encephalopathy and ascites, and data acquisition is more convenient. However, the ALBI score contains only two indicators, there is no upper limit effect, and the ALBI score is biased if the patient has hypoproteinaemia or hyperbilirubinemia (such as obstructive jaundice). In addition, this score was originally proposed based on liver cancer patients without considering the influence of other causes, and further studies are needed to confirm its practicality and accuracy for detecting liver function abnormalities caused by other causes[44]. The above studies suggest that there are certain limitations in predicting CRC liver metastasis based only on tumor markers, liver function, and other single indicators, which may easily lead to misdiagnosis and missed diagnosis. Therefore, in this study, the ALBI score was combined with conventional liver function indicators and CEA to detect CRC liver metastasis at an early stage.

This study has the following shortcomings: (1) As a single-center retrospective study, there may be bias in case selection; and (2) Because of the lack of multicenter data for external validation of the model, large sample sizes and multicenter clinical data are still needed to improve the validity and reliability of the model.

CONCLUSION

In summary, the ALBI score combined with the ALT and CEA levels has high specificity and accuracy in predicting CRC liver metastasis and will be valuable for improving the diagnosis and treatment of CRC liver metastasis patients.

FOOTNOTES

Author contributions: Wang ZM wrote the manuscript; Pan SP and Zhang JJ collected the data; Zhou J guided the study; and all authors reviewed, edited, and approved the final manuscript and revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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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 technical appendix, statistical code, and dataset are available from the corresponding author at email: dr.zhouj@163.com.

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REFERENCES

1 **Bretthauer M**, Løberg M, Wieszczy P, Kalager M, Emilsson L, Garborg K, Rupinski M, Dekker E, Spaander M, Bugajski M, Holme Ø, Zauber AG, Pilonis ND, Mroz A, Kuipers EJ, Shi J, Hernán MA, Adami HO, Regula J, Hoff G, Kaminski MF; NordICC Study Group. Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death. *N Engl J Med* 2022; **387**: 1547-1556 [PMID: 36214590 DOI: 10.1056/NEJMoa2208375]

2 **Burnett-Hartman AN**, Lee JK, Demb J, Gupta S. An Update on the Epidemiology, Molecular Characterization, Diagnosis, and Screening Strategies for Early-Onset Colorectal Cancer. *Gastroenterology* 2021; **160**: 1041-1049 [PMID: 33417940 DOI: 10.1053/j.gastro.2020.12.068]

3 **Ladabaum U**, Dominitz JA, Kahi C, Schoen RE. Strategies for Colorectal Cancer Screening. *Gastroenterology* 2020; **158**: 418-432 [PMID: 31394083 DOI: 10.1053/j.gastro.2019.06.043]

4 **Champion VL**, Christy SM, Rakowski W, Lairson DR, Monahan PO, Gathirua-Mwangi WG, Stump TE, Biederman EB, Kettler CD, Rawl SM. An RCT to Increase Breast and Colorectal Cancer Screening. *Am J Prev Med* 2020; **59**: e69-e78 [PMID: 32690203 DOI: 10.1016/j.amepre.2020.03.008]

5 **Mannucci A**, Zuppardo RA, Rosati R, Leo MD, Perea J, Cavestro GM. Colorectal cancer screening from 45 years of age: Thesis, antithesis and synthesis. *World J Gastroenterol* 2019; **25**: 2565-2580 [PMID: 31210710 DOI: 10.3748/wjg.v25.i21.2565]

6 **Bailey JR**, Aggarwal A, Imperiale TF. Colorectal Cancer Screening: Stool DNA and Other Noninvasive Modalities. *Gut Liver* 2016; **10**: 204-211 [PMID: 26934885 DOI: 10.5009/gnl15420]

7 **Wolf AMD**, Fontham ETH, Church TR, Flowers CR, Guerra CE, LaMonte SJ, Etzioni R, McKenna MT, Oeffinger KC, Shih YT, Walter LC, Andrews KS, Brawley OW, Brooks D, Fedewa SA, Manassaram-Baptiste D, Siegel RL, Wender RC, Smith RA. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J Clin* 2018; **68**: 250-281 [PMID: 29846947 DOI: 10.3322/caac.21457]

8 **Emile SH**, Barsom SH, Wexner SD. An updated review of the methods, guidelines of, and controversies on screening for colorectal cancer. *Am J Surg* 2022; **224**: 339-347 [PMID: 35367029 DOI: 10.1016/j.amjsurg.2022.03.034]

9 **Gupta S**, Sussman DA, Doubeni CA, Anderson DS, Day L, Deshpande AR, Elmunzer BJ, Laiyemo AO, Mendez J, Somsouk M, Allison J, Bhuket T, Geng Z, Green BB, Itzkowitz SH, Martinez ME. Challenges and possible solutions to colorectal cancer screening for the underserved. *J Natl Cancer Inst* 2014; **106**: dju032 [PMID: 24681602 DOI: 10.1093/jnci/dju032]

10 **Murphy CC**, Halm EA, Zaki T, Johnson C, Yekkaluri S, Quirk L, Singal AG. Colorectal Cancer Screening and Yield in a Mailed Outreach Program in a Safety-Net Healthcare System. *Dig Dis Sci* 2022; **67**: 4403-4409 [PMID: 34800219 DOI: 10.1007/s10620-021-07313-7]

11 **Holden DJ**, Harris R, Porterfield DS, Jonas DE, Morgan LC, Reuland D, Gilchrist M, Viswanathan M, Lohr KN, Lyda-McDonald B. Enhancing the use and quality of colorectal cancer screening. *Evid Rep Technol Assess (Full Rep)* 2010; 1-195, v [PMID: 20726624]

12 **Wu L**, Zheng Y, Liu J, Luo R, Wu D, Xu P, Li X. Comprehensive evaluation of the efficacy and safety of LPV/r drugs in the treatment of SARS and MERS to provide potential treatment options for COVID-19. *Aging (Albany NY)* 2021; **13**: 10833-10852 [PMID: 33879634 DOI: 10.18632/aging.202860]

13 **Wheeler SB**, Leeman J, Hassmiller Lich K, Tangka FKL, Davis MM, Richardson LC. Data-Powered Participatory Decision Making: Leveraging Systems Thinking and Simulation to Guide Selection and Implementation of Evidence-Based Colorectal Cancer Screening Interventions. *Cancer J* 2018; **24**: 136-143 [PMID: 29794539 DOI: 10.1097/PPO.0000000000000317]

14 **Berger BM**, Ahlquist DA. Stool DNA screening for colorectal neoplasia: biological and technical basis for high detection rates. *Pathology* 2012; **44**: 80-88 [PMID: 22198259 DOI: 10.1097/PAT.0b013e3283502fdf]

15 **Randel KR**, Schult AL, Botteri E, Hoff G, Bretthauer M, Ursin G, Natvig E, Berstad P, Jørgensen A, Sandvei PK, Olsen ME, Frigstad SO, Darre-Næss O, Norvard ER, Bolstad N, Kørner H, Wibe A, Wensaas KA, de Lange T, Holme Ø. Colorectal Cancer Screening With Repeated Fecal Immunochemical Test Versus Sigmoidoscopy: Baseline Results From a Randomized Trial. *Gastroenterology* 2021; **160**: 1085-1096.e5 [PMID: 33227280 DOI: 10.1053/j.gastro.2020.11.037]

16 **Wu L**, Li H, Liu Y, Fan Z, Xu J, Li N, Qian X, Lin Z, Li X, Yan J. Research progress of 3D-bioprinted functional pancreas and *in vitro* tumor models. *IJB* 2024; **10**: 1256 [DOI: 10.36922/ijb.1256]

17 **Wu L**, Zhong Y, Wu D, Xu P, Ruan X, Yan J, Liu J, Li X. Immunomodulatory Factor TIM3 of Cytolytic Active Genes Affected the Survival and Prognosis of Lung Adenocarcinoma Patients by Multi-Omics Analysis. *Biomedicines* 2022; **10** [PMID: 36140350 DOI: 10.3390/biomedicines10092248]

18 **Kisiel JB**, Eckmann JD, Limburg PJ. Multitarget Stool DNA for Average Risk Colorectal Cancer Screening: Major Achievements and Future

Directions. *Gastrointest Endosc Clin N Am* 2020; **30**: 553-568 [PMID: 32439088 DOI: 10.1016/j.giec.2020.02.008]
19 **Dodou D**, de Winter JC. Agreement between self-reported and registered colorectal cancer screening: a meta-analysis. *Eur J Cancer Care (Engl)* 2015; **24**: 286-298 [PMID: 24754544 DOI: 10.1111/ecc.12204]
20 **Williams CD**, Grady WM, Zullig LL. Use of NCCN Guidelines, Other Guidelines, and Biomarkers for Colorectal Cancer Screening. *J Natl Compr Canc Netw* 2016; **14**: 1479-1485 [PMID: 27799515 DOI: 10.6004/jnccn.2016.0154]
21 **Pettit N**, Ceppa D, Monahan P. Low Rates of Lung and Colorectal Cancer Screening Uptake Among a Safety-net Emergency Department Population. *West J Emerg Med* 2022; **23**: 739-745 [PMID: 36205665 DOI: 10.5811/westjem.2022.5.55351]
22 **Brandhof SD**, Fagerlin A, Hawley S, Toes-Zoutendijk E, Trevena L, McCaffery K, Korfage IJ. Colorectal cancer screening: Associations between information provision, attitudes and intended participation. *Patient Educ Couns* 2018; **101**: 546-550 [PMID: 28899711 DOI: 10.1016/j.pec.2017.08.021]
23 **Wu L**, Liu Q, Ruan X, Luan X, Zhong Y, Liu J, Yan J, Li X. Multiple Omics Analysis of the Role of RBM10 Gene Instability in Immune Regulation and Drug Sensitivity in Patients with Lung Adenocarcinoma (LUAD). *Biomedicines* 2023; **11** [PMID: 37509501 DOI: 10.3390/biomedicines11071861]
24 **Wu L**, Li X, Qian X, Wang S, Liu J, Yan J. Lipid Nanoparticle (LNP) Delivery Carrier-Assisted Targeted Controlled Release mRNA Vaccines in Tumor Immunity. *Vaccines (Basel)* 2024; **12** [PMID: 38400169 DOI: 10.3390/vaccines12020186]
25 **Zhu X**, Weiser E, Jacobson DJ, Griffin JM, Limburg PJ, Finney Rutten LJ. Patient preferences on general health and colorectal cancer screening decision-making: Results from a national survey. *Patient Educ Couns* 2022; **105**: 1034-1040 [PMID: 34340846 DOI: 10.1016/j.pec.2021.07.033]
26 **Ameen S**, Wong MC, Yee KC, Nøhr C, Turner P. AI Diagnostic Technologies and the Gap in Colorectal Cancer Screening Participation. *Stud Health Technol Inform* 2022; **294**: 803-804 [PMID: 35612208 DOI: 10.3233/SHTI220588]
27 **Coronado GD**, Nielson CM, Keast EM, Petrik AF, Suls JM. The influence of multi-morbidities on colorectal cancer screening recommendations and completion. *Cancer Causes Control* 2021; **32**: 555-565 [PMID: 33687606 DOI: 10.1007/s10552-021-01408-2]
28 **Heisser T**, Hoffmeister M, Brenner H. Effects of screening for colorectal cancer: Development, documentation and validation of a multistate Markov model. *Int J Cancer* 2021; **148**: 1973-1981 [PMID: 33320964 DOI: 10.1002/ijc.33437]
29 **Wu L**, Zheng Y, Ruan X, Wu D, Xu P, Liu J, Li X. Long-chain noncoding ribonucleic acids affect the survival and prognosis of patients with esophageal adenocarcinoma through the autophagy pathway: construction of a prognostic model. *Anticancer Drugs* 2022; **33**: e590-e603 [PMID: 34338240 DOI: 10.1097/CAD.0000000000001189]
30 **Van Gossum A**. Guidelines for colorectal cancer screening--a puzzle of tests and strategies. *Acta Clin Belg* 2010; **65**: 433-436 [PMID: 21268961 DOI: 10.1179/acb.2010.65.6.012]
31 **Harper DM**, Tariq M, Alhawli A, Syed N, Patel M, Resnicow K. Cancer risk perception and physician communication behaviors on cervical cancer and colorectal cancer screening. *Elife* 2021; **10** [PMID: 34427182 DOI: 10.7554/eLife.70003]
32 **Bonafede MM**, Miller JD, Pohlman SK, Troeger KA, Sprague BL, Herschorn SD, Winer IH. Breast, Cervical, and Colorectal Cancer Screening: Patterns Among Women With Medicaid and Commercial Insurance. *Am J Prev Med* 2019; **57**: 394-402 [PMID: 31377088 DOI: 10.1016/j.amepre.2019.04.010]
33 **Ladabaum U**, Mannalithara A, Mitani A, Desai M. Clinical and Economic Impact of Tailoring Screening to Predicted Colorectal Cancer Risk: A Decision Analytic Modeling Study. *Cancer Epidemiol Biomarkers Prev* 2020; **29**: 318-328 [PMID: 31796524 DOI: 10.1158/1055-9965.EPI-19-0949]
34 **Joseph DA**, Meester RG, Zauber AG, Manninen DL, Winges L, Dong FB, Peaker B, van Ballegooijen M. Colorectal cancer screening: Estimated future colonoscopy need and current volume and capacity. *Cancer* 2016; **122**: 2479-2486 [PMID: 27200481 DOI: 10.1002/cncr.30070]
35 **Sekiguchi M**, Igarashi A, Sakamoto T, Saito Y, Esaki M, Matsuda T. Cost-effectiveness analysis of colorectal cancer screening using colonoscopy, fecal immunochemical test, and risk score. *J Gastroenterol Hepatol* 2020; **35**: 1555-1561 [PMID: 32167186 DOI: 10.1111/jgh.15033]
36 **Ylitalo KR**, Camp BG, Umstattd Meyer MR, Barron LA, Benavidez G, Hess B, Laschober R, Griggs JO. Barriers and Facilitators of Colorectal Cancer Screening in a Federally Qualified Health Center (FQHC). *J Am Board Fam Med* 2019; **32**: 180-190 [PMID: 30850454 DOI: 10.3122/jabfm.2019.02.180205]
37 **Wu L**, Zhong Y, Yu X, Wu D, Xu P, Lv L, Ruan X, Liu Q, Feng Y, Liu J, Li X. Selective poly adenylation predicts the efficacy of immunotherapy in patients with lung adenocarcinoma by multiple omics research. *Anticancer Drugs* 2022; **33**: 943-959 [PMID: 35946526 DOI: 10.1097/CAD.0000000000001319]
38 **Hardin V**, Tangka FKL, Wood T, Boisseau B, Hoover S, DeGroff A, Boehm J, Subramanian S. The Effectiveness and Cost to Improve Colorectal Cancer Screening in a Federally Qualified Homeless Clinic in Eastern Kentucky. *Health Promot Pract* 2020; **21**: 905-909 [PMID: 32990049 DOI: 10.1177/1524839920954165]
39 **Mojica CM**, Vargas N, Bradley S, Parra-Medina D. Barriers and Facilitators of Colonoscopy Screening Among Latino Men in a Colorectal Cancer Screening Promotion Program. *Am J Mens Health* 2023; **17**: 15579883231179325 [PMID: 37287187 DOI: 10.1177/15579883231179325]
40 **Soodejani MT**, Mirzaei H, Manesh MM, Tabatabaei SM, Ghaderi A. Incidence of Colorectal Cancer and Adenomatous Polyps After a Two-Step Screening in Isfahan Province, Iran in 2018. *J Gastrointest Cancer* 2020; **51**: 850-854 [PMID: 31656018 DOI: 10.1007/s12029-019-00313-x]
41 **Clark GR**, Digby J, Fraser CG, Strachan JA, Steele RJ. Faecal haemoglobin concentrations in women and men diagnosed with colorectal cancer in a national screening programme. *J Med Screen* 2022; **29**: 26-31 [PMID: 34806935 DOI: 10.1177/09691413211056970]
42 **Wu L**, Chen X, Zeng Q, Lai Z, Fan Z, Ruan X, Li X, Yan J. NR5A2 gene affects the overall survival of LUAD patients by regulating the activity of CSCs through SNP pathway by OCLR algorithm and immune score. *Heliyon* 2024; **10**: e28282 [PMID: 38601554 DOI: 10.1016/j.heliyon.2024.e28282]
43 **Davis MM**, Coury J, Larson JH, Gunn R, Towey EG, Ketelhut A, Patzel M, Ramsey K, Coronado GD. Improving colorectal cancer screening in rural primary care: Preliminary effectiveness and implementation of a collaborative mailed fecal immunochemical test pilot. *J Rural Health* 2023; **39**: 279-290 [PMID: 35703582 DOI: 10.1111/jrh.12685]
44 **Krul MF**, Elferink MAG, Kok NFM, Dekker E, Lansdorp-Vogelaar I, Meijer GA, Nagtegaal ID, Breekveldt ECH, Ruers TJM, van Leerdam ME, Kuhlmann KFD. Initial Impact of National CRC Screening on Incidence and Advanced Colorectal Cancer. *Clin Gastroenterol Hepatol* 2023; **21**: 797-807.e3 [PMID: 36116753 DOI: 10.1016/j.cgh.2022.08.046]

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ORIGINAL ARTICLE

Retrospective Study

Comparative analysis of the short and medium-term efficacy of the Da Vinci robot *versus* laparoscopic total mesangectomy for rectal cancer

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Abstract

BACKGROUND

The Da Vinci robot-assisted surgery technique has been widely used in laparoscopic mesangectomy for rectal cancer. However, the short-term efficacy of these procedures compared to traditional laparoscopic surgery remains controversial. The purpose of this study was to compare and analyze the short- and medium-term efficacy of Da Vinci robot and laparoscopic surgery in total mesangectomy (TME) for rectal cancer, so as to provide guidance and reference for clinical practice.

AIM

To investigate the safety and long-term efficacy of robotic and laparoscopic total mesorectal resection for the treatment of rectal cancer.

METHODS

The clinicopathologic data of 240 patients who underwent TME for rectal cancer in the Anorectal Department of People's Hospital of Xinjiang Uygur Autonomous Region from August 2018 to March 2023 were retrospectively analyzed. Among them, 112 patients underwent laparoscopic TME (L-TME) group, and 128 patients underwent robotic TME (R-TME) group. The intraoperative, postoperative, and follow-up conditions of the two groups were compared.

RESULTS

The conversion rate of the L-TME group was greater than that of the R-TME group (5.4% *vs* 0.8%, $\chi^2 = 4.417$, $P = 0.036$). The complication rate of the L-TME

group was greater than that of the R-TME group (32.1% *vs* 17.2%, χ^2 = 7.290, P = 0.007). The percentage of positive annular margins in the L-TME group was greater than that in the R-TME group (7.1% *vs* 1.6%, χ^2 = 4.658, P = 0.031). The 3-year disease-free survival (DFS) rate and overall survival (OS) rate of the L-TME group were lower than those of the R-TME group (74.1% *vs* 85.2%, χ^2 = 4.962, P = 0.026; 81.3% *vs* 91.4%, χ^2 = 5.494, P = 0.019); in patients with American Joint Committee on Cancer stage III DFS rate and OS rate in the L-TME group were significantly lower than those in the R-TME group (52.5% *vs* 76.1%, χ^2 = 5.799, P = 0.016; 65.0% *vs* 84.8%, χ^2 = 4.787, P = 0.029).

CONCLUSION

Compared with the L-TME group, the R-TME group had a better tumor prognosis and was more favorable for patients with rectal cancer, especially for patients with stage III rectal cancer.

Key Words: Rectal tumor; Robots; Laparoscopy; Total mesangectomy; Survival prognosis; Retrospective analysis

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Core Tip: This study compared the short- and medium-term efficacy of Da Vinci robot-assisted surgery with traditional laparoscopic surgery in total mesangectomy for rectal cancer, involving indexes such as operation time, postoperative complications, postoperative pain, and postoperative rehabilitation. By comparing and analyzing the advantages and disadvantages of the two surgical methods, the influence on the treatment effect and quality of life of the patients was evaluated, and the scientific basis for clinical decision-making was provided.

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INTRODUCTION

With the continuous development of medical technology, Da Vinci robot technology and laparoscopic mesangectomy for the treatment of rectal cancer have gradually emerged[1]. Rectal cancer is a common malignant tumor, and continuous innovations in its treatment are essential for improving the survival rate and quality of life of patients[2]. Due to its precision and minimal invasiveness, Da Vinci robot technology has gradually become a popular choice for rectal cancer surgery[3]. Compared with traditional surgical methods, the Da Vinch robot is more flexible during surgery, allowing doctors to complete complex anatomical structure resection under a highly enlarged field of view, which is expected to reduce the incidence of surgical complications[4-6]. On the other hand, laparoscopic mesangectomy for rectal cancer, as a representative traditional surgical method, has achieved remarkable efficacy in the treatment of rectal cancer, but its limitations and invasiveness are still problems that cannot be ignored. Studies have shown that the Da Vinci robot may have better operability in rectal cancer surgery, but whether it is more effective than laparoscopic surgery in the short or medium term still needs further research[7-9]. Therefore, the aim of this study was to comprehensively compare the short- and medium-term treatment effects of the Da Vinci robot and laparoscopic total mesangectomy (L-TME) for rectal cancer, providing clinicians with a more scientific and objective basis to optimize the selection of rectal cancer surgical programs[10]. The purpose of this study was to provide patients with safer and more effective surgical treatment, promote continuous progress in the field of rectal cancer surgery, and contribute to patient rehabilitation and quality of life.

With the widespread application of L-TME for rectal cancer, people have begun to pay attention to its long-term oncological outcomes[11]. Previous studies have shown that the short-term efficacy of L-TME is better than that of open surgery, but the long-term efficacy is similar. At present, many studies have confirmed the short-term tumor prognosis of robotic TME (R-TME) for rectal cancer[12]. However, only a few studies have reported its long-term efficacy, and the long-term oncological outcomes of L-TME and R-TME are still controversial. This study analyzed and compared the safety and long-term efficacy of R-TME and L-TME.

MATERIALS AND METHODS

General patient data analysis

This study was a retrospective study. Clinicopathological data of 240 patients with rectal cancer undergoing TME were collected from August 2018 to March 2023 in the Anorectal Department of People's Hospital of Xinjiang Uygur Autonomous Region, including 112 patients undergoing L-TME and 128 patients undergoing R-TME. Laparoscopic model: CLV-S190.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Colorectal adenocarcinoma confirmed by pathological biopsy. Preoperative computed tomography (CT) or magnetic resonance imaging (MRI) was performed to evaluate lymph node spread and determine the depth of tumor invasion. Tumor-node-metastasis (TNM) stages I-III were used. The tumor staging criteria used were the American Joint Committee on Cancer (AJCC)/Union International Against Cancer Colorectal Cancer TNM Staging System (8th edition); (2) Imaging examination ruled out liver, lung, and other distant metastases; and (3) Surgery was generally tolerated. The exclusion criteria for patients were as follows: (1) Had a tumor invading other adjacent organs; (2) Had serious underlying disease; (3) Had combined perforation, obstruction, or emergency surgery; (4) Had received neoadjuvant chemoradiotherapy before surgery; (5) Had undergone palliative resection; and (6) Had multiple colorectal cancers. All patients and their families signed informed consent before surgery. This study was approved by the Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences.

The following data were collected: (1) General information: Age, sex, body mass index (BMI), American Society of Anesthesiologists grade, preoperative serum carcinoembryonic antigen, tumor distance from the anal margin and distribution (as determined by electronic colonoscopy), clinical stage, comorbidities, NRS2002 score, low anterior rectal resection syndrome, International Questionnaire on Erectile Function-5, and follow-up A surname; (2) Perioperative indexes: Conversion rate of laparotomy, postoperative hospital stay, postoperative complications, and Clavien-Dindo grade; (3) Oncological results: The number of lymph nodes removed, pathological grade, AJCC stage, positive rate of annular margin, vascular and nerve invasion, and mesorectal excision (complete: Complete mesenteric tissue, smooth surface, defect depth ≤ 5 mm; nearly complete: The mesangial tissue surface was irregular, the defect depth was ≥ 5 mm; and the musculi propria was not reached). Incomplete: Small mesangial tissue defects as deep as the muscularis propria; and (4) Survival analysis: Disease-free survival (DFS), overall survival (OS), local recurrence, and distant metastasis. The 3-year DFS was defined as the percentage of patients who were free of disease recurrence within 3 years; the 3-year OS was defined as the percentage of patients who were still alive at 3 years of follow-up after surgery.

Surgical method

To facilitate the free anterior rectal space, the uterus was routinely suspended for female patients, and the bladder was suspended for male patients. As shown in Figure 1A, during the procedure, robotic arm II lifted the vascular ridge of the upper rectal artery to enter the Toldt space at the level of the sacral promontory and free it upward to the root of the inferior mesenteric artery. The left colic artery was found and preserved, the superior rectal artery and the sigmoid artery were cut off, the inferior mesenteric vein was cut off, the Toldt space continued to open to the head, and the descending colon and lateral peritoneum of the sigmoid colon were cut. With the continuation of the rectum from the pelvic floor to the hiatus of the levator anal muscle, the extreme attachment margin of the mesentery indicates that total mesentery resection has been completed, as shown in Figure 1B and C.

The separation sequence was lateral first, then posterior, and finally anterior to the rectum. Because the posterior ligament is shielded by the cluster of hiatal ligaments, it is not easy to access the sphincter space. However, gently pulling the puborectal muscle around the rectum from the left and right sides can easily enter the internal and external sphincter spaces. The sphincter gap is loose and without a vascular gap, and the robot's electric hook is delicate and flexible. The three-step separation method of the robot electric hook, which is combined with "a little bit of water burning", "blunt pushing", and "tracing line burning", is adopted to achieve sharp and accurate separation in the sphincter gap, accurately control the depth and depth of the operating plane, and progress layer by layer, as shown in Figure 1D and E. When separation reaches the dentate line level, the loose sphincter space disappears, and a cluster of venous plexuses can be seen in front of the rectum, as shown in Figure 1F.

Further distal separation is prone to damaging the intestinal tube and causing easy bleeding. This is the limit distance for complete abdominal path ionization of the robot and the scope of partial intersphincteric resection (ISR) resection, as shown in Figure 1G. For subtotal ISR or complete ISR, a combined transanal path is needed, as shown in Figure 1H. The reconstruction of the digestive tract was as follows: Part of the ISR was separated from the enterotomy tube through the pelvic cavity with a straight-line cutting and closing device, and the coloanal canal anastomosis was completed under an endoscope. Subtotal and complete ISR require a combined abdominal-transanal route to free the rectum, drag out the rectum and tumor through the anus, disentangle the enterotomy under direct vision, complete colo-anal anastomosis (Figure 1I), and complete a prophylactic ileostomy in the right lower abdomen.

Follow-up method

Follow-up was conducted according to the Guidelines for Colorectal Cancer Diagnosis and Treatment of the Chinese Society of Clinical Oncology. Patients with AJCC stage I disease were followed up every 6 months. Patients with AJCC stages II to III disease were treated once every 3 months. Follow-up included: (1) Physical examination, mainly digital rectal examination; (2) Blood collection and serum tumor marker analysis; (3) Abdominal ultrasound examination; (4) Electronic colonoscopy; and (5) Enhanced CT or MRI examination of the chest, abdominal cavity, and pelvic cavity once a year. The follow-up period ends in March 2023.

Statistical analysis

SPSS 26.0 statistical software was used for data analysis. Normally distributed measurement data are expressed as the mean ± SD, and a *t* test was used for comparisons between groups. The measurement data with a skewed distribution are expressed as the median (interquartile distance), and a nonparametric test (Mann-Whitney *U* test) was used for comparisons between groups. The χ^2 test or Fisher's exact probability test was used to compare the data between groups. The Kaplan-Meier method was used for survival analysis, and the log-rank test was used for comparisons between

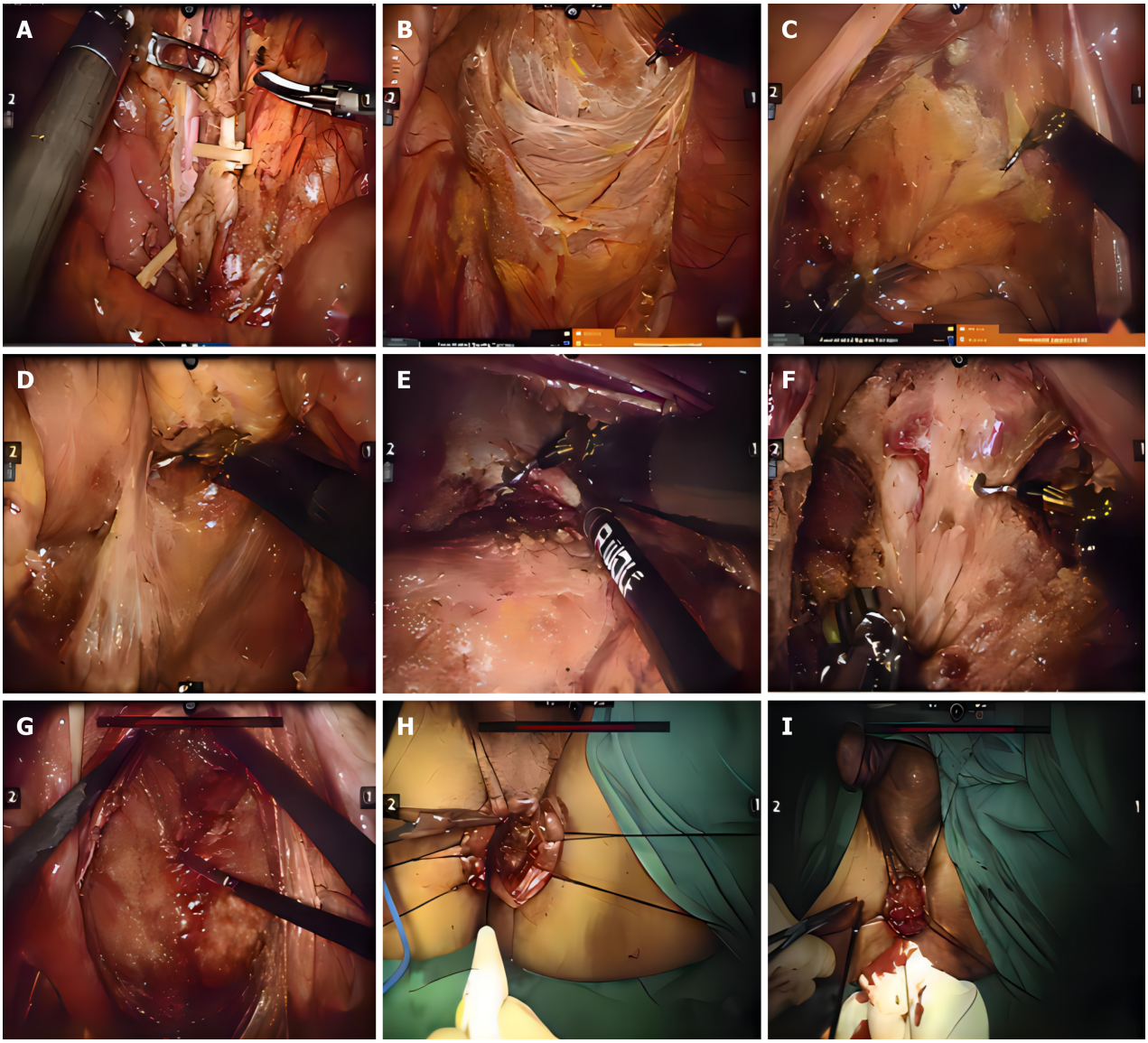


Figure 1 The surgical procedure for the Da Vinci robot diagram. A: The left colic artery was preserved, and the lymph nodes in group 253 were dissected; B: Free retrorectal space; C: Free anterior rectal space; D: Hiatal ligament; E: The puborectal muscle was redrawn to free the sphincter space through the abdominal path; F: Anterior wall venous plexus; G: Complete abdominal path intersphincter separation; H: Free the sphincter space *via* the anal route; I: Colo-anal end-to-end anastomosis.

groups. $P < 0.05$ was considered to indicate statistical significance.

RESULTS

General clinical data of the patients

A total of 240 patients with rectal cancer were included, including 151 males and 89 females. The mean age was 61 ± 9 years, ranging from 37 to 84 years. The average BMI was 23 ± 2.89 kg/m^2. There was no significant difference in the comparison of general data between the two groups (all $P > 0.05$), as shown in Table 1.

Analysis of surgical indexes

The intraoperative conversion rate of the L-TME group was greater than that of the R-TME group ($P < 0.05$). There were more postoperative complications in the L-TME group than in the R-TME group ($P < 0.05$). The hospital stay in the L-TME group was longer than that in the R-TME group ($P < 0.05$). In the L-TME group, 6 patients with anastomotic fistula were treated with enterostomy, 5 patients with intestinal obstruction were treated with adhesive release, 1 patient with urinary retention was treated with ultrasound-guided vesical puncture fistula, 2 patients with anastomotic stenosis were treated with balloon dilation, and 1 patient with sexual dysfunction was transferred to the urology department for treatment. In the R-TME group, 4 patients with anastomotic fistulas underwent enterostomy, 2 patients with intestinal obstruction underwent adhesion lysis, and 1 patient with pulmonary embolism was transferred to the intensive care unit

Table 1 Comparison of general data of rectal cancer patients between the two groups

Clinicopathological indicators	L-TME group (*n* = 112)	R-TME group (*n* = 128)	Statistical	*P* value
ASA grading			$\chi^2 = 0.006$	0.997
Class I	59	68		
Class II	39	44		
Class III	14	16		
Preoperative serum CEA	2.93 (6.06)	3.13 (4.78)	$Z = -0.005$	0.996
Tumor distance from anal margin (cm)	6 (6)	5 (6)	$Z = -0.963$	0.335
Distance distribution of tumor from anal margin			$\chi^2 = 0.592$	0.744
< 5 cm	29	34		
5-10 cm	65	69		
10-15 cm	18	25		
Comorbidities				
Diabetes	24	28	$\chi^2 = 0.007$	0.933
Dypertension	32	26	$\chi^2 = 2.223$	0.136
Chronic obstructive pulmonary disease	15	12	$\chi^2 = 0.966$	0.326
Emphysema	6	8	$\chi^2 = 0.087$	0.768
Varicose veins of the lower extremities	4	3	$\chi^2 = 0.318$	0.573
Deep vein thrombosis of the lower extremities	2	1	$\chi^2 = 0.488$	0.485
Sinus bradycardia	1	3	$\chi^2 = 0.767$	0.381
Atrial fibrillation	1	2	$\chi^2 = 0.217$	0.641
NRS2002 Score			$\chi^2 = 1.493$	0.222
0-2 points	99	106		
≥ 3 points	13	22		
TNM staging			$\chi^2 = 0.138$	0.933
Stage I	34	38		
Stage II	42	46		
Stage III	36	44		
LARS			$\chi^2 = 5.070$	0.079
None	89	115		
Mild	19	11		
Severe	4	2		
IIEF-5 score	112	128	$\chi^2 = 7.443$	0.059
Accessibility	90	118		
Mild impairment	13	5		
Moderate impairment	7	4		
Severe impairment	2	1		
Follow-up time (months)	43.5 (11.5)	42.0 (5.8)	$Z = -1.593$	0.111

L-TME: Laparoscopic total mesorectal resection; R-TME: Robotic total mesorectal resection; ASA: American Society of Anesthesiologists; CEA: Carcinoembryonic antigen; TNM: Tumor-node-metastasis; LARS: Low anterior rectal resection syndrome; IIEF-5: International Questionnaire on Erectile Function-5.

for treatment. The other complications all improved after conservative treatment without special treatment, as shown in Table 2.

Postoperative pathological findings

Compared with those in the L-TME group, the number of lymph nodes dissected was greater in the R-TME group, and the number of positive circumferential margins was lower in the R-TME group ($P < 0.05$). There were no significant differences in tumor diameter, pathological grade, AJCC stage, neurovascular invasion, or complete mesenteric resection rate between the two groups (all $P > 0.05$), as shown in Table 3.

Survival analysis and follow-up

The median follow-up time was 43 months, and the follow-up time ranged from 6 to 60 months. There were no severe complications, such as ostomy hernia, delayed anastomotic fistula, or death of the ostomy, in the two groups. There was no significant difference in the recurrence rate between the two groups ($P > 0.05$). The 3-year DFS and OS of AJCC stage III patients in the L-TME group were lower than those in the R-TME group (74.1% *vs* 85.2%, $P = 0.045$; 81.4% *vs* 91.4%, $P = 0.03$) (Figure 2 and Table 4).

DISCUSSION

L-TME has obvious advantages in terms of short-term efficacy, such as less trauma, faster recovery, and fewer complications[13]. However, due to the 2D laparoscopic surgical field of view, inflexibility of long straight-stem instruments, limited pelvic anatomical space, and complex anatomical levels, manual operation for low-position straight bowel cancer patients is more difficult[14-16]. In 2006, Pigazzi and others completed the first robotic rectal cancer surgery. The Da Vinci robotic surgery system is more suitable for accurate operation in narrow surgical spaces due to its high-definition 3D surgical field of view, automatic filtering of the operator's hand tremor, independent operating table, and high-degree-of-freedom robotic arm, which can reduce operator fatigue and ensure smooth operation[17]. The quality of surgical specimen removal should be improved, thereby reducing local recurrence and improving OS[18].

Switching to laparotomy not only increases the risk of death within 30 d but also affects local recurrence and OS in patients with rectal cancer during long-term follow-up[19]. In this study, the rate of conversion to laparotomy was 5.4% in the L-TME group and 0.8% in the R-TME group, and these differences were statistically significant. A recently published meta-analysis of randomized controlled trials of laparoscopic *vs* robotic rectal cancer surgery showed that the rate of conversion to laparotomy was lower in the robotic group than in the laparoscopic group, which is consistent with the results of this study. Technological advances in robotic systems have enabled surgeons to perform more precise dissections in the narrow pelvis, reducing the need to switch to laparotomy and thus reducing the incidence of postoperative complications[20-22].

In this study, more Clavien-Dindo grade 3 complications occurred in the L-TME group. It has been reported that grade 3 complications after radical resection of colorectal cancer have a negative impact on patient OS and DFS. The L-TME group had a relatively longer postoperative hospital stay due to the greater incidence of major postoperative complications, which could explain the poor survival rate caused by the delayed initiation of adjuvant chemotherapy[23]. The R-TME group had a lower rate of postoperative complications, which may be one reason for the improved survival rate. Previous studies have shown that R-TME and L-TME have similar long-term survival rates[24-26]. However, another study showed that L-TME and R-TME had 3-year OS rates of 70% and 93%, respectively, and 3-year DFS rates of 69% and 84%, respectively, indicating that R-TME had better long-term survival[27]. The results of this study showed that the 3-year OS and DFS rates for L-TME and R-TME patients who underwent robotic surgery were similar to those reported by the institute for patients with AJCC stage I to III rectal cancer. Local recurrence is the most common long-term complication in patients with rectal cancer[28]. The goal of the TME is to reduce local recurrence and improve OS while allowing patients to maintain an appropriate quality of life[29]. In this study, the local recurrence rate of R-TME was 2.7%, which is lower than that reported in previous studies[30-32].

Specimen quality is considered to be an important factor affecting the prognosis of rectal cancer patients, in which complete mesocrectomy and a negative circumferential margin (CRM) play important roles[33,34]. In this study, the R-TME group had a complete mesenteric resection rate similar to that of the L-TME group, which is consistent with previous findings. The results of this study showed that the rate of CRM positivity was greater in the L-TME group than in the R-TME group, and previous studies revealed that the rate of CRM positivity was greater in the L-TME group[35-37]. The unique advantages of robotic technology allow surgeons to maximize the replication of open TME principles, obtain better histopathological results, and improve the long-term survival rate of patients.

CONCLUSION

Compared with the L-TME group, the R-TME group achieved a lower conversion rate for laparotomies and a better tumor prognosis, especially for patients with AJCC stage III rectal cancer.

Table 2 Comparison of intraoperative and postoperative outcomes of rectal cancer patients

Clinical indicators	L-TME group (*n* = 112)	R-TME group (*n* = 128)	Statistical	*P* value
Conversion to laparotomy	6	1	$\chi^2 = 4.417$	0.036
Complications			$\chi^2 = 7.290$	0.007
Yes	36	22		
Not	76	106		
Complications Clavien-Dindo			$\chi^2 = 6.847$	0.144
Class I	95	118		
Class II	3	2		
Class III	14	6		
Class IV	0	1		
Level V	0	1		
Postoperative complications				
Anastomal fistula	13	5	$\chi^2 = 5.106$	0.024
Anastomotic bleeding	3	2	$\chi^2 = 0.365$	0.546
The anastomotic is narrow	4	2	$\chi^2 = 0.989$	0.32
Urinary tract infections	2	1	$\chi^2 = 0.488$	0.485
Urinary retention	3	2	$\chi^2 = 0.365$	0.546
Ileus	8	6	$\chi^2 = 0.656$	0.418
Infection of the incision in the abdominal wall	2	3	$\chi^2 = 0.091$	0.763
Pulmonary embolism	0	1	-	1
Sexual dysfunction	1	0	-	0.467
Length of postoperative hospital stay (d)	17 (3)	6 (2)	$Z = -2.541$	0.011

L-TME: Laparoscopic total mesorectal resection; R-TME: Robotic total mesorectal resection.

Table 3 Comparison of postoperative pathological examination results between the two groups of rectal cancer patients

Pathological indicators	L-TME group (*n* = 112)	R-TME group (*n* = 128)	Statistical	*P* value
Number of lymph nodes dissected	12 (7)	16 (8)	$Z = -3.295$	0.001
Tumor diameter (cm)	4.0 (1.5)	3.5 (2.4)	$Z = -0.006$	0.996
Pathological grading			$\chi^2 = 0.607$	0.738
High differentiation	5	8		
Medium differentiation	95	104		
Low differentiation	12	16		
Positive circumcision margin (case)	8	2	$\chi^2 = 4.658$	0.031
AJCC staging			$\chi^2 = 0.002$	0.999
Phase I	28	32		
Phase II	44	50		
Phase III	40	46		
Mesorectal resection (case)			$\chi^2 = 5.060$	0.08
completely	104	126		
Near-complete	6	2		

Imperfection	2	0		
Nerve invasion	23	18	$\chi^2 = 1.767$	0.184
Vascular invasion	25	20	$\chi^2 = 1.758$	0.185

L-TME: Laparoscopic total mesorectal resection; R-TME: Robotic total mesorectal resection; AJCC: American Joint Committee on Cancer.

Table 4 Comparison of the 3-year survival outcomes of rectal cancer patients

	TNM staging		Phase I		Phase II		Phase III	
	Number of cases	%	Number of cases	%	Number of cases	%	Number of cases	%
Disease-free survival	83	74.1	25	89.3	37	84.1	21	52.5
	109	85.2	30	93.8	44	88	35	76.1
	4.962		0.403		0.323		5.799	
	0.026		0.525		0.57		0.016	
Total survival	91	81.3	26	92.9	39	88.6	26	65
	117	91.4	31	96.9	47	94	39	84.8
	5.494		0.499		0.852		4.787	
	0.019		0.48		0.356		0.029	

TNM: Tumor-node-metastasis.

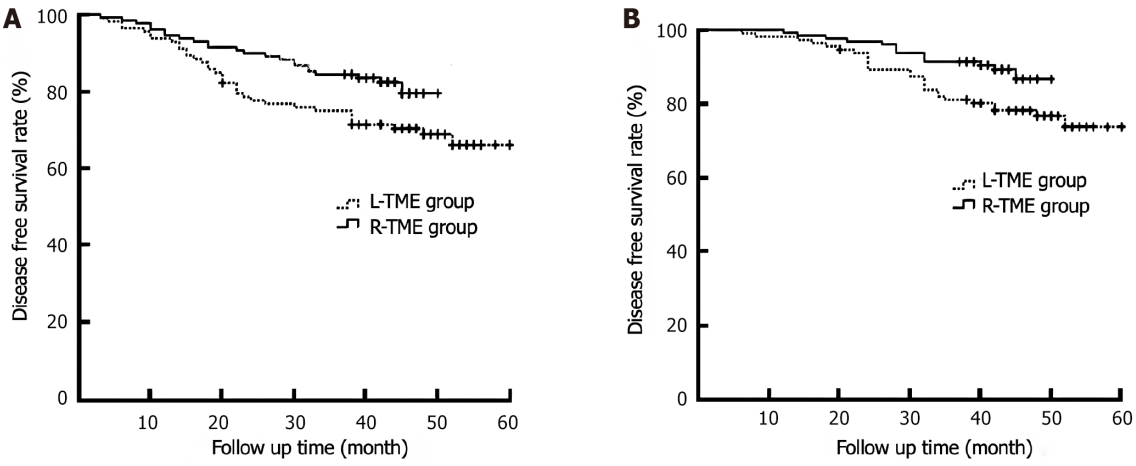


Figure 2 Comparison of the 3-year disease-free survival rate and overall survival rate between laparoscopic mesangectomy and robotic mesangectomy. A: 3-year disease-free survival rate; B: 3-year overall survival rate. L-TME: Laparoscopic total mesorectal resection; R-TME: Robotic total mesorectal resection.

FOOTNOTES

Author contributions: Gao WG wrote the manuscript; Shi W and Gong XC collected the data; Tuoheti Y and Li ZW guided the study; and all authors reviewed, edited, and approved the final manuscript and revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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REFERENCES

1 **Feng Z**, Sun Z, Zhang Q, Ren S. Analysis of clinical efficacy and safety of hand-sewn anastomosis for the digestive tract with Da Vinci robot in rectal cancer surgery. *World J Surg Oncol* 2023; **21**: 317 [PMID: 37817203 DOI: 10.1186/s12957-023-03172-w]
2 **Morelli L**, Di Franco G, Guadagni S, Rossi L, Palmeri M, Furbetta N, Gianardi D, Bianchini M, Caprili G, D'Isidoro C, Mosca F, Moglia A, Cuschieri A. Robot-assisted total mesorectal excision for rectal cancer: case-matched comparison of short-term surgical and functional outcomes between the da Vinci Xi and Si. *Surg Endosc* 2018; **32**: 589-600 [PMID: 28733738 DOI: 10.1007/s00464-017-5708-5]
3 **Takeyama H**, Danno K, Nishigaki T, Yamashita M, Oka Y. Surgical technique for mesorectal division during robot-assisted laparoscopic tumor-specific mesorectal excision (TSME) for rectal cancer using da Vinci Si surgical system: the simple switching technique (SST). *Updates Surg* 2021; **73**: 1093-1102 [PMID: 33079354 DOI: 10.1007/s13304-020-00901-8]
4 **Jiang J**, Zhu S, Yi B, Li J. Comparison of the short-term operative, Oncological, and Functional Outcomes between two types of robot-assisted total mesorectal excision for rectal cancer: Da Vinci versus Micro Hand S surgical robot. *Int J Med Robot* 2021; **17**: e2260 [PMID: 33837608 DOI: 10.1002/rcs.2260]
5 **Tsukamoto S**, Nishizawa Y, Ochiai H, Tsukada Y, Sasaki T, Shida D, Ito M, Kanemitsu Y. Surgical outcomes of robot-assisted rectal cancer surgery using the da Vinci Surgical System: a multi-center pilot Phase II study. *Jpn J Clin Oncol* 2017; **47**: 1135-1140 [PMID: 29036613 DOI: 10.1093/jjco/hyx141]
6 **Wu L**, Zhong Y, Yu X, Wu D, Xu P, Lv L, Ruan X, Liu Q, Feng Y, Liu J, Li X. Selective poly adenylation predicts the efficacy of immunotherapy in patients with lung adenocarcinoma by multiple omics research. *Anticancer Drugs* 2022; **33**: 943-959 [PMID: 35946526 DOI: 10.1097/CAD.0000000000001319]
7 **Sun Z**, Ma T, Huang Z, Lu J, Xu L, Wang Y, Li X, Wei Z, Wang G, Xiao Y. Robot-assisted radical resection of colorectal cancer using the KangDuo surgical robot versus the da Vinci Xi robotic system: short-term outcomes of a multicentre randomised controlled noninferiority trial. *Surg Endosc* 2024; **38**: 1867-1876 [PMID: 38307959 DOI: 10.1007/s00464-024-10682-5]
8 **Wang H**, Wu Y, Huang P, Chen W, Wang Z, Wang Y. Comparison of effectiveness and safety of Da Vinci robot's "3 + 1" and "4 + 1" modes of treatment for colorectal cancer. *J Robot Surg* 2023; **17**: 2807-2815 [PMID: 37735326 DOI: 10.1007/s11701-023-01717-5]
9 **Wu L**, Zheng Y, Ruan X, Wu D, Xu P, Liu J, Li X. Long-chain noncoding ribonucleic acids affect the survival and prognosis of patients with esophageal adenocarcinoma through the autophagy pathway: construction of a prognostic model. *Anticancer Drugs* 2022; **33**: e590-e603 [PMID: 34338240 DOI: 10.1097/CAD.0000000000001189]
10 **Becattini C**, Pace U, Pirozzi F, Donini A, Avruscio G, Rondelli F, Boncompagni M, Chiari D, De Prizio M, Visonà A, De Luca R, Guerra F, Muratore A, Portale G, Milone M, Castagnoli G, Righini M, Martellucci J, Persiani R, Frasson S, Dentali F, Delrio P, Campanini M, Gussoni G, Vedovati MC, Agnelli G. Rivaroxaban vs placebo for extended antithrombotic prophylaxis after laparoscopic surgery for colorectal cancer. *Blood* 2022; **140**: 900-908 [PMID: 35580191 DOI: 10.1182/blood.2022015796]
11 **Molenaar CJL**, Minnella EM, Coca-Martinez M, Ten Cate DWG, Regis M, Awasthi R, Martínez-Palli G, López-Baamonde M, Sebio-Garcia R, Feo CV, van Rooijen SJ, Schreinemakers JMJ, Bojesen RD, Gögenur I, van den Heuvel ER, Carli F, Slooter GD; PREHAB Study Group. Effect of Multimodal Prehabilitation on Reducing Postoperative Complications and Enhancing Functional Capacity Following Colorectal Cancer Surgery: The PREHAB Randomized Clinical Trial. *JAMA Surg* 2023; **158**: 572-581 [PMID: 36988937 DOI: 10.1001/jamasurg.2023.0198]
12 **Rompianesi G**, Pegoraro F, Ceresa CD, Montalti R, Troisi RI. Artificial intelligence in the diagnosis and management of colorectal cancer liver metastases. *World J Gastroenterol* 2022; **28**: 108-122 [PMID: 35125822 DOI: 10.3748/wjg.v28.i1.108]
13 **Cuk P**, Kjær MD, Mogensen CB, Nielsen MF, Pedersen AK, Ellebæk MB. Short-term outcomes in robot-assisted compared to laparoscopic colon cancer resections: a systematic review and meta-analysis. *Surg Endosc* 2022; **36**: 32-46 [PMID: 34724576 DOI: 10.1007/s00464-021-08782-7]
14 **Yang L**, Fang C, Bi T, Han J, Zhang R, Zhou S. Efficacy of robot-assisted *vs* laparoscopy surgery in the treatment of colorectal cancer: A systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol* 2023; **47**: 102176 [PMID: 37454927 DOI: 10.1016/j.clinre.2023.102176]
15 **Wu L**, Zhong Y, Wu D, Xu P, Ruan X, Yan J, Liu J, Li X. Immunomodulatory Factor TIM3 of Cytolytic Active Genes Affected the Survival and Prognosis of Lung Adenocarcinoma Patients by Multi-Omics Analysis. *Biomedicines* 2022; **10** [PMID: 36140350 DOI: 10.3390/biomedicines10092248]
16 **Shinji S**, Yamada T, Matsuda A, Sonoda H, Ohta R, Iwai T, Takeda K, Yonaga K, Masuda Y, Yoshida H. Recent Advances in the Treatment of Colorectal Cancer: A Review. *J Nippon Med Sch* 2022; **89**: 246-254 [PMID: 35082204 DOI: 10.1272/jnms.JNMS.2022_89-310]
17 **Aggarwal A**, Han L, Boyle J, Lewis D, Kuyruba A, Braun M, Walker K, Fearnhead N, Sullivan R, van der Meulen J. Association of Quality and Technology With Patient Mobility for Colorectal Cancer Surgery. *JAMA Surg* 2023; **158**: e225461 [PMID: 36350616 DOI:

10.1001/jamasurg.2022.5461]
18 **Farah E**, Abreu AA, Rail B, Salgado J, Karagkounis G, Zeh HJ 3rd, Polanco PM. Perioperative outcomes of robotic and laparoscopic surgery for colorectal cancer: a propensity score-matched analysis. *World J Surg Oncol* 2023; **21**: 272 [PMID: 37644538 DOI: 10.1186/s12957-023-03138-y]
19 **Kampman SL**, Smalbroek BP, Dijksman LM, Smits AB. Postoperative inflammatory response in colorectal cancer surgery: a meta-analysis. *Int J Colorectal Dis* 2023; **38**: 233 [PMID: 37725227 DOI: 10.1007/s00384-023-04525-3]
20 **Wu L**, Zheng Y, Liu J, Luo R, Wu D, Xu P, Li X. Comprehensive evaluation of the efficacy and safety of LPV/r drugs in the treatment of SARS and MERS to provide potential treatment options for COVID-19. *Aging (Albany NY)* 2021; **13**: 10833-10852 [PMID: 33879634 DOI: 10.18632/aging.202860]
21 **Puntambekar SP**, Rajesh KN, Goel A, Hivre M, Bharambe S, Chitale M, Panse M. Colorectal cancer surgery: by Cambridge Medical Robotics Versius Surgical Robot System-a single-institution study. Our experience. *J Robot Surg* 2022; **16**: 587-596 [PMID: 34282555 DOI: 10.1007/s11701-021-01282-9]
22 **Wei PL**, Huang YJ, Wang W, Huang YM. Comparison of robotic reduced-port and laparoscopic approaches for left-sided colorectal cancer surgery. *Asian J Surg* 2023; **46**: 698-704 [PMID: 35778241 DOI: 10.1016/j.asjsur.2022.06.079]
23 **Warps AK**, Saraste D, Westerterp M, Detering R, Sjövall A, Martling A, Dekker JWT, Tollenaar RAEM, Matthiessen P, Tanis PJ; Dutch ColoRectal Audit and Swedish Colorectal Cancer Registry. National differences in implementation of minimally invasive surgery for colorectal cancer and the influence on short-term outcomes. *Surg Endosc* 2022; **36**: 5986-6001 [PMID: 35258664 DOI: 10.1007/s00464-021-08974-1]
24 **An S**, Kim K, Kim MH, Jung JH, Kim Y. Perioperative Probiotics Application for Preventing Postoperative Complications in Patients with Colorectal Cancer: A Systematic Review and Meta-Analysis. *Medicina (Kaunas)* 2022; **58** [PMID: 36422183 DOI: 10.3390/medicina58111644]
25 **Wu L**, Liu Q, Ruan X, Luan X, Zhong Y, Liu J, Yan J, Li X. Multiple Omics Analysis of the Role of RBM10 Gene Instability in Immune Regulation and Drug Sensitivity in Patients with Lung Adenocarcinoma (LUAD). *Biomedicines* 2023; **11** [PMID: 37509501 DOI: 10.3390/biomedicines11071861]
26 **Alves Martins BA**, Filho OM, Ghezzi TL, Melani AGF, Romagnolo LGC, Moreira Júnior H, de Almeida JPP, Araújo SEA, de Sousa JB, de Almeida RM. An Overview of Robotic Colorectal Surgery Adoption and Training in Brazil. *Medicina (Kaunas)* 2023; **59** [PMID: 37763794 DOI: 10.3390/medicina59091675]
27 **Yoshida T**, Homma S, Ichikawa N, Fujiyoshi S, Shibata K, Imaizumi K, Taketomi A. Feasibility of Laparoscopic and Robotic Total Proctocolectomy for Ulcerative Colitis-related Colorectal Cancer. *Anticancer Res* 2023; **43**: 5245-5252 [PMID: 37909995 DOI: 10.21873/anticanres.16726]
28 **Romano B**, Pagano E, Iannotti FA, Piscitelli F, Brancaleone V, Lucariello G, Nanì MF, Fiorino F, Sparaco R, Vanacore G, Di Tella F, Cicia D, Lionetti R, Makriyannis A, Malamas M, De Luca M, Aprea G, D'Armiento M, Capasso R, Sbarro B, Venneri T, Di Marzo V, Borrelli F, Izzo AA. N-Acylethanolamine acid amidase (NAAA) is dysregulated in colorectal cancer patients and its inhibition reduces experimental cancer growth. *Br J Pharmacol* 2022; **179**: 1679-1694 [PMID: 34791641 DOI: 10.1111/bph.15737]
29 **Han Z**, Nan X, Ma M, Zhou R, Wang P, Liu J, Li Y. Effect of aspirin, warfarin, and proton-pump inhibitors on performance of fecal immunochemical test in colorectal cancer screening: a systematic review and meta-analysis. *Clin Exp Med* 2023; **23**: 4355-4368 [PMID: 37804359 DOI: 10.1007/s10238-023-01196-w]
30 **Kara OC**, Venkatayogi N, Ikoma N, Alambeigi F. A Reliable and Sensitive Framework for Simultaneous Type and Stage Detection of Colorectal Cancer Polyps. *Ann Biomed Eng* 2023; **51**: 1499-1512 [PMID: 36754924 DOI: 10.1007/s10439-023-03153-w]
31 **Cuk P**, Jawhara M, Al-Najami I, Helligsø P, Pedersen AK, Ellebæk MB. Robot-assisted versus laparoscopic short- and long-term outcomes in complete mesocolic excision for right-sided colonic cancer: a systematic review and meta-analysis. *Tech Coloproctol* 2023; **27**: 171-181 [PMID: 36001164 DOI: 10.1007/s10151-022-02686-x]
32 **Wu L**, Li X, Qian X, Wang S, Liu J, Yan J. Lipid Nanoparticle (LNP) Delivery Carrier-Assisted Targeted Controlled Release mRNA Vaccines in Tumor Immunity. *Vaccines (Basel)* 2024; **12** [PMID: 38400169 DOI: 10.3390/vaccines12020186]
33 **Ferrier C**, Le Gac M, Kolanska K, Boudy AS, Dabi Y, Touboul C, Bendifallah S, Daraï E. Comparison of robot-assisted and conventional laparoscopy for colorectal surgery for endometriosis: A prospective cohort study. *Int J Med Robot* 2022; **18**: e2382 [PMID: 35178837 DOI: 10.1002/rcs.2382]
34 **Yotsov T**, Karamanliev M, Maslyankov S, Iliev S, Ramadanov N, Dimitrov D. Mesenteric Vascular Evaluation with Pre-operative Multidetector Computed Tomographic Angiography and Intraoperative Indocyanine Green Angiography to Reduce Anastomotic Leaks after Minimally Invasive Surgery for Colorectal Cancer. *JSLS* 2022; **26** [PMID: 35967960 DOI: 10.4293/JSLS.2022.00022]
35 **Wu L**, Li H, Liu Y, Fan Z, Xu J, Li N, Qian X, Lin Z, Li X, Yan J. Research progress of 3D-bioprinted functional pancreas and in vitro tumor models. *IJB* 2024; **10**: 1256 [DOI: 10.36922/ijb.1256]
36 **Avella P**, Vaschetti R, Cappuccio M, Gambale F, DE Meis L, Rafanelli F, Brunese MC, Guerra G, Scacchi A, Rocca A. The role of liver surgery in simultaneous synchronous colorectal liver metastases and colorectal cancer resections: a literature review of 1730 patients underwent open and minimally invasive surgery. *Minerva Surg* 2022; **77**: 582-590 [PMID: 36409039 DOI: 10.23736/S2724-5691.22.09716-7]
37 **Hu C**, Zhang Z, Zhang L, Liu R, Yan J, Sun Q, Wang G, She J. Robot-assisted Total Mesorectal Excision and Lateral Pelvic Lymph Node Dissection for Locally Advanced Middle-low Rectal Cancer. *J Vis Exp* 2022 [PMID: 35225257 DOI: 10.3791/62919]

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ORIGINAL ARTICLE

Retrospective Study

How to apply *ex-vivo* split liver transplantation safely and feasibly: A three-step approach

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Abstract

BACKGROUND

Given the current organ shortage crisis, split liver transplantation (SLT) has emerged as a promising alternative for select end-stage liver disease patients.

AIM

To introduce an *ex-vivo* liver graft splitting approach and evaluate its safety and feasibility in SLT.

METHODS

A retrospective analysis was conducted on the liver transplantation data from cases performed at our center between April 1, 2022, and May 31, 2023. The study included 25 SLT cases and 81 whole liver transplantation (WLT) cases. Total *ex-vivo* liver splitting was employed for SLT graft procurement in three steps. Patient outcomes were determined, including liver function parameters, postoperative complications, and perioperative mortality. Group comparisons for categorical variables were performed using the χ^2-test.

RESULTS

In the study, postoperative complications in the 25 SLT cases included hepatic artery thrombosis (n = 1) and pulmonary infections (n = 3), with no perioperative mortality. In contrast, among the 81 patients who underwent WLT, complications included perioperative mortality (n = 1), postoperative pulmonary infections

(*n* = 8), abdominal infection (*n* = 1), hepatic artery thromboses (*n* = 3), portal vein thrombosis (*n* = 1), and intra-abdominal bleeding (*n* = 5). Comparative analysis demonstrated significant differences in alanine aminotransferase (176.0 *vs* 73.5, *P* = 0.000) and aspartate aminotransferase (AST) (42.0 *vs* 29.0, *P* = 0.004) at 1 wk postoperatively, and in total bilirubin (11.8 *vs* 20.8, *P* = 0.003) and AST (41.5 *vs* 26.0, *P* = 0.014) at 2 wk postoperatively. However, the overall incidence of complications was comparable between the two groups (*P* > 0.05).

CONCLUSION

Our findings suggest that the total *ex-vivo* liver graft splitting technique is a safe and feasible approach, especially under the expertise of an experienced transplant center. The approach developed by our center can serve as a valuable reference for other transplantation centers.

Key Words: Split liver transplantation; Transplantation; Liver splitting; *Ex-vivo*; *In-situ*

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Core Tip: Split liver transplantation has become a routine procedure at many transplant centers, and there are currently two main approaches for the generation of split-liver allografts: *In-situ* splitting and *ex-vivo* splitting. While *in-situ* splitting, which involves liver division within the organ donor's body before procurement, is the prevailing technique adopted by most transplant centers, the utilization of *ex-vivo* splitting, wherein the liver is divided after procurement, remains limited. Our findings suggest that the *ex-vivo* liver graft splitting technique is a safe and feasible approach, especially under the expertise of an experienced transplant center.

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INTRODUCTION

Given the current organ shortage crisis, split liver transplantation (SLT) has emerged as a promising alternative for select patients with end-stage liver disease[1-4], offering clinical outcomes akin to those achieved through whole liver transplantation (WLT)[5-7]. The techniques for SLT involve primarily splitting off the left lateral section and the right trisegment, followed by further partitioning into the left and right hemi-livers or liver segments, contingent on the compatibility conditions between the donor and recipient[8,9].

There are currently two main approaches for the generation of split-liver allografts: *In-situ* splitting and *ex-vivo* splitting. While *in-situ* splitting, which involves liver division within the organ donor's body before procurement, is the prevailing technique adopted by most transplant centers, the utilization of *ex-vivo* splitting, wherein the liver is divided after procurement, remains limited[4,10,11]. Despite its potential benefits, *ex-vivo* splitting is currently employed by only a few specialized centers. Ding *et al*[12] previously reported that out of 11 liver grafts, only 2 (18.2%) underwent *ex-vivo* splitting. Similarly, Xu *et al*[13] performed only 20 (14.3%) SLT procedures out of the 140 liver transplantations.

Interestingly, SLT has become a routine procedure at our transplant center, and the total *ex-vivo* liver graft splitting technique has become our preferred approach. Despite the significance of *ex-vivo* liver graft splitting, there are few detailed reports on this splitting technique. To address this knowledge gap, our present study presents a comprehensive summary of our center's practice and technical approach to *ex-vivo* liver graft splitting, aiming to evaluate its safety and feasibility and provide a reference for surgeons in other transplant centers.

MATERIALS AND METHODS

Study design and patients

Clinical data from 122 liver transplantation cases performed at Shenzhen Third People's Hospital were initially collected between April 1, 2022, and May 31, 2023. The study enrolled 81 cases of WLT, 16 cases of living-donor liver transplantation, and 25 cases of SLT. A total of 106 cases, comprising of SLT and WLT recipients, were eventually included in our study. Comprehensive data, including clinical records, surgical reports, laboratory findings, and imaging results, were obtained for each case. Liver function parameters, incidence of surgical complications, and perioperative mortality rate were independently analyzed for the SLT and WLT groups. All the patients provided informed consent before operation, and the study was approved by the ethics committee of Shenzhen Third People's Hospital (No. 2022-133).

Donor liver evaluation methods

Before organ procurement, all potential organ donors received comprehensive preoperative evaluations, including complete blood counts, liver function tests, renal function tests, infectious disease pathogen screening, and inflammation marker testing. Additionally, imaging studies, such as liver ultrasound or contrast-enhanced computed tomography (CT) scans, were performed.

Donor liver splitting procedure

The liver graft splitting procedure was performed using the total *ex-vivo* splitting technique. Following liver procurement, the donor liver was partitioned while immersed in a cold storage solution. The splitting of the left lateral section and the right trisegment involved three main steps: (1) Division of the first porta hepatis: The anatomical structures of the first porta hepatis were dissected, followed by the separate division of the left branch of the portal vein and the left branch of the hepatic artery. Next, the division site of the left hepatic duct was identified under biliary probe guidance. Following bile duct resection, the splitting line on the visceral surface of the liver was marked (Figure 1); (2) Division of the second porta hepatis: The suprahepatic inferior vena cava was gently elevated, and the root of the left hepatic vein was bluntly separated to fully expose the site where the left hepatic vein joins the inferior vena cava. After dividing the left hepatic vein, the surface splitting line of the liver on the diaphragmatic aspect was marked, connecting it to the visceral surface splitting line (Figure 2); and (3) Division of liver parenchyma: A clamp-crushing technique was utilized for dividing the liver parenchyma to avoid thermal injury to liver tissues. Smaller vessels were ligated with titanium clips, while larger vessels were ligated using silk or Prolene sutures. Throughout the procedure, continuous monitoring of anatomical structures with positional changes was performed to ascertain the precise division plane and avoid injuries to critical intrahepatic structures (Figure 3). After completing the division of the right trisegment and the left lateral section, the caudate lobe on the left side of the inferior vena cava was excised. The surgical procedure depicted above is further detailed in Figures 1-3.

Statistical analysis

All statistical analyses were performed using SPSS 24.0 statistical software. The descriptive statistics are expressed as frequencies (%) for categorical variables, and median (interquartile range) for continuous variables. Group comparisons for categorical variables were performed using the χ^2-test. For metric variables, the Mann-Whitney *U* test was used. A two-sided *P*-value < 0.05 was considered statistically significant.

RESULTS

Clinical data of donors

Between April 1, 2022 and May 31, 2023, 13 liver grafts were subjected to splitting. These grafts were procured from 13 brain-dead organ donors, with all exhibiting hemodynamic stability preoperatively, with minimal or no use of vasoactive drugs. The median age of the liver donors was 31 years, and they had a median preoperative total bilirubin (TB) level of 20.76 μmol/L, median alanine aminotransferase (ALT) level of 43.3 U/L, median aspartate aminotransferase (AST) level of 83 U/L, and median intensive care unit (ICU) stay duration of 4 d.

The liver graft splitting procedure was conducted using the total *ex-vivo* splitting technique, whereby both the left lateral section and the right trisegment were divided in all cases. Following the procedure, 26 liver segments were obtained (13 left lateral sections and 13 right trisegments). Among these liver segments, 25 were allocated to our transplant center by the China Organ Transplant Response System, while one right trisegment was given to another transplant center. During the liver graft splitting procedure for the 12 cases in which the right trisegment was utilized for liver transplantation, the caudate lobe located on the left side of the inferior vena cava was consistently excised. Further details regarding the donor liver information can be found in Table 1.

Clinical data of liver transplant recipients

All 106 Liver transplant procedures retrospectively analyzed in this study were successfully performed. The age of WLT cases was younger than that of SLT cases (49.00 *vs* 1.83, $P = 0.001$), and there were more decompensated cirrhosis recipients in WLT cases (48 *vs* 5, $P = 0.001$). Out of the 81 WLT cases, 66 were carried out using the classic *in-situ* liver transplantation technique, while the remaining 15 utilized the modified piggyback liver transplantation technique. As for the 25 SLT cases, 13 pediatric recipients received left lateral section grafts, and 7 adult and 5 pediatric recipients received right trisegment grafts. In the 12 patients who underwent SLT with the right trisegment graft, we conducted the removal of ischemic hepatic tissue from Segment IV while preserving the middle hepatic vein during the surgical procedure.

Postoperative results and complications

Among the 81 cases of WLT, one perioperative death occurred, while the remaining patients were successfully discharged. The postoperative complications primarily included pulmonary infections in 8 cases (9.9%), intra-abdominal infections in 1 (1.2%), incisional infections in 1 (1.2%), herpes zoster infection in 1 (1.2%), hepatic artery thrombosis in 3 (3.7%), portal vein thrombosis in 1 (1.2%), intra-abdominal bleeding in 5 (6.2%), graft-versus-host disease (GVHD) in 1 (1.2%), and acute kidney injury in 1 (1.2%). The patient with intra-abdominal bleeding underwent exploratory laparotomy to achieve hemostasis, while those with hepatic artery or portal vein thrombosis received surgical thrombectomy. The patient who experienced GVHD passed away on postoperative day 56 despite aggressive treatment.

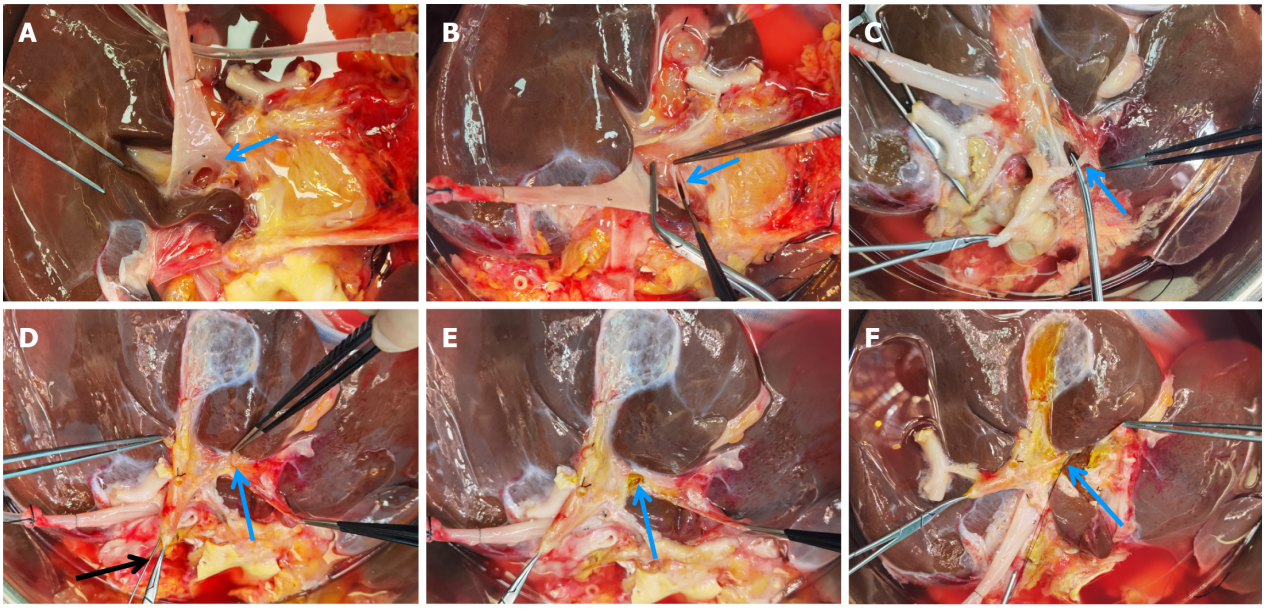


Figure 1 Procedure of splitting the first porta hepatis. A: Separation of the left and right branches of the portal vein (arrow indicating the left portal vein); B: Division of the left portal vein (arrow) followed by suturing of the proximal end; C: Identification and division of the left hepatic artery (arrow); D: Identification of the division site of the left hepatic duct (blue arrow) under biliary probe guidance (black arrow); E: Incision of the left hepatic duct anterior wall (arrow) and reconfirmation of the left hepatic duct, right hepatic duct, and suspected bile duct openings using the probe; F: Division of the left hepatic duct, confirming the landmark for the division of liver parenchyma in the first porta hepatis.

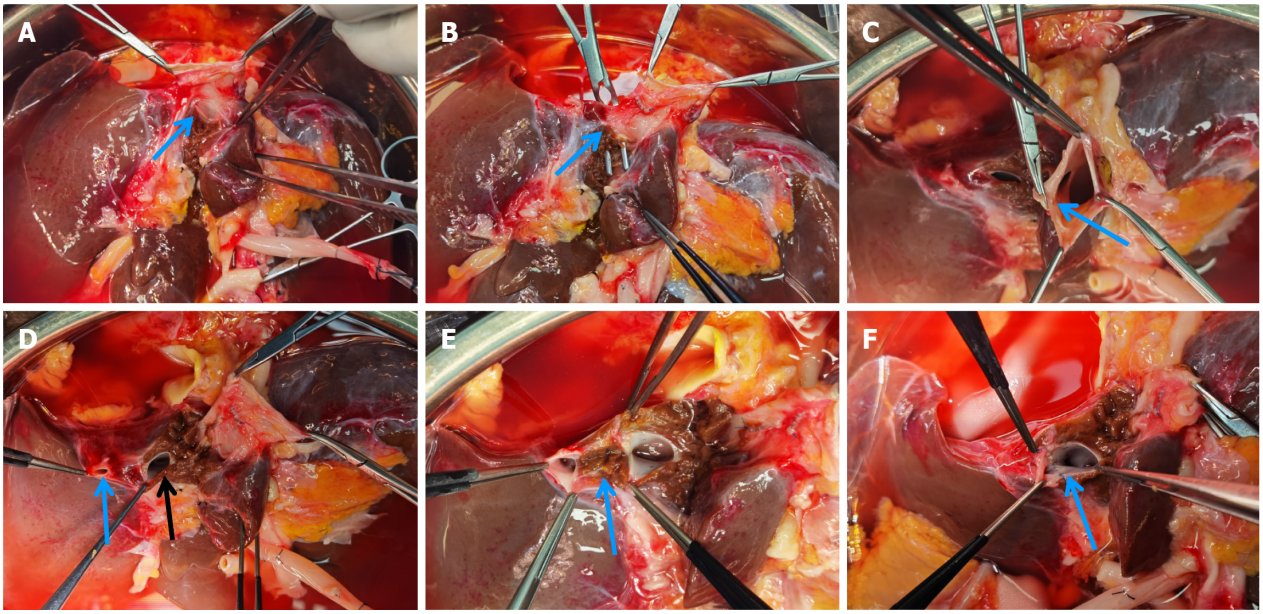


Figure 2 Step-by-step process involved in splitting the second porta hepatis. A: Elevation of the suprahepatic inferior vena cava followed by blunt dissection of the liver tissue at the junction of the left hepatic vein and the inferior vena cava (arrow) to fully expose the left hepatic vein; B: Separating and dividing the left hepatic vein (arrow) using a vascular occlusion clamp on the inferior vena cava side; C: Formation of the middle hepatic vein and the opening of the inferior vena cava (arrow points to the formed vessel opening); D: Identification of the two openings of the left hepatic vein in the left lateral segment (blue arrow and black arrow); E: Removal of the liver tissue between the two openings of the left hepatic vein (arrow) to form a single opening; F: Display of the formed opening of the left hepatic vein.

Subsequent follow-ups, ranging from 2 to 15 mo, revealed that 76 patients recovered well and had no abnormalities.

Among the 25 subjects that underwent SLT, one experienced hepatic artery thrombosis on postoperative day 3, which was successfully treated by surgical thrombectomy, leading to a favorable recovery. Another three patients developed postoperative pulmonary infections, but there were no instances of bile leakage or intestinal leakage, and no perioperative deaths were reported. All 25 patients were discharged without complications and showed no abnormalities during a follow-up period ranging from 4 to 15 mo.

Table 1 Clinical data of 13 donor liver cases

No.	Gender	Age (yr)	Type of donation	Cause of death	Preoperative Na^+ concentration (mmol/L)	Preoperative TB (μmol/L)	Preoperative ALT (U/L)	Preoperative AST (U/L)	ICU stay duration (d)
1	Male	31	DBD	Craniocerebral injury	143	57.80	37.0	41.0	3
2	Female	12	DBD	Hypoxic-ischemic encephalopathy	140	13.40	42.0	53.0	4
3	Female	42	DBD	Craniocerebral injury	146	50.80	45.0	83.0	5
4	Male	44	DBD	Cerebral hemorrhage	143	45.30	18.0	37.0	4
5	Male	36	DBD	Craniocerebral injury	150	13.80	131.0	172.0	4
6	Male	34	DBD	Cerebral hemorrhage	156	23.40	267.5	293.2	2
7	Male	12	DBD	Hypoxic-ischemic encephalopathy	136	13.00	43.3	93.1	11
8	Male	31	DBD	Cerebral hemorrhage	150	26.80	15.0	25.0	10
9	Male	25	DBD	Craniocerebral injury	143	54.50	177.0	83.0	4
10	Female	9	DBD	Hypoxic-ischemic encephalopathy	148	3.05	103.0	227.0	10
11	Male	8	DBD	Hypoxic-ischemic encephalopathy	149	10.21	22.7	22.9	4
12	Female	29	DBD	Cerebral hemorrhage	148	20.76	37.0	42.0	7
13	Male	40	DBD	Cerebral hemorrhage	132	12.20	166.0	85.0	5

DBD: Donation after brain death; TB: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; Na^+: Sodium ion; ICU: Intensive care unit.

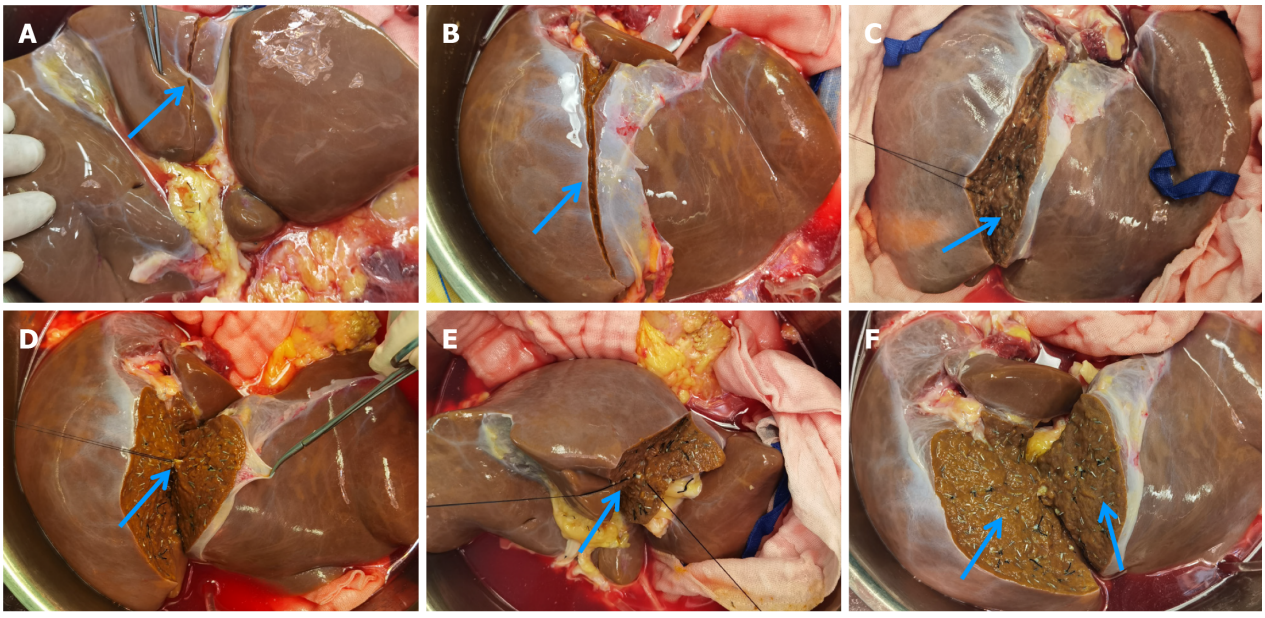


Figure 3 Procedure of liver parenchymal division. A: Identification of the landmark line on the visceral surface of the liver for liver parenchymal division (0.5-

1.0 cm to the right of the liver round ligament); B: Landmark line on the diaphragmatic surface of the liver for liver parenchymal division (on the right of the falciform ligament); C: Liver parenchymal division in the flat position, using titanium clips for small vessels (arrow); D: Adjusting the position of the liver during parenchymal division (suprahepatic inferior vena cava facing upwards), using silk sutures or ligatures for larger vessels (arrow); E: Continued liver parenchymal division with the liver flipped (suprahepatic inferior vena cava facing downward); F: Display of the two smooth liver segment surfaces after completion of the splitting process (arrow).

A comparison of postoperative data between SLT and WLT revealed statistically significant differences in ALT (176.0 *vs* 73.5, $P = 0.000$) and AST (42.0 *vs* 29.0, $P = 0.004$) levels at 1 wk post-surgery. Additionally, at 2 wk post-surgery, there were statistically significant differences in TB (11.8 *vs* 20.8, $P = 0.003$) and AST (41.5 *vs* 26.0, $P = 0.014$) levels. However, no statistically significant difference was observed in the overall incidence of postoperative complications between the two groups ($P > 0.05$). Further details can be found in Table 2.

DISCUSSION

In the face of a critical shortage of available donor organs, SLT represents a valuable approach to address this pressing issue. SLT involves the division of a single high-quality liver into two parts, thereby saving the lives of two recipients [14]. The success of SLT hinges on ensuring that each split portion of the liver maintains intact anatomical structures, encompassing the inflow vessels (hepatic artery and portal vein), outflow vessels (hepatic veins), and biliary tract. Additionally, adherence to conventional criteria for SLT, such as the graft-to-recipient weight ratio (GRWR), is crucial. Typically, a GRWR greater than 1% for adults[8,15] and between 2% to 4% for children is recommended. In our study, all the 25 recipients of SLT met these criteria and did not experience postoperative complications such as large-for-size or small-for-size graft syndromes. However, some scholars reported that the ideal graft weight is approximately 1-3% of the recipient weight[16].

Different transplant centers primarily adopt either *in-situ* or *ex-vivo* splitting approaches. Reyes *et al*[17] previously reported that the survival rates of recipients undergoing *in-situ* and *ex-vivo* liver splitting were comparable and similar to the survival rates of WLT recipients, in line with the findings of our study. Our literature review revealed that the majority of transplant centers have a preference for the *in-situ* liver-splitting approach[8,12,18]. *In-situ* liver splitting involves performing the procedure within the donor's body for liver procurement. This approach offers several advantages[19,20], including shorter cold ischemia time, simultaneous hemostasis during liver parenchymal transection, and facilitated intraoperative cholangiography. However, it may also have certain drawbacks, such as potential delays in procuring other organs and the need for coordination between transplant centers. Recent literature has explored the use of normothermic perfusion devices for liver splitting, which holds the potential to mitigate some of the limitations associated with *in-situ* splitting. Although this technology shows promise, it has not yet been widely adopted in clinical practice, and its clinical effectiveness requires further observation and research[21].

By contrast, *ex-vivo* splitting, which we primarily use, avoids these drawbacks. However, it requires a skilled surgical team familiar with *ex-vivo* liver anatomy to prevent damage to critical structures. Although some literature reported a higher incidence of biliary and vascular complications in adult recipients undergoing *ex-vivo* splitting compared to *in-situ* splitting[22], in our study, out of the 25 cases of SLT, only one adult recipient suffered from hepatic artery thrombosis postoperatively. Besides, there was no incidence of other biliary or vascular complications in the remaining cases. Importantly, the overall incidence of postoperative complications showed no statistically significant difference between the SLT and WLT groups ($P > 0.05$). As mentioned in the Methods section, recipients undergoing liver right trisegment graft surgery had the caudate lobe and ischemic segment IV of the liver excised during the procedure, likely contributing to the absence of bile leakage and intra-abdominal infections postoperatively[23,24].

Postoperative liver function tests revealed statistically significant differences between the SLT group and the WLT group in ALT (176.0 *vs* 73.5, $P = 0.000$) and AST (42.0 *vs* 29.0, $P = 0.004$) levels at 1 wk postoperatively, as well as in TB (11.8 *vs* 20.8, $P = 0.003$) and AST (41.5 *vs* 26.0, $P = 0.014$) levels at 2 wk after surgery. Herein, the higher postoperative ALT and AST levels observed in the SLT group at 1 wk and the elevated AST level at 2 wk might be associated with ischemic necrosis on the transection plane of the liver. Although the difference in TB at 2 wk showed statistical significance, both groups had median values within the normal range, indicating good postoperative liver function.

The safety of SLT relies not only on a surgical team with extensive experience but also on a comprehensive evaluation and careful selection of the donor liver prior to the surgery. Several studies[12,14,25] have emphasized the importance of choosing relatively young donors with stable hemodynamics, short ICU stays, no significant steatosis or infections, and no apparent vascular or biliary anomalies. At our center, we adhere to specific criteria for selecting split liver donors, which include individuals under 45 years of age (with a median age of 31 years in this study) exhibiting stable hemodynamics, absence of significant steatosis or infections, and no apparent vascular or biliary anomalies. It has been reported that intraoperative cholangiography is a necessary examination[14,20], but we did not perform intraoperative cholangiography in this study, because no bile duct variation was found before surgery. However, it is essential to note that cholangiography should be considered if suspicious ductal structures are encountered during the surgery. In the study, all 25 recipients had no relevant biliary complications postoperatively.

Table 2 Clinical data comparison between split liver transplantation and whole liver transplantation cases

	Split liver transplantation (*n* = 25)	Whole liver transplantation (*n* = 81)	*P* value
Gender (male/female)	17/8	65/16	0.273
Age (yr)	1.83 (0.55, 43.00)	49 (40.50, 55.00)	0.001
Underlying diseases			
Decompensated cirrhosis	5	48	0.001
Liver cancer	2	15	0.210
One-week postoperative indicators			
TB	26.400 (12.950, 34.350)	28.250 (17.525, 48.925)	0.274
ALT	176.0 (81.5, 259.5)	73.5 (43.5, 115.5)	0.000
AST	42.00 (32.00, 79.00)	29.00 (20.25, 49.25)	0.004
GGT	139.0 (102.5, 227.5)	118.0 (64.0, 174.0)	0.117
Two-week postoperative indicators			
TB	11.80 (7.95, 20.55)	20.80 (15.20, 26.30)	0.003
ALT	63.0 (29.5, 82.5)	40.0 (21.0, 82.0)	0.154
AST	41.5 (20.5, 61.5)	26.0 (17.0, 41.0)	0.014
GGT	81.0 (54.5, 182.5)	114 (56.0, 201.0)	0.528
Postoperative complications			0.584
Intra-abdominal bleeding	0	5	
Hepatic artery thrombosis	1	3	
Pulmonary infections	3	8	
Abdominal infection	0	1	
Bile leakage	0	0	
Intestinal leakage	0	0	
30-d postoperative mortality	0	1	

TB: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase.

CONCLUSION

In this retrospective analysis of consecutive *ex-vivo* SLT cases conducted over the past year, the methods and steps of *ex-vivo* liver graft splitting technique were summarized in detail, and our study demonstrated that the total *ex-vivo* liver splitting approach with three steps is safe and feasible, especially when performed in experienced transplant centers. Importantly, this approach has been found to address concerns associated with the geographical distance between organ donor hospitals and transplant centers, as well as potential risks of prolonged surgical duration during organ procurement and potential harm to other donated organs. However, follow-up studies with large samples are warranted due to the relatively small number of cases, in order to allow more donor livers suitable for cleavage to be split and to benefit more liver transplant recipients.

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FOOTNOTES

Author contributions: Zhao D contributed to study conception, design, and administrative support; Xie QH, Fang TS, Zhang KJ, Xie WG, and Tang JX contributed to provision of the study materials or patients; Jin X and Xie LJ contributed to collection and assembly of the data; Zhao D and Tang JX contributed to data analysis and interpretation; all authors contributed to manuscript writing and final

approval of the manuscript.

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Informed consent statement: All the patients provided informed consent before operation.

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Data sharing statement: If anyone needs relevant data, they can contact the corresponding author.

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REFERENCES

1 **Smith SK**, Miloh T. Pediatric Liver Transplantation. *Clin Liver Dis* 2022; **26**: 521-535 [PMID: 35868688 DOI: 10.1016/j.cld.2022.03.010]
2 **Perkins JD**, Dick AA, Healey PJ, Montenovo MI, Biggins SW, Sibulesky L, Reyes JD. New Evidence Supporting Increased Use of Split Liver Transplantation. *Transplantation* 2020; **104**: 299-307 [PMID: 31335771 DOI: 10.1097/TP.0000000000002853]
3 **Valentino PL**, Emre S, Geliang G, Li L, Deng Y, Mulligan D, Rodriguez-Davalos MI. Frequency of whole-organ in lieu of split-liver transplantation over the last decade: Children experienced increased wait time and death. *Am J Transplant* 2019; **19**: 3114-3123 [PMID: 31152483 DOI: 10.1111/ajt.15481]
4 **Herden U**, Fischer L, Koch M, Li J, Achilles EG, Nashan B. Outcome following right-extended split liver transplantation in the recent transplant era: Single-center analysis of a German transplant center. *Clin Transplant* 2018; **32**: e13288 [PMID: 29779255 DOI: 10.1111/ctr.13288]
5 **Gambaro SE**, Romero P, Pedraza N, Moulin L, Yantorno S, Ramisch D, Rumbo C, Barros-Schelotto P, Descalzi V, Gondolesi GE. Right Extended Split Liver Transplantation Compared With Whole Liver Transplantation: Lessons Learned at a Single Center in Latin America-Results From a Match Case-Control Study. *Transplant Proc* 2017; **49**: 2122-2128 [PMID: 29149972 DOI: 10.1016/j.transproceed.2017.07.019]
6 **Doyle MB**, Maynard E, Lin Y, Vachharajani N, Shenoy S, Anderson C, Earl M, Lowell JA, Chapman WC. Outcomes with split liver transplantation are equivalent to those with whole organ transplantation. *J Am Coll Surg* 2013; **217**: 102-12; discussion 113 [PMID: 23639200 DOI: 10.1016/j.jamcollsurg.2013.03.003]
7 **Hong JC**, Yersiz H, Farmer DG, Duffy JP, Ghobrial RM, Nonthasoot B, Collins TE, Hiatt JR, Busuttil RW. Longterm outcomes for whole and segmental liver grafts in adult and pediatric liver transplant recipients: a 10-year comparative analysis of 2,988 cases. *J Am Coll Surg* 2009; **208**: 682-9; discusion 689 [PMID: 19476815 DOI: 10.1016/j.jamcollsurg.2009.01.023]
8 **Zhao D**, Zhang KJ, Fang TS, Yan X, Jin X, Liang ZM, Tang JX, Xie LJ. Topological approach of liver segmentation based on 3D visualization technology in surgical planning for split liver transplantation. *World J Gastrointest Surg* 2022; **14**: 1141-1149 [PMID: 36386399 DOI: 10.4240/wjgs.v14.i10.1141]
9 **Sneiders D**, van Dijk ARM, Polak WG, Mirza DF, Perera MTPR, Hartog H. Full-left-full-right split liver transplantation for adult recipients: a systematic review and meta-analysis. *Transpl Int* 2021; **34**: 2534-2546 [PMID: 34773303 DOI: 10.1111/tri.14160]
10 **Kilic M**, Seu P, Stribling RJ, Ghalib R, Goss JA. In situ splitting of the cadaveric liver for two adult recipients. *Transplantation* 2001; **72**: 1853-1858 [PMID: 11740404 DOI: 10.1097/00007890-200112150-00028]
11 **Vagefi PA**, Parekh J, Ascher NL, Roberts JP, Freise CE. Ex vivo split-liver transplantation: the true right/left split. *HPB (Oxford)* 2014; **16**: 267-274 [PMID: 23601002 DOI: 10.1111/hpb.12113]
12 **Ding L**, Yu X, Zhang R, Qian J, Zhang W, Wu Q, Zhou L, Yang Z, Zheng S. Full-Right Full-Left Split Liver Transplantation for Two Adult Recipients: A Single-Center Experience in China. *J Clin Med* 2023; **12** [PMID: 37297977 DOI: 10.3390/jcm12113782]
13 **Xu M**, Dong C, Sun C, Wang K, Zhang W, Qin H, Han C, Yang Y, Zhang F, Wang Z, Zheng W, Wei X, Gao W, Shen Z. Impact of donor age on short-term outcomes after pediatric split liver transplantation. *Front Pediatr* 2023; **11**: 1131629 [PMID: 37114006 DOI: 10.3389/fped.2023.1131629]
14 **Hashimoto K**, Fujiki M, Quintini C, Aucejo FN, Uso TD, Kelly DM, Eghtesad B, Fung JJ, Miller CM. Split liver transplantation in adults. *World J Gastroenterol* 2016; **22**: 7500-7506 [PMID: 27672272 DOI: 10.3748/wjg.v22.i33.7500]
15 **Lee WC**, Chan KM, Chou HS, Wu TJ, Lee CF, Soong RS, Wu TH, Lee CS. Feasibility of split liver transplantation for 2 adults in the model of end-stage liver disease era. *Ann Surg* 2013; **258**: 306-311 [PMID: 23108123 DOI: 10.1097/SLA.0b013e3182754b8e]
16 **Cuenca AG**, Kim HB, Vakili K. Pediatric liver transplantation. *Semin Pediatr Surg* 2017; **26**: 217-223 [PMID: 28964477 DOI:

10.1053/j.sempedsurg.2017.07.014]

17 **Reyes J**, Gerber D, Mazariegos GV, Casavilla A, Sindhi R, Bueno J, Madariaga J, Fung JJ. Split-liver transplantation: a comparison of ex vivo and in situ techniques. *J Pediatr Surg* 2000; **35**: 283-9; discussion 289 [PMID: 10693682 DOI: 10.1016/S0022-3468(00)90026-5]

18 **Cherukuru R**, Reddy MS, Shanmugam NP, Rajalingam R, Kota V, Gunasekaran V, Narasimhan G, Kaliamoorthy I, Rela M. Feasibility and Safety of Split-Liver Transplantation in a Nascent Framework of Deceased Donation. *Liver Transpl* 2019; **25**: 450-458 [PMID: 30586233 DOI: 10.1002/lt.25405]

19 **Dalmau M**, Gómez-Gavara C, Dopazo C, Molino JA, Caralt M, Bilbao I, Charco R, Hidalgo E. Left Lateral Sector In Situ Split Liver Transplantation Technique: Step-by-Step Video Demonstration. *Transplant Proc* 2022; **54**: 2511-2514 [PMID: 36414512 DOI: 10.1016/j.transproceed.2022.09.015]

20 **Lau NS**, Jacques A, McCaughan G, Crawford M, Liu K, Pulitano C. Addressing the challenges of split liver transplantation through technical advances. A systematic review. *Transplant Rev (Orlando)* 2021; **35**: 100627 [PMID: 34052472 DOI: 10.1016/j.trre.2021.100627]

21 **Lau NS**, Ly M, Dennis C, Ewenson K, Ly H, Huang JL, Cabanes-Creus M, Chanda S, Wang C, Lisowski L, Liu K, Kench J, McCaughan G, Crawford M, Pulitano C. Liver splitting during normothermic machine perfusion: a novel method to combine the advantages of both in-situ and ex-vivo techniques. *HPB (Oxford)* 2023; **25**: 543-555 [PMID: 36858919 DOI: 10.1016/j.hpb.2023.02.003]

22 **Wan P**, Li Q, Zhang J, Xia Q. Right lobe split liver transplantation versus whole liver transplantation in adult recipients: A systematic review and meta-analysis. *Liver Transpl* 2015; **21**: 928-943 [PMID: 25832308 DOI: 10.1002/lt.24135]

23 **Mahamid A**, Chen M, Sulimani O, Amodeo S, Facciuto L, Kozato A, Bekki Y, Schiano TD, Facciuto ME. The Importance of Segment 4 Anatomy on Outcomes Following Living Donor Left Lateral Segmentectomy. *J Surg Res* 2023; **285**: 13-19 [PMID: 36638550 DOI: 10.1016/j.jss.2022.12.022]

24 **Shankar S**, Rammohan A, Rela M, Srinivasan P. Surgical anatomy of segment four of liver and its implications in hepato-biliary surgery and liver transplantation. *J Liver Transpl* 2022; **6**: 100076 [DOI: 10.1016/j.liver.2022.100076]

25 **Azoulay D**, Castaing D, Adam R, Savier E, Delvart V, Karam V, Ming BY, Dannaoui M, Krissat J, Bismuth H. Split-liver transplantation for two adult recipients: feasibility and long-term outcomes. *Ann Surg* 2001; **233**: 565-574 [PMID: 11303140 DOI: 10.1097/00000658-200104000-00013]

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ORIGINAL ARTICLE

Retrospective Study

Clinical efficacy of laparoscopic cholecystectomy combined with endoscopic papillary balloon dilation in treatment of gallbladder stones with common bile duct stones: A retrospective study

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Abstract

BACKGROUND

The incidence of cholelithiasis has been on the rise in recent years, but the choice of procedure is controversial.

AIM

To investigate the efficacy of laparoscopic cholecystectomy (LC) combined with endoscopic papillary balloon dilation (EPBD) in patients with gallbladder stones (GS) with common bile duct stones (CBDS).

METHODS

The clinical data of 102 patients with GS combined with CBDS were selected for retrospective analysis and divided into either an LC + EPBD group (n = 50) or an LC + endoscopic sphincterotomy (EST) group (n = 52) according to surgical methods. Surgery-related indexes, postoperative recovery, postoperative complications, and expression levels of inflammatory response indexes were compared between the two groups.

RESULTS

Total surgical time, stone free rate, rate of conversion to laparotomy, and successful stone extraction rate did not differ significantly between the LC + EPBD group and LC + EST group. Intraoperative hemorrhage, time to ambulation, and length of hospitalization in the LC + EPBD group were lower than those of the LC + EST group (P < 0.05). The rate of total complications of the two groups was 9.80% and 17.65%, respectively, and the difference was not statistically significant. No serious complications occurred in either group. At 48 h postoperatively, the expression levels of interleukin-6, tumor necrosis factor-α, high-sensitivity C-reactive protein, and procalcitonin were lower in the LC + EPBD group than in

the LC + EST group ($P < 0.05$). At 3 d postoperatively, the expression levels of aspartate transaminase, alanine transaminase, and total bilirubin were lower in the LC + EPBD group than in the LC + EST group ($P < 0.05$).

CONCLUSION

LC combined with EPBD and LC combined with EST are both effective procedures for the treatment of GS with CBDS, in which LC combined with EPBD is beneficial to shorten the patient's hospitalization time, reduce the magnitude of elevated inflammatory response indexes, and promote postoperative recovery.

Key Words: Gallbladder stone; Common bile duct stone; Endoscopic papillary balloon dilation; Laparoscopic cholecystectomy; Endoscopic sphincterotomy

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Core Tip: The study investigated the efficacy of laparoscopic cholecystectomy (LC) combined with endoscopic papillary balloon dilation (EPBD) and LC combined with endoscopic sphincterotomy (EST) in the treatment of gallbladder stones with common bile duct stones. The results demonstrated a significant reduction in intraoperative bleeding and postoperative recovery time in the LC + EPBD group compared to the LC + EST group. Additionally, there was a notable improvement in inflammatory indexes and liver function. Therefore, LC combined with EPBD may be beneficial to the hospitalization time and inflammatory response of such patients.

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INTRODUCTION

In recent years, there has been a notable increase in the incidence of cholelithiasis. Notably, the prevalence of gallbladder stones (GS) combined with common bile duct stones (CBDS) reaches as high as 20%[1]. The pathogenesis of GS combined with CBDS is multifactorial, involving genetic predisposition and dietary habits, and it is a common disease in clinical surgery. If not treated in time, it can lead to serious complications such as biliary obstruction, posing a life-threatening risk to the patient[2]. GS combined with CBDS is an important clinical problem. In symptomatic patients, the primary goal is to achieve complete stone removal and perform cholecystectomy, while for asymptomatic patients, there remains a lack of standardized treatment options[3]. Studies have found that approximately 25% of patients with GS experience symptoms and/or complications, with a 1%-2% incidence of serious complications. The primary etiology of complications lies in the migratory nature of stones, with common manifestations including biliary pain, pancreatitis, bile duct obstruction, and cholangitis. These complications are typically precipitated by stone migration[4].

The selection of a safer and more effective treatment method for patients with GS combined with CBDS is of paramount importance at present. In general, laparoscopic cholecystectomy (LC) is considered as the preferred method for treating benign gallbladder diseases because of its advantages of short operation time, minimal trauma, and rapid postoperative recovery[5]. In addition, LC combined with endoscopic papillary balloon dilation (EPBD) and LC combined with endoscopic sphincterotomy (EST) have been widely used to treat GS combined with CBDS[6]. The application of EPBD has been reported to result in a decreased occurrence of recurrent cholecystitis, cholangitis, and bile duct stones when compared to EST[7]. A randomized controlled trial showed that the incidence of postoperative pancreatitis after EPBD was 16.7%, which was significantly higher than that of EST surgery[8]. However, another study indicated that the incidence of pancreatitis could be reduced by prolonging the duration of EPBD balloon dilatation[9]. This implies that there remains a degree of debate concerning the selection between these two methodologies. Therefore, this retrospective clinical study aimed to compare the efficacy of LC combined with EPBD *vs* LC combined with EST for treating GS combined with CBDS in 102 patients in the Gastroenterology Department of our hospital.

MATERIALS AND METHODS

General information

The clinical data of 102 patients with GS combined with CBDS in the Department of Gastroenterology of the Third Affiliated Hospital of Qiqihar Medical University Hospital from December 2018 to December 2023 were selected for a retrospective study, and they were divided into either an EPBD + LC group ($n = 50$) or an EST + LC group ($n = 52$) according to the surgical methods.

The inclusion criteria were: (1) Patients meeting the diagnostic criteria for GS and CBDS in the 7th edition of Surgery; (2) Patients with a diagnosis of the condition confirmed by computed tomography, magnetic resonance imaging, and other imaging examinations before surgery; (3) Patients with a diameter of the common bile duct ≥ 0.8 cm, and the maximum diameter of CBDS < 2.0 cm; (4) Patients aged 42-75 years old; (5) Patients providing written informed consent; and (6) Patients with no contraindications to surgery or anesthesia.

The exclusion criteria were: (1) Patients with a prior history of upper abdominal surgery; (2) Patients diagnosed with neoplasms affecting the gallbladder or biliary system; (3) Patients with acute septic cholangitis or acute pancreatitis; and (4) Patients with incomplete clinical data. The study was approved by the Ethics Committee of the Third Affiliated Hospital of Qiqihar Medical University (No. 2023LW-3) and all participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Treatment methods

Before the treatment of choledocholithiasis, patients were required to undergo a routine preoperative evaluation to assess their cardiovascular and respiratory fitness. Additionally, they must adhere to a fasting period of 6 h prior to surgery. The LC + EPBD group was treated as follows. First, the patient was given lidocaine local anesthesia to anesthetize the pharynx. Then, operating endoscopically, a guidewire was placed at the opening of the papilla and a dilatation balloon was placed in the position of the guidewire. The balloon dilation was observed and, following confirmation of proper dilation, the guidewire and balloon catheter were withdrawn from the body. Next, the stones were removed from the common bile duct using a reticular basket to ensure that they were completely removed and the duct was clear. A nasobiliary tube was placed for drainage after the procedure and an LC was scheduled at a later time.

The LC + EST group was treated as follows. The patient was positioned in the left lateral decubitus position and received general anesthesia. A duodenoscope was then inserted through the oral cavity, followed by a precise incision made in the papillary sphincter using a high-frequency electric knife. Next, stones were removed from the common bile duct using a reticular basket for stone extraction, and a nasobiliary tube was placed for drainage. Food and water were fasted for 24 h postoperatively, and LC was performed after the patient's condition was stabilized.

Observation indicators

Observational indicators included patients' general information, surgical success rate, surgery-related indexes, post-surgical recovery, and complications (before discharge). Inflammatory indexes [interleukin-6 (IL-6), IL-10, tumor necrosis factor-α (TNF-α), high-sensitivity C-reactive protein (hs-CRP), and procalcitonin (PCT)], hepatic function indexes [aspartate transaminase (AST), alanine transaminase (ALT), and total bilirubin (TBIL)], surgery-related indexes (stone free rate, total operation time, intraoperative hemorrhage, rate of conversion to laparotomy, *etc.*), postoperative recovery [visual analogue scale (VAS) score at 6 h postoperatively, time to postoperative exhaust, time to ambulation, length of hospitalization, *etc.*], and complications (hemorrhage, cholecystitis, acute pancreatitis, *etc.*) were also recorded.

Surgical success rate was judged by the following criteria. "Significantly effective" referred to the complete resolution of clinical symptoms, total elimination of stones, and restoration of normal gastrointestinal function within 24 h post-surgery without any complications. "Effective" meant achieving clinical symptom improvement, complete stone removal, and restoration of normal gastrointestinal function within 7 d after surgery without any infections or complications. "Ineffective" meant not meeting the criteria for symptoms, stones, and gastrointestinal function mentioned above. The surgical success rate was calculated as (significantly effective + effective) cases/total cases × 100%.

Evaluation of therapeutic effects

The efficacy for a duration of 14 d was assessed based on the criteria outlined in the Surgery of Hepatobiliary Oncology: Significantly effective: Ultrasonography revealed a significant reduction in the thickness and size of the gallbladder wall, approaching normal levels. No recurrence has been observed for three consecutive months; effective: Although the volume of the gallbladder wall and lower gallbladder was not within normal range, it exhibited obvious thinning and shrinkage, leading to significant alleviation of clinical symptoms; ineffective: Absence of any alteration in the volume of the gallbladder wall and lower gallbladder, coupled with a lack of reduction or even exacerbation of clinical symptoms.

Statistical analysis

SPSS 22.0 software was used for statistical analyses. Measurement data are expressed as the mean ± SD, and comparisons between groups were conducted using a *t*-test. Count data are presented as *n* (%), and comparisons between groups were performed using a χ^2 test. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

General information of patients

The comparison of age, gender, body mass index, size of bile duct stones, diameter of common bile duct, and number of bile duct stones between the two groups of patients did not reveal any statistically significant differences ($P > 0.05$) (Table 1).

Surgical success rate

There was no significant difference in the success rates between the two groups ($P > 0.05$) (Table 2).

Table 1 General data of the two patient groups

Variable	LC + EPBD group (*n* = 50)	LC + EST group (*n* = 52)	t/χ^2	*P* value
Age (year)	57.22 ± 8.03	58.19 ± 8.74	-0.584	0.560
Gender (male/female)	25/24	24/28	0.151	0.698
BMI	22.35 ± 3.21	23.15 ± 3.91	-1.127	0.263
Size of bile duct stones (mm)	8.18 ± 2.19	8.56 ± 2.57	-0.797	0.427
Diameter of the common bile duct (mm)	11.84 ± 1.40	12.12 ± 1.59	-0.925	0.357
Number of bile duct stones (*n*)	3.02 ± 1.22	2.77 ± 1.17	1.062	0.291

LC: Laparoscopic cholecystectomy; EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; BMI: Body mass index.

Table 2 Comparison of surgical success rates between the two groups, *n* (%)

Item	LC + EPBD group (*n* = 50)	LC + EST group (*n* = 52)	χ^2	*P* value
Significantly effective	38 (76.00)	37 (71.20)	0.527	0.768
Effective	9 (18.00)	10 (19.20)		
Ineffective	3 (6.00)	5 (9.60)		
Surgical success rate	47 (94.00)	44 (90.40)		

LC: Laparoscopic cholecystectomy; EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation.

Surgery-related indicators

Total operation time, rate of conversion to laparotomy, stone removal rate, and success rate of stone extraction did not differ significantly between the two groups ($P > 0.05$). Intraoperative hemorrhage, time to ambulation, and length of hospitalization were significantly lower in the LC + EPBD group than in the LC + EST group ($P < 0.05$) (Table 3).

Comparison of postoperative recovery between the two groups

Comparison of VAS score at 6 h postoperatively and time to postoperative exhaust between the two groups showed no statistically significant difference ($P > 0.05$). The time to ambulation and hospitalization time of patients in the LC + EPBD group were significantly shorter than those of the LC + EST group ($P < 0.05$) (Table 4).

Comparison of complications after surgery in the two groups

The overall incidence of complications in the LC + EPBD and LC + EST groups was 7.84% and 9.80%, respectively. All the complications resolved after conservative treatment. Although the number of cases of pancreatitis in the LC + EPBD group was more than that of the LC + EST group, and the number of cases with cholangitis and abdominal infection was significantly less than that of the LC + EST group ($P > 0.05$) (Table 5).

Expression of inflammatory response indicators

Before surgery, IL-6, IL-10, TNF-α, hs-CRP, and PCT were not significantly different between the two groups ($P > 0.05$). At 48 h after surgery, IL-6, TNF-α, hs-CRP, and PCT in the LC + EPBD group were significantly lower than those of the LC + EST group ($P < 0.05$) (Table 6).

Comparison of preoperative and postoperative liver function indexes between the two groups

The expression levels of AST, ALT, and TBIL were not significantly different between the two groups before operation ($P > 0.05$). At 3 d after surgery, AST, ALT, and TBIL in both groups were lower than preoperative values, and AST, ALT, and TBIL in the LC + EPBD group were significantly lower than those of the LC + EST group ($P < 0.05$) (Table 7).

DISCUSSION

Cholelithiasis, a common biliary tract disease both domestically and internationally, can be categorized into cholesterol stones, pigment calculus, and combination calculus based on their composition. It is often caused by bile stasis, bacterial infections, and other factors leading to the formation of single or multiple stone obstructions in any part of the biliary tract system. Consequently, symptoms such as abdominal pain, nausea and vomiting, and jaundice may occur[10].

Table 3 Surgery-related indicators in the two groups

Item	LC + EPBD group (*n* = 50)	LC + EST group (*n* = 52)	t/χ^2	*P* value
Total operation time (min)	94.16 ± 14.32	92.37 ± 12.85	0.667	0.507
Intraoperative hemorrhage (mL)	32.98 ± 8.95	37.48 ± 8.85	-2.554	0.012
Rate of conversion to laparotomy, *n* (%)	0	0	/	/
Success rate of stone extraction, *n* (%)	48 (96.00)	49 (94.20)		1.000
Stone removal rate, *n* (%)	48 (96.00)	50 (96.20)		1.000

LC: Laparoscopic cholecystectomy; EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation.

Table 4 Comparison of postoperative recovery between the two groups

Item	LC + EPBD group (*n* = 50)	LC + EST group (*n* = 52)	*t*	*P* value
VAS score	3.06 ± 0.74	3.21 ± 0.87	-0.945	0.347
Time to postoperative exhaust (d)	1.34 ± 0.63	1.42 ± 0.67	-0.648	0.519
Time to ambulation (d)	1.32 ± 0.62	1.82 ± 0.51	-4.502	< 0.001
Hospitalization time (d)	11.52 ± 1.76	11.98 ± 1.48	-1.433	0.155

LC: Laparoscopic cholecystectomy; EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; VAS: Visual analogue scale.

Table 5 Comparison of complications after surgery in the two groups, *n* (%)

Item	LC + EPBD group (*n* = 50)	LC + EST group (*n* = 52)	χ^2	*P* value
Pancreatitis	3 (6.00)	2 (3.80)		0.675
Cholangitis	1 (2.00)	2 (3.80)		1.000
Abdominal infection	0	1 (1.90)		1.000
Death	0	0		/
Perforation	0	0		/
Overall complications	4 (8.00)	5 (9.60)		1.000

LC: Laparoscopic cholecystectomy; EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation.

Historically, surgical interventions such as open exploratory cholecystectomy and choledochotomy for stone extraction have been the primary treatments for GS combined with CBDS. The advancement of minimally invasive endoscopic techniques has led to the development of various surgical procedures for treating GS combined with CBDS, although there is still some controversy regarding the optimal treatment method. Studies have confirmed that LC is a safe and effective procedure for treating GS, observing gallbladder structures and adhesions under laparoscopic guidance, reducing perioperative stress reactions, and promoting rapid postoperative physical recovery[11]. The combination of LC with EST and EPBD represents two distinct approaches for the treatment of GS combined with CBDS, offering the advantages of reduced invasiveness, diminished pain, accelerated recovery, and shortened hospitalization duration[12]. According to the national and international literature, the combination of LC with EPBD and EST has demonstrated significant clinical benefits in the treatment of GS combined with CBDS[13,14]. The efficacy of EST in the treatment of GS combined with CBDS is widely acknowledged, although it carries potential risks including hemorrhage, perforation, and permanent impairment of sphincter function[15,16]. To mitigate these complications, the EPBD technique was introduced for the management of GS combined with CBDS. This technique involves utilizing a biliary dilatation balloon to enlarge the biliary orifice without incising the papillary sphincter, as initially reported by Ishii *et al*[17].

The incidence of bleeding and perforation during EPBD was reported to be extremely low, particularly in the presence of coagulation disorders or anatomical alterations. Additionally, the efficacy of stone removal was found to be comparable to that achieved with EST[18]. The findings of this study demonstrated that the combination of LC and EPBD exhibited advantages in terms of intraoperative hemorrhage, time to ambulation, and length of hospitalization. These results suggest that LC combined with EPBD may effectively reduce intraoperative hemorrhage and promote patient recovery. This could be attributed to the avoidance of papillary sphincter incision by EPBD, which preserves the integrity

Table 6 Expression of inflammatory response indicators in the two groups

Indicator	LC + EPBD group (*n* = 50)	LC + EST group (*n* = 52)	*t*	*P* value
IL-6 (pg/mL)				
Preoperative	12.96 ± 2.83	13.21 ± 3.25	0.426	0.671
48 h postoperatively	20.43 ± 3.02	24.84 ± 3.51	6.783	< 0.001
IL-10 (pg/mL)				
Preoperative	17.35 ± 3.94	16.21 ± 4.06	1.439	0.153
48 h postoperatively	13.43 ± 2.25	13.26 ± 2.47	0.347	0.729
TNF-α (pg/mL)				
Preoperative	18.35 ± 4.32	18.92 ± 4.75	0.624	0.534
48 h postoperatively	36.36 ± 8.35	46.22 ± 8.95	5.744	< 0.001
hs-CRP (mg/L)				
Preoperative	4.43 ± 1.38	4.78 ± 1.67	1.177	0.242
48 h postoperatively	15.07 ± 3.04	18.75 ± 5.16	4.361	< 0.001
PCT (ng/mL)				
Preoperative	0.35 ± 0.14	0.32 ± 0.16	1.039	0.301
48 h postoperatively	1.42 ± 0.47	1.51 ± 0.38	1.069	0.290

LC: Laparoscopic cholecystectomy; EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; IL: Interleukin; TNF: Tumor necrosis factor; hs-CRP: High-sensitivity C-reactive protein; PCT: Procalcitonin.

Table 7 Comparison of liver function indicators in the two groups

Indicator	LC + EPBD group (*n* = 50)	LC + EST group (*n* = 52)	*t*	*P* value
AST (U/L)				
Preoperative	54.72 ± 4.36	55.24 ± 5.55	0.525	0.600
3 d postoperatively	30.56 ± 5.64	41.91 ± 6.03	9.804	< 0.001
ALT (U/L)				
Preoperative	72.84 ± 6.92	71.43 ± 7.58	0.973	0.333
3 d postoperatively	47.94 ± 7.37	59.35 ± 7.58	7.699	< 0.001
TBIL (umol/L)				
Preoperative	52.14 ± 6.42	54.22 ± 7.15	1.537	0.127
3 d postoperatively	24.14 ± 6.45	27.22 ± 7.05	2.293	0.024

LC: Laparoscopic cholecystectomy; EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; AST: Aspartate transaminase; ALT: Alanine transaminase; TBIL: Total bilirubin.

of biliary-intestinal union and maintains its physiological function. In addition, the incidence of postoperative complications was lower in both groups, which proved that both LC combined EPBD and LC combined EST have high safety and could effectively avoid excessive injury to the body. Although the incidence of pancreatitis was higher in the LC + EPBD group compared to the LC + EST group, the difference did not reach statistical significance. Some researchers suggest that pancreatitis may be attributed to sphincter dilatation leading to intramucosal hemorrhage, edema, and subsequent obstruction of the pancreatic duct[19]. Meanwhile, several studies have demonstrated a negative correlation between the duration of EPBD and the risk of pancreatitis. Additionally, it has been observed that balloon dilatation for ≤ 1 min increases the likelihood of pancreatitis in patients with CBDS. However, prolonging the duration to at least > 3 min effectively reduces the incidence of pancreatitis[20]. Therefore, EPBD may be a safe and effective alternative to EST for the treatment of GS combined with CBDS.

In addition, patients often have different stress responses during surgery, which may suppress the immune response and heighten inflammation levels, increasing the risk of postoperative complications. The control of inflammation is a crucial determinant for disease prognosis and recovery[21]. IL-6, TNF-α, hs-CRP, and PCT are all common indicators of

inflammatory response in the body, and are associated with the risk of gallstone disease. Among them, IL-6 is an important pro-inflammatory factor, which is produced by a variety of immune cells stimulated by various factors to participate in the body's inflammatory and immune responses[22]. Studies have shown that IL-6 overexpression in the biliary epithelium causes inflammatory cell infiltration and increases the thickness of the gallbladder wall, thus inducing gallstones[23]. IL-6 also induces the liver to release the non-specific acute phase protein CRP, which is normally expressed at low levels, but when an acute inflammatory response is initiated, CRP rises dramatically, exerting an anti-inflammatory effect and reducing excessive tissue damage[24]. TNF-α production is often significantly increased during trauma, inflammation, and infection. Wan *et al*[25] confirmed that it was elevated after GS combined with CBDS, which may reflect the body's stress to inflammation and trauma.

PCT, serving as a biomarker for assessing inflammatory response, typically remains at a basal level. However, during the period of inflammation, its expression level becomes elevated, reflecting the severity of inflammation within the body [26]. The severity of acute cholecystitis is positively correlated with PCT, making it a valuable laboratory indicator for assessing the severity of this complication in gallstone patients[27]. In this study, both groups exhibited high levels of IL-6, TNF-α, hs-CRP, and PCT after surgery. However, the elevation of IL-6, TNF-α, hs-CRP, and PCT was comparatively lower in the LC + EPBD group than in the LC + EST group. This difference can be attributed to the fact that in the LC + EPBD group, repeated lithotripsy is avoided during surgery, thereby mitigating biliary tract injury and reducing traumatic operations such as resection and other stress reactions.

The liver function indexes, including ALT, AST, and TBIL, can serve as indicators of hepatocellular injury severity. In patients with GS combined with CBDS, significantly elevated levels of serum AST, ALT, and TBIL were observed. This finding may be attributed to the impact of artificial pneumoperitoneum during surgery on hepatic tissue hemodynamics and subsequent reduction in blood flow through the hepatic artery and portal vein leading to impaired liver function [28]. In addition, a meta-analysis found that CBDS was the most common etiology for significantly elevated ALT levels (> 500 IU/L), and that approximately one-third of patients with CBDS would present with ALT or AST > 500 IU/L[29]. The elevation of TBIL levels in certain pathological conditions may augment and predispose to the development of gallstones [30]. In this study, the preoperative liver function indexes of the patients were consistent with previous findings. The LC + EPBD group demonstrated a significant reduction in AST, ALT, and TBIL levels, indicating that this approach effectively improved liver function. This could be attributed to the fact that LC combined with EPBD obviated the need for incising the papillary sphincter, thereby mitigating local damage and reducing inflammatory factor release, ultimately safeguarding liver function.

This study, however, still has certain limitations, such as small sample size, which may somewhat restrict the generalizability of the findings. The limited duration of the study precluded a comprehensive evaluation of long-term outcomes and complication rates. Furthermore, potential confounding factors that were not adequately controlled for in the study, such as inter-individual variations among patients and uncertainty surrounding complications, may have influenced the objectivity of the findings. The current study necessitates further expansion of the sample size and longer follow-up periods in order to comprehensively evaluate the actual efficacy and safety of this surgical procedure.

CONCLUSION

In summary, both LC combined with EPBD and LC combined with EST are effective for the treatment of GS with CBDS. In the present study, LC combined with EPBD achieved better clinical benefits, and was conducive to shortening the hospitalization time, reducing inflammatory stress response, and improving the liver function. However, there were some limitations, which must be validated in the future by using large samples and other research methods. In addition, according to literature reports[31], traditional Chinese medicine such as Da Chaihu Tang, anti-inflammatory and bile-relieving Tang, and Xiao Chaihu Tang play a crucial role in the treatment of GS combined with CBDS. These medications have been shown to significantly reduce cholesterol and bile acid levels, expedite the body's recovery, and effectively decrease stone recurrence rates. Therefore, the the synergistic treatment program of Chinese and Western medicines can be used to improve patients' postoperative recovery and reduce the occurrence of complications.

FOOTNOTES

Author contributions: Liu HD and Jin S contributed to the conception and design of this study, collection and assembly of the data, and data analysis and interpretation; Liu HD participated in the administrative support; Liu HD, Zhang Q, Xu WS, and Jin S were involved in the provision of study materials or patients of this study; and all authors wrote the manuscript and approved the final manuscript.

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REFERENCES

1 **Scherber PR**, Zúniga SE, Glanemann M, Lammert F. [Gallstone disease - interdisciplinary treatment]. *Dtsch Med Wochenschr* 2020; **145**: 287-295 [PMID: 32120403 DOI: 10.1055/a-0944-8655]
2 **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]
3 **Cianci P**, Restini E. Management of cholelithiasis with choledocholithiasis: Endoscopic and surgical approaches. *World J Gastroenterol* 2021; **27**: 4536-4554 [PMID: 34366622 DOI: 10.3748/wjg.v27.i28.4536]
4 **Troncone E**, Mossa M, De Vico P, Monteleone G, Del Vecchio Blanco G. Difficult Biliary Stones: A Comprehensive Review of New and Old Lithotripsy Techniques. *Medicina (Kaunas)* 2022; **58** [PMID: 35056428 DOI: 10.3390/medicina58010120]
5 **Tian D**, Zhu H, Wei X. Hybrid Laparoendoscopic-Radiologic Procedure for Laparoscopic Cholecystectomy Complicated With Choledocolithiasis. *Surg Laparosc Endosc Percutan Tech* 2020; **30**: 221-226 [PMID: 31985571 DOI: 10.1097/SLE.0000000000000758]
6 **Masuda S**, Koizumi K, Shionoya K, Jinushi R, Makazu M, Nishino T, Kimura K, Sumida C, Kubota J, Ichita C, Sasaki A, Kobayashi M, Kako M, Haruki U. Comprehensive review on small common bile duct stones. *World J Gastroenterol* 2023; **29**: 1955-1968 [PMID: 37155530 DOI: 10.3748/wjg.v29.i13.1955]
7 **Wang Q**, Fu L, Wu T, Ding X. The ballooning time in endoscopic papillary balloon dilation for removal of bile duct stones: A systematic review and meta-analysis. *Medicine (Baltimore)* 2021; **100**: e24735 [PMID: 33725940 DOI: 10.1097/MD.0000000000024735]
8 **Meng W**, Leung JW, Zhang K, Zhou W, Wang Z, Zhang L, Sun H, Xue P, Liu W, Wang Q, Zhang J, Wang X, Wang M, Shao Y, Cai K, Hou S, Li Q, Zhu K, Yue P, Wang H, Zhang M, Sun X, Yang Z, Tao J, Wen Z, Chen B, Shao Q, Zhao M, Zhang R, Jiang T, Liu K, Chen K, Zhu X, Zhang H, Miao L, Li J, Yan X, Wang F, Suzuki A, Tanaka K, Nur U, Weiderpass E, Li X. Optimal dilation time for combined small endoscopic sphincterotomy and balloon dilation for common bile duct stones: a multicentre, single-blinded, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2019; **4**: 425-434 [PMID: 31003961 DOI: 10.1016/S2468-1253(19)30075-5]
9 **Yu ZY**, Liang C, Yang SY, Zhang X, Sun Y. The therapeutic effect of balloon dilatation with different duration for biliary duct calculi: A network meta-analysis. *J Minim Access Surg* 2022; **18**: 327-337 [PMID: 35708376 DOI: 10.4103/jmas.JMAS_304_20]
10 **Yu S**, Shi S, Zhu X. Clinical effect of laparoscopic cholecystectomy in the treatment of chronic cholecystitis with gallstones. *Biotechnol Genet Eng Rev* 2023; 1-13 [PMID: 37098886 DOI: 10.1080/02648725.2023.2204710]
11 **Ye Q**, Zhang J, Ou X, Zhou X, Zhu C, Li W, Yao J, Zhang G. Efficacy and safety of three endoscopic techniques for small common bile duct stones (≤ 10 mm): a multicenter, retrospective, cohort study with propensity score matching. *Surg Endosc* 2023; **37**: 1863-1869 [PMID: 36253627 DOI: 10.1007/s00464-022-09436-y]
12 **Lyu Y**, Cheng Y, Wang B, Zhao S, Chen L. Comparison of the Efficacy and Safety of Three Endoscopic Methods to Manage Large Common Bile Duct Stones: A Systematic Review and Network Meta-Analysis. *J Laparoendosc Adv Surg Tech A* 2021; **31**: 443-454 [PMID: 32762611 DOI: 10.1089/lap.2020.0511]
13 **Hu J**, Mu N, He Y. Comparing the efficacy of endoscopic balloon dilation alone and combined with endoscopic sphincterotomy for common bile duct stone: a systematic review and meta-analysis. *Ann Palliat Med* 2022; **11**: 163-172 [PMID: 35144408 DOI: 10.21037/apm-21-3557]
14 **Classen M**, Demling L. [Endoscopic sphincterotomy of the papilla of vater and extraction of stones from the choledochal duct (author's transl)]. *Dtsch Med Wochenschr* 1974; **99**: 496-497 [PMID: 4835515 DOI: 10.1055/s-0028-1107790]
15 **Asuri K**, Jain M, Maheshwari P, Prakash O, Kumar S, Garg P, Sagar R, Bansal VK. Quality of Life Outcomes Following Single-stage Laparoscopic Common Bile Duct Exploration Versus 2-stage Endoscopic Sphincterotomy Followed by Laparoscopic Cholecystectomy in Management of Cholelithiasis With Choledocholithiasis. *Surg Laparosc Endosc Percutan Tech* 2021; **31**: 285-290 [PMID: 33538548 DOI: 10.1097/SLE.0000000000000902]
16 **Yasuda I**. Pancreato-hepatobiliary endoscopy: Endoscopic management of bile duct stones. *Dig Endosc* 2022; **34** Suppl 2: 116-119 [PMID: 34505323 DOI: 10.1111/den.14113]
17 **Ishii S**, Isayama H, Ushio M, Takahashi S, Yamagata W, Takasaki Y, Suzuki A, Ochiai K, Tomishima K, Kanazawa R, Saito H, Fujisawa T, Shiina S. Best Procedure for the Management of Common Bile Duct Stones *via* the Papilla: Literature Review and Analysis of Procedural Efficacy and Safety. *J Clin Med* 2020; **9** [PMID: 33255554 DOI: 10.3390/jcm9123808]
18 **Liao WC**, Lee CT, Chang CY, Leung JW, Chen JH, Tsai MC, Lin JT, Wu MS, Wang HP. Randomized trial of 1-minute versus 5-minute endoscopic balloon dilation for extraction of bile duct stones. *Gastrointest Endosc* 2010; **72**: 1154-1162 [PMID: 20869710 DOI: 10.1016/j.gie.2010.07.009]
19 **Liao WC**, Tu YK, Wu MS, Wang HP, Lin JT, Leung JW, Chien KL. Balloon dilation with adequate duration is safer than sphincterotomy for extracting bile duct stones: a systematic review and meta-analyses. *Clin Gastroenterol Hepatol* 2012; **10**: 1101-1109 [PMID: 22642953 DOI: 10.1016/j.cgh.2012.05.017]

20 **Chou CK**, Lee KC, Luo JC, Chen TS, Perng CL, Huang YH, Lin HC, Hou MC. Endoscopic papillary balloon dilatation less than three minutes for biliary stone removal increases the risk of post-ERCP pancreatitis. *PLoS One* 2020; **15**: e0233388 [PMID: 32453738 DOI: 10.1371/journal.pone.0233388]

21 **Gümüs K**, Pirhan Y, Aydın G, Keloglan S, Tasova V, Kahveci M. The Effect of Preoperative Oral Intake of Liquid Carbohydrate on Postoperative Stress Parameters in Patients Undergoing Laparoscopic Cholecystectomy: An Experimental Study. *J Perianesth Nurs* 2021; **36**: 526-531 [PMID: 33926804 DOI: 10.1016/j.jopan.2020.10.012]

22 **Kang S**, Narazaki M, Metwally H, Kishimoto T. Historical overview of the interleukin-6 family cytokine. *J Exp Med* 2020; **217** [PMID: 32267936 DOI: 10.1084/jem.20190347]

23 **Liu Z**, Kemp TJ, Gao YT, Corbel A, McGee EE, Wang B, Shen MC, Rashid A, Hsing AW, Hildesheim A, Pfeiffer RM, Pinto LA, Koshiol J. Association of circulating inflammation proteins and gallstone disease. *J Gastroenterol Hepatol* 2018; **33**: 1920-1924 [PMID: 29671891 DOI: 10.1111/jgh.14265]

24 **Liu F**, Li L, Xu M, Wu J, Luo D, Zhu Y, Li B, Song X, Zhou X. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. *J Clin Virol* 2020; **127**: 104370 [PMID: 32344321 DOI: 10.1016/j.jcv.2020.104370]

25 **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]

26 **Zhang L**, Zhang X. Serum sTREM-1, PCT, CRP, Lac as Biomarkers for Death Risk Within 28 Days in Patients with Severe Sepsis. *Open Life Sci* 2018; **13**: 42-47 [PMID: 33817066 DOI: 10.1515/biol-2018-0006]

27 **Sakalar S**, Ozakın E, Cevik AA, Acar N, Dogan S, Kaya FB, Kara T. Plasma Procalcitonin Is Useful for Predicting the Severity of Acute Cholecystitis. *Emerg Med Int* 2020; **2020**: 8329310 [PMID: 32399305 DOI: 10.1155/2020/8329310]

28 **Zgheib H**, Wakil C, Al Souky N, Mailhac A, Jamali F, El Sayed M, Tamim H. Liver function tests as predictors of common bile duct stones in acute cholecystitis patients with a chronic history: A retrospective cohort study on the ACS-NSQIP database. *Medicine (Baltimore)* 2021; **100**: e26885 [PMID: 34414941 DOI: 10.1097/MD.0000000000026885]

29 **Mohamed MFH**, Elfert K, Wadhavkar N, Marino D, Farrakhan K, Beran A, Abdallah MA, Abdalla A, Farrell R. Choledocholithiasis Can Present with Marked Transaminases Elevation: Systematic Review and Meta-Analysis. *Dig Dis Sci* 2023; **68**: 3428-3435 [PMID: 37269372 DOI: 10.1007/s10620-023-07981-7]

30 **Chen Q**, Zhang Y, Li S, Chen S, Lin X, Li C, Asakawa T. Mechanisms Underlying the Prevention and Treatment of Cholelithiasis Using Traditional Chinese Medicine. *Evid Based Complement Alternat Med* 2019; **2019**: 2536452 [PMID: 31316569 DOI: 10.1155/2019/2536452]

31 **Li B**, Lin Y, Nie B, Zhao G, Zhang X, Zhu M, Hu J, Huang P, Feng S, Qiu R, Tian G, Zhang S, Shang H. Systematic review and pathway enrichment analysis of Chinese medicine in preventing recurrence and improving prognosis of cholelithiasis after gallbladder-preserving lithotripsy. *Ann Palliat Med* 2021; **10**: 12985-13001 [PMID: 34498482 DOI: 10.21037/apm-20-1135]

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ORIGINAL ARTICLE

Retrospective Study

Evaluation of oxaliplatin and tigio combination therapy in locally advanced gastric cancer

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Abstract

BACKGROUND

Locally advanced gastric cancer (LAGC) is a common malignant tumor. In recent years, neoadjuvant chemotherapy has gradually become popular for the treatment of LAGC.

AIM

To investigate the efficacy of oxaliplatin combined with a tigio neoadjuvant chemotherapy regimen *vs* a conventional chemotherapy regimen for LAGC.

METHODS

Ninety patients with LAGC were selected and randomly divided into control and study groups with 45 patients in each group, according to the numerical table method. The control group was treated with conventional chemotherapy, and the study group was treated with oxaliplatin combined with tigio-neoadjuvant chemotherapy. The primary outcome measures were the clinical objective response rate (ORR) and surgical resection rate (SRR), whereas the secondary outcome measures were safety and Karnofsky Performance Status score.

RESULTS

The ORR in the study group was 80.00%, which was significantly higher than that of the control group (57.78%). In the study group, SRR was 75.56%, which was significantly higher than that of the control group (57.78%). There were 15.56% adverse reactions in the study group and 35.56% in the control group. These differences were statistically significant between the two groups.

CONCLUSION

The combination of oxaliplatin and tigio before surgery as neoadjuvant chemotherapy for patients with LAGC can effectively improve the ORR and SRR and is safe.

Key Words: Locally advanced gastric cancer; Oxaliplatin and tigio; Neoadjuvant chemotherapy; Surgical resection rate; Objective response rate; Clinical efficacy

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Core Tip: This study identified the following highlights. The objective response rate in the study was 80.00%, which was significantly higher than that of the control group (57.78%). In the study group, 75.56% of the tumors were resected, which was significantly higher than that of the control group (57.78%). There were 15.56% adverse reactions in the study group and 35.56% in the control group. These differences were statistically significant between the two groups.

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INTRODUCTION

According to the Global Cancer Statistics Report 2022, stomach cancer is the fifth most common malignancy worldwide and one of the leading causes of cancer-related deaths[1]. As of 2022, there were approximately 1089103 new cases of gastric cancer (GC) worldwide and approximately 768793 deaths[2]. GC is usually diagnosed at advanced stages in Chinese patients, and surgical resection remains the primary choice of treatment. However, in locally advanced GC (LAGC), only a small percentage of cases are surgically resected, and the proportion of radical resections is even low[3]. After exploratory laparotomy, the opportunity for surgery is often lost because the tumor invades adjacent organs, has extensive infiltration and metastasis, or only palliative resection can be performed, and the postoperative survival rate is low[4].

With the advancement of diagnostic and treatment technology in recent years, comprehensive treatment of GC has made some progress[5]. However, there is still a 20% 5-year survival rate for LAGC, and the postoperative recurrence rate and mortality rate remain high[6]. It is estimated that around 60% of the patients with GC will have local recurrence or distant metastasis even after radical resection (R0 resection)[7]. The proportion of patients with GC in stages II-III in our country is as high as 58.0%[8]. To improve the rate of R0 resection and reduce the incidence of postoperative recurrence and metastasis, the addition of neoadjuvant therapy undoubtedly brings new hope for the survival and benefits of patients with GC.

Studies have shown that neoadjuvant chemotherapy is a type of systemic chemotherapy for patients before surgery that plays a role in shrinking tumors and facilitating follow-up treatment[9,10]. Compared with conventional treatment, neoadjuvant chemotherapy has more significant clinical efficacy, higher drug safety, better disease control effects, and higher application value in advanced tumors[11,12]. Japan is advocating a chemotherapy regimen based on tigio (S-1)[13]. Tigio, a derivative of fluorouracil, is an oral anticancer agent with definite efficacy in the adjuvant treatment of GC. Five-year survival data from a Japanese trial of tigio-assisted chemotherapy for GC confirmed an improvement in 5-year OS in patients receiving tigio-assisted chemotherapy (71.7% *vs* 61.1%)[14]. However, due to the limited efficacy of single-drug chemotherapy, multi-drug combination regimens are often used clinically. In the ARTIST2 trial, it was shown that postoperative adjuvant (oxaliplatin + tigio) or SOX + radiotherapy could effectively extend disease-free survival in D2-resectable stage II/ III GC patients compared to tigio monotherapy[15]. Currently, regarding the neoadjuvant treatment of LAGC, a large-scale phase III clinical trial in China has confirmed the remarkable efficacy of the neoadjuvant scheme, and thus determined that oxaliplatin plus S-1 is the first choice for neoadjuvant chemotherapy of LAGC in China[16].

In this study, we compared the effectiveness of oxaliplatin combined with a tigio neoadjuvant chemotherapy regimen to a conventional chemotherapy regimen for LAGC to further improve the clinical efficacy in patients with LAGC.

MATERIALS AND METHODS

General information

Ninety patients with clinically diagnosed LAGC between June 2022 and June 2023 were included in this study. Patients were randomly divided into a study group (45 patients) and a control group (45 patients). Both groups underwent B-ultrasonography and magnetic resonance imaging to detect abdominal lymph node metastasis, lesion infiltration, and organ metastasis. Upper gastrointestinal barium meal test revealed normal digestion.

Inclusion and exclusion criteria

The inclusion criteria[17] were as follows: pathologically diagnosed LAGC, aged between 18 and 75 years, did not receive chemotherapy or radiotherapy, no distant metastasis, signed the informed consent form, the expected survival time was

more than 6 months, and the Karnofsky Performance Status (KPS) score was > 60 points. The exclusion criteria were as follows: those whose physical signs did not meet the standards for chemotherapy, history of GC-related diagnosis and treatment, combined with other malignant tumors, and pregnant and lactating women.

Ethical approval

The hospital ethics committee approved informed consent forms for all chemotherapy patients.

Treatment methods

The 90 enrolled patients underwent routine and complete examinations, routine blood tests, liver and kidney function tests, electrocardiography, and cardiac ultrasonography. Antiemetics, stomach and liver protection, and other treatments were routinely administered before medication; specifically, 30 min before medication, patients were instructed to take intramuscular diphenhydramine and intravenously administered cimetidine (300.0 mg), and dexamethasone (7.5 mg) at 21:00 the previous night and 6 h in the morning of chemotherapy, and patients were administered antiemetic treatment with drugs, such as granisetron and metoclopramide.

In the control group, conventional chemotherapy was administered, that is, on the 1st d of chemotherapy, epirubicin 75 mg/m^2 + cisplatin 40 mg/m^2. The treatment course was 21 d.

The study group was treated with neoadjuvant chemotherapy[15], specifically, oxaliplatin and tigio combined treatment, oxaliplatin intravenous infusion on the first day of treatment at an infusion dose of 130 mg/m^2 (the first day), and tigio oral therapy at the same time at a dose of 80 mg/m^2 twice a day. Both groups were treated for 21 d, and the duration of treatment for both groups was more than two courses.

Observation indicators

Primary observation indicators: Evaluation of the objective response rate (ORR). According to RECIST1.0 standards[18]: (1) The tumor disappears completely and a complete response (CR) is achieved; (2) partial response (PR), the lesion shrinks by ≥ 50%; (3) the tumor is stable, and the lesions shrink by < 50% or increase by < 25%; and (4) tumor progression, with lesions increasing by ≥ 25%. The calculation method of clinical remission rate in each group is: (Complete remission + partial remission)/number of cases × 100%.

Surgical resection rate (SRR): Patients undergoing surgical resection/ total patients treated per group × 100%.

Secondary observation indicators: Adverse reactions: The incidence of adverse reactions in the two groups before and after treatment was analyzed. KPS scores: Before and after treatment, the KPS scores were compared between the two groups.

Statistical analysis

This group used SPSS 26.0 for the analysis and processing of the research data. Measurement data were expressed as (mean ± SD), *t*-tests were used to compare measurements, and count data were expressed as percentages (%). Chi-square tests were used to compare count data between groups, with $P < 0.05$ indicating statistically significant differences between the groups.

RESULTS

Comparison of general data

The research flowchart is presented in Figure 1. A total of 25 men and 20 women participated in this study. Average age was 48.8 ± 9.5 years and body mass index (BMI) was 23.50 ± 3.12. Of these patients, 4 had diabetes, 18 had hypertension, 9 had hyperlipidemia, and 2 had arrhythmia; 16 were smokers and 20 were alcoholics. A total of 24 men and 21 women participated in this study. Their average age was 49.5 ± 9.8 years and BMI was 24.01 ± 2.85. Among them, 5 had diabetes, 14 had hypertension, 11 had hyperlipidemia, and 1 had arrhythmia; 18 were smokers and 22 were alcoholics. There were no statistically significant differences in the general information between the two groups during the study period ($P > 0.05$), indicating comparability. Table 1 presents the results of the study.

Comparative analysis of recent treatment efficacy

Statistical analysis of the recent treatment efficacy in the two groups of patients revealed that among the 45 patients in the study group, 11 were classified as CR, 25 as PR, 6 cases as stable disease (SD), and 3 cases as progressive disease (PD). The ORR was 80.00% (36/45), and the disease control rate (DCR) was 93.33% (42/45). In the control group, there were 9 patients with CR, 17 with PR, 12 with SD, and 7 with PD. The ORR was 57.78% (26/45) and the DCR was 84.44% (38/45). The clinical efficacy was higher in the study group than that in the control group, and statistically significant differences were observed between the two groups ($P < 0.05$) (Table 2).

Comparison of the SRR

The study group had a significantly higher resection rate of 75.56% than that of the control group (57.78%). The differences between the groups were statistically significant ($P < 0.05$). The results are presented in Figure 2A.

Table 1 Comparison of clinical data between the two groups

Index	Study group (*n* = 45)	Control group (*n* = 45)	χ^2/t	*P* value
Sex			0.044	0.832
Male	25	24		
Female	20	21		
Age (yr)	48.80 ± 9.50	49.50 ± 9.80	0.639	0.524
BMI (kg/m^2)	23.50 ± 3.12	24.01 ± 2.85	0.796	0.427
Complications (*n*)			0.795	0.672
Diabetes	4	5		
Hypertension	18	14		
Hyperlipidemia	9	11		
Arrhythmia	2	1		
Smoking history (*n*)			0.189	0.664
Yes	16	18		
No	29	27		
Drinking history (*n*)			0.179	0.673
Yes	20	22		
No	25	23		

BMI: Body mass index.

Table 2 Analysis of short-term efficacy of patients between two groups

Index	Study group (*n* = 45)		Control group (*n* = 45)		χ^2	*P* value
	n	%	*n*	%		
CR	11	24.44	9	20.00		
PR	25	55.56	17	37.78		
SD	6	13.33	12	26.67		
PD	3	6.67	7	15.56		
ORR (CR + PR)	36	80.00	26	57.78	11.519	0.011
DCR (CR + PR + SD)	42	93.33	38	84.44	4.215	0.016

CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; ORR: Overall response Rate; DCR: Disease control rate.

Comparison of KPS scores

Compared with that before treatment, a significant improvement in KPS scores was observed in the study group ($P < 0.05$). The results are presented in Figure 2B.

Comparison of adverse reactions

Based on the statistical results, 15.56% of the study group experienced adverse reactions compared to 35.56% of the control group ($P < 0.05$), indicating a statistically significant difference. as shown in Table 3.

DISCUSSION

LAGC is a common malignant tumor in clinical practice. Most patients are asymptomatic in the early stages and are often treated at a later stage because of gastrointestinal reactions[19]. After gastroscopy and pathological examination, these tumors are often found in the middle and late stages, thus losing the best period for surgery[20]. Neoadjuvant chemotherapy has become a new treatment method for some patients with middle and advanced malignant tumors in

Table 3 Comparison of adverse reactions between the two groups

Index	Study group (n = 45)		Control group (n = 45)		χ^2	P value
	n	%	n	%		
Abnormal liver function	1	2.22	5	11.11		
Nausea and vomiting	3	6.67	6	13.33		
Diarrhoea	2	4.44	3	6.67		
Decreased white blood cells	1	2.22	2	4.44		
Total	7	15.56	16	35.56	10.512	< 0.001

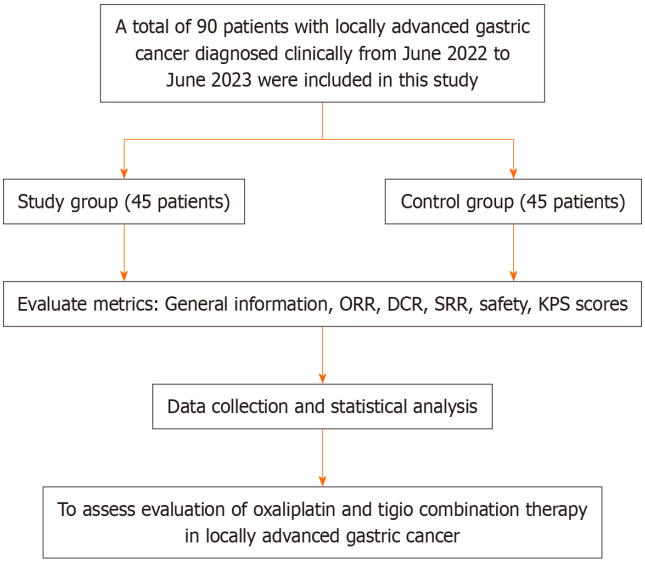


Figure 1 Flow chart. ORR: Overall response rate; DCR: Disease control rate; SRR: Surgical resection rate; KPS: Karnofsky Performance Status.

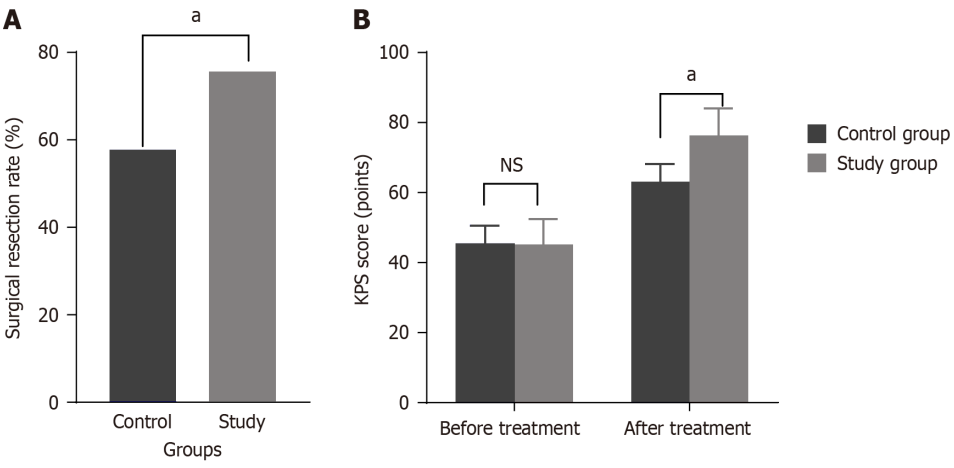


Figure 2 The surgical resection rate and Karnofsky Performance Status scores between the two groups. A: Surgical resection rate; B: Karnofsky Performance Status scores. KPS: Karnofsky Performance Status.

recent years, aiming to control and shrink the progression of the lesions through chemotherapy and then achieve therapeutic purpose through surgical treatment[21]. This type of therapy mainly uses a combination of two or three drugs; however, the number of drugs must be selected according to the patient's body indicators and tolerance before treatment[22].

The results of this study showed that the ORR of the study group was 80.00% after treatment, which was significantly higher than that of the control group (57.78%) (P < 0.05). Compared with the control group, the study group had a resection rate of 75.56%, while the control group had a resection rate of 57.78%, and the two groups differed significantly

($P < 0.05$). This finding is consistent with those of the previous studies[23-25]. Analysis of the reasons: Compared with traditional chemotherapy methods, oxaliplatin and tigio combined neoadjuvant chemotherapy regimen can effectively reduce focal diameter and control disease progression through the rational combination of multiple therapeutic drugs, thus further reducing the tumor stage of patients and providing a basis for the implementation of further treatment. In addition, neoadjuvant chemotherapy can have a good inhibitory effect on the metastasis and proliferation of cancer cells in patients, which can further improve the treatment effect, avoid the risk of patient prognosis recurrence, and improve the quality of life. However, in actual treatment, three drugs, two drugs, or single drugs should be carefully selected according to the physical strength and age of patients to reduce adverse reactions and improve the patient's quality of life.

According to this study, the study group experienced adverse reactions at a rate of 15.56% compared with the control group's 35.56%, which was statistically significant ($P < 0.05$). There was a significantly greater improvement in KPS score in the research group than that in the control group, with $P < 0.05$, which is in general agreement with the findings of Cui *et al*[26] and Dimpel *et al*[27]. This may be because the combined application of oxaliplatin and tigio can play a synergistic role in enhancing the antitumor effect. Oxaliplatin is a platinum-based anticancer drug that inhibits DNA replication and transcription, thereby inhibiting the proliferation of tumor cells. Tigio is an oral fluorouracil analog that inhibits the growth of tumor cells by inhibiting enzymes, such as thymidylate synthase, which interferes with DNA synthesis. The combined use of these two drugs is advantageous and improves their therapeutic effects. Simultaneously, the oral administration of tigio is more convenient than intravenous administration, and its metabolites are less toxic to normal cells, which can reduce the incidence of adverse reactions.

Limitation

This study has several limitations. First, this was a single-center study, and a selection bias may have influenced the results. As a retrospective study, there were some limitations, such as the lack of a thorough research plan and information bias. Second, this study did not include indicators of blood drawing in patients before and after surgery. If more detailed biochemical indicators are available and their data statistics and analyses are performed, it may further explain why neoadjuvant chemotherapy does not increase the incidence of recent postoperative complications. Third, the sample size of this study was small, and the representation of the whole population was limited; therefore, this study still needs to be verified by a prospective study with a larger sample size.

CONCLUSION

In conclusion, for patients with LAGC, compared with conventional chemotherapy, oxaliplatin combined with tigio as a preoperative neoadjuvant chemotherapy regimen can effectively increase the ORR and SRR, has certain safety, and improve its clinical therapeutic effect.

FOOTNOTES

Author contributions: Zhang LY designed this study, collected and analyzed the data; Wang T drafted the manuscript and gave final approval of the version to be published; Wang T and Zhang LY took part in this study as endoscopic operators or assistants.

Institutional review board statement: The study was reviewed and approved by the Medical Ethics Committee of Xianyang Hospital, Yan'an University (Approval No. 2023-299).

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

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REFERENCES

1 **Lordick F**, Carneiro F, Cascinu S, Fleitas T, Haustermans K, Piessen G, Vogel A, Smyth EC; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2022; **33**: 1005-1020 [PMID: 35914639 DOI: 10.1016/j.annonc.2022.07.004]

2 **Röcken C**. Predictive biomarkers in gastric cancer. *J Cancer Res Clin Oncol* 2023; **149**: 467-481 [PMID: 36260159 DOI: 10.1007/s00432-022-04408-0]

3 **Rao X**, Zhang C, Luo H, Zhang J, Zhuang Z, Liang Z, Wu X. Targeting Gastric Cancer Stem Cells to Enhance Treatment Response. *Cells* 2022; **11** [PMID: 36139403 DOI: 10.3390/cells11182828]

4 **Ajani JA**, D'Amico TA, Bentrem DJ, Chao J, Cooke D, Corvera C, Das P, Enzinger PC, Enzler T, Fanta P, Farjah F, Gerdes H, Gibson MK, Hochwald S, Hofstetter WL, Ilson DH, Keswani RN, Kim S, Kleinberg LR, Klempner SJ, Lacy J, Ly QP, Matkowskyj KA, McNamara M, Mulcahy MF, Outlaw D, Park H, Perry KA, Pimiento J, Poultsides GA, Reznik S, Roses RE, Strong VE, Su S, Wang HL, Wiesner G, Willett CG, Yakoub D, Yoon H, McMillian N, Pluchino LA. Gastric Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2022; **20**: 167-192 [PMID: 35130500 DOI: 10.6004/jnccn.2022.0008]

5 **Zhou Y**, Zhou Y, Lin X, Lin S, Li W. New strategy in hemorrhagic gastric cancer: A case report of complete pathological remission after neoadjuvant chemotherapy. *Medicine (Baltimore)* 2023; **102**: e32789 [PMID: 36820602 DOI: 10.1097/MD.0000000000032789]

6 **Kim HD**, Ryu MH, Kang YK. Adjuvant treatment for locally advanced gastric cancer: an Asian perspective. *Gastric Cancer* 2024; **27**: 439-450 [PMID: 38489111 DOI: 10.1007/s10120-024-01484-8]

7 **Zhang J**, Cui Y, Wei K, Li Z, Li D, Song R, Ren J, Gao X, Yang X. Deep learning predicts resistance to neoadjuvant chemotherapy for locally advanced gastric cancer: a multicenter study. *Gastric Cancer* 2022; **25**: 1050-1059 [PMID: 35932353 DOI: 10.1007/s10120-022-01328-3]

8 **Yin Y**, Lin Y, Yang M, Lv J, Liu J, Wu K, Liu K, Li A, Shuai X, Cai K, Wang Z, Wang G, Shen J, Zhang P, Tao K. Neoadjuvant tislelizumab and tegafur/gimeracil/octeracil (S-1) plus oxaliplatin in patients with locally advanced gastric or gastroesophageal junction cancer: Early results of a phase 2, single-arm trial. *Front Oncol* 2022; **12**: 959295 [PMID: 36158692 DOI: 10.3389/fonc.2022.959295]

9 **Yıldız İ**, Özer L, Şenocak Taşçı E, Bayoglu İV, Aytac E. Current trends in perioperative treatment of resectable gastric cancer. *World J Gastrointest Surg* 2023; **15**: 323-337 [PMID: 37032791 DOI: 10.4240/wjgs.v15.i3.323]

10 **Wang KX**, Cui TY, Yang XD, Wang GQ, Jiang QS, Sun H, Jiang NY, Yong XM, Shi CB, Ding YB, Chen XF, Fang YY. Study on Efficacy and Safety of Low-Dose Apatinib Combined with Camrelizumab and SOX Regimen as First-Line Treatment of Locally Advanced and Unresectable Gastric/Gastroesophageal Junction Cancer: A Protocol for an Open-Label, Dose Escalation and Extension Phase Ib Clinical Trial. *Onco Targets Ther* 2021; **14**: 4859-4865 [PMID: 34584426 DOI: 10.2147/OTT.S316288]

11 **Song R**, Cui Y, Ren J, Zhang J, Yang Z, Li D, Li Z, Yang X. CT-based radiomics analysis in the prediction of response to neoadjuvant chemotherapy in locally advanced gastric cancer: A dual-center study. *Radiother Oncol* 2022; **171**: 155-163 [PMID: 35490846 DOI: 10.1016/j.radonc.2022.04.023]

12 **Sisic L**, Crnovrsanin N, Nienhueser H, Jung JO, Schiefer S, Haag GM, Bruckner T, Schneider M, Müller-Stich BP, Büchler MW, Schmidt T. Perioperative chemotherapy with 5-FU, leucovorin, oxaliplatin, and docetaxel (FLOT) for esophagogastric adenocarcinoma: ten years real-life experience from a surgical perspective. *Langenbecks Arch Surg* 2023; **408**: 81 [PMID: 36763220 DOI: 10.1007/s00423-023-02822-7]

13 **Sakuramoto S**, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K; ACTS-GC Group. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007; **357**: 1810-1820 [PMID: 17978289 DOI: 10.1056/NEJMoa072252]

14 **Sasako M**, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T, Ohashi Y. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 *versus* surgery alone in stage II or III gastric cancer. *J Clin Oncol* 2011; **29**: 4387-4393 [PMID: 22010012 DOI: 10.1200/JCO.2011.36.5908]

15 **Park SH**, Lim DH, Sohn TS, Lee J, Zang DY, Kim ST, Kang JH, Oh SY, Hwang IG, Ji JH, Shin DB, Yu JI, Kim KM, An JY, Choi MG, Lee JH, Kim S, Hong JY, Park JO, Park YS, Lim HY, Bae JM, Kang WK; ARTIST 2 investigators. A randomized phase III trial comparing adjuvant single-agent S1, S-1 with oxaliplatin, and postoperative chemoradiation with S-1 and oxaliplatin in patients with node-positive gastric cancer after D2 resection: the ARTIST 2 trial(☆). *Ann Oncol* 2021; **32**: 368-374 [PMID: 33278599 DOI: 10.1016/j.annonc.2020.11.017]

16 **Yu J**, Wang Z, Li Z, Liu Y, Fan Y, Di J, Cui M, Xing J, Zhang C, Yang H, Yao Z, Zhang N, Chen L, Liu M, Xu K, Tan F, Gao P, Su X. Health-Related Quality of Life in Patients With Locally Advanced Gastric Cancer Undergoing Perioperative or Postoperative Adjuvant S-1 Plus Oxaliplatin With D2 Gastrectomy: A Propensity Score-Matched Cohort Study. *Front Oncol* 2022; **12**: 853337 [PMID: 35444949 DOI: 10.3389/fonc.2022.853337]

17 **Schulz C**, Kullmann F, Kunzmann V, Fuchs M, Geissler M, Vehling-Kaiser U, Stauder H, Wein A, Al-Batran SE, Kubin T, Schäfer C, Stintzing S, Giessen C, Modest DP, Ridwelski K, Heinemann V. NeoFLOT: Multicenter phase II study of perioperative chemotherapy in resectable adenocarcinoma of the gastroesophageal junction or gastric adenocarcinoma-Very good response predominantly in patients with intestinal type tumors. *Int J Cancer* 2015; **137**: 678-685 [PMID: 25530271 DOI: 10.1002/ijc.29403]

18 **Schirren R**, Novotny A, Friess H, Reim D. Histopathologic Response Is a Positive Predictor of Overall Survival in Patients Undergoing Neoadjuvant/Perioperative Chemotherapy for Locally Advanced Gastric or Gastroesophageal Junction Cancers-Analysis from a Large Single Center Cohort in Germany. *Cancers (Basel)* 2020; **12** [PMID: 32796715 DOI: 10.3390/cancers12082244]

19 **Shitara K**, Lordick F, Bang YJ, Enzinger P, Ilson D, Shah MA, Van Cutsem E, Xu RH, Aprile G, Xu J, Chao J, Pazo-Cid R, Kang YK, Yang J, Moran D, Bhattacharya P, Arozullah A, Park JW, Oh M, Ajani JA. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. *Lancet* 2023; **401**: 1655-1668 [PMID: 37068504 DOI: 10.1016/S0140-6736(23)00620-7]

20 **Liu L**, Wang C, Li F, Zhang X, Cheng X, Lin S, Liu Y, Yang C, Li W. The safety and efficacy of laparoscopic gastrectomy for patients with locally advanced gastric cancer following neoadjuvant chemotherapy. *Sci Rep* 2022; **12**: 10384 [PMID: 35726012 DOI: 10.1038/s41598-022-14717-6]

21 **Lin W**, Huang Z, Du Z, Wang Y, Zuo T. Case Report: Clinical application of continuous arterial infusion chemotherapy in neoadjuvant therapy for locally advanced gastric cancer. *Front Oncol* 2023; **13**: 1214599 [PMID: 37427136 DOI: 10.3389/fonc.2023.1214599]

22 **Li N**, Wang X, Tang Y, Zhao D, Chi Y, Yang L, Jiang L, Jiang J, Liu W, Fang H, Liu Y, Song Y, Wang S, Jin J, Li Y. A prospective phase I study of hypo-fractionated neoadjuvant radiotherapy for locally advanced gastric cancer. *BMC Cancer* 2018; **18**: 803 [PMID: 30089457 DOI: 10.1186/s12885-018-4707-9]

23 **Ding PA**, Liu Y, Guo HH, Yang PG, Tian Y, Fan LQ, Tan BB, Li Y, Zhao Q. [Application of laparoscopic exploration combined with abdominal exfoliative cytology in the diagnosis and treatment of locally advanced gastric cancer]. *Zhonghua Wei Chang Wai Ke Za Zhi* 2020; **23**: 170-176 [PMID: 32074798 DOI: 10.3760/cma.j.issn.1671-0274.2020.02.013]

24 **Gervaso L**, Pellicori S, Cella CA, Bagnardi V, Lordick F, Fazio N. Biomarker evaluation in radically resectable locally advanced gastric cancer treated with neoadjuvant chemotherapy: an evidence reappraisal. *Ther Adv Med Oncol* 2021; **13**: 17588359211029559 [PMID: 34484429 DOI: 10.1177/17588359211029559]

25 **Deng J**, Zhang W, Xu M, Zhou J. Imaging advances in efficacy assessment of gastric cancer neoadjuvant chemotherapy. *Abdom Radiol (NY)* 2023; **48**: 3661-3676 [PMID: 37787962 DOI: 10.1007/s00261-023-04046-1]

26 **Cui Y**, Zhang J, Li Z, Wei K, Lei Y, Ren J, Wu L, Shi Z, Meng X, Yang X, Gao X. A CT-based deep learning radiomics nomogram for predicting the response to neoadjuvant chemotherapy in patients with locally advanced gastric cancer: A multicenter cohort study. *EClinicalMedicine* 2022; **46**: 101348 [PMID: 35340629 DOI: 10.1016/j.eclinm.2022.101348]

27 **Dimpel R**, Novotny A, Slotta-Huspenina J, Langer R, Friess H, Reim D. UICC Staging after Neoadjuvant/Perioperative Chemotherapy Reveals No Significant Survival Differences Compared to Primary Surgery for Locally Advanced Gastric Cancer. *Cancers (Basel)* 2022; **14** [PMID: 36551654 DOI: 10.3390/cancers14246169]

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ORIGINAL ARTICLE

Retrospective Study

Lung ultrasound score evaluation of the effect of pressure-controlled ventilation volume-guaranteed on patients undergoing laparoscopic-assisted radical gastrectomy

Jian Tan, Cheng-Ming Bao, Xiao-Yuan Chen

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Abstract

BACKGROUND

Laparoscopic-assisted radical gastrectomy (LARG) is the standard treatment for early-stage gastric carcinoma (GC). However, the negative impact of this procedure on respiratory function requires the optimized intraoperative management of patients in terms of ventilation.

AIM

To investigate the influence of pressure-controlled ventilation volume-guaranteed (PCV-VG) and volume-controlled ventilation (VCV) on blood gas analysis and pulmonary ventilation in patients undergoing LARG for GC based on the lung ultrasound score (LUS).

METHODS

The study included 103 patients with GC undergoing LARG from May 2020 to May 2023, with 52 cases undergoing PCV-VG (research group) and 51 cases undergoing VCV (control group). LUS were recorded at the time of entering the operating room (T0), 20 minutes after anesthesia with endotracheal intubation (T1), 30 minutes after artificial pneumoperitoneum (PP) establishment (T2), and 15 minutes after endotracheal tube removal (T5). For blood gas analysis, arterial partial pressure of oxygen (PaO_2) and partial pressure of carbon dioxide ($PaCO_2$) were observed. Peak airway pressure (P_{peak}), plateau pressure (P_{plat}), mean airway pressure (P_{mean}), and dynamic pulmonary compliance (C_{dyn}) were recorded at T1 and T2, 1 hour after PP establishment (T3), and at the end of the operation (T4).

Postoperative pulmonary complications (PPCs) were recorded. Pre- and postoperative serum interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α) were measured by enzyme-linked immunosorbent assay.

RESULTS

Compared with those at T0, the whole, anterior, lateral, posterior, upper, lower, left, and right lung LUS of the research group were significantly reduced at T1, T2, and T5; in the control group, the LUS of the whole and partial lung regions (posterior, lower, and right lung) decreased significantly at T2, while at T5, the LUS of the whole and some regions (lateral, lower, and left lung) increased significantly. In comparison with the control group, the whole and regional LUS of the research group were reduced at T1, T2, and T5, with an increase in PaO_2, decrease in $PaCO_2$, reduction in P_{peak} at T1 to T4, increase in P_{mean} and C_{dyn}, and decrease in P_{plat} at T4, all significant. The research group showed a significantly lower incidence of PPCs than the control group within 3 days postoperatively. Postoperative IL-1β, IL-6, and TNF-α significantly increased in both groups, with even higher levels in the control group.

CONCLUSION

LUS can indicate intraoperative non-uniformity and postural changes in pulmonary ventilation under PCV-VG and VCV. Under the lung protective ventilation strategy, the PCV-VG mode more significantly improved intraoperative lung ventilation in patients undergoing LARG for GC and reduced lung injury-related cytokine production, thereby alleviating lung injury.

Key Words: Lung ultrasound score; Pressure-controlled ventilation volume-guaranteed; Laparoscopic-assisted radical gastrectomy; Blood gas analysis indexes; Pulmonary ventilation

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Core Tip: This study mainly analyzed the effects of pressure-controlled ventilation volume-guaranteed (PCV-VG) and volume-controlled ventilation (VCV) on blood gas analysis and pulmonary ventilation in patients with gastric carcinoma (GC) undergoing laparoscopic-assisted radical gastrectomy (LARG) based on the lung ultrasound score (LUS). We performed validation analyses by evaluating the peak airway pressure (P_{peak}), plateau pressure (P_{plat}), mean airway pressure (P_{mean}), dynamic pulmonary compliance (C_{dyn}), occurrence of postoperative pulmonary complications (PPCs), and levels of serum interleukin (IL)-1β, IL-6, and tumor necrosis factor-α before and after surgery. We confirmed that LUS can indicate non-uniformity and postural changes in lung ventilation under the two ventilation modes. However, PCV-VG is superior to VCV in significantly alleviating lung injury and inflammatory responses in patients undergoing LARG for GC, improving lung ventilation, and exerting a protective effect against PPCs. Thus, PCV-VG is a practical ventilation option in clinical practice.

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INTRODUCTION

Gastric carcinoma (GC) is the third leading cause of death from tumors worldwide and the fifth most prevalent malignancy. It often occurs in the elderly and is characterized by a progressive decline in physical function[1,2]. Risk factors include dietary factors, such as high salt, oil, and sugar intake; unhealthy lifestyle habits like smoking and alcohol consumption; and *Helicobacter pylori* infection, all of which contribute to an increased risk of developing GC[3]. Over 1 million new GC cases are diagnosed every year and nearly 800000 deaths, with a 5-year survival of 36.3%[4]. This is because of the low cure rate and high treatment difficulty due to the nonspecific manifestations in early GC cases the loss of the best time for surgery in advanced ones[5]. Laparoscopic-assisted radical gastrectomy (LARG), the standard treatment for early-stage GC, is advantageous over conventional open gastrectomy in minimal invasiveness, good visualization, lesser intraoperative bleeding, and faster postoperative recovery[6,7]. However, anesthesia, mechanical synchronization, and other factors involved in the procedure may induce various negative effects on the patient's respiratory function and cause adverse events, such as abnormal blood gas analysis indexes, uneven pulmonary ventilation, and postoperative pulmonary complications (PPCs)[8,9].

Therefore, the optimized management of LARG would be highly beneficial to avoid such adverse events and improve the efficacy and safety of patients. This paper evaluated the influence of pressure-controlled ventilation volume-guaranteed (PCV-VG) on blood gas analysis indexes and pulmonary ventilation in patients undergoing LARG for GC and compared it with volume-controlled ventilation (VCV) as the control. A comparative evaluation was also conducted

based on the lung ultrasound score (LUS), which has not been analyzed by other investigators[10]. VCV is a ventilation mode that applies a uniform flow rate, which may increase the peak airway pressure (P_{peak}) in the alveoli, leading to lung loss in patients[11]. In contrast, as a more advanced dual-control ventilation mode, PCV-VG delivers pressure-controlled gas, with the pressure control level automatically adjusted according to factors, such as the patient's lung resistance and compliance, resulting in a lower P_{peak} and higher dynamic pulmonary compliance (C_{dyn}). These features may help prevent lung pressure-related losses[12,13]. The LUS is a non-invasive and radiation-free lung scoring standard used to evaluate pulmonary ventilation[14]. This study evaluated the clinical effect of PCV-VG in LARG based on the LUS and is hereby reported in detail.

MATERIALS AND METHODS

Patients and general data

The participants were 103 patients undergoing LARG for GC at the Lishui District People's Hospital from May 2020 to May 2023. The research group (n = 52) underwent PCV-VG, whereas the control group (n = 51) underwent VCV.

Criteria for patient enrollment and exclusion

The inclusion criteria were as follows: Patients that presented GC symptoms and met the diagnostic criteria for GC; no extensive infiltration of surrounding tissues and organs or distant metastasis; underwent LARG under general anesthesia; and complete case records.

The exclusion criteria were the following: Severe dysfunction of the heart, lung, kidneys, *etc*.; psychological illness or mental disturbance; pulmonary bullae, asthma, or moderate to severe ventilation dysfunction; and neuromuscular diseases, lung surgery history, or preoperative anemia (hemoglobin ≤ 70 g/L).

Anesthesia methods

All patients were conventionally monitored for blood pressure, electrocardiography, and SpO_2 after entering the operating room. A radial artery puncture needle was inserted under local anesthesia with 1 mL of 2% lidocaine for invasive mean arterial pressure (MAP) monitoring. The anesthesia induction scheme consisted of midazolam (0.02 mg/kg), sufentanil (0.5 μg/kg), etomidate (0.2 mg/kg), and rocuronium bromide (0.6 mg/kg). Catheterization was performed in the right internal jugular deep vein. After establishing an artificial pneumoperitoneum (PP), the patient was placed in a dorsal elevated position at 30°. Sevoflurane (1%–2%), remifentanil (0.1–0.3 μg/kg/min), dexmedetomidine (0.2 μg/kg/h), and rocuronium bromide (5–6 μg/kg/min) were used for anesthesia maintenance, with the dosage adjusted depending on the anesthesia depth. The bispectral index was maintained at 40–60. The intraoperative fluctuation amplitude of MAP was controlled to not exceed 20% of the base value. If the MAP decreased > 20% of the base value after rehydration therapy, norepinephrine was given at 0.01–0.5 μg/kg/min. The patient was placed in a supine position following artificial PP. The withdrawal time of rocuronium bromide and dexmedetomidine was 40 min or so before the end of the procedure; sevoflurane was discontinued approximately 10 min before the surgery was completed, and remifentanil was withdrawn immediately postoperatively. After the patient regained consciousness and reached the indication for extubation, the tracheal catheter was removed, and a postoperative intravenous analgesia pump was used for pain relief. Subsequently, the patient was transferred to the post-anesthesia care unit.

Ventilation parameter setting

After endotracheal intubation, the patients in the research and control groups were placed under PCV-VG and VCV, respectively. Protective ventilation strategies were adopted in both groups: inhaled oxygen concentration: 60%; fresh gas velocity: 1.5 L/min; tidal volume: 8 mL/kg; respiratory rate (RR): 12 breaths/min; inspiratory/expiratory: 1:2; $PETCO_2$ (adjusted by respiratory rate): 30–35 mmHg; and pressure: 35 cmH_2O.

Detection indicators

A portable ultrasound machine was used to record the LUS of patients at the time of entering the operating room (T0), 20 min after anesthesia with endotracheal intubation (T1), 30 min after establishing artificial PP (T2), and 15 min after endotracheal tube removal (T5). The LUS was divided into 12 pulmonary zones: the chest wall was divided into anterior, lateral, and posterior sides based on the anterior and posterior axillary lines. Each part was then divided into upper and lower sections to make up 12 evaluable lung regions. The possible total score of the 12 Lung regions was 0–36 points, with a higher score indicating greater lung ventilation injury.

Arterial blood was collected at T0, T1, T2, and T5, and blood gas analysis was performed to record the arterial partial pressure of oxygen (PaO_2) and partial pressure of carbon dioxide ($PaCO_2$).

The P_{peak}, platform pressure (P_{plat}), mean airway pressure (P_{mean}), and C_{dyn} were monitored and recorded at T1, T2, T3 (1 h after PP establishment), and T4 (at the end of surgery).

For PPCs, incidence of adverse events, such as pneumonia, hypoxemia, bronchospasm, atelectasis, and pneumothorax, were recorded and the total incidence calculated.

Venous blood (3 mL) was drawn on an empty stomach pre- and postoperatively and centrifuged to obtain serum for measuring interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α) levels by enzyme-linked immunosorbent assay.

Table 1 Comparison of general patient characteristics

Indicators	Control group (*n* = 51)	Research group (*n* = 52)	χ^2/t	*P* value
Sex (male/female)	25/26	24/28	0.085	0.771
Age (years)	58.78 ± 8.01	61.13 ± 7.40	1.547	0.125
Body mass index (kg/m^2)	21.49 ± 2.40	22.12 ± 3.01	1.173	0.244
Duration of pneumoperitoneum (minutes)	66.25 ± 12.89	64.63 ± 13.6	0.620	0.537
ASA grade (II/III)	28/23	25/27	0.480	0.488

ASA: America Society of Anesthesiologists.

Statistical analyses

Continuous variables (*e.g.*, age, body mass index, PP duration, LUS, PaO_2, and $PaCO_2$) were expressed mean ± SE. To identify statistical significance (threshold: $P < 0.05$), the independent sample t-test was performed for inter-group comparisons of continuous variables and paired *t* test for intra-group comparisons before and after treatment. Categorical variables [sex, America Society of Anesthesiologist (ASA) grade, *etc.*) were expressed as rate (percentage) and compared between groups using the χ^2 test. The collected experimental data were analyzed using SPSS20.0.

RESULTS

Comparison of general data

The two patient cohorts were similar in sex, age, body mass index, PP duration, ASA grade, and other general data ($P > 0.05$; Table 1).

Comparison of LUS

We compared the LUS of the different lung regions between the two patient groups. Compared with those at T0, the whole, anterior, lateral, posterior, upper, lower, left, and right lung LUS of the research group were significantly lower at T1, T2, and T5 ($P < 0.05$). In the control group, the whole, posterior, and lower lung region LUS decreased significantly at T2 ($P < 0.05$), whereas the whole, upper, lower, left, and right lung LUS increased at T5 ($P < 0.05$). At T0, the two groups exhibited marked differences in anterior, lateral, posterior, upper, lower, left, and right lung region LUS ($P < 0.05$). At T1, T2, and T5, the research group had significantly lower LUS for the whole lung and all lung regions than the control group ($P < 0.05$; Figure 1).

Comparison of PaO_2 and $PaCO_2$

The blood gas analysis indexes at each time point were comparatively analyzed. The two groups showed similar PaO_2 and $PaCO_2$ at T0 ($P > 0.05$) and a significant increase in the two indexes at T1 and T2 ($P < 0.05$). PaO_2 and $PaCO_2$ were significantly lower at T5 but did not differ significantly with T0 Levels ($P > 0.05$). PaO_2 and $PaCO_2$ at T1 and T2 were higher in the research group than in the control group ($P < 0.05$). $PaCO_2$ initially decreased in both groups at T1, increased significantly at T2 ($P < 0.05$), and decreased significantly at T5 to a level that was still higher than that at T0 ($P < 0.05$). Significant inter-group differences was also observed in $PaCO_2$ at T1 and T5 ($P < 0.05$) (Figure 2).

Comparisons on the P_{peak}, P_{plat}, P_{mean}, and C_{dyn}

The two groups differed significantly in the P_{peak} and C_{dyn} at T1 ($P < 0.05$). P_{peak} and P_{plat} increased significantly in both groups at T2 and T3 compared at T1, while at T4, these two indicators in reduced significantly to levels that did not differ significantly from those at T1 ($P > 0.05$). The research group had lower P_{peak} at T2, T3, and T4 and P_{plat} at T4 than the control group ($P < 0.05$). Compared with T1, the P_{mean} and C_{dyn} in both groups decreased significantly at T2 and T3. At T4, the P_{mean} of both groups increased to levels comparable with those at T1 ($P > 0.05$). The C_{dyn} of both groups also rose significantly but remained significantly lower than that at T1 ($P < 0.05$). The research group showed higher P_{mean} at T2 and T4 and higher C_{dyn} at T2, T3, and T4 compared with the control group ($P < 0.05$; Figure 3).

Comparison of PPCs

The most common PPCs in the research group was hypoxemia, followed by atelectasis, bronchospasm, and pneumothorax. The most common PPC in the control group patients was hypoxemia, followed by atelectasis, pneumonia, and bronchospasm and pneumothorax. The incidence of PPCs was markedly lower in the research group than in the control group ($P < 0.05$; Table 2).

Comparisons of IL-1β, IL-6, and TNF-α

Preoperative IL-1β, IL-6, and TNF-α did not differ significantly between the groups ($P > 0.05$). However, all of them

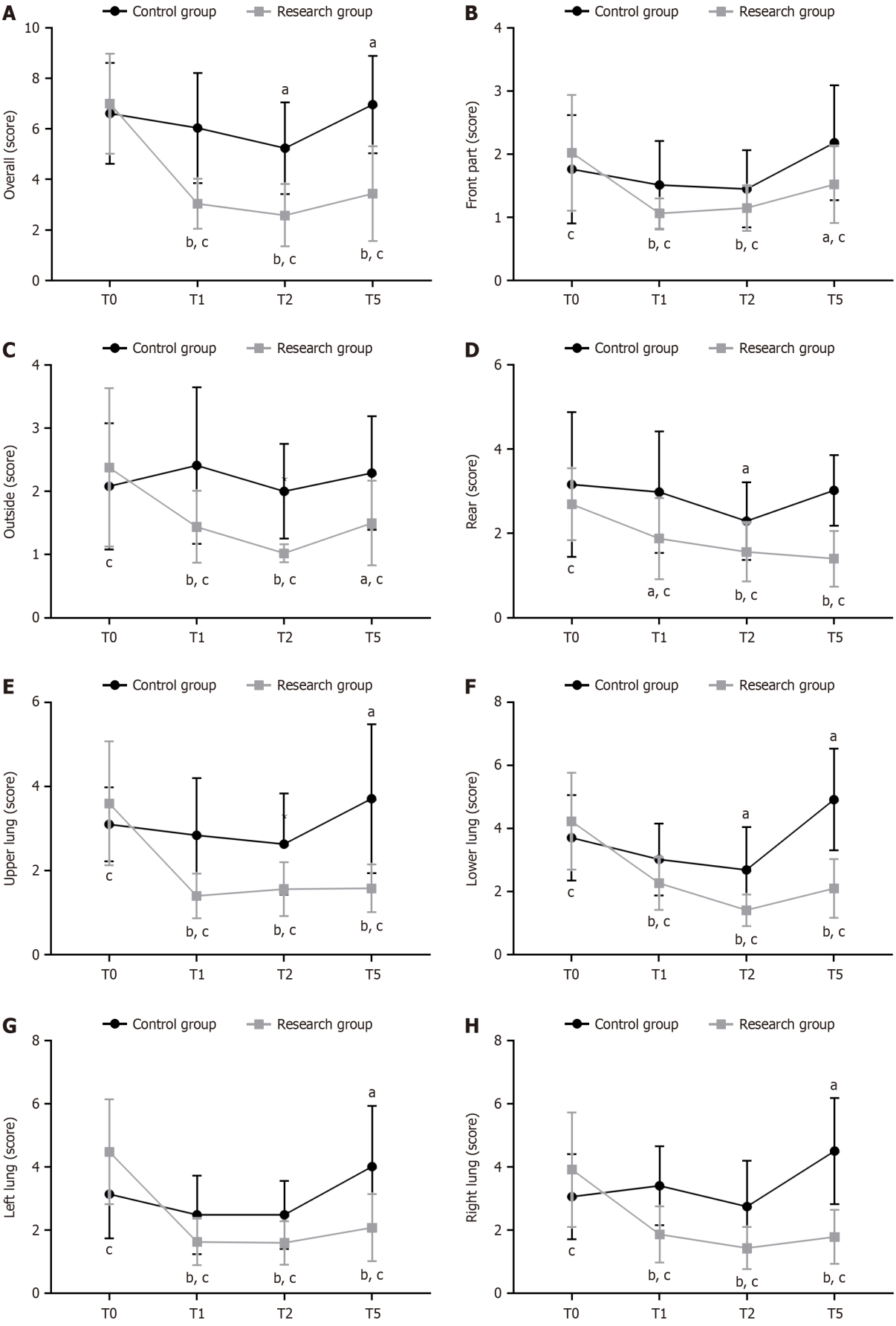


Figure 1 Comparison of lung ultrasound scores. A-H: Changes in lung ultrasound scores of the (A) whole, (B) anterior, (C) lateral, (D) posterior, (E) upper, (F) lower, (G) left, and (H) right lung regions across time points. [a]*P* < 0.05 and [b]*P* < 0.01, compared with T0; [c]*P* < 0.05, *vs* control group.

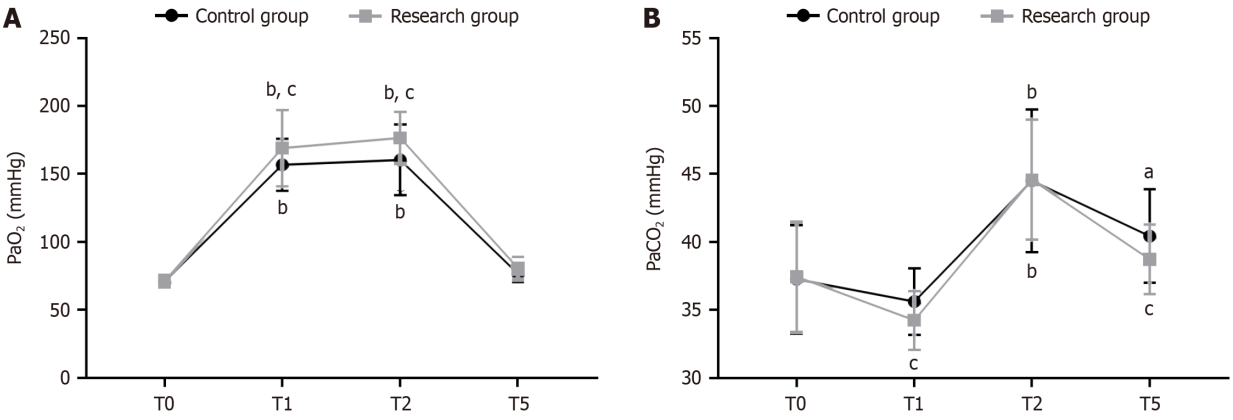


Figure 2 Comparison of (arterial partial pressure of oxygen) PaO_2 and (partial pressure of carbon dioxide) $PaCO_2$. A and B: Changes in (A) PaO_2 and (B) $PaCO_2$ at various time points. $^aP < 0.05$ and $^bP < 0.01$, compared with T0; $^cP < 0.05$ *vs* control group.

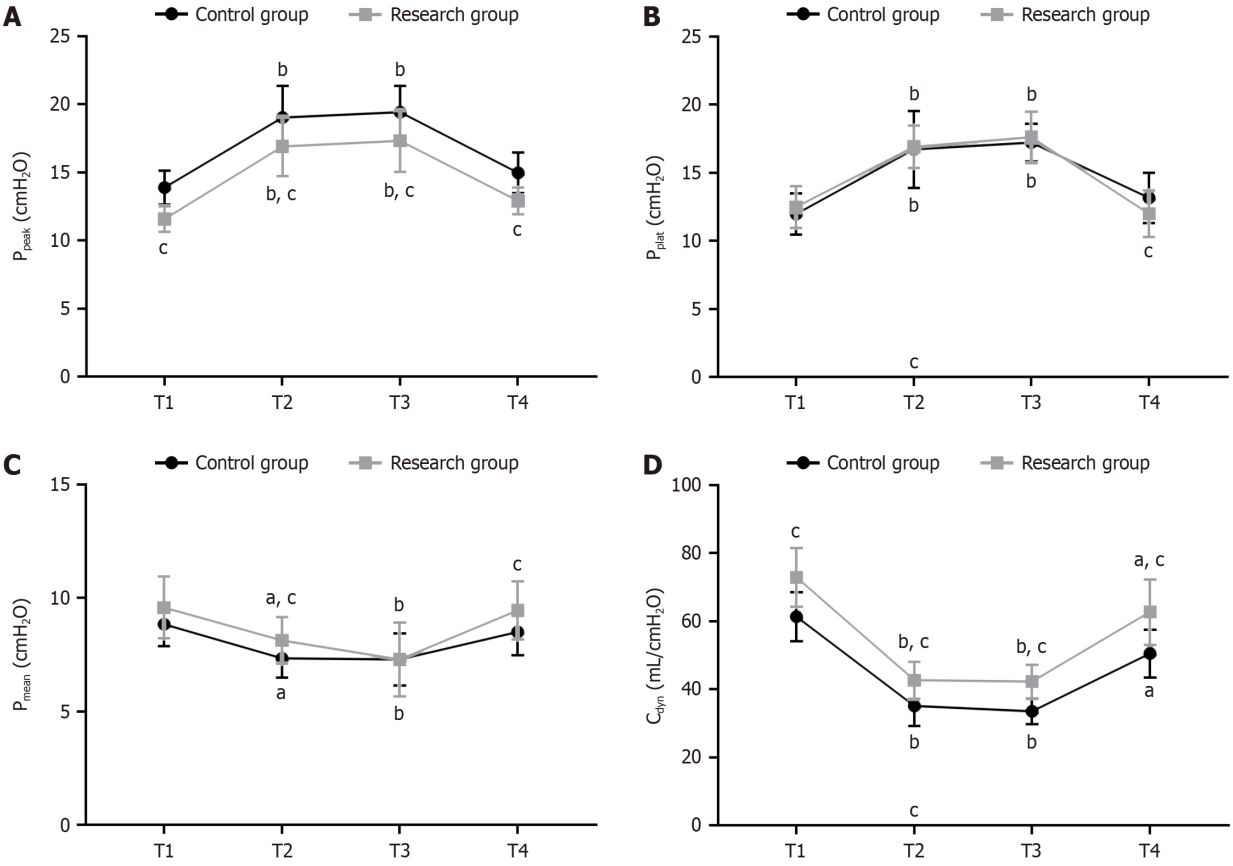


Figure 3 Comparisons of peak airway pressure (P_{peak}), plateau pressure (P_{plat}), mean airway pressure (P_{mean}), and dynamic pulmonary compliance (C_{dyn}). A-D: Changes in (A) P_{peak}, (B) P_{plat}, (C) P_{mean}, and (D) C_{dyn} across time points. $^aP < 0.05$ and $^bP < 0.01$, compared with T1; $^cP < 0.05$ *vs* control group.

increased significantly in both patient cohorts postoperatively ($P < 0.05$), with a more significant increase in the control group ($P < 0.05$; Figure 4).

DISCUSSION

Although the treatment of GC has been continuously optimized and the incidence rate reduced, LARG remains the best choice for the treatment of non-metastatic GC[15]. The advantages of LARG have been established, but this procedure still carries a risk of postoperative adverse events[16]; thus, further optimization of the management of this procedure is required.

Table 2 Comparison of postoperative pulmonary complications, *n* (%)

Indicators	Control group (*n* = 51)	Research group (*n* = 52)	χ^2	*P* value
Pneumonia	3 (5.88)	0 (0.00)		
Hypoxemia	7 (13.73)	4 (7.69)		
Bronchospasm	2 (3.92)	2 (3.85)		
Atelectasis	5 (9.80)	3 (5.77)		
Pneumothorax	2 (3.92)	1 (1.92)		
Total	19 (37.25)	10 (19.23)	4.135	0.042

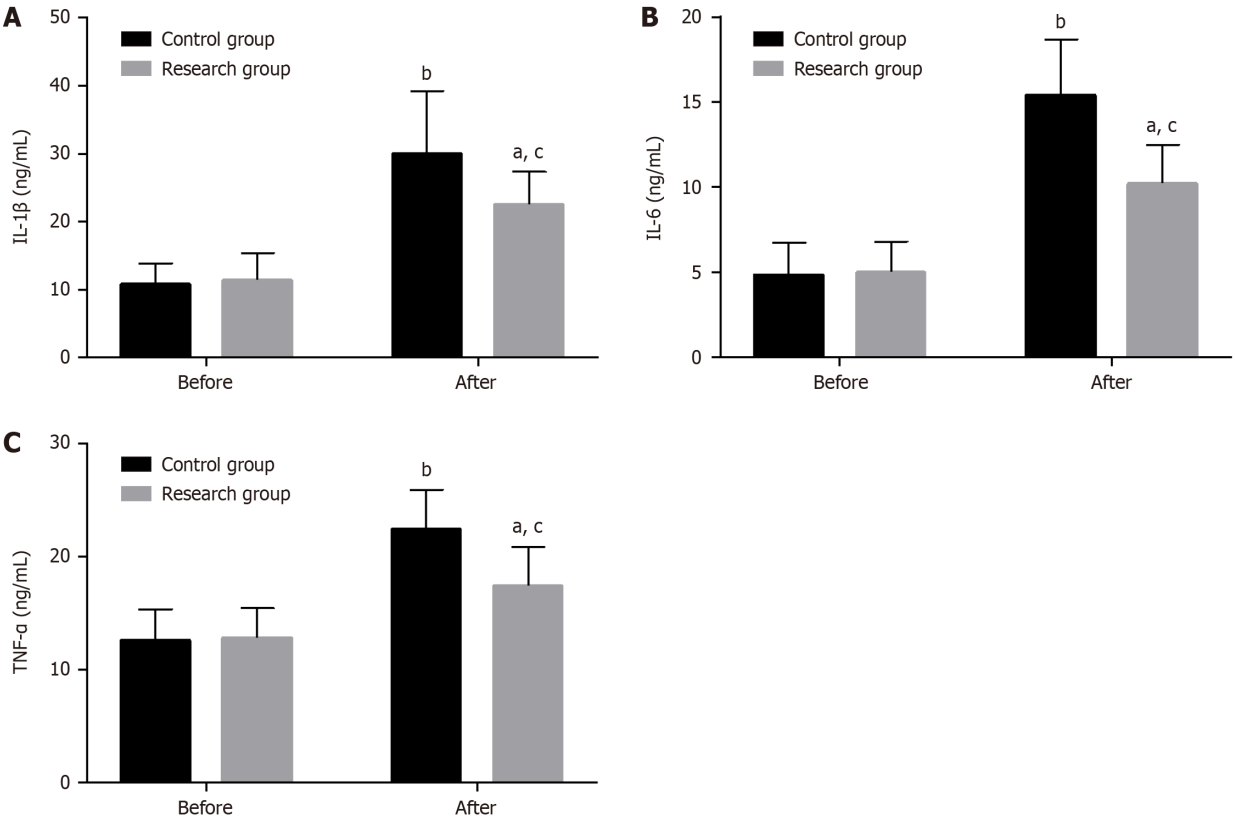


Figure 4 Comparison of interleukin-1β, interleukin-6 and tumor necrosis factor-α. A-C: Pre- and post-treatment (A) IL-1β, (B) IL-6, and (C) TNF-α levels. $^{a}P < 0.05$ and $^{b}P < 0.01$, compared with T1; $^{c}P < 0.05$ *vs* control group.

The whole, anterior, lateral, posterior, upper, lower, left, and right lung LUS decreased significantly in the research group at T1, T2, and T5, whereas the control group only showed significantly lower whole, posterior, and lower lung LUS at T2. Moreover, the research group had evidently lower LUS of the whole lung and all regional lung regions than the control group at T1, T2, and T5. These data indicate that, compared with VCV, PCV-VG can achieve uniform ventilation by expanding trapped and unventilated alveoli, thereby more effectively reducing lung ventilation damage. The LUS results in the control group indicate optimal functional residual capacity due to the patient's dorsal elevated position after VCV intervention and artificial PP establishment, in addition to the minimal pulmonary vascular resistance at this time, which ultimately resulted in more blood flow in the lower lung and the basolateral region, thereby improving the lung ventilation and the ventilation/blood flow ratio in these regions[17,18]. The lower and left lung LUS were the highest in the control group at T5, indicating that the LUS can indicate overall and regional ventilation changes perioperatively under both ventilation modes. PCV-VG, a ventilation modality optimized based on PCV and VCV, prevents ventilation–perfusion mismatches by ensuring a more uniform ventilation distribution and preventing peak inspiratory pressure from rising. This is primarily achieved by automatically changing ventilation parameters to allow the patient to inhale the target tidal volume at each forced breath on the premise of not increasing airway pressure[19,20]. Although VCV can guarantee a patient's target minute ventilation, patients are particularly susceptible to factors, such as barotrauma and changes in lung gas distribution, because of causes such as compliance or resistance[21].

Blood gas analysis revealed that the research group had significantly higher levels of PaO_2 at T1 and T2 and significantly lower levels of $PaCO_2$ at T1 and T5, indicating that PCV-VG intervention in patients undergoing LARG can

significantly optimize lung ventilation function, similar to the results reported by Toker *et al*[22]. Furthermore, the P_{peak} and P_{plat} in the research group were significantly lower than those in the control, whereas P_{mean} and C_{dyn} were significantly higher. This indicates that PCV-VG is more effective in protecting lung function under long-term mechanical ventilation in patients undergoing LARG, thereby more efficiently optimizing lung respiratory mechanics and improving the ventilation/blood flow ratio. Higher P_{peak} and lower C_{dyn} have been linked to serious imbalances in the ventilation/blood flow ratio associated with alveolar overdistension and increased pulmonary vascular resistance[23]. Turan Civraz *et al*[24] reported that PCV-VG implemented in patients undergoing laparoscopic abdominal surgery is significantly advantageous over VCV in providing optimal ventilation pressure and maintaining high dynamic compliance, similar to our findings. Hypoxemia and atelectasis were the most common PPCs in the two groups, with a notably lower incidence in the research group than in the control group. Postoperatively IL-1β, IL-6, and TNF-α were significantly increased in the research group but still considerably lower than those in the control group, indicating that PCV-VG intervention can significantly inhibit postoperative inflammatory responses in patients undergoing LARG. IL-1β is closely related to mechanical ventilation-associated inflammatory cascades, whereas IL-6 is significantly associated with the injuries of the alveolar epithelium and extracellular matrix and ventilation-related lung tissue loss. Likewise, TNF-α is strongly correlated with early inflammatory reaction related to mechanical ventilation[25,26].

This study has several limitations. First, the study was conducted at a single center, which may limit the generalizability of the results. Second, the retrospective study design may introduce selection bias and confounding variables. Third, the factors influencing the occurrence of PPCs in patients was not performed. Future studies need to address these three aspects to generate more robust results.

CONCLUSION

This study demonstrated that LUS can indicate non-uniformity and postural changes in lung ventilation under the two ventilation modes. Compared with VCV, PCV-VG intervention more significantly alleviated lung injury, improved lung ventilation, and reduced inflammation in patients undergoing LARG for GC, while exerting protective activity against PPCs, making it the more practical ventilation option in clinical practice.

FOOTNOTES

Author contributions: Tan J and Bao CM contributed equally to this work and are co-first authors; Tan J and Bao CM designed the research and wrote the first manuscript; Tan J, Bao CM and Chen XY contributed to conceiving the research and analyzing data; Tan J and Bao CM conducted the analysis and provided guidance for the research; all authors reviewed and approved the final manuscript.

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

Conflict-of-interest statement: Dr. Chen has nothing to disclose.

Data sharing statement: All data and materials are available from the corresponding author.

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REFERENCES

1 **Poorolajal J**, Moradi L, Mohammadi Y, Cheraghi Z, Gohari-Ensaf F. Risk factors for stomach cancer: a systematic review and meta-analysis. *Epidemiol Health* 2020; **42**: e2020004 [PMID: 32023777 DOI: 10.4178/epih.e2020004]

2 **Fang W**, Hu H, Jia L, Zhang J, Huang C, Hu S. Survival disparities among non-elderly American adults with locally advanced gastric cancer undergoing gastrectomy by health insurance status. *Am J Med Sci* 2022; **364**: 198-206 [PMID: 35381218 DOI: 10.1016/j.amjms.2022.03.004]

3 **Putthanachote N**, Promthet S, Hurst C, Suwanrungruang K, Chopjitt P, Wiangnon S, Chen SL, Yen AM, Chen TH. The XRCC 1 DNA repair gene modifies the environmental risk of stomach cancer: a hospital-based matched case-control study. *BMC Cancer* 2017; **17**: 680 [PMID: 29020930 DOI: 10.1186/s12885-017-3675-9]

4 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

5 **Ilson DH**. Advances in the treatment of gastric cancer: 2019. *Curr Opin Gastroenterol* 2019; **35**: 551-554 [PMID: 31436556 DOI: 10.1097/MOG.0000000000000577]

6 **Sugimoto M**, Kinoshita T, Shibasaki H, Kato Y, Gotohda N, Takahashi S, Konishi M. Short-term outcome of total laparoscopic distal gastrectomy for overweight and obese patients with gastric cancer. *Surg Endosc* 2013; **27**: 4291-4296 [PMID: 23793806 DOI: 10.1007/s00464-013-3045-x]

7 **Sun L**, Zhao B, Huang Y, Lu H, Luo R, Huang B. Feasibility of laparoscopy gastrectomy for gastric cancer in the patients with high body mass index: A systematic review and meta-analysis. *Asian J Surg* 2020; **43**: 69-77 [PMID: 31036475 DOI: 10.1016/j.asjsur.2019.03.017]

8 **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]

9 **Yajima K**, Kanda T, Tanaka R, Sato Y, Ishikawa T, Kosugi S, Honda T, Hatakeyama K. Reexpansion Pulmonary Edema following Laparoscopy-Assisted Distal Gastrectomy for a Patient with Early Gastric Cancer: A Case Report. *Case Rep Surg* 2012; **2012**: 863163 [PMID: 23227412 DOI: 10.1155/2012/863163]

10 **Ghodraty MR**, Pournajafian AR, Tavoosian SD, Khatibi A, Safari S, Motlagh SD, Abhari MB, Shafighnia S, Porhomayon J, Nader ND. A clinical trial of volume- versus pressure-controlled intraoperative ventilation during laparoscopic bariatric surgeries. *Surg Obes Relat Dis* 2021; **17**: 81-89 [PMID: 33036946 DOI: 10.1016/j.soard.2020.08.034]

11 **Schick V**, Dusse F, Eckardt R, Kerkhoff S, Commotio S, Hinkelbein J, Mathes A. Comparison of Volume-Guaranteed or -Targeted, Pressure-Controlled Ventilation with Volume-Controlled Ventilation during Elective Surgery: A Systematic Review and Meta-Analysis. *J Clin Med* 2021; **10** [PMID: 33808607 DOI: 10.3390/jcm10061276]

12 **Kim YS**, Won YJ, Lee DK, Lim BG, Kim H, Lee IO, Yun JH, Kong MH. Lung ultrasound score-based perioperative assessment of pressure-controlled ventilation-volume guaranteed or volume-controlled ventilation in geriatrics: a prospective randomized controlled trial. *Clin Interv Aging* 2019; **14**: 1319-1329 [PMID: 31409981 DOI: 10.2147/CIA.S212334]

13 **Li Bassi G**, Comaru T, Martí D, Xiol EA, Chiurazzi C, Travierso C, Carbonara M, Ranzani OT, Amaro R, Frigola G, Fuster C, Saco MA, Zanella A, De Rosa F, Rigol M, Fernandez L, Luque N, Ramirez J, Blasi F, Suen J, Fraser J, Torres A. Recruitment manoeuvres dislodge mucus towards the distal airways in an experimental model of severe pneumonia. *Br J Anaesth* 2019; **122**: 269-276 [PMID: 30686313 DOI: 10.1016/j.bja.2018.07.039]

14 **Wang F**, Wang C, Shi J, Shan Y, Miao H, Sun T, Zhou Y, Zhang Y. Lung ultrasound score assessing the pulmonary edema in pediatric acute respiratory distress syndrome received continuous hemofiltration therapy: a prospective observational study. *BMC Pulm Med* 2021; **21**: 40 [PMID: 33494739 DOI: 10.1186/s12890-021-01394-w]

15 **Feng F**, Tian Y, Zang Y, Sun L, Hong L, Yang J, Guo M, Lian X, Fan D, Zhang H. Low forced vital capacity predicts poor prognosis in gastric cancer patients. *Oncotarget* 2017; **8**: 28897-28905 [PMID: 28423645 DOI: 10.18632/oncotarget.15953]

16 **Lou S**, Yin X, Wang Y, Zhang Y, Xue Y. Laparoscopic versus open gastrectomy for gastric cancer: A systematic review and meta-analysis of randomized controlled trials. *Int J Surg* 2022; **102**: 106678 [PMID: 35589049 DOI: 10.1016/j.ijsu.2022.106678]

17 **Ordies S**, Orlitova M, Heigl T, Sacreas A, Van Herck A, Kaes J, Saez B, Vanstapel A, Ceulemans L, Vanaudenaerde BM, Vos R, Verschakelen J, Verleden GM, Verleden SE, Van Raemdonck DE, Neyrinck AP. Flow-controlled ventilation during EVLP improves oxygenation and preserves alveolar recruitment. *Intensive Care Med Exp* 2020; **8**: 70 [PMID: 33237343 DOI: 10.1186/s40635-020-00360-w]

18 **Peng Z**, Xia J, Yin N, Xue H. The effects of volume-controlled ventilation versus pressure-controlled ventilation on hemodynamic and respiratory parameters in patients undergoing lumbar spine fusion surgery: a randomized controlled trial. *Ann Palliat Med* 2021; **10**: 9553-9563 [PMID: 34628881 DOI: 10.21037/apm-21-1932]

19 **Jaju R**, Jaju PB, Dubey M, Mohammad S, Bhargava AK. Comparison of volume controlled ventilation and pressure controlled ventilation in patients undergoing robot-assisted pelvic surgeries: An open-label trial. *Indian J Anaesth* 2017; **61**: 17-23 [PMID: 28216699 DOI: 10.4103/0019-5049.198406]

20 **Assad OM**, El Sayed AA, Khalil MA. Comparison of volume-controlled ventilation and pressure-controlled ventilation volume guaranteed during laparoscopic surgery in Trendelenburg position. *J Clin Anesth* 2016; **34**: 55-61 [PMID: 27687346 DOI: 10.1016/j.jclinane.2016.03.053]

21 **Brandly JE**, Midon M, Douglas HF, Hopster K. Flow-controlled expiration reduces positive end-expiratory pressure requirement in dorsally recumbent, anesthetized horses. *Front Vet Sci* 2023; **10**: 1135452 [PMID: 37124564 DOI: 10.3389/fvets.2023.1135452]

22 **Toker MK**, Altıparmak B, Uysal Aİ, Demirbilek SG. [Comparison of pressure-controlled volume-guaranteed ventilation and volume-controlled ventilation in obese patients during gynecologic laparoscopic surgery in the Trendelenburg position]. *Braz J Anesthesiol* 2019; **69**: 553-560 [PMID: 31836201 DOI: 10.1016/j.bjan.2019.09.003]

23 **Grübler MR**, Wigger O, Berger D, Blöchlinger S. Basic concepts of heart-lung interactions during mechanical ventilation. *Swiss Med Wkly* 2017; **147**: w14491 [PMID: 28944931 DOI: 10.4414/smw.2017.14491]

24 **Turan Civraz AZ**, Saracoglu A, Saracoglu KT. Evaluation of the Effect of Pressure-Controlled Ventilation-Volume Guaranteed Mode vs. Volume-Controlled Ventilation Mode on Atelectasis in Patients Undergoing Laparoscopic Surgery: A Randomized Controlled Clinical Trial. *Medicina (Kaunas)* 2023; **59** [PMID: 37893501 DOI: 10.3390/medicina59101783]

25 **Koo BW**, Oh AY, Ryu JH, Lee YJ, Han JW, Nam SW, Park DJ, Seo KS. Effects of deep neuromuscular blockade on the stress response during laparoscopic gastrectomy Randomized controlled trials. *Sci Rep* 2019; **9**: 12411 [PMID: 31455832 DOI: 10.1038/s41598-019-48919-2]

26 **Shao RG**, Xie QW, Pan LH, Lin F, Qin K, Ming SP, Li JJ, Du XK. Necrostatin-1 attenuates Caspase-1-dependent pyroptosis induced by the RIPK1/ZBP1 pathway in ventilator-induced lung injury. *Cytokine* 2022; **157**: 155950 [PMID: 35780712 DOI: 10.1016/j.cyto.2022.155950]

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ORIGINAL ARTICLE

Retrospective Study

Effect of endoscopic sphincterotomy and endoscopic papillary balloon dilation endoscopic retrograde cholangiopancreatographies on the sphincter of Oddi

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Abstract

BACKGROUND

Endoscopic retrograde cholangiopancreatography (ERCP), with its clinical advantages of less trauma and faster recovery, has become the primary treatment for choledocholithiasis.

AIM

To investigate the effects of different ERCP procedures on the sphincter of Oddi.

METHODS

The clinical data of 91 patients who underwent ERCP at Yixing Hospital of Traditional Chinese Medicine between February 2018 and February 2021 were analyzed retrospectively. The patients were divided into endoscopic sphincterotomy (EST, n = 24) and endoscopic papillary balloon dilation (EPBD, n = 67) groups. The duration of operation, pancreatic development, pancreatic sphincterotomy, intubation difficulties, stone recurrence, and incidence of reflux cholangitis and cholecystitis were statistically analyzed in patients with a history of choledocholithiasis, pancreatitis, and Oddi sphincter dysfunction in the EST and EPBD groups.

RESULTS

Differences in hypertension, diabetes, increased bilirubin, small diameter of the

common bile duct, or ampullary diverticulum between the two groups were not significant. Statistically significant differences were observed between the two groups concerning sex and age (< 60 years). Patients with a history of choledocholithiasis, pancreatitis, and Oddi sphincter dysfunction were higher in the EST group than in the EPBD group. The number of cases of pancreatic development, pancreatic duct sphincterotomy, and difficult intubation were higher in the EST group than in the EPBD group. The number of Oddi's sphincter manometries, ERCP surgical outcomes, and guidewires entering the pancreatic duct several times in EST group were lower than those in the EPBD group. The numbers of stone recurrences, reflux cholangitis, and cholecystitis were higher in the EST group than in the EPBD group.

CONCLUSION

In summary, common bile duct stones, pancreatitis history, and multiple guided wire introductions into the pancreatic duct are independent risk factors for EST and EPBD. Based on this evidence, this study can provide actionable insights for clinicians and researchers.

Key Words: Oddi; Cholangiopancreatography; Endoscopic retrograde; Risk factors; Endoscopic sphincterotomy; Endoscopic papillary balloon dilation

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Core Tip: This study suggests that the number of cases of pancreatic development, sphincterotomy of pancreatic duct, difficulty intubation, recurrence of calculus, reflux cholangitis and cholecystitis in endoscopic sphincterotomy (EST) group were higher than those in endoscopic papillary balloon dilation (EPBD) group. Moreover, choledocholithiasis, history of pancreatitis, and multiple guides leads into the pancreatic duct are independent risk factors for EST and EPBD. Clinical re-identification of Oddi sphincter function will ensure rational and standardized patient treatment.

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INTRODUCTION

Choledocholithiasis is a common and frequently occurring disease worldwide, accounting for a substantial proportion of digestive system diseases[1,2]. It affects more than 10% of the Western population[3]. In addition to genetic factors, age, sex, nutrition, obesity, rapid weight change, and exercise are closely related to the development of choledocholithiasis[3]. With a rapidly developing economy and consequently improving living standards in China[4], the choledocholithiasis incidence in China is rising yearly owing to increasingly severe population aging and obesity[5]. Endoscopic retrograde cholangiopancreatography (ERCP) has become the chief clinical treatment for choledocholithiasis because of its clinical advantages of less trauma and faster recovery in this period of advanced science and technology and improved medical technology and hospital hardware facilities. According to multicenter clinical research data, the recurrence rate in patients with choledocholithiasis after ERCP is 4%-24%[6]. Therefore, the high recurrence rate of choledocholithiasis has become the focus of attention for surgeons worldwide[6]. Presently, domestic and foreign studies on the recurrence mechanism of choledocholithiasis mainly focus on crucial issues such as biliary microecology, duodenal papilla sphincter functional damage and abnormalities caused by surgery, and individual biliary anatomical differences[7].

Choledocholithiasis is a common digestive disease occurring in the middle and lower segments of the common bile duct[8,9]. The main symptom of the disease is suppurative cholangitis, which can be severe and even life-threatening[10]. After decades of development, ERCP has many advantages, such as less trauma, less pain, faster recovery, and fewer postoperative complications, and is widely used for diagnosing and treating choledocholithiasis[10]. The primary and emerging procedures of ERCP include endoscopic sphincterotomy (EST), endoscopic papillary balloon dilation (EPBD), endoscopic sphincterotomy plus balloon dilation (ESBD), and endoscopic endoclip papilloplasty (EEPP)[11].

The delicate and complex structure of the Oddi sphincter is composed of the common bile duct, pancreatic duct, and ampullary sphincters[12]. The common bile duct sphincter is the strongest muscle fiber of the common bile duct located at its end and the main component of the Oddi sphincter[13]. Its contraction can be close to the end of the common bile duct. The Oddi sphincter is the controlling valve of the bile-pancreatic duct passage; thus, it can effectively prevent the reflux of duodenal contents, prevent bacteria and other retrograde infections, and indirectly regulate the secretion and storage of bile and pancreatic juice[14]. It plays an irreplaceable role in maintaining the normal physiological function of the bile-pancreatic duct. Protecting the function of Oddi's sphincter during ERCP has received increasing attention from physicians[15].

This study was critical for analyzing the factors influencing post-ERCP pancreatitis (PEP), an independent risk factor for PEP, and for undertaking corresponding measures to prevent PEP. In this study, we analyzed primary indicators (common bile duct stones, history of pancreatitis, Oddi sphincter dysfunction, and pancreatic imaging) and secondary indicators (pancreatic sphincterotomy, Oddi's sphincter manometries, and ERCP operation failure). This study investigated the effects of different ERCP techniques on the Oddi sphincter.

MATERIALS AND METHODS

General information

The clinical data of 91 patients who underwent ERCP at Yixing Hospital of Traditional Chinese Medicine between February 2018 and February 2021 were analyzed retrospectively. The patients were divided into EST (n = 24) and EPBD (n = 67) groups. All experiments were conducted in accordance with the guidelines issued by the Institutional Care and Use Committee at our hospital. All selected personnel provided informed consent.

Inclusive criteria: (1) With a complete clinical history; (2) who underwent ERCP; (3) 18-70 years old; (4) with normal serum amylase levels before the operation; and (5) with signed informed consent forms.

Exclusion criteria: (1) Combination of benign or malignant biliary stricture; (2) history of biliary pancreatitis; (3) incomplete medical or follow-up data; and (4) patients with serious diseases, such as malignant tumors, cirrhosis, leukemia, *etc.*

Diagnostic criteria for pancreatitis

Diagnostic criteria: (1) Symptoms lasting more than 24 h, such as abdominal pain, nausea, and vomiting; (2) needs hospitalization for diagnosis and treatment or more than 2 d; (3) worsening and reappearing abdominal pain; and (4) a reported postoperative serum amylase level of > 500 U/L as in the literature[1].

Statistics and data collection

Data were collected from the two groups on age, sex, hypertension, diabetes, common bile duct stones, pancreatitis, bilirubin, common bile duct diameter, ampullary diverticulum, Oddi sphincter dysfunction, pancreatic imaging, ERCP type, pancreatic sphincterotomy, Oddi sphincter manometry, operation duration (> 1 h), ERCP outcome, difficulty in intubation (> 5 times), and presence of a guidewire entering numerous times into the pancreatic duct.

Statistical analyses were performed using GraphPad Prism 7 software (GraphPad Software, Inc.). Data are presented as the mean ± SD. Differences between groups were analyzed using the Student's t-test. Multiple groups were analyzed using one-way ANOVA. $P < 0.05$ was considered statistically significant.

RESULTS

Effect of ERCP on the Oddi sphincter function

Under ERCP, EST is used to treat choledocholithiasis, and the incision diameter of the papillary sphincter is usually ≥ 1 cm (Figure 1). The specific surgical method of EPBD involves reaching the duodenal papilla through the duodenoscope inserting the guidewire into the common bile duct through the imaging catheter, and then removing the catheter. Based on the size of the stone and obstruction of the bile duct, balloon catheters with different diameters were selected for expansion (Figure 2).

Comparison of clinical data between two groups

Differences in hypertension, diabetes, increased bilirubin, small common bile duct diameter, and ampullary diverticulum between the two groups were nonsignificant ($P > 0.05$). Statistically significant differences were observed between the two groups concerning sex and age < 60 years ($P < 0.05$). The number of patients with a history of choledocholithiasis, pancreatitis, and Oddi sphincter dysfunction was higher in the EST group than in the EPBD group ($P < 0.05$; Table 1).

Analysis of Influencing Factors between the two groups

No significant differences were observed between the two groups in the ERCP type, choledochal sphincterotomy, or operation duration (> 1 h; $P > 0.05$). The number of pancreatic developments, sphincterotomies of the pancreatic duct, and difficult intubations was higher in the EST group than in the EPBD group ($P < 0.05$). Meanwhile, the number of Oddi's sphincter manometries, ERCP surgical outcomes, and guidewires entering the pancreatic duct several times in the EST group were lower than those in the EPBD group ($P < 0.05$; Table 2).

Effect of main operative methods on Oddi sphincter

The number of stone recurrences, reflux cholangitis, and cholecystitis cases was higher in the EST group than in the EPBD group ($P < 0.05$; Table 3).

Table 1 Comparison of clinical data between the two groups, *n* (%)

Group	EST group (*n* = 24)	EPBD group (*n* = 67)
Gender		
Man	8 (33.33)	35 (52.24)
Woman	16 (66.67)	32 (47.76)
Age (yr)		
< 60	22 (91.67)	33 (49.25)
≥ 60	2 (8.33)	34 (50.75)
History of hypertension	13 (54.17)	33 (49.25)[a]
History of diabetes	16 (66.67)	35 (52.34)[a]
History of choledocholithiasis	18 (75.00)	36 (53.73)
History of pancreatitis	19 (79.17)	28 (41.79)
Hyperbilirubin	13 (54.17)	34 (50.75)
Small diameter of common bile duct	11 (45.83)	31 (46.27)
Ampullary diverticulum	10 (41.67)	30 (44.78)
Oddi sphincter dysfunction	20 (83.33)	21 (31.34)[a]

[a]*P* < 0.05 was considered statistically significant.
EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon.

Table 2 Analysis of influencing factors, *n* (%)

Group	EST group (*n* = 24)	EPBD group (*n* = 67)
Pancreatic development	18 (75.00)	30 (44.78)[a]
ERCP type	12 (50.00)	34 (50.75)
Sphincterotomy of pancreatic duct	14 (58.33)	27 (40.30)[a]
Oddi sphincter manometry	13 (54.17)	47 (70.15)[a]
Choledochal sphincterotomy	6 (25.00)	30 (44.78)
Operation duration (> 1 h)	5 (20.83)	14 (20.90)
ERCP surgical outcome	2 (8.33)	14 (20.90)[a]
difficult intubation	16 (66.67)	21 (31.34)[a]
The guide wire enters the pancreatic duct several times	16 (66.67)	64 (95.52)[a]

[a]*P* < 0.05 was considered statistically significant.
EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon.

DISCUSSION

Although a commonly used method for treating pancreaticobiliary system diseases, ERCP is invasive and prone to postoperative complications[16]. One such common complication is pancreatitis, which may lead to death if not treated timely[16]. The pathogenesis of PEP remains unclear; however, nipple intubation can lead to nipple water in patients, Oddi sphincter spasms, and obstruction of pancreatic juice drainage, resulting in pancreatitis[17-19]. In this study, differences in hypertension, common bile duct diameter, and ampullary diverticulum between the two groups were nonsignificant. The current study had some limitations. Large-sample clinical research on the effect of ESBD, especially EEPP, on the Oddi sphincter is still lacking, and the follow-up time for long-term complications is relatively short. This insufficiency persisted in this experiment.

The duodenal papillary sphincter, the Oddi sphincter, refers to the circular sphincter surrounding the end of the common bile duct, pancreatic ductal end, and ampulla, including the common bile duct, pancreatic duct, and ampullary sphincters[20]. It plays a "switch" role in the secretion of bile and pancreatic juice and principally maintains the fluid pressure of the biliary system, preventing the reflux of duodenal juice and the mutual communication between bile and

Table 3 Effect on Oddi sphincter of several main operative methods, *n* (%)

Group	EST group (*n* = 24)	EPBD group (*n* = 67)
Stone recurrence	3 (12.50)	4 (5.97)[a]
Refluxing cholangitis	2 (8.33)	2 (3.00)[a]
Cholecystitis	4 (16.67)	1 (1.49)[a]

[a]$P < 0.05$ was considered statistically significant.
EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon.

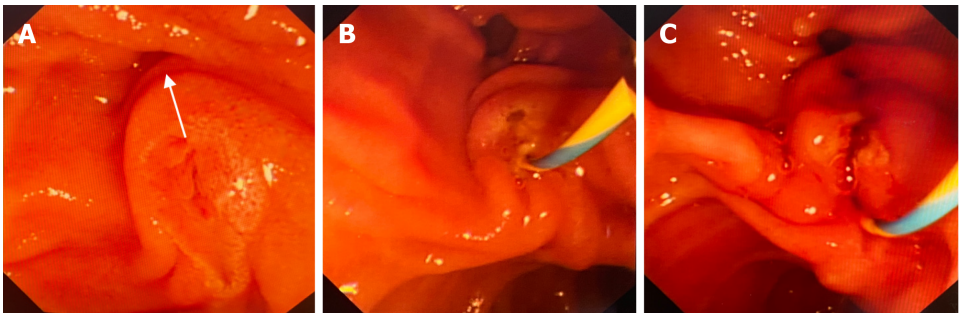


Figure 1 Operation process of endoscopic sphincterotomy. A: Duodenal papilla (arrow direction is longitudinal incision direction); B: During endoscopic sphincterotomy; C: After endoscopic sphincterotomy.

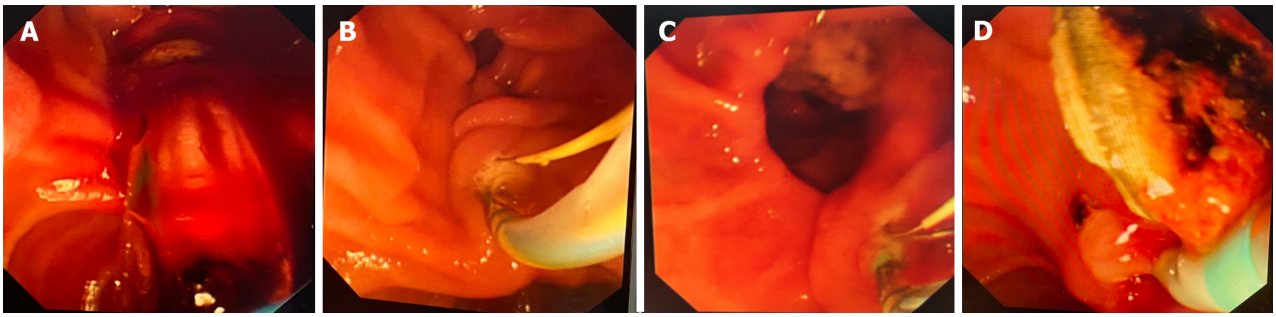


Figure 2 Operation process of endoscopic papillary balloon dilation. A: Common bile duct intubation; B: Balloon dilation of duodenal papilla; C: After airbag expansion; D: Stone extraction through expanded duodenal papilla.

pancreatic juice[21]. The dysfunction and structural damage of the Oddi sphincter will lead to diminished or loss of its "on-off" function, leading to cholestasis, duodenal fluid reflux, *etc*[22]. The clinical manifestations include biliary obstruction, biliary infection, pancreatitis, and recurrence of common bile duct stones[14,23]. In this study, the number of patients with a history of choledocholithiasis, pancreatitis, and Oddi sphincter dysfunction was higher in the EST group than in the EPBD group.

With the deepening of clinical exploration, choledocholithiasis surgery improvement, and the popularization of laparoscopy and endoscopy, laparoscopic common bile duct exploration (LCBDE) and ERCP have become the main clinical treatment methods for choledocholithiasis[24]. LCBDE is more traumatic and has a prolonged recovery period than ERCP[25]. However, regarding the long-term therapeutic effects, the stone recurrence rate was lower after LCBDE. ERCP is mainly combined with EPBD or EST, both of which are accompanied by varying degrees of damage to sphincter function and structure, leading to poor functioning of the "switch" of the Oddi sphincter postoperatively and consequently to cholestasis and infection of the biliary system, a major anatomical factor in stone recurrence[1]. In this study, the number of cases of pancreatic development, sphincterotomy of the pancreatic duct, and difficult intubation were higher in the EST group than in the EPBD group. Meanwhile, the number of Oddi's sphincter manometries, ERCP surgical outcomes, and guidewires entering the pancreatic duct several times in the EST group were lower than those in the EPBD group.

Self-factors included age, sex, choledocholithiasis, a history of pancreatitis and Oddi sphincter dysfunction, pancreatic imaging, pancreatic sphincterotomy, Oddi sphincter manometry, ERCP failure, difficulty in intubation, and multiple access of the guidewire to the pancreatic duct[1]. Therefore, preventive measures should be implemented to reduce the incidence of PEP.

Compared with the attempt of EPBD at relaxing the duodenal papillary sphincter for stone extraction utilizing balloons, the damage to the function of the duodenal papillary sphincter caused by EPBD is considerable[26]. The long-term risk of choledocholithiasis recurrence is markedly increased because of the loss of function of the duodenal papillary sphincter after surgery[27]. EST causes irreversible damage to the duodenal papillary sphincter[28]. Therefore, surgeons should carefully consider the surgical method choice for young patients to retain sphincter function as much as possible. The reasonable selection of a surgical method to reduce functional damage to the duodenal papillary sphincter should be a crucial factor in effectively preventing the recurrence of common bile duct stones after surgery[29]. However, it is challenging to strictly grasp the surgical indications since corresponding clinical guidelines to select EST and EPBD surgical methods are lacking[30].

Using a balloon in EPBD to relax the duodenal papillary sphincter for lithotomy causes more damage to the function of the duodenal papillary sphincter than intended[26]. The long-term risk of recurrent choledocholithiasis is greatly increased due to the loss of duodenal papillary sphincter function after surgery[27]. According to retrospective studies, EST causes irreversible damage to the duodenal papilla sphincter[28]. Therefore, surgeons should carefully consider that the choice of surgery for young patients should preserve sphincter function. Reasonably, choosing the surgical method to reduce functional impairment of the duodenal papillary sphincter is an important factor in effectively preventing the recurrence of choledocholithiasis after surgery[29]. However, there is a lack of corresponding clinical guidelines for strictly determining surgical indications in terms of surgical selection for EST and EPBD. In this study, the number of stone recurrences, reflux cholangitis, and cholecystitis was higher in the EST group than in the EPBD group.

The current study had some limitations. The effect of ESBD, especially EEPP, on the Oddi sphincter is still lacking in large-sample clinical research, and the follow-up time for long-term complications is short. In the future, a large amount of clinical data is needed to confirm the advantages and disadvantages of ESBD and EEPP and their specific effects on the Oddi sphincter. With the increasing importance of Oddi sphincter function in the pathogenesis of biliary and pancreatic diseases, minimizing damage to the sphincter has become a common goal of clinicians. In clinical practice, we should re-recognize the function of the Oddi sphincter and explore the ERCP method that has the least impact on it and has the best effect so that patients can receive reasonable and standard treatment as far as possible.

CONCLUSION

In conclusion, common bile duct stones, a history of pancreatitis, Oddi sphincter dysfunction, pancreatic imaging, pancreatic sphincterotomy, Oddi's sphincter manometries, ERCP operation failure, difficult intubation, and multiple guidewire entry into the pancreatic duct are all independent risk factors for PEP; thus, these findings allow to undertake corresponding countermeasures to prevent PEP after EST and EPBD in clinical practice.

FOOTNOTES

Author contributions: Fu K and Yang YY designed and performed the research and wrote the paper; Wang Y and Yin Z designed the research and supervised the report; Chen H designed the research and contributed to the analysis; Zhang GX and Chen H provided clinical advice; Wang Y and Yin Z supervised the report.

Institutional review board statement: The study was reviewed and approved by Yixing Hospital of Traditional Chinese Medicine (Approved No. 2022-052).

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

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at wy_wangyan_yx@163.com. Participants gave informed consent for data sharing.

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REFERENCES

1 **Park JC**, Park JG. A Case of Biliary Cast Syndrome After Endoscopic and Percutaneous Management of Common Bile Duct Stone. *Taehan Yongsang Uihakhoe Chi* 2022; **83**: 224-229 [PMID: 36237361 DOI: 10.3348/jksr.2021.0013]

2 **Belgau I**, Johnsen G, Græslie H, Mårvik R, Nymo S, Bjerkan K, Hyldmo Å, Klöckner C, Kulseng B, Hoff D, Sandvik J. Frequency of cholelithiasis in need of surgical or endoscopic treatment a decade or more after Roux-en-Y gastric bypass. *Surg Endosc* 2023; **37**: 1349-1356 [PMID: 36203112 DOI: 10.1007/s00464-022-09676-y]

3 **Boni L**, Huo B, Alberici L, Ricci C, Tsokani S, Mavridis D, Amer YS, Andreou A, Berriman T, Donatelli G, Forbes N, Kapiris S, Kayaalp C, Kylänpää L, Parra-Membrives P, Siersema PD, Black GF, Antoniou SA. EAES rapid guideline: updated systematic review, network meta-analysis, CINeMA and GRADE assessment, and evidence-informed European recommendations on the management of common bile duct stones. *Surg Endosc* 2022; **36**: 7863-7876 [PMID: 36229556 DOI: 10.1007/s00464-022-09662-4]

4 **Chhabra P**, On W, Paranandi B, Huggett MT, Robson N, Wright M, Maher B, Tehami N. Initial United Kingdom experience of endoscopic ultrasound-directed transgastric endoscopic retrograde cholangiopancreatography. *Ann Hepatobiliary Pancreat Surg* 2022; **26**: 318-324 [PMID: 36042580 DOI: 10.14701/ahbps.22-019]

5 **Gao F**, Zhang C, Feng Y, Zhan Y. MRI Evaluation of Indomethacin Suppositories in the Prevention of Complications of Pancreatitis and Hyperamylasemia after Choledocholithiasis ERCP Based on Image Denoising Algorithm. *Comput Math Methods Med* 2022; **2022**: 4805185 [PMID: 36051000 DOI: 10.1155/2022/4805185]

6 **Kattih O**, Velanovich V. Comparing One-Stage *vs* Two-Stage Approaches for the Management of Choledocholithiasis. *J Gastrointest Surg* 2023; **27**: 534-543 [PMID: 36127555 DOI: 10.1007/s11605-022-05458-y]

7 **Ji Z**, Wang Z, Li H. Abscess of ligamentum teres hepatis post-endoscopic retrograde cholangiopancreatography: A case report and a literature review. *SAGE Open Med Case Rep* 2022; **10**: 2050313X221110994 [PMID: 35859936 DOI: 10.1177/2050313X221110994]

8 **Lei Y**, Lethebe BC, Wishart E, Bazerbachi F, Elmunzer BJ, Thosani N, Buxbaum JL, Chen YI, Bass S, Cole MJ, Turbide C, Brenner DR, Heitman SJ, Mohamed R, Forbes N. Test Performance Characteristics of Dynamic Liver Enzyme Trends in the Prediction of Choledocholithiasis. *J Clin Med* 2022; **11** [PMID: 35956191 DOI: 10.3390/jcm11154575]

9 **Li J**, Hu J, Li P, Wu Y, Wang Y, Ji M, Hua H, Ran W, Pan Y, Zhang S. Analysis of risk factors associated with endoscopic retrograde cholangiopancreatography for patients with liver cirrhosis: a multicenter, retrospective, clinical study. *Chin Med J (Engl)* 2022; **135**: 2319-2325 [PMID: 36103988 DOI: 10.1097/CM9.0000000000002248]

10 **Liu H**, Pan W, Yan G, Li Z. A retrospective cohort study on the optimal interval between endoscopic retrograde cholangiopancreatography and laparoscopic cholecystectomy. *Medicine (Baltimore)* 2022; **101**: e29728 [PMID: 35801791 DOI: 10.1097/MD.0000000000029728]

11 **Lagouvardou E**, Martines G, Tomasicchio G, Laforgia R, Pezzolla A, Caputi Iambrenghi O. Laparo-endoscopic management of chole-choledocholithiasis: Rendezvous or intraoperative ERCP? A single tertiary care center experience. *Front Surg* 2022; **9**: 938962 [PMID: 36117813 DOI: 10.3389/fsurg.2022.938962]

12 **Coppola A**, Piacentino F, Macchi E, Marchi G, Ierardi AM, Carrafiello G, Fontana F. First use of a scoring balloon to perform Oddi sphincteroplasty for biliary stones. *Ann Gastroenterol* 2019; **32**: 416-418 [PMID: 31263365 DOI: 10.20524/aog.2019.0380]

13 **Feng Y**, Zhang J, Jiao C, Zhu H, Cheng W, Xu S, Xiao B, Ni J, Chen X. Manometric Measurement of the Sphincter of Oddi in Patients with Common Bile Duct Stones: A Consecutive Study of the Han Population of China. *Gastroenterol Res Pract* 2017; **2017**: 9031438 [PMID: 28133480 DOI: 10.1155/2017/9031438]

14 **Jia CK**, Weng J, Chen YK, Yang QZ, Fu Y, Qin QF, Yu WM. Hepatectomy with primary closure of common bile duct for hepatolithiasis combined with choledocholithiasis. *World J Gastroenterol* 2015; **21**: 3564-3570 [PMID: 25834321 DOI: 10.3748/wjg.v21.i12.3564]

15 **Chen CC**, Wu SD, Tian Y, Siwo EA, Zeng XT, Zhang GH. Sphincter of Oddi-preserving and T-tube-free laparoscopic management of extrahepatic bile duct calculi. *World J Surg* 2011; **35**: 2283-2289 [PMID: 21779932 DOI: 10.1007/s00268-011-1193-5]

16 **Long J**, Li J, Liu L, Zhou X, Lu X. Analysis of Clinical Effects of Intubation and Sphincterotomy With Wire-guided Incision Knife Plus Balloon Dilatation in the Treatment of Choledocholithiasis: A Randomized Controlled Trial. *Surg Laparosc Endosc Percutan Tech* 2022; **32**: 558-563 [PMID: 36197121 DOI: 10.1097/SLE.0000000000001096]

17 **Minakari M**, Samani RR, Shavakhi A, Jafari A, Alijanian N, Hajalikhani M. Endoscopic papillary balloon dilatation in comparison with endoscopic sphincterotomy for the treatment of large common bile duct stone. *Adv Biomed Res* 2013; **2**: 46 [PMID: 24516846 DOI: 10.4103/2277-9175.114186]

18 **Ding J**, Li F, Zhu HY, Zhang XW. Endoscopic treatment of difficult extrahepatic bile duct stones, EPBD or EST: An anatomic view. *World J Gastrointest Endosc* 2015; **7**: 274-277 [PMID: 25789099 DOI: 10.4253/wjge.v7.i3.274]

19 **Tsai TJ**, Lin CK, Lai KH, Chan HH, Wang EM, Tsai WL, Cheng JS, Yu HC, Chen WC, Hsu PI. Does preserved sphincter of Oddi function prevent common bile duct stones recurrence in patients after endoscopic papillary balloon dilation? *J Chin Med Assoc* 2018; **81**: 311-315 [PMID: 29499900 DOI: 10.1016/j.jcma.2018.01.007]

20 **Leszczyszyn J**. Choledocholithiasis diagnostics - endoscopic ultrasound or endoscopic retrograde cholangiopancreatography? *J Ultrason* 2014; **14**: 125-129 [PMID: 26672977 DOI: 10.15557/JoU.2014.0012]

21 **Masoni L**, Mari FS, Pietropaolo V, Onorato M, Meucci M, Brescia A. Laparoscopic treatment for unsuspected common bile duct stones by transcystic sphincter of Oddi pneumatic balloon dilation and pressure-washing technique. *World J Surg* 2013; **37**: 1258-1262 [PMID: 23474857 DOI: 10.1007/s00268-013-1992-y]

22 **Poincloux L**, Rouquette O, Privat J, Gorce D, Abergel A, Dapoigny M, Bommelaer G. Large-balloon dilation of the sphincter of Oddi after sphincterotomy or infundibulotomy to extract large calculi or multiple common bile duct stones without using mechanical lithotripsy. *Scand J Gastroenterol* 2013; **48**: 246-251 [PMID: 22229762 DOI: 10.3109/00365521.2011.647064]

23 **Turner GA**, Ing AJ, Connor SJ. Endoscopic large balloon sphincteroplasty is a useful, safe adjunct for difficult to treat choledocholithiasis. *ANZ J Surg* 2016; **86**: 395-398 [PMID: 24730714 DOI: 10.1111/ans.12599]

24 **Lu HS**, Yang TC, Chang CY, Huang YH, Hou MC. The risk of variceal bleeding during endoscopic retrograde cholangiopancreatography. *J Chin Med Assoc* 2022; **85**: 896-900 [PMID: 35848955 DOI: 10.1097/JCMA.0000000000000773]

25 **Lu R**, Luthra A, Han S. Combined EUS-guided gallbladder drainage with rendezvous ERCP for treatment of concomitant cholecystitis, cholelithiasis, and choledocholithiasis. *VideoGIE* 2022; **7**: 250-252 [PMID: 35815163 DOI: 10.1016/j.vgie.2022.03.003]

26 **Wu JH**, Kang JW, Wang YS, Lin HJ, Chen CY. Comparison of Different Endoscopic Methods Used for Managing Choledocholithiasis in Patients with End-Stage Renal Disease Undergoing Hemodialysis. *Dig Dis Sci* 2022; **67**: 5239-5247 [PMID: 35091841 DOI:

10.1007/s10620-021-07360-0]
27 **Mok SR**, Arif M, Diehl DL, Khara HS, Ho HC, Elfant AB. Safety and efficacy of minimal biliary sphincterotomy with papillary balloon dilation (m-EBS+EPBD) in patients using clopidogrel or anticoagulation. *Endosc Int Open* 2017; **5**: E157-E164 [PMID: 28337485 DOI: 10.1055/s-0042-120225]
28 **Testoni PA**, Mariani A, Aabakken L, Arvanitakis M, Bories E, Costamagna G, Devière J, Dinis-Ribeiro M, Dumonceau JM, Giovannini M, Gyokeres T, Hafner M, Halttunen J, Hassan C, Lopes L, Papanikolaou IS, Tham TC, Tringali A, van Hooft J, Williams EJ. Papillary cannulation and sphincterotomy techniques at ERCP: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2016; **48**: 657-683 [PMID: 27299638 DOI: 10.1055/s-0042-108641]
29 **Chung JW**, Chung JB. Endoscopic papillary balloon dilation for removal of choledocholithiasis: indications, advantages, complications, and long-term follow-up results. *Gut Liver* 2011; **5**: 1-14 [PMID: 21461066 DOI: 10.5009/gnl.2011.5.1.1]
30 **Park CH**, Jung JH, Nam E, Kim EH, Kim MG, Kim JH, Park SW. Comparative efficacy of various endoscopic techniques for the treatment of common bile duct stones: a network meta-analysis. *Gastrointest Endosc* 2018; **87**: 43-57.e10 [PMID: 28756105 DOI: 10.1016/j.gie.2017.07.038]

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ORIGINAL ARTICLE

Retrospective Study

Influence of reduced-port laparoscopic surgery on perioperative indicators, postoperative recovery, and serum inflammation in patients with colorectal carcinoma

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Abstract

BACKGROUND

Conventional five-port laparoscopic surgery, the current standard treatment for colorectal carcinoma (CRC), has many disadvantages.

AIM

To assess the influence of reduced-port laparoscopic surgery (RPLS) on perioperative indicators, postoperative recovery, and serum inflammation indexes in patients with CRC.

METHODS

The study included 115 patients with CRC admitted between December 2019 and May 2023, 52 of whom underwent conventional five-port laparoscopic surgery (control group) and 63 of whom underwent RPLS (research group). Comparative analyses were performed on the following dimensions: Perioperative indicators [operation time (OT), incision length, intraoperative blood loss (IBL), and rate of conversion to laparotomy], postoperative recovery (first postoperative exhaust, bowel movement and oral food intake, and bowel sound recovery time), serum inflammation indexes [high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6)], postoperative complications (anastomotic leakage, incisional infection, bleeding, ileus), and therapeutic efficacy.

RESULTS

The two groups had comparable OTs and IBL volumes. However, the research group had a smaller incision length; lower rates of conversion to laparotomy and postoperative total complication; and shorter time of first postoperative exhaust, bowel movement, oral food intake, and bowel sound recovery; all of which were

significant. Furthermore, hs-CRP, IL-6, and TNF-α levels in the research group were significantly lower than the baseline and those of the control group, and the total effective rate was higher.

CONCLUSION

RPLS exhibited significant therapeutic efficacy in CRC, resulting in a shorter incision length and a lower conversion rate to laparotomy, while also promoting postoperative recovery, effectively inhibiting the inflammatory response, and reducing the risk of postoperative complications.

Key Words: Reduced-port laparoscopic surgery; Colorectal carcinoma; Perioperative indicators; Postoperative recovery; Serum inflammation indexes

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Core Tip: Colorectal carcinoma (CRC) is a fatal but preventable gastrointestinal malignancy, with surgical treatment being the standard of care. However, conventional laparoscopic surgery has obvious disadvantages. This study compared reduced-port laparoscopic surgery (RPLS) and conventional laparoscopic surgery and confirmed that the former had more advantages than the latter in CRC based on perioperative indicators, postoperative recovery, serum inflammatory responses, postoperative complications, and therapeutic efficacy. RPLS not only reduced the incision length and the rate of conversion to laparotomy but also promoted postoperative recovery, effectively inhibited the inflammatory response, and reduced the risk of postoperative complications.

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INTRODUCTION

Colorectal carcinoma (CRC) is a fatal but preventable gastrointestinal malignancy and is the third most common cancer worldwide[1]. Smoking, high body fat, lack of exercise, and unhealthy eating habits, among others, may contribute to the occurrence of CRC[2]. Nearly 1.8 million new CRC cases and approximately 900000 associated deaths are reported every year, with a 5-year survival rate < 20% in patients with metastatic CRC[3,4]. Surgical treatment, the standard treatment for CRC, aims to resect the primary tumor and surrounding lymph nodes[5,6]. However, conventional laparoscopic surgery involves a five-port procedure, which not only affects the postoperative aesthetics of patients but also carries the risk of blood vessel and nerve damage in the abdominal wall and complication by trocar site hernia[7,8]. Therefore, optimizing surgical procedures based on conventional laparoscopic surgery could significantly improve the surgical outcomes and postoperative recovery of patients.

Reduced-port laparoscopic surgery (RPLS) implements an auxiliary incision combined with a single-port protocol. Port reduction (final two ports) is achieved by combining two auxiliary operation ports and one observation port in the auxiliary incision and then operating alongside the main operation port to achieve laparoscopic radical resection of CRC [9,10]. This surgical modality is minimally invasive and less labor-intensive[11]. Inaki[12] found that RPLS can be performed for bariatric surgery and sleeve gastrectomy for the resection of benign gastric submucosal tumors, providing better cosmetic effects and even achieving a permanent cure. Borodulin *et al*[13] demonstrated that the application of RPLS in bilateral salpingectomy provides good cosmetic outcomes while ensuring safety and feasibility. RPLS for patients with CRC has also been reported in previous studies as an alternative to conventional multi-port laparoscopic colectomy [14].

This study hypothesized that RPLS has superior clinical advantages over conventional five-port laparoscopic surgery in the treatment of CRC, which is hereby verified and reported in detail.

MATERIALS AND METHODS

General information

One hundred and fifteen patients with CRC admitted to The First Affiliated Hospital of Ningbo University from December 2019 to May 2023 were selected as the study subjects. The control group (n = 52) underwent conventional five-port laparoscopic surgery, while the research group (n = 63) underwent RPLS. The two case groups were clinically comparable with no significant differences in baseline data (P > 0.05).

Criteria for patient enrollment and exclusion

Inclusion criteria: All patients included in this study were clinically diagnosed with CRC[15] and met the indications for surgical treatment; and had complete clinical data, normal cognitive and communication abilities, and no water–electrolyte disturbance or acid–base imbalance.

Exclusion criteria: Minors, elderly patients aged > 80 years, and pregnant or lactating women were ineligible for this study. Also excluded were patients who had recently received chemoradiotherapy; patients with heart/lung/kidney dysfunction, coagulation dysfunction, autoimmune system defects, or other malignant tumors; and those suffering from serious gastrointestinal dysfunction, disorders, or other diseases before surgery that might affect the evaluation of gastrointestinal function.

Treatment methods

The research group underwent RPLS. The protocol involved performing an auxiliary incision, and a single port was adopted. The conventional two 5-mm auxiliary operation ports and 10-mm observation port were combined in the auxiliary incision of about 5 cm in length and used together with a 12-mm main operation port for the procedure. After general anesthesia, the patient was placed in a lithotomy position with the head low and feet high. A longitudinal incision approximately 5 cm long was made under the umbilicus into the abdomen, and a disposable retractor was placed in it and secured. After cutting the fingertips of a surgical glove, a 5-mm trocar was inserted into the thumb and little finger as the operating ports, and a 10-mm trocar was inserted into the middle finger as the observation port. A CO_2 pneumoperitoneum with an abdominal pressure of 12 mmHg was established, and a 12-mm trocar was inserted as the main operating port and positioned at the location of the CRC. Finally, laparoscopic radical resection of CRC was performed by removing the cancerous bowel segment, anastomosing the intestinal end, and dissecting the regional lymph nodes.

The control group underwent routine five-port laparoscopic surgery. Anesthesia and posture were the same as those in the research group. A pneumoperitoneum was established, the cancerous intestinal segment was removed at the tumor site, the severed intestinal end was anastomosed, and the regional lymph nodes were removed. Finally, indwelling drainage and conventional suture were performed to complete the surgery.

Endpoints

Perioperative indicators: The operation time (OT), incision length, intraoperative blood loss (IBL), and rate of conversion to laparotomy were measured and recorded.

Postoperative recovery: The first postoperative exhaust, bowel movement, and oral food intake, as well as bowel sound recovery, were monitored and documented.

Serum inflammation indexes: Early in the morning, 3 mL of venous blood was collected from the patient with an empty stomach and stored in test tubes for several minutes. After centrifugation, the serum was separated, and the supernatant was collected into EP tubes and refrigerated at −20°C for testing. Enzyme-linked immunosorbent assay was performed to quantify high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6).

Incidence of postoperative complications: Adverse events, such as anastomotic leakage (AL), incision infection, bleeding, and ileus, and their incidence rates were determined and recorded.

Efficacy: Assessment A marked response refers to the significant relief of gastrointestinal symptoms, such as diarrhea, constipation, and rectal bleeding, following treatment; complete removal of cancer lesions on imaging examination; and the absence of postoperative complications or adverse effects. A response is defined as the effective symptom control, complete resection of the cancer on imaging examination, and the presence of mild but controllable complications, such as infection and bleeding, after surgery. Non-response indicates no considerable improvement of symptoms, residual tumor resection by imaging examination, and serious postoperative complications and adverse events. The overall response rate (ORR) is the percentage of the sum of marked response and response cases to the total number of cases.

Statistical analyses

In this study, both the measurement data (expressed as mean ± SE) and counting data (expressed as number of cases and percentage) were imported into SPSS22.0 software package for statistical analyses. The chi-square test (χ^2) was used to compare counting data, and the independent sample *t*-test was used to compare measurement data between groups. In all tests, $P < 0.05$ indicated statistical significance.

RESULTS

Comparative analysis of baseline data

The comparison of baseline data revealed no significant inter-group differences in terms of sex, age, body mass index, surgical site, and tumor-nodes-metastasis staging ($P > 0.05$; Table 1).

Comparative analysis of perioperative indicators

The perioperative indicators analyzed included OT, incision length, IBL, and rate of conversion to laparotomy. OT, IBL, and rate of conversion to laparotomy were comparable between the two groups ($P > 0.05$); however, the research group

Table 1 Comparative analysis of baseline data, *n* (%)

Factors	Control group (*n* = 52)	Research group (*n* = 63)	χ^2/t	*P* value
Sex			0.151	0.697
Male	27 (51.92)	35 (55.56)		
Female	25 (48.08)	28 (44.44)		
Age (yr)	54.10 ± 9.56	55.02 ± 10.97	0.474	0.636
Body mass index (kg/m^2)	23.73 ± 2.58	24.05 ± 3.04	0.601	0.549
Surgical site			1.901	0.387
Left colon	18 (34.62)	15 (23.81)		
Right colon	20 (38.46)	31 (49.21)		
Rectum	14 (26.92)	17 (26.98)		
TNM stage			0.813	0.666
II	19 (36.54)	20 (31.75)		
III	18 (34.62)	27 (42.86)		
IV	15 (28.85)	16 (25.40)		

TNM: Tumor-nodes-metastasis.

had a significantly shorter incision length ($P < 0.05$; Figure 1).

Comparative analysis of postoperative recovery indexes

The postoperative recovery of patients was determined mainly by postoperative anal exhaust, bowel movement, oral food intake, and bowel sound recovery. The times to the first postoperative exhaust, bowel movement, and oral intake were markedly shorter and time to bowel sound recovery was faster in the research group than in the control group ($P < 0.05$; Figure 2).

Comparative analysis of serum inflammation indexes

Serum hs-CRP, TNF-α, and IL-6 levels were assessed pre- and postoperatively. No significant inter-group differences were observed in these indexes preoperatively ($P > 0.05$). However, all of them increased significantly in both groups postoperatively ($P < 0.05$). However, the levels in the research group were lower than those in the control group ($P < 0.05$; Figure 3).

Comparative analysis of postoperative complications

In terms of complications, the occurrences of AL, incision infection, bleeding, and ileus were evaluated. The incidence of total postoperative complications was markedly lower in the research group than in the control group ($P < 0.05$; Table 2).

Comparative analysis of efficacy

The ORR in the research group was 90.48%, which was significantly higher than the 75.00% of the control group ($P < 0.05$; Table 3).

DISCUSSION

Although surgery is the major treatment option for CRC, the procedure can lead to prolonged hospitalization, surgical infection, and postoperative ileus. The popularization of laparoscopic surgery has uncovered a more effective way of addressing these problems[16,17]. This study hypothesized that, compared with conventional five-port laparoscopic surgery, RPLS has a more prominent clinical effect in CRC treatment, which is hereby verified and reported.

In patients with CRC, RPLS has the same effects as five-port laparoscopic surgery in shortening OT, reducing intraoperative bleeding, and lowering the rate of conversion to laparotomy. However, RPLS more effective in shortening the incision length, as demonstrated by the evaluation of perioperative indicators. In terms of postoperative recovery, the research group exhibited significant advantages over the control group with a shorter time to first exhaust, bowel movement, oral food intake, and bowel sound recovery after surgery, indicating that RPLS can accelerate postoperative recovery. This could be attributed to the shorter incision length and less damage to gastrointestinal function in RPLS, ensuring the effective recovery of gastrointestinal function postoperatively[18,19]. Similarly, a meta-analysis indicated a shorter hospital stay in patients with gastric cancer who underwent RPLS compared with those who underwent conventional laparoscopic surgery, further demonstrating that RPLS accelerates patient recovery[20]. Similar to our results, Wu

Table 2 Comparative analysis of postoperative complications, *n* (%)

Factors	Control group (*n* = 52)	Research group (*n* = 63)	χ^2	*P* value
Anastomotic leakage	3 (5.77)	0 (0.00)		
Incision infection	10 (19.23)	3 (4.76)		
Bleeding	1 (1.92)	2 (3.17)		
Ileus	2 (3.85)	4 (6.35)		
Total	16 (30.77)	9 (14.29)	4.549	0.033

Table 3 Comparative analysis of efficacy, *n* (%)

Factors	Control group (*n* = 52)	Research group (*n* = 63)	χ^2	*P* value
Marked response	18 (34.62)	35 (55.56)		
Response	21 (40.38)	22 (34.92)		
Non-response	13 (25.00)	6 (9.52)		
Overall response rate	39 (75.00)	57 (90.48)	4.947	0.026

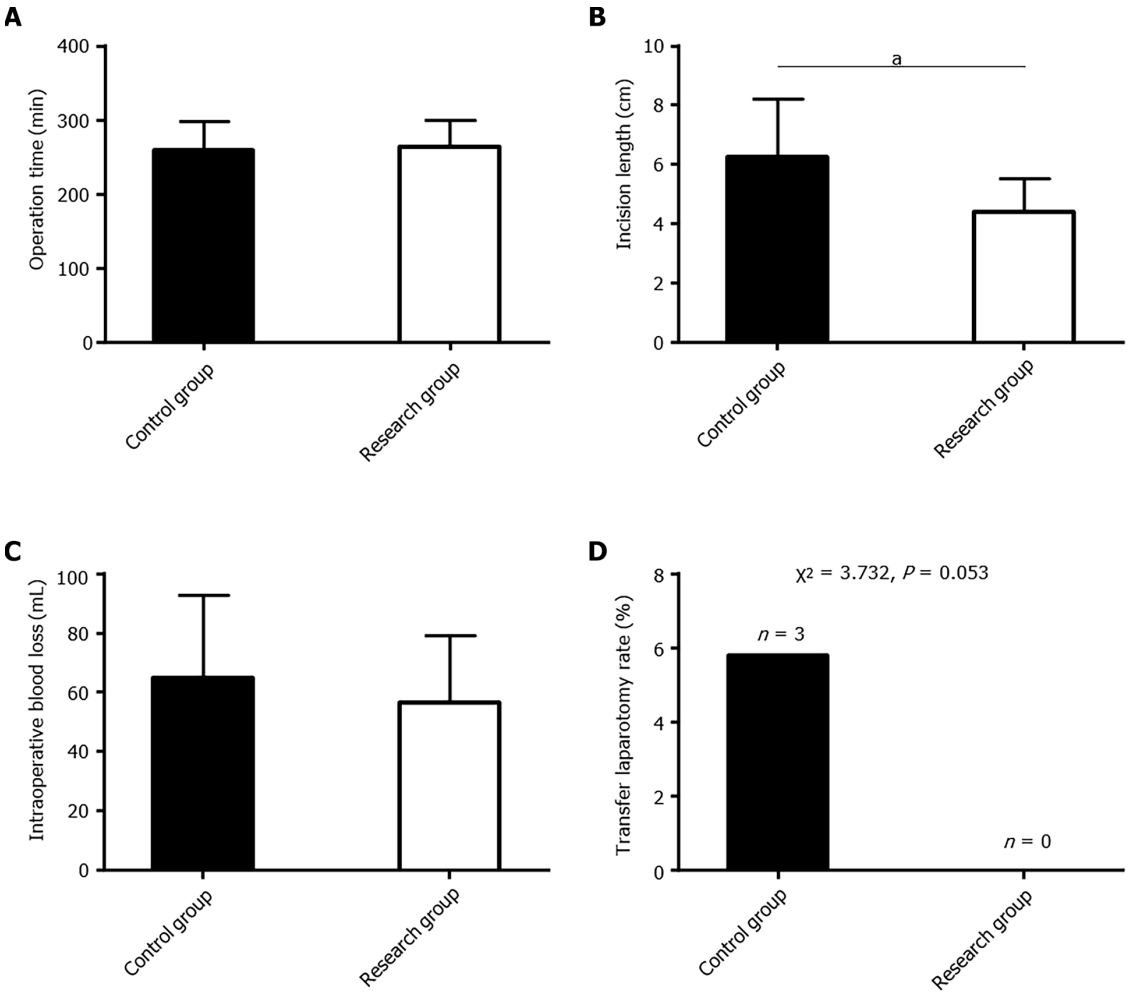


Figure 1 Comparative analysis of operation time, incision length, intraoperative blood loss, and rate of conversion to laparotomy. A: Operation time; B: Incision length; C: Intraoperative blood loss; D: Rate of conversion to laparotomy. [a]*P* < 0.01.

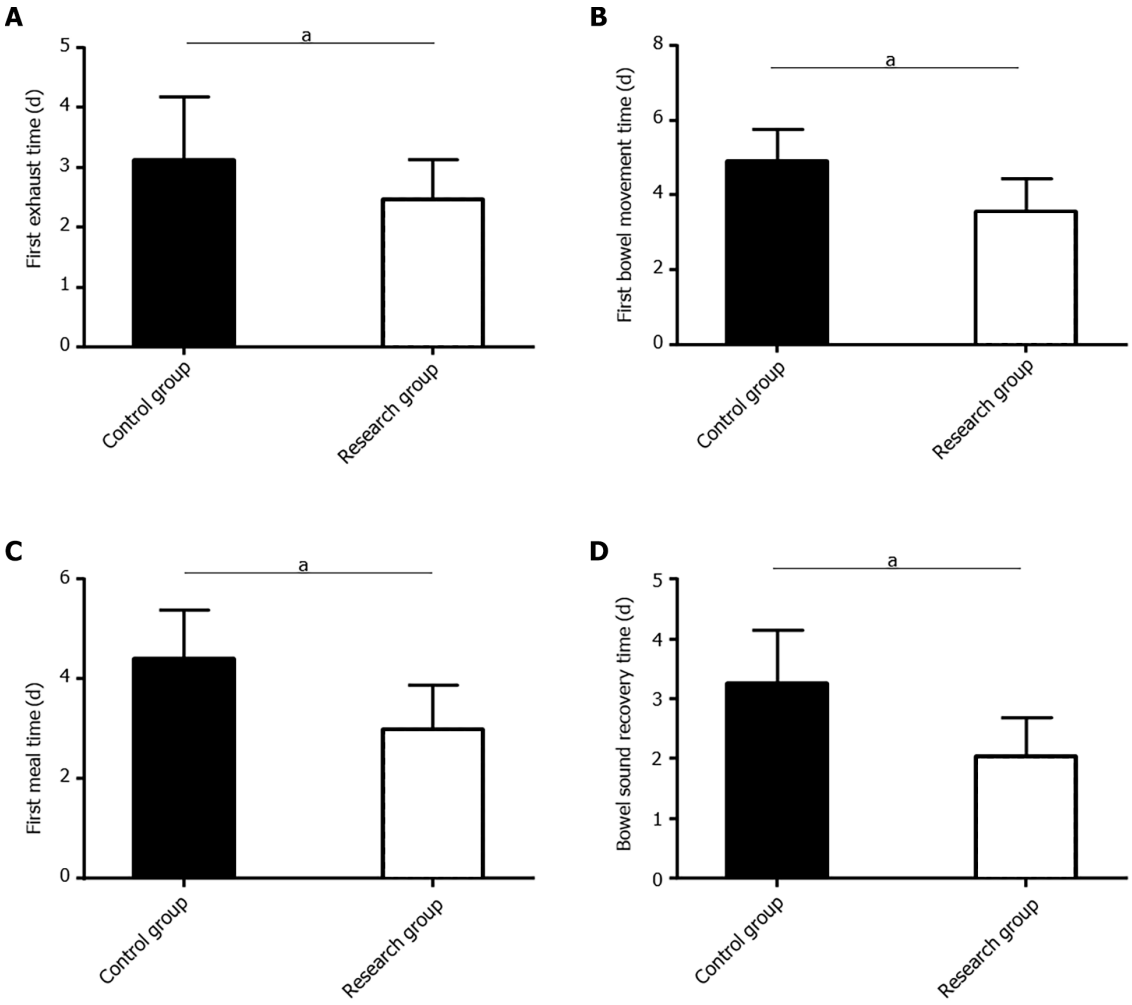


Figure 2 Comparative analysis of postoperative recovery indicators. A: First postoperative anal exhaust time; B: First postoperative bowel movement time; C: First postoperative meal time; D: First postoperative bowel sound recovery time. [a]*P* < 0.01.

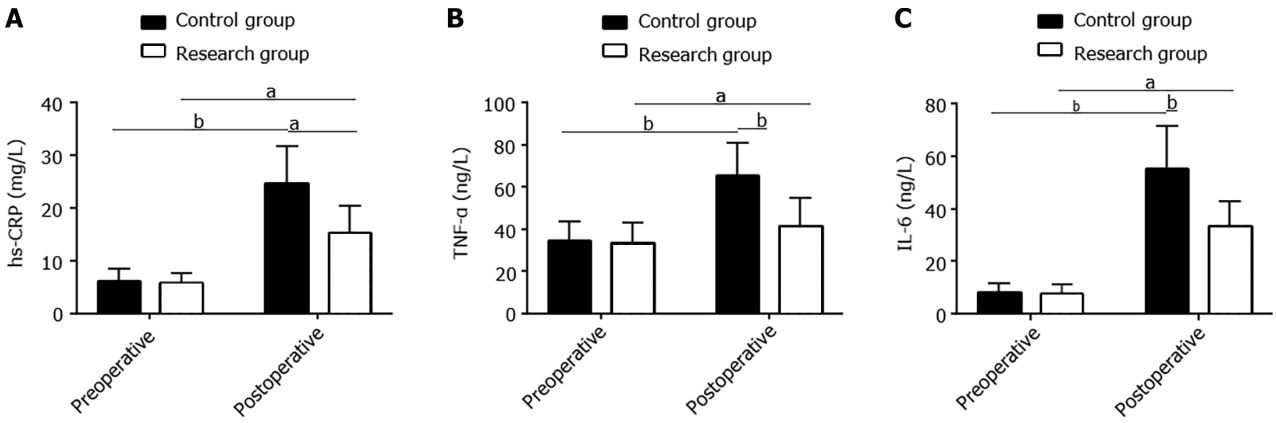


Figure 3 Comparative analysis of serum inflammatory factors. A: High-sensitivity C-reactive protein; B: Tumor necrosis factor-α; C: Interleukin-6. [a]*P* < 0.05; [b]*P* < 0.01. hs-CRP: High-sensitivity C-reactive protein; TNF-α: Tumor necrosis factor-α; IL-6: Interleukin-6.

et al[21] found that RPLS has significant advantages over multi-port laparoscopic surgery in reducing surgical incision length, alleviating postoperative pain, shortening the time to first postoperative anal exhaust, and promoting early ambulation in elderly patients with upper rectal cancer.

hs-CRP, TNF-α, and IL-6 are closely correlated with physical trauma-induced inflammatory responses in patients following RPLS[22]. In the present study, postoperative hs-CRP, TNF-α, and IL-6 Levels in the research group increased significantly but were still significantly lower than those in the control group, indicating that RPLS can significantly inhibit surgery-related inflammatory reactions in patients with CRC. In addition, the research group had a lower in-

cidence of total postoperative complications, such as AL, incision infection, bleeding, and ileus, than the control group (14.29% *vs* 30.77%, respectively). Thus, RPLS has a lower risk of postoperative adverse events. The higher safety rate of RPLS may also be attributed to the shorter incision length, indicating relatively less damage to the patient's body structure and function, thereby ensuring fewer postoperative complications[23,24]. Finally, the research group showed a significantly higher ORR than the control group (90.48% *vs* 75.00%, respectively), indicating greater therapeutic efficacy obtained with RPLS. Kim *et al*[25] reported that RPLS for gastric cancer is not only safe and feasible but also has a shorter learning curve, similar to our findings. This is partly because RPLS has no effect on the surgical field, surgical area judgment, and tumor resection, thereby confirming the safety and clinical efficacy of the procedure[26].

The current study has several limitations. First, the sample size was small, and the effect of potentially confounding factors could not be ruled out, which would limit the generalizability of the research results. Second quality of life and stress indicators were not analyzed, which would have further verified the clinical advantages of RPLS. Finally, prognostic outcomes were not assessed, which would have offered insights into the long-term impact of RPLS.

CONCLUSION

In summary, RPLS offers more advantages in the treatment of CRC than five-port laparoscopic surgery, as reflected by a shorter incision length, faster recovery, regulation of the inflammatory response, and higher rates of postoperative safety and efficacy.

FOOTNOTES

Author contributions: Wu HB designed and performed the research and wrote the paper; Wu HB, Liu DF, Liu YL and Cao YP designed the research and supervised the report; Wu HB and Wang XF collected the data; Wu HB and Cao YP provided clinical advice and supervised the report.

Institutional review board statement: This study was approved by the Ethic Committee of The First Affiliated Hospital of Ningbo University.

Informed consent statement: This study was a retrospective study using anonymized data. The review board of The First Affiliated Hospital of Ningbo University approved the study and waived informed consent.

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REFERENCES

1 **Mitsala A**, Tsalikidis C, Pitiakoudis M, Simopoulos C, Tsaroucha AK. Artificial Intelligence in Colorectal Cancer Screening, Diagnosis and Treatment. A New Era. *Curr Oncol* 2021; **28**: 1581-1607 [PMID: 33922402 DOI: 10.3390/curroncol28030149]

2 **Kuipers EJ**, Grady WM, Lieberman D, Seufferlein T, Sung JJ, Boelens PG, van de Velde CJ, Watanabe T. Colorectal cancer. *Nat Rev Dis Primers* 2015; **1**: 15065 [PMID: 27189416 DOI: 10.1038/nrdp.2015.65]

3 **Biller LH**, Schrag D. Diagnosis and Treatment of Metastatic Colorectal Cancer: A Review. *JAMA* 2021; **325**: 669-685 [PMID: 33591350 DOI: 10.1001/jama.2021.0106]

4 **Baidoun F**, Elshiwy K, Elkeraie Y, Merjaneh Z, Khoudari G, Sarmini MT, Gad M, Al-Husseini M, Saad A. Colorectal Cancer Epidemiology: Recent Trends and Impact on Outcomes. *Curr Drug Targets* 2021; **22**: 998-1009 [PMID: 33208072 DOI: 10.2174/1389450121999201117115717]

5 **Carli F**, Bousquet-Dion G, Awasthi R, Elsherbini N, Liberman S, Boutros M, Stein B, Charlebois P, Ghitulescu G, Morin N, Jagoe T, Scheede-Bergdahl C, Minnella EM, Fiore JF Jr. Effect of Multimodal Prehabilitation *vs* Postoperative Rehabilitation on 30-Day Postoperative Complications for Frail Patients Undergoing Resection of Colorectal Cancer: A Randomized Clinical Trial. *JAMA Surg* 2020; **155**: 233-242 [PMID: 31968063 DOI: 10.1001/jamasurg.2019.5474]

6 **Salibasic M**, Pusina S, Bicakcic E, Pasic A, Gavric I, Kulovic E, Rovcanin A, Beslija S. Colorectal Cancer Surgical Treatment, our Experience. *Med Arch* 2019; **73**: 412-414 [PMID: 32082011 DOI: 10.5455/medarh.2019.73.412-414]

7 **Wang Y**, Yang JW, Yan SY, Lu Y, Han JG, Pei W, Zhao JJ, Li ZK, Zhou H, Yang NN, Wang LQ, Yang YC, Liu CZ. Electroacupuncture *vs* Sham Electroacupuncture in the Treatment of Postoperative Ileus After Laparoscopic Surgery for Colorectal Cancer: A Multicenter, Randomized Clinical Trial. *JAMA Surg* 2023; **158**: 20-27 [PMID: 36322060 DOI: 10.1001/jamasurg.2022.5674]

8 **Zhao S**, Zhang L, Gao F, Wu M, Zheng J, Bai L, Li F, Liu B, Pan Z, Liu J, Du K, Zhou X, Li C, Zhang A, Pu Z, Li Y, Feng B, Tong W. Transanal Drainage Tube Use for Preventing Anastomotic Leakage After Laparoscopic Low Anterior Resection in Patients With Rectal Cancer: A Randomized Clinical Trial. *JAMA Surg* 2021; **156**: 1151-1158 [PMID: 34613330 DOI: 10.1001/jamasurg.2021.4568]

9 **Seo HS**, Kim S, Song KY, Lee HH. Feasibility and Potential of Reduced Port Surgery for Total Gastrectomy With Overlap Esophagojejunal Anastomosis Method. *J Gastric Cancer* 2023; **23**: 487-498 [PMID: 37553134 DOI: 10.5230/jgc.2023.23.e26]

10 **Nath SK**. Reduced Port Laparoscopic Cholecystectomy: Single and a Half Incision Lap Chole. *Indian J Surg* 2016; **78**: 425-427 [PMID: 27994345 DOI: 10.1007/s12262-016-1546-2]

11 **Han HJ**, Kang CM. Reduced port minimally invasive distal pancreatectomy: single-port laparoscopic versus robotic single-site plus one-port distal pancreatectomy. *Surg Endosc* 2019; **33**: 1091-1099 [PMID: 29998392 DOI: 10.1007/s00464-018-6361-3]

12 **Inaki N**. Reduced port laparoscopic gastrectomy: a review, techniques, and perspective. *Asian J Endosc Surg* 2015; **8**: 1-10 [PMID: 25496345 DOI: 10.1111/ases.12163]

13 **Borodulin O**, Stockwell E, Howard D. Cosmetic Surgery-Use of 3mm Ports and Reduced-Port Techniques for Gynecologic Surgery. *Surg Technol Int* 2020; **36**: 153-156 [PMID: 31821524]

14 **Hirano Y**, Hiranuma C, Hattori M, Douden K, Yamaguchi S. Single-incision or Single-incision Plus One-Port Laparoscopic Surgery for Colorectal Cancer. *Surg Technol Int* 2020; **36**: 132-135 [PMID: 32196563]

15 **Zehnbauer B**, Temple-Smolkin R, Monzon FA. Guidelines for Colorectal Cancer Testing: Evidence-Based Practice Recommendations. *J Mol Diagn* 2017; **19**: 183-186 [PMID: 28190460 DOI: 10.1016/j.jmoldx.2017.01.002]

16 **Kang CY**, Chaudhry OO, Halabi WJ, Nguyen V, Carmichael JC, Stamos MJ, Mills S. Outcomes of laparoscopic colorectal surgery: data from the Nationwide Inpatient Sample 2009. *Am J Surg* 2012; **204**: 952-957 [PMID: 23122910 DOI: 10.1016/j.amjsurg.2012.07.031]

17 **Thiele RH**, Rea KM, Turrentine FE, Friel CM, Hassinger TE, McMurry TL, Goudreau BJ, Umapathi BA, Kron IL, Sawyer RG, Hedrick TL. Standardization of care: impact of an enhanced recovery protocol on length of stay, complications, and direct costs after colorectal surgery. *J Am Coll Surg* 2015; **220**: 430-443 [PMID: 25797725 DOI: 10.1016/j.jamcollsurg.2014.12.042]

18 **Wei C**, Xiao J, Teng WH, Liao LH, Zang WD. [Application of single incision plus one port laparoscopic surgery in radical right hemicolon cancer surgery]. *Zhonghua Wei Chang Wai Ke Za Zhi* 2021; **24**: 54-61 [PMID: 33461253 DOI: 10.3760/cma.j.issn.441530-20200605-00344]

19 **Wang S**, Ling T, Zhao E, Cao H. The surgical treatment of gastric cancer in the era of minimally invasive surgery. *Minerva Chir* 2017; **72**: 334-346 [PMID: 28415834 DOI: 10.23736/S0026-4733.17.07347-3]

20 **Alarcón I**, Yang T, Balla A, Morales-Conde S. Single/reduced port surgery vs. conventional laparoscopic gastrectomy: systematic review and meta-analysis. *Minim Invasive Ther Allied Technol* 2022; **31**: 515-524 [PMID: 33600291 DOI: 10.1080/13645706.2021.1884571]

21 **Wu H**, Zheng Z, Xu L, Wu Y, Guan Z, Li W, Chen G. Short- And medium-term outcomes of reduced-port laparoscopic surgery in elderly patients with upper rectal cancer: A retrospective cohort study. *Cancer Med* 2020; **9**: 5320-5326 [PMID: 32490598 DOI: 10.1002/cam4.3070]

22 **Milone M**, Desiderio A, Velotti N, Manigrasso M, Vertaldi S, Bracale U, D'Ambra M, Servillo G, De Simone G, De Palma FDE, Perruolo G, Raciti GA, Miele C, Beguinot F, De Palma GD. Surgical stress and metabolic response after totally laparoscopic right colectomy. *Sci Rep* 2021; **11**: 9652 [PMID: 33958669 DOI: 10.1038/s41598-021-89183-7]

23 **Ishii Y**, Ochiai H, Sako H, Watanabe M. Long-term oncological outcome of reduced-port laparoscopic surgery (single-incision plus one port) as a technical option for rectal cancer. *Asian J Endosc Surg* 2023; **16**: 687-694 [PMID: 37365007 DOI: 10.1111/ases.13222]

24 **Fan Y**, Wu SD, Kong J, Su Y, Tian Y, Yu H. Feasibility and safety of single-incision laparoscopic splenectomy: a systematic review. *J Surg Res* 2014; **186**: 354-362 [PMID: 24135373 DOI: 10.1016/j.jss.2013.09.010]

25 **Kim HG**, Kim DY, Jeong O. Transition from Conventional to Reduced-Port Laparoscopic Gastrectomy to Treat Gastric Carcinoma: a Single Surgeon's Experience from a Small-Volume Center. *J Gastric Cancer* 2018; **18**: 172-181 [PMID: 29984067 DOI: 10.5230/jgc.2018.18.e18]

26 **Watras AJ**, Kim JJ, Ke J, Liu H, Greenberg JA, Heise CP, Hu YH, Jiang H. Large-Field-of-View Visualization with Small Blind Spots Utilizing Tilted Micro-Camera Array for Laparoscopic Surgery. *Micromachines (Basel)* 2020; **11** [PMID: 32397580 DOI: 10.3390/mi11050488]

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ORIGINAL ARTICLE

Clinical Trials Study

Clinical effect of spleen aminopeptide on improving liver function damage and immune function in children with infant hepatitis syndrome

Xiao-Qing Fang, Tian Gan, Lie-Min Wang

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Abstract

BACKGROUND

Infant hepatitis syndrome (IHS) is a clinical syndrome in infants less than one year of age with generalized skin jaundice, abnormal liver function, and hepatomegaly due to various etiologies such as infection.

AIM

To investigate the effect of IHS patients, after treatment with arsphenamine-based peptides, on patients' liver function damage and immune function.

METHODS

Of 110 patients with IHS treated in our hospital from January 2019 to January 2021 were grouped according to the randomized residual grouping method, with 5 cases in each group shed due to transfer, *etc.* Ultimately, 50 cases remained in each group. The control group was treated with reduced glutathione, and the treatment group was treated with sesquiterpene peptide based on the control group. Observe and compare the differences in indicators after treatment.

RESULTS

The comparison of serum total bilirubin, direct bilirubin, and serum alanine transferase after treatment was significantly different and lower in the treatment

group than in the control group ($P < 0.05$). The comparison of $CD4^+$, $CD3^+$, $CD4^+/CD8^+$ after treatment was significantly different and higher in the treatment group than in the control group, and the comparison was statistically significant ($P < 0.05$). The complication of the two groups showed that the rash, cough and sputum, elevated platelets, and gastrointestinal reactions in the treatment group were significantly lower than those in the control group, and the differences were statistically significant by test ($P < 0.05$).

CONCLUSION

The comparative study of IHS treated with arsphenamine combined with reduced glutathione is more effective.

Key Words: Infant hepatitis syndrome; Splenamin; Reduced glutathione; Liver function; Immune function; Complication

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Core Tip: In this study, infant hepatitis syndrome (IHS) is a clinical syndrome in infants less than one year of age with generalized skin jaundice, abnormal liver function, and hepatomegaly due to various etiologies such as infection. The comparative study of IHS was better treated with splenamine combined with reduced glutathione, which effectively improved patients' liver function and immune level, reduced adverse reactions, and provided some reference value for clinical treatment of IHS.

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INTRODUCTION

Infant hepatitis syndrome (IHS) is a clinical syndrome in infants less than one year of age with generalized skin jaundice, abnormal liver function, and hepatomegaly due to various etiologies such as infection[1]. Most of the jaundice appears within the first 12 months of life. It is accompanied by darkening of the urine and lightening of the stool, usually with hepatomegaly, and about 50% of patients also have enlarged spleen and liver function abnormalities, such as increased serum transaminases in laboratory tests. At the same time, children with IHS have inflammatory changes in the liver that cause metabolic disorders in the body, resulting in reduced protein synthesis and impaired immune function, which can seriously affect the average growth and development of infants and cause hepatic malnutrition, which can be complicated by multiple organ and systemic disorders, including secondary infections, rickets, and intracranial hemorrhage[2,3].

Splenaminopeptide is an immunomodulator, the main component of which is derived from peptides and nucleotides extracted from fresh pig spleen and is used in the treatment of cellular immune hypofunction, immunodeficiency and autoimmune dysfunctional diseases such as recurrent respiratory infections, bronchitis, pneumonia, asthma, severe herpes zoster, *etc.* It is also used in patients with malignant tumors after radiotherapy, chemotherapy, and surgery to improve the patients' autoimmunity[4]. Splenaminopeptide can inhibit the secretion of IL-4 by Th2 cells, which can enhance immunity against viruses by relieving the inhibition of lymphocytes by IL-4 and the inhibition of the ability of macrophages to phagocytose viruses[5]. By acting on three links: immune messaging, lymphocyte activation, and receptor regulation, splenaminopeptide has sufficient time to repeatedly engage with recipient lymphocytes in vivo, improving the ratio of CD4+ CD8+ cells, resulting in a significant increase in the number of lymphocytes and enhancing the cellular immune function of patients[6]. It can be seen that IHS is one of the serious diseases that threaten the health and quality of life of infants and children, and how to effectively prevent and treat this disease is a topic worthy of our in-depth study. However, whether splenamine-based peptides improve the liver function damage and immune status of patients with IHS has not been clinically reported. However, there are no clinical reports on whether splenamine improves liver function impairment and immune status in IHS patients. Based on this, we have explored the effect of splenic on liver function damage and immune function of IHS patients and analyzed the clinical efficacy. The research results are reported as follows.

MATERIALS AND METHODS

General information

The actual sample size included in this study was the 110 children who were treated in our hospital from January 2019 to January 2021, divided into control and treatment groups according to the random remainder grouping method, and 5 cases were shed in each group due to transfer, new crown epidemic, lost visits, *etc.* Finally, 50 cases were left in each group. Diagnostic criteria: all patients met the diagnostic criteria for IHS according to the diagnostic criteria for pediatric

diseases[7]: Moderate to severe yellowing of the skin over the body, abnormal liver function, lightening of stool color and deepening of urine color; palpable right subcostal liver > 2.1 cm, serum total bilirubin (TBIL) > 171 μmol/L; direct bilirubin (DBIL) < 86.5 μmol/L. Those with serum glutathione aminotransferase (ALT) > 40 U/L, liver and spleen ultrasound: showed enlarged liver, spleen may not be enlarged. In both groups, general information such as gender and age did not affect this test (Table 1).

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients with yellow skin on the face, obscure color, increasingly aggravated, abdominal fullness, enlarged liver and spleen with hard texture, short yellow urine, constipated stool, lighter color, dark red lips or tongue with petechiae, yellow coating; (2) age within one year, gender not limited, those with disease duration beyond two weeks, all cases have not used similar Chinese medicine treatment after the onset; and (3) the selected patients were treated with splenamine-based peptide for the first time. Exclusion criteria: (1) Patients with combined infectious diseases of the respiratory tract, gastrointestinal tract, and other systems, congenital diseases, central diseases, hemorrhagic diseases, *etc*.; (2) patients with other causes of jaundice and liver function impairment (such as congenital biliary atresia, endocrine hepatic glycogen accumulation disease, *etc*.); and (3) cases with an allergy to drug components such as drugs used in this study or those with incomplete clinical data.

Methods

The control group was treatment was initiated with reduced glutathione (0.3 to 0.6 g), uniformly mixed with glucose (5%) in 50 or 100 mL and administered intravenously, one time/d, for two weeks. After two weeks, it was changed to oral dose, 30 mg/kg/d, three times/d, and continued for two weeks) for liver protection; in the treatment group, based on the control group, the oral lyophilized powder of splenamine-tide (trade name: Fucoto, produced by Zhejiang Fengan Biopharmaceutical Co.). After two weeks, it can be taken orally at home with the medicine, and it should be sealed and stored in a dark place at 2-8 ℃, and it is forbidden to take medicine when its properties change. Children in both groups were treated for four weeks. All children had Liver function tests and imaging before and after treatment.

Follow-up and observation indexes

During the treatment, we observed daily changes in heart rate, heart rhythm, respiration, pulse, weight, urine volume, jaundice, stool color, *etc*. We measured blood, urine, stool routine, serum TBIL, DBIL, and ALT every week and recorded the efficacy of each course of treatment in detail every day; the Beckman CytoFLEX flow cytometer detected CD4+, CD3+, CD4+/CD8+. complete regression of yellow marks, good general condition, normal liver and spleen shrinkage, normal liver function. Improvement: Jaundice was significantly reduced, the liver and spleen shrank more than before, and the liver function of some of the indicators returned to normal. Ineffective: jaundice did not subside, and there was no change in biochemical indexes. Effective rate = (cure + improvement) - 100%.

Statistical methods

The data of this study were counted using Excel, and two physicians were available for review. The selected data were normally distributed, and the data had first, and corresponding authors entered into the computer system and proofread before using the statistical software SPSS 25.0 for relevant calculations. The measurement data were expressed as mean ± SD by independent samples *t*-test, and the count data was expressed as a percentage (%) or integer by χ^2 test, with statistical $P < 0.05$ indicating statistically significant differences.

RESULTS

Comparison of general data

The comparison of general data such as mean age mean disease duration, mean weight of patients, and patients' first symptoms in the two groups was not statistically significantly different by *t*-test and chi-square test ($P > 0.05$) (Table 1).

Comparison of liver function levels

The liver function level of the two groups of patients before treatment was not significantly different ($P > 0.05$). At the same time, the serum total bilirubin, direct bilirubin, and serum alanine transferase were significantly different after treatment. The therapy group is lower than the Control group, which is statistically significant ($P < 0.05$) (Table 2).

Comparison of immunity levels

There was no statistically significant difference between the two groups of patients in the before-therapy immune level ($P > 0.05$), while after treatment, CD4+, CD3+, and CD4+/CD8+ were significantly different, and the therapy group was higher than the Control group, which was statistically significant ($P < 0.05$) (Table 3).

Comparison of complications

The effective rate of 98.00% of the therapy group was significantly higher than that of 76.00% of the control group, and the difference was statistically significant ($P < 0.05$). The complication of the two groups of patients showed that the rash, cough, sputum, elevated platelets, and gastrointestinal reactions of the therapy group were significantly lower than those of the control group, and the difference was statistically significant ($P < 0.05$) (Table 4).

Table 1 Comparison of general data between the two groups (*n*, mean ± SD)

Group	Average age (d)	The average course of disease (d)	Patient weight (kg)	First symptoms		
				Jaundice	Pneumonia	Diarrhea
Control group (50)	41.78 ± 4.32	11.34 ± 3.25	3.34 ± 0.25	36	8	6
Therapy group (50)	41.62 ± 4.66	11.31 ± 3.64	3.31 ± 0.64	35	10	5
χ^2/t	0.169	0.043	-0.309	0.327		
P value	0.866	0.965	0.758	0.849		

Table 2 Comparison of liver function levels between the two groups (mean ± SD)

Group	TBIL (μmol/L)		DBIL (μmol/L)		Serum alanine transferase (U/L)	
	Before therapy	After treatment	Before therapy	After treatment	Before therapy	After treatment
Control group (50)	172.34 ± 32.18	75.78 ± 9.32	50.34 ± 12.25	32.51 ± 9.82	79.93 ± 19.27	69.85 ± 7.04
Therapy group (50)	173.32 ± 29.63	53.62 ± 8.66	49.36 ± 13.64	16.87 ± 3.81	73.94 ± 21.23	43.37 ± 8.30
t	-0.158	12.317	0.378	10.499	1.477	17.204
P value	0.874	0.000	0.706	0.000	0.143	0.000

DBIL: Direct bilirubin; TBIL: Total bilirubin.

Table 3 Comparison of the immune level of the two groups of patients (mean ± SD)

Group	CD4+ (%)		CD3+ (%)		CD4+/CD8+ (%)	
	Before therapy	After treatment	Before therapy	After treatment	Before therapy	After treatment
Control group (50)	32.78 ± 8.32	41.34 ± 10.25	52.51 ± 10.32	62.78 ± 10.32	0.94 ± 0.25	1.67 ± 0.12
Therapy group (50)	32.62 ± 8.66	48.26 ± 10.64	51.05 ± 10.11	73.62 ± 10.66	0.96 ± 0.24	2.49 ± 0.37
t	0.094	-3.312	0.715	-5.166	-0.408	-14.907
P value	0.925	0.000	0.477	0.000	0.684	0.000

Table 4 Comparison of clinical efficacy and complications between the two groups [*n* (%)]

Group	Cure	Improved	Ineffective	Effective	Skin rash	Cough and sputum	Elevated platelets	Gastrointestinal reaction
Control group (50)	24 (48.00)	14 (28.00)	12 (22.00)	38 (76.00)	2 (4.00)	2 (4.00)	1 (2.00)	3 (6.00)
Therapy group (50)	14 (28.00)	35 (70.00)	1 (2.00)	49 (98.00)	0	1 (2.00)	0	1 (2.00)
χ^2				10.698				4.000
P value				0.001				0.046

DISCUSSION

The pathogenesis of IHS is complex, and in infancy, the development and progression of liver lesions are associated with interactions between various types of cells in the liver[8]. Hepatocytes, blood sinusoidal endothelial cells, bile duct epithelial cells, blastocytes, and lipid storage cells of the liver can interact and interfere with each other, either directly or through some cytokines[9]. Any damage to these cells can disrupt the normal function of other cells, leading to liver dysfunction and causing apoptosis or death of hepatocytes, resulting in different pathologies and regressions. IHS varies with various etiologies[10]. In viral infections, most of the hepatocytes are either directly or immunologically damaged by the virus; many hepatocytes undergo lesions, necrosis, and apoptosis[11]. Bacterial infections are primarily seen in sepsis and urinary tract infections, which damage hepatocytes. IHS is caused by various metabolic disorders, in which hepatocytes are usually damaged by abnormal toxic metabolic intermediates[12]. IHS, caused by intrahepatic bile duct

development disorders, first causes biliary stasis in the liver, affecting the nutrient metabolism of hepatocytes and producing lesions[13]. The treatment of common IHS can be based on the condition of intravenous glycopyrrolate, glutathione, vitamin injection, and other drugs to protect the liver and bile to reduce yellowing. Those with scleral skin yellowing are given oral Injasmine oral solution, and phenobarbital can be applied orally, which improves and increases the enzyme activity and promotes bile excretion[14]. At the same time, antiviral therapy was given to those who tested positive for pathogenesis, and antiviral agents such as adenosine, ganciclovir intravenous, and interferon intramuscular injection were used for antiviral treatment[15].

In this study, the comparison of serum total bilirubin, direct bilirubin, and serum alanine transferase after treatment of IHS with arsphenamine-combined with reduced glutathione was significantly different and lower in the treatment group than in the control group, indicating that IHS was better treated with arsphenamine-combined with reduced glutathione, which effectively improved the liver function of the patients. Glutathione is a triglyceride containing Y- amide bond and sulfhydryl group, composed of glutamic acid, cysteine, and glycine, and the sulfhydryl group on cysteine is the active group of glutathione, which binds to free radicals and scavenges them from the body through oxidative dehydrogenation [16]. Combined with heavy metals, iodoacetic acid, and mustard gas, it converts harmful toxins of the organism into harmless substances. It excretes them from the body, which has a detoxifying effect, and glutathione improves the organism's immunity, making glutathione have a significant hepatoprotective effect[17]. The oral lyophilized powder of splenamine-based peptides can effectively improve the immune function of the body and enhance the antiviral ability of the body, which plays a synergistic role in treating IHS.

In this study, the differences in CD4+, CD3+, and CD4+/CD8+ after treatment were significant and higher in the treatment group than in the control group, indicating that IHS is better treated with arsphenamine-combined with reduced glutathione, which effectively improves the immune level of patients. T lymphocytes are divided into subpopulations according to their phenotypes and functions, namely, killer T cells, suppressor T cells, late metaplastic reactive T cells and inducible helper T cells[18]. The former two are CD8+ subpopulations, and the latter two are CD4+ subpopulations, which induce and regulate each other, forming a T cell regulatory network that exerts its killing effect on target cells and its positive and negative feedback regulation of immune response processes, such as anti-infection and anti-tumor immunity[19]. IHS causes dysfunctional T-cell subpopulations in the organism. The CD4+/CD8+ cell ratio decreases, and the immune regulatory network consisting of various immune cells and cytokines is imbalanced, forming a pathological vicious circle that leads to the development and progression of liver disease[20]. It has been shown that HBV can invade the peripheral blood lymphocytes of patients and affect the normal functioning of cellular functions. The lack of IL-2 in the body directly affects the normal functioning of killer T cells[21]. The low antiviral ability of the body makes HBV infect the body for a long time, on the other hand, it aggravates the autoimmune reaction in the body and aggravates the disease, while splenamine-based oral lyophilized powder has the effect of regulating immunity and inhibiting viral replication, and has better efficacy in treating chronic hepatitis B. It is easy to take and has few adverse effects, which provides a new way and method for the treatment of chronic hepatitis[22].

Although this study has some novelty, there are also shortcomings. The clinical efficacy of tegretolide-reduced glutathione treatment on IHS is significant, but the specific mechanism has not been studied in depth for a long time. The cases collected from the same hospital could have been more representative, and the exclusion and inclusion were subjective, which may lead to biased results.

CONCLUSION

In conclusion, the comparative study of IHS was better treated with splenamine combined with reduced glutathione, which effectively improved patients' liver function and immune level, reduced adverse reactions, and provided some reference value for clinical treatment of IHS.

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FOOTNOTES

Author contributions: Fang XQ and Gan T designed the research; Fang XQ, Gan T and Wang LM contributed new reagents/analytic tools; Fang XQ, Gan T and Wang LM analyzed the data; Fang XQ and Gan T wrote the paper; All authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript.

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Informed consent statement: All the families have voluntarily participated in the study and have signed informed consent forms. We explained the purpose, process, risks and benefits of the study to all individuals involved in the study orally or in writing, and obtained their informed consent. Participants have the right to know that their participation is voluntary and can withdraw from the study at any time.

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REFERENCES

1 **Watad A**, Bragazzi NL, McGonagle D, Adawi M, Bridgewood C, Damiani G, Alijotas-Reig J, Esteve-Valverde E, Quaresma M, Amital H, Shoenfeld Y. Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) demonstrates distinct autoimmune and autoinflammatory disease associations according to the adjuvant subtype: Insights from an analysis of 500 cases. *Clin Immunol* 2019; **203**: 1-8 [PMID: 30922961 DOI: 10.1016/j.clim.2019.03.007]

2 **Neupane N**, Krishnamurthy S, Jagadisan B, Dhodapkar R. Hepatitis B Seroprotection in Pediatric Nephrotic Syndrome. *Indian Pediatr* 2019; **56**: 659-662 [PMID: 31477646 DOI: 10.1007/s13312-019-1589-0]

3 **Kerkar N**, Chan A. Autoimmune Hepatitis, Sclerosing Cholangitis, and Autoimmune Sclerosing Cholangitis or Overlap Syndrome. *Clin Liver Dis* 2018; **22**: 689-702 [PMID: 30266157 DOI: 10.1016/j.cld.2018.06.005]

4 **Kang W**, Liu H, Ma L, Wang M, Wei S, Sun P, Jiang M, Guo M, Zhou C, Dou J. Effective antimicrobial activity of a peptide mutant Cbf-14-2 against penicillin-resistant bacteria based on its unnatural amino acids. *Eur J Pharm Sci* 2017; **105**: 169-177 [PMID: 28522372 DOI: 10.1016/j.ejps.2017.05.030]

5 **Borges M**, Da Silva AC, Sereno D, Ouaissi A. Peptide-based analysis of the amino acid sequence important to the immunoregulatory function of Trypanosoma cruzi Tc52 virulence factor. *Immunology* 2003; **109**: 147-155 [PMID: 12709028 DOI: 10.1046/j.1365-2567.2003.01637.x]

6 **Tsai MS**, Baratta JL, Longmuir KJ, Robertson RT. Binding patterns of peptide-containing liposomes in liver and spleen of developing mice: comparison with heparan sulfate immunoreactivity. *J Drug Target* 2011; **19**: 506-515 [PMID: 20735178 DOI: 10.3109/1061186X.2010.511227]

7 **Husby S**, Koletzko S, Korponay-Szabó I, Kurppa K, Mearin ML, Ribes-Koninckx C, Shamir R, Troncone R, Auricchio R, Castillejo G, Christensen R, Dolinsek J, Gillett P, Hróbjartsson A, Koltai T, Maki M, Nielsen SM, Popp A, Størdal K, Werkstetter K, Wessels M. European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. *J Pediatr Gastroenterol Nutr* 2020; **70**: 141-156 [PMID: 31568151 DOI: 10.1097/MPG.0000000000002497]

8 **Joshi MS**, Tandale BV, Gore MM, Bhalla S, Gurav YK, Sapkal GN, Kushwaha KP, Mishra AC, Chitambar SD. Evidence of hepatitis A virus infection in the patients with acute encephalitis syndrome in Gorakhpur region, North India. *Acta Virol* 2018; **62**: 208-213 [PMID: 29895163 DOI: 10.4149/av_2018_215]

9 **Wang X**, Qian L, Jia L, Bellah R, Wang N, Xin Y, Liu Q. Utility of Shear Wave Elastography for Differentiating Biliary Atresia From Infantile Hepatitis Syndrome. *J Ultrasound Med* 2016; **35**: 1475-1479 [PMID: 27229132 DOI: 10.7863/ultra.15.08031]

10 **Gerbi GB**, Williams R, Bakamutumaho B, Liu S, Downing R, Drobeniuc J, Kamili S, Xu F, Holmberg SD, Teshale EH. Hepatitis E as a cause of acute jaundice syndrome in northern Uganda, 2010-2012. *Am J Trop Med Hyg* 2015; **92**: 411-414 [PMID: 25448237 DOI: 10.4269/ajtmh.14-0196]

11 **Mantan M**, Pandharikar N, Yadav S, Chakravarti A, Sethi GR. Seroprotection for hepatitis B in children with nephrotic syndrome. *Pediatr Nephrol* 2013; **28**: 2125-2130 [PMID: 23800800 DOI: 10.1007/s00467-013-2538-0]

12 **Heinz N**, Griesemer A, Kinney J, Vittorio J, Lagana SM, Goldner D, Velasco M, Kato T, Lobritto S, Martinez M. A case of an Infant with SARS-CoV-2 hepatitis early after liver transplantation. *Pediatr Transplant* 2020; **24**: e13778 [PMID: 32559354 DOI: 10.1111/petr.13778]

13 **Siu SL**, Chan LW, Kwong AN. Clinical and biochemical characteristics of infants with prolonged neonatal jaundice. *Hong Kong Med J* 2018; **24**: 270-276 [PMID: 29807952 DOI: 10.12809/hkmj176990]

14 **Depreitere J**, Wang Z, Liang F, Coen E, Nouwen EJ. Presence and release of the chromogranin B-derived secretolytin-like peptide KR-11 from the porcine spleen. *Regul Pept* 2004; **122**: 99-107 [PMID: 15380927 DOI: 10.1016/j.regpep.2004.06.002]

15 **Tian Y**, Chen W, Mo G, Chen R, Fang M, Yedid G, Yan X. An Immunosuppressant Peptide from the Hard Tick Amblyomma variegatum. *Toxins (Basel)* 2016; **8** [PMID: 27153086 DOI: 10.3390/toxins8050133]

16 **Takemi S**, Ojima S, Tanaka T, Sakai T, Sakata I. Identification and characterization of an antimicrobial peptide, lysozyme, from Suncus murinus. *Cell Tissue Res* 2019; **376**: 401-412 [PMID: 30680460 DOI: 10.1007/s00441-019-02991-2]

17 **Lv YB**, Zhou Q, Fan Y, Zhang JL. Intervention on immunodeficiency mice and structural identification of enzymatic peptides from Mauremys mutica and Cuora trifasciata. *J Ethnopharmacol* 2019; **241**: 111920 [PMID: 31042594 DOI: 10.1016/j.jep.2019.111920]

18 **Putta MR**, Zhu FG, Wang D, Bhagat L, Dai M, Kandimalla ER, Agrawal S. Peptide conjugation at the 5'-end of oligodeoxynucleotides

abrogates toll-like receptor 9-mediated immune stimulatory activity. *Bioconjug Chem* 2010; **21**: 39-45 [PMID: 20020767 DOI: 10.1021/bc900425s]

19 **Lipchik AM**, Parker LL. Time-resolved luminescence detection of spleen tyrosine kinase activity through terbium sensitization. *Anal Chem* 2013; **85**: 2582-2588 [PMID: 23414415 DOI: 10.1021/ac3023422]

20 **Huff WX**, Kwon JH, Henriquez M, Fetcko K, Dey M. The Evolving Role of CD8(+)CD28(-) Immunosenescent T Cells in Cancer Immunology. *Int J Mol Sci* 2019; **20** [PMID: 31181772 DOI: 10.3390/ijms20112810]

21 **Chua C**, Salimzadeh L, Ma AT, Adeyi OA, Seo H, Boukhaled GM, Mehrotra A, Patel A, Ferrando-Martinez S, Robbins SH, La D, Wong D, Janssen HLA, Brooks DG, Feld JJ, Gehring AJ. IL-2 produced by HBV-specific T cells as a biomarker of viral control and predictor of response to PD-1 therapy across clinical phases of chronic hepatitis B. *Hepatol Commun* 2023; **7** [PMID: 38055623 DOI: 10.1097/HC9.0000000000000337]

22 **Yin Y**, Qin J, Dai Y, Zeng F, Pei H, Wang J. The CD4+/CD8+ Ratio in Pulmonary Tuberculosis: Systematic and Meta-Analysis Article. *Iran J Public Health* 2015; **44**: 185-193 [PMID: 25905052]

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ORIGINAL ARTICLE

Observational Study

Observation of therapeutic effect of lamp irradiation combined with purple gromwell oil gauze on alleviating intestinal colic in patients

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Abstract

BACKGROUND

Intestinal colic is a common complication in patients who have undergone radical surgery for colorectal cancer. Traditional Chinese medicine has advantages, including safety and stability, for the treatment of intestinal colic. Lamp irradiation for abdominal ironing has been applied in the treatment of many gastrointestinal diseases. Purple gromwell oil has the effects of clearing heat, cooling blood, reducing swelling, and relieving pain.

AIM

To investigate the impact of lamp irradiation combined with purple gromwell oil gauze on ameliorating intestinal colic in patients after radical surgery for colorectal cancer.

METHODS

A total of 120 patients who experienced postoperative intestinal colic complications after radical surgery for colorectal cancer and who were admitted to Foshan Traditional Chinese Medicine Hospital between June 2019 and March 2023 were enrolled as study subjects. The patients were divided into a control group (60 patients) and an observation group (60 patients) based on treatment method. The control group was treated with lamp irradiation, while the observation group was treated with lamp irradiation and external application of purple gromwell oil gauze. The clinical efficacy, Numeric Rating Scale (NRS) score, duration of symptoms, and rate of adverse reaction occurrence were further compared between the two groups.

RESULTS

The general effective rate in the observation group was 95.00%, which was significantly higher than that in the control group (86.67%, $P < 0.05$). Before treatment, there was no significant difference in the duration of symptoms between the groups ($P > 0.05$). After 1, 2, 3, and 4 d of treatment, the duration of

symptoms in both groups were decreased, and the duration in the observation group was significantly lower than that in the control group (96.54 ± 9.57 *vs* 110.45 ± 11.23, 87.26 ± 12.07 *vs* 104.44 ± 11.68, 80.45 ± 16.21 *vs* 99.44 ± 14.95, 73.18 ± 15.58 *vs* 92.17 ± 14.20; $P < 0.05$). After 1, 3, 5, and 7 d of treatment, the NRS scores in both groups were decreased, and the NRS scores in the observation group were significantly lower than those in the control group (3.56 ± 0.41 *vs* 4.04 ± 0.58, 3.07 ± 0.67 *vs* 3.74 ± 1.02, 2.52 ± 0.76 *vs* 3.43 ± 0.85, 2.03 ± 0.58 *vs* 3.03 ± 0.82; $P < 0.05$). There was no significant difference in the rate of adverse reaction occurrence between the groups ($P > 0.05$).

CONCLUSION

The use of lamp irradiation combined with purple gromwell oil gauze in patients with intestinal colic after radical surgery for colorectal cancer can reduce symptom duration, alleviate intestinal colic, and improve treatment efficacy, and this approach is safe. It is worth promoting the use of this treatment in clinical practice.

Key Words: Lamp irradiation; Purple gromwell oil gauze; Intestinal colic; Radical surgery for colorectal cancer; Therapeutic effect

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Core Tip: One hundred and twenty patients with colic were divided into a control group (treated with divine lamp irradiation) and an observation group (treated with divine lamp irradiation combined with purple grass oil gauze external application). The total effective rate of the observation group was higher than that of the control group, and the duration of symptoms and the Numeric Rating Scale score were lower than those of the control group; there was no significant difference in adverse reactions between the two groups. The combination of divine lamp irradiation and purple grass oil gauze is effective and safe for patients with intestinal colic.

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INTRODUCTION

Colorectal cancer is a common malignant tumor and is primarily treated with surgery. However, patients often experience intestinal colic pain after surgery, possibly related to postoperative damage to the digestive tract mucosa, abnormal gastrointestinal motility, intestinal flora imbalance, and dysfunction of the autonomic nervous system[1,2]. Intestinal colic pain significantly affects patients' quality of life, prolongs the recovery period, and increases hospitalization time. Therefore, effectively ameliorating postoperative colic pain in patients who have undergone radical colorectal cancer surgery has become a clinical focus[3]. Patients with tumors often experience physical weakness and insufficient functional recovery after surgery. Abdominal fumigation therapy, which is a treatment method in traditional Chinese medicine, has been widely used in treating gastrointestinal diseases and has been demonstrated to be a safe and stable approach for the treatment of intestinal colic pain[4].

In recent years, lamps, which are specific electromagnetic therapy devices, have been widely used as an adjunctive treatment method in clinical practice. Lamp irradiation can penetrate the epidermal tissue and reach deep tissues, acting on the patient's abdomen to promote the circulation of blood, harmonize organ functions, relieve pain, and improve abdominal discomfort through the application of heat[5]. Zi Cao (purple grass) has the effects of clearing heat, reducing swelling, cooling blood and relieving pain. The application of lamp irradiation therapy in patients who have undergone radical colorectal cancer surgery and its effect on relieving intestinal colic pain have not been sufficiently studied or explored. This study aimed to explore whether lamp irradiation combined with purple grass oil gauze could alleviate postoperative intestinal colic pain in patients who underwent radical colorectal cancer surgery, with the goal of providing strong clinical evidence to improve the quality of postoperative recovery of colorectal cancer patients as well as providing evidence-based support for the application of traditional Chinese medicine in modern medicine.

MATERIALS AND METHODS

Subject selection

A retrospective analysis of the clinical records of 120 patients who experienced postoperative intestinal colic pain after radical colorectal cancer surgery and who were admitted to Foshan Hospital of Traditional Chinese Medicine from June 2019 to March 2023 was conducted. The patients were divided into a control group (60 patients) and an observation group (60 patients) based on treatment method.

The inclusion criteria were as follows: (1) met the diagnostic criteria for colorectal cancer defined by the "Chinese Diagnosis and Treatment Guidelines for Colorectal Cancer (2020 Edition)"[6], confirmed by pathological examination, with indications for open, laparoscopic, and colonoscopic surgery for radical treatment of colorectal cancer; (2) postoperative occurrence of intestinal colic pain; (3) duration of illness ≤ 4 wk, regardless of sex; and (4) complete clinical data and ability to cooperate with the researchers.

The exclusion criteria were as follows: (1) other concomitant gastrointestinal diseases; (2) a history of allergic reactions to Chinese herbal medicine, local skin burns, scalds, or abrasions; (3) a tendency to form scars or allergies to the components of fumigant drugs or dressings; (4) significant deterioration of the condition before treatment, requiring immediate surgery, or withdrawal from the study deemed necessary by the physician; (5) poor patient compliance; and (6) serious adverse events, complications, or physiological changes that were unsuitable for continued participation in the trial, leading to self-withdrawal.

Methods

Control group: Patients in the control group were treated with lamp irradiation. Patients lay flat in a comfortable position and were treated with infrared thermal radiation therapy using the YSHT-IIA infrared heat radiation therapy device (produced by Shanghai Yuejin Medical Optical Instrument Factory, model: YSHT-IIA). The device was plugged in, the timer was set, the indicator light was illuminated, and preheating was conducted for 5 to 10 min. The device was placed 20 to 30 cm away from the lumbar and abdominal areas (adjusted based on the patient's self-perception to ensure heat without scalding). The skin surface temperature was maintained at 38-46 °C. After 30 min of irradiation, the lamp was removed. Close monitoring was conducted during lamp irradiation treatment, with particular attention given to the patient's sensations, especially for elderly people and patients who were insensitive to heat, to prevent skin burns or scalds during the irradiation process[7].

Observation group: In the observation group, the combined treatment involved the external application of purple grass oil gauze in addition to the procedures used in the control group. A single-species purple grass ointment (produced internally at Foshan Hospital of Traditional Chinese Medicine) was applied to a 4-layer sterile long strip of gauze, which was then applied to the lumbar and abdominal areas of the patient, covered with sterile gauze, and secured with adhesive tape. For individuals who were allergic to adhesive tape, bandages were used to secure the application of the medication. After 30 min of simultaneous lamp irradiation and purple grass oil gauze application, the lamp was removed. The purple grass oil gauze was left in place for 4 to 6 h, after which it was removed, any purple-red oil marks were removed with a warm, moist towel, and the clothing was tidied. During the application of the purple grass oil gauze, the nursing staff closely observed the application to promptly detect any allergic reactions on the patient's skin. If an allergic reaction occurred, the application was promptly discontinued, and appropriate treatment was administered. Patients were advised to avoid contact with cold water on the treated skin within 2 h.

Indicators for observation and criteria for evaluation of the therapeutic effect

Comparison of the recent clinical efficacy of the two groups of patients was performed according to the "Guiding Principles for Clinical Research of New Chinese Medicines"[8] for determining therapeutic efficacy. Complete remission was defined as complete disappearance of intestinal colic pain symptoms, restoration of normal gas and stool passage, and restoration of normal bowel sounds; significant effect was defined as significant reduction in abdominal pain and distension, restoration of normal gas and stool passage, absence of nausea and vomiting, and normal or slightly increased bowel sounds; effective was defined as alleviation of abdominal pain and distension, passage of gas and stool, absence of nausea and vomiting, and slight increase in bowel sounds; ineffective was defined as no improvement or exacerbation of abdominal pain and distension, no significant relief in gas and stool passage, continued presence of nausea and vomiting, and increased bowel sounds. Total effective rate = (complete remission + significant effect + effective) / total number of patients × 100%.

Pain assessment: the Numeric Rating Scale (NRS) in combination with the Weng-Baker Facial Expression Scale (facial scale) was used as a pain assessment tool. The NRS is a 100 mm line divided into ten equal parts, with numbers from 0 to 10 marked from left to right, where 0 represents no pain and 10 represents the most intense pain the patient can imagine. The patients marked a number on the line according to their pain experience to indicate the degree of pain. The facial scale consists of five facial expressions and has no age, cultural, or gender requirements, making it suitable for assessing pain in elderly individuals, children, patients with acute pain, and patients with impaired expression ability. Five facial expressions corresponding to the NRS are drawn, creating the pain assessment tool for this group, allowing patients to select their level of pain based on the facial expressions. Specifically, on the first, second, third, and fourth days after treatment, the NRS was presented to the patient, and the meaning of the numbers and facial expressions was explained in detail. Patients were instructed to accurately indicate the degree of pain at different sites on the NRS scale with their fingers, and the numbers were recorded by the nurse.

The duration of symptoms after treatment in the two groups of patients was compared, with the timing starting from the onset of abdominal pain.

The occurrence rate of adverse reactions during treatment in the two groups of patients was compared.

Statistical analysis

Statistical analysis was conducted using SPSS 26.0 software. Normally distributed quantitative data are presented as the mean ± SD, and between-group comparisons were made using independent sample *t* tests. Nonnormally distributed data are presented as medians (interquartile ranges), and between-group comparisons were conducted using the Mann-Whitney *U* test. Count data are presented as *n* (%), and between-group comparisons were conducted using the χ^2 test. A *P*

value less than 0.05 was considered to indicate statistical significance.

RESULTS

Baseline characteristics of the two groups of patients

No statistically significant differences were observed ($P > 0.05$) in baseline clinical data, including age, sex, body mass index, preoperative clinical stage, or lesion site, between the two groups. For specific data, please refer to Table 1.

Clinical efficacy

The general effective rate in the control group after treatment was 86.67%, while in the observation group, it was 95.00%. The comparison of the total effective rates between groups showed that the general effective rate in the control group was significantly lower than that in the observation group ($\chi^2 = 4.383$, $P = 0.035$). For specific data, please refer to Table 2 and Figure 1.

Duration of symptoms

Before treatment, no significant difference was observed in symptom duration between the groups ($P > 0.05$). However, after 1 d, 2 d, 3 d, and 4 d of treatment, the duration of symptoms was significantly different between the groups ($P < 0.001$, $P < 0.001$, $P = 0.007$, $P < 0.001$, respectively), with the observation group having a shorter duration of symptoms than did the control group. For specific data, please refer to Table 3 and Figure 2A.

NRS scores

After 1, 2, 3, and 4 d of treatment, there were significant differences in NRS scores between the groups ($P < 0.001$, $P = 0.001$, $P < 0.001$, $P < 0.001$, respectively), with the observation group having lower NRS scores than did the control group. For specific data, please refer to Table 4 and Figure 2B.

Adverse reactions

Two cases of skin irritation were observed in the observation group; however, no adverse reactions were reported in the control group. The difference in the occurrence rate of adverse reactions between the groups was not statistically significant ($\chi^2 = 2.0234$, $P = 0.154$).

DISCUSSION

Postoperative intestinal colic in colorectal cancer patients refers to symptoms such as abdominal pain, distension, and colic caused by incisional pain, intestinal mucosal injury, and tissue adhesions after colorectal cancer surgery. Patients experience restlessness due to abdominal pain, which significantly affects their postoperative recovery. According to traditional Chinese medicine, intestinal colic falls under the category of "abdominal pain." Postoperatively, the abdominal viscera of colorectal cancer patients are delicate and not fully recovered. Improper care may lead to the invasion of pathogenic cold, causing stagnation of cold, leading to obstruction in the meridians and stagnation of blood flow, thus resulting in abdominal pain. Thus, treatments need to focus on promoting smooth blood flow, warming the meridians, and promoting blood circulation. Traditional Chinese medicine preparations can regulate the functions of internal organs, achieving systemic efficacy.

Zicao oil, which is a topical medicine that is commonly used in clinical practice, is a single-component Zicao ointment developed internally in our hospital; it has been used in our department for more than 20 years and has shown remarkable efficacy. Zicao oil has the effects of detoxification, clearing heat, drying dampness, reducing swelling, cooling blood, and relieving pain[9]. The main chemical components of Zicao are Zicao naphthoquinones, phenols, phenolic acids, and monoterpenoid naphthoquinones, which exhibit various properties, such as anti-inflammatory and analgesic, antipyretic and pain-relieving, hepatoprotection, and transdermal absorption properties[10].

Zhou and Gao[11] reported that the modern pharmacological effects of Zicao mainly include anti-inflammatory and analgesic effects, inhibition of pathogenic microorganism growth, hemostasis, and promotion of wound healing. Lamp irradiation is a nonpharmacological treatment method. Its core component consists of coatings with dozens of elements. Following the application of electric power, specific electromagnetic waves containing various elements can be produced, covering the range of the electromagnetic wave spectrum that is emitted and absorbed by organisms. Through its electromagnetic wave effect and thermal effect, this approach can improve microcirculation, enhance the self-repair ability of tissues, strengthen immune function, and effectively increase the activity of various enzymes in the body, thereby exerting anti-inflammatory, anti-swelling, and microcirculation unblocking effects. By enhancing the secretion of endorphins and relieving muscle tension, this approach achieves analgesic effects[12,13]. Additionally, lamp irradiation can promote local blood circulation, allowing drugs to penetrate acupuncture points and meridians to the greatest extent, enabling traditional Chinese medicine to penetrate the skin and subcutaneous tissues, promote local blood circulation, unblock meridians, dispel cold and dampness, stimulate the body's self-healing power, accelerate the repair of damaged tissues, and regulate the body, thereby significantly enhancing the absorption of traditional Chinese medicine[14,15].

Table 1 Comparison of basic characteristics between groups

Item		Control group	Observation group	t/χ^2 value	*P* value
Age (yr, mean ± SD)		62.39 ± 9.51	63.13 ± 10.69	0.464	0.644
Gender [*n* (%)]	Male	33 (55.00)	31 (51.67)	0.134	0.714
	Female	27 (45.00)	29 (48.33)		
BMI/kg·cm^2 (mean ± SD)		23.71 ± 1.83	23.45 ± 1.64	1.018	0.312
TNM staging [*n* (%)]	I	11 (18.33)	13 (21.67)	0.346	0.841
	II	31 (51.67)	28 (46.67)		
	III	18 (30.00)	19 (31.67)		
Lesion site [*n* (%)]	Sigmoid colon	14 (23.33)	12 (20.00)	0.587	0.899
	Transverse colon	10 (16.67)	8 (13.33)		
	Ascending colon	19 (31.67)	21 (35.00)		
	Descending colon	17 (28.33)	19 (31.67)		

Table 2 Comparison of clinical efficacy between groups [*n* (%)]

Group	Complete remission	Significant effect	Effective	Ineffective	Total effective rate
Control group	13 (21.67)	20 (33.33)	19 (31.67)	8 (13.33)	52 (86.67)
Observation group	16 (26.67)	27 (45.00)	14 (23.33)	3 (5.00)	57 (95.00)[a]

[a]*P* < 0.05 compared with the control group.

Table 3 Comparison of symptom duration between groups (mean ± SD, min)

Group	Pretreatment	Posttreatment			
		1 d	2 d	3 d	4 d
Control group	119.26 ± 9.37	110.45 ± 11.23	104.44 ± 11.68	99.44 ± 14.95	92.17 ± 14.20
Observation group	117.89 ± 9.74	96.54 ± 9.57	87.26 ± 12.07	80.45 ± 16.21	73.18 ± 15.58
t value	0.706	4.195	6.635	2.787	6.613
P value	0.482	< 0.001	< 0.001	0.007	< 0.001

Table 4 Comparison of NRS scores between groups (mean ± SD)

Group	Posttreatment			
	1 d	2 d	3 d	4 d
Control group	4.04 ± 0.58	3.74 ± 1.02	3.43 ± 0.85	3.03 ± 0.82
observation group	3.56 ± 0.41	3.07 ± 0.67	2.52 ± 0.76	2.03 ± 0.58
t value	3.920	3.397	4.728	5.979
P value	< 0.001	0.001	< 0.001	< 0.001

In the present study, the combined use of lamp irradiation and Zicao oil gauze resulted in a higher general effective rate in the observation group than in the control group ($P < 0.05$). Before treatment, no significant difference was observed in symptom duration between the groups ($P > 0.05$). However, after 1, 2, 3, and 4 d of treatment, the duration of symptoms and NRS scores in the observation group were lower than those in the control group ($P < 0.05$). The results indicate that a lamp, through the thermal effect of electromagnetic waves, can increase blood flow, dilate local blood vessels, and enhance the permeability and absorption of the traditional Chinese medicine in Zicao oil gauze, thereby improving the treatment of postoperative intestinal colic in colorectal cancer patients, reducing the duration of

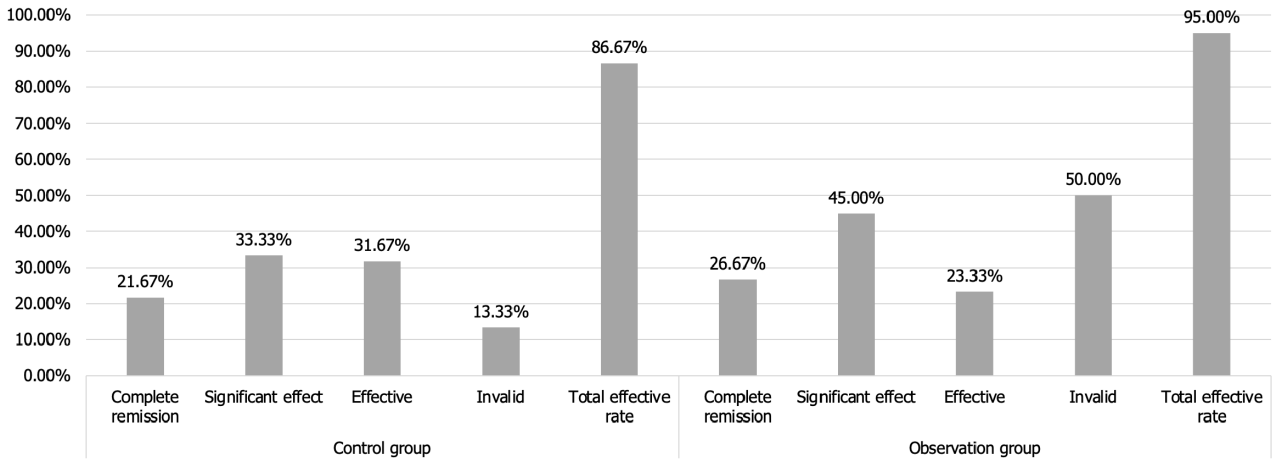


Figure 1 Comparison of clinical efficacy between groups.

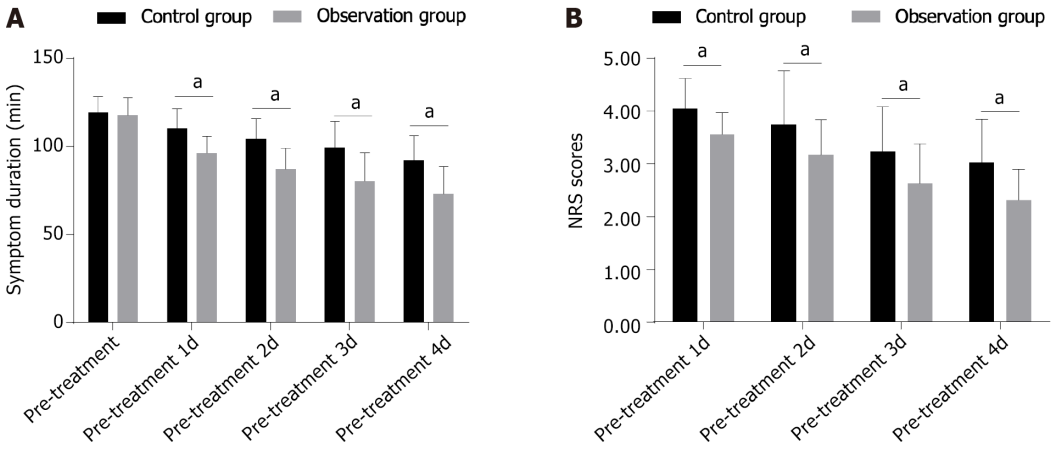


Figure 2 Comparison of symptom duration and NRS score between two groups of patients. A: Comparison of symptom duration between groups; B: Comparison of Numeric Rating Scale scores between groups. $^{a}P < 0.05$.

symptoms, and alleviating patient pain. Zicao oil is a long-standing traditional Chinese medicine therapy. In this study, the internally developed Zicao ointment, when applied externally and then irradiated with a lamp, accelerated drug absorption, enhanced efficacy, rapidly regulated local blood circulation, and enhanced analgesic and anti-inflammatory effects.

Both groups of patients in this study experienced severe adverse reactions ($P > 0.05$). This indicates that the application of Zicao oil gauze and lamp irradiation in postoperative intestinal colic patients after radical colorectal cancer surgery is a safe and reliable therapy. However, due to time constraints, the scope of observation in this study was relatively limited, and support from large data and samples was lacking, resulting in potential bias in the study conclusions. Therefore, it is necessary to conduct further high-level clinical studies, such as randomized, double-blind, multicenter, and large-sample studies, to further validate the findings of this study.

CONCLUSION

In summary, the combined application of lamp irradiation and Zicao oil gauze in postoperative intestinal colic patients who have undergone radical colorectal cancer surgery can significantly improve NRS scores for intestinal colic, reduce the duration of symptoms, and enhance treatment efficacy, and it is very safe. This approach is worthy of further clinical promotion and use.

FOOTNOTES

Author contributions: Cen BZ and Xie YF initiated the project; Chen YS and Li LP designed the experiment and conducted clinical data collection; Wu JW performed postoperative follow-up and recorded data; Cen BZ and Xie YF conducted a number of collation and statistical analysis, and wrote the original manuscript; all authors have read and approved the final manuscript.

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

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REFERENCES

1 **Tanaka M**, Kanemitsu Y, Shida D, Ochiai H, Tsukamoto S, Nagino M, Moriya Y. Prognostic Impact of Intra-abdominal/Pelvic Inflammation After Radical Surgery for Locally Recurrent Rectal Cancer. *Dis Colon Rectum* 2017; **60**: 827-836 [PMID: 28682968 DOI: 10.1097/DCR.0000000000000853]
2 **Wang YF**, Song YA, Yang WY, Zhong B. The influence of traditional and rapid intestinal preparation methods on postoperative intestinal microecology in colorectal cancer patients. *Shiyong Aizheng Zazhi* 2017; **32**: 1195-1198
3 **Feo CV**, Marcello D, Feo CF. Laparoscopic treatment of colo-colic intussusception secondary to a lipomatous polyp. *Ann Ital Chir* 2017; **6** [PMID: 28642452]
4 **Su M**, Yu W, Su Y. The influence of acupoint scraping combined with traditional Chinese medicine fumigation on gastrointestinal dysfunction and defecation after minimally invasive abdominal surgery. *Minerva Gastroenterol (Torino)* 2024 [PMID: 38287790 DOI: 10.23736/S2724-5985.23.03621-5]
5 **Zhang Y**, Zhu ST. Application effect of TDP lamp in incision healing after fracture surgery. *Jiguang Zazhi* 2018; **39**: 177-179 [DOI: 10.14016/j.cnki.jgzz.2018.07.177]
6 **Hospital Authority of National Health Commission of the People's Republic of China**; Chinese Society of Oncology, Chinese Medical Association. Diagnosis and treatment guidelines for colorectal cancer in China (2020 edition). *Zhongguo Shiyong Waike Zazhi* 2020; **40**: 601-625 [DOI: 10.19538/j.cjps.issn1005-2208.2020.06.01]
7 Subject Index. *Nonlinear Dyn* 2003; **31**: 453-454 [DOI: 10.1023/A:1023271815448]
8 **Liang MX**, Gao TS. Investigation and Analysis of Syndromes of Internal Organs in Guideline for Clinical Trials of New Patent Chinese Medicines. *Zhongguo Zhongyi Jichuyixue Zazhi* 2008; **14**: 330-331, 342
9 **Soliman AM**, Teoh SL, Ghafar NA, Das S. Molecular Concept of Diabetic Wound Healing: Effective Role of Herbal Remedies. *Mini Rev Med Chem* 2019; **19**: 381-394 [PMID: 30360709 DOI: 10.2174/1389557518666181025155204]
10 **Chen Chen T**, Yu SC, Hsu CM, Tsai FJ, Tsai Y. A water-based topical Chinese traditional medicine (Zicao) for wound healing developed using 2-hydroxypropyl-β-cyclodextrin. *Colloids Surf B Biointerfaces* 2018; **165**: 67-73 [PMID: 29454166 DOI: 10.1016/j.colsurfb.2018.02.013]
11 **Zhou YM**, Gao YS. Pharmacological effects and clinical applications of traditional Chinese medicine Zicao. *Yiyao Daobao* 2008; 786-788
12 **Huang X**. Clinical observation of abdominal acupuncture combined with specific electromagnetic wave therapy instrument in the treatment of lumbar disc herniation. *Zhongguo Yaowuyulinchuang* 2018; **18**: 1757-1758
13 **Zhang XW**, Hou DC, Jin GY, Jin HY, Zhou SQ, You X. Randomized controlled multicenter clinical trial of comprehensive traditional Chinese medicine rehabilitation treatment for knee osteoarthritis. *Liaoning Zhongyi Zazhi* 2020; **47**: 93-96 [DOI: 10.13192/j.issn.1000-1719.2020.01.031]
14 **Wen C**, Wu C, Wang X, Wu D, Cao Y, Zhang J, Zhang L, Jia M. The effect of Xiaobi decoction on minimal erythema dose of irradiation with 308 nm excimer lamp in guinea pigs. *Ann Palliat Med* 2020; **9**: 4166-4173 [PMID: 33302677 DOI: 10.21037/apm-20-2181]
15 **He T**, Xie YJ, Shu WJ. Effect of self-made medicinal liquor wet compress combined with in-frared radiation on pain,lumbar vertebral function and quality of life in patients with spinal diseases. *Zhongguo Dangdai Yiyao* 2021; **28**: 192-195

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ORIGINAL ARTICLE

Randomized Controlled Trial

Radiofrequency ablation combined with transcatheter arterial chemoembolization for recurrent liver cancer

Jin-You Guo, Li-Li Zhao, Hui-Jun Cai, Hui Zeng, Wei-Dong Mei

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Abstract

BACKGROUND

The recurrence rate of liver cancer after surgery is high. Radiofrequency ablation (RFA) combined with transcatheter arterial chemoembolization (TACE) is an effective treatment for liver cancer; however, its efficacy in recurrent liver cancer remains unclear.

AIM

To investigate the clinical effect of TACE combined with RFA in the treatment of recurrent liver cancer.

METHODS

Ninety patients with recurrent liver cancer were divided into 2 groups according to treatment plan: Control (RFA alone); and experimental [TACE combined with RFA (TACE + RFA)]. The incidence of increased alanine aminotransferase levels, complications, and other indices were compared between the two groups before and after the procedures.

RESULTS

One month after the procedures, the short-term efficacy rate and Karnofsky Performance Status scores of the experimental group were significantly higher than those of the control group ($P < 0.05$). Alpha-fetoprotein (AFP) and total bilirubin levels were lower than those in the control group ($P < 0.05$); The overall response rate was 82.22% and 66.67% in the experimental and control groups, respectively; The disease control rate was 93.33% and 82.22% in the experimental and control groups, respectively, the differences are statistically significant ($P <$

0.05). And there were no statistical differences in complications between the two groups ($P > 0.05$).

CONCLUSION
TACE + RFA was effective for the treatment of recurrent liver cancer and significantly reduced AFP levels and improved various indices of liver function.

Key Words: Transcatheter arterial chemoembolization; Radiofrequency ablation; Recurrent liver cancer; Clinical efficacy; Overall response rate; Disease control rate

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Core Tip: The postoperative recurrence rate of liver cancer is high. Although radiofrequency ablation (RFA) combined with transcatheter arterial chemoembolization (TACE) is an effective treatment for liver cancer, its efficacy in recurrent liver cancer remains unclear. Results of the present study revealed that TACE combined with RFA was effective for the treatment of recurrent liver cancer and could significantly reduce alpha-fetoprotein levels and improve various indices of liver function.

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INTRODUCTION

Primary liver cancer (PLC) is the sixth most common cancer and third leading cause of cancer-related death globally[1]. In 2020, approximately 900000 cases of PLC were newly diagnosed worldwide, and approximately 830000 related deaths were reported[2]. China accounted for approximately 410000 new cases (45.3%) and 390000 deaths (47.1%), ranking first globally[3]. Hepatocellular carcinoma, also known as liver cancer, is the most common pathological type of PLC, accounting for approximately 90% of PLC cases in China[4]. Surgery is the preferred treatment for patients with resectable liver cancer. In recent years, the overall 5-year survival rate after liver resection in patients with liver cancer has increased to 60.0%[5]. However, the postoperative recurrence rate of liver cancer is high, with rates of 40%-70% within 5 years after surgery, and most within 1-3 years after surgery[6].

Surgical resection remains the preferred treatment option for recurrent liver cancer; however, due to factors such as location, size, distant metastasis, and multicentric occurrence, only 10.4%-31.0% of patients are suitable candidates[7]. In recent years, radiofrequency ablation (RFA) has been widely used for the treatment of recurrent liver cancer due to its minimally invasive nature, simplicity of operation, broad indications, repeatability, low cost, high patient acceptance, and satisfactory therapeutic effects[8]. However, studies have found that recurrent liver cancer has a unique location and multicentric origin, as well as the characteristics of intrahepatic micrometastasis, which greatly increases the risk for recurrence[9]. Additionally, because RFA can only target locally detectable recurrent lesions, it has poor efficacy for small, undetectable lesions, resulting in a higher risk for recurrence[10]. In recent years, transcatheter arterial chemoembolization (TACE) has been used to selectively embolize recurrent intrahepatic lesions, effectively solving the problems associated with RFA[11-14]. Therefore, some investigators have proposed that the combination of TACE and RFA (TACE + RFA) may further improve clinical efficacy. However, there are currently few such studies, and treatment effects and prognosis still need to be comprehensively evaluated. As such, the present study aimed to evaluate the efficacy of TACE + RFA for the treatment of recurrent liver cancer to provide a reference for clinical treatment.

MATERIALS AND METHODS

General patient information

We retrospectively collected 90 patients diagnosed with recurrent liver cancer who were admitted to the hospital between February 2021 and February 2023. According to the method of random number table, participants were randomly assigned to the TACE + RFA group or the RFA group in a 1:1 ratio: Control [RFA (n = 45)]; and experimental [TACE + RFA (n = 45)].

Inclusion and exclusion criteria

Inclusion criteria were as follows[15]: Pathologically confirmed liver cancer and a history of curative surgical treatment; postoperative review of computed tomography (CT) or magnetic resonance imaging (MRI) and other relevant imaging examinations revealing recurrent liver cancer; fulfill treatment indications for TACE and RFA; age ≥ 18 years; liver

function classified as Child-Pugh grade A or B with no extrahepatic metastasis; and complete case information.

The exclusion criteria were as follows: Complications, such as hepatic encephalopathy, refractory ascites, or large vessel occlusion; tumor metastasis to distant sites; heart or kidney dysfunction; history of substance abuse or organic diseases; pregnancy or lactation; Karnofsky Performance Status (KPS) score < 70; and expected survival < 6 months.

Ethics approval

The present study was approved by the research ethics committee of the Second People's Hospital of Zhejiang Province Taizhou Yuhuan city (No. 2023-028), and all patients voluntarily participated.

Treatment methods

Patients in the control group underwent RFA[16], which used an radiofrequency generator (RITA 1500X) equipped with a 14-gauge StarBurst TMXL electrode needle (Angio Dynamics, Latham NY, United States). After CT positioning, an appropriate puncture pathway was selected to avoid damaging surrounding structures. All patients received local (2% lidocaine) and intravenous anesthesia (propofol and fentanyl). CT was performed after electrode needle placement to ensure that the needle tip was in the intended position. Needle tract ablation was performed at the end of treatment to prevent bleeding and tumor implantation. For larger tumors, the position of the ablation needle was adjusted multiple times based on the size and shape of the tumor to achieve as much ablation range as possible, exceeding the tumor boundary by 0.5-10 cm, to ensure the elimination of potentially infiltrated tumor portions. Immediate postoperative CT was performed to check for complications such as bleeding, pneumothorax, and/or perforation.

Patients in the experimental group underwent TACE + RFA[17]. RFA was performed 1 week after TACE, and the patients underwent treatment under anesthesia and intravenous anesthesia. The experimental group first underwent TACE using the Seldinger method to puncture the femoral artery, guiding the catheter to the hepatic artery through digital subtraction angiography (DSA), to comprehensively evaluate tumor size, number, blood supply artery, venous patency, and venous fistula, followed by intravascular administration of 500-750 mg of fluorouracil, 50-200 mg of oxaliplatin, and 10-30 mg of irinotecan. The embolic agents included a 38.0% hypertonic iodine solution and gelatin sponge particles at a dose of 5-20 mL. Accurate dosage of the drug was adjusted according to tumor size, quantity, liver function, and iodine oil filling in the tumor. At the conclusion of treatment, another DSA examination was performed to confirm complete tumor vascular embolization. Repeat embolization was performed if necessary. Hemostasis was applied to the puncture site after catheter removal and compression was applied for 12 h on the puncture side. Bed rest was prescribed for 24 h to prevent bleeding and hematoma formation at the puncture site. TACE + RFA was performed in the experimental group and compared with that in the control group. Immediate CT scans were performed postoperatively to rule out complications, such as pneumothorax, bleeding, and perforation. Observations were performed for 2 wk, with routine blood examinations twice per week, and liver and kidney function examinations once per week. Interleukin-11 treatment was administered to patients with blood platelet counts < 25×10^9/L, and granulocyte colony-stimulating factor treatment was administered to patients with a white blood cell count < 2.5×10^9/L or neutrophil count < 1.0×10^9/L.

Observation indicators

Postoperative evaluation of short-term efficacy[18]: According to the modified response evaluation criteria in solid tumors (mRECIST), accurately measurable and reproducible target lesions were selected. CT- or MRI-enhanced scans were used to measure the enhanced region of the tumor within the lesion. If all lesions exhibited no enhancement during the arterial phase, it was considered a complete response (CR); if the sum of the diameters of the lesions during the arterial phase decreased by at least 30%, it was considered a partial response (PR); if the sum of the diameters of the lesions increased by at least 20%, it was considered progressive disease (PD); and if neither meets the criteria for PR nor PD, it was considered stable disease (SD). Overall response rate (ORR) was calculated as (CR + PR) cases/total cases × 100%, and the disease control rate (DCR) as calculated as (CR + PR + SD) cases/total cases × 100%.

KPS scores of the two groups before and 1 month after the end of treatment[19]: The KPS score ranges from 0 to 100 and is directly proportional to patient health status.

Liver function indicators (alanine aminotransferase and total bilirubin) and alpha-fetoprotein tumor marker levels before and 1 month after treatment: The incidence of complications within 1 month of treatment was calculated for both groups of patients.

Statistical methods

Statistical analysis was performed using SPSS version 24.0 (IBM Corporation, Armonk, NY, United States). Continuous variables are expressed as mean ± SD, and comparisons were performed using the *t*-test. In order to perform the *t* tests, the data had been tested for normality using the Kolmogorov simirnov test. Categorical data are expressed as number (percentage) and comparisons were performed using the chi-squared test. Differences with $P < 0.05$ were considered to be statistically significant.

Table 1 Comparison of general data of two groups of patients

Index	TACE + RFA group (*n* = 45)	RFA group (*n* = 45)	χ^2/t	*P* value
Age (years)	57.9 ± 8.3	60.1 ± 9.6	1.163	0.248
Sex			0.067	0.796
Male	35	36		
Female	10	9		
Recurrence time (months)	1.9 ± 0.8	1.7 ± 0.6	1.342	0.183
Tumor diameter (cm)			0.179	0.673
≤ 3	23	25		
> 3	22	20		
Number of lesions			0.180	0.671
Single	26	24		
Multiple	19	21		
Hepatitis B surface antigen			0.620	0.431
Positive	43	40		
Negative	2	5		
Child–Pugh class			0.189	0.664
A	18	16		
B	27	29		
AFP (ng/mL)			0.053	0.818
≤ 400	31	32		
> 400	14	13		
Complications (*n*)			0.228	0.893
Diabetes	13	11		
Hypertension	15	16		
No	17	18		

TACE: Transcatheter arterial chemoembolization; RFA: Radiofrequency ablation; AFP: Alpha-fetoprotein.

RESULTS

Comparison of general data between the control and experimental groups

The TACE + RFA group included 35 males and 10 females, with average age of 57.9 ± 8.3 years. Tumor diameter was ≤ 3 cm in 23 cases and > 3 cm in 22 cases. Alpha-fetoprotein (AFP) level was ≤ 400 ng/mL in 31 cases and > 400 ng/mL in 14 cases. The mean time to recurrence was 1.9 ± 0.8 months. The Child-Pugh liver function classification was class A in 18 patients and class B in 27 cases. Tumor diameter and number were distributed as follows: ≤ 3 cm (*n* = 23); > 3 cm (*n* = 22); single tumor (*n* = 26); and multiple tumors (*n* = 19). Among these patients, 43 were positive for the hepatitis B surface antigen, 2 were negative, 13 had diabetes, and 15 had hypertension. Seventeen patients had no history of hypertension or diabetes mellitus.

The RFA group included 36 males and 9 females, with a mean age of 60.1 ± 9.6 years. Tumor diameter was ≤ 3 cm in 25 cases and > 3 cm in 20 cases. AFP level was ≤ 400 ng/mL in 32 cases and > 400 ng/mL in 13 cases. The mean time to recurrence was 1.7 ± 0.6 months. The Child-Pugh liver function classification was class A in 16 patients and class B in 29 cases. Tumor diameter and number were distributed as follows: ≤ 3 cm (*n* = 25); > 3 cm (*n* = 20); single tumor (*n* = 24); and multiple tumors (*n* = 21). Among these patients, 40 were positive for hepatitis B surface antigen, 5 were negative, 11 had diabetes, and 16 had hypertension. Eighteen patients had no history of hypertension or diabetes mellitus. There were no statistical differences in baseline data including age, sex, tumor diameter, AFP level, Child-Pugh classification of liver function, and average time of recurrence ($P > 0.05$), indicating comparability (Table 1).

Comparison of short-term therapeutic effects

One month after treatment, the short-term therapeutic effects in the two groups of patients were compared. The ORR was 82.22% and 66.67% in the experimental and control groups, respectively; this difference was statistically significant ($P <$

Table 2 Comparison of efficacy between two groups, *n* (%)

Index	TACE + RFA group (*n* = 45)	RFA group (*n* = 45)	χ^2	*P* value
CR	15	9		
PR	22	21		
SD	5	7		
PD	3	8		
ORR	37 (82.22)	30 (66.67)	6.355	0.012
DCR	42 (93.33)	37 (82.22)	5.752	0.017

TACE: Transcatheter arterial chemoembolization; RFA: Radiofrequency ablation; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; ORR: Overall response rate; DCR: Disease control rate.

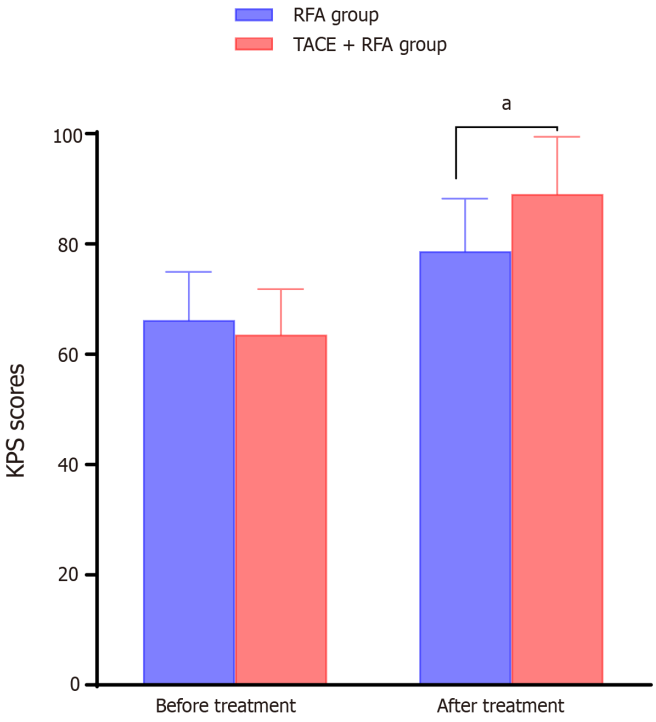


Figure 1 Comparison of Karnofsky Performance Status scores between the two groups. [a]*P* < 0.05. KPS: Karnofsky Performance Status; RFA: Radiofrequency ablation; TACE: Transcatheter arterial chemoembolization.

0.05). The DCR was 93.33% and 82.22% in the experimental and control groups, respectively. Once again, this difference was statistically significant ($P < 0.05$, Table 2).

Comparison of AFP, alanine aminotransferase, and total bilirubin levels

Before treatment, there were no statistically significant differences in AFP, alanine aminotransferase (ALT), and total bilirubin (TBiL) levels between the two groups ($P > 0.05$). After treatment, the mean levels of AFP, ALT, and TBiL in both groups significantly decreased compared with before treatment, and the experimental group was significantly lower than the control group, with a statistically significant difference ($P < 0.001$; Table 3).

Comparison of KPS scores

After treatment, the KPS scores of both groups of patients increased compared to those before treatment, and the KPS scores of the experimental group were significantly higher than those of the control group ($P < 0.05$; Figure 1).

Comparison of incidence of complications

The incidence of complications in the experimental group was 26.67% (12/45), which was higher than that in the control group [17.78% (8/45)], although the difference was not statistically significant ($P > 0.05$; Table 4).

Table 3 Comparison of alpha-fetoprotein, alanine aminotransferase, and total bilirubin between two groups of patients (mean ± SD)

Index		TACE + RFA group (*n* = 45)	RFA group (*n* = 45)	*t*	*P* value
AFP (ng/L)	Before treatment	423.35 ± 25.64	422.47 ± 24.85	0.165	0.869
	After treatment	86.21 ± 26.71[a]	126.70 ± 38.21[a]	5.826	< 0.001
ALT (U/L)	Before treatment	283.61 ± 21.63	279.82 ± 20.09	0.861	0.392
	After treatment	47.34 ± 5.22[a]	109.23 ± 25.32[a]	16.059	< 0.001
TBiL (μmol/L)	Before treatment	91.37 ± 8.58	91.64 ± 8.94	0.146	0.884
	After treatment	36.26 ± 4.23[a]	48.83 ± 4.54[a]	13.589	< 0.001

[a]$P < 0.05$, compared with before treatment.

TACE: Transcatheter arterial chemoembolization; RFA: Radiofrequency ablation; AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; TBiL: Total bilirubin.

Table 4 Comparison of complication rates between the two groups, *n* (%)

Index	TACE + RFA group (*n* = 45)	RFA group (*n* = 45)	χ^2	*P* value
Fever	3	2		
Bleeding	1	1		
Liver abscess	1	0		
Nausea and vomiting	1	1		
Upper gastrointestinal bleeding	1	0		
Abdominal pain	1	1		
Abnormal liver function	4	3		
Total incidence rate	12 (26.67)	8 (17.78)	2.286	0.131

TACE: Transcatheter arterial chemoembolization; RFA: Radiofrequency ablation.

DISCUSSION

For patients with liver cancer, surgical resection is the main treatment method, but the recurrence and metastasis rates are high[20,21]. Postoperative recurrence is the main obstacle to long-term survival of patients with liver cancer[22].With the continuous development of minimally invasive surgeries in recent years, TACE and other local treatments have been widely used in clinical practice[23]. However, repeated chemotherapy can worsen liver function damage, which may affect treatment outcomes. With the continuous advancement of medical technology, RFA has gradually become a new treatment option that can be combined with TACE[24]. However, due to the limited ablation range of RFA, there may be a zone of incomplete ablation of small metastatic lesions. Therefore, in clinical practice, TACE is often combined with RFA. A study by Feng[25] found that combined RFA and TACE for recurrent liver cancer resulted in better disease-free survival and overall survival than RFA alone, indicating that combination therapy is more effective in preventing tumor progression and recurrence.

The results of the present study also showed that 1 month after surgery, the ORR in the study group was 82.22%, while in the control group it was 66.67%, with a statistically significant difference ($P < 0.05$). The DCR in the experimental group was 93.33%, while that in the control group was 82.22%, with a statistically significant difference between the two groups ($P < 0.05$). This indicated that the short-term clinical efficacy of combination therapy was superior to that of monotherapy [26,27]. These results suggest that TACE + RFA may enhance the body's absorption and sensitivity to chemotherapeutic drugs. Simultaneously, TACE can occlude the tumor's blood-supplying artery, significantly reducing the cooling effect of blood on thermal ablation, thereby enhancing — to some extent — the tumor-killing effect of RFA and achieving a synergistic effect, resulting in a higher treatment effectiveness rate.

Results of this study also revealed that, after treatment, the levels of liver function indicators (ALT and TBiL) and AFP tumor markers in both groups decreased to some extent. However, liver function indicators (ALT and TBiL) and AFP tumor markers were significantly lower in the experimental group than in the control group ($P < 0.05$). This is because combination therapy can completely kill tumor cells, prevent invasion or metastasis, and lower the risk for postoperative recurrence. These findings were consistent with those reported by Ouyang *et al*[28].

In addition, the incidence rates of complications in the 2 groups were compared, and no statistically significant differences were found ($P > 0.05$). According to a study by Wang *et al*[29], TACE combined with RFA did not significantly

increase the rate of complications in patients with liver cancer. This result is consistent with those reported in the literature. The results of this study also demonstrated that KPS scores for both patient groups before and 4 weeks after treatment were higher than those before treatment, and the KPS scores of the experimental group were significantly higher than those of the control group ($P < 0.05$). This is consistent with results reported by Bholee *et al*[30]. Possible explanations for this are as follows. RFA has a stronger destructive effect on deep liver cancer tissues, especially lesions around liver lobules, effectively avoiding residual lesions after TACE treatment. At the same time, RFA can induce secondary destruction of chemotherapy-resistant cancer cells by causing DNA damage, promoting the degradation of chromosomes and absorption of nuclear fragments, thereby improving patient quality of life.

Limitations

The present study had some limitations, the first of which was its single-center design and small sample size, with inherent risks for selection bias. Second, it had a short follow-up; as such, long-term efficacy needs to be assessed with a larger sample size and multiple centers. A randomized controlled clinical study should be conducted for further verification. Finally, another limitation of this study was that the patients were not further grouped according to clinical stage, which may — to some extent — have affected the reliability of the results. In future studies, the sample size will be expanded, multiple control groups will be established, and multicenter comparative studies will be conducted.

CONCLUSION

In summary, TACE + RFA yielded greater efficacy for the treatment of recurrent liver cancer. TACE + RFA significantly decreased AFP levels and improved various indicators of liver function. This finding should be promoted in future clinical trials.

FOOTNOTES

Author contributions: Guo JY, Zhao LL, Cai HJ, Zeng H, and Mei WD designed research; Cai HJ and Zeng H performed research; Mei WD contributed new reagents/analytic tools; Cai HJ and Mei WD analyzed data; Guo JY and Zhao LL wrote paper.

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REFERENCES

1 **Xia C**, Dong X, Li H, Cao M, Sun D, He S, Yang F, Yan X, Zhang S, Li N, Chen W. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. *Chin Med J (Engl)* 2022; **135**: 584-590 [PMID: 35143424 DOI: 10.1097/CM9.0000000000002108]
2 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020; **70**: 7-30 [PMID: 31912902 DOI: 10.3322/caac.21590]
3 **Cao W**, Chen HD, Yu YW, Li N, Chen WQ. Changing profiles of cancer burden worldwide and in China: a secondary analysis of the global

cancer statistics 2020. *Chin Med J (Engl)* 2021; **134**: 783-791 [PMID: 33734139 DOI: 10.1097/CM9.0000000000001474]

4 **Bhatt A**, Wu J. Immunotherapy for recurrent hepatocellular carcinoma. *World J Gastroenterol* 2023; **29**: 2261-2271 [PMID: 37124885 DOI: 10.3748/wjg.v29.i15.2261]

5 **Kim TH**, Koh YH, Kim BH, Kim MJ, Lee JH, Park B, Park JW. Proton beam radiotherapy vs. radiofrequency ablation for recurrent hepatocellular carcinoma: A randomized phase III trial. *J Hepatol* 2021; **74**: 603-612 [PMID: 33031846 DOI: 10.1016/j.jhep.2020.09.026]

6 **Sugawara Y**, Hibi T. Surgical treatment of hepatocellular carcinoma. *Biosci Trends* 2021; **15**: 138-141 [PMID: 33746184 DOI: 10.5582/bst.2021.01094]

7 **Jiang C**, Cheng G, Liao M, Huang J. Individual or combined transcatheter arterial chemoembolization and radiofrequency ablation for hepatocellular carcinoma: a time-to-event meta-analysis. *World J Surg Oncol* 2021; **19**: 81 [PMID: 33741001 DOI: 10.1186/s12957-021-02188-4]

8 **Takayama T**, Hasegawa K, Izumi N, Kudo M, Shimada M, Yamanaka N, Inomata M, Kaneko S, Nakayama H, Kawaguchi Y, Kashiwabara K, Tateishi R, Shiina S, Koike K, Matsuyama Y, Omata M, Makuuchi M, Kokudo N. Surgery versus Radiofrequency Ablation for Small Hepatocellular Carcinoma: A Randomized Controlled Trial (SURF Trial). *Liver Cancer* 2022; **11**: 209-218 [PMID: 35949295 DOI: 10.1159/000521665]

9 **Shi T**, Xu C, Feng Y, Wei Y, Lv H, Zhu Q. Surgical resection versus radiofrequency ablation for early recurrent hepatocellular carcinoma. *Eur J Gastroenterol Hepatol* 2022; **34**: 844-851 [PMID: 35694799 DOI: 10.1097/MEG.0000000000002393]

10 **Gou H**, Liu S, Zhu G, Peng Y, Li X, Yang X, He K. Effectiveness of radiofrequency ablation versus transarterial chemoembolization for recurrent hepatocellular carcinoma: A meta-analysis. *Acta Radiol Open* 2022; **11**: 20584601221085514 [PMID: 35368406 DOI: 10.1177/20584601221085514]

11 **Zhang Y**, Qin Y, Dong P, Ning H, Wang G. Liver resection, radiofrequency ablation, and radiofrequency ablation combined with transcatheter arterial chemoembolization for very-early- and early-stage hepatocellular carcinoma: A systematic review and Bayesian network meta-analysis for comparison of efficacy. *Front Oncol* 2022; **12**: 991944 [PMID: 36387091 DOI: 10.3389/fonc.2022.991944]

12 **Zhang YJ**, Chen MS, Chen Y, Lau WY, Peng Z. Long-term Outcomes of Transcatheter Arterial Chemoembolization Combined With Radiofrequency Ablation as an Initial Treatment for Early-Stage Hepatocellular Carcinoma. *JAMA Netw Open* 2021; **4**: e2126992 [PMID: 34570206 DOI: 10.1001/jamanetworkopen.2021.26992]

13 **Shin SW**, Ahn KS, Kim SW, Kim TS, Kim YH, Kang KJ. Liver Resection Versus Local Ablation Therapies for Hepatocellular Carcinoma Within the Milan Criteria: A Systematic Review and Meta-analysis. *Ann Surg* 2021; **273**: 656-666 [PMID: 33074898 DOI: 10.1097/SLA.0000000000004350]

14 **Keshavarz P**, Raman SS. Comparison of combined transarterial chemoembolization and ablations in patients with hepatocellular carcinoma: a systematic review and meta-analysis. *Abdom Radiol (NY)* 2022; **47**: 1009-1023 [PMID: 34982183 DOI: 10.1007/s00261-021-03368-2]

15 **Bureau of Medical Administration**, National Health Commission of the People's Republic of China. [Standardization for diagnosis and treatment of hepatocellular carcinoma (2022 edition)]. *Zhonghua Gan Zang Bing Za Zhi* 2022; **30**: 367-388 [PMID: 35545562 DOI: 10.3760/cma.j.cn501113-20220413-00193]

16 **Liu W**, Xu H, Ying X, Zhang D, Lai L, Wang L, Tu J, Ji J. Radiofrequency Ablation (RFA) Combined with Transcatheter Arterial Chemoembolization (TACE) for Patients with Medium-to-Large Hepatocellular Carcinoma: A Retrospective Analysis of Long-Term Outcome. *Med Sci Monit* 2020; **26**: e923263 [PMID: 32667906 DOI: 10.12659/MSM.923263]

17 **Peng Z**, Chen S, Wei M, Lin M, Jiang C, Mei J, Li B, Wang Y, Li J, Xie X, Chen M, Qian G, Kuang M. Advanced Recurrent Hepatocellular Carcinoma: Treatment with Sorafenib Alone or in Combination with Transarterial Chemoembolization and Radiofrequency Ablation. *Radiology* 2018; **287**: 705-714 [PMID: 29390197 DOI: 10.1148/radiol.2018171541]

18 **Cucchetti A**, Serenari M, Sposito C, Di Sandro S, Mosconi C, Vicentin I, Garanzini E, Mazzaferro V, De Carlis L, Golfieri R, Spreafico C, Vanzulli A, Buscemi V, Ravaioli M, Ercolani G, Pinna AD, Cescon M. Including mRECIST in the Metroticket 2.0 criteria improves prediction of hepatocellular carcinoma-related death after liver transplant. *J Hepatol* 2020; **73**: 342-348 [PMID: 32201284 DOI: 10.1016/j.jhep.2020.03.018]

19 **Thuluvath PJ**, Thuluvath AJ, Savva Y. Karnofsky performance status before and after liver transplantation predicts graft and patient survival. *J Hepatol* 2018; **69**: 818-825 [PMID: 29883596 DOI: 10.1016/j.jhep.2018.05.025]

20 **Agsalda-Garcia M**, Shieh T, Souza R, Kamada N, Loi N, Oda R, Acosta-Maeda T, Choi SY, Lim E, Misra A, Shiramizu B. Raman-Enhanced Spectroscopy (RESpect) Probe for Childhood Non-Hodgkin Lymphoma. *SciMed J* 2020; **2**: 1-7 [PMID: 34085057 DOI: 10.28991/scimedj-2020-0201-1]

21 **Zhang X**, Bai Y, Xu L, Zhang B, Feng S, Xu L, Zhang H, Xu L, Yang P, Niu T, Zheng S, Liu J. Clinical and morpho-molecular classifiers for prediction of hepatocellular carcinoma prognosis and recurrence after surgical resection. *Hepatol Int* 2019; **13**: 715-725 [PMID: 31531761 DOI: 10.1007/s12072-019-09978-9]

22 **Colasanti M**, Berardi G, Mariano G, Ferretti S, Meniconi RL, Guglielmo N, Ettorre GM. Laparoscopic Left Hepatectomy for Hepatocellular Carcinoma Recurrence Following Liver Transplantation. *Ann Surg Oncol* 2022; **29**: 2984 [PMID: 35006508 DOI: 10.1245/s10434-021-11275-5]

23 **Ouchi K**, Sugawara T, Fujiya T, Kamiyama Y, Kakugawa Y, Mikuni J, Yamanami H, Nakagawa K. Prediction of recurrence and extratumor spread of hepatocellular carcinoma following resection. *J Surg Oncol* 2000; **75**: 241-245 [PMID: 11135264 DOI: 10.1002/1096-9098(200012)75:4<241::AID-JSO3>3.0.CO;2-C]

24 **Dong H**, Ge D, Qu B, Zhu P, Wu Q, Wang T, Wang J, Li Z. Transarterial chemoembolization with or without multikinase inhibitors for patients with unresectable hepatocellular carcinoma: a systematic review and meta-analysis of randomized controlled trials. *Front Oncol* 2023; **13**: 1139025 [PMID: 37361570 DOI: 10.3389/fonc.2023.1139025]

25 **Feng Z**. Minshan Chen: combination of TACE and RFA can improve the treatment of HCC. *Ann Transl Med* 2013; **1**: 10 [PMID: 25332955 DOI: 10.3978/j.issn.2305-5839.2013.01.07]

26 **Orimo T**, Kamiyama T, Yokoo H, Wakayama K, Shimada S, Einama T, Kamachi H, Taketomi A. Salvage Hepatectomy for Recurrent Hepatocellular Carcinoma after Radiofrequency Ablation and/or Transcatheter Arterial Chemoembolization: A Propensity Score-Matched Analysis. *Dig Surg* 2018; **35**: 427-434 [PMID: 28903105 DOI: 10.1159/000480521]

27 **Dan Y**, Meng W, Li W, Chen Z, Lyu Y, Yu T. Transarterial Chemoembolization Combined With Radiofrequency Ablation Versus Hepatectomy for Hepatocellular Carcinoma: A Meta-Analysis. *Front Surg* 2022; **9**: 948355 [PMID: 35898584 DOI: 10.3389/fsurg.2022.948355]

28 **Ouyang T**, Cao Y, Chen L, Zheng C. Comparison of the Efficacy Among Transcatheter Arterial Chemoembolization (TACE)-Radiofrequency

Ablation Plus Apatinib, TACE Plus Apatinib, and TACE Alone for Hepatocellular Carcinoma: A Retrospective Study. *Cardiovasc Intervent Radiol* 2022; **45**: 780-790 [PMID: 35410405 DOI: 10.1007/s00270-022-03141-y]

29 **Wang C**, Liao Y, Qiu J, Yuan Y, Zhang Y, Li K, Zou R, Wang Y, Zuo D, He W, Zheng Y, Li B, Yuan Y. Transcatheter arterial chemoembolization alone or combined with ablation for recurrent intermediate-stage hepatocellular carcinoma: a propensity score matching study. *J Cancer Res Clin Oncol* 2020; **146**: 2669-2680 [PMID: 32449005 DOI: 10.1007/s00432-020-03254-2]

30 **Bholee AK**, Peng K, Zhou Z, Chen J, Xu L, Zhang Y, Chen M. Radiofrequency ablation combined with transarterial chemoembolization versus hepatectomy for patients with hepatocellular carcinoma within Milan criteria: a retrospective case-control study. *Clin Transl Oncol* 2017; **19**: 844-852 [PMID: 28070766 DOI: 10.1007/s12094-016-1611-0]

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ORIGINAL ARTICLE

Randomized Clinical Trial

Effect of high-protein peptide-based formula compared with isocaloric isonitrogenous polymeric formula in critically ill surgical patient

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Abstract

BACKGROUND

Malnutrition is common in critically ill patients, and it is associated with an increased risk of complications. Early enteral nutrition with adequate caloric and protein intake is critical nevertheless it is difficult to achieve. Peptide-based formulas have been shown to be beneficial in patients with feeding intolerance. However, there are limited studies showing the efficacy and safety of high-protein peptide-based formula in critically ill surgical patients.

AIM

To determine the effects of a high-protein peptide formulation on gastrointestinal tolerance, nutritional status, biochemical changes, and adverse events in patients

in the surgery intensive care unit (SICU) compared to an isocaloric isonitrogenous standard polymeric formulation.

METHODS
This study was a multi-center double-blind, randomized controlled trial. We enrolled adult patients in the surgical intensive care unit, age ≥ 15 years and expected to receive enteral feeding for at least 5-14 d post-operation. They were randomly assigned to receive either the high-protein peptide-based formula or the isocaloric isonitrogenous standard formula for 14 d. Gastric residual volume (GRV), nutritional status, body composition and biochemical parameters were assessed at baseline and on days 3, 5, 7, 9, 11, and 14.

RESULTS
A total of 19 patients were enrolled, 9 patients in the peptide-based formula group and 10 patients in the standard formula group. During the study period, there were no differences of the average GRV, body weight, body composition, nutritional status and biochemical parameters in the patients receiving peptide-based formula, compared to the standard regimen. However, participants in the standard formula lost their body weight, body mass index (BMI) and skeletal muscle mass significantly. While body weight, BMI and muscle mass were maintained in the peptide-based formula, from baseline to day 14. Moreover, the participants in the peptide-based formula tended to reach their caloric target faster than the standard formula.

CONCLUSION
The study emphasizes the importance of early nutritional support in the SICU and showed the efficacy and safety of a high-protein, peptide-based formula in meeting caloric and protein intake targets while maintaining body weight and muscle mass.

Key Words: Peptide-based formula; Surgical intensive care; Hydrolyzed protein; Surgery; Nutritional support

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Core Tip: This study is to focus on early nutrition support by novel high protein, peptide-based formula in various surgical intensive care patients. The formula could help maintaining body weight and muscle mass of patients and help them to meet calories and protein requirement. In addition, this nutrition support improved serum albumin, prealbumin and retinol binding protein which lead to decrease risk of malnutrition. Besides nutritional status outcomes evaluation, we investigate wound healing improvement by plasma fibronectin which is protein for cell adhesion, wound healing and blood clotting in this study. This finding would be helpful for recovery surgical patients after operation.

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INTRODUCTION

Malnutrition is common in critically ill patients, and it is associated with an increased risk of complications, particularly in surgical intensive care (SICU) patients. Malnutrition increases infectious complications, delayed wound healing, prolonged hospital stays, and increased hospital cost and overall mortality[1,2]. Early enteral nutrition with adequate caloric and protein intake have been shown to successfully handle the metabolic demands that arise during the acute phase of critical illness, especially in surgical patients which increased metabolic needs for recovery and wound healing. Early enteral feeding could reduce length of hospital stay, ICU stay, ventilator days and mortality in critically ill patients [3]. Moreover, high protein intake during peri-operative period results in less negative nitrogen balance and decrease risk of muscle wasting. Nevertheless, high caloric and protein intake is difficult to achieve. Since the greater volumes and concentrations of enteral nutrition may be required, which may raise the risk of feeding intolerance. Using high volume enteral feeding may increase gastric residual volume (GRV) which leads to increased risk of aspiration pneumonia[4,5]. Fibronectin is a protein that is essential for cell adhesion, wound healing, and blood clotting. Plasma fibronectin is essential for host defense in critically ill patients, especially during sepsis. Low plasma fibronectin levels can promote phagocytic failure, reticuloendothelial system malfunction, and multiple organ failure[6,7].

Peptide-based formula is an enteral formula that incorporates partially or totally hydrolyzed protein in the form of dipeptides or tripeptides. Additionally, a peptide-based formula usually contains a significant amount of medium chain triglyceride (MCT) which is easier to absorb and utilize[8]. This form of enteral formula has several advantages over other forms of enteral nutrition. It contains smaller protein fragments that can be absorbed and utilize more efficiently[9]. It is also a beneficial nutrition support for patients with tube feeding-related diarrhea, feeding intolerance or malabsorption

[10]. However, there are limited studies showing the efficacy and safety of high-protein peptide-based formula in critically ill surgical patients. Thus, this study aimed to determine the effect of high-protein peptide-based formula, compared to the isocaloric isonitrogenous standard polymeric formula, on the gastrointestinal (GI) tolerability and changes of fibronectin levels in patients who were admitted to the SICU. The secondary objective was to investigate the nutritional status, biochemical changes (serum albumin, prealbumin, and retinol-binding protein) and adverse events of this peptide-based formula compared to the standard regimen. The study's findings will be beneficial and guide physicians in choosing the appropriate nutritional regimen for critically ill surgical patients.

MATERIALS AND METHODS

Participants

This study was a multi-center double-blind, randomized controlled trial. It was conducted at SICU of Ramathibodi Hospital (Mahidol University), Chonburi Hospital and Surin Hospital, Thailand. We enrolled adult patients, age 15 years or older, who were admitted to the SICU and expected to receive enteral feeding for at least 5-14 d post-operation. Any acute surgical conditions patients, not the high-risk postoperative observation, could be enrolled to cover clinical scenarios which have problem to achieve goal of calories by enteral feeding. They were randomly assigned to receive either the high-protein peptide-based formula or the isocaloric isonitrogenous standard formula. Block randomization was generated from computerized system by statistical center and transferred to study site location as opaque sealed envelopes at a ratio of 1:1. We excluded patients who required parenteral nutrition, high doses sedative agents (fentanyl > 2 mg/kg/h or morphine > 0.05 mg/kg/h), history of aspiration pneumonia, thyroid disease, severe hepatic or renal impairment, abdominal hypertension, fluid overload, allergy to any research food components, end stage cancer, and severe burn (grade 2 or grade 3 burn with a lesion greater than 50% of the body surface area).

The study was approved by the Institutional Review Board from all institutes and the study was registered at the Thai Clinical Trials Registry (TCTR20220507003) before the first patient's enrollment. All patients voluntarily signed and dated the written informed consent.

Research diets

The study formula is a high-protein peptide-based formula with a Protein: Carbohydrate: Fat ratio of 20:45:35. It contains whey protein hydrolysate and leucine as protein sources and MCT, fish oil and canola oil as fat sources. The formula is fiber-free and it has low osmotic properties. For the control group, casein is added to the standard polymeric formula to pro-duce isocaloric and isonitrogenous formula. The ingredients and nutritional content of both enteral diets are displayed in Table 1. Both diets were prepared at a concentration of 1 kcal/mL.

Feeding protocol

The feeding was started within 48 h after ICU admission and delivered continuously through NG tube. The daily calorie intake for the first 7 d was 20-25 kcal/kg body weight/d, then it was gradually increased to 25-30 kcal/kg of body weight/d over the following 8-14 d. The feeding started by providing at least 50% of the patient's total daily energy requirement, and then gradually increased the feeding rate until the protocol-set feeding rate is reached.

GRV assessment

GRV was measured before feeding, 6 times daily at 4-h intervals. If the GRVs was less than 250 mL, feeding was gradually increased until the target is reached. If the GRV was between 250-400 mL, the feeding was withholded for 1 h before reassessing GRV. If the amount is still over 250 mL, the feeding was stopped for another hour before reassessing the gastric content and the prokinetic agents was administered according to the physician judgement. If the GRV exceeded 400 mL, feeding was stopped, and medication was administered. Symptoms of GI intolerance including diarrhea (assessed using by the Hart and Dobb scale) nausea and vomiting during the study period were recorded daily.

Fibronectin and other biochemical outcomes

Serum fibronectin concentrations were analyzed using a Human Fibronectin Detection kit, PerkinElmer, Inc. The data was generated by white OptiplatedTM 384 microplate and the Envision® plate reader 2103, PerkinElmer, Inc. At baseline (day 1) and on days 3, 5, 11, and 14. The other blood samplings such as complete blood count, blood urea nitrogen, creatinine, glomerular filtration rate, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, albumin, prealbumin, retinol binding protein (RBP), total lymphocyte count (TLC), prothrombin time, total bilirubin, international normalized ratio, fasting blood glucose, free thyroxine, free triiodothyronine, thyroid stimulating hormone, serum electrolyte were also performed.

Other outcomes

The nutritional status was determined on days 1, 3, 5, 7, 9, 11, and 14 using Bhumibol Nutrition Triage (BNT) which was endorsed by Society of Parenteral and Enteral Nutrition of Thailand[10]. Body composition using Bioelectrical Impedance Analysis (Inbody®, Korea), and Sequential Organ Failure Assessment score on day 1 and 14 and Glasgow Coma Scale were also recorded on day 1, 3, 5, 7, 9, 11 and 14.

Table 1 The study formula (once peptide) at concentration of 1 kcal:1 mL

	Peptide-based formula	Standard formula
Caloric distribution (Protein: Carbohydrate: Fat)	20:45:35	20:52:28
Source of protein	Whey protein hydrolysate (96%); Leucine (4%)	Sodium caseinate (8%); Soy protein isolate (92%)
Source of carbohydrate	Maltodextrin (79%); Potato starch (21%)	Maltodextrin (64%); Sucrose (32%); Fructo-oligosaccharide (4%)
Source of fat	Fish oil (5%); Canola oil (43%); MCT oil (52%)	Rice bran oil (92%); MCT oil (8%)
Osmolality (mOsm/kg H_2O)	290	364
Osmolarity (mOsm/L)	242	307

MCT: Medium chain triglyceride.

Statistical analysis

The sample size calculation was based on estimated serum fibronectin amount of ICU patients who received small-peptide and whole protein enteral feeding[11]. Considering standard deviation of serum fibronectin in post-operative patients as 20[12], a 95% confidence level, 80% power of study, and a 10% drop-out rate, 10 subjects were required in each group.

Statistical analysis was carried out using the SPSS version 18.0 (SPSS Inc, Chicago, IL, United States). Continuous data are presented as mean ± SD or median (interquartile range) while categorical data are shown as number (percentage). Independence sample *t*-test or Mann-Whitney *U* test were used to determine the differences of continuous variables between groups. While dependence sample *t*-test or Wilcoxon signed-rank test were used to compare within-subject parameters. Test results of categorical variables were evaluated by Chi-square and Fisher exact tests as appropriate. Results were deemed statistically significant at *P*-value < 0.05.

RESULTS

Baseline characteristics

A total of 19 patients were enrolled, 9 patients were randomized to the peptide-based formula and 10 patients were randomized to the standard formula. Most of the subjects (77.8%) were men. Mean (SD) age of the participants in the peptide-based formula was slightly higher than the standard formula (60.1 ± 21.6 *vs* 49.1 ± 26.0 years, $P = 0.333$). Eighty percent of participants were classified as having a risk of malnutrition or mild malnutrition according to the BNT. Baseline characteristics were similar between groups (Table 2). Causes of ICU admission and type of surgery are shown in Table 3.

Primary outcome

GRV was measured before feeding, 6 times a day then it was calculated as a daily average GRV. There were no significant differences between groups in average GRV measurement over the first three, five, or seven days of ICU admission (Figure 1). There was no difference between the two groups' percentage changes in serum fibronectin levels between days 1 and 3, 5, 11, and 14 (Table 4).

Secondary outcomes and subgroup analysis

During the SICU admission, body weight, body mass index (BMI), skeletal muscle index were not significantly different between groups at day 14 after ICU admission. Mean calorie intake were slightly higher in the control group (peptide-based formula 25.6 ± 4.1 *vs* standard formula 27.3 ± 3.7 kcal/kg/d, $P = 0.402$). However, on day 14, participants in the standard formula lost their body weight, BMI and skeletal muscle mass significantly. While body weight, BMI and muscle mass were maintained in the peptide-based formula, from baseline to day 14 (Table 5).

Serum albumin, prealbumin, RBP and TLC increased from baseline in all participants from both groups. However, only serum prealbumin and RBP significantly increased at day 14 ($P \leq 0.05$) (Figure 2). The actual caloric and protein intake were similar between groups. Duration to achieved target calories, at 25 kcal/kg BW/d and 30 kcal/kg BW/d, in peptide-based formula was shorter than standard formula both as shown in Table 6. There was no observed readmission in either group within 90 d following hospital discharge, and the survival rate was 100% in both group at day 180.

Side effects

There were no severe adverse event, and the frequency of GI complications was similar between groups.

Table 2 Baseline characteristics of study participants, *n* (%)/mean ± SD

	Peptide-based formula (*n* = 9)	Standard formula (*n* = 10)	*P* value
Demographic			
Age (yr)	60.1 ± 21.6	49.1 ± 26.0	0.333
Gender (Male)	7 (77.8)	9 (90.0)	0.466
Weight (kg)	66.2 ± 14.3	62.6 ± 10.4	0.533
BMI (kg/m^2)	24.2 ± 3.1	22.4 ± 3.8	0.275
GCS score	10.7 ± 3.0	10.0 ± 3.1	0.864
SOFA score	4.0 ± 2.0	4.2 ± 2.0	0.769
[1]Nutrition status assessment			
Risk of malnutrition	4 (44.4)	3 (30.0)	0.752
Mild malnutrition	4 (44.4)	5 (50.0)	
Moderate malnutrition	0 (0.0)	1 (10.0)	
Severe malnutrition	1 (11.1)	1 (10.0)	
Biochemistry			
Hemoglobin (g/dL)	9.8 ± 2.4	10.1 ± 1.8	0.793
White blood cells count (× 10^3/μL)	14.8 ± 4.2	15.0 ± 7.5	0.955
Platelets count (× 10^3/μL)	218.8 ± 112.7	175.5 ± 85.5	0.253
Neutrophils	84.3 ± 8.5	83.5 ± 5.8	0.826
Monocytes	6.3 ± 3.5	7.2 ± 3.8	0.513
Total lymphocytes count (cell/μL)	1267.1± 1164.8	1006.0 ± 1005.6	0.288
Blood urea nitrogen (mg/dL)	22.3 ± 8.7	21.3 ± 20.6	0.327
Creatinine (mg/dL)	1.1 ± 0.4	1.0 ± 0.9	0.102
Urine urea nitrogen	12.0 ± 6.4	15.4 ± 22.2	0.441
GFR (mL/min/1.73 m²)	74.7± 31.6	103.5 ± 35.8	0.082
Fasting plasma glucose (mg/dL)	128.0 ± 26.7	128.1 ± 49.1	0.374
Alkaline phosphatase (U/L)	92.1 ± 41.2	96.3 ± 64.6	0.859
Aspartate transaminase (U/L)	84.5 ± 52.0	104.3 ± 66.5	0.501
Alanine transaminase (U/L)	32.5 ± 26.0	86.8 ± 99.8	0.154
Nutritional status			
Albumin (g/dL)	2.6 ± 0.6	2.5 ± 0.5	0.821
Prealbumin (mg/dL)	10.2 ± 5.3	14.1 ± 8.2	0.236
Retinol binding protein (mg/dL)	2.1 ± 1.7	2.0 ± 1.3	1.000

[1]Nutrition status were assessed with Bhumibol Nutrition Triage which is endorsed by Society of Parenteral and Enteral Nutrition of Thailand. NT-1 (score 0-4): Normal or risk of malnutrition; NT-2 (score 5-7): Mild malnutrition; NT-3 (score 8-10): Moderate malnutrition; NT-4 (score >10): Severe malnutrition. BMI: Body mass index; GCS: Glasgow coma scale; SOFA: Sequential organ failure assessment; GFR: Glomerular filtration rate.

DISCUSSION

Our study demonstrated that early nutrition support can lead to improvement of nutritional status for patients in SICU. Within the first week of ICU admission, all patients in this study reached their energy and protein targets according to the European Society for Parenteral and Enteral Nutrition guideline[3]. Even though, there were no differences of GRV and changes of body weight, body composition, nutritional status and biochemical parameters, including fibronectin levels, in patients receiving high-protein peptide-based formula, compared to the standard regimen. The participants in the standard formula lost their body weight, BMI and muscle mass significantly, while the participants receiving peptide-based formula could maintain their weight, BMI and muscle mass on day 14. Moreover, the participants in the peptide-

Table 3 Subject characteristics

Subject number	Cause of ICU admission	Type of surgery
1	Traumatic subdural hematoma	Non operative management, close neurological observation
2	Acute calculus cholecystitis, adult respiratory distress syndrome	Open cholecystectomy
3	Closed fracture of shaft of right of humerus, closed fracture of right tibia and fibula severe head injury, maxillofacial injury, traumatic subdural hematoma	Open reduction of fracture with internal fixation humerus. Closed reduction of fracture without internal fixation tibia and fibula. Non operative management, close neurological observation
4	AAST grade II liver injury severe head injury, traumatic subdural hematoma thoracic blunt aortic injury	Craniotomy, tracheostomy, thoracic endovascular repair of the aorta
5	Splenic injury grade 5 left hemothorax	Exploratory laparotomy with splenectomy
6	Large gastric ulcer perforation	Exploratory laparotomy, simple suture with omental patch
7	Omental twist causing omental infarction	Exploratory laparotomy, omentectomy with drainage
8	Sigmoid colon diverticulitis with perforation	Exploratory laparotomy c sigmoidectomy with Hartmann operation
9	Gastric ulcer perforation	Exploratory laparotomy, simple suture with omental patch
10	Traumatic subdural hematoma	Craniotomy
11	AAST grade 4 pancreatic injury	Exploratory laparotomy, distal pancreatectomy, total splenectomy
12	Malignant neoplasm of adrenal gland, gallstone	Unilateral adrenalectomy, total cholecystectomy
13	Acute calculus cholecystitis	Laparoscopic cholecystectomy
14	Closed fracture of acetabulum, fracture of right radius and ulnar bones	Open reduction of fracture with internal fixation of radius and ulnar bones
15	Severe head injury, traumatic subdural hematoma	Craniectomy for clot removal
16	Epidural hematoma, fracture zygoma, fracture orbit, fracture rib with hemothorax right	Craniotomy with clot removal, open reduction with internal fixation facial fractures
17	Distal rectal cancer	Abdominoperineal resection
18	Necrotizing fasciitis with septic shock	Debridement right leg
19	Necrotizing fasciitis right leg	Debridement right leg

AAST: The American Association for the Surgery of Trauma; ICU: Intensive care unit.

Table 4 Percentage change of serum fibronectin level, median (25th-75th percentiles)

	Peptide-based formula	Standard formula	*P* value
Day 3 *vs* Day 1	17.8 (39.5)	17.5 (100.4)	0.790
Day 5 *vs* Day 1	21.4 (41.9)	63.4 (150.4)	0.290
Day 11 *vs* Day 1	65.1 (106.8)	59.1 (211.8)	0.641
Day 14 *vs* Day 1	11.0 (115.6)	80.5 (357.0)	0.157

based formula tended to reach their caloric target faster than the standard formula.

Peptide-based formula is the enteral formula which contains proteins that are partially hydrolyzed to dipeptides or tripeptides. Moreover, it usually includes higher MCT content compared to the standard polymeric formula which can be absorbed in GI tract and used as source of energy immediately[13]. Previous studies indicated that peptide-based formula could ameliorate feeding intolerance in critically ill patients[14] particularly in malnourished patients who underwent abdominal surgery[15]. In our study, the average GRV were similar between patients receiving either the peptide-based formula or the standard regimen. The discrepancy of the result might be explained by the fact that there were only few patients who had moderate to severe malnutrition in our study. Moreover, clinical characteristics of our study participants were various and not all patients had undergone abdominal surgery. Moreover, the participants in both groups did not have any GI intolerance at baseline and the average GRV were in the normal range throughout the study period [16].

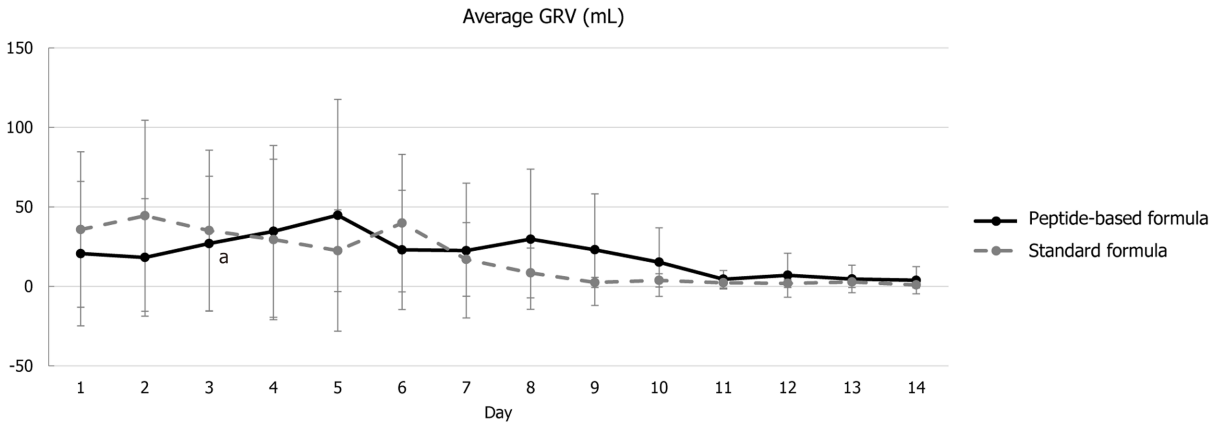
Table 5 Comparison of anthropometry between peptide-based formula and standard formula, mean ± SD

	Peptide-based formula			Standard formula			*P* value (compare between group for day 14)
	Day 1	Day 14	*P* value	Day 1	Day 14	*P* value	
Body weight (kg)	66.2 ± 14.3	65.2 ± 13.1	0.389	62.6 ± 10.4	58.4 ± 10.5	0.037	0.288
BMI (kg/m^2)	24.2 ± 3.1	23.0 ± 2.4	0.471	22.4 ± 3.8	20.9 ± 4.1	0.032	0.273
SMI (kg/m^2)	18.4 ± 5.0	15.7 ± 3.7	0.139	16.1 ± 3.2	13.6 ± 3.2	0.003	0.419

BMI: Body mass index; SMI: Skeletal muscle mass index.

Table 6 Comparison of duration to achieve goal of calories between peptide-based formula and standard formula, mean ± SD

Day to reach goal	Peptide-based formula	Standard formula	*P* value
Step 1 (25 kcal/kg/d up)	2.7 ± 0.6	3.8 ± 2.5	0.462
Step 2 (30 kcal/kg/d up)	7.5 ± 3.5	8.5 ± 0.7	0.733



Average GRV	Peptide-based formula (mean ± SD)	Standard formula (mean ± SD)	*P* value (compare between group)
First 3 d of study	22.03 ± 40.42	38.53 ± 51.79	0.380
First 5 d of study	29.09 ± 50.28	33.72 ± 47.26	0.955
First 7 d of study	27.27 ± 47.00	32.24 ± 44.15	0.885

Figure 1 Comparison of average daily gastric residual volume during study between peptide-based formula and standard formula. [a]*P* value ≤ 0.05. GRV: Gastric residual volume.

Even though, there were no differences of body weight, body composition, nutritional status and biochemical parameters between groups of patients on day 14. Interestingly, the participants in the standard formula lost their weight, BMI and muscle mass significantly, while the participants receiving peptide-based formula could maintain their weight, BMI and muscle mass during baseline through day 14. Muscle wasting is a crucial factor on the recovery of critically ill patients. Sarcopenia can lead to functional disability which can persists for years after discharge from the intensive care unit[17,18]. In a recent clinical study, it was found that patients who receiving peptide-based formula lost less weight and lean mass, compared to the isocaloric and isonitrogenous enteral nutrition[19]. The study suggests that a peptide-based formula is more effective in term of maintaining body weight and muscle mass in patients undergoing surgery. Notably, both groups included the same amount of protein, but the peptide-based formula, composed of whey protein and leucine which could accelerate muscle protein synthesis[20]. Recent study demonstrated that peptide-based formula could prevent significant muscle loss, in comparison with standard formula or β-hydroxymethy β-butyrate-rich product, in obese patients who underwent Roux-en-Y gastric bypass[21]. Moreover, the peptide-based formula contains leucine, a branch-chain amino acid that the World Health Organization recommends people get 39 micrograms/kg of body weight/d[22]. This may be helpful for ICU patients, as shown by the previous research, which presented leucine concentrations that lower normal range lead to decreased cumulative survival rate[23].

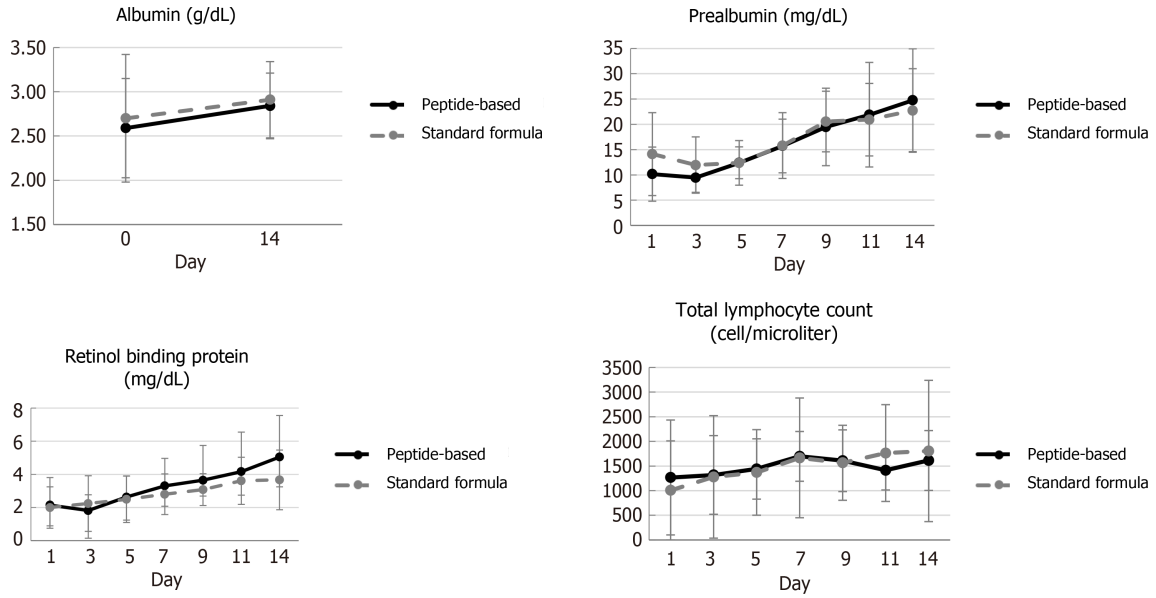


Figure 2 Comparison of nutritional status parameters during study between peptide-based formula and standard formula.

The average calorie and protein intake were similar between groups however participants in the peptide-based formula had a tendency to reach their energy goals earlier, compared to the control group. the study's finding were similar to the previous study which indicated that peptide-based formulas are more effective in achieving nutritional targets within a 7-d period compared to the intact-protein enteral nutrition formulas[24].

There was no significant difference in the change in plasma fibronectin levels between groups. This could be attributed to the fact that the level of plasma fibronectin varied greatly and was unpredictable. Previous research has shown that this value can be affected by several factors, such as the type of disease, severity of the infection, type of cancer, and blood transfusion[25-27]. Unlike previous studies[28,29], we only evaluated fibronectin levels after surgery, as we could not assess fibronectin levels before ICU admission[28,29]. Considering the factors mentioned above, the researcher concluded that the serum fibronectin value used in this study has a large variation, making it difficult to compare the degree of improvement among patients. Furthermore, it may not be specific enough to accurately measure the effect of the interventions.

This study has several strengths. Firstly, it was a multicenter, double-blind randomized controlled trial. Secondly, we used the isocaloric, isonitrogenous polymeric standard formula as a control. Thirdly, the feeding protocol was progressive and adjusted individually according to physician's judgement. Lastly, the study measured various outcomes including body composition, biochemistry, and gastrointestinal complications. Our important limitation of this study was the small sample size since we conducted the study during the coronavirus disease pandemic. The small sample size limits the ability to draw a definitive conclusion. Therefore, further study should be conducted to determine the long-term effect of peptide-based formula in larger patient populations, including various patient groups.

CONCLUSION

This study's results suggest that early nutritional support is a crucial aspect of health care for patients in the SICU. The high-protein, peptide-based enteral formula was not only well-received but also effective in helping critically ill patients meet their caloric and protein intake targets. This peptide-based enteral formula plays a significant role in preserving body weight and muscle mass. These findings have substantial implications for muscle strength, physical performance, and an individual's ability to participate in physical medicine and rehabilitation.

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FOOTNOTES

Author contributions: Sumritpradit P conceived the original idea, designed the study, enrolled subjects, patient care, performed the interpretation of data, wrote manuscript, and revised the manuscript and corresponding to submit for publication; Shantavasinkul PC

performed biochemistry analysis, took responsibility for integrity of data, wrote manuscript and revised the manuscript; Ungpinitpong W enrolled subjects, patient care, performed the statistical analysis data, took responsibility for accuracy of data, reviewed the manuscript and provided critical comments; Noorit P enrolled subjects, patient care, performed the interpretation of data, took responsibility for integrity of data, reviewed the manuscript and provided critical comments; Gajaseni C collected the data, coordinate with participants and site staff team for intervention. All authors read and approved the final manuscript.

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REFERENCES

1 **Heyland DK**. Nutritional support in the critically ill patients. A critical review of the evidence. *Crit Care Clin* 1998; **14**: 423-440 [PMID: 9700440 DOI: 10.1016/s0749-0704(05)70009-9]
2 **Singer P**, Berger MM, Van den Berghe G, Biolo G, Calder P, Forbes A, Griffiths R, Kreyman G, Leverve X, Pichard C, ESPEN. ESPEN Guidelines on Parenteral Nutrition: intensive care. *Clin Nutr* 2009; **28**: 387-400 [PMID: 19505748 DOI: 10.1016/j.clnu.2009.04.024]
3 **Kreymann KG**, Berger MM, Deutz NE, Hiesmayr M, Jolliet P, Kazandjiev G, Nitenberg G, van den Berghe G, Wernerman J; DGEM (German Society for Nutritional Medicine), Ebner C, Hartl W, Heymann C, Spies C; ESPEN (European Society for Parenteral and Enteral Nutrition). ESPEN Guidelines on Enteral Nutrition: Intensive care. *Clin Nutr* 2006; **25**: 210-223 [PMID: 16697087 DOI: 10.1016/j.clnu.2006.01.021]
4 **Mentec H**, Dupont H, Bocchetti M, Cani P, Ponche F, Bleichner G. Upper digestive intolerance during enteral nutrition in critically ill patients: frequency, risk factors, and complications. *Crit Care Med* 2001; **29**: 1955-1961 [PMID: 11588461 DOI: 10.1097/00003246-200110000-00018]
5 **Blaser AR**, Starkopf J, Kirsimägi Ü, Deane AM. Definition, prevalence, and outcome of feeding intolerance in intensive care: a systematic review and meta-analysis. *Acta Anaesthesiol Scand* 2014; **58**: 914-922 [PMID: 24611520 DOI: 10.1111/aas.12302]
6 **Magnusson MK**, Mosher DF. Fibronectin: structure, assembly, and cardiovascular implications. *Arterioscler Thromb Vasc Biol* 1998; **18**: 1363-1370 [PMID: 9743223 DOI: 10.1161/01.atv.18.9.1363]
7 **Grossman JE**. Plasma fibronectin and fibronectin therapy in sepsis and critical illness. *Rev Infect Dis* 1987; **9** Suppl 4: S420-S430 [PMID: 3326138 DOI: 10.1093/clinids/9.supplement_4.s420]
8 **Silk DB**. Progress report. Peptide absorption in man. *Gut* 1974; **15**: 494-501 [PMID: 4604970 DOI: 10.1136/gut.15.6.494]
9 **Meredith JW**, Ditesheim JA, Zaloga GP. Visceral protein levels in trauma patients are greater with peptide diet than with intact protein diet. *J Trauma* 1990; **30**: 825-8; discussion 828 [PMID: 2116533 DOI: 10.1097/00005373-199007000-00011]
10 **Brinson RR**, Kolts BE. Diarrhea associated with severe hypoalbuminemia: a comparison of a peptide-based chemically defined diet and standard enteral alimentation. *Crit Care Med* 1988; **16**: 130-136 [PMID: 3125004]
11 **Heimburger DC**, Geels VJ, Bilbrey J, Redden DT, Keeney C. Effects of small-peptide and whole-protein enteral feedings on serum proteins and diarrhea in critically ill patients: a randomized trial. *JPEN J Parenter Enteral Nutr* 1997; **21**: 162-167 [PMID: 9168369 DOI: 10.1177/014860719702100316 2]
12 **Hackbarth R**, Sarnaik AP, Meert K, Deshmukh DR, Arciniegas E. Changes in plasma fibronectin in children after elective repair of congenital heart defects. *J Thorac Cardiovasc Surg* 1993; **105**: 31-36 [PMID: 8419706]
13 **Mohamed Elfadil O**, Shah RN, Hurt RT, Mundi MS. Peptide-based formula: Clinical applications and benefits. *Nutr Clin Pract* 2023; **38**: 318-328 [PMID: 36802281 DOI: 10.1002/ncp.10961]
14 **Wang K**, Zhang Z. Peptide-based enteral nutrition for critically ill patients. *J Transl Crit Care Med* 2021; **3**: 2 [DOI: 10.4103/jtccm.jtccm_11_21]
15 **Liu MY**, Tang HC, Hu SH, Chang SJ. Peptide-based enteral formula improves tolerance and clinical outcomes in abdominal surgery patients

relative to a whole protein enteral formula. *World J Gastrointest Surg* 2016; **8**: 700-705 [PMID: 27830042 DOI: 10.4240/wjgs.v8.i10.700]

16 **Montejo JC**, Miñambres E, Bordejé L, Mesejo A, Acosta J, Heras A, Ferré M, Fernandez-Ortega F, Vaquerizo CI, Manzanedo R. Gastric residual volume during enteral nutrition in ICU patients: the REGANE study. *Intensive Care Med* 2010; **36**: 1386-1393 [PMID: 20232036 DOI: 10.1007/s00134-010-1856-y]

17 **Mayer KP**, Thompson Bastin ML, Montgomery-Yates AA, Pastva AM, Dupont-Versteegden EE, Parry SM, Morris PE. Acute skeletal muscle wasting and dysfunction predict physical disability at hospital discharge in patients with critical illness. *Crit Care* 2020; **24**: 637 [PMID: 33148301 DOI: 10.1186/s13054-020-03355-x]

18 **Schefold JC**, Wollersheim T, Grunow JJ, Luedi MM, Z'Graggen WJ, Weber-Carstens S. Muscular weakness and muscle wasting in the critically ill. *J Cachexia Sarcopenia Muscle* 2020; **11**: 1399-1412 [PMID: 32893974 DOI: 10.1002/jcsm.12620]

19 **Alexander DD**, Bylsma LC, Elkayam L, Nguyen DL. Nutritional and health benefits of semi-elemental diets: A comprehensive summary of the literature. *World J Gastrointest Pharmacol Ther* 2016; **7**: 306-319 [PMID: 27158547 DOI: 10.4292/wjgpt.v7.i2.306]

20 **Wamiti J**, Kogi-Makau W, Onyango FE, Ngala S. Leucine supplementation in the management of protein energy malnutrition: A review article. *East African Med J* 2017; **94** Suppl 1: 20-24

21 **Comas Martínez M**, Fidilio Meli E, Palmas Candia F, Cordero E, Hernández I, Vilallonga R, Burgos R, Vila A, Simó R, Ciudin A. Protein Supplementation with Short Peptides Prevents Early Muscle Mass Loss after Roux-en-Y-Gastric Bypass. *Nutrients* 2022; **14** [PMID: 36501125 DOI: 10.3390/nu14235095]

22 **Joint WHO/FAO/UNU Expert Consultation**. Protein and amino acid requirements in human nutrition. *World Health Organ Tech Rep Ser* 2007; 1-265 [PMID: 18330140]

23 **Wang MY**, Wang CH, Chen WS, Chu CM, Wu HP, Liu MH, Lin YT, Kao KC, Liang CY, Chen WH, Wang HJ, Lee SC. U-Shape Relationship between Plasma Leucine Level and Mortality in the Intensive Care Unit. *Dis Markers* 2022; **2022**: 7389258 [PMID: 35035612 DOI: 10.1155/2022/7389258]

24 **Wang YQ**, Li YH, Li YT, Li HX, Zhang D. Comparisons between short-peptide formula and intact-protein formula for early enteral nutrition initiation in patients with acute gastrointestinal injury: a single-center retrospective cohort study. *Ann Transl Med* 2022; **10**: 573 [PMID: 35722435 DOI: 10.21037/atm-22-1837]

25 **Stathakis NE**, Fountas A, Tsianos E. Plasma fibronectin in normal subjects and in various disease states. *J Clin Pathol* 1981; **34**: 504-508 [PMID: 7251892 DOI: 10.1136/jcp.34.5.504]

26 **Boughton BJ**, Simpson A, Baar S, Ala F, Casson J, Gower J. The concentration of plasma fibronectin in burns patients treated with fresh frozen plasma or plasma protein fraction. *Resuscitation* 1984; **12**: 41-45 [PMID: 6330824 DOI: 10.1016/0300-9572(84)90057-1]

27 **Gironi A**, Niccolai J, Fabbri LP, Niccolai M, Chisci C. [Determination of plasma fibronectin (Fn) levels. Comparison between normal subjects and patients with various pathological conditions]. *Quad Sclavo Diagn* 1982; **18**: 392-405 [PMID: 6764670]

28 **Chadwick SJ**, Mowbray JF, Dudley HA. Plasma fibronectin and complement in surgical patients. *Br J Surg* 1984; **71**: 718-720 [PMID: 6478167 DOI: 10.1002/bjs.1800710926]

29 **Gauperaa T**, Giercksky KE, Revhaug A, Rekvig OP. Fibronectin, complement and immunoglobulins in serum after surgery. *Br J Surg* 1985; **72**: 59-62 [PMID: 3967133 DOI: 10.1002/bjs.1800720123]

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ORIGINAL ARTICLE

Clinical and Translational Research

Metabolic disorders and hepatitis: Insights from a Mendelian randomization study

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Abstract

BACKGROUND

Hepatitis is a systemic disease that often results in various comorbidities. Metabolic disorders, the most common comorbidities in clinical practice, were selected for this study.

AIM

To investigate the causal relationship between comorbidities and hepatitis treatment outcomes.

METHODS

A total of 23583378 single nucleotide polymorphisms from 1248743 cases and related summaries of genome-wide association studies were obtained from online public databases. A two-sample Mendelian randomization (MR) was performed to investigate causality between exposure [type 2 diabetes mellitus (T2D), hyperlipidemia, and hypertension] and outcome (chronic hepatitis B or C infections).

RESULTS

The data supported the causal relationship between comorbidities and hepatitis infections, which will affect the severity of hepatitis progression and will also provide a reference for clinical researchers. All three exposures showed a link with progression of both hepatitis B (T2D, $P = 0.851$; hyperlipidemia, $P = 0.596$; and hypertension, $P = 0.346$) and hepatitis C (T2D, $P = 0.298$; hyperlipidemia, $P = 0.141$; and hypertension, $P = 0.035$).

CONCLUSION

The results of MR support a possible causal relationship between different ex-

posures (T2D, hyperlipidemia, and hypertension) and chronic hepatitis progression; however, the potential mechanisms still need to be elucidated.

Key Words: Hepatitis; Comorbidity; Type 2 diabetes mellitus; Hyperlipidemia; Hypertension

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Core Tip: In our study, the randomization model was well defined for the exposures [type 2 diabetes mellitus (T2D), hyperlipidemia, and hypertension] and outcomes (chronic hepatitis B and chronic hepatitis C) by two-sample Mendelian randomization (MR) analysis, and they showed capabilities for interaction with chronic hepatitis infection. The results of our MR support a possible causal relationship between different exposures (T2D, hyperlipidemia, and hypertension) and chronic hepatitis progression.

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INTRODUCTION

According to the Global Hepatitis Report 2017 by the World Health Organization, more than 1.34 million people died of hepatitis virus infection worldwide in 2015; more than half of the patients died because of progression to cirrhosis and the other half died due to hepatocellular carcinoma[1]. Hepatitis can be caused by infections with different viruses: Hepatitis A virus, hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus. However, only HBV, HCV, and HDV can induce chronic hepatitis, leading to severe cirrhosis and hepatocellular carcinoma[1]. Because chronic hepatitis is mainly caused by HBV and HCV[2], we investigated the comorbidities of these two types in this study.

HBV is a DNA virus, whereas HCV is an RNA virus. HBV can activate severe immune responses in patients and can be removed by the human body in the short term[3]. However, HBV can also induce a chronic form in the long term; approximately 40% of HBV patients progress to cirrhosis[4], which could be attributable to the long half-life of HBV covalently closed circular DNA[5,6]. Meanwhile, other risk factors such as aging[5], other concomitant diseases, or consumption of alcohol, could significantly increase the probability of being diagnosed with cirrhosis, based on the theory of Sagnelli *et al*[7]. Similar to HBV, the chances of progression to cirrhosis and hepatocellular carcinoma among patients with HCV infection also increase with age[8]. Other potential risk factors, such as gastrointestinal diseases of the esophagus, stomach, and duodenum (41.7%), could induce comorbidities with hepatitis[9].

Researchers have recently explored the relationship between hepatitis and related comorbidities. According to Hsu *et al* [10], comorbidities accompanying hepatitis are often caused by hypertension, diabetes, and ischemic heart disease. In addition, circulatory diseases[9], renal diseases, and non-liver cancers can worsen hepatitis progression accompanied by comorbidities[8]. Therefore, in this study, we investigated the role of the following typical comorbidities in influencing hepatitis: Type 2 diabetes mellitus (T2D), hyperlipidemia, and hypertension.

As the risk factors and pathology of hepatitis comorbidities vary, analyzing the relationship between clinical treatment and hepatitis progression among different comorbidities becomes challenging. Meanwhile, knowledge in this field is still rather limited; therefore, we employed a Mendelian randomization (MR) protocol to explore this pair of causations. Currently, MR is a widely used research method based on genome-wide association studies (GWAS) and the theory of nucleotide polymorphisms. As a newly developed tool, MR inherits the principles of the equal, random, and independent distribution method, which adopts genetic variants to reveal causal relationships[11,12], thus providing more reliable and authentic results[13,14]. Regarding hepatitis research, MR will help establish the causal linkage between hepatitis comorbidities and disease outcomes. In this study, patients with different comorbidities were regarded as having a functional variation of specific genes, and MR analysis will guide researchers to better understand hepatitis comorbidities and progression.

MATERIALS AND METHODS

Study design

In this study, a two-sample MR analysis was employed to investigate the causal relationship between comorbidities and hepatitis treatment outcomes. Meanwhile, the inverse variance weighting (IVW) method was applied to determine the causal relationship between exposures and outcomes, where comorbidities were regarded as exposures and indicators from various aspects were regarded as outcomes. Consequently, single nucleotide polymorphisms (SNPs) associated with

Table 1 Description of included traits

Group	Trait	ID	Sample size	Year	Case/control	SNPs
Exposures	T2D	ebi-a-GCST90093109	50533	2022	16677/33856	13403040
	Hyperlipidemia	ebi-a-GCST90090994	9714	2022	3310/6404	592502
	Hypertension	ebi-a-GCST90038604	484598	2021	129909/354689	9587836
Outcomes	CHB	ebi-a-GCST90018804	351885	2021	145/351740	19079722
	CHC	ebi-a-GCST90018805	352013	2021	273/351740	19074546

T2D: Type 2 diabetes mellitus; CHB: Chronic hepatitis B; CHC: Chronic hepatitis C; Chronic hepatitis B; CHC: Chronic hepatitis C.

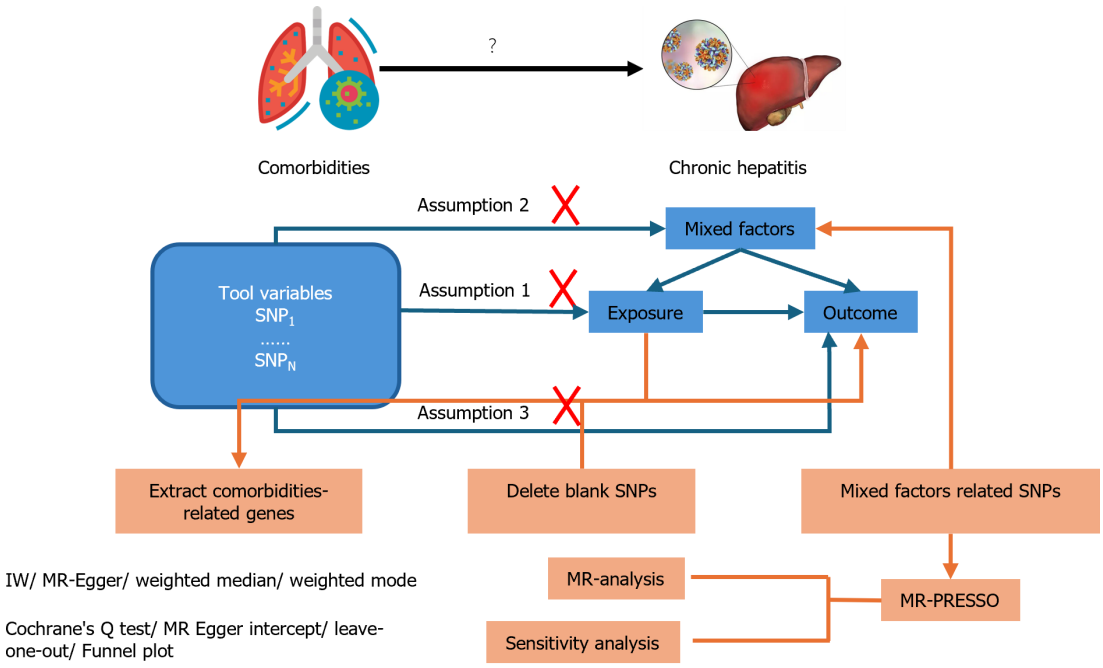


Figure 1 Mendelian randomization analysis. MR: Mendelian randomization; SNP: Single nucleotide polymorphism.

hepatitis comorbidities were used as instrumental variables, while their clinical conditions were used as outcome variables. Based on this condition, three important assumptions should be satisfied.

Assumption 1: The selected SNPs should be significantly related to the exposure variable. Assumption 2: SNPs should remain independent of factors that could play a role in exposure and outcomes. Assumption 3: SNPs should not have a direct impact on inducing changes in hepatitis status but can only alter the status *via* comorbidities to exhibit a causal relationship.

Based on the descriptions above, we conducted an MR analysis as depicted in Figure 1.

Data of exposure and outcome

The included SNPs and related GWAS summaries were obtained from the online public databases IEU OpenGWAS (https://gwas.mrcieu.ac.uk/) and FinnGen Biobank (https://r8.finngen.fi/), which provide genetic insights from a well-phenotyped isolated population[15]. Online calculations were performed using the MR-Base platform (http://app.mrbase.org/, version 1.4.3 8a77eb; accessed on 08 January 2024)[11]. In this study, different pairs of exposures and outcomes were formed to examine their relationships, where T2D (total 50,533 samples, 16677 cases/33856 controls), hyperlipidemia (total 9714 samples, 3310 cases/6404 controls), and hypertension (total 484598 samples, 129909 cases/354689 controls) comprised the exposures, and chronic hepatitis B (CHB; total 351885 samples, 145 cases/351740 controls) and chronic hepatitis C (CHC) infections (total 352013 samples, 273 cases/351740 controls). Table 1 lists the characteristics of these pairs. These data were accessed and investigated on 06 January 2024.

MR analysis

MR analysis was deployed to investigate the association between metabolic disorders and chronic hepatitis, which leveraged genetic variants as instrumental variables to infer causal relationships. The MR-base GWAS catalog served as a crucial tool for selecting appropriate SNPs as instrumental variables during the MR analysis. Meanwhile, rigorous criteria

were adopted to ensure the high authenticity of the SNP statistics: *P* value threshold of less than 5×10^{-8} and LD Rsq threshold of 0.001.

Meanwhile, we utilized various models to test the theory that comorbidities affect chronic hepatitis. For instance, the IVW method as a commonly used approach in MR analysis, was used to estimate the causal effect between exposure and outcome. Additionally, the MR-Egger model was utilized to detect and correct for potential horizontal pleiotropy with a non-zero *P* value indicating statistical significance ($P < 0.05$). To ensure a convincing conclusion, the Cochrane Q test was applied with the IVW and MR-Egger tests to test for heterogeneity.

To verify the robustness of this MR analysis, sensitivity analyses were conducted by using various MR methods, including MR-Egger regression, weighted median, and weighted mode methods. The weighted mode was examined by leave-one-out analysis, where the impact of each instrumental SNP on exposures and outcomes could be detected. In addition, the odds ratio (OR) and its 95% confidence interval (95%CI) were calculated using the MR results to predict the integrity of the causal relationship between exposure and outcome factors.

Presentation of the results was meticulously executed through the creation of comprehensive visualizations, including forest plots, funnel plots, leave-one-out plots, and scatter plots. These plots provided insights into the effects of each SNP on both exposure and outcome variables, facilitating a deeper understanding of the observed associations.

The statistical analyses were conducted using R (version 4.0.3) and R/TwoSampleMR (https://mrcieu.github.io/TwoSampleMR, version 0.5.5) were used with the online analysis tool for computational efficiency. By employing these rigorous statistical approaches, the study aimed to provide robust evidence regarding the relationship between metabolic disorders and chronic hepatitis, contributing to the broader understanding of disease etiology and potential therapeutic interventions.

RESULTS

MR estimates

We chose three typical comorbidities among patients with chronic hepatitis, namely T2D, hyperlipidemia, and hypertension, as exposure factors and found their GWAS summary for detailed MR. In this study, we found that these factors were significantly associated with the progression of chronic hepatitis. As shown in Table 1, the overall SNP exposure was 23583378 and the total sample accounted for 1248743 cases. In the outcome group, the number of patients with hepatitis B and C infections was 418 of 703898 cases. These data were retrieved from public research worldwide and, therefore, present extensive human research.

Detailed data of the two-sample MR are presented in Table 2. All three exposures exhibited a role in promoting the progress of hepatitis: T2D showed a link with hepatitis B progression examined by IVW (OR = 1.01676, 95%CI = 0.854–1.210, $P = 0.851$), as did hyperlipidemia (OR = 0.97827, 95%CI = 0.902–1.061, $P = 0.596$), and hypertension (OR = 1.35243, 95%CI = 0.721–2.535, $P = 0.346$). For the other outcomes of CHC infection, T2D promoted its progression with OR = 0.94825, 95%CI = 0.858–1.048, $P = 0.298$; hyperlipidemia with OR = 0.96140, 95%CI = 0.912–1.013, $P = 0.141$; and hypertension with OR = 0.67301, 95%CI = 0.465–0.973, $P = 0.035$).

Consistent with the findings in Table 2, the effects of the SNPs on exposure and outcomes are illustrated below (Figure 2).

Sensitivity analyses

As mentioned in the MR section, different statistical models were applied to examine the quality of the analysis. For example, to examine the horizontal pleiotropy of this MR, the MR-Egger intercept was calculated based on the mode with $P > 0.05$, suggesting a correct scientific basis for this analysis. Directional horizontal pleiotropy was drawn in funnel plots (Figure 3), where the data dots were distributed in a symmetrical form. In addition, no heterogeneity was found in this study because the *P* values were greater than 0.05. Meanwhile, the leave-one-out analysis results indicated a significant relationship between different exposures and outcomes (Figures 4 and 5).

DISCUSSION

Currently, with faster transportation and a changeable lifestyle in modern societies, the probability of a person diagnosed with two or more diseases are increasing[16]. Since the mortality rate for patients with chronic hepatitis remains low, and the situations for the patients carrying an additional disease become complicated, we performed this MR to analyze the potential effects of comorbidities during hepatitis and the disease progression among the patients, and the first category went to cardiovascular disease after we looked up the related findings.

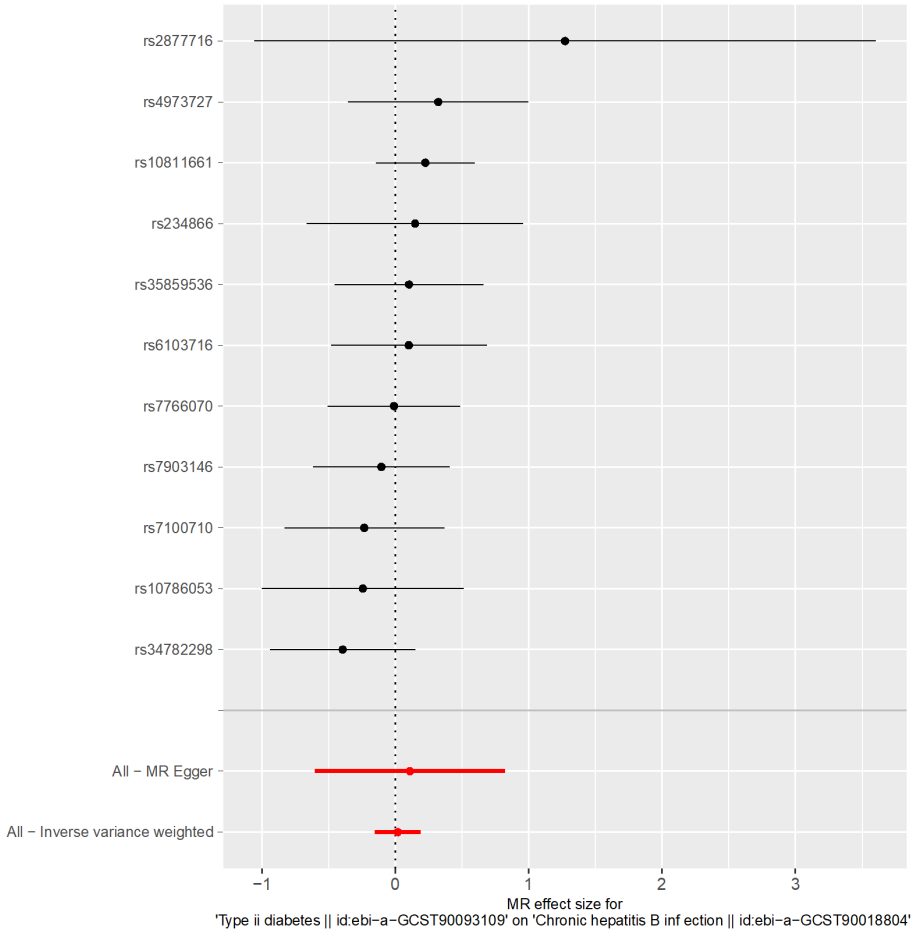
According to our findings, comorbidities associated with metabolic disorders and cardiovascular disease promote the progression of chronic hepatitis. A meta-analysis by Naing *et al*[17], which included 17 studies with 286084 patients demonstrated a strong relationship between T2D and CHC infection. This correlation was first proposed by Allison *et al*[18] in 1994, based on the finding of abnormalities in carbohydrate metabolism, such as glucose intolerance, in cirrhosis. The exact molecular mechanisms remain to be further explored, but MR could help answer this question since the underlying mechanisms are related to genetic specificity[19]. In addition, a meta-analysis found that T2D is associated with hepatitis B infection, and that T2D could promote hepatitis B progression into hepatocellular carcinoma[20]. The pathology remains to be further explored, but studies have indicated that altered microbiome caused by HBV affect both

Table 2 Mendelian randomization for the association between comorbidities and chronic hepatitis

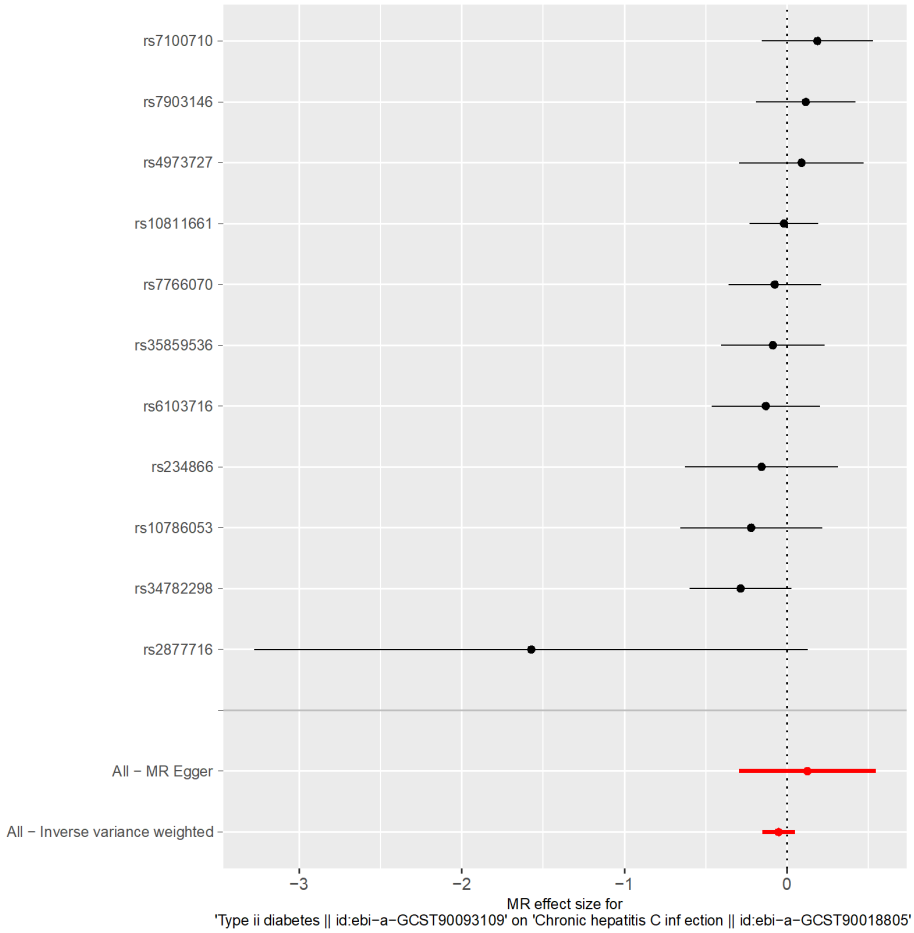
Outcome	Exposure	Number of instruments	Method	OR	95%CI	*P* value	Heterogeneity			Pleiotropy	
							Q	Q_df	Q p	Intercept	*P* value
CHB infection	T2D	11	MR Egger	1.11338	0.546-2.271	0.774	6.861	9	0.6516	-0.011	0.803
			Weighted median	1.08022	0.860-1.357	0.504	-	-	-		
			IVW	1.01676	0.854-1.210	0.851	6.927	10	0.7323		
			Weighted mode	1.10321	0.815-1.493	0.576	-	-	-		
	Hyperlipidemia	5	MR Egger	1.00996	0.804-1.269	0.938	3.888	3	0.2738	-0.013	0.784
			Weighted median	1.00910	0.918-1.110	0.857	-	-	-		
			IVW	0.97827	0.902-1.061	0.596	4.004	4	0.4055		
			Weighted mode	1.01660	0.912-1.133	0.765	-	-	-		
	Hypertension	277	MR Egger	1.845401	0.350-9.728	0.471	279.1	258	0.1751	-0.0028	0.693
			Weighted median	1.56894	0.604-4.077	0.346	-	-	-		
			IVW	1.35243	0.721-2.535	0.346	279.3	259	0.1846		
			Weighted mode	1.81921	0.519-6.379	0.359	-	-	-		
CHC infection	T2D	11	MR Egger	1.13338	0.744-1.726	0.574	9.143	9	0.4242	-0.022	0.414
			Weighted median	0.94250	0.825-1.077	0.391	-	-	-		
			IVW	0.94825	0.858-1.048	0.298	9.887	10	0.4504		
			Weighted mode	0.94916	0.810-1.112	0.550	-	-	-		
	Hyperlipidemia	5	MR Egger	0.89288	0.793-1.005	0.158	3.222	3	0.3587	0.03	0.274
			Weighted median	0.94627	0.898-0.997	0.038	-	-	-		
			IVW	0.96140	0.912-1.013	0.141	5.134	4	0.2738		
			Weighted mode	0.94262	0.891-0.998	0.108	-	-	-		
	Hypertension	260	MR Egger	0.59067	0.223-1.566	0.291	289.5	258	0.08644	0.0012	0.777
			Weighted median	0.69088	0.391-1.220	0.206	-	-	-		
			Inverse variance weighted	0.67301	0.465-0.973	0.035	289.6	259	0.09284		
			Weighted mode	0.83477	0.408-1.707	0.617	-	-	-		

MR: Mendelian randomization; IVW: Inverse variance weighting; T2D: Type 2 diabetes mellitus; CHB: Chronic hepatitis B; CHC: Chronic hepatitis C.

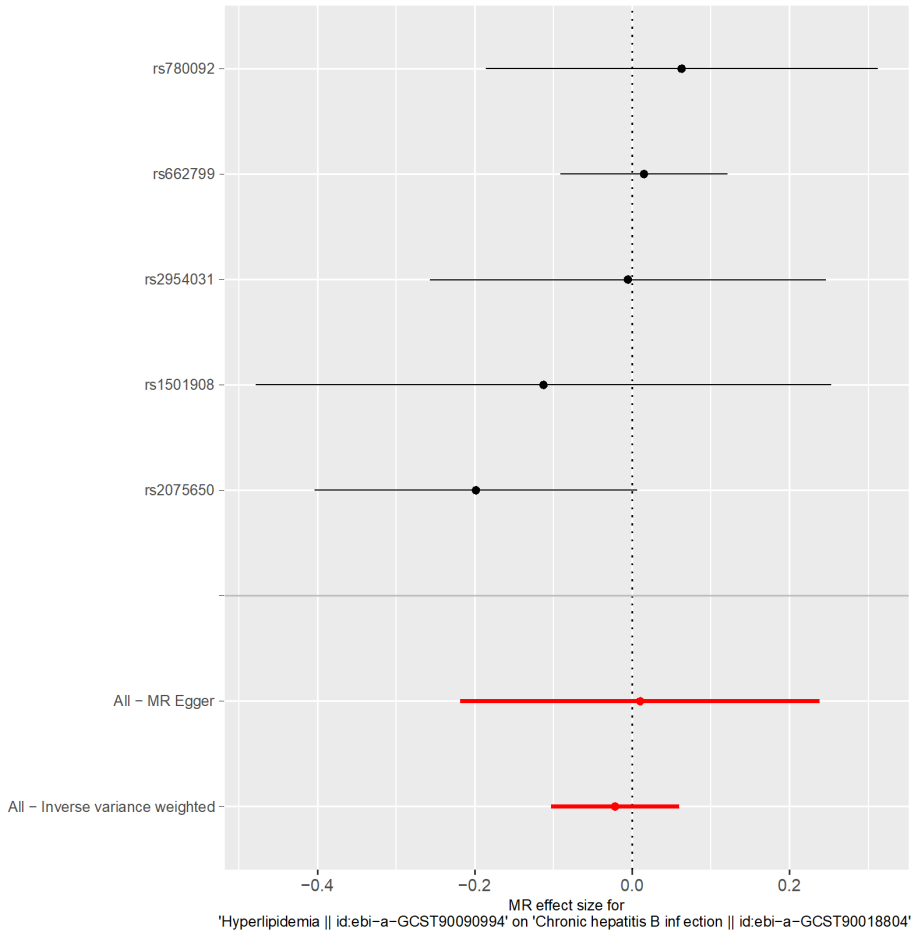
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All − MR Egger
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MR effect size for
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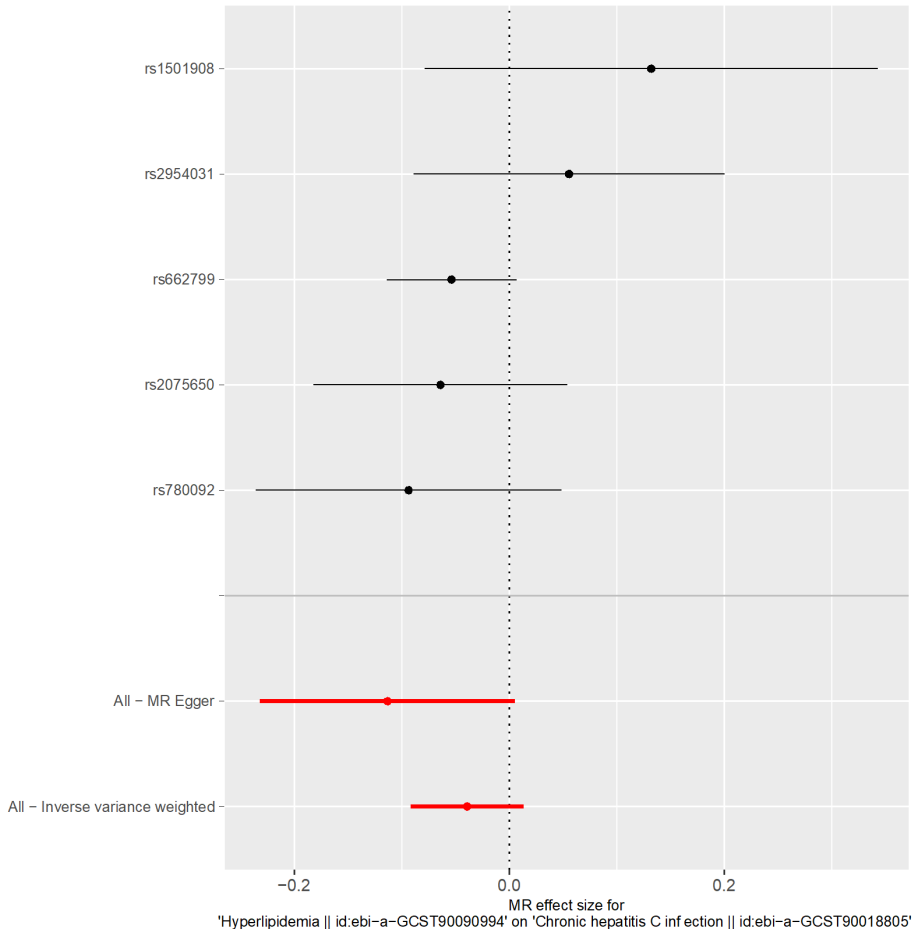
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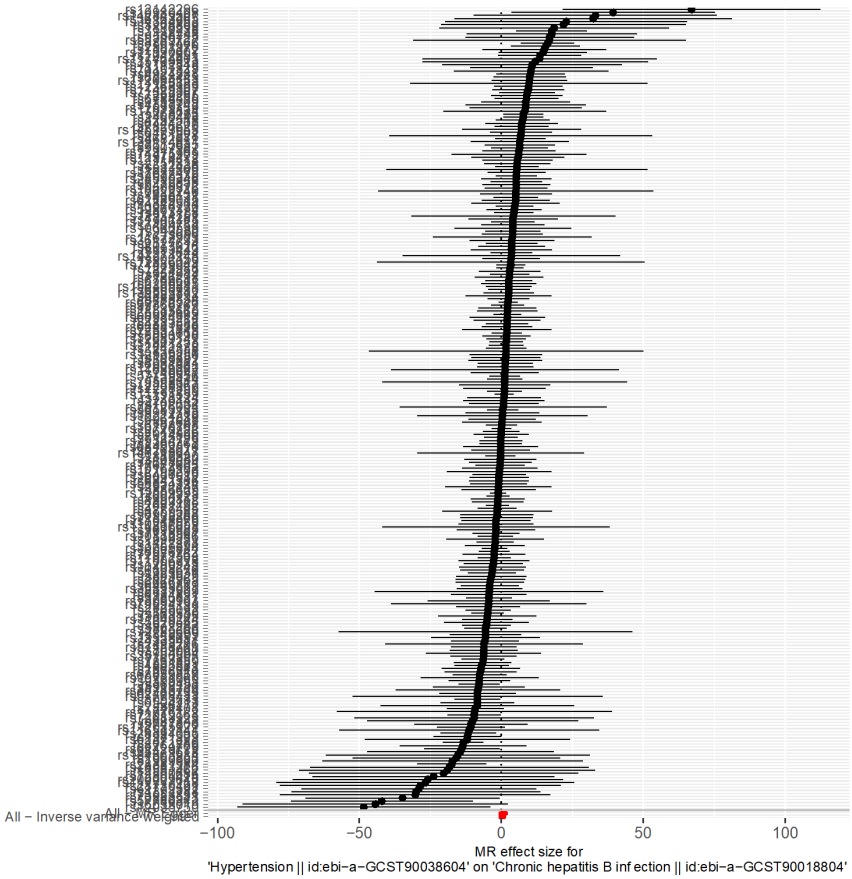
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E



F

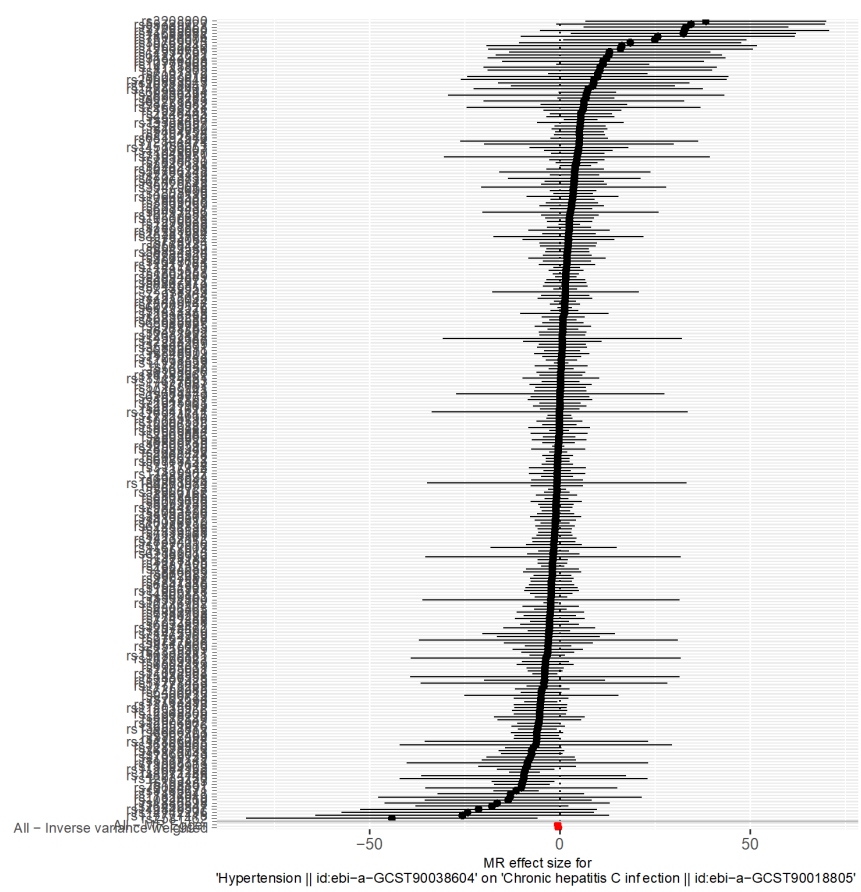


Figure 2 Forest plot of the comorbidities. A and B: type 2 diabetes mellitus; C and D: Hyperlipidemia; E and F: Hypertension affecting chronic hepatitis B infection (upper panel) and chronic hepatitis C infection (lower panel). MR: Mendelian randomization.

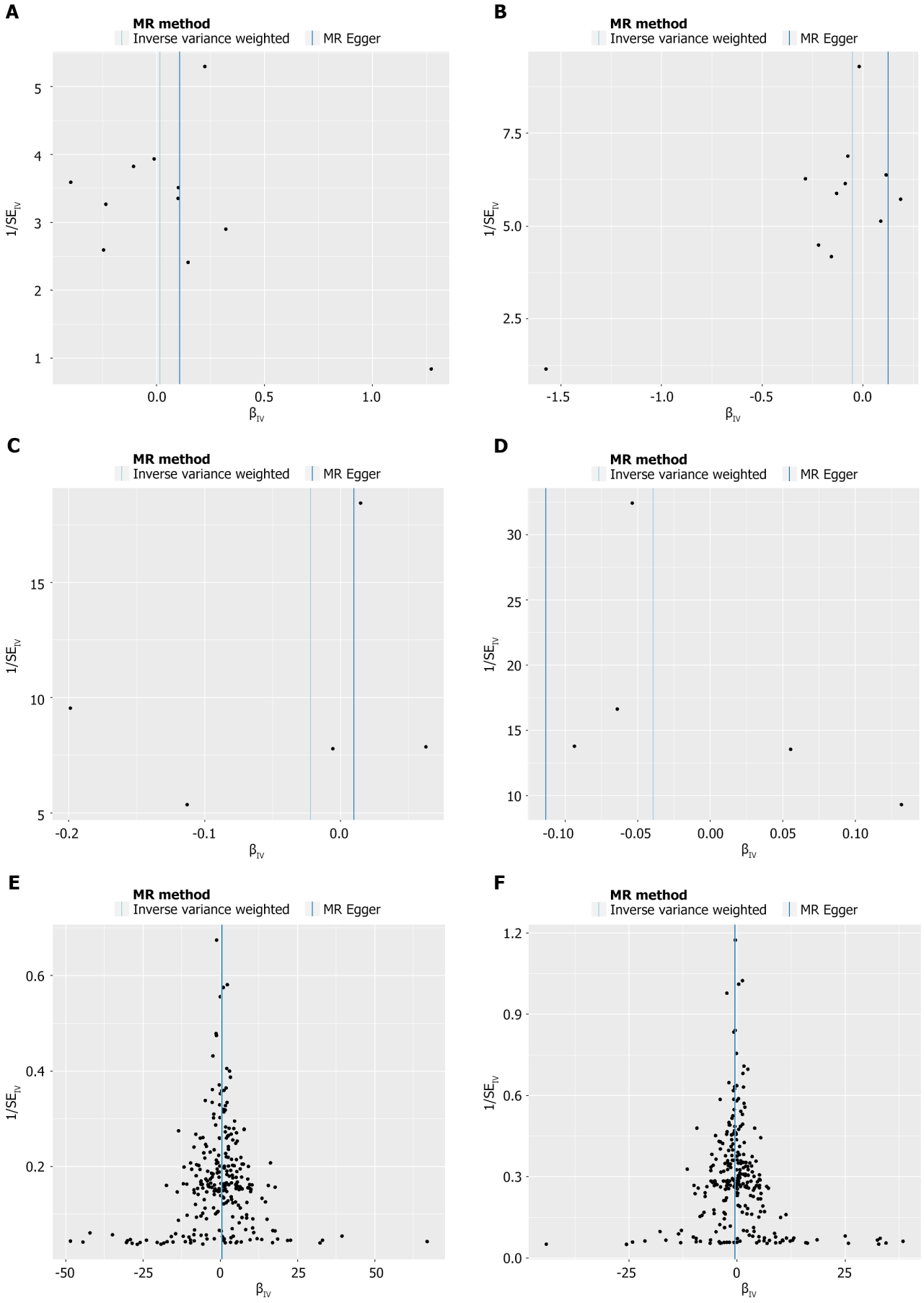
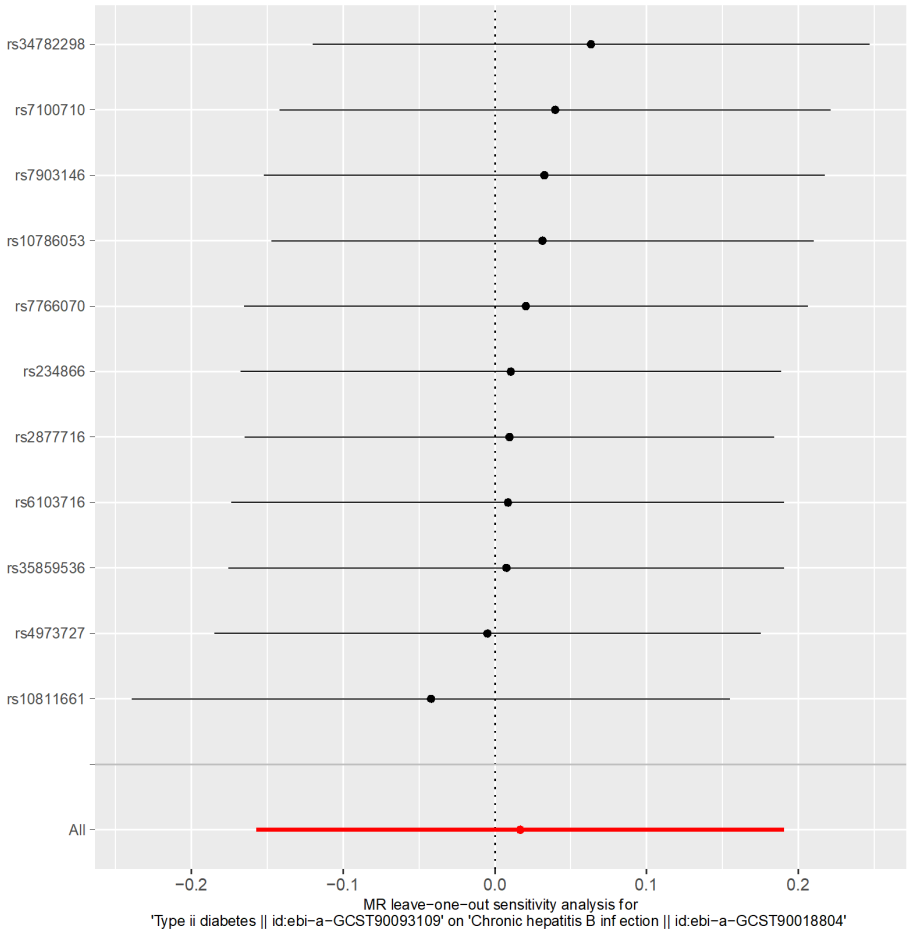
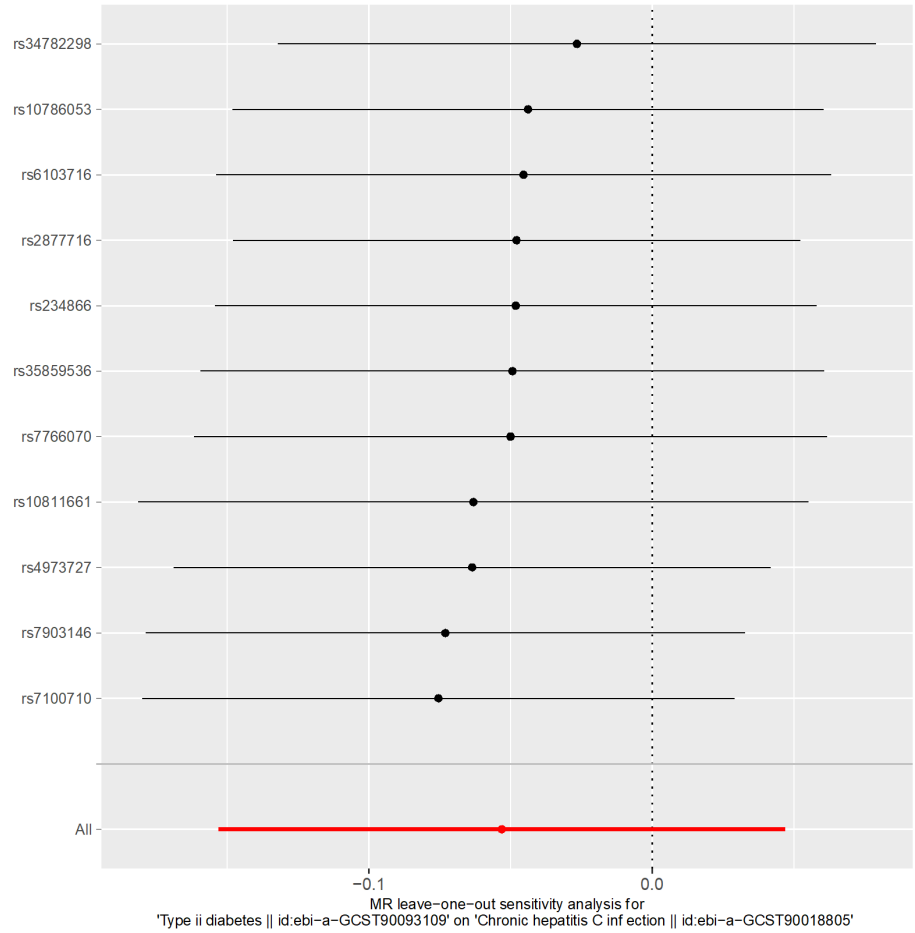


Figure 3 Funnel plot of the comorbidities. A and B: Type 2 diabetes mellitus; C and D: Hyperlipidemia; E and F: Hypertension affecting chronic hepatitis B infection (upper panel) and chronic hepatitis C infection (lower panel). MR: Mendelian randomization.

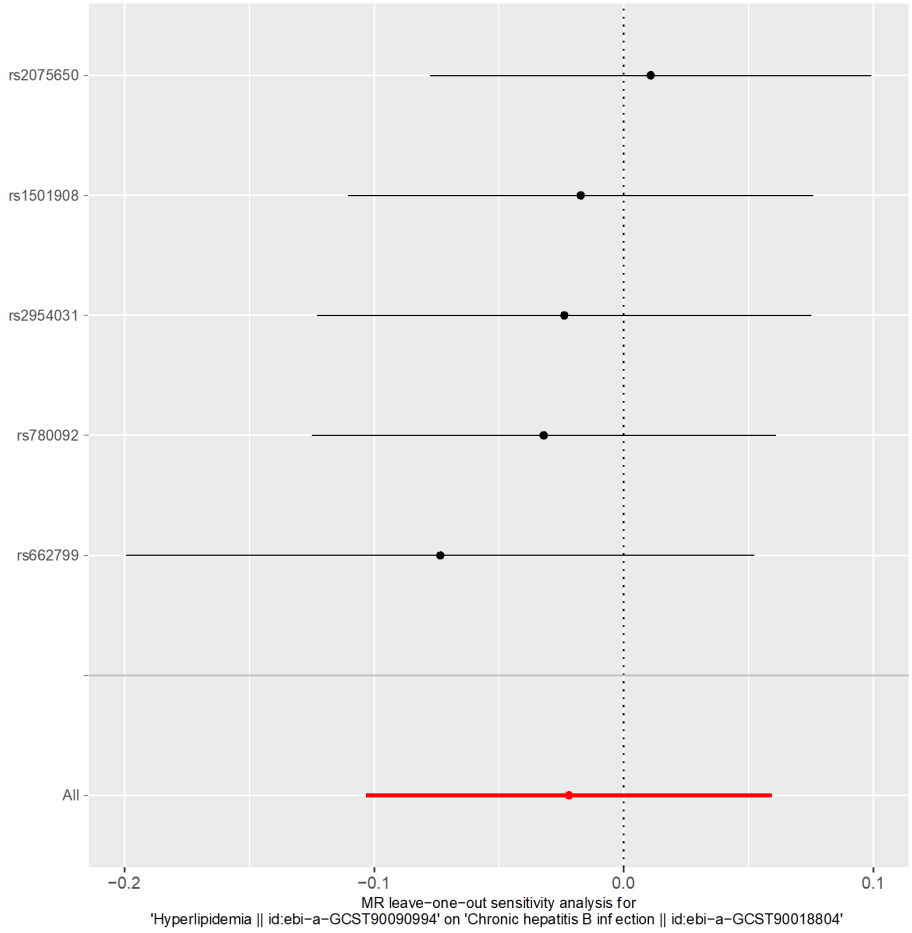
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MR leave−one−out sensitivity analysis for
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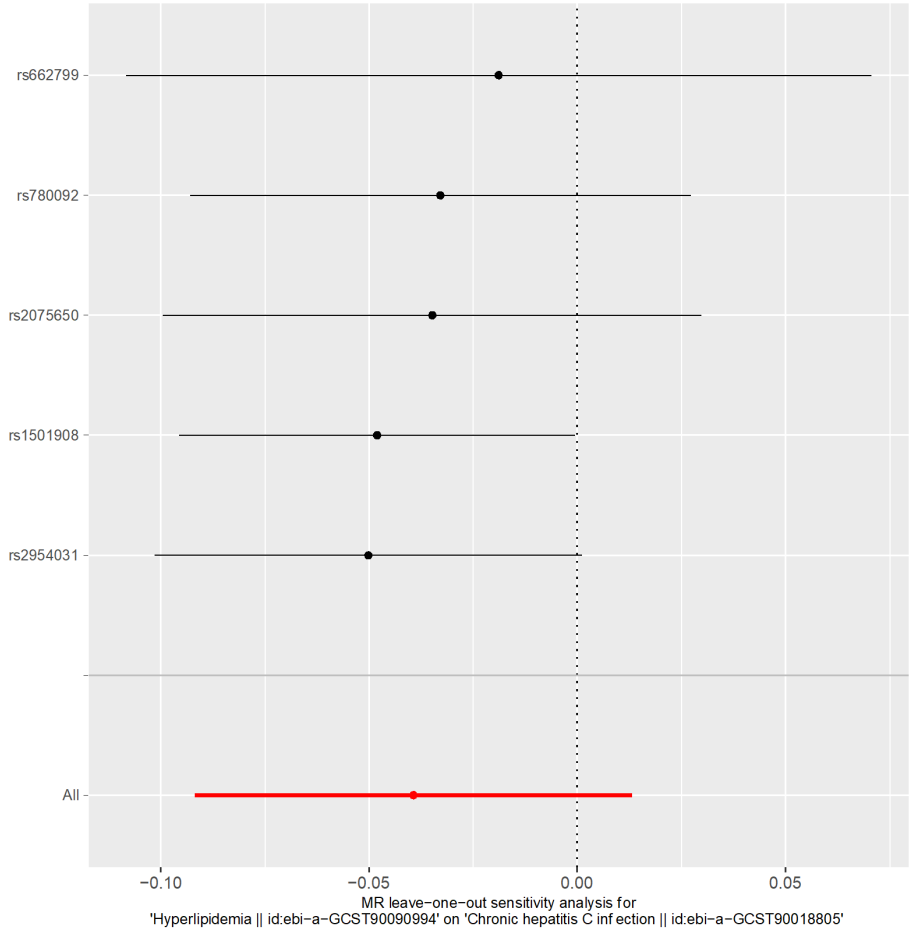
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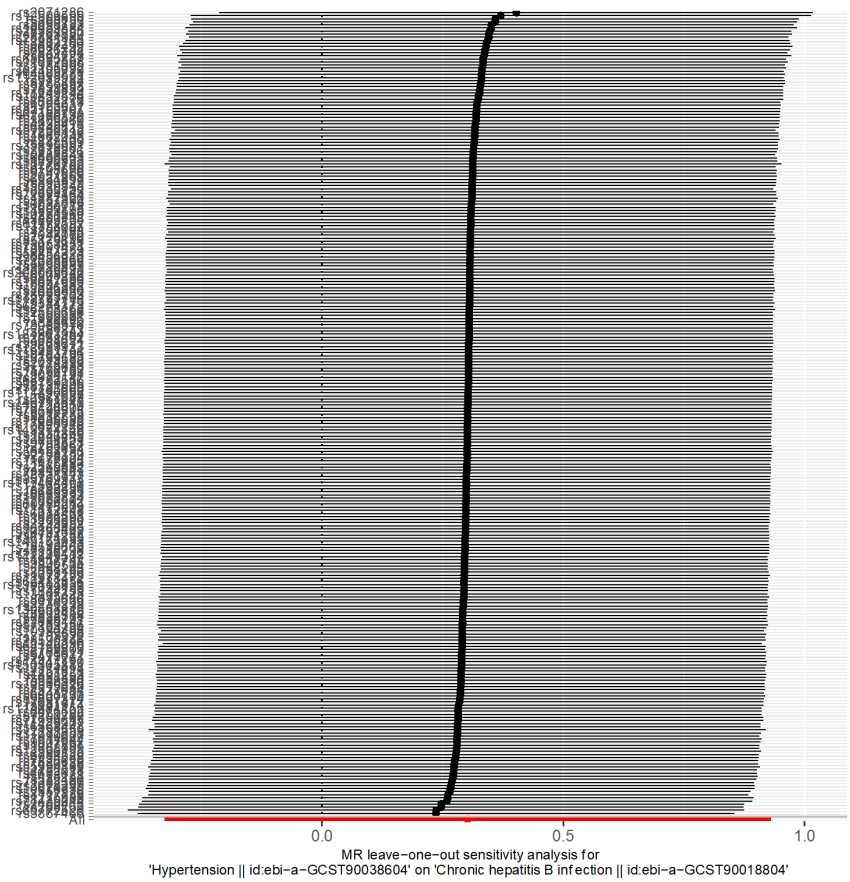
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F

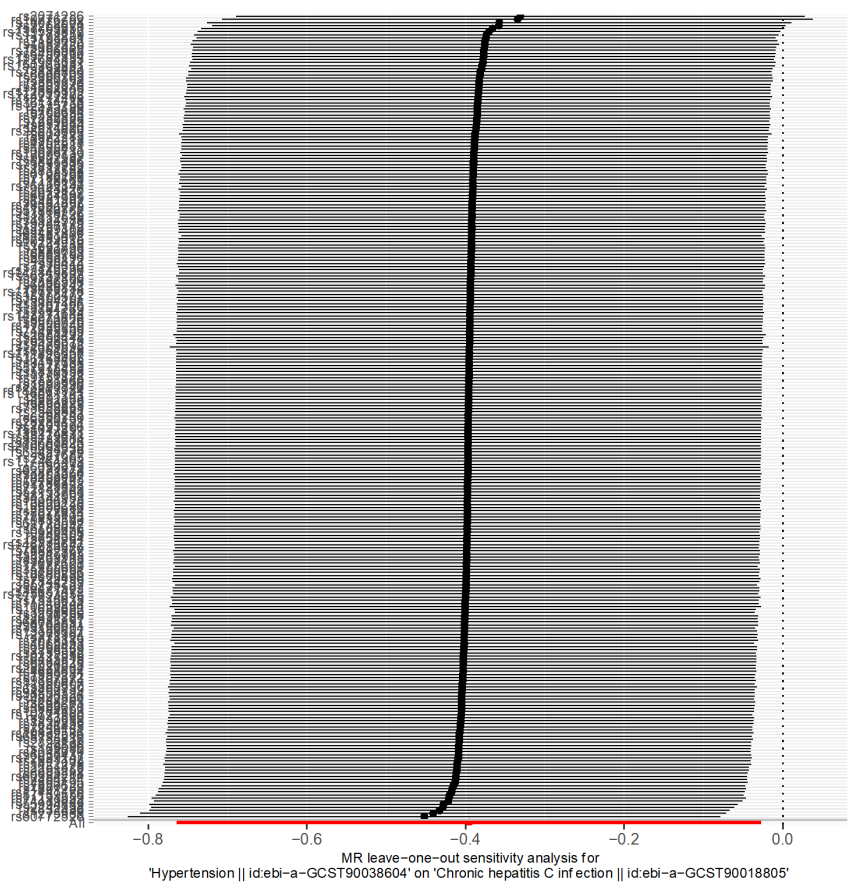


Figure 4 Leave one-out plot of the comorbidities. A and B: Type 2 diabetes mellitus; C and D: Hyperlipidemia; E and F: Hypertension affecting chronic hepatitis B infection (upper panel) and chronic hepatitis C infection (lower panel). MR: Mendelian randomization.

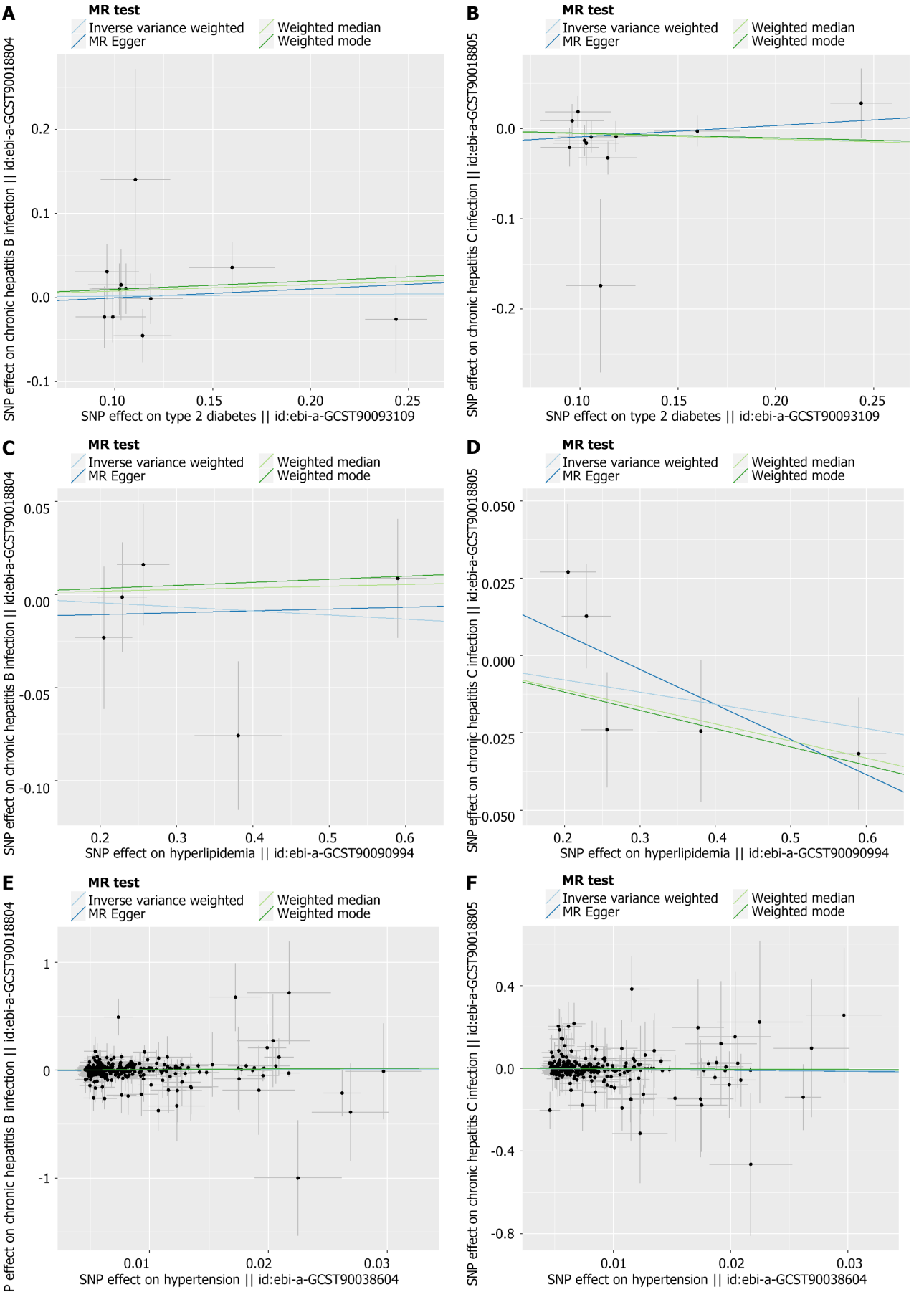


Figure 5 Scatter plot of the comorbidities. A and B: Type 2 diabetes mellitus; C and D: Hyperlipidemia; E and F: Hypertension affecting chronic hepatitis B infection (upper panel) and chronic hepatitis C infection (lower panel). MR: Mendelian randomization.

lipid and glucose metabolism, thus increasing the severity of the chronic hepatitis infection until non-alcoholic fatty liver disease (NAFLD) develops[21]. Multiple studies have revealed that parenteral viral hepatitis can affect insulin resistance in the body, thus increasing the severity of hepatitis progression in patients[22]. Hepatitis infection with comorbid T2D eventually progresses to NAFLD[21,23], hepatic steatosis[24], hepatocarcinoma, and fibrosis[25].

Hyperlipidemia is also a frequently observed comorbidity of chronic hepatitis infections in clinical practice[26]. According to a cohort study of 1927 patients from 2005 to 2015, hyperlipidemia was correlated with hepatitis progression into hepatocarcinoma without cirrhosis[27]. Meanwhile, a new type of HBV infection, occult HBV (HBV DNA-positive, but HBV surface antigen-negative), is more likely to occur in patients with hyperlipidemia[28]. The molecular mechanisms by which hyperlipidemia interacts with hepatitis remain unknown; however, an interesting phenomenon between hyperlipidemia and HBV infection has been reported. Statins, which were originally used to treat hyperlipidemia, have been widely used in clinical hepatitis treatment, and they could reduce the risks of progression to cirrhosis [29] and hepatocarcinoma[30,31].

Hypertension, which shares most instrumental SNPs with hepatitis, exhibits a strong association with hepatitis B and C infections. In clinical research, hypertension has been reported to be a risk factor for HCV patients with severe progression[32], and the overall effect in patients (*e.g.*, ascites) with both hypertension and HCV is dependent on the severity of liver damage[33]. However, if patients receive antihypertensive treatment, they present with a mild viral syndrome upon exposure to HBV infection[34]. Researchers have attempted to explain this relationship, and one recent finding is that among patients with hypertension, the estimated glomerular filtration rate (eGFR) is lower in patients with HCV than those without HCV infection[35]. eGFR and other pathways may link hepatitis progression to hypertension; however, further research is required to support this theory.

In our study, the randomization model was well defined for the exposures (T2D, hyperlipidemia, and hypertension) and outcomes (CHB and CHC) by two-sample MR analysis, and they showed capabilities for interaction with chronic hepatitis infection; however, this study lacks clinical experimental data and other supporting materials to strengthen this theory. However, this shortage does not hinder this finding from being further explored, and as the next step in continued research, in-depth research on both clinical and molecular levels will be conducted to determine the exact molecular mechanisms and pathology of this linkage.

CONCLUSION

The results of our MR support a possible causal relationship between different exposures (T2D, hyperlipidemia, and hypertension) and chronic hepatitis progression; however, the potential mechanisms still need to be elucidated, and more supported data should come together to support the theory that these common comorbidities will surely affect the clinical treatment of chronic hepatitis infections.

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FOOTNOTES

Author contributions: Su QL and Liang LB and Mao TR designed and performed the experiments; Liang LB and Liu XP provided support for data analysis and writing the manuscript; Su QL provided the supervision, resources, discussion, design and peer review process; all the authors have seen and approved the manuscript.

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REFERENCES

1 **World Health Organization**. Global hepatitis report 2017. Apr 19, 2017. [cited 30 April 2024]. Available from: https://www.who.int/publications/i/item/9789241565455

2 **Shin EC**, Sung PS, Park SH. Immune responses and immunopathology in acute and chronic viral hepatitis. *Nat Rev Immunol* 2016; **16**: 509-523 [PMID: 27374637 DOI: 10.1038/nri.2016.69]

3 **Ferri C**, Govoni M, Calabrese L. The A, B, Cs of viral hepatitis in the biologic era. *Curr Opin Rheumatol* 2010; **22**: 443-450 [PMID: 20386453 DOI: 10.1097/BOR.0b013e328338f6df]

4 **Sarin SK**, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, Chen DS, Chen HL, Chen PJ, Chien RN, Dokmeci AK, Gane E, Hou JL, Jafri W, Jia J, Kim JH, Lai CL, Lee HC, Lim SG, Liu CJ, Locarnini S, Al Mahtab M, Mohamed R, Omata M, Park J, Piratvisuth T, Sharma BC, Sollano J, Wang FS, Wei L, Yuen MF, Zheng SS, Kao JH. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016; **10**: 1-98 [PMID: 26563120 DOI: 10.1007/s12072-015-9675-4]

5 **Zhu JY**. Analysis of the correlation between CONUT score and hepatitis B cirrhosis. M.Sc. Thesis, Shandong University. 2023. Available from: https://kns.cnki.net/kcms2/article/abstract?v=BQVG6Ge829Y-qHI3Y5tUWGw8m9QqwGqqup_xu90qFn3ceRLdP2CUfKGZnQ7s_vjK9dWWGzOfnnAt6mVLuwZ34Qr4c1jgF_YpOfJpheuTFEjV7mh4XYXKwpjLnAanFjIIyY9mygto1_ykLHm3Ms9Cvw==&uniplatform=NZKPT&language=CHS

6 **Zhang H**, Tu T. Approaches to quantifying hepatitis B virus covalently closed circular DNA. *Clin Mol Hepatol* 2022; **28**: 135-149 [PMID: 34674513 DOI: 10.3350/cmh.2021.0283]

7 **Sagnelli E**, Stroffolini T, Mele A, Imparato M, Sagnelli C, Coppola N, Almasio PL. Impact of comorbidities on the severity of chronic hepatitis B at presentation. *World J Gastroenterol* 2012; **18**: 1616-1621 [PMID: 22529690 DOI: 10.3748/wjg.v18.i14.1616]

8 **Lee MH**, Yang HI, Lu SN, Jen CL, You SL, Wang LY, Wang CH, Chen WJ, Chen CJ; R. E.V.E.A.L.-HCV Study Group. Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. *J Infect Dis* 2012; **206**: 469-477 [PMID: 22811301 DOI: 10.1093/infdis/jis385]

9 **Ruzicka DJ**, Tetsuka J, Fujimoto G, Kanto T. Comorbidities and co-medications in populations with and without chronic hepatitis C virus infection in Japan between 2015 and 2016. *BMC Infect Dis* 2018; **18**: 237 [PMID: 29793436 DOI: 10.1186/s12879-018-3148-z]

10 **Hsu PY**, Wei YJ, Liang PC, Lee JJ, Niu SW, Huang JC, Hsu CT, Jang TY, Huang CI, Lin YH, Hsieh MY, Hsieh MH, Chen SC, Dai CY, Lin ZY, Huang JF, Chang JM, Yeh ML, Huang CF, Chiu YW, Hwang SJ, Chuang WL, Yu ML. Comorbidities in patients with chronic hepatitis C and hepatitis B on hemodialysis. *J Gastroenterol Hepatol* 2021; **36**: 2261-2269 [PMID: 33651428 DOI: 10.1111/jgh.15480]

11 **Hemani G**, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, Laurin C, Burgess S, Bowden J, Langdon R, Tan VY, Yarmolinsky J, Shihab HA, Timpson NJ, Evans DM, Relton C, Martin RM, Davey Smith G, Gaunt TR, Haycock PC. The MR-Base platform supports systematic causal inference across the human phenome. *Elife* 2018; **7** [PMID: 29846171 DOI: 10.7554/eLife.34408]

12 **Goto A**, Yamaji T, Sawada N, Momozawa Y, Kamatani Y, Kubo M, Shimazu T, Inoue M, Noda M, Tsugane S, Iwasaki M. Diabetes and cancer risk: A Mendelian randomization study. *Int J Cancer* 2020; **146**: 712-719 [PMID: 30927373 DOI: 10.1002/ijc.32310]

13 **Hartwig FP**, Borges MC, Horta BL, Bowden J, Davey Smith G. Inflammatory Biomarkers and Risk of Schizophrenia: A 2-Sample Mendelian Randomization Study. *JAMA Psychiatry* 2017; **74**: 1226-1233 [PMID: 29094161 DOI: 10.1001/jamapsychiatry.2017.3191]

14 **Lee K**, Lim CY. Mendelian Randomization Analysis in Observational Epidemiology. *J Lipid Atheroscler* 2019; **8**: 67-77 [PMID: 32821701 DOI: 10.12997/jla.2019.8.2.67]

15 **Kurki MI**, Karjalainen J, Palta P, Sipilä TP, Kristiansson K, Donner KM, Reeve MP, Laivuori H, Aavikko M, Kaunisto MA, Loukola A, Lahtela E, Mattsson H, Laiho P, Della Briotta Parolo P, Lehisto AA, Kanai M, Mars N, Rämö J, Kiiskinen T, Heyne HO, Veerapen K, Rüeger S, Lemmelä S, Zhou W, Ruotsalainen S, Pärn K, Hiekkalinna T, Koskelainen S, Paajanen T, Llorens V, Gracia-Tabuenca J, Siirtola H, Reis K, Elnahas AG, Sun B, Foley CN, Aalto-Setälä K, Alasoo K, Arvas M, Auro K, Biswas S, Bizaki-Vallaskangas A, Carpen O, Chen CY, Dada OA, Ding Z, Ehm MG, Eklund K, Färkkilä M, Finucane H, Ganna A, Ghazal A, Graham RR, Green EM, Hakanen A, Hautalahti M, Hedman ÅK, Hiltunen M, Hinttala R, Hovatta I, Hu X, Huertas-Vazquez A, Huilaja L, Hunkapiller J, Jacob H, Jensen JN, Joensuu H, John S, Julkunen V, Jung M, Junttila J, Kaarniranta K, Kähönen M, Kajanne R, Kallio L, Kälviäinen R, Kaprio J; FinnGen, Kerimov N, Kettunen J, Kilpeläinen E, Kilpi T, Klinger K, Kosma VM, Kuopio T, Kurra V, Laisk T, Laukkanen J, Lawless N, Liu A, Longerich S, Mägi R, Mäkelä J, Mäkitie A, Malarstig A, Mannermaa A, Maranville J, Matakidou A, Meretoja T, Mozaffari SV, Niemi MEK, Niemi M, Niiranen T, O Donnell CJ, Obeidat ME, Okafo G, Ollila HM, Palomäki A, Palotie T, Partanen J, Paul DS, Pelkonen M, Pendergrass RK, Petrovski S, Pitkäranta A, Platt A, Pulford D, Punkka E, Pussinen P, Raghavan N, Rahimov F, Rajpal D, Renaud NA, Riley-Gillis B, Rodosthenous R, Saarentaus E, Salminen A, Salminen E, Salomaa V, Schleutker J, Serpi R, Shen HY, Siegel R, Silander K, Siltanen S, Soini S, Soininen H, Sul JH, Tachmazidou I, Tasanen K, Tienari P, Toppila-Salmi S, Tukiainen T, Tuomi T, Turunen JA, Ulirsch JC, Vaura F, Virolainen P, Waring J, Waterworth D, Yang R, Nelis M, Reigo A, Metspalu A, Milani L, Esko T, Fox C, Havulinna AS, Perola M, Ripatti S, Jalanko A, Laitinen T, Mäkelä TP, Plenge R, McCarthy M, Runz H, Daly MJ, Palotie A. FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature* 2023; **613**: 508-518 [PMID: 36653562 DOI: 10.1038/s41586-022-05473-8]

16 **Nettleton S**. The sociology of health and illness. [cited 30 April 2024]. Available from: https://www.wiley.com/en-us/The+Sociology+of+Health+and+Illness%2C+4th+Edition-p-9781509512737

17 **Naing C**, Mak JW, Ahmed SI, Maung M. Relationship between hepatitis C virus infection and type 2 diabetes mellitus: meta-analysis. *World J Gastroenterol* 2012; **18**: 1642-1651 [PMID: 22529694 DOI: 10.3748/wjg.v18.i14.1642]

18 **Allison ME**, Wreghitt T, Palmer CR, Alexander GJ. Evidence for a link between hepatitis C virus infection and diabetes mellitus in a cirrhotic population. *J Hepatol* 1994; **21**: 1135-1139 [PMID: 7699240 DOI: 10.1016/S0168-8278(05)80631-2]

19 **Negro F**, Alaei M. Hepatitis C virus and type 2 diabetes. *World J Gastroenterol* 2009; **15**: 1537-1547 [PMID: 19340895 DOI: 10.3748/wjg.15.1537]

20 **Tan Y**, Wei S, Zhang W, Yang J, Yan L. Type 2 diabetes mellitus increases the risk of hepatocellular carcinoma in subjects with chronic hepatitis B virus infection: a meta-analysis and systematic review. *Cancer Manag Res* 2019; **11**: 705-713 [PMID: 30679924 DOI: 10.2147/CMAR.S188238]

21 **Han W**, Huang C, Ji Y, Zhou L, Chen J, Hou J. Alterations in the Gut Microbiota and Hepatitis-B-Virus Infection in Southern Chinese Patients With Coexisting Non-Alcoholic Fatty Liver Disease and Type-2 Diabetes Mellitus. *Front Med (Lausanne)* 2021; **8**: 805029 [PMID: 34993216 DOI: 10.3389/fmed.2021.805029]

22 **Merza MA**. Seroprevalence and risk factors of hepatitis B and C viruses among diabetes mellitus patients in Duhok province, Iraqi Kurdistan.

J Family Med Prim Care 2020; **9**: 642-646 [PMID: 32318396 DOI: 10.4103/jfmpc.jfmpc_1158_19]

23 **Zhu L**, Jiang J, Zhai X, Baecker A, Peng H, Qian J, Zhou M, Song C, Zhou Y, Xu J, Liu H, Hang D, Hu Z, Shen H, Zhang ZF, Zhu F. Hepatitis B virus infection and risk of non-alcoholic fatty liver disease: A population-based cohort study. *Liver Int* 2019; **39**: 70-80 [PMID: 30025200 DOI: 10.1111/liv.13933]

24 **Yu MW**, Lin CL, Liu CJ, Huang YW, Hu JT, Wu WJ, Wu CF. Hepatic steatosis and development of type 2 diabetes: Impact of chronic hepatitis B and viral specific factors. *J Formos Med Assoc* 2022; **121**: 1478-1487 [PMID: 34764005 DOI: 10.1016/j.jfma.2021.10.014]

25 **Mak LY**, Hui RW, Lee CH, Mao X, Cheung KS, Wong DK, Lui DT, Fung J, Yuen MF, Seto WK. Glycemic burden and the risk of adverse hepatic outcomes in patients with chronic hepatitis B with type 2 diabetes. *Hepatology* 2023; **77**: 606-618 [PMID: 36130882 DOI: 10.1002/hep.32716]

26 **Wang X**, Xie Q. Metabolic Dysfunction-associated Fatty Liver Disease (MAFLD) and Viral Hepatitis. *J Clin Transl Hepatol* 2022; **10**: 128-133 [PMID: 35233381 DOI: 10.14218/JCTH.2021.00200]

27 **Phan J**, Ng V, Sheinbaum A, French S, Choi G, El Kabany M, Durazo F, Saab S, Tong M, Busuttil R, Han SH. Hyperlipidemia and Nonalcoholic Steatohepatitis Predispose to Hepatocellular Carcinoma Development Without Cirrhosis. *J Clin Gastroenterol* 2019; **53**: 309-313 [PMID: 29912756 DOI: 10.1097/MCG.0000000000001062]

28 **Yang L**, Li T, Li W, Tang X, Li J, Long R, Fu Y, Allain JP, Li C. Occult Hepatitis B Virus Infection in Hyperlipidemia Patients. *Tohoku J Exp Med* 2017; **241**: 255-261 [PMID: 28381700 DOI: 10.1620/tjem.241.255]

29 **Chang FM**, Wang YP, Lang HC, Tsai CF, Hou MC, Lee FY, Lu CL. Statins decrease the risk of decompensation in hepatitis B virus- and hepatitis C virus-related cirrhosis: A population-based study. *Hepatology* 2017; **66**: 896-907 [PMID: 28318053 DOI: 10.1002/hep.29172]

30 **Goh MJ**, Sinn DH, Kim S, Woo SY, Cho H, Kang W, Gwak GY, Paik YH, Choi MS, Lee JH, Koh KC, Paik SW. Statin Use and the Risk of Hepatocellular Carcinoma in Patients With Chronic Hepatitis B. *Hepatology* 2020; **71**: 2023-2032 [PMID: 31556128 DOI: 10.1002/hep.30973]

31 **Simon TG**, Duberg AS, Aleman S, Hagstrom H, Nguyen LH, Khalili H, Chung RT, Ludvigsson JF. Lipophilic Statins and Risk for Hepatocellular Carcinoma and Death in Patients With Chronic Viral Hepatitis: Results From a Nationwide Swedish Population. *Ann Intern Med* 2019; **171**: 318-327 [PMID: 31426090 DOI: 10.7326/M18-2753]

32 **Fujinaga K**, Usui M, Yamamoto N, Ishikawa E, Nakatani A, Kishiwada M, Mizuno S, Sakurai H, Tabata M, Isaji S. Hypertension and hepatitis C virus infection are strong risk factors for developing late renal dysfunction after living donor liver transplantation: significance of renal biopsy. *Transplant Proc* 2014; **46**: 804-810 [PMID: 24767353 DOI: 10.1016/j.transproceed.2013.11.103]

33 **Valla D**, Flejou JF, Lebrec D, Bernuau J, Rueff B, Salzmann JL, Benhamou JP. Portal hypertension and ascites in acute hepatitis: clinical, hemodynamic and histological correlations. *Hepatology* 1989; **10**: 482-487 [PMID: 2777210 DOI: 10.1002/hep.1840100414]

34 **Parrilli G**, Manguso F, Orsini L, Coccoli P, Vecchione R, Terracciano L, De Luca N, Cirillo N, Abazia C, Budillon G, Marchesini G. Essential hypertension and chronic viral hepatitis. *Dig Liver Dis* 2007; **39**: 466-472 [PMID: 17369113 DOI: 10.1016/j.dld.2007.01.009]

35 **Gantumur G**, Batsaikhan B, Huang CI, Yeh ML, Huang CF, Lin YH, Lin TC, Liang PC, Liu TW, Lee JJ, Lin YC, Lin IL, Huang JF, Chuang WL, Yu ML, Tu HP, Dai CY. The association between hepatitis C virus infection and renal function. *J Chin Med Assoc* 2021; **84**: 757-765 [PMID: 34074934 DOI: 10.1097/JCMA.0000000000000561]

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ORIGINAL ARTICLE

Clinical and Translational Research

Analysis of cancer-specific survival in patients with metastatic colorectal cancer: A evidence-based medicine study

Yin-Jie Zhou, Zhi-E Tan, Wei-Da Zhuang, Xin-Hua Xu

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Abstract

BACKGROUND

Metastatic colorectal cancer (mCRC) is a common malignancy whose treatment has been a clinical challenge. Cancer-specific survival (CSS) plays a crucial role in assessing patient prognosis and treatment outcomes. However, there is still limited research on the factors affecting CSS in mCRC patients and their correlation.

AIM

To predict CSS, we developed a new nomogram model and risk grading system to classify risk levels in patients with mCRC.

METHODS

Data were extracted from the United States Surveillance, Epidemiology, and End Results database from 2018 to 2023. All eligible patients were randomly divided into a training cohort and a validation cohort. The Cox proportional hazards model was used to investigate the independent risk factors for CSS. A new nomogram model was developed to predict CSS and was evaluated through internal and external validation.

RESULTS

A multivariate Cox proportional risk model was used to identify independent risk

factors for CSS. Then, new CSS columns were developed based on these factors. The consistency index (C-index) of the histogram was 0.718 (95%CI: 0.712-0.725), and that of the validation cohort was 0.722 (95%CI: 0.711-0.732), indicating good discrimination ability and better performance than tumor-node-metastasis staging (C-index: 0.712-0.732). For the training set, 0.533, 95%CI: 0.525-0.540; for the verification set, 0.524, 95%CI: 0.513-0.535. The calibration map and clinical decision curve showed good agreement and good potential clinical validity. The risk grading system divided all patients into three groups, and the Kaplan-Meier curve showed good stratification and differentiation of CSS between different groups. The median CSS times in the low-risk, medium-risk, and high-risk groups were 36 months (95%CI: 34.987-37.013), 18 months (95%CI: 17.273-18.727), and 5 months (95%CI: 4.503-5.497), respectively.

CONCLUSION

Our study developed a new nomogram model to predict CSS in patients with synchronous mCRC. In addition, the risk-grading system helps to accurately assess patient prognosis and guide treatment.

Key Words: Colorectal tumor; Surveillance epidemiology and end results database; Nomogram analysis; Survival prognosis; Retrospective study

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Core Tip: This study utilized an evidence-based approach to analyze cancer-specific survival (CSS) in patients with metastatic colorectal cancer (mCRC). By systematically collecting, integrating, and analyzing relevant data, we explored CSS in mCRC patients and its influencing factors to provide clinicians with more accurate prognostic assessments and treatment decision support. The importance of this study is that it can provide a basis for individualized treatment of mCRC patients and promote the maximization of treatment effects, thereby improving the quality of life and survival rate of patients.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignant neoplasms, ranking third in incidence (10.2%) and second in mortality (9.2%)[1-3]. In countries in Eastern Europe, Latin America, and Asia, the incidence and mortality of CRC are increasing annually[4]. There are no obvious signs or symptoms of CRC in the early stages, and more than one-fifth of patients have developed distant metastases at the time of diagnosis[5]. Among patients with CRC, patients with simultaneous metastases have lower survival rates than patients with heterochronous metastases[6]. The most common metastatic organs for CRC are the liver and lung, while bone metastases are rare, and brain metastases occur in only 1% of CRC patients[7]. Although metastatic CRC (mCRC) has the worst prognosis, there are large differences in survival outcomes between patients with different metastatic organs. The 1-year survival rate for patients with liver and lung metastases is greater than 80%, while the 1-year survival rates for patients with bone and brain metastases are 30% and 11%, respectively[8]. Therefore, accurate screening for different risk factors is critical for physicians to predict mCRC outcomes.

Currently, the American Joint Committee on Cancer (AJCC) staging system is the primary method for predicting survival outcomes in patients with mCRC[9]. However, the T stage, N stage, and M stage are the only factors for distinguishing different prognoses, and this scheme is far from satisfactory in terms of prediction accuracy[10]. A nomogram is a visual tool used to predict the probability of an endpoint occurring and to quantify survival risk. According to the different regression coefficients, the columniogram can include significant factors to improve the prediction accuracy. To date, nomograms have been successfully used to predict the prognosis of patients with CRC but have rarely been used for patients with mCRC[11].

Therefore, our goal was to develop a new nomographic model to predict tumor-specific survival for patients with simultaneous mCRC and to divide this model into different risk levels to accurately assess patient prognosis.

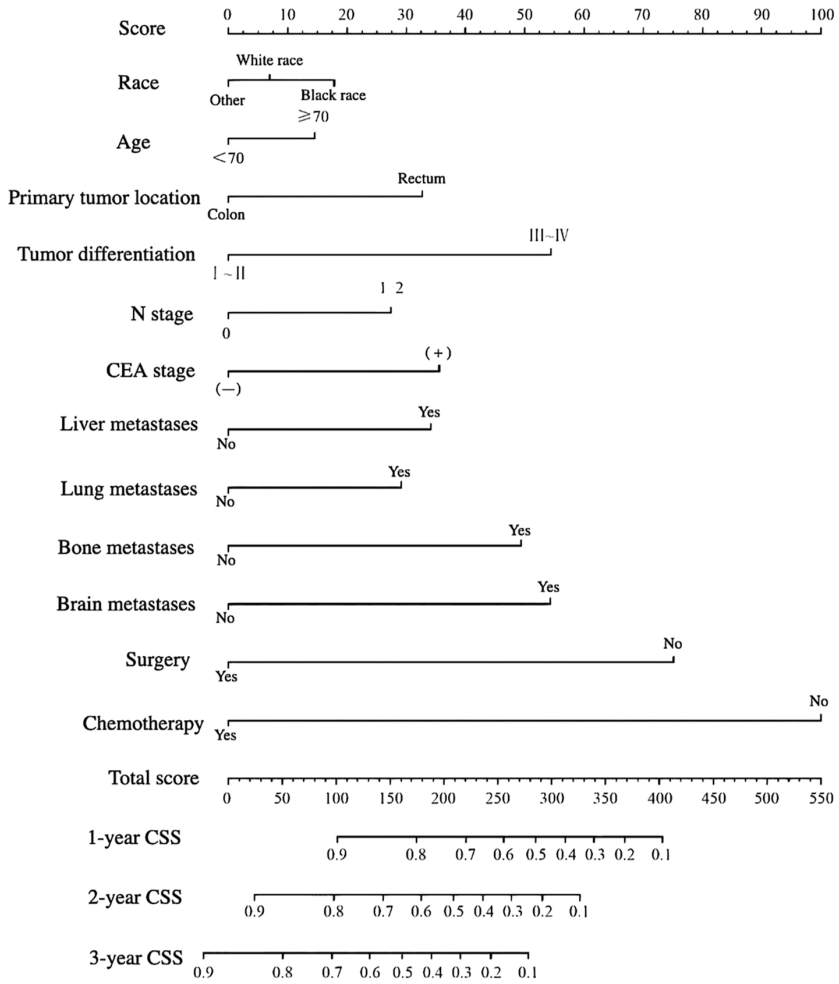


Figure 1 Nomogram for predicting the tumor-specific survival of patients with metastatic colorectal cancer. CEA: Carcinoembryonic antigen; CSS: Cancer-specific survival.

MATERIALS AND METHODS

Research subjects

This study obtained all the data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute using SEER Stat software (version 8.3.6). The data were collected and reported using data items and codes recorded by the North American Association of Central Cancer Registries. The inclusion criteria for patients were as follows: (1) Were diagnosed with CRC between 2018 and 2023; (2) were diagnosed with simultaneous metastasis; and (3) had a histological diagnosis. The exclusion criteria were as follows: (1) No patients with distant metastasis; and (2) unknown missing data, such as race, primary tumor site, T stage, N stage, carcinoembryonic antigen (CEA) status, surgical status, and survival time.

The following variables were collected: Race, sex, age at diagnosis, primary site, grade, T stage, N stage, CEA status, distant metastatic status (liver, lung, bone, brain), surgery (primary tumor resection), chemotherapy, cancer-specific survival (CSS), and survival time. CSS was assessed by 1-, 2-, and 3-year survival rates, defined as the time from the date of diagnosis to the date of death or study due to CRC, according to the eighth edition of the AJCC tumor-node-metastasis staging system.

Research method

All eligible patients were randomly divided into training and validation groups (at a ratio of 7:3). The Pearson chi-square test was used to examine demographic differences between all coqueues, training coqueues, and validation coqueues. A multivariate Cox proportional risk model was used to explore independent risk factors for CSS, and a predictive nomogram model was built using a training cohort. The C-index, calibration curve, and decision curve analysis (DCA) were used for internal and external verification.

Nomogram analysis

X-tile software was used to determine the optimal critical value according to the total score of the column graph to establish a risk grading system, and all patients were divided into low-, medium-, and high-risk groups. Kaplan-Meier (K-M) curves of CSS were constructed and compared with a logarithmic rank test. Statistical analysis was performed

Table 1 Demographic characteristics, *n* (%)

Variable	Total cohort (*n* = 15838)	Training cohort (*n* = 11088)	Validation cohort (*n* = 4750)	χ^2	*P* value
Race				1.36	0.507
Black people	2303 (14.5)	1590 (14.3)	713 (15.0)		
White race	12075 (76.2)	8480 (76.5)	3595 (75.7)		
Other	1460 (9.2)	1018 (9.2)	442 (9.3)		
Sex				0.027	0.869
Male	8560 (54.0)	5988 (54.0)	2572 (54.1)		
Female	7278 (46.0)	5100 (46.0)	2178 (45.9)		
Age at diagnosis (yr)				1.73	0.188
< 70	10 735 (67.8)	7480 (67.5)	3255 (68.5)		
≥ 70	5103 (32.2)	3608 (32.5)	1495 (31.5)		
Primary tumor location				0.264	0.607
Colon	7063 (44.6)	4930 (44.5)	2133 (44.9)		
Rectum	8775 (55.4)	6158 (55.5)	2617 (55.1)		
Tumor differentiation				0.014	0.906
I-II	11127 (70.3)	7793 (70.3)	3334 (70.2)		
III-IV	4711 (29.7)	3295 (29.7)	1416 (29.8)		
T staging				0.08	0.777
1-2	2079 (13.1)	1461 (13.2)	618 (13.0)		
3-4	13759 (86.9)	9627 (86.8)	4132 (87.0)		
N stage				0.576	0.448
0	4209 (26.6)	2966 (26.7)	1243 (26.2)		
1-2	11629 (73.4)	8122 (73.3)	3507 (73.8)		
CEA status				2.721	0.099
Masculine	12378 (78.2)	8705 (78.5)	3673 (77.3)		
Feminine	3460 (21.8)	2383 (21.5)	1077 (22.7)		
Liver metastases				0.286	0.593
No	4731 (29.9)	3298 (29.7)	1433 (30.2)		
Yes	11107 (70.1)	7790 (70.3)	3317 (69.8)		
Lung metastases				2.202	0.138
No	12673 (80.0)	8838 (79.7)	3835 (80.7)		
Yes	3165 (20.0)	2250 (20.3)	915 (19.3)		
Bone metastases				0.724	0.395
No	15226 (96.1)	10669 (96.2)	4557 (95.9)		
Yes	612 (3.9)	419 (3.8)	193 (4.1)		
Brain metastases				1.032	0.31
No	15682 (99.0)	10973 (99.0)	4709 (99.1)		
Yes	156 (1.0)	115 (1.0)	41 (0.9)		
Surgical				0.014	0.906
No	3495 (22.1)	2444 (22.0)	1051 (22.1)		
Yes	12343 (77.9)	8644 (78.0)	3699 (77.9)		
Chemotherapy				0.026	0.872

None/unknown	4235 (26.7)	2969 (26.8)	1266 (26.7)
Yes	11603 (73.3)	8119 (73.2)	3484 (73.3)

CEA: Carcinoembryonic antigen.

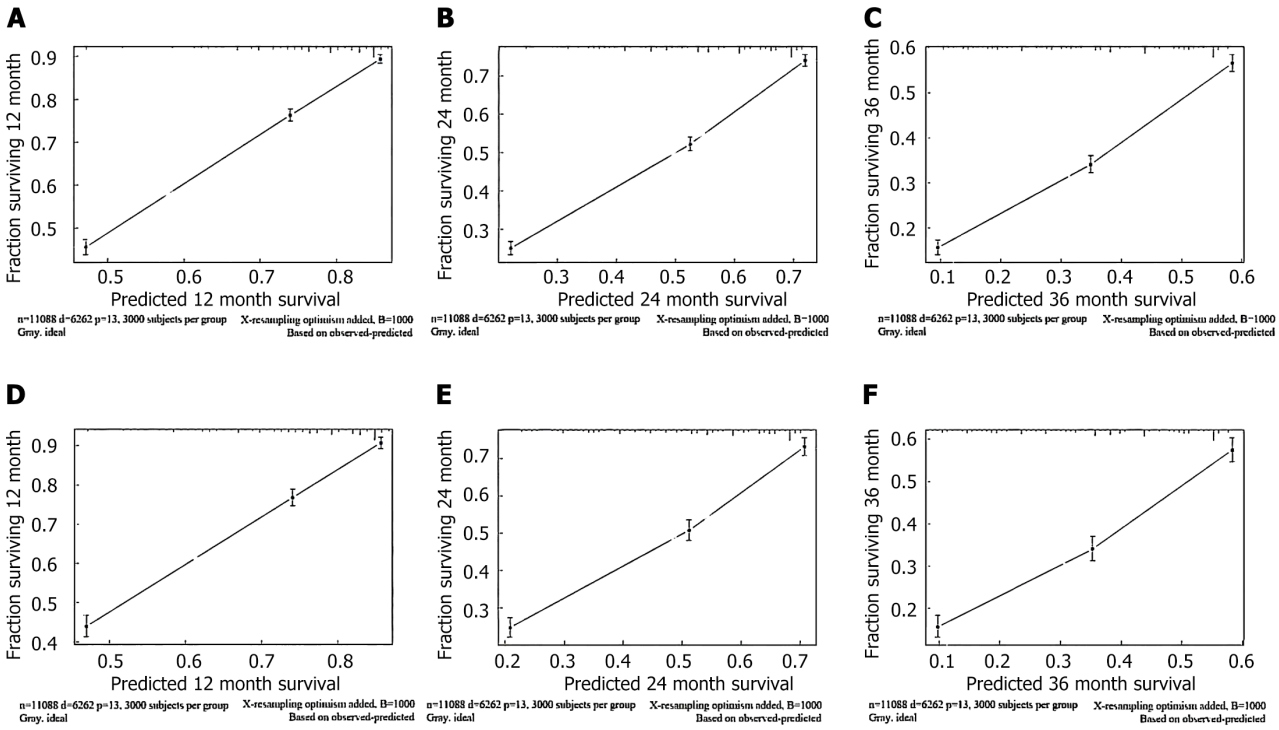


Figure 2 Calibration curves based on cancer-specific survival for metastatic colorectal cancer patients. A-C: Calibration curves based on 1-, 2-, and 3-year cancer-specific survival (CSS) of the training cohort; D-F: Calibration curves based on 1-, 2-, and 3-year CSS of the validation cohort.

using SPSS 21.0 statistical software (IBM SPSS Statistics for Windows; Armonk, NY, United States), GraphPad Prism 6 (GraphPad Software), X-Tile software (Yale University), and R Statistical Software 3.6.2 (www.r-project.org/).

Statistical analysis

SPSS 23.0 statistical software was used for analysis. The χ^2 test was used for comparison of counting data, and the t test was used for comparison of measurement data. The survival rate was calculated by the life table method, the survival curve was plotted by the K-M method, and comparisons were performed by the log-rank method. Multiple factor analysis was performed by the Cox proportional risk regression model, and $P < 0.050$ was considered to indicate statistical significance.

RESULTS

Baseline population information

According to the inclusion criteria, a total of 15838 patients eligible for inclusion were included in this study, among whom 11088 (70.0%) patients were randomly assigned to the training cohort and 4750 (30.0%) patients were randomly assigned to the verification cohort. The demographic characteristics of this study population are shown in Table 1.

In this study, there were 8560 males (54.0%) and 7278 females (46.0%), of which the majority were white (76.2%), 13759 (86.9%) were T3-4, 11629 (73.4%) were N1-2, and CEA was positive (78.2%). The incidence of distant metastasis in the liver, lung, bone, and brain was 11107 (70.1%), 3165 (20.0%), 612 (3.9%), and 156 (1.0%), respectively. A total of 12343 patients (77.9%) received surgery, and 11603 patients (73.3%) received chemotherapy. There was no significant difference between the training cohort and the verification cohort ($P > 0.05$).

Prediction factor determination

The Cox proportional hazards model was used to identify independent risk factors for CSS. Multivariate analysis revealed that the independent risk factors in the training cohort were race, age at diagnosis, primary site, tumor grade, N stage, CEA status, liver metastasis, lung metastasis, bone metastasis, brain metastasis, surgery, and chemotherapy

(Table 2).

Based on the significant risk factors for CSS, a predictive nomogram model of CSS was established (Figure 1). The regression coefficients and estimates of the training queue are shown in Table 3. The nomogram was evaluated with internal and external validation. The C-index of the column chart was 0.718 (95%CI: 0.712-0.725), and the C-finger number of the verification set was 0.722 (95%CI: 0.711-0.732), indicating good identification ability and better performance than TNM staging (C-index: Training set, 0.533, 95%CI: 0.525-0.540; verification set, 0.524, 95%CI: 0.513-0.535). A calibration diagram of the CSS showed good agreement between the predicted and actual values of the training and validation samples, with 1000 bootstrap samples (Figure 2). The DCA curve showed a large net gain between most threshold probabilities at different time points, indicating good potential clinical validity for predicting CSS (Figure 3).

Establishment of the risk classification system

In addition, X-Tile software was used to determine the optimal cutoff value and establish a risk classification system (Figure 4). All patients were classified as low risk (5852/11088, 52.78%, score: 0-164), medium risk (3487/11088, 31.45%, score: 165-247) or high risk (1749/11088, 15.77%, score: 248-524). In theory, the total score ranges from 0 to 524. K-M curves showed that the risk grading system had good layering and differentiation ability for different CSS groups (Table 4, Figure 5).

DISCUSSION

The prognosis of mCRC patients is significantly worse than that of non-mCRC patients. mCRC mortality varies widely from patient to patient, suggesting the importance and necessity of reclassifying the exact risk level based on the AJCC staging system[12-14]. However, due to the limitations of the included factors, the existing prediction models lack individualization and comprehensive evaluation, and the sample sizes of most studies[15-17] are small, which also limits their universal applicability. In this study, we developed a new CSS predictive nomogram based on simultaneous mCRC data from large population cohorts.

We identified predictors of CSS that were consistent with previous studies, including race, age at diagnosis, primary site, grade, N stage, CEA status, liver metastasis, lung metastasis, bone metastasis, brain metastasis, surgery, and chemotherapy[18]. For patients with mCRC, both surgery and chemotherapy are important for improving outcomes, as recommended by the United States National Comprehensive Cancer Network (NCCN) guidelines and the European Society of Medical Oncology guidelines[19]. Modest suggested that the effective rate of first-line systemic treatment is 38% to 65%, and the disease control rate is 81% to 90%[20]. Compared to earlier studies, this column chart is the first to include chemotherapy status as a risk predictor for predicting CSS. The highest score of mCRC patients who did not receive chemotherapy was 100, which was greater than that of mCRC patients who did not receive surgery, indicating that the regression coefficient of the effect of chemotherapy on CSS was greater than that of surgery[21-23]. In addition, patients who did not receive chemotherapy or who did not receive chemotherapy were not separately recorded in the SEER database as confounding risk factors in this study, which may reduce the actual regression coefficient of not receiving chemotherapy[24-26]. According to previous studies[27-29], chemotherapy is positively associated with survival benefits in patients with mCRC, and our study further highlights the unique advantages of simultaneous mCRC chemotherapy.

In addition to chemotherapy, our study revealed that primary tumor resection is also important for prognosis. Several studies[30-32] support this idea in mCRC, especially in patients with liver or lung metastases. The NCCN guidelines recommend that patients with mCRC should be evaluated by a multidisciplinary team and, if possible, that the metastatic disease and primary tumor should be removed. Therefore, primary tumor resection remains controversial for mCRC patients whose metastases cannot be resected. Studies[33-35] have shown that primary tumor resection significantly extends overall survival (OS) in mCRC patients with unresectable metastases (median OS: 13.8 months *vs* 6.3 months, $P = 0.0001$). Another study[36] also supported the idea that primary tumor removal resulted in better survival for mCRC patients with unresectable metastases (2-year CSS: 50.2% *vs* 28.1%, $P < 0.001$). In conclusion, primary tumor resection has a positive impact on patient survival. As mentioned above, the liver and lungs are the most common sites of CRC metastasis, and bone and brain metastases are very rare. In addition, the prognostic significance of different metastatic organs was inconsistent. The occurrence of brain metastases is often associated with the worst survival, and studies[37-39] have reported that the median survival of CRC patients with brain metastases is 3 to 6 months, that of CRC patients with bone metastases is 5 to 7 months, that of CRC patients with liver metastases is 22.8 months, and that of CRC patients with lung metastases is 36.2 to 49 months. Another study confirmed this idea, with brain metastases having the largest coefficient of impact among the four metastatic organs of CRC. Our study showed that the regression coefficients of CSS in descending order were brain metastasis, bone metastasis, liver metastasis, and lung metastasis. Due to the presence of the blood-brain barrier (BBB) and blood–cerebrospinal fluid barrier (CSF), brain metastases are often the ultimate organs of metastasis for CRC, while other extracranial metastases occur in areas such as the liver and lungs. The BBB and CSF also hinder chemotherapy efficacy, which may be another reason for the poor prognosis.

On the basis of multiple regression analysis, we developed a new nomograph to integrate multiple predictors and help accurately predict the survival of patients with synchronous mCRC. One study constructed a nomogram for predicting the survival of CRC patients. Another study also developed an OS nomogram model for predicting mCRC with strong consistency. Compared to existing predictive models, our column charts integrate more predictive variables, such as chemotherapy and surgery, to provide comprehensive predictions for CSS. In addition, through X-Tile software, we established a risk classification system with an optimal cutoff value that is more accurate and reliable. This approach

Table 2 Multivariate analysis of COX based on training cohorts

Variable	Multivariate analysis	
	HR (95%CI)	*P* value
Race		
Black people	1	
White race	0.894 (0.834-0.959)	0.002
Other	0.835 (0.752-0.928)	0.001
Sex		
Male	1	
Female	0.965 (0.918-1.015)	0.17
Age at diagnosis (yr)		
< 70	1	
≥ 70	1.162 (1.099-1.228)	< 0.001
Primary tumor location		
Colon	1	
Rectum	0.715 (0.678-0.754)	< 0.001
Tumor differentiation		
I-II	1	
III-IV	1.721 (1.630-1.817)	< 0.001
T staging		
1-2	1	
3-4	1.085 (0.999-1.179)	0.053
N stage		
0	1	
1-2	1.304 (1.226-1.386)	< 0.001
CEA status		
Masculine	1	
Feminine	0.699 (0.655-0.746)	< 0.001
Liver metastases		
No	1	
Yes	1.406 (1.326-1.490)	< 0.001
Lung metastases		
No	1	
Yes	1.341 (1.260-1.426)	< 0.001
Bone metastases		
No	1	
Yes	1.621 (1.438-1.827)	< 0.001
Brain metastases		
No	1	
Yes	1.718 (1.370-2.155)	< 0.001
Surgical		
No	1	
Yes	0.459 (0.429-0.492)	< 0.001

Chemotherapy		
None/unknown	1	
Yes	0.368 (0.348-0.390)	< 0.001

CEA: Carcinoembryonic antigen; HR: Hazard ratio.

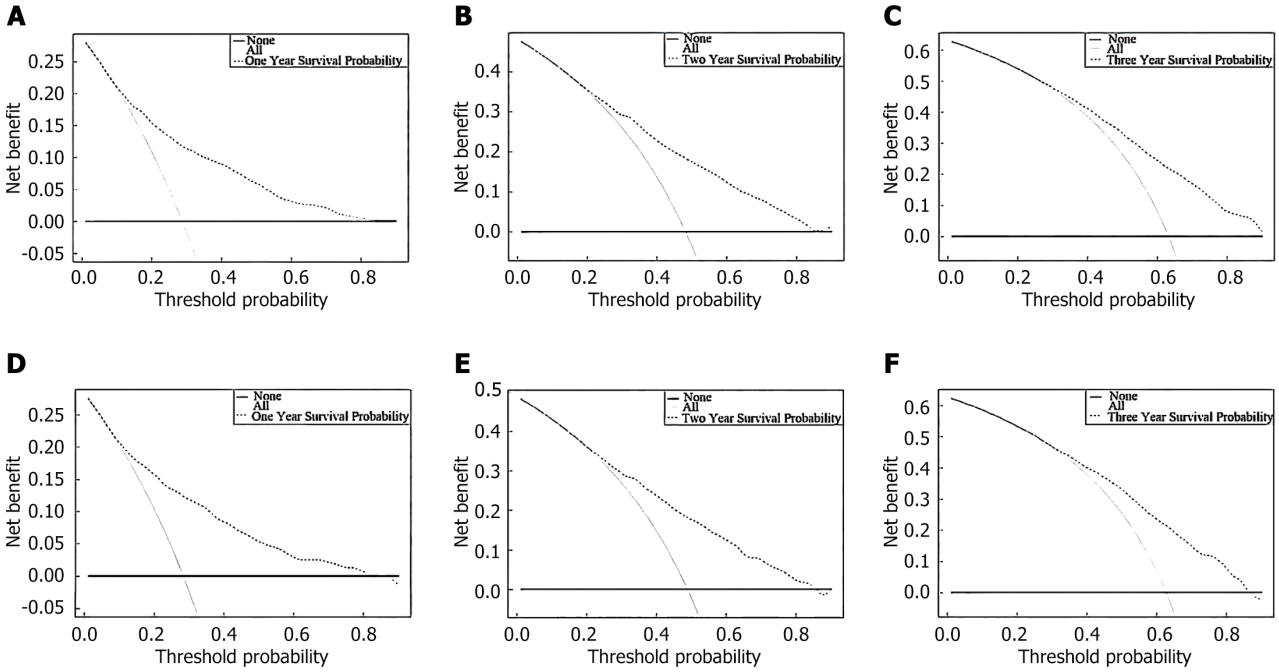


Figure 3 The nomogram model predicts the clinical decision curve of cancer-specific survival in metastatic colorectal cancer patients. A-C: Clinical decision curves based on 1-, 2-, and 3-year cancer-specific survival (CSS) in the training cohort; D-F: Clinical decision curves based on 1-, 2-, and 3-year CSS in the validation cohort.

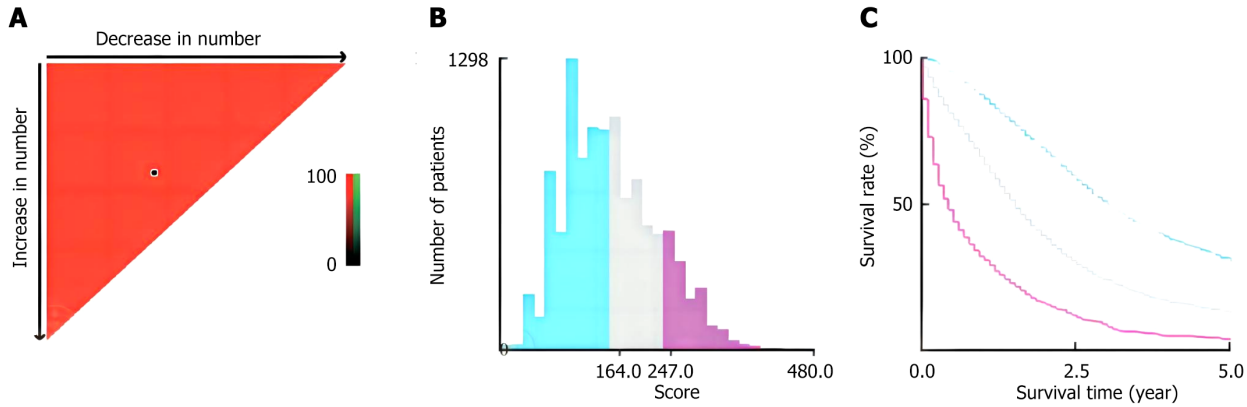


Figure 4 X-tile software was used to calculate the optimal truncation value and establish a risk classification system. A and B: The optimal cutoff values of the predicted total scores, including the low-risk group (score: 0-164), medium-risk group (score: 165-247) and high-risk group (score: 248-480); C: Kaplan-Meier curves for different risk levels according to the cancer-specific survival of the training cohort.

helps to assess the level of risk in patients with mCRC, allowing for individualized treatment and an accurate prognosis. In addition, we provide estimated points for each important prognostic factor to improve clinical application[40].

There are several limitations to our study. First, this study is a retrospective analysis of existing selection bias. Furthermore, the SEER database does not contain detailed information on chemotherapy regimens or targeted therapies, which hinders further subgroup analysis. Then, the SEER data are used to verify the validity of the column graph prediction, which lacks the verification of real data.

Table 3 Regression coefficients and estimated scores for building a Nomogram prediction model based on a training cohort

Variable	Nomogram	
	Regression coefficients	Estimated score
Race		
Black people	17.846261	18
White race	6.960746	7
Other	0	0
Age at diagnosis (yr)		
< 70	0	0
≥ 70	14.55836	15
Primary tumor location		
Colon	32.76881	33
Rectum	0	0
Tumor differentiation		
I-II	0	0
III-IV	54.39289	54
N stage		
0	0	0
1-2	27.38794	27
CEA status		
Masculine	35.56051	36
Feminine	0	0
Liver metastases		
No	0	0
Yes	34.12213	34
Lung metastases		
No	0	0
Yes	29.0965	29
Bone metastases		
No	0	0
Yes	49.30787	49
Brain metastases		
No	0	0
Yes	54.35879	54
Surgical		
No	75.074	75
Yes	0	0
Chemotherapy		
None/unknown	100	100
Yes	0	0
Range	0-524.474061	0-524
Score	531.434807	531

CEA: Carcinoembryonic antigen.

Table 4 Analyzes tumor-specific survival rates in patients with different risk classes, %

Variable	Low-risk group	Medium-risk group	High-risk group
	(*n* = 8140)	(*n* = 4737)	(*n* = 2013)
1 yr CSS	86.10	63.00	31.50
2 yr CSS	67.30	38.00	16.10
3 yr CSS	49.70	24.60	8.90
5 yr CSS	31.30	14.20	4.30
Median CSS	36 months	18 months	5 months
95%CI	34.987-37.013	17.273-18.727	4.503-5.497

CSS: Cancer-specific survival.

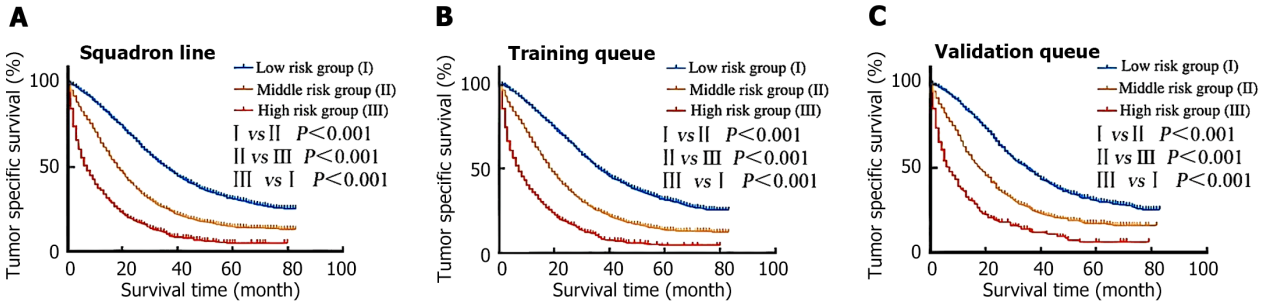


Figure 5 Kaplan-Meier survival curves for patients with different risk levels were drawn according to their cancer-specific survival. A: Platoon line; B: Training queue; C: Authentication queue.

CONCLUSION

In summary, we developed a new nomogram model to predict CSS in patients with synchronous mCRC. The verification of the model showed that the model has good discriminability and consistency. The risk grading system can grade the risk level of mCRC patients, accurately evaluate patient prognosis, and guide treatment.

FOOTNOTES

Author contributions: Zhou YJ wrote the manuscript; Tan ZE and Zhuang WD collected the data; and Xu XH guided the study; All authors reviewed, edited, and approved the final manuscript and revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Conflict-of-interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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REFERENCES

1 **Chen J**, Feng B, Hu M, Huang F, Chen Y, Ma X, Long W. A transfer learning nomogram for predicting prostate cancer and benign conditions on MRI. *BMC Med Imaging* 2023; **23**: 200 [PMID: 38036991 DOI: 10.1186/s12880-023-01163-7]

2 **Park JK**, Park JE, Bang S, Jeon HJ, Kim JW, Lee WS. Development and validation of a nomogram for predicting ongoing pregnancy in single vitrified-warmed blastocyst embryo transfer cycles. *Front Endocrinol (Lausanne)* 2023; **14**: 1257764 [PMID: 38075065 DOI: 10.3389/fendo.2023.1257764]

3 **Zhu S**, Liao X, Jiang W, Sun Y, Chen X, Zheng B. Development and validation of a nomogram model for predicting clinical pregnancy in endometriosis patients undergoing fresh embryo transfer. *BMC Pregnancy Childbirth* 2023; **23**: 764 [PMID: 37907870 DOI: 10.1186/s12884-023-06082-7]

4 **Garajova I**, Balsano R, Tommasi C, Dalla Valle R, Pedrazzi G, Ravaioli M, Spallanzani A, Leonardi F, Santini C, Caputo F, Riefolo M, Giuffrida M, Gelsomino F. Synchronous and metachronous colorectal liver metastases: impact of primary tumor location on patterns of recurrence and survival after hepatic resection. *Acta Biomed* 2020; **92**: e2021061 [PMID: 33682832 DOI: 10.23750/abm.v92i1.11050]

5 **Xiong F**, Sun Q, Wang S, Yao Z, Chen P, Wan C, Zhong H, Zeng Y. A nomogram to assist blastocyst selection in vitrified-warmed embryo transfer cycles. *J Obstet Gynaecol Res* 2022; **48**: 1816-1828 [PMID: 35373468 DOI: 10.1111/jog.15138]

6 **Liu X**, Zhang D, Liu Z, Li Z, Xie P, Sun K, Wei W, Dai W, Tang Z, Ding Y, Cai G, Tong T, Meng X, Tian J. Deep learning radiomics-based prediction of distant metastasis in patients with locally advanced rectal cancer after neoadjuvant chemoradiotherapy: A multicentre study. *EBioMedicine* 2021; **69**: 103442 [PMID: 34157487 DOI: 10.1016/j.ebiom.2021.103442]

7 **Zhang Q**, Wang X, Zhang Y, Lu H, Yu Y. Nomogram prediction for the prediction of clinical pregnancy in Freeze-thawed Embryo Transfer. *BMC Pregnancy Childbirth* 2022; **22**: 629 [PMID: 35941542 DOI: 10.1186/s12884-022-04958-8]

8 **Feng B**, Huang L, Liu Y, Chen Y, Zhou H, Yu T, Xue H, Chen Q, Zhou T, Kuang Q, Yang Z, Chen X, Chen X, Peng Z, Long W. A Transfer Learning Radiomics Nomogram for Preoperative Prediction of Borrmann Type IV Gastric Cancer From Primary Gastric Lymphoma. *Front Oncol* 2021; **11**: 802205 [PMID: 35087761 DOI: 10.3389/fonc.2021.802205]

9 **Yue M**, Ma L, Cao Y, Zhai J. Application of a Nomogram for Predicting the Risk of Subchorionic Hematoma in Early Pregnancy With In Vitro Fertilization-Embryo Transfer/Frozen Embryo Transfer. *Front Endocrinol (Lausanne)* 2021; **12**: 631097 [PMID: 33737911 DOI: 10.3389/fendo.2021.631097]

10 **Zeng Z**, Ma Y, Zeng H, Huang P, Liu W, Jiang M, Xiang X, Deng D, Liao X, Chen P, Chen Y. Simple nomogram based on initial laboratory data for predicting the probability of ICU transfer of COVID-19 patients: Multicenter retrospective study. *J Med Virol* 2021; **93**: 434-440 [PMID: 32603535 DOI: 10.1002/jmv.26244]

11 **Wu L**, Zheng Y, Liu J, Luo R, Wu D, Xu P, Wu D, Li X. Comprehensive evaluation of the efficacy and safety of LPV/r drugs in the treatment of SARS and MERS to provide potential treatment options for COVID-19. *Aging (Albany NY)* 2021; **13**: 10833-10852 [PMID: 33879634 DOI: 10.18632/aging.202860]

12 **Jiang X**, Liu R, Liao T, He Y, Li C, Guo P, Zhou P, Cao Y, Wei Z. A Predictive Model of Live Birth Based on Obesity and Metabolic Parameters in Patients With PCOS Undergoing Frozen-Thawed Embryo Transfer. *Front Endocrinol (Lausanne)* 2021; **12**: 799871 [PMID: 35095766 DOI: 10.3389/fendo.2021.799871]

13 **Zhang H**, Hu S, Xu D, Shen H, Jin H, Yang J, Zhang X. Risk Factors for Carbapenem Resistant Gram Negative Bacteria (CR-GNB) Carriage Upon Admission to the Gastroenterology Department in a Tertiary First Class Hospital of China: Development and Assessment of a New Predictive Nomogram. *Infect Drug Resist* 2022; **15**: 7761-7775 [PMID: 36597451 DOI: 10.2147/IDR.S396596]

14 **Sun J**, Huang L, Yang Y, Liao H. Risk assessment and clinical prediction model of planned transfer to the ICU after hip arthroplasty in elderly individuals. *BMC Surg* 2023; **23**: 305 [PMID: 37805523 DOI: 10.1186/s12893-023-02204-2]

15 **Wu L**, Zhong Y, Wu D, Xu P, Ruan X, Yan J, Liu J, Li X. Immunomodulatory Factor TIM3 of Cytolytic Active Genes Affected the Survival and Prognosis of Lung Adenocarcinoma Patients by Multi-Omics Analysis. *Biomedicines* 2022; **10** [PMID: 36140350 DOI: 10.3390/biomedicines10092248]

16 **Guo Z**, Chen W, Wang Y, Chu R, Xu X, Zhang L, Yan L, Ma J. Nomogram to predict an endometrial thickness above 7.5 mm in the frozen embryo transfer cycle of women with a thin endometrium. *Reprod Biomed Online* 2022; **44**: 324-332 [PMID: 35031241 DOI: 10.1016/j.rbmo.2021.10.022]

17 **Si M**, Jiang H, Zhao Y, Qi X, Li R, Long X, Qiao J. Nomogram for Predicting Live Birth after the First Fresh Embryo Transfer in Patients with PCOS Undergoing IVF/ICSI Treatment with the GnRH-Ant Protocol. *Diagnostics (Basel)* 2023; **13** [PMID: 37296779 DOI: 10.3390/diagnostics13111927]

18 **Sheng Y**, Wang Q, Liu H, Wang Q, Chen W, Xing W. Prognostic nomogram model for selecting between transarterial chemoembolization plus lenvatinib, with and without PD-1 inhibitor in unresectable hepatocellular carcinoma. *Br J Radiol* 2024; **97**: 668-679 [PMID: 38303541 DOI: 10.1093/bjr/tqae018]

19 **Duan C**, Hao D, Cui J, Wang G, Xu W, Li N, Liu X. An MRI-Based Deep Transfer Learning Radiomics Nomogram to Predict Ki-67 Proliferation Index of Meningioma. *J Imaging Inform Med* 2024; **37**: 510-519 [PMID: 38343220 DOI: 10.1007/s10278-023-00937-3]

20 **Wu L**, Liu Q, Ruan X, Luan X, Zhong Y, Liu J, Yan J, Li X. Multiple Omics Analysis of the Role of RBM10 Gene Instability in Immune Regulation and Drug Sensitivity in Patients with Lung Adenocarcinoma (LUAD). *Biomedicines* 2023; **11** [PMID: 37509501 DOI: 10.3390/biomedicines11071861]

21 **Kim JH**, Jee BC, Suh CS, Kim SH. Nomogram to predict ongoing pregnancy using age of women and serum biomarkers after in vitro fertilization cycles. *Eur J Obstet Gynecol Reprod Biol* 2014; **172**: 65-69 [PMID: 24183986 DOI: 10.1016/j.ejogrb.2013.10.015]

22 **Wu Y**, Yang R, Lin H, Cao C, Jiao X, Zhang Q. A Validated Model for Individualized Prediction of Live Birth in Patients With Adenomyosis Undergoing Frozen-Thawed Embryo Transfer. *Front Endocrinol (Lausanne)* 2022; **13**: 902083 [PMID: 35685210 DOI: 10.3389/fendo.2022.902083]

23 **Diao L**, Cai S, Huang C, Li L, Yu S, Wang L, Liu S, Li Y, Zeng Y. New endometrial immune cell-based score (EI-score) for the prediction of implantation success for patients undergoing IVF/ICSI. *Placenta* 2020; **99**: 180-188 [PMID: 32829188 DOI: 10.1016/j.placenta.2020.07.025]

24 **Vivanti AJ**, Maraux B, Bornes M, Daraï E, Richard F, Rouzier R. Threatened preterm birth: Validation of a nomogram to predict the individual risk of very preterm delivery in a secondary care center. *J Gynecol Obstet Hum Reprod* 2019; **48**: 501-507 [PMID: 30980998 DOI: 10.1016/j.jogoh.2019.04.004]

25 **Wu L**, Zheng Y, Ruan X, Wu D, Xu P, Liu J, Wu D, Li X. Long-chain noncoding ribonucleic acids affect the survival and prognosis of patients with esophageal adenocarcinoma through the autophagy pathway: construction of a prognostic model. *Anticancer Drugs* 2022; **33**: e590-e603 [PMID: 34338240 DOI: 10.1097/CAD.0000000000001189]

26 **Wang R**, Dai W, Gong J, Huang M, Hu T, Li H, Lin K, Tan C, Hu H, Tong T, Cai G. Development of a novel combined nomogram model integrating deep learning-pathomics, radiomics and immunoscore to predict postoperative outcome of colorectal cancer lung metastasis patients. *J Hematol Oncol* 2022; **15**: 11 [PMID: 35073937 DOI: 10.1186/s13045-022-01225-3]

27 **Huang YQ**, Liang CH, He L, Tian J, Liang CS, Chen X, Ma ZL, Liu ZY. Development and Validation of a Radiomics Nomogram for Preoperative Prediction of Lymph Node Metastasis in Colorectal Cancer. *J Clin Oncol* 2016; **34**: 2157-2164 [PMID: 27138577 DOI: 10.1200/JCO.2015.65.9128]

28 **Wu L**, Zhong Y, Yu X, Wu D, Xu P, Lv L, Ruan X, Liu Q, Feng Y, Liu J, Li X. Selective poly adenylation predicts the efficacy of immunotherapy in patients with lung adenocarcinoma by multiple omics research. *Anticancer Drugs* 2022; **33**: 943-959 [PMID: 35946526 DOI: 10.1097/CAD.0000000000001319]

29 **Lee JH**, Jung S, Park WS, Choe EK, Kim E, Shin R, Heo SC, Lee JH, Kim K, Chai YJ. Prognostic nomogram of hypoxia-related genes predicting overall survival of colorectal cancer-Analysis of TCGA database. *Sci Rep* 2019; **9**: 1803 [PMID: 30755640 DOI: 10.1038/s41598-018-38116-y]

30 **Yan S**, Ding H, Zhao X, Wang J, Deng W. Development and validation of a nomogram for further decision of radical surgery in pT1 colorectal cancer after local resection. *Int J Colorectal Dis* 2021; **36**: 1499-1506 [PMID: 33864506 DOI: 10.1007/s00384-021-03928-4]

31 **Wu L**, Li H, Liu Y, Fan Z, Xu J, Li N, Qian X, Lin Z, Li X, Yan J. Research progress of 3D-bioprinted functional pancreas and in vitro tumor models. *IJB* 2024; **10**: 1256 [DOI: 10.36922/ijb.1256]

32 **Liu Y**, Meng Y, Zhou C, Liu Y, Tian S, Li J, Dong W. Creation and Validation of a Survival Nomogram Based on Immune-Nutritional Indexes for Colorectal Cancer Patients. *J Oncol* 2022; **2022**: 1854812 [PMID: 35368901 DOI: 10.1155/2022/1854812]

33 **Qin X**, Zhao M, Deng W, Huang Y, Cheng Z, Chung JPW, Chen X, Yang K, Chan DYL, Wang H. Development and Validation of a Novel Prognostic Nomogram Combined With Desmoplastic Reaction for Synchronous Colorectal Peritoneal Metastasis. *Front Oncol* 2022; **12**: 826830 [PMID: 35359399 DOI: 10.3389/fonc.2022.826830]

34 **Hong T**, Cai D, Jin L, Zhang Y, Lu T, Hua D, Wu X. Development and validation of a nomogram to predict survival after curative resection of nonmetastatic colorectal cancer. *Cancer Med* 2020; **9**: 4126-4136 [PMID: 32314876 DOI: 10.1002/cam4.3010]

35 **Wu L**, Li X, Qian X, Wang S, Liu J, Yan J. Lipid Nanoparticle (LNP) Delivery Carrier-Assisted Targeted Controlled Release mRNA Vaccines in Tumor Immunity. *Vaccines (Basel)* 2024; **12** [PMID: 38400169 DOI: 10.3390/vaccines12020186]

36 **Zhang Y**, Zhang Z, Wei L, Wei S. Construction and validation of nomograms combined with novel machine learning algorithms to predict early death of patients with metastatic colorectal cancer. *Front Public Health* 2022; **10**: 1008137 [PMID: 36605237 DOI: 10.3389/fpubh.2022.1008137]

37 **Kajiwara Y**, Oka S, Tanaka S, Nakamura T, Saito S, Fukunaga Y, Takamatsu M, Kawachi H, Hotta K, Ikematsu H, Kojima M, Saito Y, Yamada M, Kanemitsu Y, Sekine S, Nagata S, Yamada K, Kobayashi N, Ishihara S, Saitoh Y, Matsuda K, Togashi K, Komori K, Ishiguro M, Kuwai T, Okuyama T, Ohuchi A, Ohnuma S, Sakamoto K, Sugai T, Katsumata K, Matsushita HO, Yamano HO, Eda H, Uraoka T, Akimoto N, Kobayashi H, Ajioka Y, Sugihara K, Ueno H. Nomogram as a novel predictive tool for lymph node metastasis in T1 colorectal cancer treated with endoscopic resection: a nationwide, multicenter study. *Gastrointest Endosc* 2023; **97**: 1119-1128.e5 [PMID: 36669574 DOI: 10.1016/j.gie.2023.01.022]

38 **Wu L**, Chen X, Zeng Q, Lai Z, Fan Z, Ruan X, Li X, Yan J. NR5A2 gene affects the overall survival of LUAD patients by regulating the activity of CSCs through SNP pathway by OCLR algorithm and immune score. *Heliyon* 2024; **10**: e28282 [PMID: 38601554 DOI: 10.1016/j.heliyon.2024.e28282]

39 **Tang X**, Hu N, Huang S, Jiang J, Rao H, Yang X, Yuan Y, Zhang Y, Xia G. Prognostic nomogram for colorectal cancer patients with multi-organ metastases: a Surveillance, Epidemiology, and End Results program database analysis. *J Cancer Res Clin Oncol* 2023; **149**: 12131-12143 [PMID: 37428251 DOI: 10.1007/s00432-023-05070-w]

40 **Xie Z**, Zhang Q, Wang X, Chen Y, Deng Y, Lin H, Wu J, Huang X, Xu Z, Chi P. Development and validation of a novel radiomics nomogram for prediction of early recurrence in colorectal cancer. *Eur J Surg Oncol* 2023; **49**: 107118 [PMID: 37844471 DOI: 10.1016/j.ejso.2023.107118]

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ORIGINAL ARTICLE

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FDX1 as a novel biomarker and treatment target for stomach adenocarcinoma

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Abstract

BACKGROUND

Stomach adenocarcinoma (STAD) is one of the main reasons for cancer-related deaths worldwide. This investigation aimed to define the connection between STAD and Cuproptosis-related genes (CRGs). Cuproptosis is a newly identified form of mitochondrial cell death triggered by copper.

AIM

To explore the identification of potential biomarkers for STAD disease based on cuproptosis.

METHODS

A predictive model using Gene Ontology (GO), Least Absolute Shrinkage and Selection Operator (LASSO), Kyoto Encyclopedia of Genes and Genomes (KEGG), Gene Set Variation Analysis (GSVA), and Gene Set Enrichment Analysis analyzed gene interconnections, focusing on 3 copper-related genes and their expression in The Cancer Genome Atlas-STAD. Networks for mRNA-miRNA and mRNA-transcription factor interactions were constructed. The prognostic significance of CRG scores was evaluated using time-receiver operating characteristic, Kaplan-Meier curves, and COX regression analysis. Validation was conducted with datasets GSE26942, GSE54129, and GSE66229. Expression of copper-related differentially expressed genes was also analyzed in various human tissues and gastric cancer subpopulations using the human protein atlas.

RESULTS
Three significant genes (*FDX1*, *LIAS*, *MTF1*) were identified and selected *via* LASSO analysis to predict and classify individuals with STAD into high and low CRG score subgroups. These genes were down-regulated in both risk categories. GO and KEGG analyses highlighted their involvement mainly in the electron transport chain. After validating their differential expression, *FDX1* emerged as the most accurate diagnostic marker for gastric cancer. Additionally, the RCircos package localized *FDX1* on chromosome 11.

CONCLUSION
Our study revealed that *FDX1* could be a potential biomarker and treatment target for gastric malignancy, providing new ideas for further scientific research.

Key Words: Stomach adenocarcinoma disease; Copper death; *FDX1*; prognostic biomarkers; Cuproptosis-related genes

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Core Tip: This study explores the novel link between cuproptosis-related genes (CRGs) and stomach adenocarcinoma (STAD), identifying *FDX1* as a potential biomarker and therapeutic target. Utilizing comprehensive analyses, including Gene Set Enrichment Analysis and Least Absolute Shrinkage and Selection Operator regression, we categorized STAD patients into high and low risk based on CRG scores. *FDX1*, along with two other genes, demonstrated significant diagnostic and prognostic potential, suggesting a new avenue for targeted therapies in gastric cancer treatment.

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INTRODUCTION

With an estimated more than one million new cases annually, gastric cancer, specifically gastric adenocarcinoma (STAD), is the third most frequent cause of malignancy mortality globally and the fifth most common cancer[1]. And it has a high recurrence and mortality rate[1]. Significant advances in the treatment of STAD have been made in the previous decades, particularly with the cisplatin start, which has delayed the life expectancy of patients with gastric adenocarcinoma to some extent[2]. However, the development of drug resistance has reduced the effectiveness of cisplatin, leading to local infiltration of tumor cells and distant metastases. As a result, the STAD prognosis is still discouraging, with a 5-year survival rate of less than 30%[3]. And STAD risk factors are diverse, including but not restricted to age, sex, *Helicobacter pylori* (*H. pylori*) infection, and a high nitrite diet[4]. To enhance STAD diagnosis, prevention, and therapy, finding novel STAD biomarkers or treatment targets is vital.

Copper is a vital trace element in the body and significantly maintains enzyme activity[5]. Recently, copper function in cancer has been extensively explored, with numerous studies showing elevated levels in various tumor tissues such as lung, breast, cervical, ovarian, prostate, stomach, and colorectal cancers[6]. Copper also exhibits cytotoxicity when its concentration exceeds the threshold for maintaining homeostatic mechanisms, and the researchers named this mechanism of copper ion-induced cell death as copper death[7]. Therefore, by analyzing the phenomenon, mechanism, and disease model, the researchers found that copper death happens *via* the binding of copper to the tricarboxylic acid cycle lipidated elements. This causes iron-sulfur cluster protein loss and lipid-acylated protein aggregation, which induces proteotoxic stress and apoptosis[8]. Moreover, copper enhances tumor angiogenesis for metabolic waste and nutrient transportation [9].

According to these investigations, copper is a valuable target for treating malignancy.

Given the critical role of copper element disorders in cancer, this investigation aimed to systematically discover the molecular function (MF) and medical relevance of genes connected with copper death in STAD. We analyzed information from 353 individuals with STAD in the The Cancer Genome Atlas (TCGA) database, showing the results of cuproptosis-related genes (CRGs) expression and functional enrichment analysis. Notably, three CRGs were determined to be connected with survival and prognosis in hepatocellular carcinoma patients. And more validation was obtained in the external The Gene Expression Omnibus (GEO) datasets GSE26942, GSE54129, and GSE66229, culminating in the screening of *FDX1* as a highly significant gene. Studying the connection between STAD and genes connected with copper death will help us grasp STAD patients' immune status and continuously optimize treatment strategies to prolong prognosis. In conclusion, our investigation offers a comprehensive analysis of CRGs' function in different parts of STAD, highlighting the CRGs' significance in STAD progression and giving a guideline for applying copper death-related genes in STAD treatment. The technology road map is shown in Figure 1.

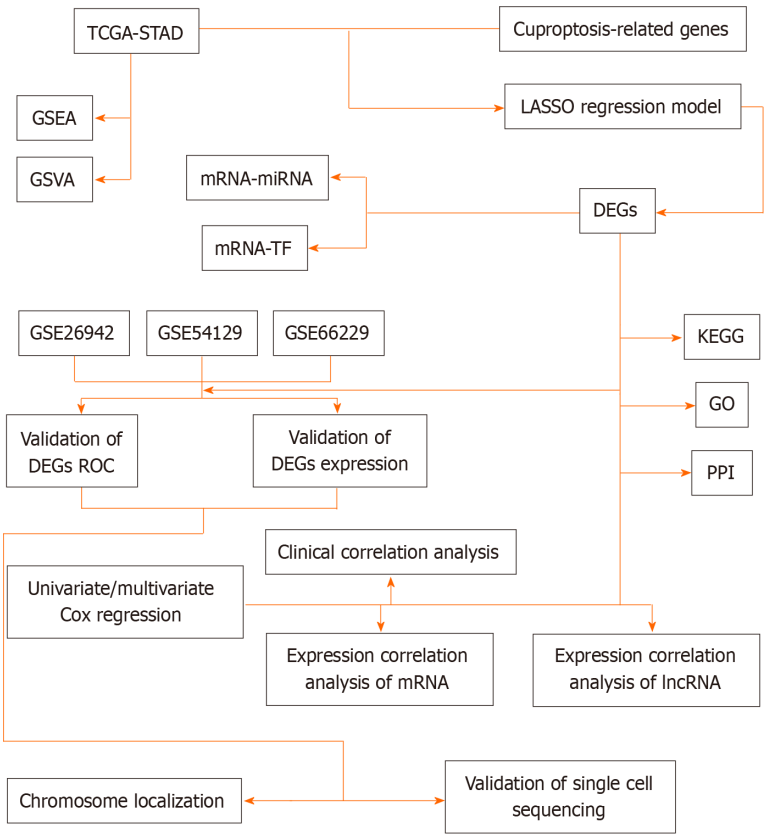


Figure 1 Technology roadmap. STAD: Stomach adenocarcinoma; TCGA: The Cancer Genome Atlas; GSEA: Gene Set Enrichment Analysis; GSVA: Gene Set Variation Analysis; LASSO: Least Absolute Shrinkage and Selection Operator; DEGs: Differentially expressed genes; KEGG: Kyoto Encyclopedia of Genes and Genomes; GO: Gene Ontology; PPI: Protein-protein interaction; ROC: Receiver operating characteristic curve.

MATERIALS AND METHODS

Data download

Expression profiling datasets of STAD patients were downloaded from GEO (http://www.ncbi.nlm.nih.gov/geo/) database using the R package GEO query[10]. GSE26942[11], GSE66229 and GSE54129. In the dataset GSE26942, we selected 202 STAD samples and 12 control samples for follow-up analysis. The data set GSE54129 has 132 pieces, including 111 STAD samples and 21 control samples. Data set GSE66229 consisted of 300 STAD models and 100 control samples; we selected these samples for follow-up analysis.

In addition, we have used the TCGA biolinks package[12] from the Tumor Genome Project (https://portal.gdc.cancer.gov/) to download the count sequencing data of the STAD dataset (TCGA-STAD), which included a total of 407 samples, including 375 STAD and 32 control specimens. By excluding models without predictive data from the UCSC Xena database, the medical information of 353 samples was also obtained (http://genome.ucsc.edu), and these 353 samples were used for follow-up analysis (Table 1).

Construction of a predictive model for genes linked to copper death

To obtain predictive models for genes connected to copper death, we selected the overall survival (OS) from the dataset TCGA-STAD clinical data and the expression profiles of genes linked to copper death (LASSO) from 353 samples of STAD for which clinical data were available in the dataset TCGA-STAD. Expression profiles of cuproptosis-related genes from 353 STAD samples with medical data in the dataset TCGA-STAD were selected utilizing a ten-fold cross-validation seed to apply LASSO regression for 2000. The results were visualized, prognosis-related genes for copper death were obtained, and Kaplan-Meier curves for prognosis-related genes were plotted.

Differentially expressed genes related to copper death prognosis

We first utilized the limma package[13] to standardize the profile information of gene expression of 353 patients with STAD in the dataset TCGA-STAD. Depending on the risk scores from the Least Absolute Shrinkage and Selection Operator (LASSO) regression analysis, samples with risk scores more than the median were then used as a high-risk group, and samples with risk scores less than the median were used as the low-risk group, using the median risk score as the criterion. Differential analysis with subgroups of low and high risk was conducted to acquire all differentially expressed genes (DEGs) with $|\log FC| > 0$ and P value < 0.05. The DEGs intersected with the prognosis-related genes of copper death to acquire the prognosis-related DEGs of copper death. Then the expression profile data of DEGs of copper death associated with the prognosis in the dataset TCGA-STAD were extracted and displayed in a heat map using the

Table 1 Patient Characteristics of individuals with stomach adenocarcinoma in The Cancer Genome Atlas datasets, *n* (%)

Characteristic	Levels	Overall (*n* = 375)
T stage	T1	19 (5.2)
	T2	80 (21.8)
	T3	168 (45.8)
	T4	100 (27.2)
N stage	N0	111 (31.1)
	N1	97 (27.2)
	N2	75 (21)
	N3	74 (20.7)
M stage	M0	330 (93)
	M1	25 (7)
Pathologic stage	Stage I	53 (15.1)
	Stage II	111 (31.5)
	Stage III	150 (42.6)
	Stage IV	38 (10.8)
Gender	Female	134 (35.7)
	Male	241 (64.3)
Age	≤ 65	164 (44.2)
	> 65	207 (55.8)
OS event	Alive	228 (60.8)
	Dead	147 (39.2)
DSS event	Alive	263 (74.3)
	Dead	91 (25.7)
PFI event	Alive	251 (66.9)
	Dead	124 (33.1)
Age, median (IQR)		67 (58, 73)

OS: Overall survival; DSS: Disease-specific survival; PFI: Progression-free interval.

ComplexHeatmap package.

Functional enrichment (Gene Ontology) and pathway enrichment (Kyoto Encyclopedia of Genes and Genomes) analyses of prognostically DEGs

Gene Ontology (GO)[10] analysis is a frequent technique for large-scale functional enrichment investigations, like biological process (BP), MF and cellular component (CC). Kyoto Encyclopedia of Genes and Genomes (KEGG) is a broadly utilized database for keeping genomes, diseases, biological mechanisms, and medicines data. We initially conducted a molecular correlation study of prognosis-related DEGs for copper death using the dataset TCGA-STAD, taking $P < 0.05$ positive correlation Top5 genes and negative correlation Top5 genes, using the R package clusterProfiler KEGG and GO annotation analyses were conducted. Entry screening criteria were P value < 0.05, and false discovery rate (FDR) value (q value) < 0.05 was reflected as statistically significant, with P value correction by Benjamini-Hochberg (BH).

Gene Set Enrichment Analysis and Gene Set Variation Analysis

We extracted the gene expression profile data of 353 cases with STAD from the dataset TCGA-STAD for LASSO regression analysis. The median risk score was employed as the criterion for the outcome, with samples with risk scores more than the median as a group of high-risk and samples with risk scores less than the median were considered as the low-risk group. Then, the Molecular Signatures Database (MSigDB) was utilized to obtain the samples. The gene set "h.all.v7.5.2.symbols.gmt" was obtained from the MSigDB database as the reference gene set, and all genes in the gastric cancer dataset TCGA-STAD were enriched according to groups of low and high-risk utilizing the clusterProfiler package. The following were factors employed in this Gene Set Enrichment Analysis (GSEA): Seeds of 2000 with a count of 10000, a

minimum of 10 genes, and a maximum of 500 genes per gene set, and a *P* value correction manner of BH. The screening criteria for significant enrichment were FDR and *P* values; both were less than 0.05. The Top4 results were visualized based on the NES.

Gene Set Variation Analysis (GSVA) is an unsupervised non-parametric analysis method. Gene expression matrices between specimens are transformed into gene set expression matrices between samples to analyze the gene set enrichment outcomes of the microarray nuclear transcriptome. This is employed to assess whether different pathways are enriched among various models. We retrieved "h.all.v7.5.2.symbols.gmt" from the MSigDB database and conducted a GSVA study on the TCGA-STAD dataset. Analyze differences in functional enrichment between high- and low-risk groups in the dataset TCGA-STAD.

Protein-protein interaction

In the present investigation, we utilized the STRING database to obtain the top 10 genes with the least necessary interaction score for prognosis-related differential expression of genes associated with copper death to create a protein-protein interaction (PPI) network and use Cytoscape (version 3.9.1). Visualization of the PPI network model.

Constructing mRNA-miRNA, mRNA-TF interactions networks

We used the Starbase and miRDB databases to predict miRNAs interacting with prognostically relevant DEGs for copper death. The intersection of the two database results was then taken, and the mRNA-miRNA interaction network was plotted using Cytoscape software.

Utilizing ChIP-seq data of DNA-binding proteins, the CHIPBase database (version 2.0; https://rna.sysu.edu.cn/chipbase/) detects thousands of binding motif matrices and their binding sites and anticipates millions of transcriptional regulatory connections between genes and transcription factors (TFs). hTFtarget database (http://bioinfo.life.hust.edu.cn/hTFtarget) is an extensive human TFs and their target modulation. Utilizing the Cytoscape program, we identified and visualized TFs that bind to DEGs linked to the prognosis of copper mortality using the hTFtarget and CHIPBase (version 2.0) databases.

Receiver operating characteristic curves

Receiver operating characteristic curve (ROC) is a composite marker of a continuous variable of specificity and sensitivity, with values generally ranging from 0.5 to 1 of the area under curve (AUC). When the AUC is near 1, the diagnosis is more accurate. We plotted ROC curves for genes based on expression profile data of prognostically relevant DEGs for copper death in the dataset TCGA-STAD.

Expression and molecular correlation analysis of prognosis-related DEGs between different single cell subpopulations

Utilizing the database of human protein atlas (HPA, www.proteinatlas.org/), DEGs' expression connected to copper death prognosis in different human tissues was obtained, and the outcomes were displayed. We used the RCircos package. They were locating prognosis-associated DEGs in chromosomes. After using the expression profile data from the dataset TCGA-STAD to calculate the connection of other molecules in the dataset with prognosis-related DEGs, the positive Top5 and negative Top5 correlations were selected for protein-coding molecules of gene type to plot co-expression heatmaps. Then the positive Top5 and negative Top5 correlations were determined for LncRNA molecules of gene type to plot co-expression heatmaps.

Analysis of clinical relevance

To investigate the clinical predictive value of prognosis-related DEGs for copper death in STAD. We subjected prognosis-related DEGs for copper death in STAD to univariate Cox regression analysis. The factors with $P < 0.05$ were also selected for inclusion in the multi-factor Cox regression analysis to construct a multi-factor Cox regression model. We created a nomogram based on the one-way Cox regression analysis results to predict the survival of patients with STAD at one year, three years, and five years. Decision curve analysis (DCA) is a simple method for evaluating clinical predictive models, diagnostic tests, and molecular markers. We used the survival package to assess the effect of the nomogram model on patient survival at 1, 3, and 5 years. We analyzed the prognosis-related differential expression gene expression levels of copper death in STAD cancer tissues on the overall tumor survival overall survival, disease-specific survival, and progression-free interval effects.

Statistical analysis

The R programming (version 4.2.1) was employed for all data processing and analysis. Independent Student t-tests were utilized to determine the statistical significance of customarily distributed variables to compare two groups of continuous data. Mann-Whitney *U*-tests were utilized to examine differences between non-normally distributed data (*i.e.*, Wilcoxon rank sum tests). To compare and analyze the statistical significance between the two groups of subjected prognosis-related DEGs for copper death in STAD to univariate Cox regression analysis was employed to conduct survival analysis, the Kaplan-Meier survival curve was utilized to detect changes in survival and the log-rank test was used to evaluate the statistical significance of variations in survival time between the two patient groups. The survival R program was the basis for the univariate and multifactorial Cox analyses, while the lasso analyses used the glmnet R package. At $P < 0.05$, each statistical P value was two-sided and statistically significant.

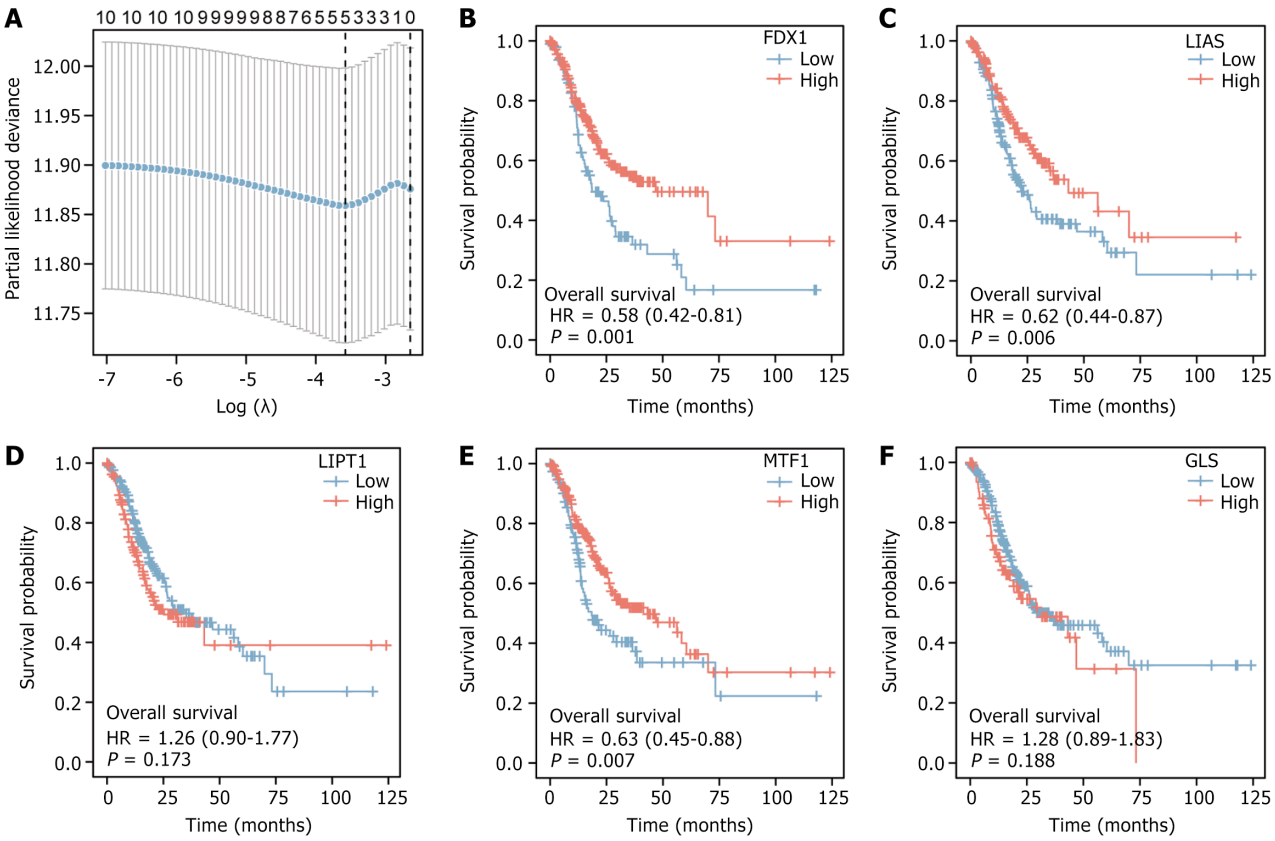


Figure 2 Visualisation of Least Absolute Shrinkage and Selection Operator regression results and Kaplan-Meier curves. A: Visualization of Least Absolute Shrinkage and Selection Operator regression results for dataset The Cancer Genome Atlas (TCGA)-stomach adenocarcinoma (STAD); B: Kaplan-Meier (K-M) curves for gene FDX1 in dataset TCGA-STAD; C: K-M curves for gene LIAS in dataset TCGA-STAD; D: K-M curves for gene LIPT1 in dataset TCGA-STAD; E: K-M curves for gene MTF1 in dataset TCGA-STAD; F: K-M curves for gene GLS in dataset TCGA-STAD.

RESULTS

A predictive model construction for genes associated with copper death

We selected the OS from the dataset TCGA-STAD clinical data and the expression profile data of genes connected to copper death (cuproptosis-related genes) from the dataset TCGA-STAD to construct the LASSO regression prognostic model to obtain five genes (*FDX1, LIAS, LIPT1, MTF1, GLS*, Figure 2A). Based on the prognostic information of the dataset TCGA-STAD, we plotted these five genes [*FDX1* (P = 0.001, Figure 2B), *LIAS* (P = 0.006, Figure 2C), *LIPT1*(P = 0.173, Figure 2D), *MTF1* (P = 0.007, Figure 2E), *GLS* (P = 0.188, Figure 2F)] K-M curves, of which we selected three genes (*FDX1*, *LIAS*, *MTF1*) that were statistically significant (P < 0.05) as prognosis-related genes for copper death.

Differential expression analysis of genes related to copper death prognosis

Using the limma package, we first normalized the GEP data of 353 subjects with STAD in the dataset TCGA-STAD. Then, depending on the risk scores from the LASSO regression analysis outcomes, the samples with risk scores more than the median were considered as the group of high risk, and those with risk scores less than the median were considered as the low-risk group. DEGs were obtained by differential analysis in low and high-risk groups and volcano plotting of the differential analysis results (Figure 3A). The results were as follows: the data set TCGA-STAD had a total of 7330 DEGs satisfying $|\log FC| > 0$ and P value < 0.05. DEGs were intersected with copper death prognosis-related genes to obtain three copper death prognosis-related differentially expressed genes (*FDX1*, *LIAS*, *MTF1*). The expression profile data of copper death prognosis-related DEGs were then extracted, and heatmaps were drawn utilizing the ComplexHeatmap package (Figure 3B). To demonstrate the expression of copper death prognosis-related DEGs in the dataset TCGA-STAD. The outcomes show that gene *FDX1*, gene *LIAS*, and gene *MTF1* are differentially expressed genes down-regulated in both high and low-risk groupings.

Finally, we plotted group comparison plots for gene *FDX1* (Figure 3C), gene *LIAS* (Figure 3D), and gene *MTF1* (Figure 3E) based on the different groupings in the dataset TCGA-STAD to demonstrate the DEGs linked with copper death prognosis in different sets of expression in various groups. The outcomes exhibited P < 0.001 for *FDX1*, *LIAS*, and *MTF1* in the low and high-risk subgroups.

DEGs' molecular correlation analysis in the prognosis of copper death

We used the expression profile data from the dataset TCGA-STAD to calculate the association of other molecules in the dataset with the gene *FDX1*, the gene *LIAS* and the gene *MTF1*. We selected the results of the correlation analysis of gene

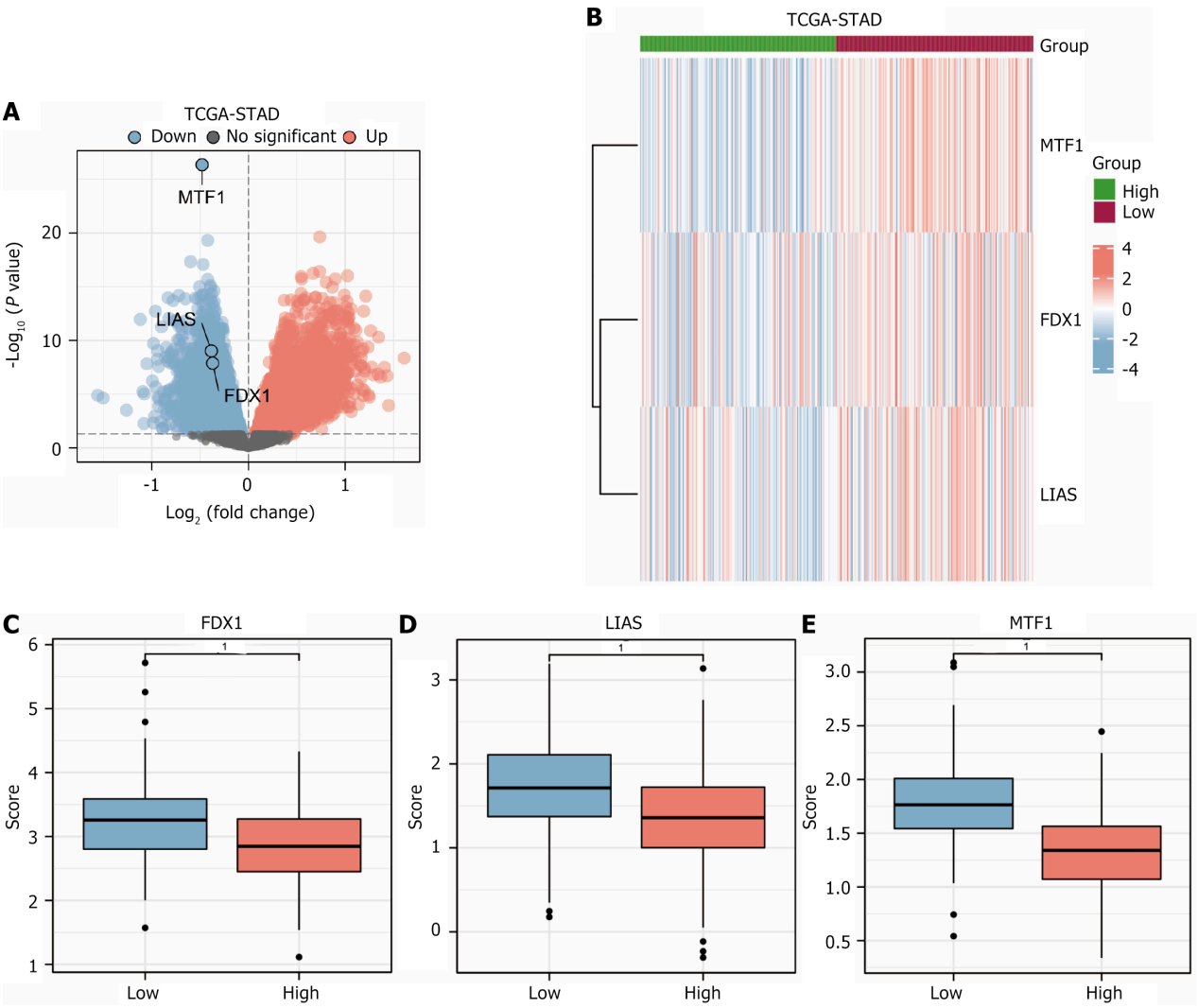


Figure 3 Volcano plot of The Cancer Genome Atlas-stomach adenocarcinoma differential analysis results for dataset, heat map of prognostic differentially expressed genes and group comparison plot. A: Volcano plot of results of differential analysis in dataset The Cancer Genome Atlas (TCGA)-stomach adenocarcinoma (STAD; genes marked in the plot are copper death prognosis-related differentially expressed genes); B: Heat map of expression of copper death prognosis-related differentially expressed genes in dataset TCGA-STAD according to high and low risk subgroups; C: Comparison plot of gene FDX1 in high and low risk groups (subgroups: High and low) in dataset TCGA-STAD; D: Comparative plot of gene LIAS; E: Comparative plot of gene MTF1. TCGA: The Cancer Genome Atlas; STAD: Stomach adenocarcinoma; Up: Up-regulated genes; Down: Down-regulated genes. [1]$P < 0.001$, which is highly statistically significant.

FDX1 in molecular type for protein-coding molecules ($P < 0.05$) to take positive correlation Top5 and negative correlation Top5 to plot the co-expression heat map of gene *FDX1* in the dataset TCGA-STAD (Figure 4A). Then the molecules with gene type lncRNA ($P < 0.05$) were selected to take positive correlation Top5 and negative correlation Top5 to plot the co-expression heat map of gene *FDX1* in the dataset TCGA-STAD (Figure 4B). The correlation analysis outcomes of gene *LIAS* were then selected for the molecular type of protein-coding molecules ($P < 0.05$) to plot the co-expression heat map of gene *LIAS* in the dataset TCGA-STAD by taking the positive correlation Top5 and negative correlation Top5 (Figure 4C). Then the molecules with gene type lncRNA ($P < 0.05$) were selected to take positive correlation Top5 and negative correlation Top5 to plot the co-expression heat map of gene *LIAS* in the dataset TCGA-STAD (Figure 4D). Finally, the results of correlation analysis of gene *MTF1* were selected for the molecular type of protein-coding molecules ($P < 0.05$) to take positive correlation Top5 and negative correlation Top5 to plot the co-expression heat map of gene *MTF1* in dataset TCGA-STAD (Figure 4E) After selecting molecules with gene type lncRNA ($P < 0.05$) taking positive correlation Top5 and negative correlation Top5 to plot the co-expression heat map of gene *MTF1* in dataset TCGA-STAD (Figure 4F).

The correlation between gene *LIAS* and protein-coding molecules *GUF1*, *MRPL35*, *SMIM20*, *SEPSECS*, and *MTIF2* gradually increased with increasing gene expression. In contrast, the association between gene LIAS and protein-coding molecules *RTL8C*, *MFGE8*, *PDLIM4*, *VASN*, *KLHL30* gradually decreased with increasing gene expression. The connection between gene *LIAS* and LncRNA molecules AC008966.1, STX18-AS1, LINC00909, SNHG3, RPARP-AS1 gradually increased with increasing gene expression, and the relationship between gene *LIAS* and LncRNA molecules TGFB2-AS1, AC015922.2, AL391422.4 AC019205.1, AL391121.1 correlated progressively lower with increasing gene expression.

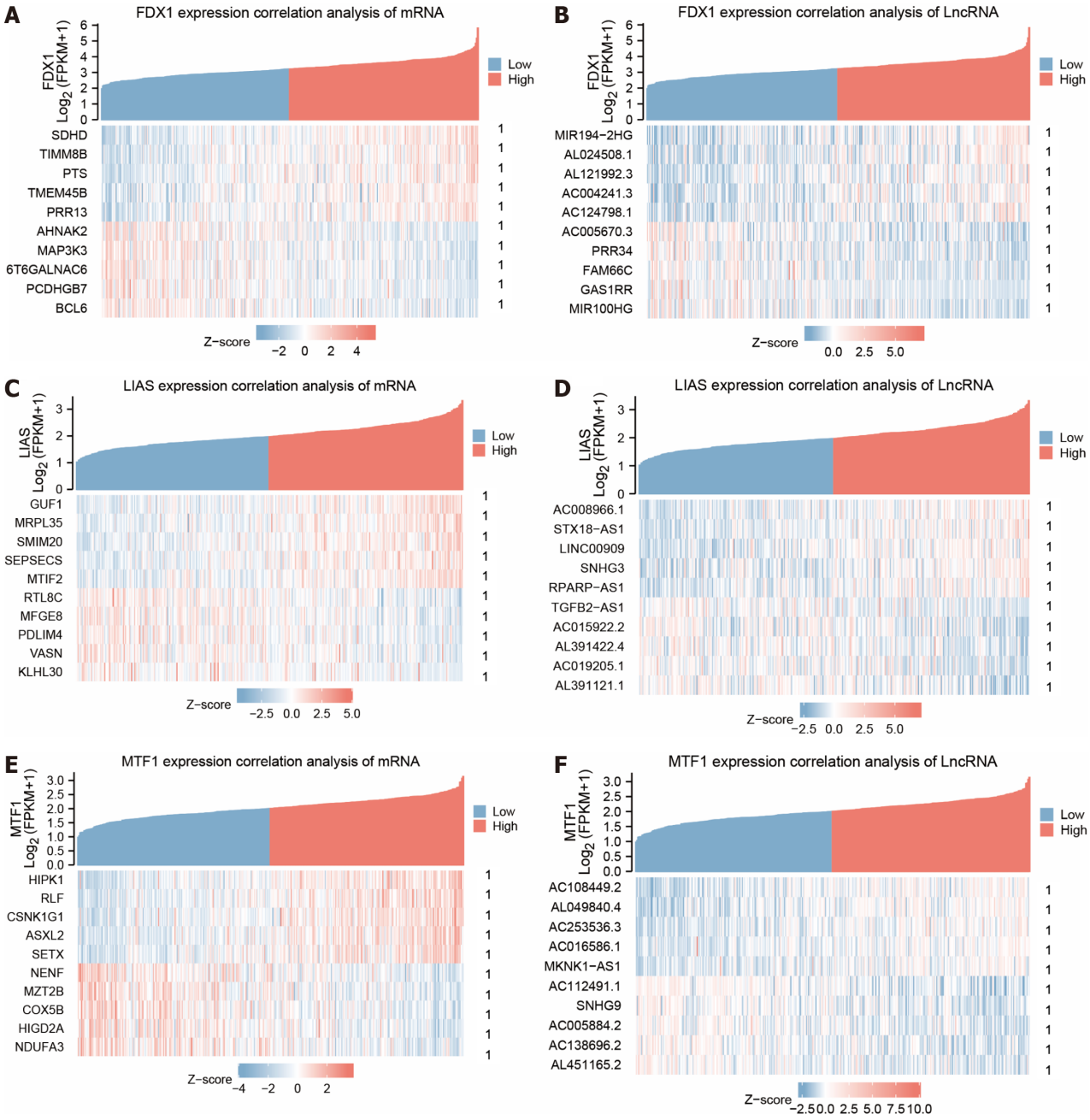


Figure 4 Co-expression heat map of differentially expressed genes for copper death prognosis. A: Heat map of gene FDX1 co-expression with genotypes of protein-coding molecules with positive correlation Top5 and negative correlation Top5 genes; B: Heat map of gene FDX1 co-expression with genotypes of LncRNA molecules with positive correlation Top5 and negative correlation Top5 genes; C: Heat map of gene LIAS co-expression with genotypes of protein-coding molecules with positive correlation Top5 and negative correlation Top5 genes; D: Co-expression heat map of gene LIAS with genotype LncRNA molecules for positively associated Top5 and negatively associated Top5 genes; E: Co-expression heat map of gene MTF1 with genotype protein-coding molecules for positively associated Top5 and negatively associated Top5 genes; F: Co-expression heat map of gene MTF1 with genotype LncRNA molecules for positively associated Top5 and negatively associated Top5 genes. Negatively related Top5 genes co-expression heat map. $^1P < 0.001$, which is highly statistically significant.

The association between gene *MTF1* and protein-coding molecules *HIPK1*, *RLF*, *CSNK1G1*, *ASXL2*, and *SETX* gradually increased with increasing gene expression, and the connection between gene *MTF1* and protein-coding molecules *NENF*, *MZT2B*, *COX5B*, *HIGD2A*, *NDUFA3* gradually decreased with the increase in gene expression. The relationship between gene *MTF1* and LncRNA molecules AC108449.2, AL049840.4, AC253536.3, AC016586.1, MKNK1-AS1 gradually increased with increasing gene expression, and the correlation between gene *MTF1* and LncRNA molecules AC112491.1, SNHG9, AC005884.2 AC138696.2, AL451165.2 correlated progressively lower with increasing gene expression.

Gene function enrichment (GO) and pathway enrichment (KEGG) analyses of DEGs connected to copper death prognosis

We selected the gene *FDX1*, the gene LIAS and the gene *MTF1* with the molecule type used in the co-expression heat map

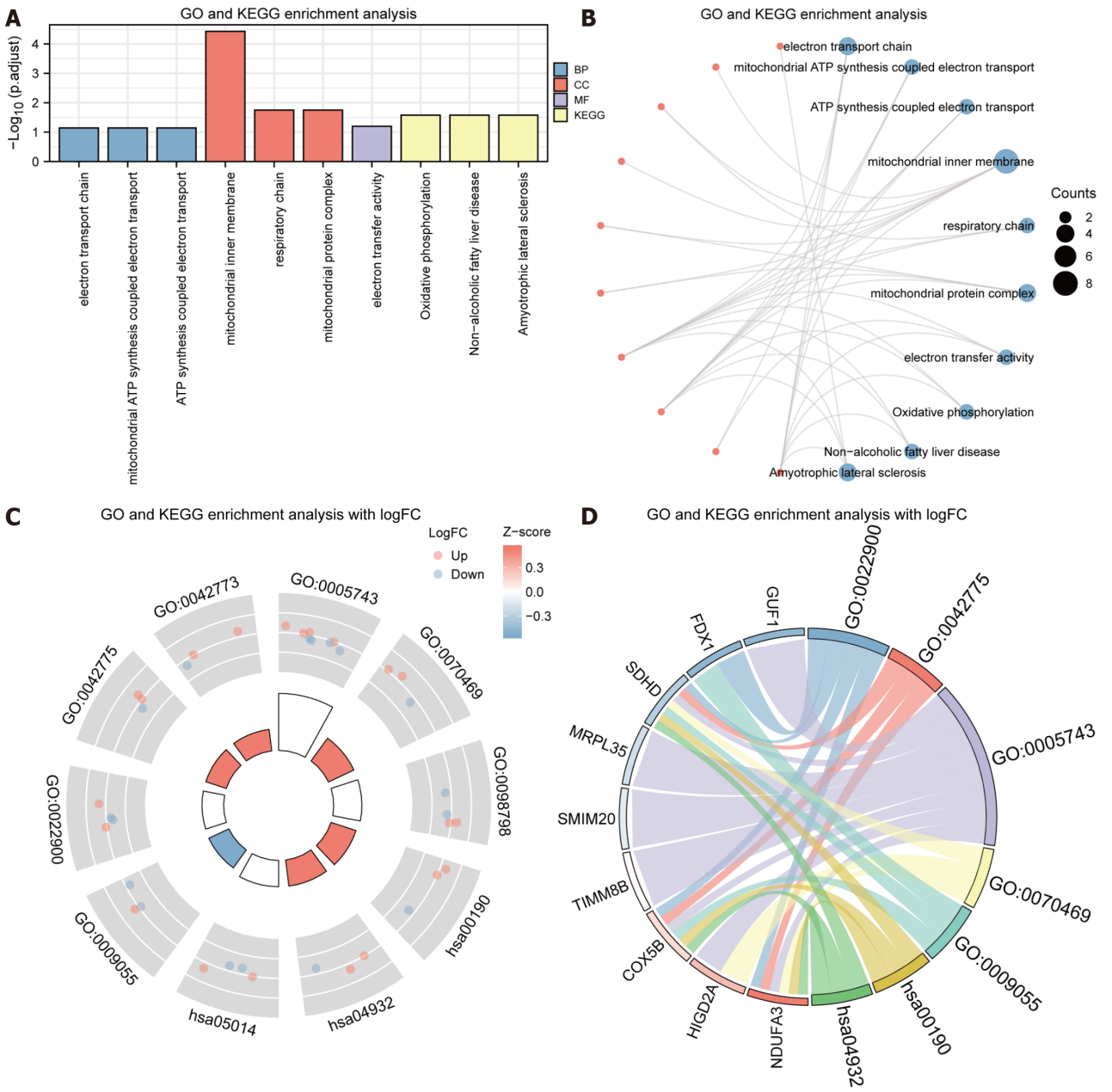


Figure 5 Visualization of functional enrichment (Gene Ontology) and pathway enrichment (Kyoto Encyclopedia of Genes and Genomes) analyses outcomes. A: Histogram of functional enrichment [Gene Ontology (GO)] and pathway enrichment [Kyoto Encyclopedia of Genes and Genomes (KEGG)] analyses outcomes; B: Ring network of functional enrichment (GO) and pathway enrichment (KEGG) analyses outcomes; C: Circle plot of the combined logFC outcomes of functional enrichment (GO) and pathway enrichment (KEGG) analyses; D: String plot of the combined logFC outcomes of functional enrichment (GO) and pathway enrichment (KEGG) analyses. STAD: Stomach adenocarcinoma. GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; BP: Biological process; CC: Bellular component; MF: Molecular function; Up: Up-regulated genes; Down: Down-regulated genes.

drawn for the protein code as co-expressed genes for the three genes for 30 co-expressed genes. We enriched these 30 genes along with the three copper death prognosis-related DEGs for a total of 33 genes for analysis. These 33 genes were utilized for GO and KEGG gene functional enrichment analysis, which demonstrated that they were primarily enriched in the BP, including the ATP synthesis coupled electron transport, electron transport chain, mitochondrial ATP synthesis related electron transport, mitochondrial inner membrane, mitochondrial protein complex, respiratory chain CC, and MF of electron transfer activity. It was also enriched in KEGG pathways like Non-alcoholic fatty liver disorder and Oxidative phosphorylation. The GO and the KEGG gene functional enrichment analyses outcomes are visualized in a bar chart (Figure 5A and Table 2).

Meanwhile, network diagrams were drawn based on the outcomes of GO functional and KEGG pathway enrichment analyses (Figure 5B). The connecting lines illustrate the corresponding molecules and the annotations of the related entries; the more significant the node, the greater the number of molecules contained in the entry. Finally, we used the logFC values of 32 of these 33 genes from the TCGA-STAD differential analysis to perform a combined logFC analysis of function enrichment and KEGG pathway enrichment, and depending on the enrichment analysis, the logFC of the molecules was employed to detect the standard score (Z-score) for each entry) and visualized by circle plot (Figure 5C)

Table 2 Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analysis results

Ontology	ID	Description	*P* value	*P* adjust	*Q* value
BP	GO: 0022900	Electron transport chain	1.62e-04	0.072	0.060
BP	GO: 0042775	Mitochondrial ATP synthesis coupled electron transport	4.05e-04	0.072	0.060
BP	GO: 0042773	ATP synthesis coupled electron transport	4.18e-04	0.072	0.060
BP	GO: 2000773	Negative regulation of cellular senescence	4.92e-04	0.072	0.060
BP	GO: 0022904	Respiratory electron transport chain	7.01e-04	0.078	0.065
CC	GO: 0005743	Mitochondrial inner membrane	5.02e-07	3.72e-05	3.07e-05
CC	GO: 0070469	Respiratory chain	5.13e-04	0.018	0.015
CC	GO: 0098798	Mitochondrial protein complex	7.23e-04	0.018	0.015
MF	GO: 0009055	Electron transfer activity	8.42e-04	0.063	0.047
KEGG	hsa00190	Oxidative phosphorylation	0.001	0.026	0.016
KEGG	hsa04932	Non-alcoholic fatty liver disease	0.002	0.026	0.016
KEGG	hsa05014	Amyotrophic lateral sclerosis	0.003	0.026	0.016
KEGG	hsa04714	Thermogenesis	0.007	0.046	0.028
KEGG	hsa05012	Parkinson disease	0.008	0.046	0.028

GO: Gene Ontology; BP: Biological process; MF: Molecular function; CC: Cellular component; KEGG: Kyoto Encyclopedia of Genes and Genomes.

and chord plot (Figure 5D).

GSEA and GSVA

To detect all gene impacts on pathway expression levels in the STAD dataset TCGA-STAD, we used the cluster profile package to perform GSEA on all genes in the dataset TCGA-STAD according to groups of low and high risk. GSEA was conducted to take the NES of the star pathways and plot the mountain range (Figure 6A) are significantly enriched in HALLMARK EPITHELIAL MESENCHYMAL TRANSITION (Figure 6B), HALLMARK MYOGENESIS (Figure 6C), HALLMARK COAGULATION (Figure 6D) HALLMARK_APICAL_JUNCTION (Figure 6E) and other biologically relevant functions and signaling pathways.

To explore the variations in the hallmark gene sets between high and low-risk groups for STAD, we conducted a GSVA of all genes expression data in the dataset TCGA-STAD according to the standard and high-risk groups for STAD samples. The outcomes showed that a total of 28 hallmark gene sets showed variations ($P < 0.05$) among the high and low-risk groups. Subgroup comparison plots (Figure 7A) and heat maps (Figure 7B) of the outcomes of the differences between the groups of high and low risk for these 28 gene sets were plotted (Table 3).

The results show that: gene sets HALLMARK_GLYCOLYSIS, HALLMARK_INTERFERON_ALPHA_RESPONSE, HALLMARK_P53_PATHWAY, HALLMARK_TGF_BETA_SIGNALING in the high and low risk groups of dataset TCGA-STAD between $P < 0.05$. Gene sets HALLMARK_ANGIOGENESIS, HALLMARK_HEDGEHOG_SIGNALING, HALLMARK_BILE_ACID_METABOLISM, HALLMARK_ESTROGEN_ RESPONSE_LATE, HALLMARK_MYC_TARGETS_V2, HALLMARK_KRAS_SIGNALING_DN, HALLMARK_PANCREAS_BETA_CELLS between high and low risk groups in dataset TCGA-STAD $P < 0.01$. Gene sets HALLMARK_MYOGENESIS, HALLMARK_PROTEIN_SECRETION, HALLMARK_MITOTIC_SPINDLE, HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION HALLMARK_G2M_CHECKPOINT, HALLMARK_PI3K_AKT_MTOR_SIGNALING, HALLMARK_PEROXISOME, HALLMARK_SPERMATOGENESIS, HALLMARK_MTORC1_SIGNALING HALLMARK_E2F_TARGETS, HALLMARK_MYC_TARGETS_V1, HALLMARK_UNFOLDED_PROTEIN_RESPONSE, HALLMARK_COAGULATION, HALLMARK_FATTY_ACID_ METABOLISM, HALLMARK_ANDROGEN_RESPONSE, HALLMARK_HYPOXIA between high and low risk groups in dataset TCGA-STAD at $P < 0.001$.

Construction of PPI, mRNA-miRNA, and mRNA-TF interaction networks

Protein-protein interactions were analyzed for three copper death prognosis-related DEGs (*FDX1*, *LIAS*, *MTF1*) utilizing the STRING database, and the interactions were visualized employing Cytoscape software (Figure 8A). The target and CHIPBase (version 2.0) databases were used to find TF that bind to three copper death prognosis-related DEGs (*FDX1*, *LIAS*, *MTF1*). In the CHIPBase database, we used D1kbToTalSite > 1 as the screening principle to acquire 29 pairs of mRNA-TF, and in the target database, we used NO of dataset > 1 as the screening principle to receive 476 pairs of mRNA-TF. Typically, 23 mRNA-TF pairs were obtained by intersecting the results of the two databases. The Cytoscape program was utilized to display the mRNA-TF interaction network (Figure 8B). We used mRNA-miRNA data from the Starbase and the miRDB databases to anticipate miRNAs interacting with these three copper death prognosis-related DEGs (*FDX1*, *LIAS*, *MTF1*). In the Starbase database, we screened for cancernum > 0 to obtain 92 pairs of mRNA-miRNAs, and in the

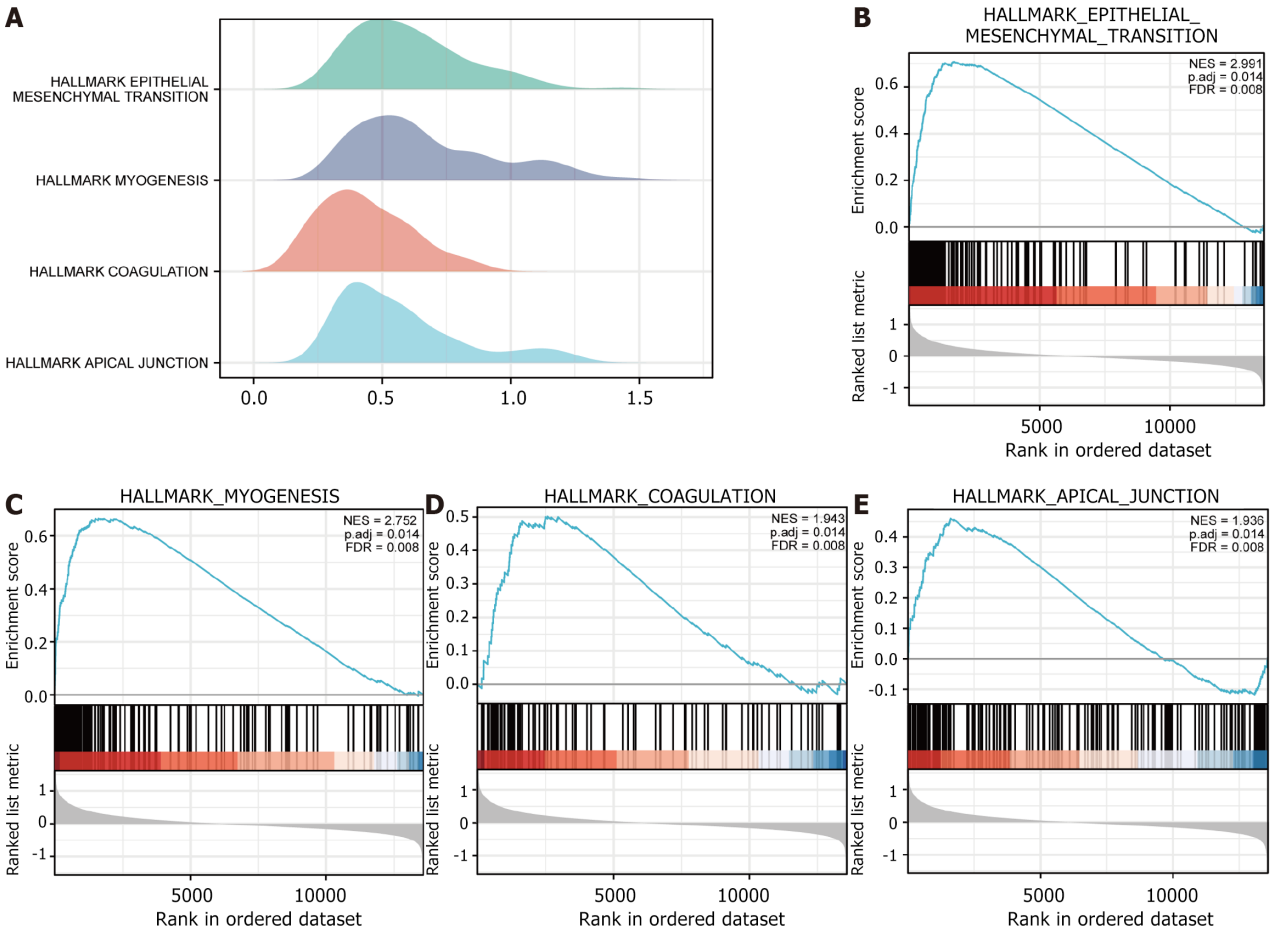


Figure 6 Gene Set Enrichment Analysis of the dataset The Cancer Genome Atlas-stomach adenocarcinoma. A: Mountain plot of Gene Set Enrichment Analysis (GSEA) results for the dataset The Cancer Genome Atlas (TCGA)-stomach adenocarcinoma (STAD) for gastric cancer (STAD); B: GSEA of all genes in the dataset TCGA-STAD in high and low risk subgroups (subgroup: High and subgroup: Low) *vs* HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION; C: Visualization of GSEA outcomes of all genes in the dataset TCGA-STAD in high and low risk groupings (grouping: High and grouping: Low) *vs* HALLMARK_MYOGENESIS; D: Visualization of GSEA outcomes of all genes in the dataset TCGA-STAD in high and low risk groupings (grouping: High and grouping: Low) *vs* visualization of GSEA results for HALLMARK_COAGULATION; E: Visualization of GSEA results for all genes in the dataset TCGA-STAD in high and low risk groupings (grouping: High and grouping: Low) *vs* HALLMARK_APICAL_JUNCTION. FDR: False discovery rate.

miRDB database, to obtain 515 pairs of mRNA-miRNAs. The intersection of the two databases resulted in 43 teams of mRNA-miRNAs. The mRNA-miRNA interaction network was mapped by Cytoscape software for visualization (Figure 8C).

Prognostic analysis and performance of predictive DEGs

Using risk factor plots, we visualized the risk factor groupings of the created LASSO regression predictive model (Figure 9A). Then, to validate our LASSO regression predictive model, we employed multivariate and univariate Cox regressions in the TCGA-STAD dataset to clinically analyze the association between increased and reduced DEGs expression associated with copper death prognosis and prognosis. We selected the statistically significant ($P < 0.05$) parts of the results from the univariate Cox regressions in the form of forest plots for presentation (Figure 9B).

In addition, we performed Calibration analyses and plotted calibration curves for the 1-, 3- and 5-year prognosis of the statistically significant (P <0 .05) factors in the univariate and multivariate Cox regression analyses of the one-way outcomes (Figure 9C), and analyzed and plotted nomogram for these univariate outcome nomograms based on prognostic information (Figure 9D). The results show that the best fit was achieved for the 1-year model constructed.

Finally, we used DCA to assess the medical efficacy of the constructed LASSO regression predictive model at one year (Figure 9E), three years (Figure 9F), and five years (Figure 9G). The results showed that the LASSO regression prognostic model with DEGs (*FDX1*, *LIAS*, *MTF1*) associated with copper death prognosis as variables predicted gastric cancer better with increasing disease duration.

Expression validation and ROC validation of prognosis-related differential genes

We initially standardized the GEO datasets GSE26942, GSE54129, and GSE66229 using the limma package to plot three copper deaths using STAD samples and control samples as subgroups prognosis-related DEGs (*FDX1*, *LIAS*, *MTF1*) in data GSE26942 (Figure 10A), dataset GSE54129 (Figure 10B) and dataset GSE66229 (Figure 10C) respectively, before plotting group comparison for dataset TCGA-STAD based on grouping of low and high risk (Figure 10D). The differential

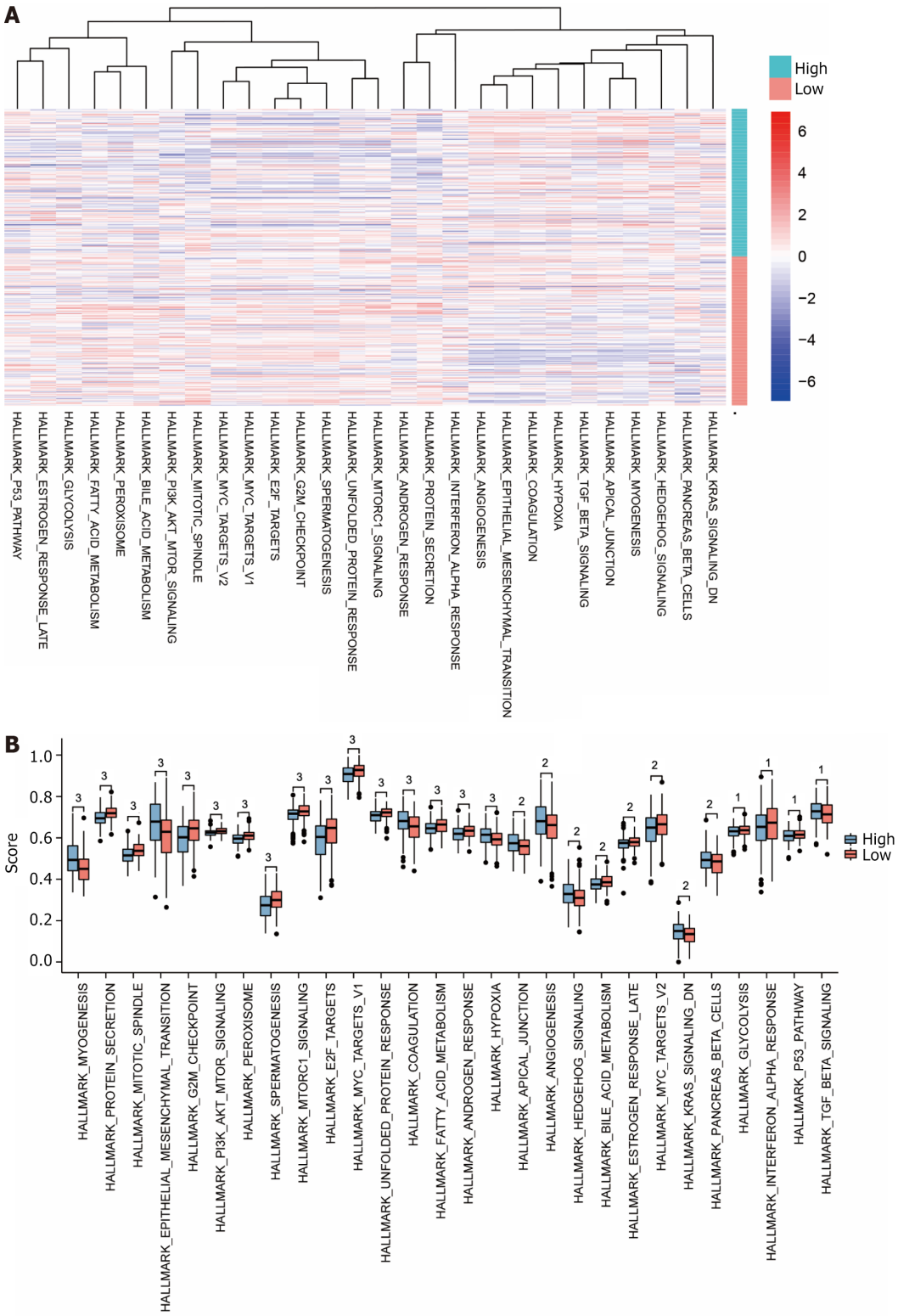


Figure 7 Visualisation of Gene Set Variation Analysis results. A: Complex heat map of gene sets showing differences ($P < 0.05$) between datasets The Cancer Genome Atlas (TCGA)-stomach adenocarcinoma (STAD) high and low risk subgroups (subgroup: High and subgroup: Low); B: Subgroup comparison map of gene sets showing differences ($P < 0.05$) between datasets TCGA-STAD high and low risk subgroups (subgroup: High and subgroup: Low); C: Comparison of gene sets showing differences ($P < 0.05$) between datasets TCGA-STAD high and low risk subgroups (subgroup: High and subgroup: Low). Up: Up-regulated genes; Down: Down-regulated genes. $^{1}P < 0.05$, indicating statistical significance. $^{2}P < 0.01$, which is highly statistically significant. $^{3}P < 0.001$ and highly statistically significant.

Table 3 Gene Set Enrichment Analysis enrichment analysis results

ID	Enrichment score	NES	*P* value	*Q* values
HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION	0.708105259	2.990707978	0.001305483	0.008457298
HALLMARK_HYPOXIA	0.403129656	1.699699999	0.00130719	0.008457298
HALLMARK_APICAL_JUNCTION	0.461587301	1.935939035	0.001310616	0.008457298
HALLMARK_MYOGENESIS	0.66612	2.752470842	0.001331558	0.008457298
HALLMARK_COAGULATION	0.50179623	1.942687567	0.00143472	0.008457298
HALLMARK_UV_RESPONSE_DN	0.406876695	1.662984536	0.002702703	0.009857419
hallmark_interferon_alpha_response	-0.423867587	-1.8197451	0.003257329	0.009857419
HALLMARK_G2M_CHECKPOINT	-0.566300626	-2.681102853	0.004255319	0.009857419
hallmark_interferon_gamma_response	-0.329292011	-1.559005425	0.004255319	0.009857419
HALLMARK_E2F_TARGETS	-0.562672699	-2.6759039	0.004329004	0.009857419
HALLMARK_MYC_TARGETS_V1	-0.454693047	-2.162384814	0.004329004	0.009857419
HALLMARK_MITOTIC_SPINDLE	-0.367141984	-1.748758241	0.004347826	0.009857419
HALLMARK_MTORC1_SIGNALING	-0.385874626	-1.837984926	0.004347826	0.009857419
HALLMARK_MYC_TARGETS_V2	-0.448665513	-1.728129282	0.005617978	0.011827321
HALLMARK_INFLAMMATORY_RESPONSE	-0.318801368	-1.472576393	0.00862069	0.016938899
HALLMARK_PROTEIN_SECRETION	-0.367157298	-1.567228573	0.009771987	0.018001029
HALLMARK_ANGIOGENESIS	0.547725076	1.690092924	0.014802632	0.025664005
HALLMARK_IL6_JAK_STAT3_SIGNALING	-0.367388389	-1.508170458	0.018181818	0.029771398
HALLMARK_KRAS_SIGNALING_DN	0.371059103	1.431772189	0.024425287	0.037786775
hallmark_estrogen_response_late	-0.291604703	-1.348128819	0.025641026	0.037786775
HALLMARK_UNFOLDED_PROTEIN_RESPONSE	-0.323403998	-1.423443484	0.029315961	0.041145208
HALLMARK_HEDGEHOG_SIGNALING	0.472117157	1.469309232	0.045602606	0.0610944

expression of three copper death prognosis-related DEGs in STAD was verified to be significant. The outcomes exhibited that the gene *FDX1* was statistically significant and was lowly expressed in STAD samples, and it could be concluded that the gene *FDX1* is an oncogene in STAD.

Finally, we used 407 samples from dataset TCGA-STAD (Figure 10E), dataset GSE26942 (Figure 10F), dataset GSE54129 (Figure 10G), and dataset GSE66229 (Figure 10H) to draw ROC curves based on STAD samples and control samples were grouped to plot ROC curves for the DEGs (*FDX1*, *LIAS*, *MTF1*) connected with copper death prognosis. The results showed that the genes *FDX1* (AUC = 0.823) and *LIAS* (AUC = 0.728) had some accuracy, and *MTF1* (AUC = 0.597) had low accuracy in STAD sample and control sample subgroups of dataset GSE26942. Gene *FDX1* (AUC = 0.970), and *LIAS* (AUC = 0.985) had high accuracy, and gene *MTF1* (AUC = 0.813) had some accuracy in the STAD sample and control sample subgroup of the dataset GSE54129. Gene *FDX1* (AUC = 0.610), *LIAS* (AUC = 0.550), and *MTF1* (AUC = 0.519) had low accuracy STAD sample and control sample of the dataset GSE66229. Gene *FDX1* (AUC = 0.620), *LIAS* (AUC = 0.543), and *TF1* (AUC = 0.625) had low accuracy in STAD sample and control sample subgroup of the GSETCGA-STAD dataset. In summary, the gene *FDX1* had the highest diagnostic accuracy in STAD (Table 4).

Expression of the gene FDX1 between different single cell subpopulations and in various human tissues

We obtained gene *FDX1* expression in different human tissues (Figure 11) and among different STAD single-cell subpopulations (Figure 12A) through the HPA database and visualized the results. The results show that gene *FDX1* has high expression of both RNA and protein in endocrine tissues, higher protein expression in kidney and urinary bladder tissues, and high protein expression in male and female tissues. Gene *FDX1* was highly expressed in gastric cancer cell lines, mainly in T-cells, Plasma cells. We utilized the RCircos package to localize prognosis related DEGs in chromosomes (Figure 12) The results show that the gene *FDX1* is on chromosome 11.

DISCUSSION

STAD is a widespread malignant tumor with a worse prognosis and an elevated rate of death. Intestinal mucosa cancer cells that grow abnormally and create ulcers are the causes of STAD. Diagnosis is always delayed since this process is

Table 4 Univariate/multivariate Cox regression

Characteristics	Total (*n*)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95%CI)	*P* value	Hazard ratio (95%CI)	*P* value
FDX1	370				
High	184	Reference			
Low	186	1.282 (0.922-1.784)	0.140		
LIAS	370				
High	183	Reference			
Low	187	1.501 (1.075-2.095)	0.017	1.414 (0.981-2.038)	0.063
MTF1	370				
High	185	Reference			
Low	185	1.368 (0.985-1.900)	0.061	1.346 (0.936-1.936)	0.109
T stage	362				
T1	18	Reference			
T2	78	6.725 (0.913-49.524)	0.061	4.323 (0.548-34.111)	0.165
T3	167	9.548 (1.326-68.748)	0.025	5.338 (0.613-46.515)	0.129
T4	99	9.634 (1.323-70.151)	0.025	5.141 (0.576-45.881)	0.143
N stage	352				
N0	107	Reference			
N1	97	1.629 (1.001-2.649)	0.049	1.152 (0.578-2.296)	0.688
N2	74	1.655 (0.979-2.797)	0.060	1.298 (0.553-3.050)	0.549
N3	74	2.709 (1.669-4.396)	< 0.001	1.818 (0.772-4.281)	0.171
M stage	352				
M0	327	Reference			
M1	25	2.254 (1.295-3.924)	0.004	1.038 (0.430-2.504)	0.935
Pathologic stage	347				
Stage I	50	Reference			
Stage II	110	1.551 (0.782-3.078)	0.209	1.132 (0.399-3.212)	0.816
Stage III	149	2.381 (1.256-4.515)	0.008	1.181 (0.304-4.588)	0.810
Stage IV	38	3.991 (1.944-8.192)	< 0.001	2.082 (0.513-8.445)	0.305

often slower and difficult to identify at an early phase[11]. Though the occurrence and death rates of STAD have decreased over the past century, the total cases of gastric cancer numbers continue to increase due to the aging population [12]. Moreover, the healthcare burden of gastric cancer is high, accounting for 20% of the total global cancer burden[14]. Despite advances in targeted therapy over the past decades, surgery is still considered to be the only curative treatment for gastric cancer to date.

Furthermore, metastasis of cancer cells and resistance to chemotherapy are the main barriers limiting malignancy treatment efficacy[15]. Unfortunately, despite substantial efforts in preclinical and clinical studies, the STAD prognosis is still unsatisfactory, with a 5-year survival rate of only 20%-30% for patients with progressive STAD[16]. Therefore, new strategies and directions for the treatment of STAD are urgently needed.

A new investigation explored that an imbalance in intracellular copper ion accumulation triggers mitochondrial lipoproteins aggregation, causing a distinct type of cell death known as copper death[9]. Copper death largely depends on mitochondrial respiration, unlike apoptosis, scorch death, necrosis, and iron death[17]. Upon excessive accumulation of Cu^{2+} in cells dependent on mitochondrial respiration (Cu^{2+} is transferred into cells *via* copper ion carriers), Cu^{2+} binds to thioredoxylated DLAT, inducing heterodimerization of DLAT. The insoluble DLAT rise causes cytotoxicity and induces cell death[18]. More interestingly, in some cancers, we found higher levels of copper ions in tumor tissue and the serum of tumor patients than in normal subjects[19]. Breast cancer and cuproptosis-related genes are also very closely related [20]. However, the relationship between gastric adenocarcinoma and copper death-related genes and prognosis has not been elucidated.

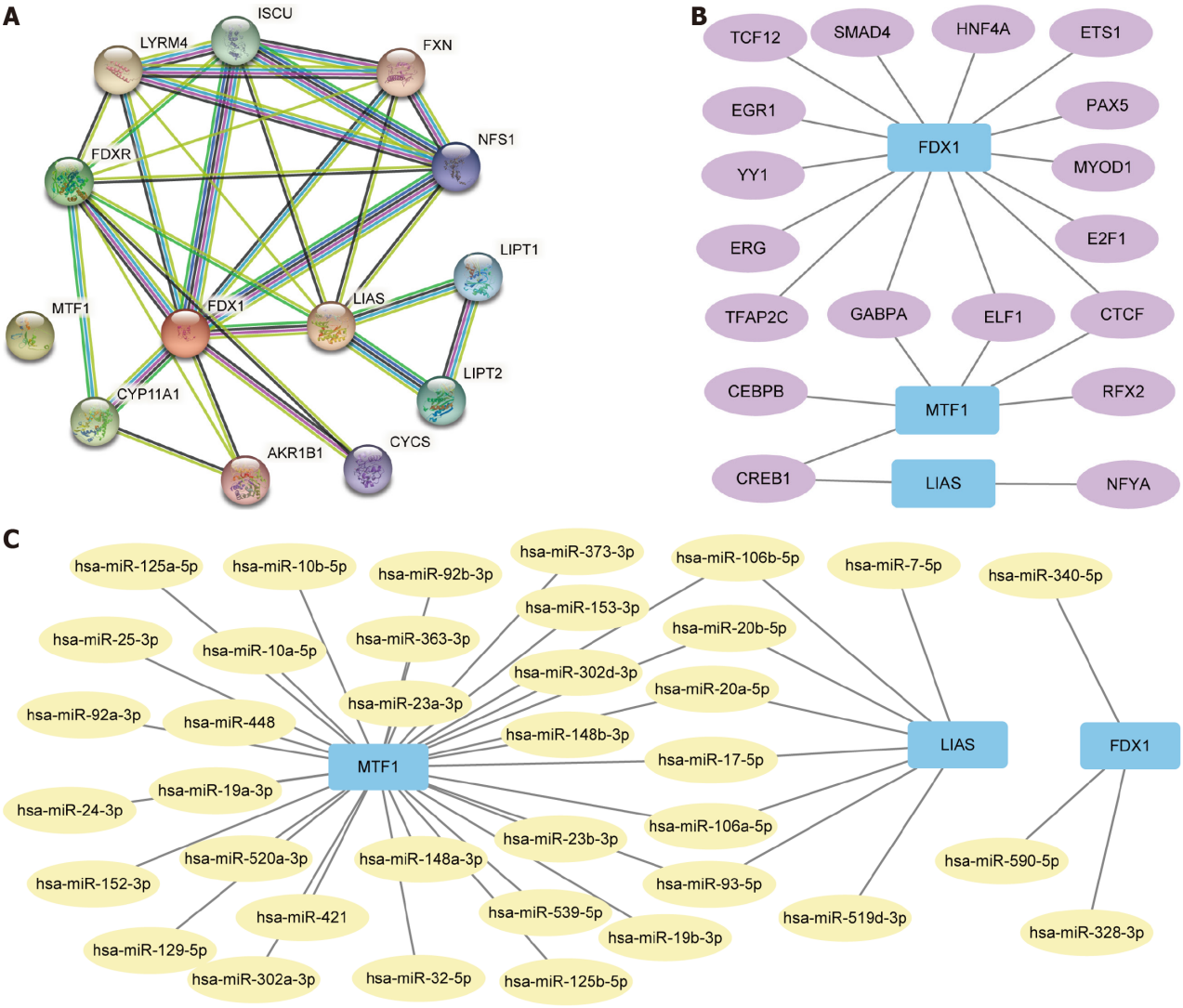


Figure 8 Construction of protein-protein interaction, mRNA-miRNA, and mRNA-transcription factor interactions networks. A: protein-protein interaction network of differentially expressed genes (DEGs) connected with copper death prognosis; B: mRNA-transcription factor (TF) interaction network of DEGs related to copper death prognosis and TF; C: mRNA-miRNA interaction network of DEGs linked with copper death prognosis and miRNA. Blue rectangles are mRNA molecules. Yellow circles are miRNA molecules. Purple circles are TF.

In our investigation, we explored the CRGs' differential expression in STAD and healthy samples and identified three important prognostic genes, *FDX1*, *LIAS* and *MTF1*, by univariate cox regression analysis. These genes have previously been informed to have a crucial function in cancer progression.

FDX1 is a mitochondrial iron-oxygen-reducing protein with essential roles in steroid synthesis, heme, and Fe/S cluster biosynthesis. *FDX1* is important in steroid synthesis, hemoglobin, and Fe/S cluster biosynthesis[21]. It also reduces steroid synthesis by mitochondrial cytochrome P450[22]. *FDX1* is also an important biomarker in clear renal cell carcinoma[23]. The protein encoded by *LIAS* is related to the biotin and lipoic acid synthase family. *FDX*1 regulates cellular proteolipid acylation by binding directly to *LIAS*[24].

Furthermore, *LIAS* is essential in identifying cupulocyte-associated subtypes of gastric cancer and constructing predictive models[25]. *MTF1* induces the expression of metallothionein and other genes related to metal homeostasis in reaction to heavy metals like copper, zinc, cadmium, and silver. It could bind to the metal response element in the promoter and activate the transcription of metallothionein genes such as metallothionein-2/MT2A[26]. In lung adenocarcinoma, *MTF1* is vital in identifying two molecular subtypes and developing predictive models[27]. Another study revealed that zinc promotes epithelial cell transformation to mesenchymal stromal cells (EMT) through an *MTF1*-dependent pathway, contributing to ovarian tumor metastasis[28]. In summary, *FDX1*, *LIAS*, and *MTF1* play essential roles in cancer and are likely potential targets for STAD.

Functional enrichment analysis using GO and KEGG exhibited that these genes are enriched in mitochondrial ATP synthesis coupled electron transport, electron transport chain, ATP synthesis coupled electron transport and are closely related to STAD development. The enzymes on the electron transport chain catalyze the oxidation of biological substrates and the synthesis of ATP and are involved in bioenergetic conversion[29]. It has been shown that *H. pylori* infection of gastric adenocarcinoma cells leads to mitochondrial DNA mutations and reduced mitochondrial DNA content, affecting the ATP synthesis coupled electron transport pathway and reducing the level and activity of the electron transport chain

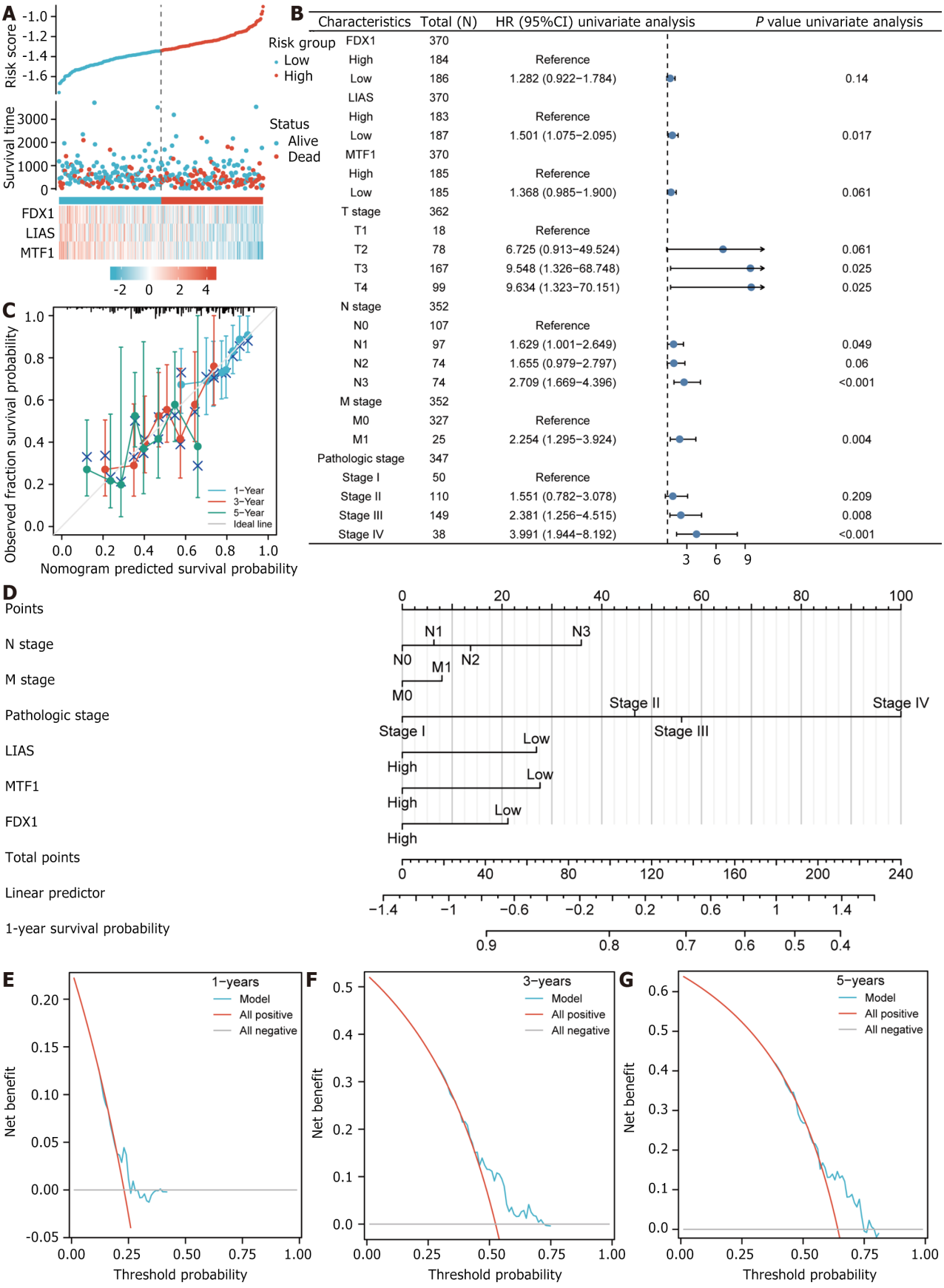


Figure 9 Prognostic analysis and performance of predictive differentially expressed genes. A: Risk factor plot; B: Forest plot for univaiate Cox regression analysis of differentially expressed genes for copper death prognosis; C: 1-, 3- and 5-year calibration curve plots; D: Nomogram; E: 1-year decision curve analysis (DCA) plot for Least Absolute Shrinkage and Selection Operator (LASSO) regression prognosis model; F: 3-year DCA plot for LASSO regression prognosis model; G: 5-year DCA plot for LASSO regression prognosis model.

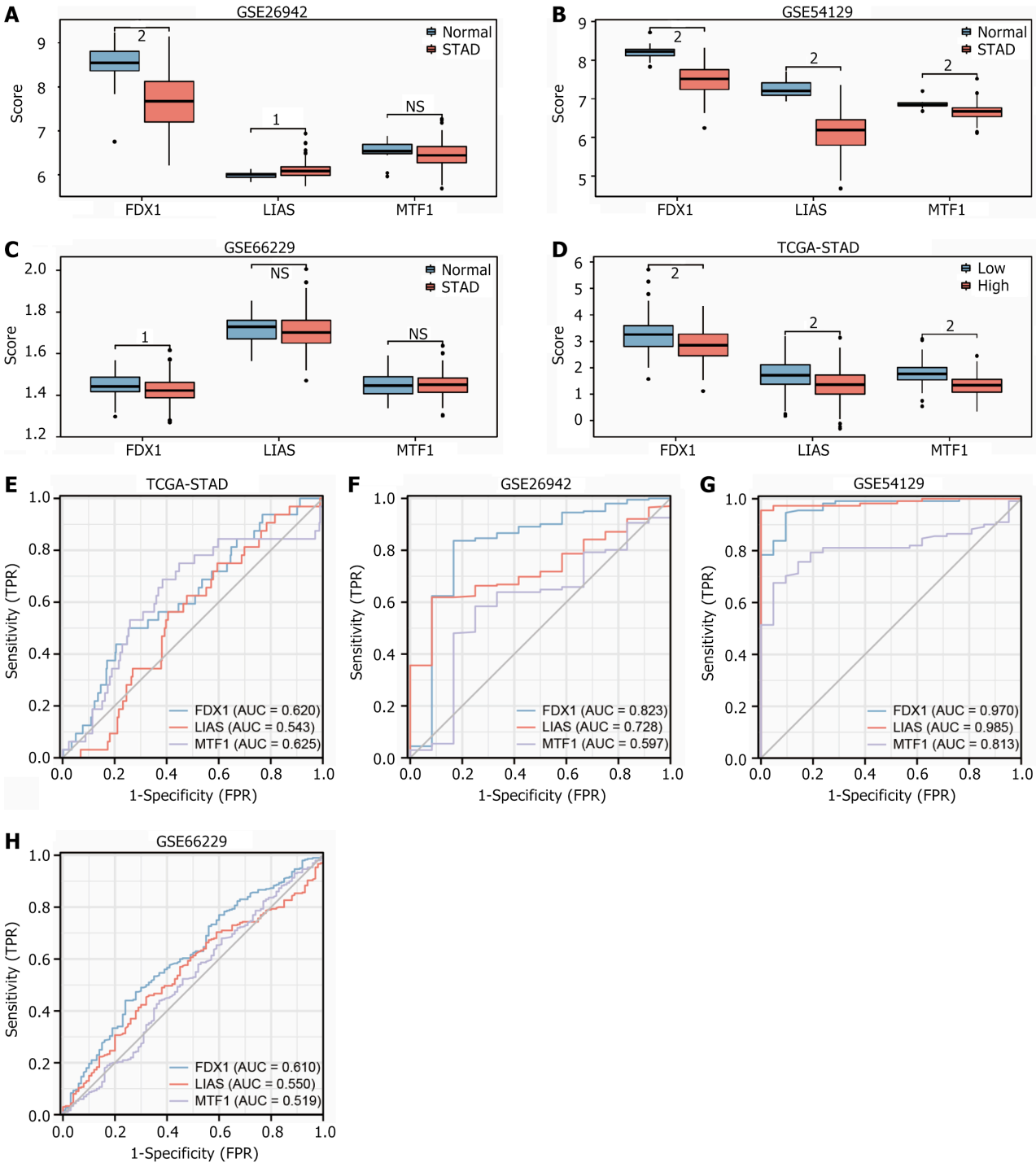


Figure 10 Expression and receiver operating characteristic curve validation of the The Gene Expression Omnibus dataset for prognosis-related differentially expressed genes. A: Expression validation plot of gene FDX1, LIAS, MTF1 in data set GSE26942; B: Expression validation plot of gene FDX1, LIAS, MTF1 in data set GSE54129; C: Expression validation plot of gene FDX1, LIAS, MTF1 in data set GSE66229; D: Expression validation plot of gene FDX1, LIAS, MTF1 in data set The Cancer Genome Atlas (TCGA)-stomach adenocarcinoma (STAD). MTF1 expression validation plot in dataset TCGA-STAD; E: Receiver operating characteristic curves (ROCs) for gene FDX1, LIAS, MTF1 in dataset GSE26942; F: ROC validation of gene FDX1, LIAS, MTF1 in dataset GSE54129; G: ROC curves for gene FDX1, LIAS, MTF1 in dataset ROC validation in dataset GSE66229; H: ROC validation of gene FDX1, LIAS, MTF1 in dataset TCGA-STAD; I: ROC validation of gene FDX1, LIAS, MTF1 in dataset TCGA-STAD. Up: Up-regulated genes; Down: Down-regulated genes; AUC: Aera under the curve. $^{1}P < 0.01$, which is highly statistically significant. $^{2}P < 0.001$ and highly statistically significant.

complex I[30].

This research established a new predictive model dependent on three prognostic CRGs (*i.e.*, FDX1, LIAS, and MTF1) by LASSO-Cox regression, univariate, and multivariate Cox regression analyses. The outcomes exhibited that patients who died were primarily concentrated in the high-risk group and that the expression levels of DEGs associated with copper death prognosis were lower in the high-risk group than in the low-risk group. To validate our LASSO regression predictive model, we also employed univariate and multivariate Cox regression in the TCGA-STAD dataset to analyze the relationship between elevated and decreased expression of DEGs associated with copper death prognosis and clinical

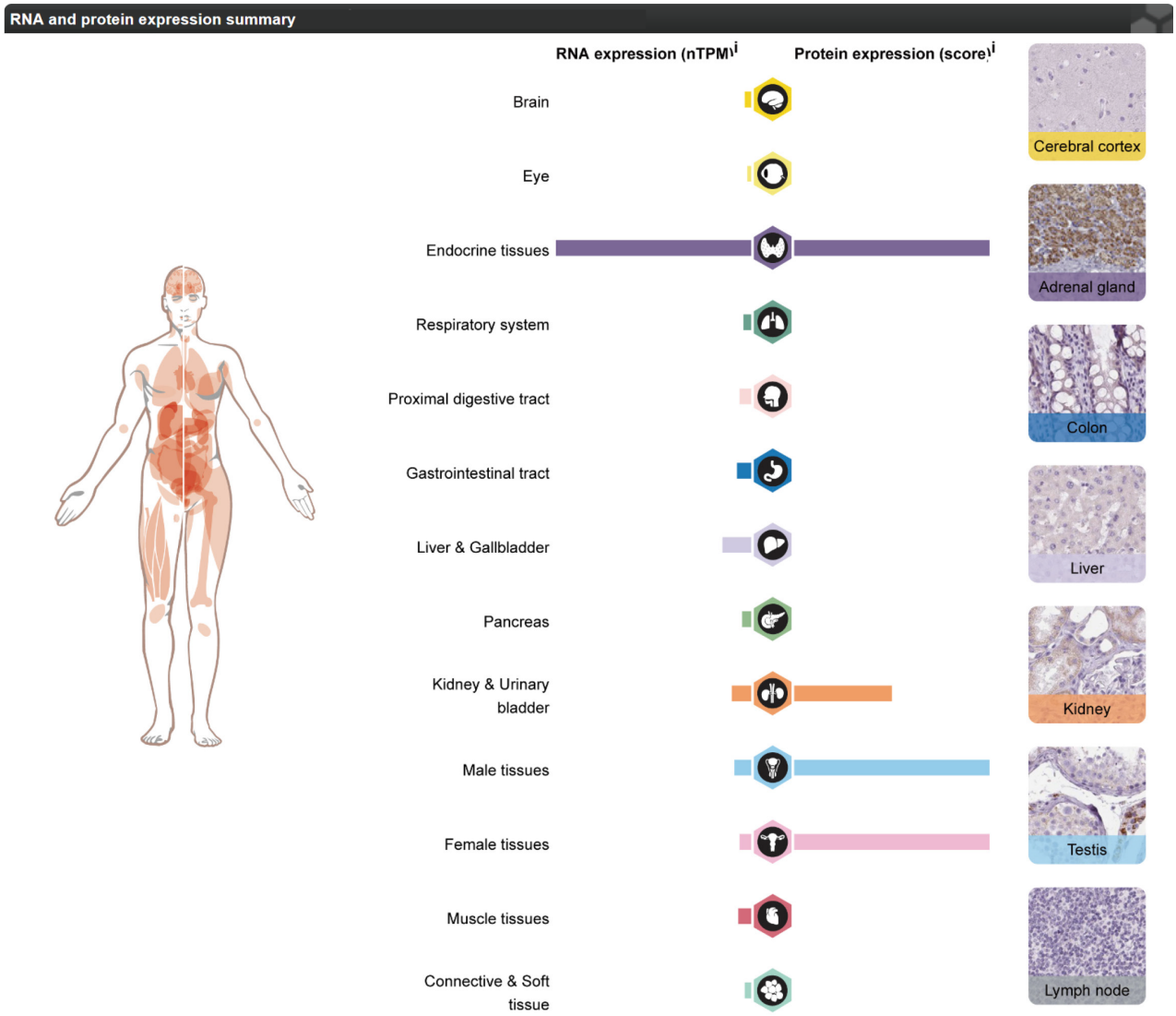


Figure 11 Expression of gene FDX1 in different human tissues.

prognosis, showing that the 1-year model was the best fit and that *FDX1*, *LIAS*, and *MTF1* as variables predicted gastric cancer with increasing duration of disease The better the model indicated.

Most importantly, we finally validated *FDX1*, *LIAS*, and *MTF1* in data sets GSE26942 and GSE54129. Data set GSE66229, respectively, and the results showed that $P < 0.001$ for gene *FDX1* in data set GSE26942, $P < 0.01$ for gene *LIAS*, and P& gt;0.05. in dataset GSE54129 P for gene *FDX1*, *P* for gene *LIAS* and *P* for gene *MTF1* were all less than 0.001. in dataset GSE66229 $P < 0.01$ for gene *FDX1*, $P > 0.05$ for gene *LIAS* and $P > 0.05$ for gene *MTF1*. And, in dataset TCGA- *P* for gene *FDX1*, gene *LIAS*, and gene *MTF1* were all less than 0.001 in the data set STAD. In summary, gene FDX1 could be considered an oncogene of gastric cancer.

FDX1, a protein-coding gene, has been associated with iron death and copper death[31]. *FDX1* encodes a small iron-sulfur protein that transfers electrons from NADPH to mitochondrial cytochrome P450 *via* adrenocortical ferric oxidoreductase and is involved in steroid, vitamin D, and bile acid metabolism[21]. Our study above suggests that *FDX1* is a key gene associated with copper death. Bioinformatics and clinical tissue validation revealed that *FDX1* was highly expressed in STAD tumor tissues, and it was hypothesized that *FDX1* might function in STAD treatment. Furthermore, previous studies by Yang *et al*[32] found that *FDX1* was poorly expressed in most malignancies but highly expressed in gastric adenocarcinoma, glioblastoma, and endometrial cancer of the uterine corpus. And it was demonstrated by *in vitro* experiments that *FDX1* down-regulation inhibited cell viability in bladder malignancy, clear cell renal cell carcinoma, and prostate tumor cells. They inferred that *FDX1* could be a potential therapeutic target for STAD. Their findings are consistent with our conclusions, which validate our data mining results.

We obtained the gene *FDX1* expression in different human tissues and, among other gastric cancer, single-cell subpopulations utilizing the HPA database and visualized the outcomes. The results show that gene *FDX1* is greatly expressed in T-cells, Plasma cells in gastric cancer cell lines. In conclusion, these studies were analyzed in conjunction with relevant clinical data, further strengthening the convincing case and confirming our speculation above about the role of CRGs in STAD.

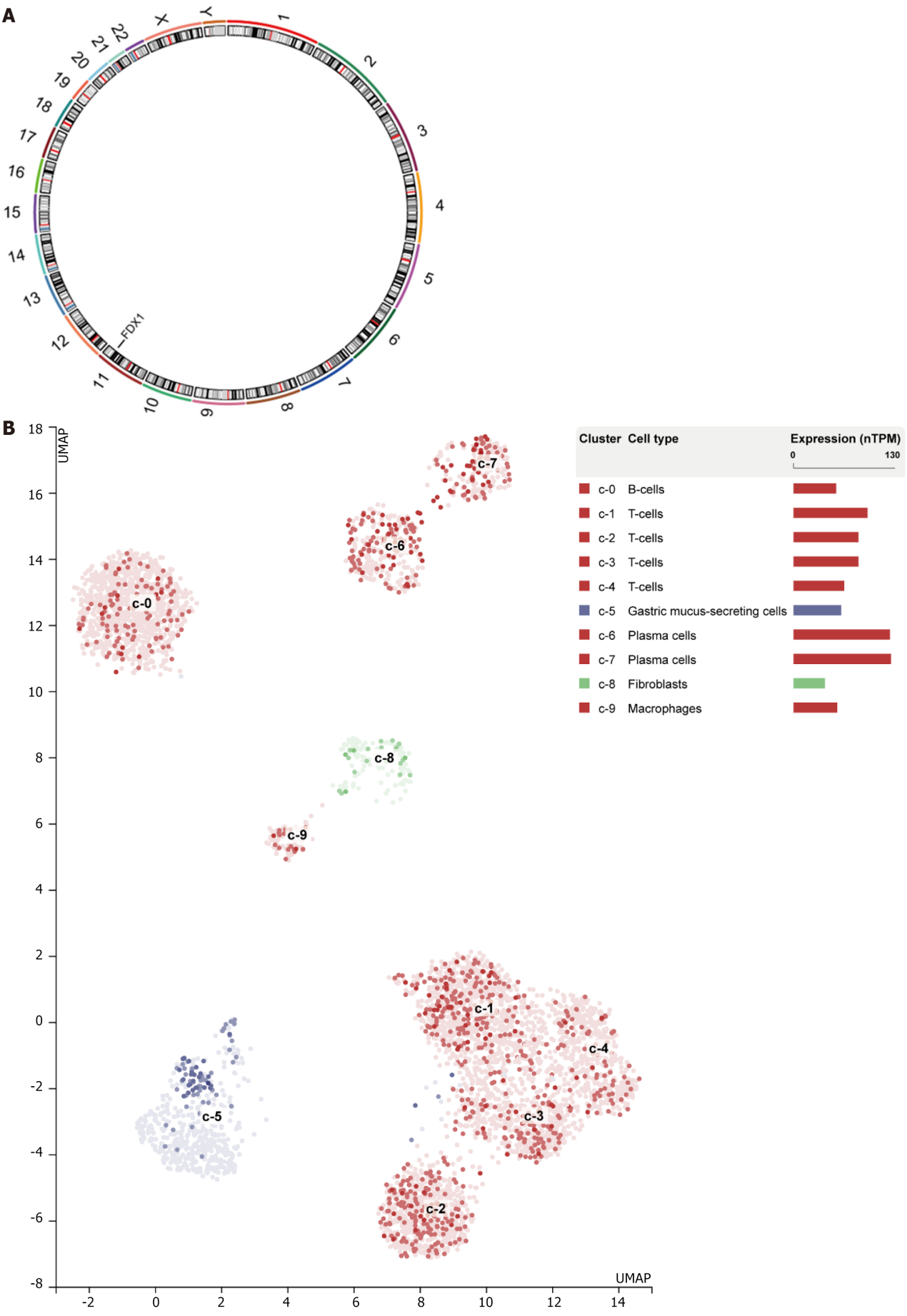


Figure 12 Expression and chromosomal localization of the gene FDX1 in different single cell subpopulations of gastric cancer. A: Gene

FDX1 expression in gastric malignancy cell lines; B: Gene FDX1 Localization in chromosomes.

Of course, the absence of experimental conditions to further validate this with experiments is a limitation of this study. This is a pity for researchers. And there needs to be more appropriate clinical correlation studies that can be analyzed in conjunction with clinical information. And the large number of data sets for this analysis may cause unavoidable inter-batch differences. Next, we will elucidate the role of related genes in STAD onset, migration, and invasion by further exploration.

CONCLUSION

This investigation systematically revealed the function of copper death-related genes in STAD, providing a reliable, comprehensive analysis. Moreover, we established a CRGs score predictive model including these three prognostic markers (*FDX1*, *LIAS*, and *MTF1*), which indicated good validity in predicting survival outcomes in the STAD *cohort*. Most importantly, we identified *FDX1* as an independent factor influencing STAD prognosis. These outcomes provide novel visions into the molecular mechanisms of STAD and contribute to the STAD diagnosis development and new therapeutic strategies.

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FOOTNOTES

Author contributions: Xie XZ and Zuo L designed the research; Huang W, Fan QM, Weng YY, Yao WD, Jiang JL and Jin JQ contributed new reagents/analytic tools; Huang W, Fan QM, Weng YY, Yao WD, Jiang JL and Jin JQ analyzed the data; Xie XZ and Zuo L wrote the paper; all authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. Xie XZ and Zuo L contributed equally to this work as co-first authors equally to this work. Xie XZ and Zhuo L were named co-first authors on three grounds. First of all, the research is a collaborative effort, which precisely reflects the distribution of responsibilities and ensures efficient communication and post-submission management, thus improving the quality and reliability of the paper. Second, the research team brings together diverse expertise in different fields, a designation that highlights the diversity of the team's characteristics and promotes multiple perspectives for deeper understanding. Third, both authors have made equal contributions in the research process, and this naming principle recognizes their equal contributions while emphasizing the spirit of teamwork.

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REFERENCES

1 **Trama A**, Botta L, Foschi R, Ferrari A, Stiller C, Desandes E, Maule MM, Merletti F, Gatta G; EUROCARE-5 Working Group. Survival of European adolescents and young adults diagnosed with cancer in 2000-07: population-based data from EUROCARE-5. *Lancet Oncol* 2016; **17**: 896-906 [PMID: 27237614 DOI: 10.1016/S1470-2045(16)00162-5]

2 **Zheng P**, Chen L, Yuan X, Luo Q, Liu Y, Xie G, Ma Y, Shen L. Exosomal transfer of tumor-associated macrophage-derived miR-21 confers cisplatin resistance in gastric cancer cells. *J Exp Clin Cancer Res* 2017; **36**: 53 [PMID: 28407783 DOI: 10.1186/s13046-017-0528-y]

3 **Banks M**, Graham D, Jansen M, Gotoda T, Coda S, di Pietro M, Uedo N, Bhandari P, Pritchard DM, Kuipers EJ, Rodriguez-Justo M, Novelli

MR, Ragunath K, Shepherd N, Dinis-Ribeiro M. British Society of Gastroenterology guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma. *Gut* 2019; **68**: 1545-1575 [PMID: 31278206 DOI: 10.1136/gutjnl-2018-318126]

4 **Tsugane S**, Sasazuki S. Diet and the risk of gastric cancer: review of epidemiological evidence. *Gastric Cancer* 2007; **10**: 75-83 [PMID: 17577615 DOI: 10.1007/s10120-007-0420-0]

5 **Kim BE**, Nevitt T, Thiele DJ. Mechanisms for copper acquisition, distribution and regulation. *Nat Chem Biol* 2008; **4**: 176-185 [PMID: 18277979 DOI: 10.1038/nchembio.72]

6 **Wang F**, Zhang S, Jeon R, Vuckovic I, Jiang X, Lerman A, Folmes CD, Dzeja PD, Herrmann J. Interferon Gamma Induces Reversible Metabolic Reprogramming of M1 Macrophages to Sustain Cell Viability and Pro-Inflammatory Activity. *EBioMedicine* 2018; **30**: 303-316 [PMID: 29463472 DOI: 10.1016/j.ebiom.2018.02.009]

7 **Wang Y**, Zhang L, Zhou F. Cuproptosis: a new form of programmed cell death. *Cell Mol Immunol* 2022; **19**: 867-868 [PMID: 35459854 DOI: 10.1038/s41423-022-00866-1]

8 **Tsvetkov P**, Coy S, Petrova B, Dreishpoon M, Verma A, Abdusamad M, Rossen J, Joesch-Cohen L, Humeidi R, Spangler RD, Eaton JK, Frenkel E, Kocak M, Corsello SM, Lutsenko S, Kanarek N, Santagata S, Golub TR. Copper induces cell death by targeting lipoylated TCA cycle proteins. *Science* 2022; **375**: 1254-1261 [PMID: 35298263 DOI: 10.1126/science.abf0529]

9 **Ge EJ**, Bush AI, Casini A, Cobine PA, Cross JR, DeNicola GM, Dou QP, Franz KJ, Gohil VM, Gupta S, Kaler SG, Lutsenko S, Mittal V, Petris MJ, Polishchuk R, Ralle M, Schilsky ML, Tonks NK, Vahdat LT, Van Aelst L, Xi D, Yuan P, Brady DC, Chang CJ. Connecting copper and cancer: from transition metal signalling to metalloplasia. *Nat Rev Cancer* 2022; **22**: 102-113 [PMID: 34764459 DOI: 10.1038/s41568-021-00417-2]

10 **Mi H**, Muruganujan A, Ebert D, Huang X, Thomas PD. PANTHER version 14: more genomes, a new PANTHER GO-slim and improvements in enrichment analysis tools. *Nucleic Acids Res* 2019; **47**: D419-D426 [PMID: 30407594 DOI: 10.1093/nar/gky1038]

11 **Zhang L**, Kang W, Lu X, Ma S, Dong L, Zou B. Weighted gene co-expression network analysis and connectivity map identifies lovastatin as a treatment option of gastric cancer by inhibiting HDAC2. *Gene* 2019; **681**: 15-25 [PMID: 30266498 DOI: 10.1016/j.gene.2018.09.040]

12 **Smyth EC**, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. *Lancet* 2020; **396**: 635-648 [PMID: 32861308 DOI: 10.1016/S0140-6736(20)31288-5]

13 **Ritchie ME**, Phipson B, Wu D, Hu Y, Law CW, Shi W, Smyth GK. limma powers differential expression analyses for RNA-sequencing and microarray studies. *Nucleic Acids Res* 2015; **43**: e47 [PMID: 25605792 DOI: 10.1093/nar/gkv007]

14 **Soerjomataram I**, Lortet-Tieulent J, Parkin DM, Ferlay J, Mathers C, Forman D, Bray F. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. *Lancet* 2012; **380**: 1840-1850 [PMID: 23079588 DOI: 10.1016/S0140-6736(12)60919-2]

15 **Norouzi S**, Gorgi Valokala M, Mosaffa F, Zirak MR, Zamani P, Behravan J. Crosstalk in cancer resistance and metastasis. *Crit Rev Oncol Hematol* 2018; **132**: 145-153 [PMID: 30447920 DOI: 10.1016/j.critrevonc.2018.09.017]

16 **Howlader N**, Ries LA, Stinchcomb DG, Edwards BK. The impact of underreported Veterans Affairs data on national cancer statistics: analysis using population-based SEER registries. *J Natl Cancer Inst* 2009; **101**: 533-536 [PMID: 19318639 DOI: 10.1093/jnci/djn517]

17 **Ren F**, Logeman BL, Zhang X, Liu Y, Thiele DJ, Yuan P. X-ray structures of the high-affinity copper transporter Ctr1. *Nat Commun* 2019; **10**: 1386 [PMID: 30918258 DOI: 10.1038/s41467-019-09376-7]

18 **Li SR**, Bu LL, Cai L. Cuproptosis: lipoylated TCA cycle proteins-mediated novel cell death pathway. *Signal Transduct Target Ther* 2022; **7**: 158 [PMID: 35562341 DOI: 10.1038/s41392-022-01014-x]

19 **da Silva DA**, De Luca A, Squitti R, Rongioletti M, Rossi L, Machado CML, Cerchiaro G. Copper in tumors and the use of copper-based compounds in cancer treatment. *J Inorg Biochem* 2022; **226**: 111634 [PMID: 34740035 DOI: 10.1016/j.jinorgbio.2021.111634]

20 **Deng J**, Fu F, Zhang F, Xia Y, Zhou Y. Construct ceRNA Network and Risk Model of Breast Cancer Using Machine Learning Methods under the Mechanism of Cuproptosis. *Diagnostics (Basel)* 2023; **13** [PMID: 36980514 DOI: 10.3390/diagnostics13061203]

21 **Sheftel AD**, Stehling O, Pierik AJ, Elsässer HP, Mühlenhoff U, Webert H, Hobler A, Hannemann F, Bernhardt R, Lill R. Humans possess two mitochondrial ferredoxins, Fdx1 and Fdx2, with distinct roles in steroidogenesis, heme, and Fe/S cluster biosynthesis. *Proc Natl Acad Sci U S A* 2010; **107**: 11775-11780 [PMID: 20547883 DOI: 10.1073/pnas.1004250107]

22 **Strushkevich N**, MacKenzie F, Cherkesova T, Grabovec I, Usanov S, Park HW. Structural basis for pregnenolone biosynthesis by the mitochondrial monooxygenase system. *Proc Natl Acad Sci U S A* 2011; **108**: 10139-10143 [PMID: 21636783 DOI: 10.1073/pnas.1019441108]

23 **Jiang A**, Ye J, Zhou Y, Zhu B, Lu J, Ge S, Qu L, Xiao J, Wang L, Cai C. Copper Death Inducer, FDX1, as a Prognostic Biomarker Reshaping Tumor Immunity in Clear Cell Renal Cell Carcinoma. *Cells* 2023; **12** [PMID: 36766692 DOI: 10.3390/cells12030349]

24 **Dreishpoon MB**, Bick NR, Petrova B, Warui DM, Cameron A, Booker SJ, Kanarek N, Golub TR, Tsvetkov P. FDX1 regulates cellular protein lipoylation through direct binding to LIAS. *J Biol Chem* 2023; **299**: 105046 [PMID: 37453661 DOI: 10.1016/j.jbc.2023.105046]

25 **Wang J**, Qin D, Tao Z, Wang B, Xie Y, Wang Y, Li B, Cao J, Qiao X, Zhong S, Hu X. Identification of cuproptosis-related subtypes, construction of a prognosis model, and tumor microenvironment landscape in gastric cancer. *Front Immunol* 2022; **13**: 1056932 [PMID: 36479114 DOI: 10.3389/fimmu.2022.1056932]

26 **Brugnera E**, Georgiev O, Radtke F, Heuchel R, Baker E, Sutherland GR, Schaffner W. Cloning, chromosomal mapping and characterization of the human metal-regulatory transcription factor MTF-1. *Nucleic Acids Res* 1994; **22**: 3167-3173 [PMID: 8065932 DOI: 10.1093/nar/22.15.3167]

27 **Zhou J**, Chen D, Zhang S, Wang C, Zhang L. Identification of two molecular subtypes and a novel prognostic model of lung adenocarcinoma based on a cuproptosis-associated gene signature. *Front Genet* 2022; **13**: 1039983 [PMID: 36712848 DOI: 10.3389/fgene.2022.1039983]

28 **Zhang X**, Yang Q. Association between serum copper levels and lung cancer risk: A meta-analysis. *J Int Med Res* 2018; **46**: 4863-4873 [PMID: 30296873 DOI: 10.1177/0300060518798507]

29 **Sazanov LA**, Hinchliffe P. Structure of the hydrophilic domain of respiratory complex I from Thermus thermophilus. *Science* 2006; **311**: 1430-1436 [PMID: 16469879 DOI: 10.1126/science.1123809]

30 **Machado AM**, Desler C, Bøggild S, Strickertsson JA, Friis-Hansen L, Figueiredo C, Seruca R, Rasmussen LJ. Helicobacter pylori infection affects mitochondrial function and DNA repair, thus, mediating genetic instability in gastric cells. *Mech Ageing Dev* 2013; **134**: 460-466 [PMID: 24012633 DOI: 10.1016/j.mad.2013.08.004]

31 **Zhang C**, Zeng Y, Guo X, Shen H, Zhang J, Wang K, Ji M, Huang S. Pan-cancer analyses confirmed the cuproptosis-related gene FDX1 as an immunotherapy predictor and prognostic biomarker. *Front Genet* 2022; **13**: 923737 [PMID: 35991547 DOI: 10.3389/fgene.2022.923737]

32 **Yang L**, Zhang Y, Wang Y, Jiang P, Liu F, Feng N. Ferredoxin 1 is a cuproptosis-key gene responsible for tumor immunity and drug

sensitivity: A pan-cancer analysis. *Front Pharmacol* 2022; **13**: 938134 [PMID: 36210836 DOI: 10.3389/fphar.2022.938134]

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ORIGINAL ARTICLE

Basic Study

Peritoneal fluid indocyanine green test for diagnosis of gut leakage in anastomotic leakage rats and colorectal surgery patients

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Abstract

BACKGROUND

Application of indocyanine green (ICG) fluorescence has led to new developments in gastrointestinal surgery. However, little is known about the use of ICG for the diagnosis of postoperative gut leakage (GL). In addition, there is a lack of rapid and intuitive methods to definitively diagnose postoperative GL.

AIM

To investigate the effect of ICG in the diagnosis of anastomotic leakage in a surgical rat GL model and evaluate its diagnostic value in colorectal surgery patients.

METHODS

Sixteen rats were divided into two groups: GL group (n = 8) and sham group (n = 8). Approximately 0.5 mL of ICG (2.5 mg/mL) was intravenously injected postoperatively. The peritoneal fluid was collected for the fluorescence test at 24 and 48 h. Six patients with rectal cancer who had undergone laparoscopic rectal cancer resection plus enterostomies were injected with 10 mL of ICG (2.5 mg/mL) on postoperative day 1. Their ostomy fluids were collected 24 h after ICG injection to identify the possibility of the ICG excreting from the peripheral veins to the enterostomy stoma. Participants who had undergone colectomy or rectal cancer resection were enrolled in the diagnostic test. The peritoneal fluids from drainage were collected 24 h after ICG injection. The ICG fluorescence test was conducted using OptoMedic endoscopy along with a near-infrared fluorescent imaging system.

RESULTS

The peritoneal fluids from the GL group showed ICG-dependent green fluorescence in contrast to the sham group. Six samples of ostomy fluids showed green fluorescence, indicating the possibility of ICG excreting from the peripheral veins to the enterostomy stoma in patients. The peritoneal fluid ICG test exhibited a sensitivity of 100% and a specificity of 83.3% for the diagnosis of GL. The positive

predictive value was 71.4%, while the negative predictive value was 100%. The likelihood ratios were 6.0 for a positive test result and 0 for a negative result.

CONCLUSION
The postoperative ICG test in a drainage tube is a valuable and simple technique for the diagnosis of GL. Hence, it should be employed in clinical settings in patients with suspected GL.

Key Words: Gut leakage; Indocyanine green; Anastomotic leakage model; Diagnostic test; Diagnostic technique

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Core Tip: This study demonstrates the effectiveness of the peritoneal fluid indocyanine green (ICG) test in detecting postoperative gut leakage (GL) using rat models of surgical GL. The ICG test is a highly useful tool for diagnosing GL in patients with colorectal surgery. Our proposed method is a simple technique that can be used for both diagnosing and ruling out GL.

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INTRODUCTION

Gut leakage (GL) is a serious yet common postoperative complication of gastrointestinal (GI) surgery. It has an incidence rate of 2.4%–27.0% and a mortality rate of up to 18% among patients with resected colorectal carcinoma[1-4]. Postoperative GL may result in reoperation, delayed discharge, and increased morbidity and mortality, as well as a risk of local recurrence[5-7]. It also reduces the quality of life of the patient after discharge[8].

Despite these serious adverse effects of postoperative GL, no simple method for its definitive diagnosis has yet been developed. Patients with GL generally display systemic inflammatory response symptoms, such as severe abdominal pain, high fever, rapid heart and respiratory rates, peritonitis, fecal matter in the drainage tube, and increased leukocytes postoperative day (POD) 5–8[9,10]. However, it is not easy to diagnose GL based on clinical symptoms alone. Postoperative monitoring of combined changes in C-reactive protein (CRP) and procalcitonin (PCT) tests affords both good positive and negative predictive values for GL, usually diagnosed at POD 3–5[11,12]. The drainage matrix metalloprotein 9 (MMP9) levels on POD 3 can be used to predict the risk of GL[13]. However, the currently available evidence for MMP9 is inconsistent[14]. At present, the abdominal computed tomography (CT) scan is the most commonly used postoperative imaging method to diagnose or rule out GL. However, the CT scan is an expensive technology. In addition, it may lead to false-negative results, which may delay re-intervention[15]. Therefore, it is necessary to develop simpler methods for the diagnosis of GL.

Indocyanine green (ICG) fluorescence has helped advance the field of GI surgery. Intraoperative usage of ICG for assessing anastomosis perfusion has been well studied[16,17]. However, little is known about using ICG for diagnosing postoperative GL. In the present study, we design a GL rat model by conducting surgical abscission of the sigmoid colon and test the effectiveness of ICG for diagnosing postoperative GL in rat models. In addition, we investigate whether ICG can be used for the diagnosis of postoperative GL in human patients who have undergone colorectal cancer resections.

MATERIALS AND METHODS

Study design

We designed an enterostomy test to identify any possible leakage of ICG from the peripheral veins to the enterostomy stoma. In addition, we developed a diagnostic test to explore the diagnostic effect of the ICG test on GL in patients with colorectal surgery. The human study was approved by the Research Ethics Committee of the Guangzhou First People's Hospital (Approval No. K-2019-173-01). This study was registered in the Chinese Clinical Trial Registry (registration number: ChiCTR1900028537).

Diagnostic criteria for leakage

We employed the following criteria to diagnose leakage: (1) Feces or pus discharged from an abdominal drainage tube, the rectum, or rectovaginal fistula[18]; and (2) peritonitis with sepsis, or with one of the following clinical features: Leukocytosis (> 12 × 10^9/L), elevated CRP (> 10 mg/L), PCT (> 0.5 ng/mL), abnormal drainage volume (> 100 mL lasting 3 d), significant increase in reduced drainage (increased > 30 mL from the previous day), or abnormal drainage color

(turbid or brown)[18]. The ICG index test for the diagnosis of leakage involved the detection of green fluorescence emitted by the collected peritoneal fluid under near-infrared light.

Sample size

The sample size was estimated as follows: $n = Z^2P\ (1\text{-}P)/d^2$[19]. P is a pre-determined value of sensitivity ascertained based on our previous clinician experience, and d is the marginal error. Here, $P = 0.95$, $Z = 1.96$, $a = 0.05$, $d = 0.1$. Hence, the total required sample size was calculated as follows: $n = 1.96^2 \times 0.95 \times (1\text{-}0.95) / 0.1^2 = 18$.

Human patients

Six patients were enrolled in the enterostomy test. We used the following inclusion criteria for enrollment: (1) Patients that underwent a temporary or permanent enterostomy, including a colostomy or ileostomy for the first time; (2) patients should not have any postoperative intestinal obstructions and have smooth draining from the stoma; and (3) patients should be ≥ 18 years of age. Patients with a history of adverse reactions or known allergies to ICG, iodine, or iodine dyes were excluded from the test.

For the diagnostic test, we assessed 21 patients for eligibility. However, we enrolled only 17. Patients aged ≥ 18 years who had undergone GI reconstruction surgery, including colectomy or rectal cancer resection, were enrolled in the diagnostic test. We employed the following inclusion criteria for the diagnostic test: (1) The abdominal drainage tube, rectum, or rectovaginal fistula should contain feces or pus; (2) peritonitis, sepsis, or any of the following clinical features: leukocytosis (> 12 × 10^9/L), elevated CRP (> 10 mg/L), PCT (> 0.5 ng/mL), abnormal drainage volume (> 100 mL lasting 3 d), significant increase in reduced drainage (increased > 30 mL from the previous day), or abnormal color of the drainage (turbid or brown); and (3) patients with one of the following features[20]: Tumor location (lower rectum), distance from the anal verge (< 6 cm), clinical T stage (T3/4), intraoperative blood loss (> 50 mL), number of linear staples (> 2), operative time (> 3 h), tachycardia POD 1 (≥ 100 bpm), and postoperative fever (≥ 38°C). We used the following exclusion criteria: (1) Patients with a history of adverse reactions or known allergies to ICG, iodine, or iodine dyes; and (2) patients who underwent a temporary or permanent enterostomy. All patients provided written informed consent before participating in the study.

Animals

Sixteen male Sprague–Dawley rats aged 7 wk and weighing 220 ± 20 g were purchased from Guangdong Medical Laboratory Animal Center (Guangdong, China). All rats were housed in smooth-bottomed plastic cages in a pathogen-free animal room with controlled temperature (22 ± 2°C), humidity (50% ± 10%), and light (12 h light-dark cycles), with free access to rodent chow and water. To acclimate the animals to the laboratory environment, an acclimation period of 1 wk was allowed before the initiation of the experiment. This animal study was approved by the Institutional Animal Care and Use Committee of the Second Affiliated Hospital of South China University of Technology (Protocol No. 2022079).

Surgical anastomotic leakage model

Eight rats were first anesthetized with inhaled isoflurane and then a laparotomy was performed in their inferior middle abdomen. Their colon was exposed approximately 6–8 cm from the anus and incised with scissors. The disassociated ends of the colon were then anastomosed with non-absorbable monofilament sutures at two diagonal points (GL group, $n = 8$). The abdomen was closed using 5-0 braided silk sutures in layers. The remaining eight rats did not undergo colon surgery for leakage and were used as controls (sham group, $n = 8$).

ICG administration in rats

ICG was obtained from the Department of Pharmacy of Guangzhou First People's Hospital. The ICG solution was diluted to 2.5 mg/mL, according to the instruction manual. Approximately 1.25 mg (0.5 mL) of diluted ICG was intravenously injected into the penile vein of the rats.

ICG administration in human patients

ICG was administered immediately post-surgery to human patients. On POD 1, 25 mg (10 mL) of diluted ICG was intravenously injected into six patients who had undergone enterostomy with a stoma. Next, 17 patients diagnosed with or suspected to have GL were intravenously injected with 25 mg (10 mL) of diluted ICG at the following times: POD 1 for 4 cases, POD 2 for 8 cases, POD 4 for 1 case, and POD 6 for 4 cases.

Peritoneal fluid collection

The rats were anesthetized with inhaled isoflurane at 24 and 48 h after post-surgical ICG injection. Their abdominal cavity was opened, and their intestines at the surgical points were exposed. After photographing the site, the abdominal cavity was washed with 5 mL of saline solution containing 2% v/v of fetal bovine serum albumin. The wash solution containing leaked stool, ingested food, bile, and digestive juices was collected and preserved at 4°C until fluorescence detection.

In human patients, the ostomy fluid or drainage liquid was collected from the enterostomy stoma or abdominal drainage tubes on the second day after ICG administration. This drainage liquid was also preserved at 4°C until the fluorescence test.

Fluorescence test

This test was performed using a fluorescence laparoscope equipped with a near-infrared fluorescence imaging system

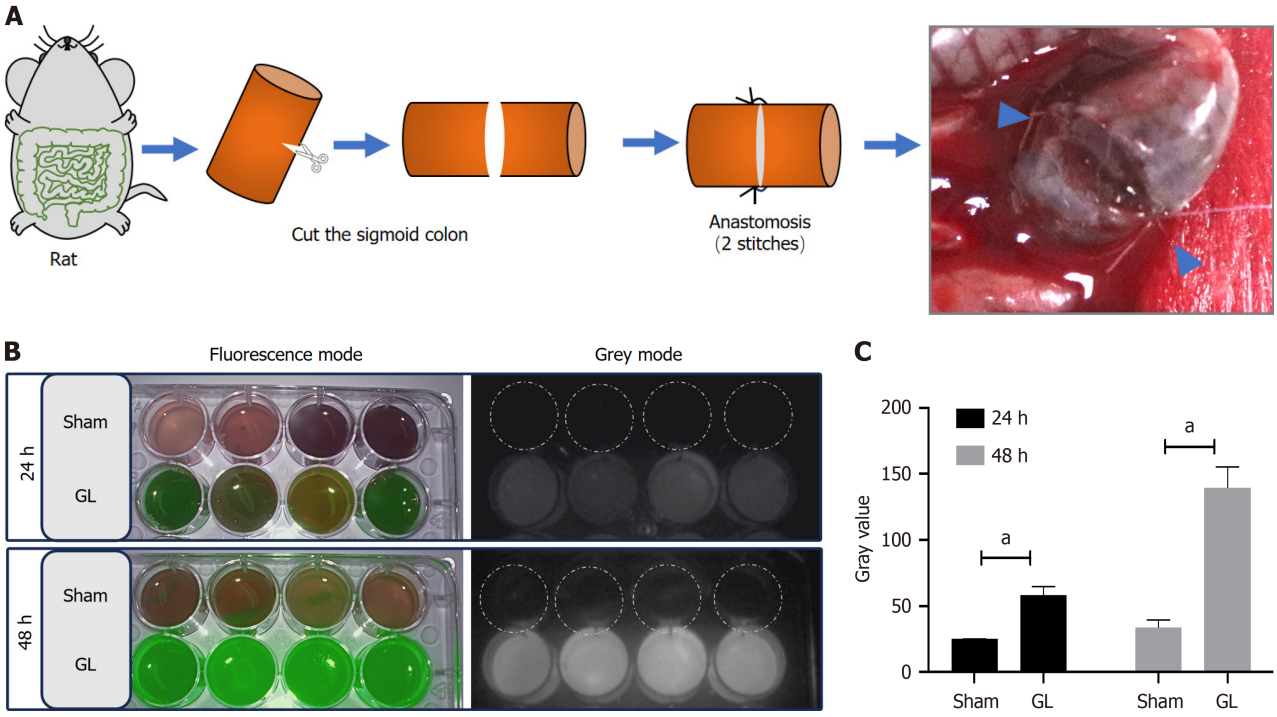


Figure 1 Indocyanine green test diagnosed leakage in rat gut leakage model. A: Gut anastomotic leakage model in rat. The sigmoid colon was cut, disassociated, and anastomosed with two stitches (blue triangles); B: Indocyanine green (ICG) test results of peritoneal fluids between gut leakage (GL) group and sham group at 24 and 48 h. Data show green fluorescence in the GL model; C: Gray values indicate ICG test results in each group at 24 and 48 h. Data show increased gray values in the GL model compared with that in the sham group. Data are presented as a bar graph with mean ± SD and were compared using the student's *t* test, $^{a}P < 0.0001$.

(OptoMedic Technologies Inc., Guangzhou, China). The images were collected in three modes: white light, fluorescence, and gray. The fluorescence intensities were measured by ImageJ software with the gray-mode pictures.

Statistical analysis

The data were presented as the mean ± SD or the actual number of cases. A two-sided *P* value of < 0.05 was considered statistically significant. Intergroup comparisons of continuous variables were conducted using a two-sided Student's *t* test. Statistical analysis was performed using SPSS 26.0, and the figures were generated using GraphPad Prism.

RESULTS

ICG test diagnosed leakage in rat

To simulate clinical postoperative GL in the colon, we established a GL rat model by surgically incising the sigmoid colon with an incomplete colon anastomosis sutured by only two stitches (Figure 1A). The incomplete anastomosis caused a state of intestinal discontinuity for at least 2 d postoperative. During this period, the stool comprising ingested food, bile, and digestive juices leaked into the abdominal cavity. The sham group showed no fluorescence, while the GL group showed green fluorescence in the collected peritoneal fluids at 24 and 48 h (Figure 1B). The semiquantitative analysis of gray values in the images showed that the GL group exhibited increased fluorescence intensity at 24 and 48 h compared to that shown by the sham group (Figure 1C).

ICG detected in ostomy fluids in enterostomy stoma patients

To test the status of ICG from the peripheral veins to the enterostomy port in patients, six patients (four women and two men), with an average age of 66.3 ± 10.6 years, who had undergone laparoscopic rectal cancer resection along with enterostomies, were selected for ICG injection on POD 1 (Table 1). The ostomy fluid at the stoma was collected on POD 2 and used to detect the ICG-dependent fluorescence (Figure 2). Five samples of stoma fluids from the aforementioned six cases showed strong green fluorescence, while one exhibited weak green fluorescence (Figure 2).

Diagnostic test

In the diagnostic test (Figure 3), 21 patients were assessed for eligibility. Of these, four patients were excluded. Three of these excluded patients did not meet the inclusion criteria, while one patient refused to participate. Finally, 17 were enrolled for the ICG test analysis. The baseline demographic and clinical characteristics of the participants are listed in Table 2. In the ICG test, seven of the 17 patients showed green fluorescence, while the other did not (Figure 4A). When

Table 1 Characteristics of six patients with enterostomy stomas

Patients	*n* = 6
Age (yr), mean ± SD	66.3 ± 10.6
Gender (male/female)	2/4
Diagnose	6 (100%)
Rectal cancer	
Surgery approach	6 (100%)
Laparoscopic rectal cancer resection plus ileostomy	

Table 2 Patient characteristics in the diagnostic test

Characteristic	Value (*n* = 17) (percentage)
Age (yr), mean ± SD	58.6 ± 11.4
Gender (male/female)	10/7
Diagnosis, *n* (%)	
Ascending colon cancer	3 (17.6)
Descending colon cancer	2 (11.8)
Sigmoid colon cancer	4 (23.5)
Rectal cancer	8 (47.1)
Surgery, *n* (%)	
Laparoscopic right hemicolectomy	3 (17.6)
Laparoscopic left hemicolectomy	2 (11.8)
Laparoscopic sigmoidectomy	4 (23.5)
Laparoscopic rectal cancer resection	8 (47.1)
Enrollment criteria	
Feces or pus discharged from drainage tube, *n* (%)	2 (11.8)
Peritonitis with leukocytosis, *n* (%)	5 (29.4)
Peritonitis with procalcitonin, *n* (%)	5 (29.4)
Peritonitis with C-reactive protein, *n* (%)	3 (17.6)
Abnormal drainage volume (> 100 mL lasting 3 d), *n* (%)	2 (11.8)
Postoperative fever (> 38°C), *n* (%)	7 (41.2)
Intraoperative blood loss > 50 mL, *n* (%)	3 (17.6)
Operative time > 3 h, *n* (%)	6 (35.3)
Tachycardia POD 1 (≥ 100 bpm), *n* (%)	2 (11.8)
Clinical T stage (T3/T4)	7/3

tested with a reference standard, five of the seven patients who tested positive in the index test were diagnosed as GL positive, while all the other 10 who tested negative were diagnosed as GL negative (Table 3). The ICG test exhibited 100% sensitivity and 83.3% specificity for the diagnosis of GL. The positive predictive value was 71.4% and the negative predictive value was 100%. The likelihood ratios were 6.0 for a positive test result and 0 for a negative result. We ranked the fluorescence intensity based on the gray values of the 17 drainage collections and generated the receiver operating curve (ROC) to determine the predictive values of ICG for identifying postoperative GL. The ROC analysis showed the area under the curve as 0.933 (95%CI: 0.813–1.000; Figure 4B).

Table 3 Contingency table evaluating the accuracy of indocyanine green measurement for the diagnosis of postoperative gut leakage

ICG test	Postoperative gut leakage		Total
	Positive	Negative	
Positive	5	2	7
Negative	0	10	10
Total	5	12	17

ICG: Indocyanine green.

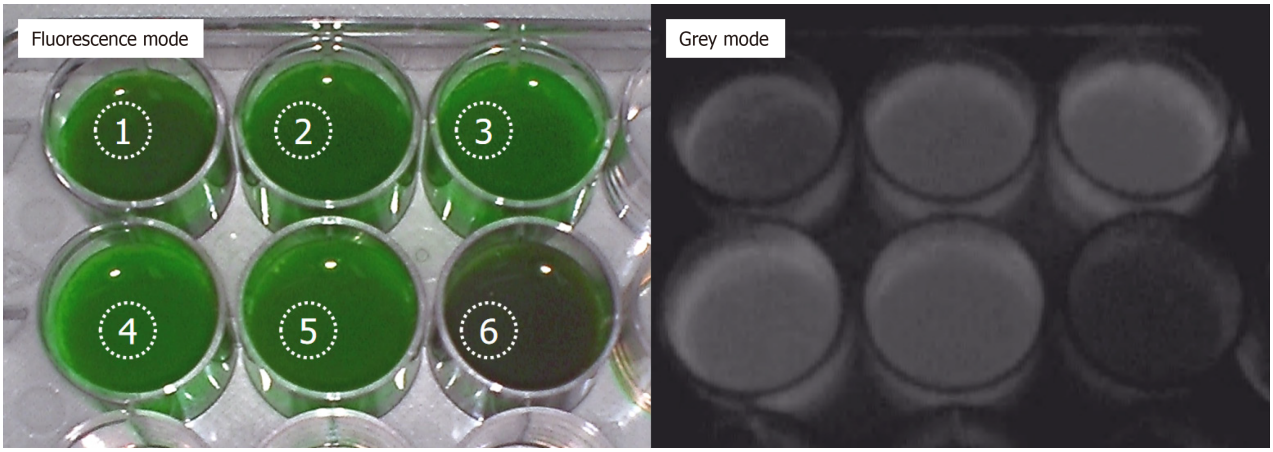


Figure 2 Indocyanine green detected in ostomy fluids in patients with enterostomy stomas. Indocyanine green test results of ostomy liquids from six patients using fluorescence and gray modes. The collection can be seen in green in the fluorescence mode.

DISCUSSION

We demonstrated the effectiveness of the peritoneal fluid ICG test in identifying postoperative GL in surgical GL rat models. We also showed the diagnostic value of the ICG test for diagnosing GL in patients undergoing colorectal surgery. Experimental models have become essential for verifying the effectiveness of ICG in diagnosing postoperative leakage. Previously reported GL models have mainly been used to study the mechanisms of intestinal wound healing[21]. Usually, in models of intestinal anastomotic sutures after segmental colonic resection, five stitches were needed to achieve a probability of 50% leakage[21,22]. A recent report also showed that a colonoscopy leakage model can be used to study the different stages of intestinal wound healing[22]. In the present study, we used only two stitches after surgically removing the sigmoid colon in rats. This technique afforded 100% leakage, with stool consisting of ingested food, bile, and digestive juices leaking into the abdominal cavity, which can be detected 24 and 48 h postoperatively. Thus, our model was suitable for testing GL as early as 24 h postoperatively.

The intravenously injected ICG was taken up by hepatocytes. It was then initially excreted into the bile and later into the bowel. If no leakage occurred, there would be no green fluorescence in the peritoneal fluid when exposed to near-infrared light. Inversely, green peritoneal fluid is indicative of leakage, because the ICG cannot enter the enterohepatic circulation. Our animal experiment demonstrated that the ICG test can be used to detect postoperative GL because all peritoneal fluids of GL model rats showed green fluorescence. Furthermore, the ICG test of the ostomy fluids showed that this test can be used to detect postoperative GL in human patients. These results support the high sensitivity (nearly 100%) of ICG for detecting leakage.

Leakage is traditionally diagnosed based on clinical symptoms; laboratory tests such as markers of leukocytosis, CRP, and PCT; or imaging with an abdominopelvic CT scan or endoscopy[18]. Several biomarkers have been employed for diagnosing GL, such as postoperative fever, time to first defecation after operation[20], gut microbiota[23], MMP9[14], cytokines IL6 and TNFα[24,25], and ischemia biomarkers such as lactic acid and pH[26]. Usually, the most effective evidence of postoperative GL is a direct clinical manifestation, such as feces or pus discharged from an abdominal drainage tube, the rectum, or rectovaginal fistula[18]. In our diagnostic data, two cases discharged feces in the abdominal drainage tube, seven had postoperative fever (≥ 38°C), four had leukocytosis, and five had elevated CRP or PCT.

The intraoperative use of ICG for assessing anastomosis perfusion has been well documented[16,17]. It has been reported that the intraoperative use of fluorescence with ICG could reduce GL rates in rectal cancer surgery[27,28]. Despite that, the postoperative application of ICG for the diagnosis of postoperative anastomotic leakage has not yet been studied. Our diagnostic test demonstrated that the ICG test conducted using drainage tubes for the diagnosis of GL had a sensitivity of 100% and a specificity of 83.3%. Hence, ICG can be used intraoperatively to assess anastomosis perfusion. In addition, it can be used postoperatively to diagnose postoperative anastomotic leakage.

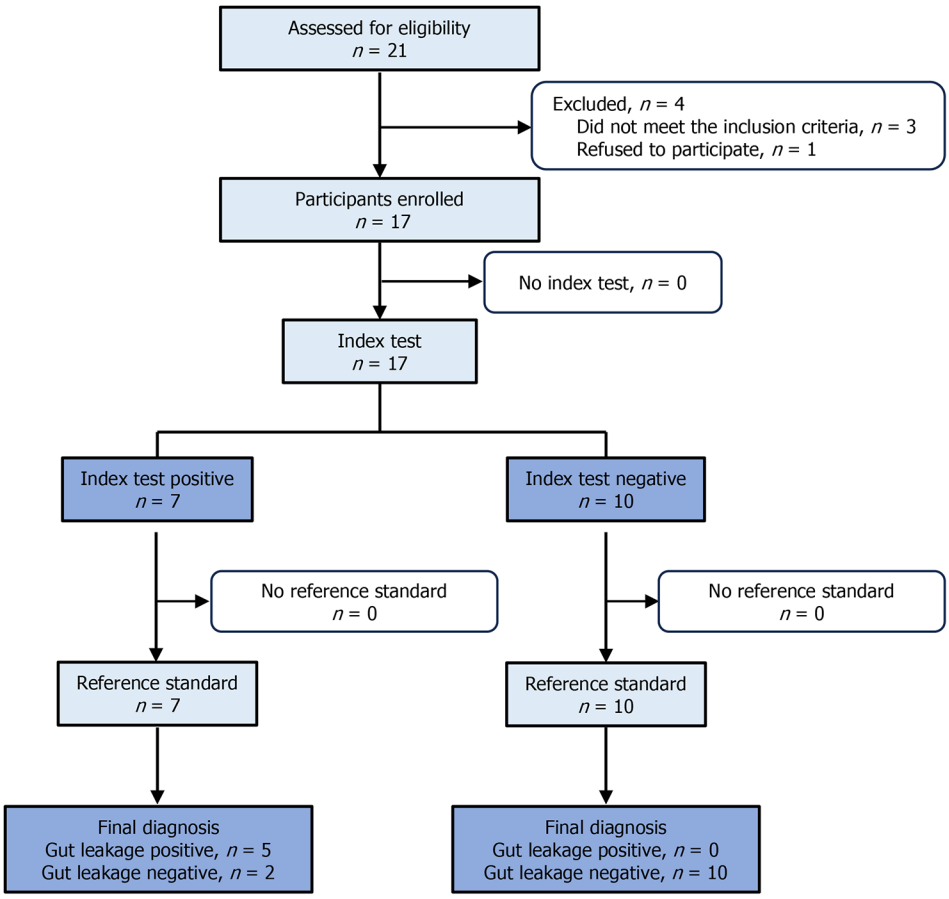


Figure 3 STARD flow diagram of the diagnostic test.

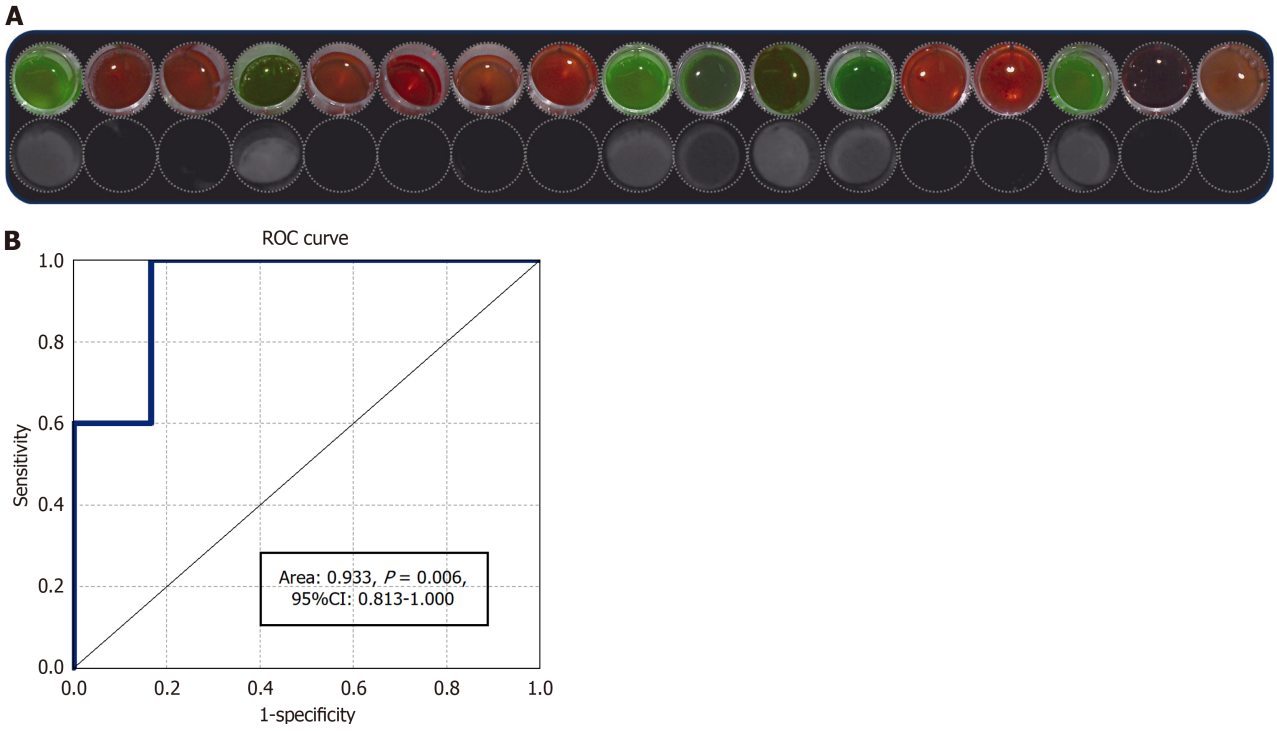


Figure 4 Diagnostic test results. A: Indocyanine green (ICG) test results of drainage fluids from 17 patients using fluorescence and gray modes; B: Receiver operating curves of predictive values of ICG for identifying postoperative gut leakage in patients.

Our study has some limitations as well. The rat model of anastomotic leakage has not been previously reported. To verify the leakage, we used only two stitches for anastomosis in the rat model, which is not a common practice in clinical surgery for patients. Nonetheless, it was still acceptable and appropriate for this study because we needed 100% leakage. In addition, the fluorescence was detected by collecting the drainage liquid. However, this method can be applied only in patients with an abdominal drainage tube. Finally, the sample size for the diagnostic test was small. In addition, all the enrolled patients were from a single center. Therefore, it is necessary to conduct multicenter studies with a large sample size.

CONCLUSION

In conclusion, our study showed that the postoperative ICG test using the drainage tube is a valuable and simple technique for the diagnosis of GL. This simple technique is worthy of clinical promotion and application for diagnosing or ruling out GL. This method may help in proactive or early interventions in cases of postoperative GL.

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FOOTNOTES

Author contributions: Huang Y and Gu WL conceived and designed the study; Huang Y and Li TY performed the animal research and collected the data; Huang Y and Weng JF performed the human research and collected the data and wrote the manuscript; Huang Y, Li TY and Zhang S analyzed and interpreted the data; Xu YJ and Liu H revised the manuscript; all authors have read and approved the final manuscript.

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REFERENCES

1 **Platell C**, Barwood N, Dorfmann G, Makin G. The incidence of anastomotic leaks in patients undergoing colorectal surgery. *Colorectal Dis* 2007; **9**: 71-79 [PMID: 17181849 DOI: 10.1111/j.1463-1318.2006.01002.x]

2 **Matsubara N**, Miyata H, Gotoh M, Tomita N, Baba H, Kimura W, Nakagoe T, Simada M, Kitagawa Y, Sugihara K, Mori M. Mortality after common rectal surgery in Japan: a study on low anterior resection from a newly established nationwide large-scale clinical database. *Dis Colon Rectum* 2014; **57**: 1075-1081 [PMID: 25101603 DOI: 10.1097/DCR.0000000000000176]

3 **Matthiessen P**, Hallböök O, Rutegård J, Simert G, Sjödahl R. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. *Ann Surg* 2007; **246**: 207-214 [PMID: 17667498 DOI: 10.1097/SLA.0b013e3180603024]

4 **Matthiessen P**, Strand I, Jansson K, Törnquist C, Andersson M, Rutegård J, Norgren L. Is early detection of anastomotic leakage possible by intraperitoneal microdialysis and intraperitoneal cytokines after anterior resection of the rectum for cancer? *Dis Colon Rectum* 2007; **50**: 1918-1927 [PMID: 17763907 DOI: 10.1007/s10350-007-9023-4]

5 **Krarup PM**, Nordholm-Carstensen A, Jorgensen LN, Harling H. Anastomotic leak increases distant recurrence and long-term mortality after curative resection for colonic cancer: a nationwide cohort study. *Ann Surg* 2014; **259**: 930-938 [PMID: 24045445 DOI: 10.1097/SLA.0b013e3182a6f2fc]

6 **Smith JD**, Paty PB, Guillem JG, Temple LK, Weiser MR, Nash GM. Anastomotic leak is not associated with oncologic outcome in patients undergoing low anterior resection for rectal cancer. *Ann Surg* 2012; **256**: 1034-1038 [PMID: 22584695 DOI: 10.1097/SLA.0b013e318257d2c1]

7 **Ha GW**, Kim JH, Lee MR. Oncologic Impact of Anastomotic Leakage Following Colorectal Cancer Surgery: A Systematic Review and Meta-Analysis. *Ann Surg Oncol* 2017; **24**: 3289-3299 [PMID: 28608118 DOI: 10.1245/s10434-017-5881-8]

8 **Shearer R**, Gale M, Aly OE, Aly EH. Have early postoperative complications from laparoscopic rectal cancer surgery improved over the past 20 years? *Colorectal Dis* 2013; **15**: 1211-1226 [PMID: 23711242 DOI: 10.1111/codi.12302]

9 **Zhang YB**, Pan XF, Chen J, Cao A, Zhang YG, Xia L, Wang J, Li H, Liu G, Pan A. Combined lifestyle factors, incident cancer, and cancer mortality: a systematic review and meta-analysis of prospective cohort studies. *Br J Cancer* 2020; **122**: 1085-1093 [PMID: 32037402 DOI: 10.1038/s41416-020-0741-x]

10 **Kulu Y**, Ulrich A, Bruckner T, Contin P, Welsch T, Rahbari NN, Büchler MW, Weitz J; International Study Group of Rectal Cancer. Validation of the International Study Group of Rectal Cancer definition and severity grading of anastomotic leakage. *Surgery* 2013; **153**: 753-761 [PMID: 23623834 DOI: 10.1016/j.surg.2013.02.007]

11 **Italian ColoRectal Anastomotic Leakage (iCral) Study Group**. Anastomotic leakage after elective colorectal surgery: a prospective multicentre observational study on use of the Dutch leakage score, serum procalcitonin and serum C-reactive protein for diagnosis. *BJS Open* 2020; **4**: 499-507 [PMID: 32134216 DOI: 10.1002/bjs5.50269]

12 **Giaccaglia V**, Salvi PF, Antonelli MS, Nigri G, Pirozzi F, Casagranda B, Giacca M, Corcione F, de Manzini N, Balducci G, Ramacciato G. Procalcitonin Reveals Early Dehiscence in Colorectal Surgery: The PREDICS Study. *Ann Surg* 2016; **263**: 967-972 [PMID: 26528879 DOI: 10.1097/SLA.0000000000001365]

13 **Sparreboom CL**, Komen N, Rizopoulos D, Verhaar AP, Dik WA, Wu Z, van Westreenen HL, Doornebosch PG, Dekker JWT, Menon AG, Daams F, Lips D, van Grevenstein WMU, Karsten TM, Bayon Y, Peppelenbosch MP, Wolthuis AM, D'Hoore A, Lange JF. A multicentre cohort study of serum and peritoneal biomarkers to predict anastomotic leakage after rectal cancer resection. *Colorectal Dis* 2020; **22**: 36-45 [PMID: 31344302 DOI: 10.1111/codi.14789]

14 **Edomskis P**, Goudberg MR, Sparreboom CL, Menon AG, Wolthuis AM, D'Hoore A, Lange JF. Matrix metalloproteinase-9 in relation to patients with complications after colorectal surgery: a systematic review. *Int J Colorectal Dis* 2021; **36**: 1-10 [PMID: 32865714 DOI: 10.1007/s00384-020-03724-6]

15 **Doeksen A**, Tanis PJ, Vrouenraets BC, Lanschot van JJ, Tets van WF. Factors determining delay in relaparotomy for anastomotic leakage after colorectal resection. *World J Gastroenterol* 2007; **13**: 3721-3725 [PMID: 17659732 DOI: 10.3748/wjg.v13.i27.3721]

16 **De Nardi P**, Elmore U, Maggi G, Maggiore R, Boni L, Cassinotti E, Fumagalli U, Gardani M, De Pascale S, Parise P, Vignali A, Rosati R. Intraoperative angiography with indocyanine green to assess anastomosis perfusion in patients undergoing laparoscopic colorectal resection: results of a multicenter randomized controlled trial. *Surg Endosc* 2020; **34**: 53-60 [PMID: 30903276 DOI: 10.1007/s00464-019-06730-0]

17 **Alekseev M**, Rybakov E, Shelygin Y, Chernyshov S, Zarodnyuk I. A study investigating the perfusion of colorectal anastomoses using fluorescence angiography: results of the FLAG randomized trial. *Colorectal Dis* 2020; **22**: 1147-1153 [PMID: 32189424 DOI: 10.1111/codi.15037]

18 **Rahbari NN**, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, Holm T, Wong WD, Tiret E, Moriya Y, Laurberg S, den Dulk M, van de Velde C, Büchler MW. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. *Surgery* 2010; **147**: 339-351 [PMID: 20004450 DOI: 10.1016/j.surg.2009.10.012]

19 **Hajian-Tilaki K**. Sample size estimation in diagnostic test studies of biomedical informatics. *J Biomed Inform* 2014; **48**: 193-204 [PMID: 24582925 DOI: 10.1016/j.jbi.2014.02.013]

20 **Fukada M**, Matsuhashi N, Takahashi T, Imai H, Tanaka Y, Yamaguchi K, Yoshida K. Risk and early predictive factors of anastomotic leakage in laparoscopic low anterior resection for rectal cancer. *World J Surg Oncol* 2019; **17**: 178 [PMID: 31677643 DOI: 10.1186/s12957-019-1716-3]

21 **Pommergaard HC**, Rosenberg J, Schumacher-Petersen C, Achiam MP. Choosing the best animal species to mimic clinical colon anastomotic leakage in humans: a qualitative systematic review. *Eur Surg Res* 2011; **47**: 173-181 [PMID: 21968050 DOI: 10.1159/000330748]

22 **Bachmann R**, Van Hul M, Leonard D, Delzenne NM, Kartheuser A, Cani PD. The colonoscopic leakage model: a new model to study the intestinal wound healing at molecular level. *Gut* 2020; **69**: 2071-2073 [PMID: 32398223 DOI: 10.1136/gutjnl-2020-321234]

23 **Hajjar R**, Santos MM, Dagbert F, Richard CS. Current evidence on the relation between gut microbiota and intestinal anastomotic leak in colorectal surgery. *Am J Surg* 2019; **218**: 1000-1007 [PMID: 31320106 DOI: 10.1016/j.amjsurg.2019.07.001]

24 **Su'a BU**, Mikaere HL, Rahiri JL, Bissett IB, Hill AG. Systematic review of the role of biomarkers in diagnosing anastomotic leakage following colorectal surgery. *Br J Surg* 2017; **104**: 503-512 [PMID: 28295255 DOI: 10.1002/bjs.10487]

25 **Sparreboom CL**, Wu Z, Dereci A, Boersema GS, Menon AG, Ji J, Kleinrensink GJ, Lange JF. Cytokines as Early Markers of Colorectal Anastomotic Leakage: A Systematic Review and Meta-Analysis. *Gastroenterol Res Pract* 2016; **2016**: 3786418 [PMID: 27051416 DOI: 10.1155/2016/3786418]

26 **Wright EC**, Connolly P, Vella M, Moug S. Peritoneal fluid biomarkers in the detection of colorectal anastomotic leaks: a systematic review. *Int J Colorectal Dis* 2017; **32**: 935-945 [PMID: 28401350 DOI: 10.1007/s00384-017-2799-3]

27 **Arezzo A**, Bonino MA, Ris F, Boni L, Cassinotti E, Foo DCC, Shum NF, Brolese A, Ciarleglio F, Keller DS, Rosati R, De Nardi P, Elmore U, Fumagalli Romario U, Jafari MD, Pigazzi A, Rybakov E, Alekseev M, Watanabe J, Vettoretto N, Cirocchi R, Passera R, Forcignanò E, Morino M. Intraoperative use of fluorescence with indocyanine green reduces anastomotic leak rates in rectal cancer surgery: an individual participant data analysis. *Surg Endosc* 2020; **34**: 4281-4290 [PMID: 32556696 DOI: 10.1007/s00464-020-07735-w]

28 **Song M**, Liu J, Xia D, Yao H, Tian G, Chen X, Liu Y, Jiang Y, Li Z. Assessment of intraoperative use of indocyanine green fluorescence imaging on the incidence of anastomotic leakage after rectal cancer surgery: a PRISMA-compliant systematic review and meta-analysis. *Tech Coloproctol* 2021; **25**: 49-58 [PMID: 32885328 DOI: 10.1007/s10151-020-02335-1]

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SYSTEMATIC REVIEWS

Global geoepidemiology of gastrointestinal surgery rates in Crohn's disease

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Abstract

BACKGROUND

Data regarding the worldwide gastrointestinal surgery rates in patients with Crohn's disease (CD) remains limited.

AIM

To systematically review the global variation in the rates of surgery in CD.

METHODS
A comprehensive search analysis was performed using multiple electronic databases from inception through July 1, 2020, to identify all full text, randomized controlled trials and cohort studies pertaining to gastrointestinal surgery rates in adult patients with CD. Outcomes included continent based demographic data, CD surgery rates over time, as well as the geoepidemiologic variation in CD surgery rates. Statistical analyses were conducted using R.

RESULTS
Twenty-three studies spanning four continents were included. The median proportion of persons with CD who underwent gastrointestinal surgery in studies from North America, Europe, Asia, and Oceania were 30% (range: 1.7%-62.0%), 40% (range: 0.6%-74.0%), 17% (range: 16.0%-43.0%), and 38% respectively. No clear association was found regarding the proportion of patients undergoing gastrointestinal surgery over time in North America (R^2 = 0.035) and Europe (R^2 = 0.100). A moderate, negative association was seen regarding the proportion of patients undergoing gastrointestinal surgery over time (R^2 = 0.520) in Asia.

CONCLUSION
There appears to be significant inter-continental variation regarding surgery rates in CD. Homogenous evidence-based guidelines accounting for the geographic differences in managing patients with CD is prudent. Moreover, as a paucity of data on surgery rates in CD exists outside the North American and European continents, future studies, particularly in less studied locales, are warranted.

Key Words: Gastrointestinal surgery; Crohn's disease; Geoepidemiology; Inflammatory bowel disease; Prevalence

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Core Tip: Surgical intervention in patents with Inflammatory bowel disease and particularly Crohn's disease (CD) to prevent complications remain a controversial subject. Significant inter-continental variation was observed regarding surgery rates in patients with CD. Our study provides insight for future studies targeting pathophysiology, genetics, risk factors, and management based upon the global variations detected. In addition, it serves to encourage the development of homogenous evidence-based guidelines accounting for the geographic differences in managing patients with CD: With an ultimate goal of helping clinicians make informed decisions for their patients independent of the region they practice. Additionally, as a paucity of data on surgery rates in patients with CD exists outside the North American and European continents, future studies, particularly in less studied locales, are warranted.

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INTRODUCTION

Inflammatory bowel disease (IBD), mainly comprised of Crohn's disease (CD) and ulcerative colitis, is an autoimmune, inflammatory condition marked by periods of clinical remission and disease flares. Unique to CD, it has its transmural inflammatory nature and innate ability to involve any segment along the gastrointestinal tract[1]. Although predominantly seen in industrialized nations, the incidence and prevalence of CD is increasing worldwide[2-4]. While rates in Northern America and Europe have stabilized, studies have shown a significant increase in incidence rates in Eastern European and Asian countries, parallel to their social and economic growth[5-7]. Despite extensive studies, the pathogenesis of this complex disease is still poorly understood; but exposure to environmental risk factors in genetically susceptible individuals is suspected to be one of the primary drivers of inflammation[4]. Differences in diet with subsequent changes in intestinal microbiota, temperature differences, socioeconomic status, and hygiene are some of the environmental factors thought to result in geographical variation and a rising trend with modernization[7-9].

CD can be difficult to manage despite medical expertise, as patients often experience recurrent flares throughout their lifetime, with up to 50% of patients developing an intestinal complication (stricture, abscess, or fistula) within 20 years of diagnosis[10,11]. Despite a dramatic expansion in the therapeutic arsenal for CD and its subsequent ability to be medically managed, surgery remains a crucial option, notably for patients with complications or refractory diseases[12,13]. Although the risk of gastrointestinal surgery in patients with CD has been reported to have decreased in recent years, almost 50% of patients with CD undergo surgery within 10 years of diagnosis[14-16]. GI surgery is defined as any procedure involving bowel resection or strictureplasty. For perianal disease, surgery is defined as requirement of fistulae

resection and/or abscess drainage. Surgery for treatment of perianal disease was also analyzed since it is an important feature in the treatment of penetrating CD affecting the anorectum[17]. Some studies report an estimated 70%-80% of patients with CD may require surgery at some point during their lifetime[18]. However, data regarding the worldwide gastrointestinal surgery rates in patients with CD remains limited.

As the global geographic and ethnic variations noticed in the prevalence rates of CD have inevitably led to a discrepancy in management, in particular surgery rates, a detailed knowledge of the inter-continental differences in surgical rates is paramount[18-39]. This will allow clinicians to evaluate the impact of therapeutic strategies, identify risk factors for disease severity, help facilitate shared decision-making, and potentially guide clinical practice[16]. In this setting, we sought to perform a systematic review to investigate the global variation of gastrointestinal surgery rates in patients with CD. In addition, we attempt to review the inter-continental surgery rates in patients with CD over time.

MATERIALS AND METHODS

Search strategy

A comprehensive search analysis was performed using the electronic databases MEDLINE/PubMed, EMBASE, and Cochrane, through July 1, 2020, to identify all pertinent articles. MeSH terms "Inflammatory bowel disease", "Crohn's disease", "surgery", and "epidemiology" were used in different combinations to generate a comprehensive and up-to-date list of articles. Two individual reviewers (SW and MA) performed the search independently and shortlisted the articles for final review. Any disagreement was resolved through mutual discussion and screening by a third reviewer (JDF) using a modified delphi system[40]. References of the initially identified studies were subsequently reviewed manually to find additional studies that may have been missed on initial search. Articles were initially screened by titles and abstracts. Full text was obtained for final shortlisted studies. We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to conduct our systematic review (Figure 1)[41,42].

Inclusion and exclusion criteria

Studies pertaining to adult patients (over age 18) with CD undergoing gastrointestinal surgery were included. We limited our search strategy to include full text, randomized controlled trials and cohort studies. We excluded review articles, case reports, studies with 10 or fewer patients, and letters to the editor. The search strategy was not restricted by language or date.

Outcomes

Outcomes included: (1) Continent based demographic data (gender and age at CD diagnosis); and (2) CD surgery rates over time, as well as iii) the geoepidemiologic variation in CD surgery rates. Figure 1 depicts the screening methodology and inclusion parameters used. The PICO (population, intervention, control group and outcome) description was used as an organizing framework for the study question to ensure *a priori* establishment of the study methodology[42].

Data collection

Demographic data, number of study participants, and surgery rates were extracted from each study. The data collection was performed by 2 individual reviewers (SW and MA) and any discrepancy was resolved by a third reviewer (JDF) using a modified delphi system[40].

Data synthesis and statistical analysis

All articles were screened for bias using the Newcastle-Ottawa Scale[43]. Individual study data are reported when available and regional rates are reported as weighted averages or median and range. To identify region-specific changes in the proportion of patients undergoing gastrointestinal surgery over time these data were plotted and correlation coefficients were generated. Statistical analysis was conducted using R version 3.6.1.

RESULTS

Literature search

The literature search identified 1397 articles of which 135 were deemed eligible for further assessment. Of these, 112 studies did not report on CD surgery rates and were thus excluded. The remaining 23 studies (examining 24 populations) met inclusion criteria and were deemed eligible for data analysis (Figure 1)[18-39,44]. Table 1 lists the baseline characteristics of the included studies. Meta-analysis was planned for this study, however unaccountable heterogeneity precluded such analysis.

North America

Nine North American studies published between 2004 and 2019 were included (seven in The United States, two in Canada). The median sample size was 400 (range: 99-8985), the median age at CD diagnosis was 27 (range: 15-38), and the median proportion of males was 44% (range: 27%-59%). The median proportion of persons with CD who underwent gastrointestinal surgery was 30.0% (range: 1.7%-62.0%). No clear association was found regarding the proportion of pa-

Table 1 Baseline characteristics of the included studies

Ref.	Region	Total (*N*)	Surgeries (*n*)
Chow *et al*[22], 2009	Asia	132	57
Jeon *et al*[29], 2010	Asia	96	15
Lee *et al*[32], 2017	Asia	165	28
Pandey *et al*[34], 2015	Asia	430	112
Varma *et al*[38], 2019[1]	Asia	103	16
Kariyawasam *et al*[30], 2014	Australia	1035	388
Alvarez-Lobos *et al*[17], 2005	Europe	170	59
Bernell *et al*[19], 2000	Europe	1936	1424
Chhaya *et al*[20], 2015	Europe	5235	32
Chhaya *et al*[21], 2016	Europe	9391	1714
Cosnes *et al*[23], 2005	Europe	2573	1070
Golovics *et al*[28], 2013	Europe	506	204
González-Lama *et al*[44], 2016	Europe	467	210
Szántó *et al*[37], 2018	Europe	428	228
Zaharie *et al*[39], 2016	Europe	478	78
Cushing *et al*[24], 2018	North America	400	198
Dubinsky *et al*[25], 2013	North America	1115	444
Feagan *et al*[26], 2008	North America	778	13
Forcione *et al*[27], 2004	North America	345	69
Kuenzig *et al*[31], 2018	North America	2113	532
Nguyen *et al*[33], 2017	North America	8985	2648
Peyrin-Biroulet *et al*[35], 2012	North America	310	152
Reutemann *et al*[36], 2017	North America	135	84
Varma *et al*[38], 2019[1]	North America	99	16

[1]Data from same study.

tients undergoing gastrointestinal surgery over time (R^2 = 0.035) (Figure 2A).

Europe

Nine European studies published between 2000 and 2018 were included. The median sample size was 506 (range: 170-9391), the median age at CD diagnosis was 32.0 (range: 27.9-38.5), and the median proportion of males was 48% (range: 44%-54%). The median proportion of persons with CD who underwent gastrointestinal surgery was 40.0% (range: 0.6%-74.0%). No clear association was found regarding the proportion of patients undergoing gastrointestinal surgery over time (R^2 = 0.100) (Figure 2B).

Asia

Five Asian studies were included. Median sample size was 132 (range: 96-430). The median proportion of persons with CD who underwent gastrointestinal surgery was 17% (range: 16%-43%). A moderate, negative association was seen regarding the proportion of patients undergoing gastrointestinal surgery over time (R^2 = 0.52) (Figure 2C).

Oceania

Only one study was identified from Oceania. The mean age at CD diagnosis reported by that study was 29; 44% of study participants were male. The study included 1035 patients with CD, of whom 38% (388) underwent gastrointestinal surgery. As only one study, published in 2014, from this region was included, surgery trends over time could not be assessed. See Figure 3 for a summary of the regions reporting studies on CD surgery rates. See Table 2 for the continent-based variation in CD surgery rates. See Table 3 for a summary of included studies based on population basis, time period, follow up period, and journal publication.

Table 2 Continent based variation in Crohn's disease surgery rates

Region	*n* (median, range)	GI surgery (median, range)	Proportion surgery (median, range)
North America	400 (99-8985)	152 (13-2648)	29.0% (1.6%-62.0%)
Europe	506 (170-9391)	210 (32-1714)	40.0% (0.6%-74.0%)
Asia	132 (96-430)	28 (15-112)	17.0% (16.0%-43.0%)
Oceania	1035	388	38.0%

Table 3 Summary of included studies based on population basis, time period, follow up period, and journal publication

Ref.	Population based	Time period	Follow up period	Journal publication
Chow *et al*[22], 2009	No	1987-2007	5.0 yr	*Inflammatory Bowel Diseases Journal*
Jeon *et al*[29], 2010	No	-	36.0 months	*Korean Journal of Gastroenterology*
Lee *et al*[32], 2017	No	2000-2015	6.0 months	*World Journal of Gastroenterology*
Pandey *et al*[34], 2015	Yes	1970-2013	7.3 years	*Inflammatory Bowel Diseases Journal*
Varma *et al*[38], 2019[1]	Yes	2014-2018	-	*Journal of Gastroenterology & Hepatology Foundation*
Kariyawasam *et al*[30], 2014	No	1970-2009	12.0 months	*Inflammatory Bowel Diseases Journal*
Alvarez-Lobos *et al*[17], 2005	No	2002-2004	7.4 yr	*Annals of Surgery*
Bernell *et al*[19], 2000	Yes	1955-1989	14.9 yr	*Annals of Surgery*
Chhaya *et al*[20], 2015	Yes	1995-2009	4.8 yr	*Inflammatory Bowel Diseases Journal*
Chhaya *et al*[21], 2016	Yes	1989-2009	5.8 yr	*European Journal of Gastroenterology & Hepatology*
Cosnes *et al*[23], 2005	No	1978-2002	5.0 yr	*Gut Journal*
Golovics *et al*[28], 2013	Yes	1977-2008	1.0 yr	*World Journal of Gastroenterology*
González-Lama *et al*[44], 2016	No	-	10.7 yr	*Inflammatory Bowel Diseases Journal*
Szántó *et al*[37], 2018	No	2007-2015	3.6 yr	*PLOS One Journal*
Zaharie *et al*[39], 2016	Yes	2006-2014	-	*Journal of Crohn's and Colitis*
Cushing *et al*[24], 2018	No	2014-2016	-	*Inflammatory Bowel Diseases Journal*
Dubinsky *et al*[25], 2013	No	-	60.0 months	*Inflammatory Bowel Diseases Journal*
Feagan *et al*[26], 2008	No	-	12.0 months	*Gastroenterology Journal*
Forcione *et al*[27], 2004	No	1991-1999	3.0 yr	*Gut Journal*
Kuenzig *et al*[31], 2018	Yes	1994-2010	2.0 yr	*American Journal of Gastroenterology*
Nguyen *et al*[33], 2017	Yes	1999-2008	-	*Inflammatory Bowel Diseases Journal*
Peyrin-Biroulet *et al*[35], 2012	Yes	2000-2009	12.0 yr	*American Journal of Gastroenterology*
Reutemann *et al*[36], 2017	No	2006-2014	41.7 months	*Inflammatory Bowel Diseases Journal*
Varma *et al*[38], 2019[1]	No	2014-2018	12.0 months	*Journal of Gastroenterology & Hepatology Foundation*

[1]Data from same study.

DISCUSSION

Our systematic review pertaining to global CD surgery rates and rates over time yielded considerable inter-continental differences. The median proportion of persons with CD who underwent gastrointestinal surgery in studies from North America, Europe, Asia, and Oceania were 30% (range: 1.7%-62.0%), 40% (range: 0.6%-74.0%), 17% (range: 16.0%-43.0%), and 38% respectively. While no clear association was found regarding the proportion of patients undergoing gastrointestinal surgery over time in North America (R^2 = 0.035) and Europe (R^2 = 0.100), a moderate, negative association was seen (R^2 = 0.520) in Asia. In addition, studies emerging from Asia had the greatest median proportion of males, namely 68% (with a range of 59% to 76%).

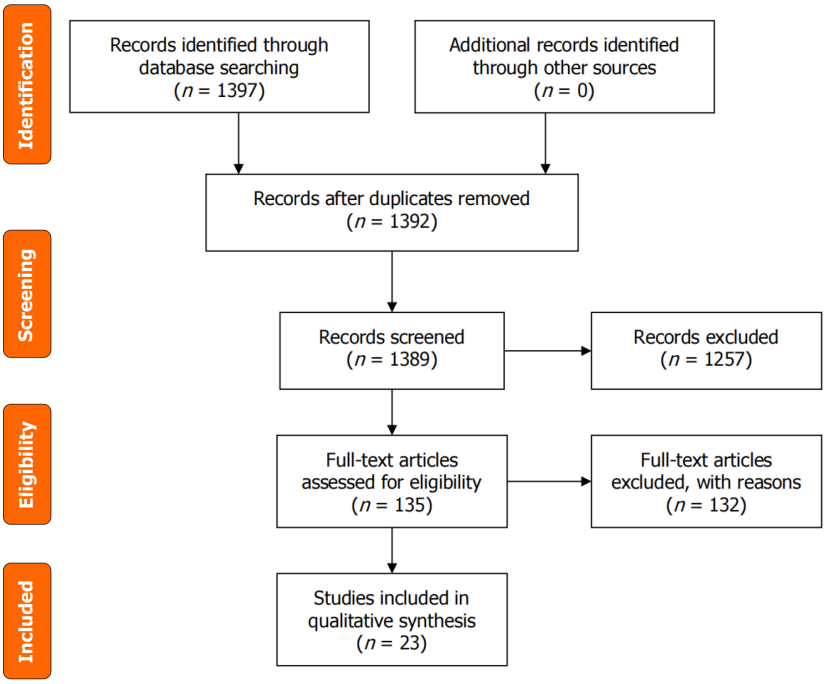


Figure 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement diagram delineating the process by which articles were screened and ultimately included.

The complexity of CD is multifactorial: Variable disease presentations, progression, complications, and therapeutic options (medical, surgical). The therapeutic options themselves are varied in terms of type of therapy, administration, patient adherence, and follow-up[45]. As the understanding of the risk/benefits for each option continues to evolve, clinicians face an arduous task of selecting the appropriate management for their patients[46]. The utility of an appropriate therapeutic/management strategy is paramount and needs to be individualized, *i.e.*, based upon patient factors. In the age of biologics, the rate of surgical interventions has dropped, nonetheless, it still remains as a viable alternative option for certain complications of CD such as strictures, fistulas, perforations, abscess, and malignancy and for patients who do not tolerate medical therapy[1,3]. The types of surgery include small bowel or ileocecal resection, small bowel strictureplasty, colorectal resection, perianal surgery, and combined procedures for any combination of the previous stated procedures[14].

As illustrated within, we observed marked variation in the inter-regional surgery rates according to region with proportions ranging from as low as 17% to as high as a staggering 40%. This is likely due to several factors including socioeconomic status, healthcare delivery model, regional difference in practices, type of surgery, and patient factors. The variation was also noted within the region, for example in North America, Feagan *et al*[26] noted a surgical rate of 1.7% while Reutemann *et al*[36] noted rate of 62.2%. In addition to the factors described above, these variations can also reflect the uncertainty in best clinical practice, hence suggesting a need for updated, and perhaps more global, evidence-based guidelines for the management of patients with CD.

The variation in patient demographics and surgical rates are perhaps also due to the lower incidence of CD in certain geographical regions such as Asia[2]. Indeed, the incidence and prevalence of CD in Asia is somewhat lower compared to rest of the world, however, this trend has changed in the last few years. Some of the disease characteristics are also different such as higher male proportions, older age of onset, lower rates of family history, extra-intestinal manifestations, and surgery. Despite the lack of strong family history, the postulated mechanisms for increasing IBD prevalence in Asian countries are attributable to a host of factors including vaccinations, antibiotics, western diet, contact with west, and alteration in gut microbiota[47]. Future research targeted to understanding the differences in these factors in the various populations (and variations in disease manifestations) are important to develop improved health care models and guidelines to cater to different populations more appropriately.

Alternate therapies such as herbal medications in India/Pakistan and Chinese medications in China can lead to a delayed presentation to conventional medical practitioners. The mechanism of action, drug interactions, and adverse events are not clear for these medications[48]. The use of these medications needs to be regulated after establishing safety and efficacy using the appropriate process (research, marketing surveillance, and FDA approval, *etc*). Awareness should be created in patients regarding the potential adverse outcomes of using inappropriate therapies for CD. A delayed presentation can potentially lead to higher surgical complications necessitating surgical corrections.

European countries were observed to have higher surgical rates amongst patients with CD (approximately 40%). The higher surgical rate, particularly from centers in Northern Europe, is thought to be secondary to aggressive disease phenotype, higher prevalence, attitude towards surgery, and/or genetics[49]. The surgery rates in Europe were higher likely because of the public insurance system in majority of the countries compared to the private insurance in United States. Studies have showed people with IBD had thrice the direct cost of treatment for IBD compared to a non-IBD



Figure 2 Gastrointestinal surgery rates in Crohn's disease. A: Gastrointestinal surgery rates in Crohn's disease (CD) in North America over time as reported by the included studies; B: Gastrointestinal surgery rates in CD in Europe over time as reported by the included studies; C: Gastrointestinal surgery rates in CD in Asia over time as reported by the included studies.

patient and twice the out-of-pocket expenses[50]. In Asia, the surgery rates for IBD were likely lower because of the low socio-economic status and limited access to surgical care[51].

Our systematic review has some limitations. First, data was gathered primarily from observational studies which have significant bias (recall, information, selection, subjective *etc.*). Second, there was significant variation in the reporting of data and follow-ups. Studies with longer follow-up/study duration period tended to have increased proportions of surgical rates. Third, we were not able to account for the type of surgery that CD patients underwent. Further, surgery based on urgency (elective, urgent, and emergent) was also not accounted for. Lastly, we were also not able to account residual

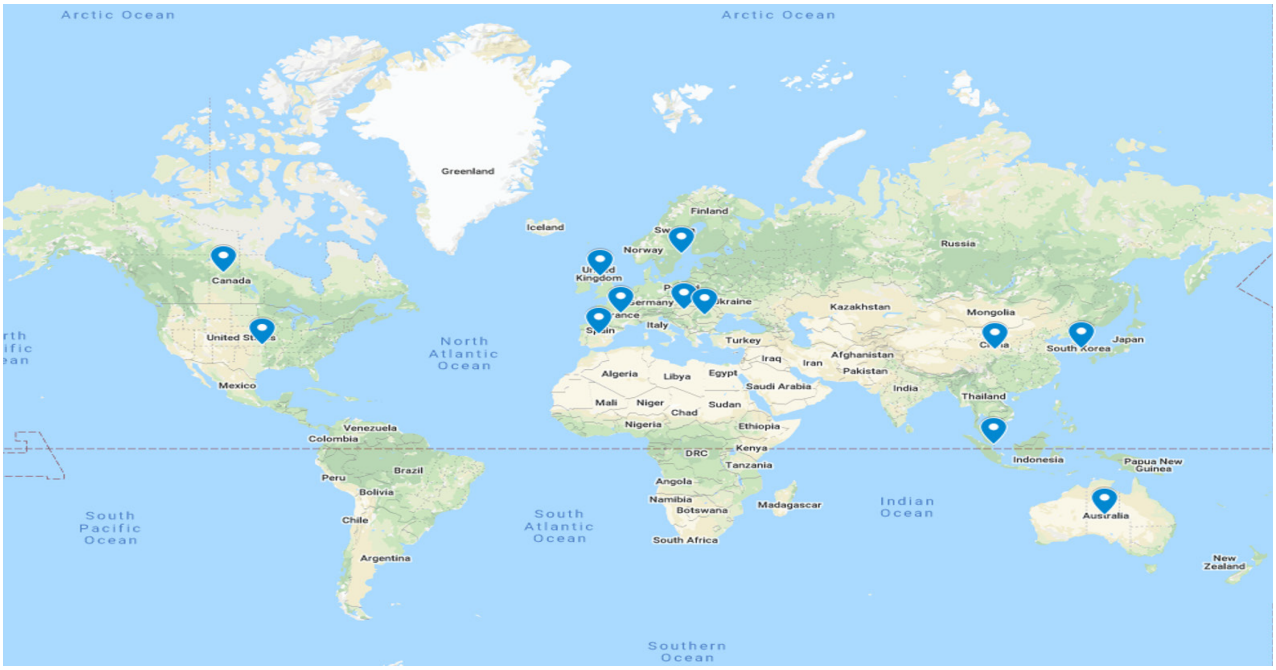


Figure 3 Map summary of the epidemiology of Crohn's disease surgery rates based upon study region.

confounders such as concomitant IBD medications (particularly biologics), co-morbidities, and disease flares. Despite the limitations, we included a large number of studies with a diverse and robust number of patients. Moreover, this is the first study reporting the geoepidemiological variations in the rate of surgery for CD patients.

CONCLUSION

In summary, significant inter-continental variation was observed regarding surgery rates in patients with CD. Our study provides insight for future studies targeting pathophysiology, genetics, risk factors, and management based upon the global variations detected. In addition, it serves to encourage the development of homogenous evidence-based guidelines accounting for the geographic differences in managing patients with CD, with an ultimate goal of helping clinicians make informed decisions for their patients independent of the region they practice. Additionally, as a paucity of data on surgery rates in patients with CD exists outside the North American and European continents, future studies—particularly in less studied locales, are warranted.

FOOTNOTES

Author contributions: Weissman S, Aziz M, and Bangolo A searched the literature, wrote, and revised the manuscript; Aung H, Mathew M, Garcia L, Chandar SA, Karamthoti P, Bawa H, Alshimari A, Kejela Y, Mehdi N, Joseph CA, Kodali A, Kumar R, Goyal P, Satheesha S, Nivedita F, Nagesh VK, Tesoro N, Sethi T, Singh G, Belal A, Intisar A, Khalid H, Cornwell S, Suresh SB, Ahmed K, Marole KK, Anand OP, and Reshi RB revised and edited the manuscript; Mehta TI, Elias S, and Feuerstein JD revised and approved the final version and are the article's guarantors; and all authors certify that they contributed sufficiently to the intellectual content and data analysis, and have reviewed the final version of the manuscript and approves it for publication.

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REFERENCES

1 **Torres J**, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. *Lancet* 2017; **389**: 1741-1755 [PMID: 27914655 DOI: 10.1016/S0140-6736(16)31711-1]
2 **Han M**, Jung YS, Cheon JH, Park S. Regional variations in the use of biologics and immunomodulators among Korean patients with inflammatory bowel diseases. *J Gastroenterol Hepatol* 2019; **34**: 1166-1174 [PMID: 30672608 DOI: 10.1111/jgh.14609]
3 **Wong DJ**, Roth EM, Feuerstein JD, Poylin VY. Surgery in the age of biologics. *Gastroenterol Rep (Oxf)* 2019; **7**: 77-90 [PMID: 30976420 DOI: 10.1093/gastro/goz004]
4 **Molodecky NA**, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012; **142**: 46-54.e42; quiz e30 [PMID: 22001864 DOI: 10.1053/j.gastro.2011.10.001]
5 **Vegh Z**, Kurti Z, Lakatos PL. Epidemiology of inflammatory bowel diseases from west to east. *J Dig Dis* 2017; **18**: 92-98 [PMID: 28102560 DOI: 10.1111/1751-2980.12449]
6 **Park SJ**, Kim WH, Cheon JH. Clinical characteristics and treatment of inflammatory bowel disease: a comparison of Eastern and Western perspectives. *World J Gastroenterol* 2014; **20**: 11525-11537 [PMID: 25206259 DOI: 10.3748/wjg.v20.i33.11525]
7 **Ng SC**, Bernstein CN, Vatn MH, Lakatos PL, Loftus EV Jr, Tysk C, O'Morain C, Moum B, Colombel JF; Epidemiology and Natural History Task Force of the International Organization of Inflammatory Bowel Disease (IOIBD). Geographical variability and environmental risk factors in inflammatory bowel disease. *Gut* 2013; **62**: 630-649 [PMID: 23335431 DOI: 10.1136/gutjnl-2012-303661]
8 **Loftus EV Jr**. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology* 2004; **126**: 1504-1517 [PMID: 15168363 DOI: 10.1053/j.gastro.2004.01.063]
9 **Baumgart DC**, Sandborn WJ. Crohn's disease. *Lancet* 2012; **380**: 1590-1605 [PMID: 22914295 DOI: 10.1016/S0140-6736(12)60026-9]
10 **Fichera A**, McCormack R, Rubin MA, Hurst RD, Michelassi F. Long-term outcome of surgically treated Crohn's colitis: a prospective study. *Dis Colon Rectum* 2005; **48**: 963-969 [PMID: 15785882 DOI: 10.1007/s10350-004-0906-3]
11 **Lichtenstein GR**, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol* 2018; **113**: 481-517 [PMID: 29610508 DOI: 10.1038/ajg.2018.27]
12 **Ma C**, Moran GW, Benchimol EI, Targownik LE, Heitman SJ, Hubbard JN, Seow CH, Novak KL, Ghosh S, Panaccione R, Kaplan GG. Surgical Rates for Crohn's Disease are Decreasing: A Population-Based Time Trend Analysis and Validation Study. *Am J Gastroenterol* 2017; **112**: 1840-1848 [PMID: 29087396 DOI: 10.1038/ajg.2017.394]
13 **Hazlewood GS**, Rezaie A, Borman M, Panaccione R, Ghosh S, Seow CH, Kuenzig E, Tomlinson G, Siegel CA, Melmed GY, Kaplan GG. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. *Gastroenterology* 2015; **148**: 344-54.e5; quiz e14 [PMID: 25448924 DOI: 10.1053/j.gastro.2014.10.011]
14 **Frolkis AD**, Dykeman J, Negrón ME, Debruyn J, Jette N, Fiest KM, Frolkis T, Barkema HW, Rioux KP, Panaccione R, Ghosh S, Wiebe S, Kaplan GG. Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. *Gastroenterology* 2013; **145**: 996-1006 [PMID: 23896172 DOI: 10.1053/j.gastro.2013.07.041]
15 **Gomollón F**, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, Peyrin-Biroulet L, Cullen GJ, Daperno M, Kucharzik T, Rieder F, Almer S, Armuzzi A, Harbord M, Langhorst J, Sans M, Chowers Y, Fiorino G, Juillerat P, Mantzaris GJ, Rizzello F, Vavricka S, Gionchetti P; ECCO. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis* 2017; **11**: 3-25 [PMID: 27660341 DOI: 10.1093/ecco-jcc/jjw168]
16 **Rieder F**, Fiocchi C, Rogler G. Mechanisms, Management, and Treatment of Fibrosis in Patients With Inflammatory Bowel Diseases. *Gastroenterology* 2017; **152**: 340-350.e6 [PMID: 27720839 DOI: 10.1053/j.gastro.2016.09.047]
17 **Alvarez-Lobos M**, Arostegui JI, Sans M, Tassies D, Plaza S, Delgado S, Lacy AM, Pique JM, Yagüe J, Panés J. Crohn's disease patients carrying Nod2/CARD15 gene variants have an increased and early need for first surgery due to stricturing disease and higher rate of surgical recurrence. *Ann Surg* 2005; **242**: 693-700 [PMID: 16244543 DOI: 10.1097/01.sla.0000186173.14696.ea]
18 **Larson DW**, Pemberton JH. Current concepts and controversies in surgery for IBD. *Gastroenterology* 2004; **126**: 1611-1619 [PMID: 15168371 DOI: 10.1053/j.gastro.2004.03.063]
19 **Bernell O**, Lapidus A, Hellers G. Risk factors for surgery and postoperative recurrence in Crohn's disease. *Ann Surg* 2000; **231**: 38-45 [PMID: 10636100 DOI: 10.1097/00000658-200001000-00006]
20 **Chhaya V**, Saxena S, Cecil E, Subramanian V, Curcin V, Majeed A, Pollok RC. Impact of timing and duration of thiopurine treatment on first perianal surgery in Crohn's disease: UK population-based study (1995-2009). *Inflamm Bowel Dis* 2015; **21**: 385-391 [PMID: 25569740 DOI: 10.1097/MIB.0000000000000290]
21 **Chhaya V**, Saxena S, Cecil E, Subramanian V, Curcin V, Majeed A, Pollok RC. Emerging trends and risk factors for perianal surgery in Crohn's disease: a 20-year national population-based cohort study. *Eur J Gastroenterol Hepatol* 2016; **28**: 890-895 [PMID: 27128719 DOI: 10.1097/MEG.0000000000000651]
22 **Chow DK**, Sung JJ, Wu JC, Tsoi KK, Leong RW, Chan FK. Upper gastrointestinal tract phenotype of Crohn's disease is associated with early surgery and further hospitalization. *Inflamm Bowel Dis* 2009; **15**: 551-557 [PMID: 19067420 DOI: 10.1002/ibd.20804]
23 **Cosnes J**, Nion-Larmurier I, Beaugerie L, Afchain P, Tiret E, Gendre JP. Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery. *Gut* 2005; **54**: 237-241 [PMID: 15647188 DOI: 10.1136/gut.2004.045294]
24 **Cushing KC**, Chiplunker A, Li A, Sung YJ, Geisman T, Chen LS, Cresci S, Gutierrez AM. Smoking Interacts With CHRNA5, a Nicotinic Acetylcholine Receptor Subunit Gene, to Influence the Risk of IBD-Related Surgery. *Inflamm Bowel Dis* 2018; **24**: 1057-1064 [PMID: 29688464 DOI: 10.1093/ibd/izx094]
25 **Dubinsky MC**, Kugathasan S, Kwon S, Haritunians T, Wrobel I, Wahbeh G, Quiros A, Bahar R, Silber G, Farrior S, Stephens M, Teleten N,

Panikkath D, Ippoliti A, Vasiliauskas E, Fleshner P, Williams C, Landers C, Rotter JI, Targan SR, Taylor KD, McGovern DP. Multidimensional prognostic risk assessment identifies association between IL12B variation and surgery in Crohn's disease. *Inflamm Bowel Dis* 2013; **19**: 1662-1670 [PMID: 23665963 DOI: 10.1097/MIB.0b013e318281f275]

26 **Feagan BG**, Panaccione R, Sandborn WJ, D'Haens GR, Schreiber S, Rutgeerts PJ, Loftus EV Jr, Lomax KG, Yu AP, Wu EQ, Chao J, Mulani P. Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. *Gastroenterology* 2008; **135**: 1493-1499 [PMID: 18848553 DOI: 10.1053/j.gastro.2008.07.069]

27 **Forcione DG**, Rosen MJ, Kisiel JB, Sands BE. Anti-Saccharomyces cerevisiae antibody (ASCA) positivity is associated with increased risk for early surgery in Crohn's disease. *Gut* 2004; **53**: 1117-1122 [PMID: 15247177 DOI: 10.1136/gut.2003.030734]

28 **Golovics PA**, Lakatos L, Nagy A, Pandur T, Szita I, Balogh M, Molnar C, Komaromi E, Lovasz BD, Mandel M, Veres G, Kiss LS, Vegh Z, Lakatos PL. Is early limited surgery associated with a more benign disease course in Crohn's disease? *World J Gastroenterol* 2013; **19**: 7701-7710 [PMID: 24282358 DOI: 10.3748/wjg.v19.i43.7701]

29 **Jeon SJ**, Lee KJ, Lee MH, Lim SK, Kang CJ, Kim JH. Rates of early surgery and associated risk factors in Crohn's disease. *Korean J Gastroenterol* 2010; **56**: 236-241 [PMID: 20962559 DOI: 10.4166/kjg.2010.56.4.236]

30 **Kariyawasam VC**, Selinger CP, Katelaris PH, Jones DB, McDonald C, Barr G, Chapman G, Colliwshaw J, Lunney PC, Middleton K, Wang RR, Huang T, Andrews J, Leong RW. Early use of thiopurines or methotrexate reduces major abdominal and perianal surgery in Crohn's disease. *Inflamm Bowel Dis* 2014; **20**: 1382-1390 [PMID: 24991785 DOI: 10.1097/MIB.0000000000000119]

31 **Kuenzig ME**, Sadatsafavi M, Aviña-Zubieta JA, Burne RM, Abrahamowicz M, Beauchamp ME, Kaplan GG, Benchimol EI. Asthma is not associated with the need for surgery in Crohn's disease when controlling for smoking status: a population-based cohort study. *Clin Epidemiol* 2018; **10**: 831-840 [PMID: 30038523 DOI: 10.2147/CLEP.S156772]

32 **Lee DW**, Koo JS, Choe JW, Suh SJ, Kim SY, Hyun JJ, Jung SW, Jung YK, Yim HJ, Lee SW. Diagnostic delay in inflammatory bowel disease increases the risk of intestinal surgery. *World J Gastroenterol* 2017; **23**: 6474-6481 [PMID: 29085197 DOI: 10.3748/wjg.v23.i35.6474]

33 **Nguyen GC**, Bernstein CN, Benchimol EI. Risk of Surgery and Mortality in Elderly-onset Inflammatory Bowel Disease: A Population-based Cohort Study. *Inflamm Bowel Dis* 2017; **23**: 218-223 [PMID: 27997435 DOI: 10.1097/MIB.0000000000000993]

34 **Pandey A**, Salazar E, Kong CS, Lim WC, Ong J, Ong DE, Ong C, Aw M, Wee E, Chuah SW, Tan V, Tay WL, Nadkarni N, Ling KL. Risk of Major Abdominal Surgery in an Asian Population-based Crohn's Disease Cohort. *Inflamm Bowel Dis* 2015; **21**: 2625-2633 [PMID: 26240999 DOI: 10.1097/MIB.0000000000000525]

35 **Peyrin-Biroulet L**, Harmsen WS, Tremaine WJ, Zinsmeister AR, Sandborn WJ, Loftus EV Jr. Surgery in a population-based cohort of Crohn's disease from Olmsted County, Minnesota (1970-2004). *Am J Gastroenterol* 2012; **107**: 1693-1701 [PMID: 22945286 DOI: 10.1038/ajg.2012.298]

36 **Reutemann BA**, Turkeltaub JA, Al-Hawary M, Waljee AK, Higgins PDR, Stidham RW. Endoscopic Balloon Dilation Size and Avoidance of Surgery in Stricturing Crohn's Disease. *Inflamm Bowel Dis* 2017; **23**: 1803-1809 [PMID: 28691940 DOI: 10.1097/MIB.0000000000001181]

37 **Szántó K**, Nyári T, Bálint A, Bor R, Milassin Á, Rutka M, Fábián A, Szepes Z, Nagy F, Molnár T, Farkas K. Biological therapy and surgery rates in inflammatory bowel diseases-Data analysis of almost 1000 patients from a Hungarian tertiary IBD center. *PLoS One* 2018; **13**: e0200824 [PMID: 30059523 DOI: 10.1371/journal.pone.0200824]

38 **Varma S**, Hu J, Mehta A, Song Y, Park A, Zhi M, Hutfless S. Initial medical and surgical management of inflammatory bowel disease in the biologic era: A comparison between the United States and China. *JGH Open* 2019; **3**: 234-241 [PMID: 31276042 DOI: 10.1002/jgh3.12146]

39 **Zaharie R**, Tantau A, Zaharie F, Tantau M, Gheorghe L, Gheorghe C, Gologan S, Cijevschi C, Trifan A, Dobru D, Goldis A, Constantinescu G, Iacob R, Diculescu M; IBDPROSPECT Study Group. Diagnostic Delay in Romanian Patients with Inflammatory Bowel Disease: Risk Factors and Impact on the Disease Course and Need for Surgery. *J Crohns Colitis* 2016; **10**: 306-314 [PMID: 26589956 DOI: 10.1093/ecco-jcc/jjv215]

40 **Eubank BH**, Mohtadi NG, Lafave MR, Wiley JP, Bois AJ, Boorman RS, Sheps DM. Using the modified Delphi method to establish clinical consensus for the diagnosis and treatment of patients with rotator cuff pathology. *BMC Med Res Methodol* 2016; **16**: 56 [PMID: 27206853 DOI: 10.1186/s12874-016-0165-8]

41 **Moher D**, Altman DG, Liberati A, Tetzlaff J. PRISMA statement. *Epidemiology* 2011; **22**: 128; author reply 128 [PMID: 21150360 DOI: 10.1097/EDE.0b013e3181fe7825]

42 **Shea BJ**, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017; **358**: j4008 [PMID: 28935701 DOI: 10.1136/bmj.j4008]

43 **Wells G**, Shea B, O'Connell D, Peterson J, Losos WM, Tugwell P, Ga SW, Zello G, Petersen J. Newcastle-Ottawa Scale for assessing the quality of studies in the meta-analysis. 2014. [cited 20 March 2024]. Available from: https://api.semanticscholar.org/CorpusID:79550924

44 **González-Lama Y**, Suárez C, González-Partida I, Calvo M, Matallana V, de la Revilla J, Magaz M, Bernardo C, Agudo B, Ibarrola P, Relea L, Arévalo J, Vera MI, Abreu L. Timing of Thiopurine or Anti-TNF Initiation Is Associated with the Risk of Major Abdominal Surgery in Crohn's Disease: A Retrospective Cohort Study. *J Crohns Colitis* 2016; **10**: 55-60 [PMID: 26520164 DOI: 10.1093/ecco-jcc/jjv187]

45 **Ananthakrishnan AN**, Kwon J, Raffals L, Sands B, Stenson WF, McGovern D, Kwon JH, Rheaume RL, Sandler RS. Variation in treatment of patients with inflammatory bowel diseases at major referral centers in the United States. *Clin Gastroenterol Hepatol* 2015; **13**: 1197-1200 [PMID: 25460565 DOI: 10.1016/j.cgh.2014.11.020]

46 **Kane S**. If variety is the spice of life, we need to rethink our recipe: variation in inflammatory bowel disease practice among tertiary centers. *Clin Gastroenterol Hepatol* 2015; **13**: 1201-1203 [PMID: 25638587 DOI: 10.1016/j.cgh.2015.01.020]

47 **Prideaux L**, Kamm MA, De Cruz PP, Chan FK, Ng SC. Inflammatory bowel disease in Asia: a systematic review. *J Gastroenterol Hepatol* 2012; **27**: 1266-1280 [PMID: 22497584 DOI: 10.1111/j.1440-1746.2012.07150.x]

48 **Ke F**, Yadav PK, Ju LZ. Herbal medicine in the treatment of ulcerative colitis. *Saudi J Gastroenterol* 2012; **18**: 3-10 [PMID: 22249085 DOI: 10.4103/1319-3767.91726]

49 **Burisch J**, Jess T, Martinato M, Lakatos PL; ECCO -EpiCom. The burden of inflammatory bowel disease in Europe. *J Crohns Colitis* 2013; **7**: 322-337 [PMID: 23395397 DOI: 10.1016/j.crohns.2013.01.010]

50 **Park KT**, Ehrlich OG, Allen JI, Meadows P, Szigethy EM, Henrichsen K, Kim SC, Lawton RC, Murphy SM, Regueiro M, Rubin DT, Engel-Nitz NM, Heller CA. Corrigendum to The Cost of Inflammatory Bowel Disease: An Initiative From the Crohn's & Colitis Foundation. *Inflamm Bowel Dis* 2020; **26**: 1118 [PMID: 32374862 DOI: 10.1093/ibd/izaa081]

51 **Sewell JL**, Velayos FS. Systematic review: The role of race and socioeconomic factors on IBD healthcare delivery and effectiveness. *Inflamm Bowel Dis* 2013; **19**: 627-643 [PMID: 22623078 DOI: 10.1002/ibd.22986]

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META-ANALYSIS

Compare clinical efficacy and safety of neoadjuvant therapy and neoadjuvant chemoradiotherapy for locally advanced rectal cancer: Meta-analysis

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Abstract

BACKGROUND

To compare the efficacy and safety of total neoadjuvant therapy (TNT) and neoadjuvant chemoradiotherapy (nCRT) in the treatment of middle and low locally advanced rectal cancer. Our study will systematically collect and integrate studies to evaluate the ability of these two treatments to improve tumor shrinkage rates, surgical resection rates, tumor-free survival, and severe adverse events.

AIM

To provide clinicians and patients with more reliable treatment options to optimize treatment outcomes and quality of life for patients with locally advanced rectal cancer by comparing the advantages and disadvantages of the two treatment options.

METHODS

A full search of all clinical studies on the effectiveness and safety of TNT and nCRT for treating locally advanced rectal cancer identified in Chinese (CNKI, Wanfang, China Biomedical Literature Database) and English (PubMed, Embase) databases was performed. Two system assessors independently screened the studies according to the inclusion and exclusion criteria. Quality evaluation and

data extraction were performed for the included literature. We used RevMan 5.3 software to perform a meta-analysis of the pathologic complete response (pCR) rate, T stage degradation rate, resection 0 (R0) rate, anal grade 3/4 acute toxicity rate, perioperative complications, overall survival (OS), and disease-free survival (DFS) in the TNT and nCRT groups.

RESULTS

Finally, 14 studies were included, six of which were randomized controlled studies. A total of 3797 patients were included, including 1865 in the TNT group and 1932 in the nCRT group. The two sets of baseline data were comparable. The results of the meta-analysis showed that the pCR rate [odds ratio (OR) = 1.57, 95% confidence interval (CI): 1.30-1.90, $P < 0.00001$], T stage degradation rate (OR = 2.16, 95%CI: 1.63-2.57, $P < 0.00001$), and R0 resection rate (OR = 1.42, 95%CI: 1.09-1.85, $P = 0.009$) were significantly greater in the nCRT group than in the nCRT group. There was no significant difference in the incidence of grade 3/4 acute toxicity or perioperative complications between the two groups. The 5-year OS [hazard ratio (HR) = 0.84, 95%CI: 0.69-1.02, $P = 0.08$] and DFS (HR = 0.94, 95%CI: 0.03-1.39, $P = 0.74$) of the TNT group were similar to those of the nCRT group.

CONCLUSION

TNT has greater clinical efficacy and safety than nCRT in the treatment of locally advanced rectal cancer.

Key Words: Neoadjuvant therapy; Neoadjuvant chemoradiotherapy; Advanced rectal cancer; Clinical efficacy; Meta-analysis

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Core Tip: The main aim of this study was to perform a meta-analysis and compare the clinical efficacy and safety of neoadjuvant therapy and neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer. We will collect and synthesize relevant research data to evaluate the performance of the two treatments in terms of the tumor shrinkage rate, surgical resection rate, tumor-free survival rate and other clinical indicators and analyze the safety differences between the two treatments in terms of the incidence of serious adverse events and other aspects. Through in-depth exploration of the advantages and disadvantages of the two treatment schemes, the aim is to provide more guiding treatment suggestions for clinicians to optimize the choice of treatment schemes for patients and improve the treatment effect and quality of life.

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INTRODUCTION

Neoadjuvant chemoradiotherapy (nCRT), total mesorectal excision (TME), and postoperative adjuvant chemotherapy are the standard treatment strategies for low- and medium-locally advanced rectal cancer[1]. The diagnosis and treatment mode of "nCRT + TME + postoperative adjuvant chemotherapy" have significantly improved the local control rate of tumors, and the local recurrence rate of rectal cancer after surgery has decreased from 35% to 5%-10%, but the distant metastasis rate is still as high as 25%-30%, and it is the main factor affecting the survival prognosis. The CAO/ARO/AIO-94 study and the EORTC22921 study both showed that nCRT did not improve the long-term survival prognosis of patients with rectal cancer, and patients' compliance with postoperative adjuvant chemotherapy was poor[2-5].

To further reduce the rate of distant metastasis in patients with rectal cancer and improve survival, some scholars have proposed an "intensive treatment" program[6]. One is to increase the dose of radiotherapy, and the second is to add another cytotoxic drug, such as oxaliplatin, to the 5-fluorouracil-based synchronous chemotherapy regimen[7]. The third is postoperative adjuvant chemotherapy before TME, that is, total neoadjuvant therapy (TNT). TNT has two modes of induction chemotherapy, in which several cycles of systemic chemotherapy are administered before nCRT and consolidation chemotherapy is administered between nCRT and the TME. The National Comprehensive Cancer Care Consortium listed TNT as one of the recommended treatment strategies for locally advanced rectal cancer[8-10]. This study aimed to determine how well TNTs work and how long people are likely to live. The safety and effectiveness of TNT and nCRT for treating low to medium locally advanced rectal cancer will be compared.

MATERIALS AND METHODS

Document inclusion criteria

Literature type: Clinical studies related to TNT in the treatment of locally advanced rectal cancer, limited to Chinese and English; study subjects: Patients with middle and low locally advanced rectal cancer confirmed by colonoscopy pathology; intervention measures: Experimental group received TNT, control group received nCRT; outcome measures: (1) Main index: Pathologic complete response (pCR) rate, R0 resection rate, incidence of grade 3/4 acute toxicity, 5-year overall survival (OS) and disease-free survival (DFS); and (2) Secondary index: Tumor down phase rate, anal preservation rate, perioperative complication rate, local recurrence and distant metastasis rate, *etc*.

Document exclusion criteria

Single-arm study; reviews, case reports or summaries of meetings; biological therapy, such as cetuximab, bevacizumab, *etc*.; no studies on any of these outcomes.

Search strategy

Chinese databases (CNKI, Wanfang, China Biomedical Literature Database) and English databases (PubMed, Embase) were comprehensively searched. The search strategy used was "neoadjuvant chemoradiotherapy" OR "total neoadjuvant therapy" OR "induction therapy" OR "consolidation therapy" AND "rectal cancer" OR "rectal tumor". To avoid bias caused by language limitations, this study searched both English studies. To avoid missing relevant studies, relevant references listed in the articles and conference abstracts found in the search were traced (Figure 1).

Data collection and data extraction

Literature screening was performed by two independent researchers according to the inclusion and exclusion criteria[11-14]. Disagreements over the search results were resolved through discussion. If there was still a dispute after negotiation, it was resolved by a third researcher[15]. Data extraction was carried out in strict accordance with the designed table[16]. The main contents included author, publication year, country, study type, baseline data, observation indicators, *etc.*

Literature quality evaluation

The quality of randomized controlled studies was assessed using bias assessment tools recommended by the Cochrane Collaboration, including six aspects: Randomization, assignment concealment, blindness, integrity of results, selective reporting of findings, and other sources of bias. Each indicator was evaluated as "low risk", "unclear" or "high risk". The Newcastle-Ottawa Scale (NOS) was selected for the methodological evaluation of nonrandomized controlled studies[17-20]. The evaluation included four aspects: Population selection, comparability, exposure and result evaluation. The NOS uses a semiquantitative star system, with a full score of 9 stars and a score greater than 5 points included in the analysis [21].

Bias analysis

Heterogeneity between studies was assessed using I^2 statistics, with 25%, 50%, and 75% representing low, medium and high heterogeneity, respectively; $I^2 < 50\%$ and $P > 0.1$ between studies using fixed effect models; and $I^2 > 50\%$ and $P < 0.1$ from χ^2 analysis indicating study heterogeneity[22-24]. Meta-analysis by random effects models was performed, and possible heterogeneity was determined by subgroup analysis. The sensitivity analysis removed the included studies one by one to determine whether the pooled effect values were stable or reliable.

Statistical analysis

The Cochrane Collaboration provided RevMan 5.3 software for the statistical analysis. The odds ratio (OR) and 95% confidence interval (CI) of the binary measurement data were calculated. The hazard ratio (HR) and 95%CI of the survival data were calculated. For heterogeneity tests, the statistics I^2 and Q tests were selected. An $I^2 > 0.5$ indicated that the heterogeneity was high, and a random effects model was selected. If $I^2 < 0.5$, the fixed effects model was chosen. A funnel plot was constructed for publication-offset analysis of the included studies. $P < 0.05$ indicated that the difference was statistically significant.

RESULTS

Literature retrieval results and included research characteristics

A total of 14 studies meeting the criteria were included in the study, including 6 randomized controlled studies, 5 retrospective case-control studies, and 3 prospective studies (Figure 1). A total of 3797 patients with rectal cancer were included, including 1865 in the TNT group and 1932 in the nCRT group. The general characteristics of the included studies are shown in Table 1, and the chemoradiotherapy protocols adopted in each study are shown in Table 2. The quality evaluation results of randomized controlled studies are shown in Figure 2, and the quality evaluation scores of nonrandomized controlled studies were no less than 5 points.

Table 1 General characteristics of included studies

Ref.	Country	Study type	Cases	Sample size		Inclusion in research quality evaluation
				TNT	nCRT	
Garcia-Aguilar *et al*[9], 2015	America	Prospective study	259	199	60	6
Zhai *et al*[11], 2020	China	Retrospective study	134	79	55	6
Cercek *et al*[12], 2018	America	Retrospective study	628	308	320	8
Markovina *et al*[13], 2017	America	Prospective study	138	69	69	6
Zhu *et al*[14], 2019	America	Retrospective study	1079	372	707	8
Fernandez-Martos *et al*[15], 2015	America	Randomized controlled study	103	54	49	7
Maréchal *et al*[18], 2012	Belgium	Randomized controlled study	57	28	29	8
Calvo *et al*[19], 2014	Spain	Retrospective study	335	207	128	7
Bhatti *et al*[20], 2015	Pakistan	Retrospective study	154	93	61	7
Bujko *et al*[21], 2016	Poland	Randomized controlled study	515	261	254	8
Kim *et al*[22], 2018	South Korea	Randomized controlled study	110	54	56	7
Liang *et al*[23], 2019	China	Prospective study	156	76	80	5
Moore *et al*[24], 2017	Australia	Randomized controlled study	49	25	24	8
Wu *et al*[25], 2022	China	Randomized controlled study	80	40	40	8

TNT: Total neoadjuvant therapy; nCRT: Neoadjuvant chemoradiotherapy.

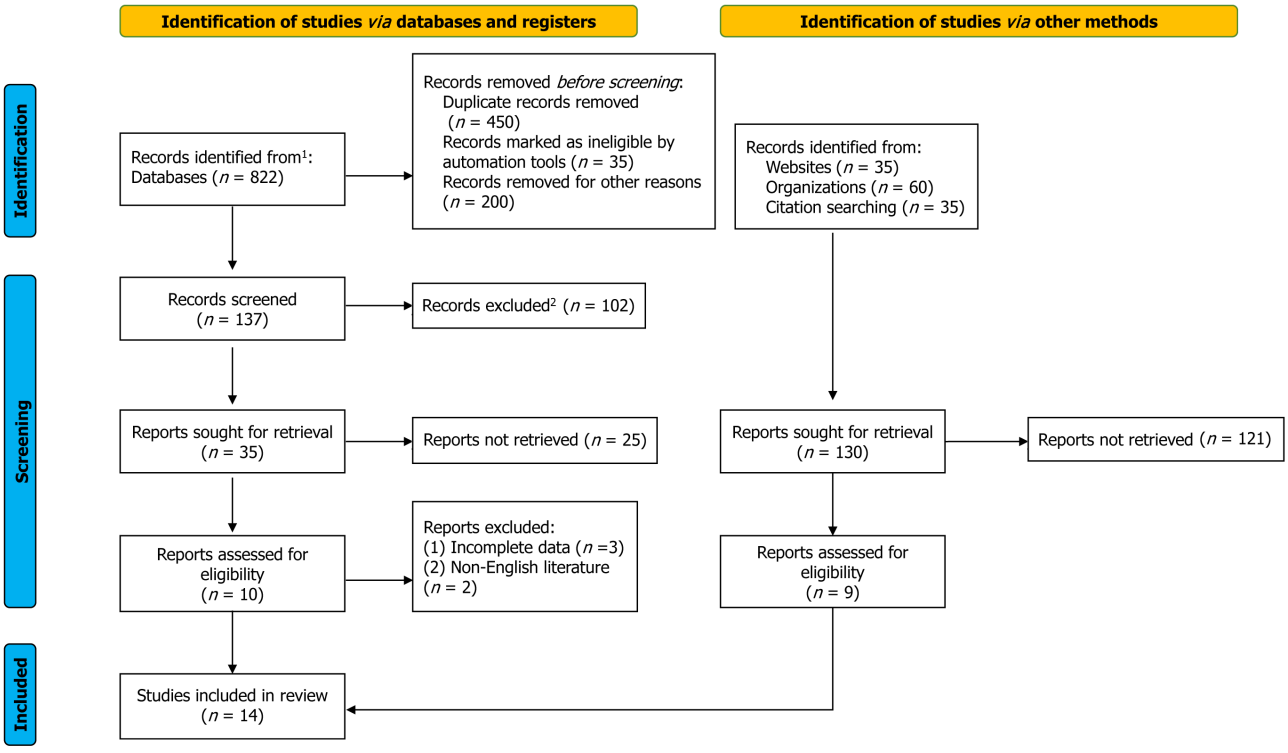


Figure 1 Flow chart of the literature screening. [1]Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). [2]If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

TNT safety evaluation analysis

Grade 3/4 acute toxic reactions: A total of 10 studies reported the incidence of grade 3/4 acute toxic reactions during the TNT or nCRT stage[9,11,13,15,18,19,21-23,25]. There was great heterogeneity among the studies (I^2 = 80%), so the random effects model was selected. The results of the meta-analysis showed that there was no significant difference in the incidence of grade 3/4 acute toxicity between the TNT group and the nCRT group (OR = 0.79, 95%CI: 0.47-1.32, P = 0.36) (Figure 3A).

Perioperative complications: A total of 10 studies reported perioperative complications[7,11,15-19,21,23,24]. There was little heterogeneity among the studies (P = 0.62, I^2 = 0%), and the fixed-effects model was chosen. The results of the meta-analysis showed that there was no significant difference in the incidence of perioperative complications between the two groups (OR = 1.02, 95%CI: 0.78-1.33, P = 0.87) (Figure 3B).

Evaluation of the perioperative efficacy of TNT

pCR rate analysis: A total of 14 studies used pCR as the main outcome index[11-18,20-25]. There was little heterogeneity among the studies (P = 0.54, I^2 = 0%), and the fixed-effects model was chosen. The results of the meta-analysis showed that the pCR rate in the TNT group was significantly greater than that in the nCRT group (OR = 1.57, 95%CI: 1.30-1.90, P < 0.00001) (Figure 3C).

Analysis of the tumor downphase rate: A total of 6 studies reported the T stage regression rate[13,18,19,22,23,25]. There was little heterogeneity among the studies (P = 0.26, I^2 = 24%), and the fixed-effects model was chosen. The results of the meta-analysis showed that the T stage decline rate in the TNT group was significantly greater than that in the nCRT group (OR = 2.16, 95%CI: 1.63-2.57, P < 0.00001) (Figure 3D).

R0 removal rate analysis: A total of 14 studies reported R0 removal rates after TNT or nCRT[7,11,14-25]. There was little heterogeneity among the studies (P = 0.10, I^2 = 38%), and the fixed-effects model was chosen. The results of the meta-analysis showed that the R0 removal rate in the TNT group was significantly greater than that in the nCRT group (OR = 1.42, 95%CI: 1.09-1.85, P = 0.009) (Figure 3E).

Anal retention rate analysis: A total of 14 studies reported anal preservation rates after TNT or nCRT[7,11-13,15-24]. There was little heterogeneity among the studies (P = 0.08, I^2 = 41%), and the fixed-effects model was chosen. The results of the meta-analysis showed that there was no significant difference in the anal preservation rate between the TNT and nCRT groups (OR = 0.99, 95%CI: 0.82-1.19, P = 0.88) (Figure 3F).

TNT survival prognosis analysis

Analysis of local recurrence and distant metastasis: Local recurrence and distant metastasis were reported in four studies each during the follow-up period[16,20,23,25], as was distant metastasis[16,20,22,25]. There was little heterogeneity among the studies (both I^2 = 0%), and the fixed-effects model was selected. The results of the meta-analysis showed that there was no statistically significant difference in local recurrence rates between the TNT group and the nCRT group (OR = 0.89, 95%CI: 0.47-1.69; P = 0.73) (Figure 3G). The rates of distant metastasis were similar between the two groups (OR = 1.11, 95%CI: 0.81-1.52; P = 0.5) (Figure 3H).

OS and DFS analysis: Seven studies reported 5-year OS in both groups[13-15,20,21,23,25]. There was little heterogeneity among the studies (P = 0.24, I^2 = 25%), and the fixed-effects model was chosen. The results of the meta-analysis showed that there was no significant difference in 5-year OS between the TNT group and the nCRT group (HR = 0.84, 95%CI: 0.69-1.02; P = 0.08) (Figure 4A). Four studies reported 5-year DFS in the TNT and nCRT groups[13,15,20,23]. There was little heterogeneity among the studies (P = 0.95, I^2 = 0%), and the fixed-effects model was selected. Meta-analysis revealed no significant difference in 5-year DFS between the two groups (HR = 0.94, 95%CI: 0.03-1.39, P = 0.74) (Figure 4B).

Literature publication bias analysis: A funnel plot was used to analyze the publication bias of the included studies for each outcome index, and it was found that the distributions on both sides of the funnel plot were basically symmetrical with no significant publication bias, indicating good stability. Taking pCR as an example, the funnel plot of the 4 included studies was basically distributed within the 95%CI, indicating no significant publication bias (Figure 5).

DISCUSSION

A number of studies have shown that TNT can significantly improve the treatment compliance of rectal cancer patients; increase the pCR rate, tumor down phase rate, and R0 resection rate; increase the anal preservation rate and organ retention rate; eliminate occult micrometastases; shorten the duration of surgery; and further reduce the rate of local recurrence and distant metastasis by increasing the local control of tumors[26-28]. In addition, these treatments improve long-term survival outcomes. In this study, the pCR rate, R0 removal rate, and T stage degradation rate in the TNT group were significantly greater than those in the nCRT group, while the incidences of grade 3/4 acute toxic reactions and perioperative complications were similar to those in the nCRT group[29]. There were no significant differences in the local recurrence rate, distant metastasis rate, 5-year OS, or DFS between the two groups. Compared with nCRT, TNT did not significantly increase the rate of grade 3/4 acute toxic reactions or perioperative complications[30]. The incidence of grade 3/4 acute toxic reactions reported during TNT treatment ranged from 4% to 55%, mainly diarrhea and hematological toxicity (neutropenia, thrombocytopenia, *etc.*). Overall, the incidence of toxic reactions with TNT (27%) was similar

Table 2 Radiochemotherapy regimens and specific doses for total neoadjuvant therapy and neoadjuvant chemoradiotherapy groups

Ref.	TNT			nCRT	
	IT/CT	Chemotherapy	Dose	Radiation therapy	Synchronous chemotherapy
Garcia-Aguilar *et al* [9], 2015	CT	mFOFLOX	5-FU 400 mg/m²; LV 200 mg/m²; OX 85 mg/m^2	45.0 Gy/25 f	5-FU 225 mg/m^2
Zhai *et al*[11], 2020	CT	CAPEOX	CAP 1000 mg/m²; OX 130 mg/m^2	50.4 Gy/28f	CAP 850 mg/m²
Cercek *et al*[12], 2018	IT	mFOFLOX	5-FU 400 mg/m²; LV 200 mg/m²; OX 85 mg/m²	45.0 Gy/25 f	5-FU 225 mg/m²/CAP 850 mg/m²
Markovina *et al*[13], 2017	IT	mFOFLOX FOFLOX	5-FU/LV/OX	45.0 Gy/25 f, 45.0 Gy/25 f	5-FU/CAP
Zhu *et al*[14], 2019	IT	CAPEOX		50.4 Gy/25-28 f	
Fernandez-Martos *et al* [15], 2015	IT	CAPEOX	CAP/OX	45.0 Gy/25 f	CAP
Maréchal *et al*[18], 2012	IT	mFOFLOX	5-FU 400 mg/m²; LV 400 mg/m²; OX 100 mg/m²	45.0 Gy/25 f	5-FU 225 mg/m²
Calvo *et al*[19], 2014	IT	mFOFLOX	5-FU 400 mg/m²; LV 200 mg/m²; OX 85 mg/m^2	45.0 Gy/25 f	5-FU 425 mg/m^2
Bhatti *et al*[20], 2015	IT	CAPEOX	CAP 1000 mg/m²; OX 130 mg/m²	50.4 Gy/25-28 f	CAP 825 mg/m²
Bujko *et al*[21], 2016	CT	mFOFLOX	5-FU/LV/OX	50.4 Gy/25-28 f	5-FU 325 mg/m²/LV 20 mg/m²
Kim *et al*[22], 2018	CT	CAPEOX, CAPEOX	CAP 1700 mg/m²; OX 100 mg/m²	50.4 Gy/25-28 f	CAP
Liang *et al*[23], 2019	CT	FOFLOX	CAP 1000 mg/m²; OX 130 mg/m²; 5-FU 400 mg/m²; LV 400 mg/m²; OX 85 mg/m^2	50.4 Gy/25-28 f	CAP 825 mg/m²
Moore *et al*[24], 2017	CT	5-FU/LV	5-FU 450 mg/m²; LV 50 mg/m^2	45.0 Gy/25 f	5-FU 225 mg/m²
Wu *et al*[25], 2022	CT	FOFLOX	5-FU 400 mg/m²; LV200 mg/m²; OX 85 mg/m²	50.4 Gy/25-28 f	5-FU 225 mg/m^2

IT: Immunotherapy; CT: Chemotherapy; TNT: Total neoadjuvant therapy; nCRT: Neoadjuvant chemoradiotherapy; 5-FU: 5-fluorouracil; CAPEOX: Capecitabine; CAP: Community-acquired pneumonia; OX: Oxaliplatin; LV: Leucovorin; FOFLOX: Fluorouracil, oxaliplatin, leucovorin; mFOFLOX: Modified fluorouracil, oxaliplatin, leucovorin.

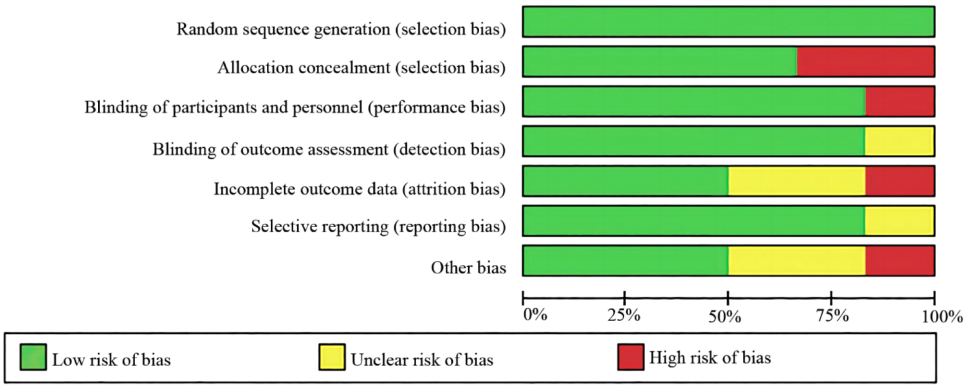


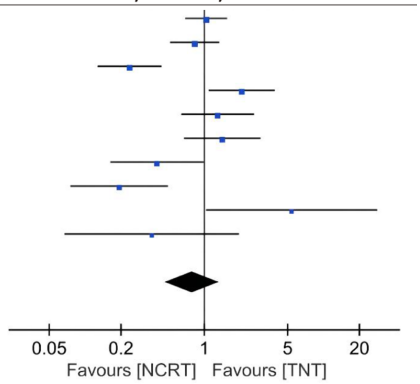
Figure 2 Risk of bias graph of the literature quality evaluation chart.

to that with nCRT (31%). Some studies also reported that the incidence of toxic side effects of TNT is lower, possibly because patients have not yet received surgical treatment, the body's immune system and general condition are better, and the tolerance of systemic chemotherapy is better[31-34]. The results of this study revealed that the incidence of perioperative complications in the TNT group was similar to that in the nCRT group, which was consistent with the conclusions of most studies. Among these complications, incision complications and anastomosis-related complications (anastomotic leakage and anastomotic stenosis) were more common[35]. The above studies indicate that the safety of TNT and nCRT is comparable and that TNT may achieve better oncological efficacy without increasing the incidence of toxic

A

Study or subgroup	TNT Events	TNT Total	NCRT Events	NCRT Total	Weight	Odds ratio M-H, random, 95%CI
Bujko et al.2016	62	256	61	259	12.7%	1.04 [0.69, 1.56]
Calvo et al.2014	60	208	42	128	12.3%	0.83 [0.52, 1.34]
Garcia et al.2015	38	199	30	60	11.5%	0.24 [0.13, 0.44]
Liang et al.2019	42	76	30	80	11.4%	2.06 [1.09, 3.90]
Markovina et al.2019	26	69	22	69	11.0%	1.29 [0.64, 2.61]
Zhai Zhiwei, et al.2020	29	79	16	55	10.7%	1.41 [0.67, 2.96]
Li Leilei, et al.2017	15	40	24	40	9.7%	0.40 [0.16, 0.98]
Fernandez et al.2015	10	54	20	37	9.4%	0.19 [0.08, 0.50]
Maréchal et al.2012	8	28	2	29	5.7%	5.40 [1.03, 28.23]
Kim et al.2018	2	55	5	53	5.6%	0.36 [0.07, 1.95]
Total (95% *CI*)		**1064**		**810**	**100.0%**	**0.79 [0.47, 1.32]**
Total events	292		252			

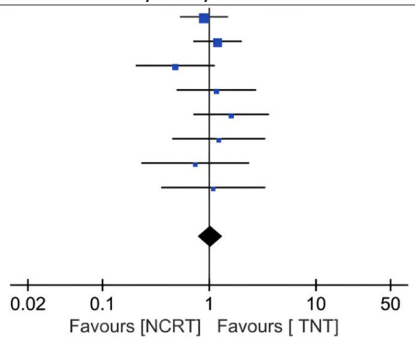
Heterogeneity: Tau² = 0.51; Chi² = 45.94, *df* = 9 (*P* < 0.00001); I^2 = 80%
Test for overall effect: *Z* = 0.91 (*P* = 0.36)



B

Study or subgroup	TNT Events	TNT Total	NCRT Events	NCRT Total	Weight	Odds ratio M-H, fixed, 95%CI
Bujko et al.2016	35	178	37	172	27.9%	0.89 [0.53, 1.50]
Calvo et al.2014	52	207	28	128	24.0%	1.20 [0.71, 2.02]
Garcia et al.2015	15	199	10	69	12.7%	0.48 [0.21, 1.13]
Liang et al.2019	13	76	12	80	9.0%	1.17 [0.50, 2.75]
Fernandez et al.2015	24	52	16	46	8.5%	1.61 [0.71, 3.63]
Zhai zhiwei,et al.2020	12	79	7	55	6.5%	1.23 [0.45, 3.35]
Maréchal et al.2012	7	28	9	29	6.1%	0.74 [0.23, 2.37]
Moore et al.2017	12	25	11	24	5.4%	1.09 [0.36, 3.35]
Total (95% *CI*)		**844**		**603**	**100.0%**	**1.02 [0.78, 1.33]**
Total events	170		130			

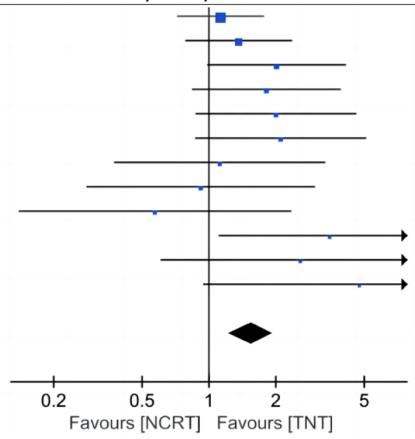
Heterogeneity: Chi² = 5.33, *df* = 7 (*P* = 0.62); I^2 = 0%
Test for overall effect: *Z* = 0.16 (*P* = 0.87)



C

Study or subgroup	TNT Events	TNT Total	NCRT Events	NCRT Total	Weight	Odds ratio M-H, fixed, 95%CI
Cercek et al.2018	43	235	49	296	30.0%	1.13 [0.72, 1.77]
Bujko et al.2016	35	220	25	205	18.4%	1.36 [0.78, 2.37]
Garcia et al.2015	62	199	11	60	9.8%	2.02 [0.98, 4.14]
Bhatti et al.2015	28	91	12	61	8.4%	1.81 [0.84, 3.93]
Markovina et al.2019	19	69	11	69	6.7%	2.00 [0.87, 4.61]
Liang et al.2019	16	76	9	80	5.9%	2.10 [0.87, 5.10]
Fernandez et al.2015	8	54	7	52	5.1%	1.12 [0.37, 3.34]
Maréchal et al.2012	7	27	8	29	4.8%	0.92 [0.28, 3.00]
Moore et al.2017	4	25	6	24	4.3%	0.57 [0.14, 2.35]
Zhai Zhiwei et al.2020	17	79	4	55	3.1%	3.50 [1.11, 11.05]
Kim et al.2018	6	44	3	52	2.0%	2.58 [0.61, 10.99]
Li Leilei et al.2017	8	40	2	40	1.4%	4.75 [0.94, 23.98]
Total (95% *CI*)		**1159**		**1023**	**100.0%**	**1.55 [1.23, 1.95]**
Total events	253		147			

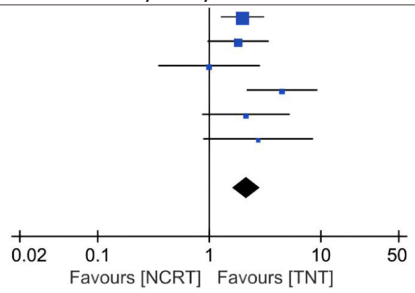
Heterogeneity: Chi² = 10.84, *df* = 11 (*P* = 0.46); I^2 = 0%
Test for overall effect: *Z* = 3.73 (*P* = 0.0002)



D

Study or subgroup	TNT Events	TNT Total	NCRT Events	NCRT Total	Weight	Odds ratio M-H, fixed, 95%CI
Calvo et al.2014	124	207	55	128	41.7%	1.98 [1.27, 3.10]
Liang et al.2019	50	79	39	80	21.7%	1.81 [0.96, 3.42]
Maréchal et al.2012	13	27	14	29	10.7%	0.99 [0.35, 2.84]
Markovina et al.2019	52	69	28	69	10.5%	4.48 [2.16, 9.28]
Kim et al.2018	16	44	11	52	9.8%	2.13 [0.86, 5.27]
Li Leilei et al.2017	24	31	15	27	5.5%	2.74 [0.88, 8.52]
Total (95% *CI*)		**457**		**385**	**100.0%**	**2.16 [1.63, 2.87]**
Total events	279		162			

Heterogeneity: Chi² = 6.55, *df* = 5 (*P* = 0.26); I^2 = 24%
Test for overall effect: *Z* = 5.34 (*P* < 0.00001)



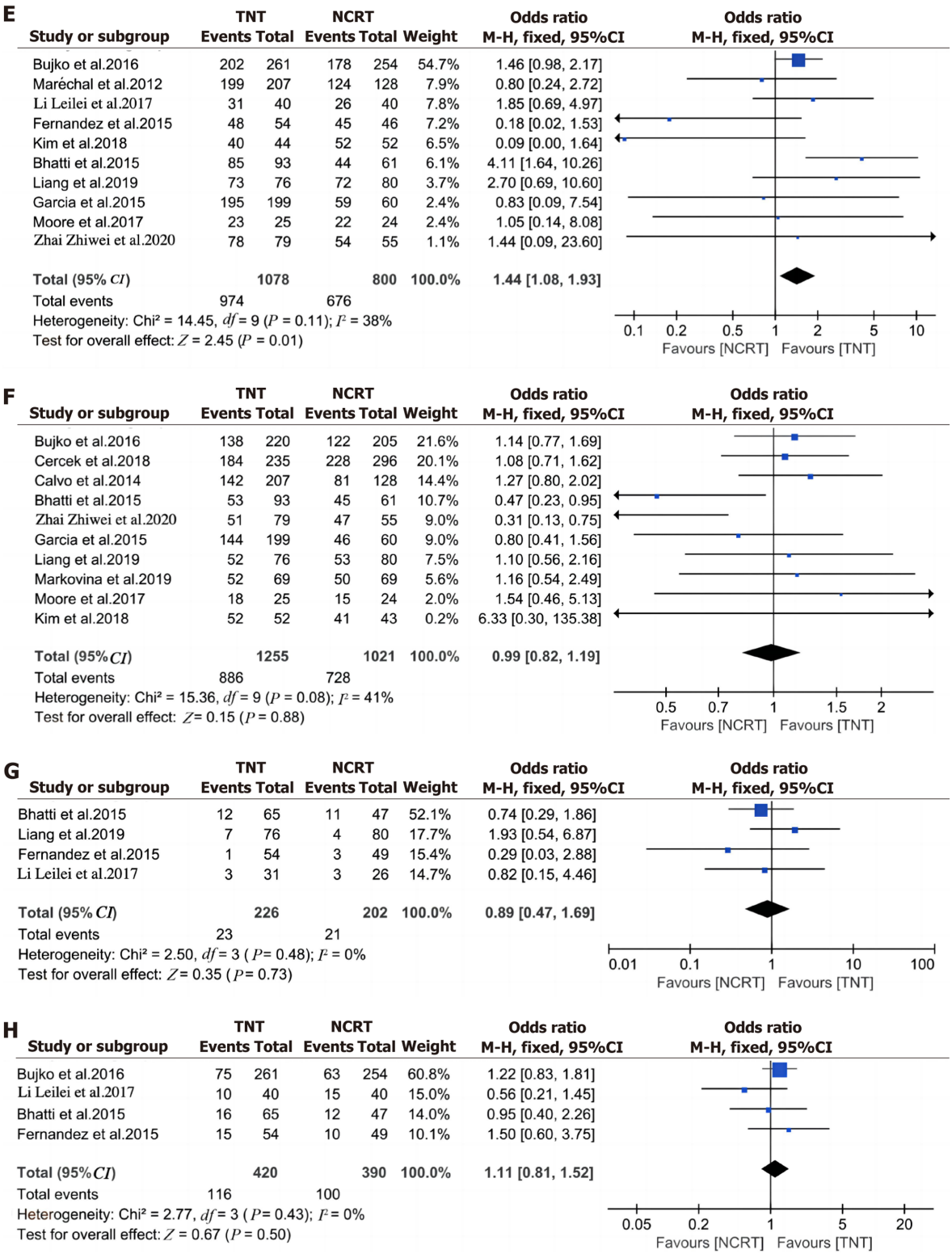


Figure 3 Comparative analysis of acute grade 3/4 toxicity, perioperative complications, pathologic complete response rates, the rate of decrease in tumor T stage, the R0 removal rate, anal preservation rates, local recurrence, and distant metastasis between total neoadjuvant therapy and neoadjuvant chemoradiotherapy. A: Comparative analysis of acute grade 3/4 toxicity between total neoadjuvant therapy (TNT) and neoadjuvant chemoradiotherapy (nCRT); B: Comparative analysis of perioperative complications between the TNT and nCRT groups; C: Comparative analysis of pathologic complete response rates between the TNT and nCRT groups; D: Comparative analysis of the rate of decrease in tumor T stage between the TNT and nCRT groups; E: Comparative analysis of the R0 removal rate between the TNT and nCRT groups; F: Comparative analysis of anal preservation rates between the TNT and nCRT groups; G: Comparative analysis of local recurrence between the TNT and nCRT groups; H: Comparative analysis of distant metastasis between the TNT and nCRT groups. TNT: Total neoadjuvant therapy; nCRT: Neoadjuvant chemoradiotherapy; CI: Confidence interval.

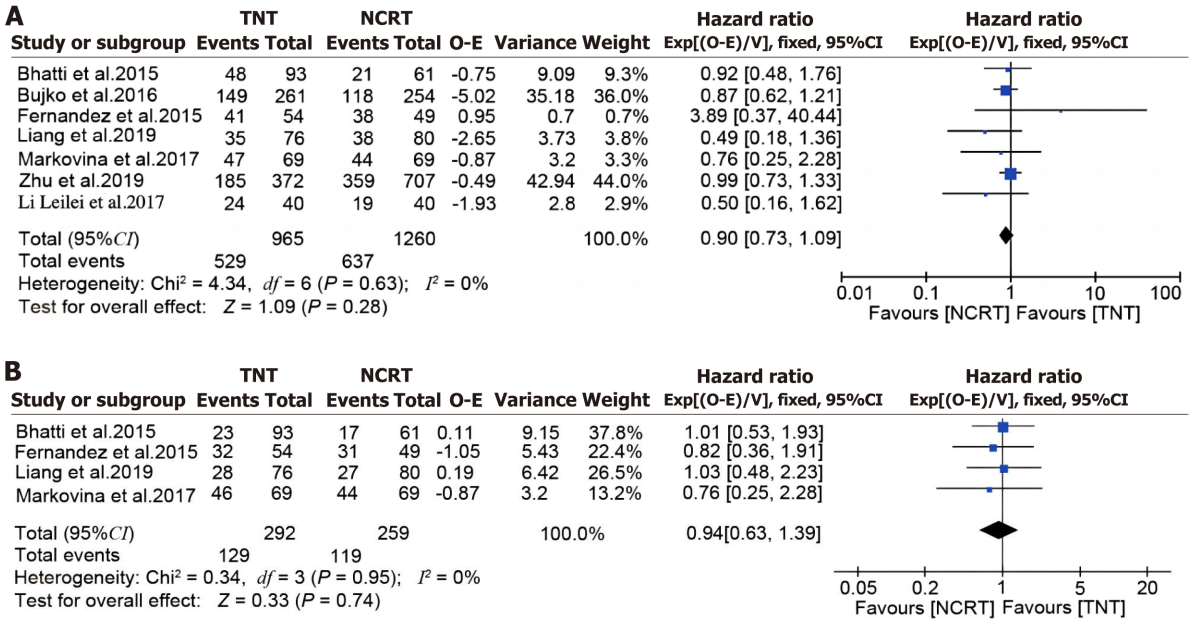


Figure 4 Comparative analysis of 5-year overall survival and disease-free survival between the total neoadjuvant therapy and neoadjuvant chemoradiotherapy groups. A: 5-year overall survival; B: 5-year disease-free survival. TNT: Total neoadjuvant therapy; nCRT: Neoadjuvant chemoradiotherapy; CI: Confidence interval.

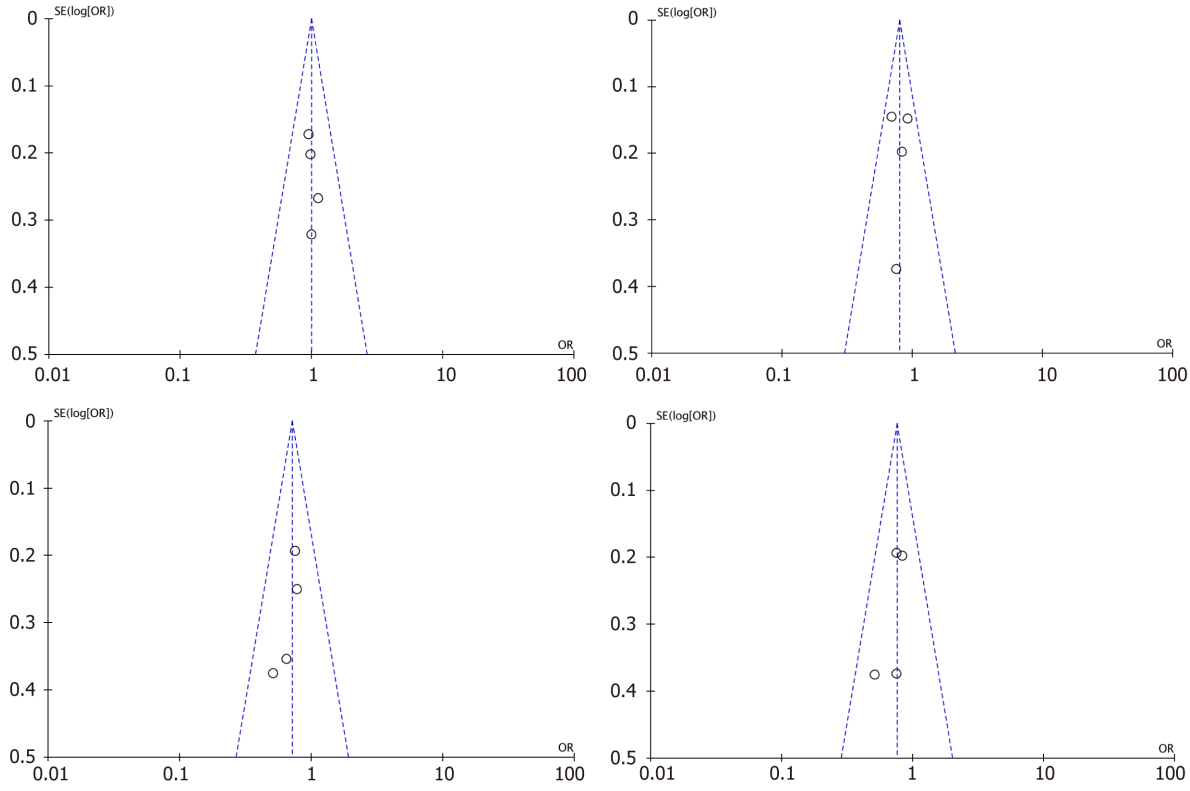


Figure 5 Publication bias of included studies. OR: Odds ratio.

side effects or postoperative complications.

As shown in the results of this study[36], the total pCR rate in the TNT group was 21.3%, which was significantly greater than that in the nCRT group (13.9%, $P < 0.05$), which was consistent with the results of the meta-analysis (22.4% *vs* 13.7%, $P = 0.01$). TNT can significantly increase the pCR rate of patients with locally advanced rectal cancer. Another study divided patients with locally advanced rectal cancer into four groups who received 0, 2, 4, or 6 wk of "mFOLFOX6" consolidation chemotherapy between nCRT and the TME and achieved pCR rates of 18%, 25%, 30%, and 38%, respectively. This showed that the pCR rate increased with an increase in the number of TNT cycles[37]. A retrospective

study from Memorial Sloan-Kettering Cancer Center showed that pCR rates were significantly greater in the TNT group than in the nCRT group (35.7% *vs* 21.3%, $P < 0.05$)[38]. However, other studies, such as the GCR-3 study and the EXPECT-C study, have shown that TNT does not significantly improve the pCR rate of patients with rectal cancer.

The opposite conclusions of different studies may be related to the time interval between the end of neoadjuvant therapy and the time before radical surgery[39-41]. The Lyon R90-01 study showed that the efficacy of TNT was time dependent, and the pCR rate increased with increasing time intervals. After this time interval is significantly extended, the tumor tissue will have enough time to shrink to achieve better tumor reduction and down phase effects and a higher pCR rate. However, the time interval of the EXPECT C study was only 5-6 wk, which is significantly lower than the 8-12 wk of other studies, which may be the main reason why the pCR rate of this study was not significantly improved[42].

This study showed that although there was no statistically significant difference in the operative anal preservation rate between the two groups, the time to return to the stoma was significantly shorter in the TNT group. The study revealed that 87.5% and 85.5% of patients in the TNT and nCRT groups, respectively, received protective ostomies after low anterior resection. Within six months after surgery, the reduction rate was significantly greater in the TNT group than in the nCRT group (71.9% *vs* 8.8%, $P < 0.001$). Patients in the nCRT group usually needed to complete postoperative adjuvant chemotherapy before the stoma was restored, while patients in the TNT group mostly completed systemic chemotherapy before surgery and could generally restore the stoma within six months. Therefore, TNT significantly shortened the duration of ostomy restoration and significantly improved the postoperative quality of life of patients with rectal cancer. Domestic studies also suggested that TNT did not significantly improve the survival prognosis of rectal cancer patients. A subgroup analysis of several studies showed that the OS and DFS of pCR patients were much better than those of nonpCR patients[43,44]. This suggests that the survival prognosis of rectal cancer patients may be linked to local tumor control. Some studies have also shown that TNT can significantly eliminate occult micrometastases and improve the survival of patients with rectal cancer. Among the 14 studies included in this paper, only 4 discussed the long-term efficacy of TNT, with a small sample size and mainly retrospective studies, which may have led to a large bias in the results of this study.

This meta-analysis also has certain limitations: (1) Only six randomized controlled studies were included in this study, and the sample size was relatively small, which may have deficiencies such as publication bias; and (2) The included studies mainly reported the short-term efficacy and safety of TNT, such as pCR, clinical complete response, and the R0 resection rate. Few studies on long-term survival prognosis exist, and most of them were retrospective studies.

CONCLUSION

In summary, TNT has the advantages of eliminating occult micrometastases, shortening the time of ostomy restoration, improving treatment compliance in patients with rectal cancer, significantly increasing the pCR rate of locally advanced rectal cancer, and improving the R0 resection rate and tumor downphase rate. Follow-up studies on TNT after long-term survival preconditioning, such as the RAPIDO, NCT03177382, and NCT02031939 studies, are underway, and it is expected that the results of these studies can further clarify the clinical efficacy of TNT.

FOOTNOTES

Author contributions: Wang Y wrote the manuscript; Yang Y and Liu QQ collected the data; Wang SZ guided the study; and all authors reviewed, edited, and approved the final manuscript and revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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REFERENCES

1 **Boublikova L**, Novakova A, Simsa J, Lohynska R. Total neoadjuvant therapy in rectal cancer: the evidence and expectations. *Crit Rev Oncol Hematol* 2023; **192**: 104196 [PMID: 37926376 DOI: 10.1016/j.critrevonc.2023.104196]

2 **Kasi A**, Abbasi S, Handa S, Al-Rajabi R, Saeed A, Baranda J, Sun W. Total Neoadjuvant Therapy vs Standard Therapy in Locally Advanced Rectal Cancer: A Systematic Review and Meta-analysis. *JAMA Netw Open* 2020; **3**: e2030097 [PMID: 33326026 DOI: 10.1001/jamanetworkopen.2020.30097]

3 **Body A**, Prenen H, Lam M, Davies A, Tipping-Smith S, Lum C, Liow E, Segelov E. Neoadjuvant Therapy for Locally Advanced Rectal Cancer: Recent Advances and Ongoing Challenges. *Clin Colorectal Cancer* 2021; **20**: 29-41 [PMID: 33531256 DOI: 10.1016/j.clcc.2020.12.005]

4 **Narang AK**, Meyer J. Neoadjuvant Short-Course Radiation Therapy for Rectal Cancer: Trends and Controversies. *Curr Oncol Rep* 2018; **20**: 68 [PMID: 29978358 DOI: 10.1007/s11912-018-0714-x]

5 **Ominelli J**, Valadão M, Araujo ROC, Cristina de Melo A, Araujo LH. The Evolving Field of Neoadjuvant Therapy in Locally-advanced Rectal Cancer: Evidence and Prospects. *Clin Colorectal Cancer* 2021; **20**: 288-298 [PMID: 34340916 DOI: 10.1016/j.clcc.2021.06.005]

6 **Salem ME**, Hartley M, Unger K, Marshall JL. Neoadjuvant Combined-Modality Therapy for Locally Advanced Rectal Cancer and Its Future Direction. *Oncology (Williston Park)* 2016; **30**: 546-562 [PMID: 27306709]

7 **Stepanyan A**, Fassan M, Spolverato G, Castagliuolo I, Scarpa M, Scarpa M; IMMUNOREACT Study Group. IMMUNOREACT 0: Biopsy-based immune biomarkers as predictors of response to neoadjuvant therapy for rectal cancer-A systematic review and meta-analysis. *Cancer Med* 2023; **12**: 17878-17890 [PMID: 37537787 DOI: 10.1002/cam4.6423]

8 **Guida AM**, Sensi B, Formica V, D'Angelillo RM, Roselli M, Del Vecchio Blanco G, Rossi P, Capolupo GT, Caricato M, Sica GS. Total neoadjuvant therapy for the treatment of locally advanced rectal cancer: a systematic minireview. *Biol Direct* 2022; **17**: 16 [PMID: 35698084 DOI: 10.1186/s13062-022-00329-7]

9 **Garcia-Aguilar J**, Chow OS, Smith DD, Marcet JE, Cataldo PA, Varma MG, Kumar AS, Oommen S, Coutsoftides T, Hunt SR, Stamos MJ, Ternent CA, Herzig DO, Fichera A, Polite BN, Dietz DW, Patil S, Avila K; Timing of Rectal Cancer Response to Chemoradiation Consortium. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. *Lancet Oncol* 2015; **16**: 957-966 [PMID: 26187751 DOI: 10.1016/S1470-2045(15)00004-2]

10 **Yuval JB**, Garcia-Aguilar J. Watch-and-wait Management for Rectal Cancer After Clinical Complete Response to Neoadjuvant Therapy. *Adv Surg* 2021; **55**: 89-107 [PMID: 34389102 DOI: 10.1016/j.yasu.2021.05.007]

11 **Zhai ZW**, Zhang KN, Wang C, Han JG, Ma HC, Wei GH, Yang Y, Wang ZJ. [Comparison of short-term efficacy and perioperative safety between neoadjuvant therapy and total neoadjuvant therapy in patients with locally advanced rectal cancer]. *Zhonghua Wei Chang Wai Ke Za Zhi* 2020; **23**: 274-280 [PMID: 32192307 DOI: 10.3760/cma.j.cn.441530-20190819-00312]

12 **Cercek A**, Roxburgh CSD, Strombom P, Smith JJ, Temple LKF, Nash GM, Guillem JG, Paty PB, Yaeger R, Stadler ZK, Seier K, Gonen M, Segal NH, Reidy DL, Varghese A, Shia J, Vakiani E, Wu AJ, Crane CH, Gollub MJ, Garcia-Aguilar J, Saltz LB, Weiser MR. Adoption of Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer. *JAMA Oncol* 2018; **4**: e180071 [PMID: 29566109 DOI: 10.1001/jamaoncol.2018.0071]

13 **Markovina S**, Youssef F, Roy A, Aggarwal S, Khwaja S, DeWees T, Tan B, Hunt S, Myerson RJ, Chang DT, Parikh PJ, Olsen JR. Improved Metastasis- and Disease-Free Survival With Preoperative Sequential Short-Course Radiation Therapy and FOLFOX Chemotherapy for Rectal Cancer Compared With Neoadjuvant Long-Course Chemoradiotherapy: Results of a Matched Pair Analysis. *Int J Radiat Oncol Biol Phys* 2017; **99**: 417-426 [PMID: 28871992 DOI: 10.1016/j.ijrobp.2017.05.048]

14 **Zhu S**, Brodin NP, English K, Ohri N, Chuy JW, Rajdev LN, Narang R, Kalnicki S, Guha C, Garg MK, Kabarriti R. Comparing outcomes following total neoadjuvant therapy and following neoadjuvant chemoradiation therapy in patients with locally advanced rectal cancer. *EClinicalMedicine* 2019; **16**: 23-29 [PMID: 31832617 DOI: 10.1016/j.eclinm.2019.09.009]

15 **Fernandez-Martos C**, Garcia-Albeniz X, Pericay C, Maurel J, Aparicio J, Montagut C, Safont MJ, Salud A, Vera R, Massuti B, Escudero P, Alonso V, Bosch C, Martin M, Minsky BD. Chemoradiation, surgery and adjuvant chemotherapy versus induction chemotherapy followed by chemoradiation and surgery: long-term results of the Spanish GCR-3 phase II randomized trial†. *Ann Oncol* 2015; **26**: 1722-1728 [PMID: 25957330 DOI: 10.1093/annonc/mdv223]

16 **Rödel C**, Trojan J, Bechstein WO, Woeste G. Neoadjuvant short- or long-term radio(chemo)therapy for rectal cancer: how and who should be treated? *Dig Dis* 2012; **30** Suppl 2: 102-108 [PMID: 23207941 DOI: 10.1159/000342038]

17 **Wu L**, Zheng Y, Liu J, Luo R, Wu D, Xu P, Wu D, Li X. Comprehensive evaluation of the efficacy and safety of LPV/r drugs in the treatment of SARS and MERS to provide potential treatment options for COVID-19. *Aging (Albany NY)* 2021; **13**: 10833-10852 [PMID: 33879634 DOI: 10.18632/aging.202860]

18 **Maréchal R**, Vos B, Polus M, Delaunoit T, Peeters M, Demetter P, Hendlisz A, Demols A, Franchimont D, Verset G, Van Houtte P, Van de Stadt J, Van Laethem JL. Short course chemotherapy followed by concomitant chemoradiotherapy and surgery in locally advanced rectal cancer: a randomized multicentric phase II study. *Ann Oncol* 2012; **23**: 1525-1530 [PMID: 22039087 DOI: 10.1093/annonc/mdr473]

19 **Calvo FA**, Sole CV, Serrano J, Del Valle E, Rodriguez M, Muñoz-Calero A, García-Sabrido JL, Garcia-Alfonso P, Peligros I, Alvarez E. Preoperative chemoradiation with or without induction oxaliplatin plus 5-fluorouracil in locally advanced rectal cancer. Long-term outcome analysis. *Strahlenther Onkol* 2014; **190**: 149-157 [PMID: 24306062 DOI: 10.1007/s00066-013-0469-0]

20 **Bhatti AB**, Waheed A, Hafeez A, Akbar A, Syed AA, Khattak S, Kazmi AS. Can induction chemotherapy before concurrent chemoradiation impact circumferential resection margin positivity and survival in low rectal cancers? *Asian Pac J Cancer Prev* 2015; **16**: 2993-2998 [PMID: 25854395 DOI: 10.7314/apjcp.2015.16.7.2993]

21 **Bujko K**, Wyrwicz L, Rutkowski A, Malinowska M, Pietrzak L, Kryński J, Michalski W, Olędzki J, Kuśnierz J, Zając L, Bednarczyk M, Szczepkowski M, Tarnowski W, Kosakowska E, Zwoliński J, Winiarek M, Wiśniowska K, Partycki M, Bęczkowska K, Polkowski W, Styliński R, Wierzbicki R, Bury P, Jankiewicz M, Paprota K, Lewicka M, Ciseł B, Skórzewska M, Mielko J, Bębenek M, Maciejczyk A, Kapturkiewicz B, Dybko A, Hajac Ł, Wojnar A, Leśniak T, Zygulska J, Jantner D, Chudyba E, Zegarski W, Las-Jankowska M, Jankowski M, Kołodziejski L, Radkowski A, Żelazowska-Omiotek U, Czeremszyńska B, Kępka L, Kolb-Sielecki J, Toczko Z, Fedorowicz Z, Dziki A, Danek A, Nawrocki G, Sopyło R, Markiewicz W, Kędzierawski P, Wydmański J; Polish Colorectal Study Group. Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. *Ann Oncol* 2016; **27**: 834-842 [PMID: 26884592 DOI: 10.1093/annonc/mdw062]

22 **Kim SY**, Joo J, Kim TW, Hong YS, Kim JE, Hwang IG, Kim BG, Lee KW, Kim JW, Oh HS, Ahn JB, Zang DY, Kim DY, Oh JH, Baek JY. A

Randomized Phase 2 Trial of Consolidation Chemotherapy After Preoperative Chemoradiation Therapy Versus Chemoradiation Therapy Alone for Locally Advanced Rectal Cancer: KCSG CO 14-03. *Int J Radiat Oncol Biol Phys* 2018; **101**: 889-899 [PMID: 29976501 DOI: 10.1016/j.ijrobp.2018.04.013]

23 **Liang HQ**, Dong ZY, Liu ZJ, Luo J, Zeng Q, Liao PY, Wu DH. Efficacy and safety of consolidation chemotherapy during the resting period in patients with local advanced rectal cancer. *Oncol Lett* 2019; **17**: 1655-1663 [PMID: 30675225 DOI: 10.3892/ol.2018.9804]

24 **Moore J**, Price T, Carruthers S, Selva-Nayagam S, Luck A, Thomas M, Hewett P. Prospective randomized trial of neoadjuvant chemotherapy during the 'wait period' following preoperative chemoradiotherapy for rectal cancer: results of the WAIT trial. *Colorectal Dis* 2017; **19**: 973-979 [PMID: 28503826 DOI: 10.1111/codi.13724]

25 **Wu L**, Zhong Y, Wu D, Xu P, Ruan X, Yan J, Liu J, Li X. Immunomodulatory Factor TIM3 of Cytolytic Active Genes Affected the Survival and Prognosis of Lung Adenocarcinoma Patients by Multi-Omics Analysis. *Biomedicines* 2022; **10** [PMID: 36140350 DOI: 10.3390/biomedicines10092248]

26 **Johnson D**, Li L, Lee KC, Lam KO, Wong KH, Ho WM, Ma B. Total Neoadjuvant Therapy for High Risk Rectal Cancer in Western and Asian Populations - Current Evidence and Clinical Applications. *Clin Colorectal Cancer* 2022; **21**: 45-54 [PMID: 35033429 DOI: 10.1016/j.clcc.2021.12.004]

27 **Kokaine L**, Gardovskis A, Gardovskis J. Evaluation and Predictive Factors of Complete Response in Rectal Cancer after Neoadjuvant Chemoradiation Therapy. *Medicina (Kaunas)* 2021; **57** [PMID: 34684080 DOI: 10.3390/medicina57101044]

28 **Borelli B**, Germani MM, Carullo M, Mattioni R, Manfredi B, Sainato A, Rossi P, Vagli P, Balestri R, Buccianti P, Morelli L, Antoniotti C, Cremolini C, Masi G, Moretto R. Total neoadjuvant treatment and organ preservation strategies in the management of localized rectal cancer: A narrative review and evidence-based algorithm. *Crit Rev Oncol Hematol* 2023; **186**: 103985 [PMID: 37059274 DOI: 10.1016/j.critrevonc.2023.103985]

29 **Ludmir EB**, Palta M, Willett CG, Czito BG. Total neoadjuvant therapy for rectal cancer: An emerging option. *Cancer* 2017; **123**: 1497-1506 [PMID: 28295220 DOI: 10.1002/cncr.30600]

30 **Wu L**, Li X, Qian X, Wang S, Liu J, Yan J. Lipid Nanoparticle (LNP) Delivery Carrier-Assisted Targeted Controlled Release mRNA Vaccines in Tumor Immunity. *Vaccines (Basel)* 2024; **12** [PMID: 38400169 DOI: 10.3390/vaccines12020186]

31 **Battersby NJ**, Moran B, Yu S, Tekkis P, Brown G. MR imaging for rectal cancer: the role in staging the primary and response to neoadjuvant therapy. *Expert Rev Gastroenterol Hepatol* 2014; **8**: 703-719 [PMID: 24954622 DOI: 10.1586/17474124.2014.906898]

32 **Kimura C**, Crowder SE, Kin C. Is It Really Gone? Assessing Response to Neoadjuvant Therapy in Rectal Cancer. *J Gastrointest Cancer* 2023; **54**: 703-711 [PMID: 36417142 DOI: 10.1007/s12029-022-00889-x]

33 **Wu L**, Liu Q, Ruan X, Luan X, Zhong Y, Liu J, Yan J, Li X. Multiple Omics Analysis of the Role of RBM10 Gene Instability in Immune Regulation and Drug Sensitivity in Patients with Lung Adenocarcinoma (LUAD). *Biomedicines* 2023; **11** [PMID: 37509501 DOI: 10.3390/biomedicines11071861]

34 **Massaras D**, Pantiora E, Sotirova E, Dellaportas D, Dafnios N, Zygogianni A, Theodosopoulos T. Neoadjuvant chemoradiotherapy in rectal cancer and anorectal sphincter dysfunction: Review of the literature. *J BUON* 2020; **25**: 35-39 [PMID: 32277612]

35 **Recio-Boiles A**, Hammad H, Howell K, Kalb BT, Nfonsam VN, Scott AJ, Babiker HM, Elquza E. Locally Advanced Rectal Cancer Evaluation by Magnetic Resonance Imaging after Neoadjuvant Therapy on Decision Making: Cancer Center Experience and Literature Review. *J Gastrointest Cancer* 2020; **51**: 254-259 [PMID: 31054106 DOI: 10.1007/s12029-019-00246-5]

36 **Franke AJ**, Parekh H, Starr JS, Tan SA, Iqbal A, George TJ Jr. Total Neoadjuvant Therapy: A Shifting Paradigm in Locally Advanced Rectal Cancer Management. *Clin Colorectal Cancer* 2018; **17**: 1-12 [PMID: 28803718 DOI: 10.1016/j.clcc.2017.06.008]

37 **Gefen R**, Garoufalia Z, Horesh N, Freund MR, Emile SH, Parlade A, Berho M, Allende D, DaSilva G, Wexner SD. How reliable is restaging MRI after neoadjuvant therapy in rectal cancer? *Colorectal Dis* 2023; **25**: 1631-1637 [PMID: 37376824 DOI: 10.1111/codi.16641]

38 **Wu L**, Zheng Y, Ruan X, Wu D, Xu P, Liu J, Wu D, Li X. Long-chain noncoding ribonucleic acids affect the survival and prognosis of patients with esophageal adenocarcinoma through the autophagy pathway: construction of a prognostic model. *Anticancer Drugs* 2022; **33**: e590-e603 [PMID: 34338240 DOI: 10.1097/CAD.0000000000001189]

39 **De Paoli A**, Innocente R, Buonadonna A, Boz G, Sigon R, Canzonieri V, Frustaci S. Neoadjuvant therapy of rectal cancer new treatment perspectives. *Tumori* 2004; **90**: 373-378 [PMID: 15510978 DOI: 10.1177/030089160409000402]

40 **Petrelli F**, Trevisan F, Tomasello G, De Stefani A, Viti M, Garrone O, Luciani A, Ghidini M. Different neoadjuvant therapies for locally advanced rectal cancer: A systematic review and network meta-analysis. *Crit Rev Oncol Hematol* 2022; **180**: 103853 [PMID: 36252747 DOI: 10.1016/j.critrevonc.2022.103853]

41 **De Felice F**, Musio D, Tombolini V, Cortesi E. Neoadjuvant Therapy for Rectal Cancer: Updates From the UNICANCER-PRODIGE 23 Trial. *Clin Colorectal Cancer* 2022; **21**: e21 [PMID: 34949551 DOI: 10.1016/j.clcc.2021.11.005]

42 **Wu L**, Zhong Y, Yu X, Wu D, Xu P, Lv L, Ruan X, Liu Q, Feng Y, Liu J, Li X. Selective poly adenylation predicts the efficacy of immunotherapy in patients with lung adenocarcinoma by multiple omics research. *Anticancer Drugs* 2022; **33**: 943-959 [PMID: 35946526 DOI: 10.1097/CAD.0000000000001319]

43 **Bedrikovetski S**, Traeger L, Vather R, Moore JW, Sammour T. Clinical and biochemical predictors of tumor response after neoadjuvant therapy in rectal cancer. *Asia Pac J Clin Oncol* 2023; **19**: 365-373 [PMID: 36305516 DOI: 10.1111/ajco.13877]

44 **Zhao Y**, Zhu J, Yang B, Gao Q, Xu Y, Wei X, Kong D, Ji S, Fei B. Retrospective study of total neoadjuvant therapy for locally advanced rectal cancer. *Future Oncol* 2022; **18**: 691-700 [PMID: 34878307 DOI: 10.2217/fon-2021-0644]

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META-ANALYSIS

Sarcopenia adversely impacts clinical outcomes in patients undergoing pancreaticoduodenectomy: A systematic review and meta-analysis

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Abstract

BACKGROUND

Sarcopenia is a syndrome marked by a gradual and widespread reduction in skeletal muscle mass and strength, as well as a decline in functional ability, which is associated with malnutrition, hormonal changes, chronic inflammation, disturbance of intestinal flora, and exercise quality. Pancreatoduodenectomy is a commonly employed clinical intervention for conditions such as pancreatic head cancer, ampulla of Vater cancer, and cholangiocarcinoma, among others, with a notably high rate of postoperative complications. Sarcopenia is frequent in patients undergoing pancreatoduodenectomy. However, data regarding the effects of sarcopenia in patients undergoing pancreaticoduodenectomy (PD) are both limited and inconsistent.

AIM

To assess the influence of sarcopenia on outcomes in patients undergoing PD.

METHODS

The PubMed, Cochrane Library, Web of Science, and Embase databases were screened for studies published from the time of database inception to June 2023 that described the effects of sarcopenia on the outcomes and complications of PD. Two researchers independently assessed the quality of the data extracted from the studies that met the inclusion criteria. Meta-analysis using RevMan 5.3.5 and Stata 14.0 software was conducted. Forest and funnel plots were used, respectively, to demonstrate the outcomes of the sarcopenia group *vs* the non-sarcopenia group after PD and to evaluate potential publication bias.

RESULTS

Sixteen studies encompassing 2381 patients were included in the meta-analysis. The patients in the sarcopenia group (n = 833) had higher overall postoperative complication rates [odds ratio (OR) = 3.42, 95% confidence interval (CI): 1.95-5.99, P < 0.0001], higher Clavien-Dindo class ≥ III major complication rates (OR = 1.41, 95%CI: 1.04-1.90, P = 0.03), higher bacteremia rates (OR = 4.46, 95%CI: 1.42-13.98, P = 0.01), higher pneumonia rates (OR = 2.10, 95%CI: 1.34-3.27, P = 0.001), higher pancreatic fistula rates (OR = 1.42, 95%CI: 1.12-1.79, P = 0.003), longer hospital stays (OR = 2.86, 95%CI: 0.44-5.28, P = 0.02), higher mortality rates (OR = 3.17, 95%CI: 1.55-6.50, P = 0.002), and worse overall survival (hazard ratio = 2.81, 95%CI: 1.45-5.45, P = 0.002) than those in the non-sarcopenia group (n = 1548). However, no significant inter-group differences were observed regarding wound infections, urinary tract infections, biliary fistulas, or postoperative digestive bleeding.

CONCLUSION

Sarcopenia is a common comorbidity in patients undergoing PD. Patients with preoperative sarcopenia have increased rates of complications and mortality, in addition to a poorer overall survival rate and longer hospital stays after PD.

Key Words: Pancreaticoduodenectomy; Sarcopenia; Postoperative complications; Length of stay; Meta-analysis

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Core Tip: Muscle wasting has a significant impact on the clinical outcomes and prognosis of patients undergoing major surgery, but there is limited research on the impact of muscle wasting on patients undergoing pancreaticoduodenectomy (PD), and the conclusions are inconsistent. This article aims to evaluate the impact of sarcopenia on the clinical outcomes of PD patients through meta-analysis, in order to provide evidence-based management for PD patients during the perioperative period. Strictly screen articles based on pre-set inclusion and exclusion criteria.

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INTRODUCTION

Sarcopenia is a syndrome characterized by a gradual, widespread reduction in mass within the skeletal musculature, together with decreased muscle strength or impaired capacity to engage in routine daily activities. Afflicted individuals often experience compromised mobility, reduced quality of life, and heightened susceptibility to undesirable outcomes including falls and mortality[1]. The development of sarcopenia is associated with *e.g.*, malnutrition, hormonal changes, chronic inflammation, disturbance of intestinal flora, and exercise quality, as well as genetic and psychosocial factors[2]. Sarcopenia is a risk factor for poor prognosis in patients with pancreatic cancer, gastric cancer, lung cancer, and other surgical procedures[3]. Pancreatoduodenectomy is clinically used to treat pancreatic head cancer, ampulla of Vater cancer, cholangiocarcinoma, and other diseases, and the incidence of postoperative complications is extremely high[4]. In light of this complication risk, the perioperative management of patients is crucial. According to the literature, the prevalence of sarcopenia in patients undergoing pancreatoduodenectomy is high[5-7]. However, the effects of sarcopenia on clinical outcomes and prognosis following pancreaticoduodenectomy (PD) remain unclear. Therefore, the purpose of the present systematic review and meta-analysis was to assess the influence of sarcopenia on postoperative results in patients undergoing PD. Additionally, we aimed to provide an evidence-based foundation for the management of patients in the perioperative period after PD.

MATERIALS AND METHODS

Literature search strategy

Zhang QH and Ma JD conducted a thorough search of credible databases; *i.e.*, PubMed, Cochrane Library, Web of Science, and Embase, to gather relevant literature. The search was conducted from the initiation of the databases until June 2023 and was limited to English-language publications. The search terms used included "sarcopenia", "frailty", "muscle weakness", "muscle atrophy", "pancreaticoduodenectomy", "Whipple procedure", "pancreaticoduodenectomies", "duodenopancreatectomy", and "pancreatoduodenectomy". To refine the results, the search terms were combined utilizing the Boolean operators "AND" and "OR". Synonyms of all terms were considered during the search.

Inclusion and exclusion criteria

To be considered for inclusion in the meta-analysis, studies needed to meet a series of specific criteria. These included having well-defined standards for assessing sarcopenia and measuring skeletal muscle, focusing on patients who were undergoing PD, and examining the correlation between sarcopenia and clinical outcomes after surgery. It was essential that the original text was accessible and that the study data could be accurately extracted. Furthermore, the studies had to be published in their entirety and fall into the category of cohort studies. Specific exclusion criteria included non-randomized controlled trials including reviews, systematic reviews, case reports, and commentaries, non-clinical trials, and any repeated publications reporting on the same study population. Studies with incomplete data on crucial clinical outcome indicators or significant bias were also excluded.

Data extraction

Data of studies were extracted separately by two authors (Zhang QH and Ma JD). In cases of disagreement, the authors discussed and resolved the issue. If necessary, a third investigator was consulted for judgment. The following main parameters were considered: Basic information (*i.e.*, first author, country, publication date, study duration, type of literature, number of cases, sex ratio, mean age, type of disease, body mass index, diagnostic criteria and prevalence of sarcopenia), clinical outcome parameters [*i.e.*, overall complications, complications classified as Clavien-Dindo (C-D) class ≥ III, wound infection, bacteremia, urinary tract infection, pneumonia, pancreatic fistula, biliary fistula, and death], and length of stay. Means and standard deviations were utilized to describe continuous outcome variables in the context of meta-analysis. When the initial data were presented as medians or ranges, the averages and standard deviations were approximated using the approach outlined by Hozo *et al*[8].

Quality assessment

The quality of each study was evaluated separately by two authors. In cases where the evaluations differed, a third investigator was consulted to decide whether the literature should be included or not. The Newcastle-Ottawa Scale was applied to evaluate the methodological rigor of the literature, taking into account three factors: Selection of the study population (4 points), comparability between groups (2 points), and outcome parameters (3 points). A maximum of nine points could be obtained, with studies having a score of six or more deemed as being of high quality[9].

Statistical analysis

To conduct the meta-analysis, we utilized RevMan 5.3.5 and Stata 14.0 software (Cochrane Collaboration, Oxford, United Kingdom). For continuous variables, we calculated the weighted mean differences along with their corresponding 95% confidence intervals (CIs). Similarly, for categorical variables, we computed odds ratios (ORs) with their respective 95%CIs. To assess heterogeneity, we performed a chi-square test, considering $P > 0.05$ as non-significant. Statistical heterogeneity was assessed using I^2 values, with a threshold of 50% or higher indicating the presence of heterogeneity. When the studies exhibited homogeneity ($I^2 < 50\%$), we adopted the fixed-effects model. Conversely, if studies presented heterogeneity ($I^2 \geq 50\%$), we utilized the random-effects model.

Risk of bias

We employed funnel plots to assess potential publication bias based on major complication rates (C-D ≥ III).

RESULTS

Eligible studies

Initially, 398 relevant publications were retrieved. After layer-by-layer screening, 16 studies with a total of 2381 patients were finally included (n = 833 and n = 1548 in the sarcopenia and non-sarcopenia groups, respectively). All studies were cohort studies. The screening process is shown in Figure 1. The basic information and results of the literature quality evaluation are shown in Tables 1-3.

Overall rates of sarcopenia

Sixteen studies reported the overall prevalence of sarcopenia at 37% (0.29, 0.45), as shown in Figure 2.

Overall rates of postoperative and major complications (C-D ≥ III)

Four studies reported the overall rate of postoperative complications, which was statistically significant after combining the effects across studies (OR = 3.42, 95%CI: 1.95-5.99, $P < 0.0001$)[7,14,18,21] (Figure 3A). Nine studies reported major postoperative complications (C-D ≥ III), yielding statistically significant combined effects (OR = 1.41, 95%CI: 1.04-1.90, P = 0.03)[5-7,12,15,16,19,20,22] (Figure 3B).

Infectious complications

Three studies reported the occurrence rate of bacteremia, which was statistically significant after combining effects (OR = 4.46, 95%CI: 1.42-13.98, P = 0.01)[5,14,17] (Figure 3C). Six studies reported that of pneumonia, yielding statistically significant combined effects (OR = 2.10, 95%CI: 1.34-3.27, P = 0.001)[5,7,13,14,21,23] (Figure 3D). No inter-group statistical difference was noted regarding wound (OR = 1.39, 95%CI: 0.89-2.19, P = 0.15) (Figure 3E) or urinary tract (OR = 1.25,

Table 1 General characteristics of the included studies

Ref.	Region	Diagnosed period	Sarcopenia/no sarcopenia			Prevalence of sarcopenia	Study design
			Sample size	Sex ratio	Median age		
Nishida *et al*[10], 2016	Japan	January 2010 to December 2014	132/134	70/111	68.79/66.17	49.62%	Cohort study
Sandini *et al*[11], 2016	Italy	2007 to February 2015	30/94	10/53	-/-	24.19%	Cohort study
Takagi *et al*[12], 2017	Japan	January 2007 to May 2013	55/164	36/107	-/-	25.11%	Cohort study
Stretch *et al*[13], 2018	Canada	2003 to 2011	50/73	29/42	68.50/66.10	40.65%	Cohort study
Tankel *et al*[14], 2018	Israel	December 2014 to February 2017	16/45	8/24	75.0/64.0	26.23%	Cohort study
Umetsu *et al*[6], 2018	Japan	February 2008 to March 2015	48/17	12/35	71.02/61.77	73.85%	Cohort study
Centonze *et al*[15], 2020	Italy	2010 to 2017	36/74	20/42	70.93/64.94	32.73%	Cohort study
Xu *et al*[16], 2020	China	January 2016 to December 2018	59/93	-/-	-/-	38.82%	Cohort study
Peng *et al*[17], 2021	China	October 2005 to August 2018	20/96	12/56	72.1/65.0	17.24%	Cohort study
Pessia *et al*[18], 2021	Italy	June 2013 to May 2019	32/36	-/-	-/-	47.06%	Cohort study
Duan *et al*[19], 2021	China	January 2014 to December 2019	108/157	52/84	62.70/55.30	40.75%	Cohort study
Nauheim *et al*[20], 2022	United States	October 2017 to January 2020	83/250	40/121	70.6/65.4	24.92%	Cohort study
Aoki *et al*[21], 2022	Japan	January 2016 to March 2020	19/161	15/87	77.9/71.0	10.56%	Cohort study
Umezawa *et al*[7], 2022	Japan	January 2006 to April 2020	44/44	35/30	73/70.5	50.00%	Cohort study
La Vaccara *et al*[5], 2023	Italy	February 2004 to January 2016	54/28	37/13	-/-	65.85%	Cohort study
Cai *et al*[22], 2023	China	January 2018 to January 2021	47/82	28/50	65.4/60.7	36.43%	Cohort study

95%CI: 0.56-2.80, P = 0.59) infections (Figure 3F).

Non-infectious complications

Eleven studies presented statistically significant combined effects for the occurrence of pancreatic fistula (OR = 1.42, 95%CI: 1.12-1.79, P = 0.003)[5,7,12-17,21,23,24] (Figure 3G). There was no significant difference of the occurrence rate of biliary fistula between the two groups (OR = 1.22, 95%CI: 0.75-1.99, P = 0.43) (Figure 3H) or postoperative bleeding (OR = 1.44, 95%CI: 0.90-2.29, P = 0.13) (Figure 3I).

Hospital length of stay

The length of hospitalization was recorded in six studies[6,14,15,18,19,21]. The duration of stay was significantly longer for the sarcopenia group than that of the non-sarcopenia group (OR = 2.86, 95%CI: 0.44-5.28, P = 0.02) (Figure 3J).

Mortality

Postoperative mortality was described in six studies[7,12,14,16,18,21]. The sarcopenia group had a higher rate of postoperative mortality than that of the non-sarcopenia group (OR = 3.17, 95%CI: 1.55-6.50, P = 0.002) (Figure 3K).

Overall survival

Overall survival was reported in two studies included in the literature. The sarcopenic group had a worse overall survival (multivariate analysis: Hazard ratio = 2.81, 95%CI: 1.45-5.45, P = 0.002) compared with the non-sarcopenic group as shown in (Figure 3L).

Publication bias

Major complications (C-D ≥ III), a main parameter of clinical outcome, were well represented and included in a large number of studies. Evaluation for publication bias revealed a roughly symmetrical distribution within the inverted funnel plot, suggesting a low risk of publication bias (Figure 4).

Table 2 Clinical and surgical characteristics of the included studies

Ref.	Surgical procedure	Sarcopenia/no sarcopenia			Measurements of sarcopenia	Sarcopenia definition
		Original cancer type	BMI	Outcomes		
Nishida *et al*[10], 2016	PD	Pancreatic tumor = 80/83; bile duct tumor = 42/40; other malignant disease = 9/10; benign disease = 1/1	21.15 ± 3.45/22.89 ± 3.67	Complications (C-D ≥ III), wound infection, pancreatic fistula, death	L3 SMI	Males < 43 cm^2/m^2 with BMI < 25 kg/m^2, < 53 cm^2/m^2 with BMI ≥ 25 kg/m^2; females < 41 cm^2/m^2
Sandini *et al*[11], 2016	Whipple or pylorus-preserving PD	-	-	Wound infection, urinary tract infection, pneumonia, pancreatic fistula, biliary fistula	CT TAMA	Males < 43 cm^2/m^2 with BMI < 25 kg/m^2, < 53 cm^2/m^2 with BMI ≥ 25 kg/m^2; females < 41 cm^2/m^2
Takagi *et al*[12], 2017	PD	Pancreatic adenocarcinoma = 25/61; bile duct carcinoma = 7/20; periampullar adenocarcinoma = 10/18; duodenal adenocarcinoma = 1/9; intraductal papillary mucinous neoplasm = 6/26; others = 6/30	21.70 ± 3.00/22.00 ± 3.40	Overall complications, wound infection, bacteremia, urinary tract infection, pneumonia, pancreatic fistula, total length of hospital stay, death	CT L3 SBI	Male < 68.5 cm^2/m^2; female < 52.5 cm^2/m^2
Stretch *et al*[13], 2018	Whipple	Pancreatic tumor = 37/47; non-pancreatic tumor = 13/26	23.5 ± 3.6/26.3 ± 6.5	Complications (C-D ≥ III), total length of hospital stay	CT L3 SMI	Male < 47.7 cm^2/m^2; female < 36.5 cm^2/m^2
Tankel *et al*[14], 2018	Pylorus-preserving PD	-	21.9 ± 2.0/25.0 ± 3.2	Complications (C-D ≥ III), pancreatic fistula, total length of hospital stay	CT L3 TPAI	Male < 83.41 cm^2/m^2; female < 65.28 cm^2/m^2
Umetsu *et al*[6], 2018	Whipple	Distal cholangiocarcinoma = 48/17	21.70 ± 2.63/24.34 ± 2.84	Complications (C-D ≥ III), pancreatic fistula, death	CT L3 PMI	Male < 5.93 cm^2/m^2; female < 3.54 cm^2/m^2
Centonze *et al*[15], 2020	Whipple	Pancreatic carcinoma or pancreatitis = 21/44; other = 15/30	25.36 ± 3.86/24.35 ± 2.27	Wound infection, bacteremia, urinary tract infection, pancreatic fistula, biliary fistula	CT L3 HUAC	Male < 16.37 HU; female < 14.21 HU
Xu *et al*[16], 2020	PD	-	-	Overall complications, total length of hospital stay, death	CT L3 TPAI	Male < 4.78 cm^2/m^2; female < 3.46 cm^2/m^2
Peng *et al*[17], 2021	PD	Pancreatic cancer = 20/96	21.2 ± 2.2/22.9 ± 2.80	Complications (C-D ≥ III), total length of hospital stay	CT L3 SMI	Male < 42.2 cm^2/m^2; female < 33.9 cm^2/m^2
Pessia *et al*[18], 2021	PD	Pancreatic head adenocarcinoma = 32/36	19.60/21.40	Complications (C-D ≥ III)	CT L3 SMI	Male < 52.4 cm^2/m^2; female < 38.5 cm^2/m^2
Duan *et al*[19], 2021	Pylorus-preserving PD	Pancreatic ductal adenocarcinoma = 48/77; pancreatic cystic tumor = 14/20; pancreatic neuroendocrine tumors = 6/9; periampullar tumor = 35/43; trauma = 1/3; others = 4/5	22.50 ± 4.1/23.20 ± 3.9	Overall complications, pneumonia, pancreatic fistula, biliary fistula, total length of hospital stay, death	CT L3 SMI	Male < 47.32 cm^2/m^2; female < 40.65 cm^2/m^2
Nauheim *et al*[20], 2022	PD	Pancreatic ductal adenocar-	25.9 ± 4.4/27.9 ± 5.5	Overall complications, complic-	CT L3 PMI	Lowest quartile

		cinoma = 50/141; periampullar/duodenal carcinoma = 10/24; cholangiocarcinoma = 3/8; other = 6/10; benign/premalignant = 14/67		ations (C-D ≥ III), wound infection, urinary tract infection; pneumonia, pancreatic fistula, death		
Aoki *et al*[21], 2022	PD	Pancreatic carcinoma = 14/69; bile duct carcinoma = 2/21; intraductal papillary mucinous neoplasm = 2/40; periampullar carcinoma = 1/13; others = 0/18	20.14 ± 1.36/22.11 ± 3.52	Complications (C-D ≥ III), wound infection, bacteremia, pneumonia, pancreatic fistula	EWGSOP2	Male: SMI < 7 kg/m^2; grip strength < 27 kg; gait speed < 0.8 m/s; female: SMI < 6 kg/m^2; grip strength < 16 kg; gait speed < 0.8 m/s
Umezawa *et al*[7], 2022	PD	Distal cholangiocarcinoma = 44/44	21.47 ± 3.45/22.37 ± 3.07	Complications (C-D ≥ III)	CT L3 PMI	Male < 6.36 cm^2/m^2; female < 3.98 cm^2/m^2
La Vaccara *et al*[5], 2023	PD	Periampullary cancers = 54/28	-	Urinary tract infection, pneumonia, pancreatic fistula, biliary fistula	CT L3 SMI	Male < 55.4 m^2/m^2; female < 38.9 cm^2/m^2
Cai *et al*[22], 2023	PD	Periampullar neoplasms = 47/82	21.50 ± 2.50/24.20 ± 3.30	Pancreatic fistula, biliary fistula	CT L3 SMI	Male < 44.2 cm^2/m^2; female < 33.9 cm^2/m^2

SMI: Skeletal muscle index; TAMA: Total abdominal muscle area; SBI: SMA/BSA index; TPA: Total psoas muscle area index; PMI: Psoas muscle mass index; PD: Pancreaticoduodenectomy; BMI: Body mass index; C-D: Clavien-Dindo.

DISCUSSION

Sarcopenia, first described by Rosenberg in 1989, is mainly observed in the elderly population and in patients with chronic diseases[23,24]. Following an investigation of 58 studies encompassing different regions within China, Chen *et al* [25] revealed that the occurrence rates of sarcopenia were 12.9% and 11.2% for elderly men and women within the community, respectively. Moreover, recent research has indicated a greater occurrence among individuals requiring surgical intervention, particularly in those diagnosed with malignant tumors; for example, the frequency of sarcopenia in patients diagnosed with liver cancer is estimated to range from 11% to 45%[26]. Similarly, patients diagnosed with cholangiocarcinoma and gallbladder cancer exhibited a sarcopenia rate of 33%[27], whereas those undergoing pancreatic surgery exhibited a range of 17% to 62%[28]. Pancreaticobiliary tumors in particular, which are accompanied by obstructive jaundice, malnutrition, impairment of the intestinal mucosal barrier function, and dysbiosis of the intestinal flora, result in the occurrence of preoperative sarcopenia[29]. In line with these findings, the results of the current meta-analysis showed that the occurrence rate of sarcopenia in individuals who undergo PD was 37% (0.29, 0.45). Therefore, preoperative screening and evaluation of sarcopenia in patients undergoing pancreatoduodenectomy is essential, and sarcopenia may adversely affect the clinical outcome of patients undergoing pancreatoduodenectomy.

Only a few comprehensive research studies have examined the effects of sarcopenia on the clinical outcomes of patients who undergo PD. To address this gap, we conducted a meta-analysis incorporating 16 studies, comprising a total of 2381 participants, of whom 833 were diagnosed with sarcopenia. We evaluated 14 factors, including the duration of the operation, rates of overall and major (C-D ≥ III) complications[30], wound infection, bacteremia, urinary tract infection, pneumonia, pancreatic fistula, biliary fistula, and postoperative digestive hemorrhage, together with length of hospital stay and overall survival. Our results indicate a notable correlation between sarcopenia and different negative consequences in comparison to that in patients without sarcopenia. Specifically, patients within the sarcopenia group exhibited

Table 3 Study quality evaluation

Ref.	Selection of study population	Comparability between the two groups	Outcome indicators	Total quality assessment score
Nishida *et al*[10]	4	2	1	7
Sandini *et al*[11]	4	2	1	7
Takagi *et al*[12]	4	2	2	8
Stretch *et al*[13]	4	2	3	9
Tankel *et al*[14]	4	2	1	7
Umetsu *et al*[6]	4	2	2	8
Centonze *et al*[15]	4	2	2	8
Xu *et al*[16]	4	2	1	7
Peng *et al*[17]	3	2	1	6
Pessia *et al*[18]	4	2	2	8
Duan *et al*[19]	4	2	2	8
Nauheim *et al*[20]	4	2	2	8
Aoki *et al*[21]	4	2	3	9
Umezawa *et al*[7]	4	2	1	7
La Vaccara *et al*[5]	4	2	2	8
Cai *et al*[22]	4	2	3	9

an increase in postoperative complications (both overall and major), occurrences of bacteremia, pneumonia, and pancreatic fistula, in addition to a poorer overall survival rate and prolonged hospital length of stay. However, no significant differences were noted between the two cohorts regarding postoperative digestive hemorrhage, wound infection, biliary fistula, and urinary tract infection.

Sarcopenia has a significant effect on patients during their perioperative phase. Decreased muscle function may render patients undergoing major abdominal surgery less active, whereas respiratory muscle weakness predisposes them to hypoxia and respiratory function impairment[31]. Furthermore, the metabolic processes involving proteins and carbohydrates heavily rely on skeletal muscle tissue; accordingly, the depletion of muscle mass disrupts metabolism, resulting in functional disruption. In addition, recent research indicates that individuals with sarcopenia experience immune abnormalities, persistent elevation of inflammatory biomarkers including tumor necrosis factor-α, interleukin-6, and dysbiosis of the gut microbiota. Notably, these biomarkers have the potential to increase the perioperative hazards associated with PD[29,31-34].

The results of the present meta-analysis revealed that preexisting sarcopenia has a significant impact on the negative clinical outcomes observed in patients following PD. Previous research indicates that muscle loss also has a detrimental impact on the long-term survival of patients undergoing major surgical interventions for gastric cancer or hepatocellular carcinoma[35,36]. The occurrence of complications reduces the immune function of patients, and also delays adjuvant therapy (such as chemotherapy, radiotherapy, *etc*.), thereby shortening the survival of patients.

The SARC-F questionnaire[37] can be used for preoperative screening to identify the population at risk. Subsequently, an evaluation and diagnosis of sarcopenia can be performed by assessing muscle strength, muscle mass, and physical fitness. Methods for assessing skeletal muscle mass comprise computed tomography or magnetic resonance scans at the L3 level, bioelectrical impedance techniques, and dual-energy X-ray absorptiometry scans. Grip strength can be utilized to measure muscle strength. Assessment of physical functional status can be achieved by measuring gait speed and five sit-to-stand times, among other methods. In the studies analyzed in the present meta-analysis, sarcopenia was mainly diagnosed by measuring muscle mass *via* imaging. However, less attention was paid to muscle strength and physical functional status taking into account the concept of prehabilitation, a combination of nutrition and exercise could potentially be employed to maintain muscle mass, improve muscle strength and functional status, and enhance patient safety during surgical procedures, ultimately enhancing positive surgical outcomes and overall quality of life[38]. This study has some limitations. Validation of the cohort studies included in the meta-analysis is required through randomized controlled trials. The limited number of studies may have resulted in an incomplete inclusion.

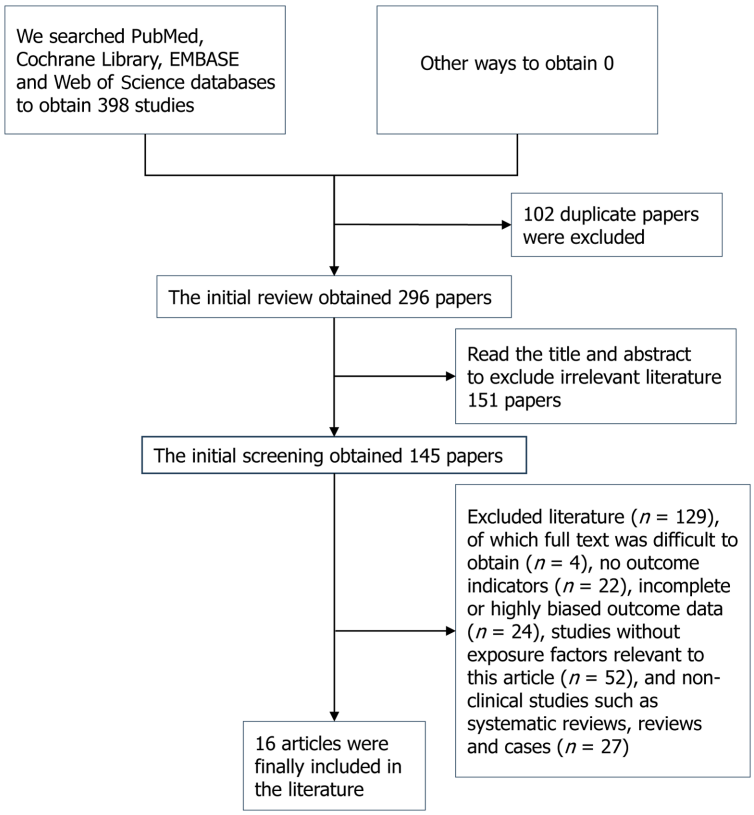


Figure 1 Flowchart of the literature search strategy.

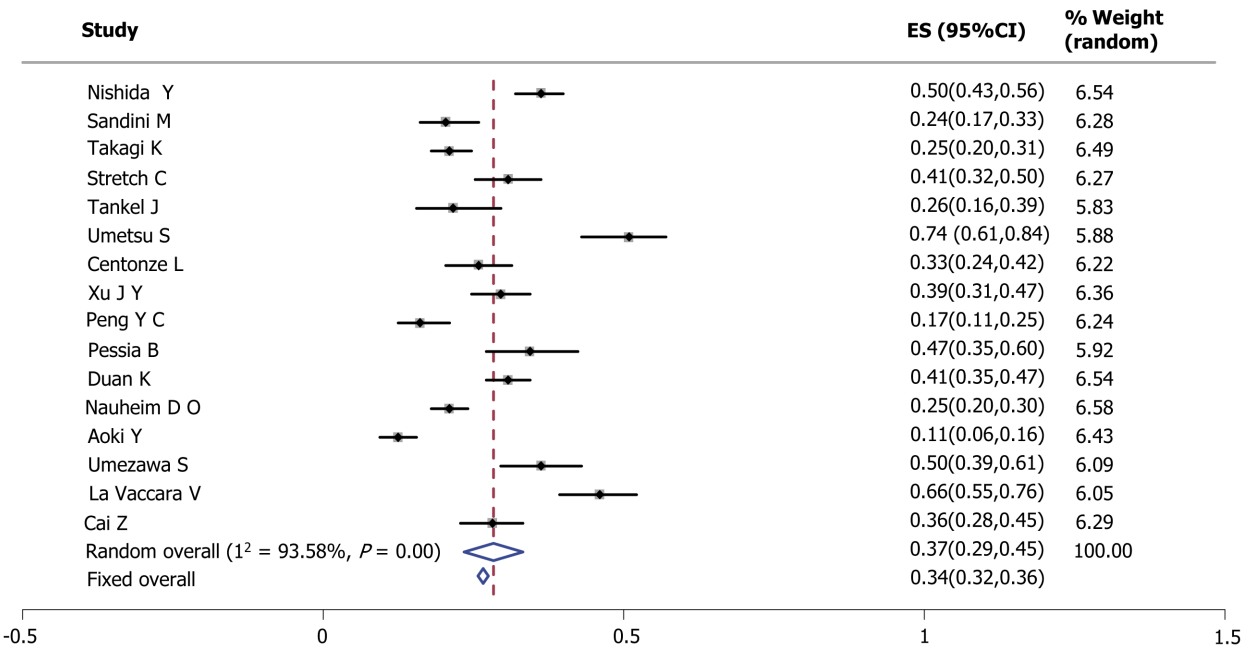


Figure 2 The overall incidence of sarcopenia.

CONCLUSION

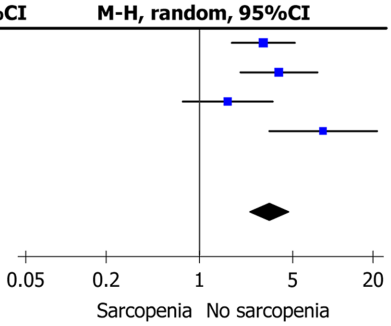
The high occurrence of preoperative sarcopenia in patients who undergo PD significantly adversely affects postoperative clinical outcomes, such as an elevated likelihood of postoperative complications and a longer duration of hospitalization. To enhance the clinical outcome and prognosis of patients after PD, it is imperative to conduct preoperative screening for sarcopenia and implement suitable interventions.

A

Study or subgroup	Sarcopenia Events	Sarcopenia Total	No sarcopenia Events	No sarcopenia Total	Weight	Odds ratio M-H, random, 95%CI
Duan K	48	108	33	157	30.4%	3.01 [1.75, 5.16]
Nauheim D O	22	83	21	250	26.6%	3.93 [2.03, 7.62]
Takagi K	12	55	24	164	23.4%	1.63 [0.75, 3.53]
Xu J Y	24	59	7	93	19.6%	8.42 [3.33, 21.33]
Total (95%CI)		**305**		**664**	**100.0%**	**3.42 [1.95, 5.99]**
Total events	106		85			

Heterogeneity: Tau² = 0.19; Chi²= 7.51, df = 3 (*P* = 0.06); I^2 = 60%

Test for overall effect: Z = 4.30 (*P* < 0.0001)

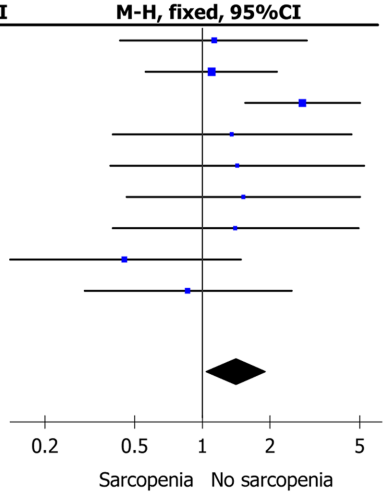


B

Study or subgroup	Sarcopenia Events	Sarcopenia Total	No sarcopenia Events	No sarcopenia Total	Weight	Odds ratio M-H, fixed, 95%CI
Aoki Y	10	19	80	161	11.4%	1.13 [0.43, 2.91]
Nauheim D O	14	83	39	250	23.1%	1.10 [0.56, 2.14]
Nishida Y	45	132	21	134	19.6%	2.78 [1.55, 5.01]
Peng Y C	4	20	15	96	5.9%	1.35 [0.40, 4.60]
Pessia B	6	32	5	36	5.5%	1.43 [0.39, 5.23]
Stretch C	6	50	6	73	6.1%	1.52 [0.46, 5.02]
Tankel J	5	16	11	45	5.7%	1.40 [0.40, 4.94]
Umetsu S	25	48	12	17	12.1%	0.45 [0.14, 1.48]
Umezawa S	8	44	9	44	10.5%	0.86 [0.30, 2.49]
Total (95%CI)		**444**		**856**	**100.0%**	**1.41 [1.04, 1.90]**
Total events	123		198			

Heterogeneity: Chi²= 10.24, df = 8 (*P* = 0.25); I^2 = 22%

Test for overall effect: Z = 2.21 (*P* = 0.03)

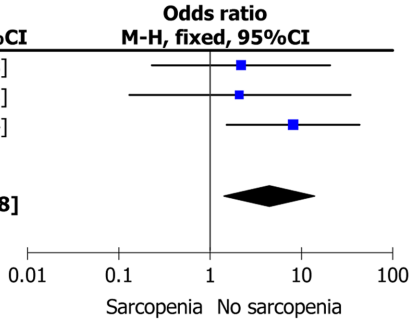


C

Study or subgroup	Sarcopenia Events	Sarcopenia Total	No sarcopenia Events	No sarcopenia Total	Weight	Odds ratio M-H, fixed, 95%CI
Aoki Y	1	19	4	161	34.0%	2.18 [0.23, 20.58]
Centonze L	1	36	1	74	27.1%	2.09 [0.13, 34.33]
Takagi K	5	55	2	164	38.9%	8.10 [1.52, 43.04]
Total (95%CI)		**110**		**399**	**100.0%**	**4.46 [1.42, 13.98]**
Total events	7		7			

Heterogeneity: Chi²= 1.16, df = 2 (*P* = 0.56); I^2 = 0%

Test for overall effect: Z = 2.56 (*P* = 0.01)

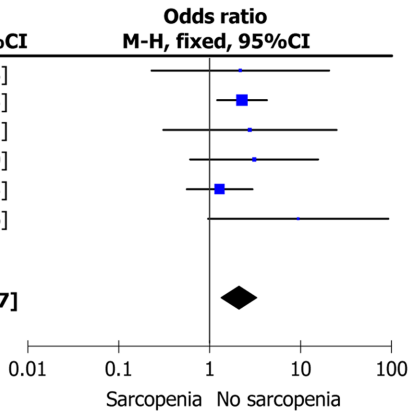


D

Study or subgroup	Sarcopenia Events	Sarcopenia Total	No sarcopenia Events	No sarcopenia Total	Weight	Odds ratio M-H, fixed, 95%CI
Aoki Y	1	19	4	161	3.0%	2.18 [0.23, 20.58]
Duan K	28	108	21	157	48.0%	2.27 [1.21, 4.25]
La Vaccara V	5	54	1	28	4.5%	2.76 [0.31, 24.81]
Nauheim D O	3	83	3	250	5.5%	3.09 [0.61, 15.60]
Sandini M	14	30	38	94	37.1%	1.29 [0.56, 2.95]
Takagi K	3	55	1	164	1.8%	9.40 [0.96, 92.36]
Total (95%CI)		**349**		**854**	**100.0%**	**2.10 [1.34, 3.27]**
Total events	54		68			

Heterogeneity: Chi² = 3.32, df = 5 (*P* = 0.65); I^2 = 0%

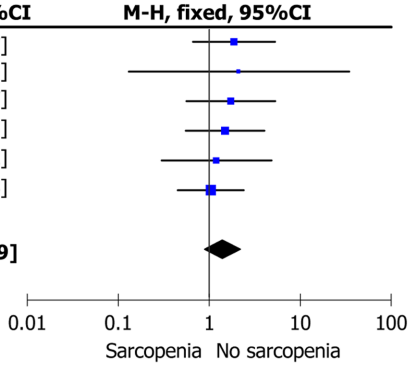
Test for overall effect: Z = 3.26 (*P* = 0.001)



E

Study or subgroup	Sarcopenia Events	Sarcopenia Total	No sarcopenia Events	No sarcopenia Total	Weight	Odds ratio M-H, fixed, 95%CI
Aoki Y	6	19	32	161	15.3%	1.86 [0.66, 5.27]
Centonze L	1	36	1	74	2.1%	2.09 [0.13, 34.33]
Nauheim D O	5	83	9	250	13.9%	1.72 [0.56, 5.27]
Nishida Y	10	132	7	134	21.2%	1.49 [0.55, 4.03]
Sandini M	3	30	8	94	11.5%	1.19 [0.30, 4.82]
Takagi K	9	55	26	164	36.0%	1.04 [0.45, 2.38]
Total (95%CI)		**355**		**877**	**100.0%**	**1.39 [0.89, 2.19]**
Total events	34		83			

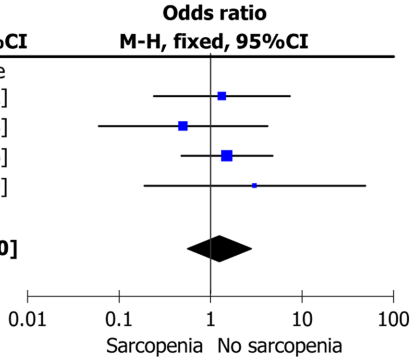
Heterogeneity: Chi² = 1.06, df = 5 (*P* = 0.96); I^2 = 0%
Test for overall effect: Z = 1.43 (*P* = 0.15)



F

Study or subgroup	Sarcopenia Events	Sarcopenia Total	No sarcopenia Events	No sarcopenia Total	Weight	Odds ratio M-H, fixed, 95%CI
Centonze L	0	36	0	74		Not estimable
La Vaccara V	5	54	2	28	23.3%	1.33 [0.24, 7.32]
Nauheim D O	1	83	6	250	28.8%	0.50 [0.06, 4.18]
Sandini M	5	30	11	94	43.2%	1.51 [0.48, 4.76]
Takagi K	1	55	1	164	4.8%	3.02 [0.19, 49.09]
Total (95%CI)		**258**		**610**	**100.0%**	**1.25 [0.56, 2.80]**
Total events	12		20			

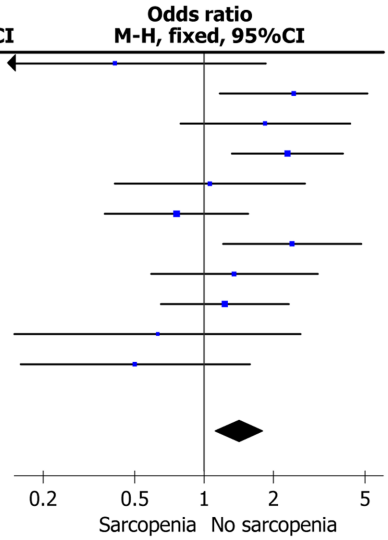
Heterogeneity: Chi²= 1.22, df = 3 (*P* = 0.75); I^2 = 0%
Test for overall effect: Z = 0.54 (*P* = 0.59)



G

Study or subgroup	Sarcopenia Events	Sarcopenia Total	No sarcopenia Events	No sarcopenia Total	Weight	Odds ratio M-H, fixed, 95%CI
Aoki Y	2	19	36	161	5.9%	0.41 [0.09, 1.85]
Cai Z	25	47	26	82	7.6%	2.45 [1.17, 5.12]
Centonze L	14	36	19	74	6.5%	1.84 [0.79, 4.31]
Duan K	39	108	31	157	13.9%	2.30 [1.32, 4.00]
La Vaccara V	20	54	10	28	7.1%	1.06 [0.41, 2.74]
Nauheim D O	11	83	42	250	15.6%	0.76 [0.37, 1.55]
Nishida Y	29	132	14	134	9.3%	2.41 [1.21, 4.81]
Sandini M	13	30	34	94	8.0%	1.35 [0.59, 3.11]
Takagi K	20	55	52	164	14.3%	1.23 [0.65, 2.33]
Tankel J	3	16	12	45	4.4%	0.63 [0.15, 2.62]
Umetsu S	23	48	11	17	7.3%	0.50 [0.16, 1.58]
Total (95%CI)		**628**		**1206**	**100.0%**	**1.42 [1.12, 1.79]**
Total events	199		287			

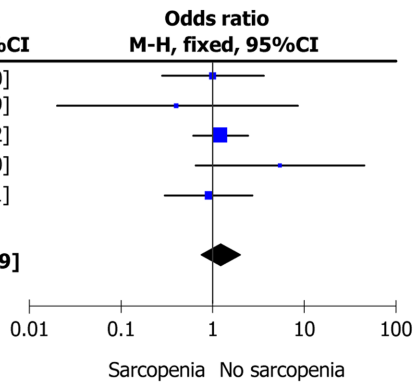
Heterogeneity: Chi²= 18.17, df = 10 (*P* = 0.05); I^2 = 45%
Test for overall effect: Z = 2.93 (*P* = 0.003)



H

Study or subgroup	Sarcopenia Events	Sarcopenia Total	No sarcopenia Events	No sarcopenia Total	Weight	Odds ratio M-H, fixed, 95%CI
Cai Z	4	47	7	82	16.3%	1.00 [0.28, 3.60]
Centonze L	0	36	2	74	5.7%	0.40 [0.02, 8.49]
Duan K	17	108	21	157	50.3%	1.21 [0.61, 2.42]
La Vaccara V	9	54	1	28	3.8%	5.40 [0.65, 45.00]
Sandini M	5	30	17	94	23.9%	0.91 [0.30, 2.71]
Total (95%CI)		**275**		**435**	**100.0%**	**1.22 [0.75, 1.99]**
Total events	35		48			

Heterogeneity: Chi²= 2.78, df = 4 (*P* = 0.59); I^2 = 0%
Test for overall effect: Z = 0.78 (*P* = 0.43)



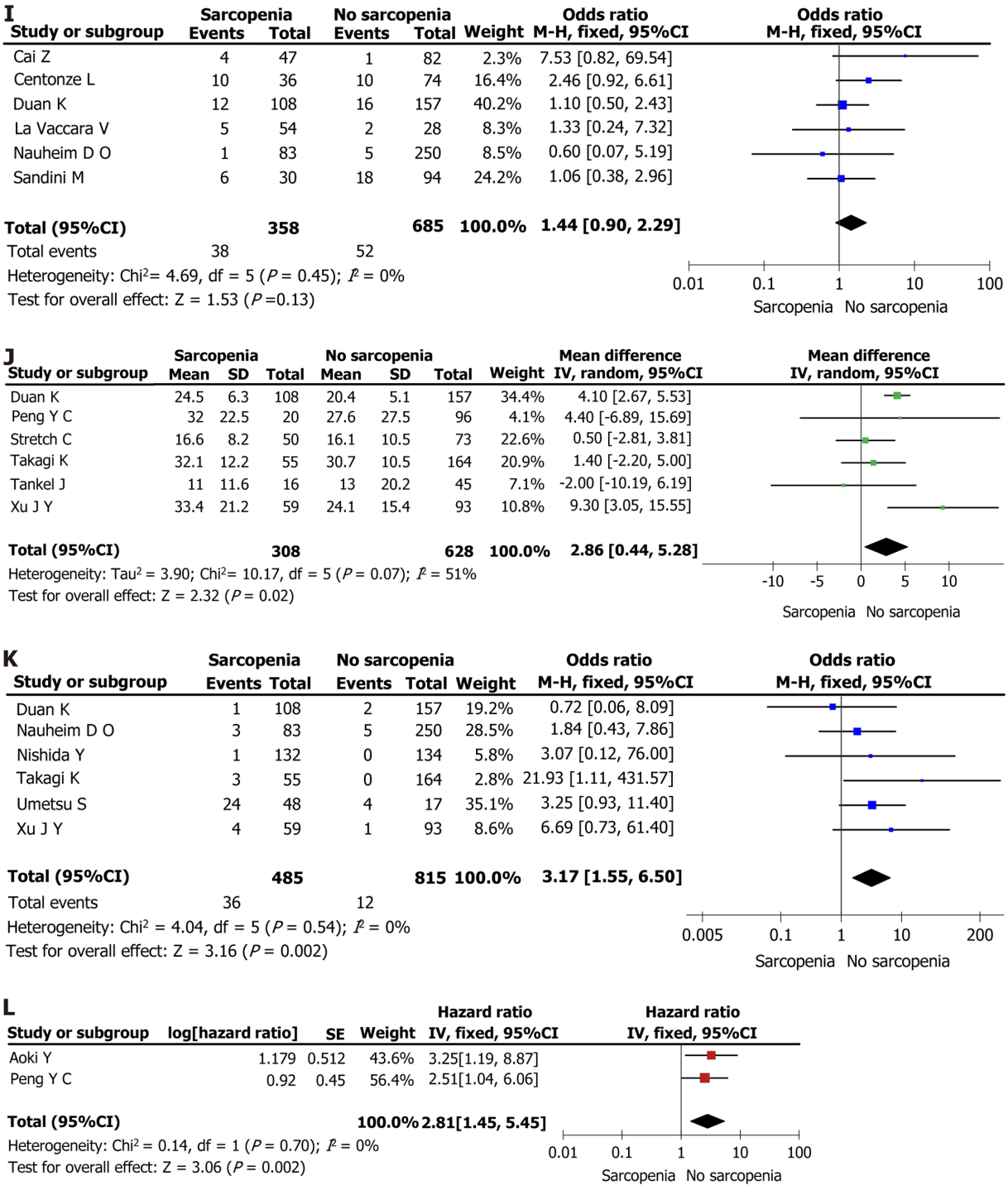


Figure 3 Comparison of the overall rate of postoperative complications, major complications (Clavien-Dindo ≥ III), the occurrence of bacteremia, the occurrence of pneumonia, wound infection rates, urinary tract infection rates, the incidence of pancreatic fistula, biliary fistula rates, the occurrence of postoperative bleeding, length of stay, postoperative mortality rates, and overall survival between the sarcopenia and non-sarcopenia groups. A: Comparison of the overall rate of postoperative complications between the sarcopenia and non-sarcopenia groups; B: Comparison of major complications (Clavien-Dindo ≥ III) between the sarcopenia and non-sarcopenia groups; C: Comparison of the occurrence of bacteremia between the sarcopenia and non-sarcopenia groups; D: Comparison of the occurrence of pneumonia between the sarcopenia and non-sarcopenia groups; E: Comparison of wound infection rates between the sarcopenia and non-sarcopenia groups; F: Comparison of urinary tract infection rates between the sarcopenia and non-sarcopenia groups; G: Comparison of the incidence of pancreatic fistula between the sarcopenia and non-sarcopenia groups; H: Comparison of biliary fistula rates between the sarcopenia and non-sarcopenia groups; I: Comparison of the occurrence of postoperative bleeding between the sarcopenia and non-sarcopenia groups; J: Comparison of length of stay between the sarcopenia and non-sarcopenia groups; K: Comparison of postoperative mortality rates between the sarcopenia and non-sarcopenia groups; L: Comparison of overall survival between the sarcopenia and non-sarcopenia groups. (multivariate analysis). CI: Confidence interval.

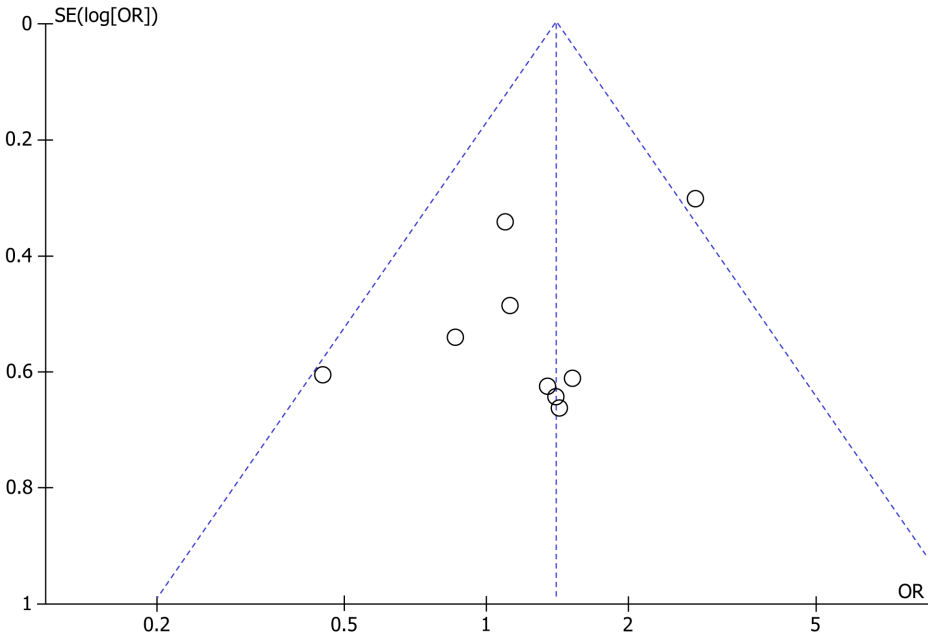


Figure 4 Funnel plot of the observed complications (Clavien-Dindo ≥ III). OR: Odds ratio.

FOOTNOTES

Author contributions: Zhang QH and Ma JD contributed equally to this work and are co-first authors. Zhang QH, Ma JD, Lu YM, Zhang RN, and Zhao ZH participated in the data curation; Zhang QH, Ma JD, Lu YM, Zhang RN, Zhao ZH, Li YT, and Chen QP were involved in the writing - review and editing; Zhang QH and Ma JD contributed to the software, validation, and writing - original draft of this manuscript; Lu YM and Chen QP took part in conceptualization and supervision; Zhang QH was involved in the methodology of this study.

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REFERENCES

1 **Cruz-Jentoft AJ**, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, Zamboni M; Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019; **48**: 16-31 [PMID: 30312372 DOI: 10.1093/ageing/afy169]

2 **Damanti S**, Azzolino D, Roncaglione C, Arosio B, Rossi P, Cesari M. Efficacy of Nutritional Interventions as Stand-Alone or Synergistic Treatments with Exercise for the Management of Sarcopenia. *Nutrients* 2019; **11** [PMID: 31443594 DOI: 10.3390/nu11091991]

3 **Xia L**, Zhao R, Wan Q, Wu Y, Zhou Y, Wang Y, Cui Y, Shen X, Wu X. Sarcopenia and adverse health-related outcomes: An umbrella review of meta-analyses of observational studies. *Cancer Med* 2020; **9**: 7964-7978 [PMID: 32924316 DOI: 10.1002/cam4.3428]

4 **Fan Y**, Li N, Zhang J, Fu Q, Qiu Y, Chen Y. The Effect of immunonutrition in patients undergoing pancreaticoduodenectomy: a systematic

review and meta-analysis. *BMC Cancer* 2023; **23**: 351 [PMID: 37069556 DOI: 10.1186/s12885-023-10820-7]

5 **La Vaccara V**, Cascone C, Coppola A, Farolfi T, Cammarata R, Emerenziani S, Coppola R, Caputo D. Role of preoperative sarcopenia in predicting postoperative complications and survival after pancreatoduodenectomy for pancreatic cancer. *Ann Ital Chir* 2023; **94**: 45-51 [PMID: 36810297]

6 **Umetsu S**, Wakiya T, Ishido K, Kudo D, Kimura N, Miura T, Toyoki Y, Hakamada K. Effect of sarcopenia on the outcomes after pancreaticoduodenectomy for distal cholangiocarcinoma. *ANZ J Surg* 2018; **88**: E654-E658 [PMID: 29388312 DOI: 10.1111/ans.14304]

7 **Umezawa S**, Kobayashi S, Otsubo T. Low preoperative psoas muscle mass index is a risk factor for distal cholangiocarcinoma recurrence after pancreatoduodenectomy: a retrospective analysis. *World J Surg Oncol* 2022; **20**: 176 [PMID: 35655260 DOI: 10.1186/s12957-022-02627-w]

8 **Hozo SP**, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005; **5**: 13 [PMID: 15840177 DOI: 10.1186/1471-2288-5-13]

9 **Khan H**, Garg A, Yasmeen, Agarwal NB, Yadav DK, Ashif Khan M, Hussain S. Zolpidem use and risk of suicide: A systematic review and meta-analysis. *Psychiatry Res* 2022; **316**: 114777 [PMID: 35985088 DOI: 10.1016/j.psychres.2022.114777]

10 **Nishida Y**, Kato Y, Kudo M, Aizawa H, Okubo S, Takahashi D, Nakayama Y, Kitaguchi K, Gotohda N, Takahashi S, Konishi M. Preoperative Sarcopenia Strongly Influences the Risk of Postoperative Pancreatic Fistula Formation After Pancreaticoduodenectomy. *J Gastrointest Surg* 2016; **20**: 1586-1594 [PMID: 27126054 DOI: 10.1007/s11605-016-3146-7]

11 **Sandini M**, Bernasconi DP, Fior D, Molinelli M, Ippolito D, Nespoli L, Caccialanza R, Gianotti L. A high visceral adipose tissue-to-skeletal muscle ratio as a determinant of major complications after pancreatoduodenectomy for cancer. *Nutrition* 2016; **32**: 1231-1237 [PMID: 27261062 DOI: 10.1016/j.nut.2016.04.002]

12 **Takagi K**, Yoshida R, Yagi T, Umeda Y, Nobuoka D, Kuise T, Fujiwara T. Radiographic sarcopenia predicts postoperative infectious complications in patients undergoing pancreaticoduodenectomy. *BMC Surg* 2017; **17**: 64 [PMID: 28549466 DOI: 10.1186/s12893-017-0261-7]

13 **Stretch C**, Aubin JM, Mickiewicz B, Leugner D, Al-Manasra T, Tobola E, Salazar S, Sutherland FR, Ball CG, Dixon E, Vogel HJ, Damaraju S, Baracos VE, Bathe OF. Sarcopenia and myosteatosis are accompanied by distinct biological profiles in patients with pancreatic and periampullary adenocarcinomas. *PLoS One* 2018; **13**: e0196235 [PMID: 29723245 DOI: 10.1371/journal.pone.0196235]

14 **Tankel J**, Dagan A, Vainberg E, Boaz E, Mogilevsky L, Hadas I, Reissman P, Ben Haim M. Sarcopenia is associated with a greater incidence of delayed gastric emptying following pancreaticoduodenectomy. *Clin Nutr ESPEN* 2018; **27**: 105-109 [PMID: 30144881 DOI: 10.1016/j.clnesp.2018.05.011]

15 **Centonze L**, Di Sandro S, Lauterio A, De Carlis R, Botta F, Mariani A, Bagnardi V, De Carlis L. The Impact of Sarcopenia on Postoperative Course following Pancreatoduodenectomy: Single-Center Experience of 110 Consecutive Cases. *Dig Surg* 2020; **37**: 312-320 [PMID: 31958796 DOI: 10.1159/000504703]

16 **Xu JY**, Li C, Zhang H, Liu Y, Wei JM. Total Psoas Area Index is Valuable to Assess Sarcopenia, Sarcopenic Overweight/Obesity and Predict Outcomes in Patients Undergoing Open Pancreatoduodenectomy. *Risk Manag Healthc Policy* 2020; **13**: 761-770 [PMID: 32753989 DOI: 10.2147/RMHP.S257677]

17 **Peng YC**, Wu CH, Tien YW, Lu TP, Wang YH, Chen BB. Preoperative sarcopenia is associated with poor overall survival in pancreatic cancer patients following pancreaticoduodenectomy. *Eur Radiol* 2021; **31**: 2472-2481 [PMID: 32974690 DOI: 10.1007/s00330-020-07294-7]

18 **Pessia B**, Giuliani A, Romano L, Bruno F, Carlei F, Vicentini V, Schietroma M. The role of sarcopenia in the pancreatic adenocarcinoma. *Eur Rev Med Pharmacol Sci* 2021; **25**: 3670-3678 [PMID: 34109576 DOI: 10.26355/eurrev_202105_25933]

19 **Duan K**, Gao X, Wei L, Gong M, Feng B, Zhou J, Zhu D. Skeletal muscle depletion and nutrition support affected postoperative complications in patients who underwent pancreatoduodenectomy. *Eur J Clin Nutr* 2021; **75**: 1218-1226 [PMID: 33483631 DOI: 10.1038/s41430-020-00851-9]

20 **Nauheim DO**, Hackbart H, Papai E, Moskal D, Yeo CJ, Lavu H, Nevler A. Preoperative sarcopenia is a negative predictor for enhanced postoperative recovery after pancreaticoduodenectomy. *Langenbecks Arch Surg* 2022; **407**: 2355-2362 [PMID: 35593934 DOI: 10.1007/s00423-022-02558-w]

21 **Aoki Y**, Furukawa K, Suzuki D, Takayashiki T, Kuboki S, Takano S, Kawasaki Y, Shiko Y, Ohtsuka M. Influence of sarcopenia as defined by EWGSOP2 on complications after pancreaticoduodenectomy and on the prognosis of pancreatic head cancer: A prospective cohort study. *Nutrition* 2022; **99-100**: 111660 [PMID: 35576875 DOI: 10.1016/j.nut.2022.111660]

22 **Cai Z**, Yang Y, Fu X, Mao L, Qiu Y. Predictive Value of Body Composition Parameters for Postoperative Complications in Patients Who Received Pancreaticoduodenectomy. *Eur Surg Res* 2023; **64**: 252-260 [PMID: 36754029 DOI: 10.1159/000529429]

23 **Yuan S**, Larsson SC. Epidemiology of sarcopenia: Prevalence, risk factors, and consequences. *Metabolism* 2023; **144**: 155533 [PMID: 36907247 DOI: 10.1016/j.metabol.2023.155533]

24 **Mballa Yene BV**, Lee SY, Park KS, Kang YJ, Seo SH, Yoo JI. Prevalence of Sarcopenia in Africa: A Systematic Review. *Clin Interv Aging* 2023; **18**: 1021-1035 [PMID: 37427010 DOI: 10.2147/CIA.S407917]

25 **Chen Z**, Li WY, Ho M, Chau PH. The Prevalence of Sarcopenia in Chinese Older Adults: Meta-Analysis and Meta-Regression. *Nutrients* 2021; **13** [PMID: 33923252 DOI: 10.3390/nu13051441]

26 **Takada H**, Kurosaki M, Nakanishi H, Takahashi Y, Itakura J, Tsuchiya K, Yasui Y, Tamaki N, Takaura K, Komiyama Y, Higuchi M, Kubota Y, Wang W, Okada M, Enomoto N, Izumi N. Impact of pre-sarcopenia in sorafenib treatment for advanced hepatocellular carcinoma. *PLoS One* 2018; **13**: e0198812 [PMID: 29912922 DOI: 10.1371/journal.pone.0198812]

27 **Chakedis J**, Spolverato G, Beal EW, Woelfel I, Bagante F, Merath K, Sun SH, Chafitz A, Galo J, Dillhoff M, Cloyd J, Pawlik TM. Pre-operative Sarcopenia Identifies Patients at Risk for Poor Survival After Resection of Biliary Tract Cancers. *J Gastrointest Surg* 2018; **22**: 1697-1708 [PMID: 29855867 DOI: 10.1007/s11605-018-3802-1]

28 **Kuan LL**, Dennison AR, Garcea G. Prevalence and Impact of Sarcopenia in Chronic Pancreatitis: A Review of the Literature. *World J Surg* 2021; **45**: 590-597 [PMID: 33165641 DOI: 10.1007/s00268-020-05828-0]

29 **Churchward-Venne TA**, Breen L, Phillips SM. Alterations in human muscle protein metabolism with aging: Protein and exercise as countermeasures to offset sarcopenia. *Biofactors* 2014; **40**: 199-205 [PMID: 24105883 DOI: 10.1002/biof.1138]

30 **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]

31 **Deniz O**, Coteli S, Karatoprak NB, Pence MC, Varan HD, Kizilarslanoglu MC, Oktar SO, Goker B. Diaphragmatic muscle thickness in older people with and without sarcopenia. *Aging Clin Exp Res* 2021; **33**: 573-580 [PMID: 32406014 DOI: 10.1007/s40520-020-01565-5]

32 **Ticinesi A**, Nouvenne A, Cerundolo N, Catania P, Prati B, Tana C, Meschi T. Gut Microbiota, Muscle Mass and Function in Aging: A Focus on Physical Frailty and Sarcopenia. *Nutrients* 2019; **11** [PMID: 31319564 DOI: 10.3390/nu11071633]

33 **Bilen MA**, Martini DJ, Liu Y, Shabto JM, Brown JT, Williams M, Khan AI, Speak A, Lewis C, Collins H, Kissick HT, Carthon BC, Akce M, Shaib WL, Alese OB, Pillai RN, Steuer CE, Wu CS, Lawson DH, Kudchadkar RR, El-Rayes BF, Ramalingam SS, Owonikoko TK, Harvey RD, Master VA. Combined Effect of Sarcopenia and Systemic Inflammation on Survival in Patients with Advanced Stage Cancer Treated with Immunotherapy. *Oncologist* 2020; **25**: e528-e535 [PMID: 32162807 DOI: 10.1634/theoncologist.2019-0751]

34 **Shi Y**, Zhou L, Yan E, Yang L, Yang C, Liu C. Sarcopenia and perioperative management of elderly surgical patients. *Front Biosci (Landmark Ed)* 2021; **26**: 882-894 [PMID: 34719213 DOI: 10.52586/4995]

35 **Voron T**, Tselikas L, Pietrasz D, Pigneur F, Laurent A, Compagnon P, Salloum C, Luciani A, Azoulay D. Sarcopenia Impacts on Short- and Long-term Results of Hepatectomy for Hepatocellular Carcinoma. *Ann Surg* 2015; **261**: 1173-1183 [PMID: 24950264 DOI: 10.1097/SLA.0000000000000743]

36 **Simonsen C**, de Heer P, Bjerre ED, Suetta C, Hojman P, Pedersen BK, Svendsen LB, Christensen JF. Sarcopenia and Postoperative Complication Risk in Gastrointestinal Surgical Oncology: A Meta-analysis. *Ann Surg* 2018; **268**: 58-69 [PMID: 29373365 DOI: 10.1097/SLA.0000000000002679]

37 **Malmstrom TK**, Morley JE. SARC-F: a simple questionnaire to rapidly diagnose sarcopenia. *J Am Med Dir Assoc* 2013; **14**: 531-532 [PMID: 23810110 DOI: 10.1016/j.jamda.2013.05.018]

38 **Shen Y**, Shi Q, Nong K, Li S, Yue J, Huang J, Dong B, Beauchamp M, Hao Q. Exercise for sarcopenia in older people: A systematic review and network meta-analysis. *J Cachexia Sarcopenia Muscle* 2023; **14**: 1199-1211 [PMID: 37057640 DOI: 10.1002/jcsm.13225]

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META-ANALYSIS

Comparison efficacy and safety of total laparoscopic gastrectomy and laparoscopically assisted total gastrectomy in treatment of gastric cancer

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Abstract

BACKGROUND

The development of laparoscopic technology has provided a new choice for surgery of gastric cancer (GC), but the advantages and disadvantages of laparoscopic total gastrectomy (LTG) and laparoscopic-assisted total gastrectomy (LATG) in treatment effect and safety are still controversial. The purpose of this study is to compare the efficacy and safety of the two methods in the treatment of GC, and to provide a basis for clinical decision-making.

AIM

To compare the efficacy of totally LTG (TLTG) and LATG in the context of radical gastrectomy for GC. Additionally, we investigated the safety and feasibility of the total laparoscopic esophagojejunostomy technique.

METHODS

Literature on comparative studies of the above two surgical methods for GC (TLTG group and LATG group) published before September 2022 were searched in the PubMed, Web of Science, Wanfang Database, CNKI, and other Chinese and English databases. In addition, the following search keywords were used: Gastric

cancer, total gastrectomy, total laparoscopy, laparoscopy-assisted, esophagojejunal anastomosis, gastric/stomach cancer, total gastrectomy, totally/completely laparoscopic, laparoscopic assisted/laparoscopy assisted/laparoscopically assisted, and esophagojejunostomy/esophagojejunal anastomosis. Review Manager 5.3 software was used for the meta-analysis after two researchers independently screened the literature, extracted the data, and evaluated the risk of bias in the included studies.

RESULTS

After layer-by-layer screening, 258 pieces of literature were recovered, and 11 of those pieces were eventually included. This resulted in a sample size of 2421 instances, with 1115 cases falling into the TLTG group and 1306 cases into the LATG group. Age or sex differences between the two groups were not statistically significant, according to the meta-analysis, however the average body mass index of the TLTG group was considerably higher than that of the LATG group ($P = 0.01$). Compared with those in the LATG group, the incision length in the TLTG group was significantly shorter ($P < 0.001$), the amount of intraoperative blood loss was significantly lower ($P = 0.003$), the number of lymph nodes removed was significantly greater ($P = 0.04$), and the time of first postoperative feeding and postoperative hospitalization were also significantly shorter ($P = 0.03$ and 0.02, respectively). There were no significant differences in tumor size, length of proximal incisal margin, total operation time, anastomotic time, postoperative pain score, postoperative anal exhaust time, postoperative anastomosis-related complications (including anastomotic fistula, anastomotic stenosis, and anastomotic hemorrhage), or overall postoperative complication rate ($P > 0.05$).

CONCLUSION

TLTG and esophagojejunostomy are safe and feasible. Compared with LATG, TLTG has the advantages of less trauma, less bleeding, easier access to lymph nodes, and faster postoperative recovery, and TLTG is also suitable for obese patients.

Key Words: Total laparoscopic gastrectomy; Laparoscopically assisted total gastrectomy; Gastric cancer; Meta-analysis

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Core Tip: This study used a systematic review and meta-analysis to determine how well and safely laparoscopic total gastrectomy and laparoscopically assisted total gastrectomy can treat gastric cancer (GC). Clinical trial data from relevant literature were collected and analyzed to evaluate the differences between the two surgical methods in terms of surgical effect, postoperative complications, and postoperative quality of life. Through the systematic synthesis of the results, an objective evaluation of the advantages and disadvantages of these two surgical methods is provided, which provides a scientific basis for clinicians to optimize the treatment of GC patients.

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INTRODUCTION

Surgery has been used for more advanced cases of gastric cancer (GC) as well as earlier cases of the disease[1]. Additionally, surgical methods have changed from laparoscopic-assisted radical gastrectomy to total laparoscopic radical gastrectomy[2]. However, reconstructing the digestive tract through total laparoscopic surgery is difficult. This is especially true for totally laparoscopic total gastrectomy (TLTG) and esophagojejunostomy, which require advanced endoscopic techniques and are not sure how well they work. There is also debate about whether they are safe and possible[3].

This study will conduct a meta-analysis of published comparative studies on TLTG and laparoscopic-assisted total gastrectomy (LATG) in the treatment of GC, aiming to observe the difference in efficacy of the two surgical methods in the treatment of GC and discuss the safety and feasibility of TLTG for GC and esophagojejunostomy. The aim is to obtain the best evidence to guide clinical practice.

MATERIALS AND METHODS

Literature retrieval strategy

The subject of this study was a controlled clinical study of TLTG and LATG for GC published before September 2023. The search databases used were PubMed, Web of Science, Wanfang Database, CNKI, and other Chinese and English databases. Keywords in the Chinese search were GC, total gastrectomy, total laparoscopy, and laparoscopy-assisted esophagojejunostomy. The key words in English were gastric/stomach cancer, total gastrectomy, totally/completely laparoscopic, laparoscopic assisted/laparoscopic assisted/laparoscopic assisted, and esophagojejunostomy/esophagojejunal anastomosis. The literature was reviewed by hand.

Inclusion criteria

All patients were confirmed by pathological examination to have GC; (2) all studies involved the comparison of the efficacy of TLTG and LATG in GC; (3) accurate and important clinical data should be provided, especially the incidence of postoperative anastomosis-related complications; (4) original statistical data should be provided, such as the mean and standard deviation of continuous variables and specific values of binary variables; and (5) for the literature of the same unit, recently published literature with higher quality statistics should be selected.

Exclusion criteria

(1) Patients with cancers other than those of the stomach; (2) patients who underwent distal gastrectomy, proximal gastrectomy, or palliative total gastrectomy; (3) patients who received neoadjuvant chemotherapy before surgery; and (4) patients whose clinical data, such as the rate of anastomosis-related complications, were not available.

Data extraction and quality evaluation

Using a unified data collection table, two system evaluators independently extracted the following data from the included literature: first author, data source (country), publication time, number of cases, patient age, sex, body mass index (BMI), length of surgical incision, total surgical time, anastomosis time, intraoperative blood loss, number of lymph node removals, tumor size, length of proximal incisal margin, postoperative pain score (visual analog scale), postoperative anal exhaust time, postoperative eating time, postoperative hospital stay, postoperative surgery overall complication rate, postoperative anastomosis-related complication rate, and other indicators. Disagreements were resolved after discussion with a third researcher.

The Newcastle-Ottawa Scale (NOS) was used to score the quality of the included studies. The evaluation content included three main aspects: research selection, research comparison, and interesting research results. The maximum possible score was 9 points, and an overall score > 6 was considered to indicate high-quality research.

Statistical analysis

The Cochrane Collaboration provided RevMan 5.3 software for statistical analysis. The odds ratio of binary data was calculated as the combined statistic, and the weighted mean difference (WMD) of continuous variable data was calculated as the combined statistic. The results were expressed with a 95%CI, and the test level was $\alpha = 0.05$. The incidence of postoperative anastomosis-related complications was measured by a funnel plot to determine publication bias. A heterogeneity test was conducted for all included studies. An $I^2 \leq 50\%$ indicated that there was no significant heterogeneity among all studies. A fixed effects model (F model) was used for combined analysis; otherwise, a random effects model (R model) was used. To avoid the influence of different surgical operators and surgical methods on the results, the R model was adopted for the analysis of clinical data related to surgery.

RESULTS

Literature retrieval results and included research characteristics

Based on the inclusion and exclusion criteria (Figure 1), 11 papers[4-14] about clinical control studies of TLTG and LATG in GC were ultimately included. These were all nonrandomized controlled studies. There were 2421 clinical cases, including 1115 in the TLTG group and 1306 in the LATG group, mainly from China, South Korea, and Japan. According to the NOS quality score, nine studies[4-12] were considered to be of high quality, all of which compared the two groups by age and sex. Seven of them[4-6,8-11] also compared the body mass indices of the two groups, and the results showed that there was no significant difference in age or sex between the two groups ($P = 0.60$ and 0.61, respectively), while the average BMI of the TLTG group was significantly greater than that of the LATG group ($P = 0.01$). The basic information and quality evaluation of the included studies are shown in Table 1.

Meta-analysis results

The meta-analysis results of this study showed that, compared with those in the LATG group, the length of surgical incisions in the TLTG group was significantly shorter ($P < 0.001$), the amount of intraoperative blood loss was significantly less ($P = 0.003$), and the number of lymph nodes removed was significantly greater ($P = 0.04$). The time of first feeding and hospital stay were also significantly shorter ($P = 0.03$ and 0.02, respectively), but there were no significant differences in tumor size, length of proximal incisal margin, operation time, postoperative pain score, postoperative anal exhaust time, or postoperative complication rate ($P > 0.05$). Table 2 summarizes the intraoperative and

Table 1 Basic information of included literature

Ref.	Countries	Sample size		Age (yr, mean ± SD)		Body mass index (kg/m²), mean ± SD)		NOS score
		TLTG group	LATG group	TLTG group	LATG group	TLTG group	LATG group	
Kim *et al*[4], 2013	South Korea	90	23	58.0 ± 10.8	56.8 ± 14.2	23.2 ± 2.9	22.2 ± 1.8	7
Kim *et al*[5], 2016	South Korea	27	29	60.8 ± 9.1	59.3 ± 13.1	24.0 ± 2.9	23.3 ± 3.2	7
Chen *et al*[6]	China	108	145	59.4 ± 11.1	57.3 ± 12.5	23.5 ± 3.5	23.1 ± 4.2	8
Gong *et al*[7], 2017	South Korea	421	266	57.78 ± 11.2	55.69 ± 11.96	/	/	7
Huang *et al*[8], 2017	China	51	456	55.5 ± 12.1	61.6 ± 11.2	22.5 ± 13.1	22.3 ± 13.5	7
Lu *et al*[9], 2016	China	25	25	59+8.9	58.4 ± 7.7	22.5 ± 2.5	22.9 ± 3.7	8
Cui *et al*[10]	China	16	47	61.3 ± 13.	67.6+13	22.8 ± 1.2	23.2+1.3	8
Hong *et al*[11], 2017	China	183	190	58 ± 11	60 ± 10	23 ± 3	22 ± 3	8
Hua *et al*[12], 2017	China	47	47	48.51 ± 2.47	48.67 ± 2.51		/	7
Xiao *et al*[13], 2015	China	30	32	/	/		/	6
Ito *et al*[14], 2014	Japan	117	46			/	/	6

TLTG: Totally laparoscopic total gastrectomy; LATG: Laparoscopic-assisted total gastrectomy; NOS: Newcastle-Ottawa Scale.

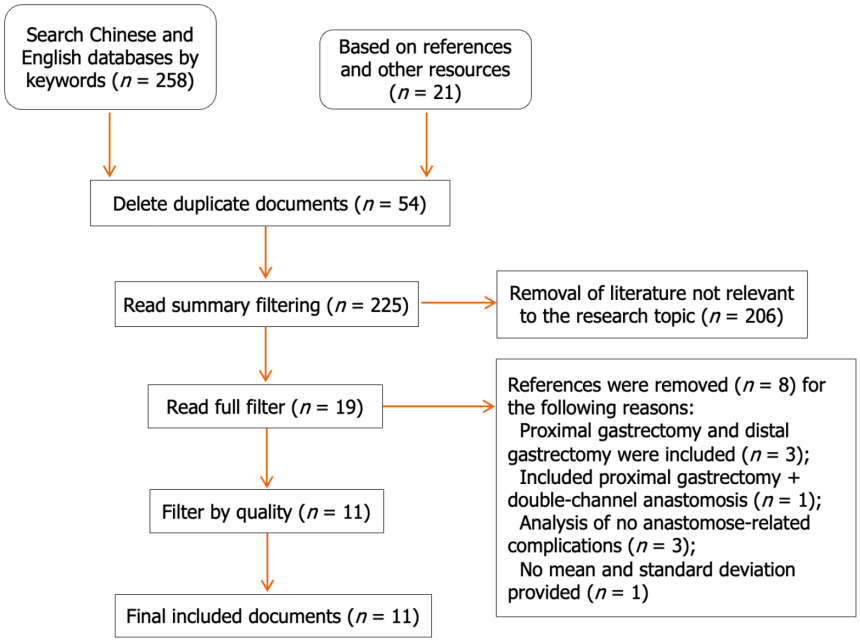


Figure 1 Flow chart of literature retrieval and screening.

postoperative information of the 11 studies included in this paper.

Intraoperative data comparison

Four of the eleven studies in this paper[10-13] examined the length of surgical incisions. The incisions in the TLTG group were significantly shorter than those in the LATG group (WMD = -4.21, 95%CI: -5.51 to -2.91, $P < 0.001$; Figure 2A). The total operation time was compared in nine studies[4-6,8-12,14]. There was no statistically significant difference in the total operation time between the two groups (WMD = 7.62, 95%CI: -4.35–19.59, $P = 0.21$; Figure 2B). Three studies[5,6,13] compared surgical anastomosis time, and the results indicated that there was no statistically significant difference in the anastomosis time between the TLTG group and the LATG group (WMD = 6.40, 95%CI: -2.28-15.08, $P = 0.15$; Figure 2C). Nine studies[5,6,8-14] compared the amount of blood loss during surgery. Much less blood was lost in the TLTG group than in the LATG group (WMD = -26.29, 95%CI: -43.70 to -8.88, $P = 0.003$; Figure 2D).

Table 2 Intraoperative and postoperative clinical data and analysis results included in the literature

Observation indicators	References	Sample size (examples)		Heterogeneity	Effect model	Comprehensive effect value	95%CI	*P* value
		TLTG group	LATG group					
Operative time	9	664	1008	< 0.001, 83%	R	WMD = 7.62	-4.35-19.59	0.21
Match time	3	165	206	< 0.001, 86%	R	WMD = 6.40	-2.28-15.08	0.15
Tumor size	7	905	1134	0.02, 61%	R	WMD = -0.29	-0.65-0.17	0.12
Proximal edge distance	5	597	512	< 0.001, 84%	R	WMD = -0.22	-0.86-0.41	0.49
Intraoperative bleeding volume	9	604	1017	< 0.001, 84%	R	WMD = -26.29	-43.70 to -8.88	0.003
Number of lymph node removals	9	973	1235	0.02, 57%	R	WMD = 1.78	0.06-3.50	0.04
Postoperative pain score								
On the first day after surgery (8:00 am)	2	511	289	0.91, 0%	R	WMD = 0.03	-0.20-0.27	0.78
On the 3rd day after surgery (8:00 am)	2	511	289	0.46, 0%	R	WMD = 0.08	-0.13-0.28	0.45
Postoperative peak pain	2	511	289	0.09, 66%	R	WMD = 0.17	-0.71-1.05	0.70
Postoperative anal exhaust time	8	547	962	< 0.001, 89%	R	WMD = -0.22	-0.56-0.13	0.22
Postoperative feeding time	8	547	962	< 0.001, 86%	R	WMD = -0.56	-1.07 to -0.06	0.03
Postoperative hospitalization time	9	577	994	< 0.001, 93%	R	WMD = -1.53	-2.83 to -0.23	0.02
The incidence of anastomotic complications	11	1115	1306	0.74, 0%	R	OR = 0.71	0.47-1.06	0.09
Anastomotic fistula	11	1115	1306	0.53, 0%	R	OR = 0.70	0.42-1.18	0.18
Anastomotic stenosis	11	1115	1306	0.85, 0%	R	OR = 0.84	0.41-1.71	0.63
Anastomotic bleeding	8	439	817	0.93, 0%	R	OR = 0.86	0.34-2.15	0.74
Overall incidence of complications	9	947	804	0.81, 0%	R	OR = 0.93	0.71-1.21	0.58

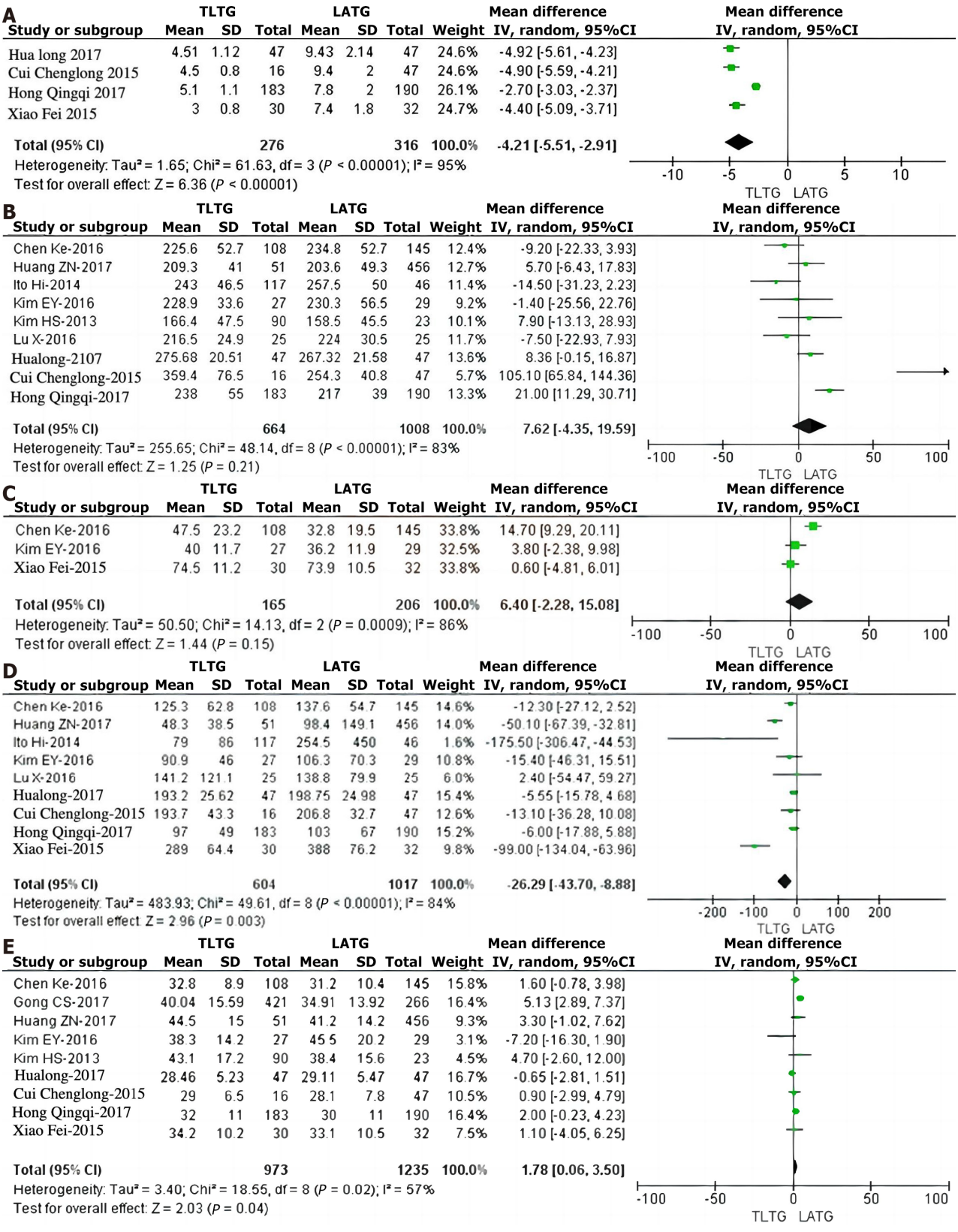
TLTG: Totally laparoscopic total gastrectomy; LATG: Laparoscopic-assisted total gastrectomy; WMD: Weighted mean difference.

In nine studies[4-8,10-13], the number of lymph nodes removed during surgery was compared. More lymph nodes were removed in the TLTG group than in the LATG group (WMD = 1.78, 95%CI: 0.06-3.50; *P* = 0.04; Figure 2E). Seven studies[4-9,11] examined the sizes of tumors that had been removed. The results showed that there was no statistically significant difference in the sizes of the tumors between the two groups (WMD = -0.29, 95%CI: -0.65-0.07, *P* = 0.12; Figure 2F). Five studies[5-7,9,10] compared the length of the proximal incisal margin, and the results indicated that there was no statistically significant difference in the length of the proximal incisal margin between the TLTG group and the LATG group (WMD = -0.22, 95%CI: -0.86-0.41, *P* = 0.49; Figure 2G).

Postoperative data comparison

Two studies[4,7] compared postoperative pain scores, and the results indicated that there was no statistically significant difference in postoperative pain peak values or pain scores at the 1st and 3rd days after surgery between the TLTG group and the LATG group (*P* = 0.70, *P* = 0.78, and *P* = 0.45, respectively). In 8 studies[4-6,8-12], the postoperative anal exhaust time was compared. There was no significant difference between the two groups (WMD = -0.22, 95%CI: -0.56-0.13, *P* = 0.22; Figure 2H). Eight studies[4-6,8-12] compared the first feeding after surgery. The first feeding in the TLTG group occurred significantly earlier than that in the LATG group (WMD = -0.56, 95%CI: -1.07 to -0.06, *P* = 0.03; Figure 2I).

A total of nine studies[4-6,8-13] compared the length of hospital stay after surgery. The TLTG group had a significantly shorter length of hospital stay than did the LATG group (WMD = -1.53, 95%CI: -2.83 to -0.23, *P* = 0.02; Figure 2J). The 11 studies included in this study all compared the incidence of postoperative anastomosis-related complications, and the results indicated that there was no significant difference between the two groups (OR = 0.71, 95%CI: 0.47-1.06, *P* = 0.09; Figure 3 and Table 2). The incidence of anastomotic fistula in the TLTG and LATG groups was 2.51% and 3.98%, respectively (OR = 0.70, 95%CI: 0.42-1.18, *P* = 0.18); the incidence of anastomotic stenosis was 1.43% and 1.45%,


A
Study or subgroup | TLTG Mean SD Total | LATG Mean SD Total | Weight | Mean difference IV, random, 95%CI
Hua long 2017 4.51 1.12 47 9.43 2.14 47 24.6% -4.92 [-5.61, -4.23]
Cui Chenglong 2015 4.5 0.8 16 9.4 2 47 24.6% -4.90 [-5.59, -4.21]
Hong Qingqi 2017 5.1 1.1 183 7.8 2 190 26.1% -2.70 [-3.03, -2.37]
Xiao Fei 2015 3 0.8 30 7.4 1.8 32 24.7% -4.40 [-5.09, -3.71]
Total (95% CI) 276 316 100.0% -4.21 [-5.51, -2.91]
Heterogeneity: Tau² = 1.65; Chi² = 61.63, df = 3 (P < 0.00001); I² = 95%
Test for overall effect: Z = 6.36 (P < 0.00001)
Mean difference IV, random, 95%CI
-10 -5 0 5 10
TLTG LATG
B
Study or subgroup | TLTG Mean SD Total | LATG Mean SD Total | Weight | Mean difference IV, random, 95%CI
Chen Ke-2016 225.6 52.7 108 234.8 52.7 145 12.4% -9.20 [-22.33, 3.93]
Huang ZN-2017 209.3 41 51 203.6 49.3 456 12.7% 5.70 [-6.43, 17.83]
Ito Hi-2014 243 46.5 117 257.5 50 46 11.4% -14.50 [-31.23, 2.23]
Kim EY-2016 228.9 33.6 27 230.3 56.5 29 9.2% -1.40 [-25.56, 22.76]
Kim HS-2013 166.4 47.5 90 158.5 45.5 23 10.1% 7.90 [-13.13, 28.93]
Lu X-2016 216.5 24.9 25 224 30.5 25 11.7% -7.50 [-22.93, 7.93]
Hualong-2107 275.68 20.51 47 267.32 21.58 47 13.6% 8.36 [-0.15, 16.87]
Cui Chenglong-2015 359.4 76.5 16 254.3 40.8 47 5.7% 105.10 [65.84, 144.36]
Hong Qingqi-2017 238 55 183 217 39 190 13.3% 21.00 [11.29, 30.71]
Total (95% CI) 664 1008 100.0% 7.62 [-4.35, 19.59]
Heterogeneity: Tau² = 255.65; Chi² = 48.14, df = 8 (P < 0.00001); I² = 83%
Test for overall effect: Z = 1.25 (P = 0.21)
Mean difference IV, random, 95%CI
-100 -50 0 50 100
TLTG LATG
C
Study or subgroup | TLTG Mean SD Total | LATG Mean SD Total | Weight | Mean difference IV, random, 95%CI
Chen Ke-2016 47.5 23.2 108 32.8 19.5 145 33.8% 14.70 [9.29, 20.11]
Kim EY-2016 40 11.7 27 36.2 11.9 29 32.5% 3.80 [-2.38, 9.98]
Xiao Fei-2015 74.5 11.2 30 73.9 10.5 32 33.8% 0.60 [-4.81, 6.01]
Total (95% CI) 165 206 100.0% 6.40 [-2.28, 15.08]
Heterogeneity: Tau² = 50.50; Chi² = 14.13, df = 2 (P = 0.0009); I² = 86%
Test for overall effect: Z = 1.44 (P = 0.15)
Mean difference IV, random, 95%CI
-100 -50 0 50 100
TLTG LATG
D
Study or subgroup | TLTG Mean SD Total | LATG Mean SD Total | Weight | Mean difference IV, random, 95%CI
Chen Ke-2016 125.3 62.8 108 137.6 54.7 145 14.6% -12.30 [-27.12, 2.52]
Huang ZN-2017 48.3 38.5 51 98.4 149.1 456 14.0% -50.10 [-67.39, -32.81]
Ito Hi-2014 79 86 117 254.5 450 46 1.6% -175.50 [-306.47, -44.53]
Kim EY-2016 90.9 46 27 106.3 70.3 29 10.8% -15.40 [-46.31, 15.51]
Lu X-2016 141.2 121.1 25 138.8 79.9 25 6.0% 2.40 [-54.47, 59.27]
Hualong-2017 193.2 25.62 47 198.75 24.98 47 15.4% -5.55 [-15.78, 4.68]
Cui Chenglong-2015 193.7 43.3 16 206.8 32.7 47 12.6% -13.10 [-36.28, 10.08]
Hong Qingqi-2017 97 49 183 103 67 190 15.2% -6.00 [-17.88, 5.88]
Xiao Fei-2015 289 64.4 30 388 76.2 32 9.8% -99.00 [-134.04, -63.96]
Total (95% CI) 604 1017 100.0% -26.29 [-43.70, -8.88]
Heterogeneity: Tau² = 483.93; Chi² = 49.61, df = 8 (P < 0.00001); I² = 84%
Test for overall effect: Z = 2.96 (P = 0.003)
Mean difference IV, random, 95%CI
-200 -100 0 100 200
TLTG LATG
E
Study or subgroup | TLTG Mean SD Total | LATG Mean SD Total | Weight | Mean difference IV, random, 95%CI
Chen Ke-2016 32.8 8.9 108 31.2 10.4 145 15.8% 1.60 [-0.78, 3.98]
Gong CS-2017 40.04 15.59 421 34.91 13.92 266 16.4% 5.13 [2.89, 7.37]
Huang ZN-2017 44.5 15 51 41.2 14.2 456 9.3% 3.30 [-1.02, 7.62]
Kim EY-2016 38.3 14.2 27 45.5 20.2 29 3.1% -7.20 [-16.30, 1.90]
Kim HS-2013 43.1 17.2 90 38.4 15.6 23 4.5% 4.70 [-2.60, 12.00]
Hualong-2017 28.46 5.23 47 29.11 5.47 47 16.7% -0.65 [-2.81, 1.51]
Cui Chenglong-2015 29 6.5 16 28.1 7.8 47 10.5% 0.90 [-2.99, 4.79]
Hong Qingqi-2017 32 11 183 30 11 190 16.4% 2.00 [-0.23, 4.23]
Xiao Fei-2015 34.2 10.2 30 33.1 10.5 32 7.5% 1.10 [-4.05, 6.25]
Total (95% CI) 973 1235 100.0% 1.78 [0.06, 3.50]
Heterogeneity: Tau² = 3.40; Chi² = 18.55, df = 8 (P = 0.02); I² = 57%
Test for overall effect: Z = 2.03 (P = 0.04)
Mean difference IV, random, 95%CI
-100 -50 0 50 100
TLTG LATG

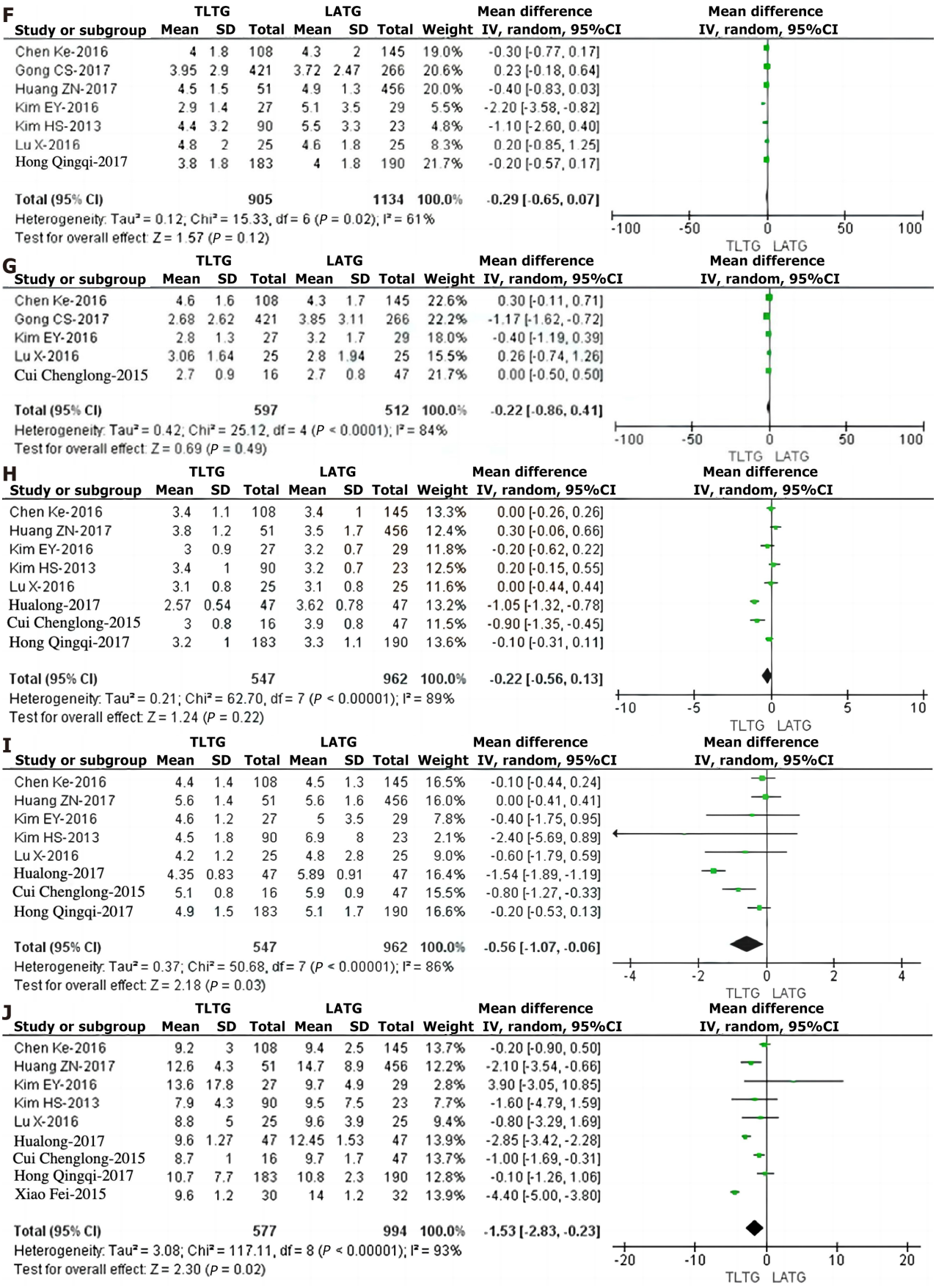


Figure 2 Meta-analysis of efficacy and safety of totally laparoscopic total gastrectomy and laparoscopic-assisted total gastrectomy in the treatment of gastric cancer. A: Surgical incision length; B: Operative time; C: Surgical anastomosis time; D: Intraoperative blood loss; E: The number of lymph nodes removed; F: Tumor size; G: Proximal incisal margin length; H: Postoperative anal exhaust time; I: Postoperative eating time; J: Postoperative hospital stay meta-analysis. TLTG: Totally laparoscopic total gastrectomy; LATG: Laparoscopic-assisted total gastrectomy.

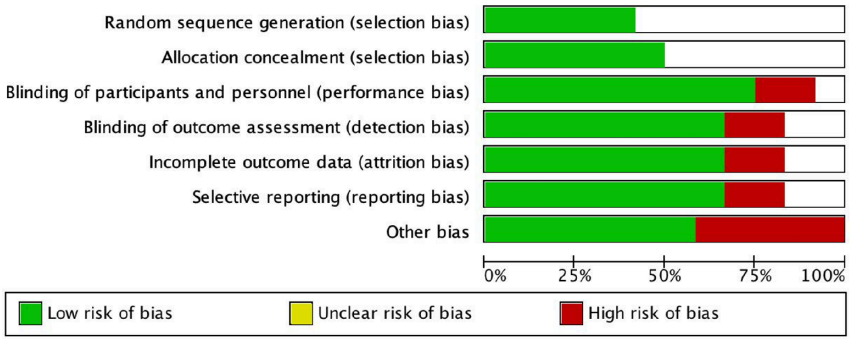


Figure 3 Literature quality evaluation chart.

respectively (OR = 0.84, 95%CI: 0.41-1.71, P = 0.63); and the incidence of anastomotic hemorrhage was 1.59% and 1.22%, respectively (OR = 0.86, 95%CI: 0.34-2.15, P = 0.74; Figure 4). Nine studies[4-7,9-13] examined the overall rate of complications after surgery. The results showed that there was no statistically significant difference between the two groups in this rate (OR = 0.93, 95%CI: 0.71-1.21; P = 0.58). In all the studies included in this study, no surgery-related deaths occurred in either group, and no second surgery was reported.

Sensitivity analysis

The incidence of postoperative anastomosis-related complications is an important index for evaluating surgical efficacy, and it is also the focus of this study. Since low-quality research data may affect the overall research results[15], when the two studies of lower quality[13,14] were removed, the incidence data of postoperative anastomosis-related complications from nine high-quality studies[4-12] were pooled and analyzed. The number of complications related to the anastomosis after surgery did not differ significantly between the TLTG and LATG groups (OR = 0.72, 95%CI: 0.47-1.09, P = 0.12), which suggests that the addition of two lower-quality studies did not change the initial results.

This study focused on the safety and feasibility of *in vivo* esophagojejunostomy. Different anastomosis methods or anastomosis instruments may have affected the final results of the study. Among the 11 studies included in this paper[4-14], 9 items[4,5,7-13] were reconstructed by Roux-en-Y anastomosis. Among them, 8 items[4,5,7-10,12,13] were all esophagojejunostomies using linear staplers. Huang *et al*[8] reported a new anastomosis method (the isometric retrocut and overlap method of the jejunum). Ito *et al*[14] used circular staplers for anastomosis, and the other two[6,11] used various anastomosis methods. Therefore, the last four studies[6,8,11,14] were removed from further sensitivity analysis. When the four studies were removed, there was no significant change in the results of any of the studies (Figure 3).

Publication bias

In this paper, funnel plots were drawn for the incidence of postoperative anastomosis-related complications in the TLTG group and the LATG group. The results of the plots showed basic symmetry, suggesting no clear publication bias (Figure 4). Egger linear regression analysis further confirmed that there was no significant publication bias in the included literature (P > 0.05).

DISCUSSION

Laparoscopic-assisted radical gastrectomy has become the most commonly used surgical method for treating GC[15]. With the improvement of endoscopy technology, the surgical path for treating GC has gradually moved toward full laparoscopy. However, due to the late development of total laparoscopic radical gastrectomy, high technical requirements, and difficulty, most medical units do not regard it as the preferred method for GC surgery[16]. Digestive tract reconstruction is the focus and difficulty of laparoscopic radical gastrectomy for treating GC. In total laparoscopic radical gastrectomy for GC, esophagojejunal anastomosis is very difficult due to its "anatomical particularity" (high anastomosis site, narrow operating space, *etc.*), and it is also the key to successful surgery. Therefore, the safety and feasibility of TLTG and esophagojejunostomy are of great concern.

There are many ways to reconstruct the digestive tract after laparoscopic total gastrectomy[17]. Roux-en-Y anastomosis, which is currently the main surgical method for reconstruction, can effectively reduce reflux esophagitis and maintain good nutritional status[18]. In previous studies, two methods of *in vivo* esophagojejunostomy were introduced, including manual suturing and mechanical suturing (linear stapling and circular stapling)[19]. Using linear staplers for reconstruction inside the body during endoscopy can make tension-free anastomosis possible, preventing damage to nearby structures[20]. Unlike circular staplers, linear staplers can be inserted into the abdominal cavity through a cannula hole (Tocar) to complete digestive tract reconstruction without the need for an auxiliary incision. Gong *et al*[7] suggested that TLTG with a linear stapler was more suitable for endoscopic surgery than LATG with a circular stapler and recommended it for the treatment of upper GC. Nine of the eleven studies in this paper[4,5,7-13] used Roux-en-Y anastomosis to reconstruct the digestive tract. Huang *et al*[8] reported a new anastomosis method called the isometric retroincision and overlapping jejunum method. Eight studies[4,5,7-10,12,13] used linear staplers to connect the esophagus

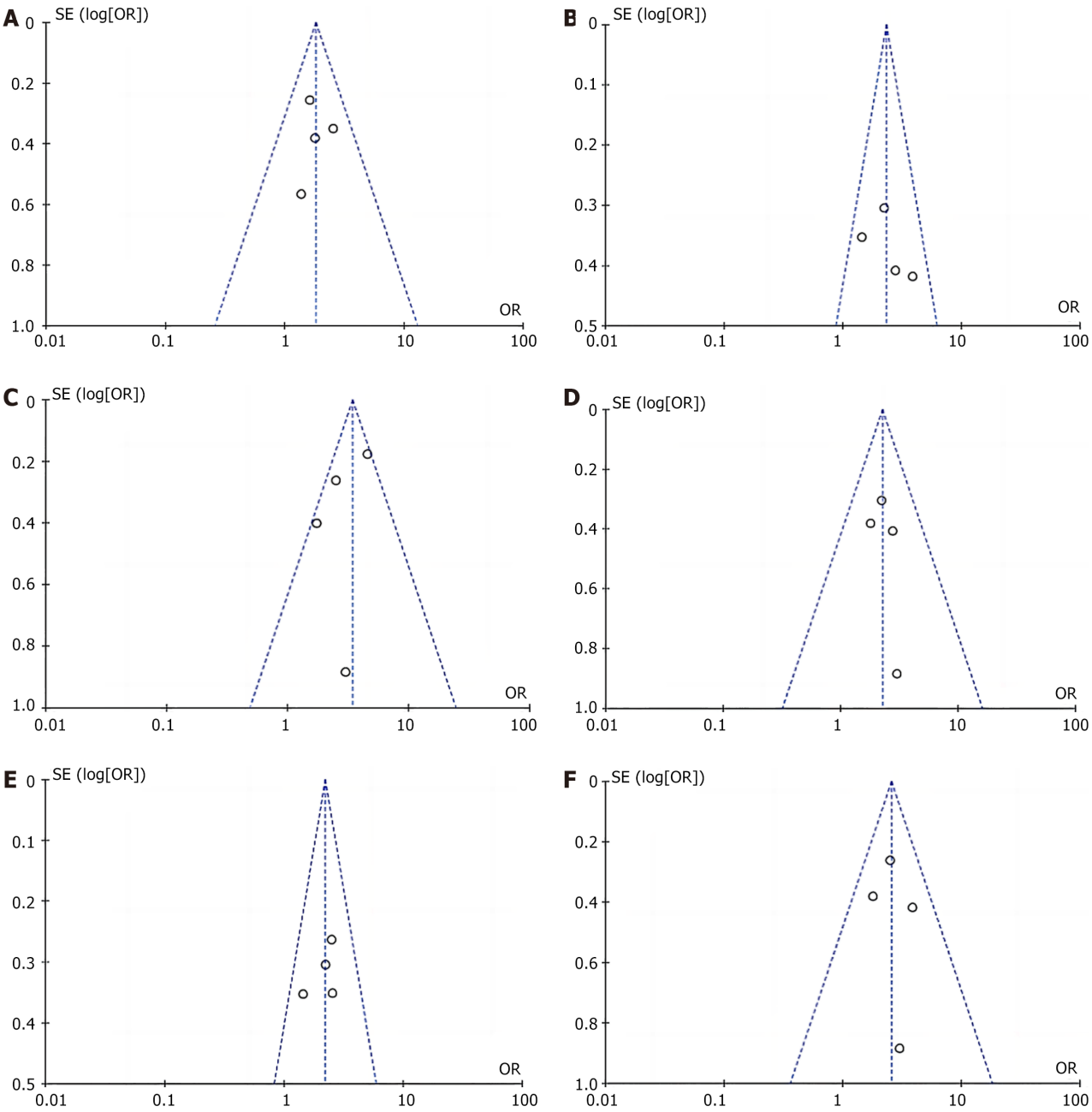


Figure 4 Funnel plot of literature publication bias. A: Funnel plot of publication bias in surgical incision length; B: Funnel plot of publication bias in operative time; C: Funnel plot of publication bias in surgical anastomosis time; D: Funnel plot of publication bias in intraoperative blood loss; E: Funnel plot of publication bias in the number of lymph nodes removed; F: Funnel plot of publication bias in tumor size.

and jejunum. Ito *et al*[14] used circular staplers, and two studies[6,11] used more than one method of anastomosis. The results of this meta-analysis showed that the incidence of postoperative anastomosis-related complications (including anastomotic fistula, anastomotic stenosis, and anastomotic hemorrhage) was lower in the TLTG group than in the LATG group (4.39% and 6.20%, respectively), and there was no statistically significant difference between the two groups (P = 0.09). Some studies[6,8,11,14] that used different anastomosis methods or devices were removed from the sensitivity analysis in this paper. The results of these studies did not change significantly. Therefore, *in vivo* digestive tract reconstruction is safe and feasible. To confirm the effectiveness of different anastomotic methods, further long-term and large-scale randomized controlled trials are needed.

Studies[21-25] have shown that total laparoscopic radical gastrectomy and esophagojejunostomy for GC can increase the duration of surgery and even cause much more blood to be lost during surgery. The results of this meta-analysis showed that there were no statistically significant differences in the total operation time or anastomotic time between the TLTG group and the LATG group, and the intraoperative blood loss in the TLTG group was significantly less than that in the LATG group[26-28]. The reasons for the low blood loss in the TLTG group were as follows: (1) there was no auxiliary abdominal incision in the TLTG, and the intraperitoneal wound was small; (2) TLTG can reduce excessive tissue traction and reduce the risk of bleeding; and (3) laparoscopic surgical techniques may affect intraoperative blood loss, and operators differ between the TLTG and LATG groups. According to relevant studies, TLTG will take much less time after

the surgeon learns and practices total laparoscopic distal gastrectomy (residual stomach and duodenal anastomosis). Therefore, this may be related to the operator's proficiency in endoscopic surgery.

The main difference between complete laparoscopic and laparoscopic-assisted radical gastrectomy for GC lies in the different paths of digestive tract reconstruction[29]. The former is completed under laparoscopy (*in vivo*), while the latter requires an auxiliary incision in vitro. However, for obese patients, total gastrectomy and esophagojejunal anastomosis *in vitro* with the aid of an abdominal incision are very difficult to perform, and the surgical incision must be prolonged, which ultimately extends the operation time and even increases the surgical risk and postoperative pain of patients[30-33]. The results of this meta-analysis showed that the average BMI of the TLTG group was significantly greater than that of the LATG group, and the length of surgical incision was significantly shorter than that of the LATG group; however, there were no statistically significant differences in the total operation time, anastomotic time, or postoperative pain score between the two groups. In conclusion, complete LGT and esophagojejunostomy in obese patients are still safe, feasible, and even more advantageous.

Most of the studies[34-38] included in this paper only compared the short-term efficacy of TLTG and LATG, and the results showed that the postoperative feeding time and postoperative hospital stay in the TLTG group were significantly shorter than those in the LATG group, while there were no significant differences in the postoperative anal venting time, postoperative anastomosis-related complications, or overall complications between the two groups[39-41]. Therefore, compared with patients in the LATG group, patients in the TLTG group achieved faster postoperative recovery.

This study has several limitations. First, we focused on the safety and feasibility of *in vivo* esophagojejunostomy, but laparoscopic surgical skills may affect surgical outcomes, and surgical operators differ between the TLTG and LATG groups. Second, most of the studies that were examined did not report or evaluate the long-term effectiveness of total laparoscopic radical gastrectomy for GC. This means that the differences in long-term effectiveness between TLTG and LATG need to be studied further. In addition, all the included studies were retrospective studies and did not include blinded or randomized controlled trials, and the sample size may not be sufficient; therefore, a large-scale randomized care trial study of the two groups is needed in the future.

CONCLUSION

TLTG under full laparoscopy is technically safe and feasible, and it is equally suitable or even more beneficial for obese patients. Compared with LATG, TLTG has the advantages of less trauma, less bleeding, easier access to lymph nodes, faster postoperative recovery, *etc.* Total laparoscopic radical gastrectomy is likely to be a future direction for the treatment of GC.

FOOTNOTES

Author contributions: Li L and Liu DY wrote the manuscript; Tao XM collected the data; Wu HQ submitted the manuscript to the journal; Zhu YP guided the study; all authors reviewed, edited, and approved the final manuscript and revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work. Li L and Liu DY contributed equally to this work as co-first authors. The reasons for designating Li L and Liu DY as co-first authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-first authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability; Second, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of co-first authors best reflect this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives; Third, Li L and Liu DY contributed efforts of equal substance throughout the research process. The choice of these researchers as co-first authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Li L and Liu DY as co-first authors is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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REFERENCES

1 **Etoh T**, Ohyama T, Sakuramoto S, Tsuji T, Lee SW, Yoshida K, Koeda K, Hiki N, Kunisaki C, Tokunaga M, Otsubo D, Takagane A, Misawa K, Kinoshita T, Cho H, Doki Y, Nunobe S, Shiraishi N, Kitano S; Japanese Laparoscopic Surgery Study Group (JLSSG). Five-Year Survival Outcomes of Laparoscopy-Assisted *vs* Open Distal Gastrectomy for Advanced Gastric Cancer: The JLSSG0901 Randomized Clinical Trial. *JAMA Surg* 2023; **158**: 445-454 [PMID: 36920382 DOI: 10.1001/jamasurg.2023.0096]

2 **Wu L**, Li X, Qian X, Wang S, Liu J, Yan J. Lipid Nanoparticle (LNP) Delivery Carrier-Assisted Targeted Controlled Release mRNA Vaccines in Tumor Immunity. Vaccines (Basel) 2024; 12 [PMID: 38400169 DOI: 10.3390/vaccines12020186]

3 **Makuuchi R**, Terashima M, Terada M, Mizusawa J, Kita R, Tokunaga M, Omori T, Ojima T, Ehara K, Watanabe M, Yanagimoto Y, Nunobe S, Kinoshita T, Ito S, Nishida Y, Hihara J, Boku N, Kurokawa Y, Yoshikawa T; Stomach Cancer Study Group of Japan Clinical Oncology Group. Randomized controlled phase III trial to investigate superiority of robot-assisted gastrectomy over laparoscopic gastrectomy for clinical stage T1-4aN0-3 gastric cancer patients (JCOG1907, MONA LISA study): a study protocol. *BMC Cancer* 2023; **23**: 987 [PMID: 37845660 DOI: 10.1186/s12885-023-11481-2]

4 **Kim HS**, Kim MG, Kim BS, Lee IS, Lee S, Yook JH. Comparison of totally laparoscopic total gastrectomy and laparoscopic-assisted total gastrectomy methods for the surgical treatment of early gastric cancer near the gastroesophageal junction. *J Laparoendosc Adv Surg Tech A* 2013; **23**: 204-210 [PMID: 23256584 DOI: 10.1089/lap.2012.0393]

5 **Kim EY**, Choi HJ, Cho JB, Lee J. Totally Laparoscopic Total Gastrectomy Versus Laparoscopically Assisted Total Gastrectomy for Gastric Cancer. *Anticancer Res* 2016; **36**: 1999-2003 [PMID: 27069193]

6 **Chen K**, Pan Y, Cai JQ, Wu D, Yan JF, Chen DW, Yu HM, Wang XF. Totally laparoscopic versus laparoscopic-assisted total gastrectomy for upper and middle gastric cancer: a single-unit experience of 253 cases with meta-analysis. *World J Surg Oncol* 2016; **14**: 96 [PMID: 27036540 DOI: 10.1186/s12957-016-0860-2]

7 **Gong CS**, Kim BS, Kim HS. Comparison of totally laparoscopic total gastrectomy using an endoscopic linear stapler with laparoscopic-assisted total gastrectomy using a circular stapler in patients with gastric cancer: A single-center experience. *World J Gastroenterol* 2017; **23**: 8553-8561 [PMID: 29358863 DOI: 10.3748/wjg.v23.i48.8553]

8 **Huang ZN**, Huang CM, Zheng CH, Li P, Xie JW, Wang JB, Lin JX, Lu J, Chen QY, Cao LL, Lin M, Tu RH, Lin JL. Digestive tract reconstruction using isoperistaltic jejunum-later-cut overlap method after totally laparoscopic total gastrectomy for gastric cancer: Short-term outcomes and impact on quality of life. *World J Gastroenterol* 2017; **23**: 7129-7138 [PMID: 29093621 DOI: 10.3748/wjg.v23.i39.7129]

9 **Lu X**, Hu Y, Liu H, Mou T, Deng Z, Wang D, Yu J, Li G. Short-term outcomes of intracorporeal esophagojejunostomy using the transorally inserted anvil *vs* extracorporeal circular anastomosis during laparoscopic total gastrectomy for gastric cancer: a propensity score matching analysis. *J Surg Res* 2016; **200**: 435-443 [PMID: 26421708 DOI: 10.1016/j.jss.2015.08.013]

10 **Cui CL**, Liang W, Zhu ZQ, YAO HH, Wu Y, Liu L, Guan JJ. Feasibility, safety and short-term efficacy of totally laparoscopic total gastrectomy for upper stomach cancer. *Zhongguo Putongwaike Zazhi* 2015; **24**: 1377-1382

11 **Hong QQ**, Wang W, Zhang J, Fan L, Zhu JM, Ji G, Yan S, You J. Clinical efficacies of totally laparoscopic and laparoscopy-assisted radical total gastrectomies in 373 patients: a multicentre retrospective study. *Zhonghua Xiaohua Waike Zazhi* 2017; **16**: 822-827 [DOI: 10.3760/cma.j.issn.1673-9752.2017.08.013]

12 **Hua L**, Wang CY. Comparison of totally laparoscopic total gastrectomy and laparoscopic-assisted total gastrectomy in patients with upper gastric cancer. *Aizheng Jinzhan* 2017; **15**: 186-188,192 [DOI: 10.11877/j.issn.1672-1535.2017.15.02.24]

13 **Xiao F**, Hu B, Song YF, You J. Comparison of clinical efficacy of total gastrectomy assisted by endoscopy and total gastrectomy for gastric cancer. *Wuhandax Xuebao (Yixueban)* 2015; **36**: 786-791 [DOI: 10.14188/j.1671-8852.2015.05.031]

14 **Ito H**, Inoue H, Odaka N, Satodate H, Onimaru M, Ikeda H, Takayanagi D, Nakahara K, Kudo SE. Evaluation of the safety and efficacy of esophagojejunostomy after totally laparoscopic total gastrectomy using a trans-orally inserted anvil: a single-center comparative study. *Surg Endosc* 2014; **28**: 1929-1935 [PMID: 24488351 DOI: 10.1007/s00464-014-3417-x]

15 **Fan Y**, Liu M, Li S, Yu J, Qi X, Tan F, Xu K, Zhang N, Yao Z, Yang H, Zhang C, Xing J, Wang Z, Cui M, Su X. Surgical and oncological efficacy of laparoscopic-assisted total gastrectomy *vs* open total gastrectomy for gastric cancer by propensity score matching: a retrospective comparative study. *J Cancer Res Clin Oncol* 2021; **147**: 2153-2165 [PMID: 33415526 DOI: 10.1007/s00432-020-03503-4]

16 **Zhou D**, Yu X, Wang Y, Tang F, Yang C, Luo D. Laparoscopically Assisted, Tubular, Stomach Construction for the Radical Resection of Esophageal Cancer. *Altern Ther Health Med* 2023; **29**: 200-205 [PMID: 36480679]

17 **Wu Q**, Wang Y, Peng Q, Bai M, Shang Z, Li L, Tian F, Jing C. Safety and effectiveness of totally laparoscopic total gastrectomy *vs* laparoscopic-assisted total gastrectomy: a meta-analysis. *Int J Surg* 2024; **110**: 1245-1265 [PMID: 38016295 DOI: 10.1097/JS9.0000000000000921]

18 **Illuminati G**, D'Urso A, Fiori E, Cerasari S, Nardi P, Lapergola A, Pasqua R, Sorrenti S, Pironi D, Lauro A, D'Andrea V. Laparoscopy-assisted *vs* open total gastrectomy with D2 Lymphadenectomy for advanced gastric cancer: results of a retrospective, multicenter study. *Updates Surg* 2023; **75**: 1645-1651 [PMID: 36854994 DOI: 10.1007/s13304-023-01476-w]

19 **Wu L**, Liu Q, Ruan X, Luan X, Zhong Y, Liu J, Yan J, Li X. Multiple Omics Analysis of the Role of RBM10 Gene Instability in Immune Regulation and Drug Sensitivity in Patients with Lung Adenocarcinoma (LUAD). *Biomedicines* 2023; **11** [PMID: 37509501 DOI: 10.3390/biomedicines11071861]

20 **Seo HS**, Kim S, Song KY, Lee HH. Feasibility and Potential of Reduced Port Surgery for Total Gastrectomy With Overlap Esophagojejunal Anastomosis Method. *J Gastric Cancer* 2023; **23**: 487-498 [PMID: 37553134 DOI: 10.5230/jgc.2023.23.e26]

21 **Motamiez A**, Maximous D, Salem AAS, Ahmed BM, Kong SH, Park DJ, Lee HJ, Yang HK. Surgical Outcomes of Laparoscopic-assisted Distal Gastrectomy Versus Totally Laparoscopic Distal Gastrectomy Billroth I for Gastric Cancer. *Surg Laparosc Endosc Percutan Tech* 2024; **34**: 80-86 [PMID: 38134380 DOI: 10.1097/SLE.0000000000001255]

22 **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]

23 **Wu L**, Zhong Y, Yu X, Wu D, Xu P, Lv L, Ruan X, Liu Q, Feng Y, Liu J, Li X. Selective poly adenylation predicts the efficacy of immunotherapy in patients with lung adenocarcinoma by multiple omics research. *Anticancer Drugs* 2022; **33**: 943-959 [PMID: 35946526 DOI: 10.1097/CAD.0000000000001319]

24 **Lin GT**, Chen JY, Chen QY, Que SJ, Liu ZY, Zhong Q, Wang JB, Lin JX, Lu J, Lin M, Huang ZN, Xie JW, Li P, Huang CM, Zheng CH. Patient-Reported Outcomes of Individuals with Gastric Cancer Undergoing Totally Laparoscopic Versus Laparoscopic-Assisted Total Gastrectomy: A Real-World, Propensity Score-Matching Analysis. *Ann Surg Oncol* 2023; **30**: 1759-1769 [PMID: 36414907 DOI: 10.1245/s10434-022-12764-x]

25 **Xu SZ**, Cai JC. Laparoscopic-Assisted Natural Orifice Specimen Extraction Gastrectomy Using an Auxiliary Incision-Free Tube for Gastric Cancer. *J Surg Res* 2022; **270**: 31-38 [PMID: 34628161 DOI: 10.1016/j.jss.2021.08.026]

26 **Wu L**, Zhong Y, Wu D, Xu P, Ruan X, Yan J, Liu J, Li X. Immunomodulatory Factor TIM3 of Cytolytic Active Genes Affected the Survival and Prognosis of Lung Adenocarcinoma Patients by Multi-Omics Analysis. *Biomedicines* 2022; **10** [PMID: 36140350 DOI: 10.3390/biomedicines10092248]

27 **Wu CY**, Lin JA, Huang QZ, Xu JH, Zhong WJ, Kang WG, Wang JT, Chen JX, Zheng HD, Ye K. Comparison of short-term and long-term clinical effects of modified overlap anastomosis and conventional incision-assisted anastomosis in laparoscopic total gastrectomy. *BMC Surg* 2023; **23**: 306 [PMID: 37817168 DOI: 10.1186/s12893-023-02212-2]

28 **Lin J**, Liang H, Zheng H, Li S, Liu H, Ge X. CONUT can be a predictor of postoperative complications after laparoscopic-assisted radical gastrectomy for elderly gastric cancer patients. *Medicine (Baltimore)* 2023; **102**: e35424 [PMID: 37800831 DOI: 10.1097/MD.0000000000035424]

29 **Wu L**, Zheng Y, Ruan X, Wu D, Xu P, Liu J, Li X. Long-chain noncoding ribonucleic acids affect the survival and prognosis of patients with esophageal adenocarcinoma through the autophagy pathway: construction of a prognostic model. *Anticancer Drugs* 2022; **33**: e590-e603 [PMID: 34338240 DOI: 10.1097/CAD.0000000000001189]

30 **Hoeppner J**. [Robot-assisted Total Gastrectomy with D2 Lymphadenectomy and Intracorporal Reconstruction]. *Zentralbl Chir* 2022; **147**: 427-429 [PMID: 35038755 DOI: 10.1055/a-1707-1437]

31 **Charalabopoulos A**, Davakis S, Paraskeva P, Machairas N, Kapelouzou A, Kordzadeh A, Sakarellos P, Vailas M, Baili E, Bakoyiannis C, Felekouras E. Feasibility and Short-Term Outcomes of Three-Dimensional Hand-Sewn Esophago-Jejunal Anastomosis in Completely Laparoscopic Total Gastrectomy for Cancer. *Cancers (Basel)* 2021; **13** [PMID: 34572936 DOI: 10.3390/cancers13184709]

32 **Li Z**, Ai S, Wang F, Tao L, Sun F, Song P, Shen X, Hu Q, Li X, Liu S, Wang M, Guan W. Comparison of short-term outcomes between robotic-assisted and laparoscopic gastrectomy guided by carbon nanoparticle suspension injection in gastric cancer. *World J Surg Oncol* 2022; **20**: 282 [PMID: 36058930 DOI: 10.1186/s12957-022-02755-3]

33 **Wu L**, Zheng Y, Liu J, Luo R, Wu D, Xu P, Li X. Comprehensive evaluation of the efficacy and safety of LPV/r drugs in the treatment of SARS and MERS to provide potential treatment options for COVID-19. *Aging (Albany NY)* 2021; **13**: 10833-10852 [PMID: 33879634 DOI: 10.18632/aging.202860]

34 **Du GS**, Jiang EL, Qiu Y, Wang WS, Yin JH, Wang S, Li YB, Chen YH, Yang H, Xiao WD. Single-incision plus one-port laparoscopic gastrectomy *vs* conventional multi-port laparoscopy-assisted gastrectomy for gastric cancer: a retrospective study. *Surg Endosc* 2022; **36**: 3298-3307 [PMID: 34313862 DOI: 10.1007/s00464-021-08643-3]

35 **Alzahrani K**, Park JH, Lee HJ, Park SH, Choi JH, Wang C, Alzahrani F, Suh YS, Kong SH, Park DJ, Yang HK. Short-term Outcomes of Pylorus-Preserving Gastrectomy for Early Gastric Cancer: Comparison Between Extracorporeal and Intracorporeal Gastrogastrostomy. *J Gastric Cancer* 2022; **22**: 135-144 [PMID: 35534450 DOI: 10.5230/jgc.2022.22.e16]

36 **Wu L**, Chen X, Zeng Q, Lai Z, Fan Z, Ruan X, Li X, Yan J. NR5A2 gene affects the overall survival of LUAD patients by regulating the activity of CSCs through SNP pathway by OCLR algorithm and immune score. *Heliyon* 2024; **10**: e28282 [PMID: 38601554 DOI: 10.1016/j.heliyon.2024.e28282]

37 **Zhao RY**, Li HH, Zhang KC, Cui H, Deng H, Gao JW, Wei B. Comparison of short-term efficacy between totally laparoscopic gastrectomy and laparoscopic assisted gastrectomy for elderly patients with gastric cancer. *World J Gastrointest Surg* 2022; **14**: 950-962 [PMID: 36185561 DOI: 10.4240/wjgs.v14.i9.950]

38 **Zhong X**, Wei M, Ouyang J, Cao W, Cheng Z, Huang Y, Liang Y, Zhao R, Yu W. Efficacy and Safety of Totally Laparoscopic Gastrectomy Compared with Laparoscopic-Assisted Gastrectomy in Gastric Cancer: A Propensity Score-Weighting Analysis. *Front Surg* 2022; **9**: 868877 [PMID: 36034374 DOI: 10.3389/fsurg.2022.868877]

39 **Wu L**, Li H, Liu Y, Fan Z, Xu J, Li N, Qian X, Lin Z, Li X, Yan J. Research progress of 3D-bioprinted functional pancreas and in vitro tumor models. *IJB* 2024; **10**: 1256 [DOI: 10.36922/ijb.1256]

40 **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]

41 **Luo G**, Xiang Q, Wang X, Li Y, Cao Y, Gong J. Hand-assisted laparoscopic *vs* laparoscopic-assisted radical gastrectomy in the treatment of advanced distal gastric cancer: final results of a single-center randomized study. *J Int Med Res* 2022; **50**: 3000605221109361 [PMID: 35822251 DOI: 10.1177/03000605221109361]

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META-ANALYSIS

Application value of indocyanine green fluorescence imaging in guiding sentinel lymph node biopsy diagnosis of gastric cancer: Meta-analysis

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Abstract

BACKGROUND

Gastric cancer is a common malignant tumor of the digestive system worldwide, and its early diagnosis is crucial to improve the survival rate of patients. Indocyanine green fluorescence imaging (ICG-FI), as a new imaging technology, has shown potential application prospects in oncology surgery. The meta-analysis to study the application value of ICG-FI in the diagnosis of gastric cancer sentinel lymph node biopsy is helpful to comprehensively evaluate the clinical effect of this technology and provide more reliable guidance for clinical practice.

AIM

To assess the diagnostic efficacy of optical imaging in conjunction with indocyanine green (ICG)-guided sentinel lymph node (SLN) biopsy for gastric cancer.

METHODS

Electronic databases such as PubMed, Embase, Medline, Web of Science, and the Cochrane Library were searched for prospective diagnostic tests of optical imaging combined with ICG-guided SLN biopsy. Stata 12.0 software was used for analysis by combining the "bivariable mixed effect model" with the "midas" command. The true positive value, false positive value, false negative value, true negative value, and other information from the included literature were extracted. A literature quality assessment map was drawn to describe the overall quality of the included literature. A forest plot was used for heterogeneity analysis, and $P <$ 0.01 was considered to indicate statistical significance. A funnel plot was used to

assess publication bias, and $P < 0.1$ was considered to indicate statistical significance. The summary receiver operating characteristic (SROC) curve was used to calculate the area under the curve (AUC) to determine the diagnostic accuracy. If there was interstudy heterogeneity ($I^2 > 50\%$), meta-regression analysis and subgroup analysis were performed.

RESULTS

Optical imaging involves two methods: Near-infrared (NIR) imaging and fluorescence imaging. A combination of optical imaging and ICG-guided SLN biopsy was useful for diagnosis. The positive likelihood ratio was 30.39 (95%CI: 0.92-1.00), the sensitivity was 0.95 (95%CI: 0.82-0.99), and the specificity was 1.00 (95%CI: 0.92-1.00). The negative likelihood ratio was 0.05 (95%CI: 0.01-0.20), the diagnostic odds ratio was 225.54 (95%CI: 88.81-572.77), and the SROC AUC was 1.00 (95%CI: The crucial values were sensitivity = 0.95 (95%CI: 0.82-0.99) and specificity = 1.00 (95%CI: 0.92-1.00). The Deeks method revealed that the "diagnostic odds ratio" funnel plot of SLN biopsy for gastric cancer was significantly asymmetrical ($P = 0.01$), suggesting significant publication bias. Further meta-subgroup analysis revealed that, compared with fluorescence imaging, NIR imaging had greater sensitivity (0.98 *vs* 0.73). Compared with optical imaging immediately after ICG injection, optical imaging after 20 minutes obtained greater sensitivity (0.98 *vs* 0.70). Compared with that of patients with an average SLN detection number < 4, the sensitivity of patients with a SLN detection number ≥ 4 was greater (0.96 *vs* 0.68). Compared with hematoxylin-eosin (HE) staining, immunohistochemical (+ HE) staining showed greater sensitivity (0.99 *vs* 0.84). Compared with subserous injection of ICG, submucosal injection achieved greater sensitivity (0.98 *vs* 0.40). Compared with 5 g/L ICG, 0.5 and 0.05 g/L ICG had greater sensitivity (0.98 *vs* 0.83), and cT1 stage had greater sensitivity (0.96 *vs* 0.72) than cT2 to cT3 clinical stage. Compared with that of patients ≤ 26, the sensitivity of patients > 26 was greater (0.96 *vs* 0.65). Compared with the literature published before 2010, the sensitivity of the literature published after 2010 was greater (0.97 *vs* 0.81), and the differences were statistically significant (all $P < 0.05$).

CONCLUSION

For the diagnosis of stomach cancer, optical imaging in conjunction with ICG-guided SLN biopsy is a therapeutically viable approach, especially for early gastric cancer. The concentration of ICG used in the SLN biopsy of gastric cancer may be too high. Moreover, NIR imaging is better than fluorescence imaging and may obtain higher sensitivity.

Key Words: Gastric neoplasms; Sentinel lymph nodes; Near infrared imaging; Fluorescence imaging; Indocyanine green; Meta-analysis

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Core Tip: To explore Indocyanine green fluorescence imaging (ICG-FI) in guiding the diagnosis of gastric cancer sentinel lymph node biopsy through meta-analysis. We will collect and analyze relevant literature to systematically evaluate the clinical manifestations of ICG-FI in gastric cancer patients and compare its diagnostic effectiveness with that of traditional methods. This study will provide clinicians with a more accurate intraoperative evaluation method for gastric cancer, which will help guide surgical decision making and improve patient prognosis.

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INTRODUCTION

At present, the main treatment for gastric cancer is surgical resection. If lymph node metastasis can be evaluated accurately and in real time during surgery and then lymph node dissection can be performed, operative complications can be reduced, and postoperative quality of life can be improved[1]. According to the different reagents used, the traditional methods for sentinel lymph node (SLN) biopsy can be divided into the biological dye method, the isotope method, and the double reagent method. Although these methods have made some progress in research, they also present their own disadvantages: The deposition of biological dyes at lymph node sites is poor, and the isotopes are characterized by background scattering around the injection site[2].

Gastric cancer is one of the most common malignant tumors in the world, and SLN biopsy, as a means of early diagnosis, is of great value for accurate treatment[3]. Indocyanine green fluorescence imaging (ICG-FI), a new imaging guidance technology, has been widely used in cancer surgery in recent years. Its unique biocompatibility and high selectivity make it an ideal tool to guide SLN biopsy. The purpose of this study was to systematically evaluate the

diagnostic efficacy of ICG-FI in guiding SLN biopsy for gastric cancer through meta-analysis and to provide a scientific basis for its application in clinical practice[4]. The comprehensive evaluation of the application of ICG-FI in SLN biopsy of gastric cancer not only provides clinicians with more accurate and reliable intraoperative navigation, improves surgical accuracy, and reduces surgical risk but is also expected to promote further innovation in SLN biopsy technology and provide new ideas for the early diagnosis and treatment of gastric cancer[5]. This study has far-reaching clinical significance for promoting the wide application of ICG-FI technology in the field of gastric cancer and improving the level of surgical treatment.

Since the beginning of the 21st century, many scholars have reported the application of ICG to guide SLN biopsy for gastric cancer patients. These studies have shown good application prospects, but the results reported by each study are inconsistent: The sensitivity and specificity fluctuate between 0.40 and 1.00 and between 0.60 and 1.00, respectively. In view of the large numerical fluctuation range of effect indicators, we conducted a meta-analysis on the diagnostic value of SLN biopsy guided by optical imaging combined with ICG to provide guidance for the treatment of gastric cancer.

MATERIALS AND METHODS

Retrieval method

The search strategy followed the Cochrane Handbook of Systematic Reviews.

The search terms "gastric/stomach" and "sentinel lymph node" and the subject terms "near-infrared/NIR or fluorescent imaging" and "indocyanine green/ICG" (as well as all free words, synonyms, and MeSH words) were used. Electronic databases such as PubMed, Embase, Medline, Web of Science, and the Cochrane Library were searched for relevant literature in any language, the search period was from the establishment of the database to the present, and the search was expanded according to the corresponding references. If the original data in the literature were incomplete or missing, the original author was contacted by email to request the original or missing data.

Literature inclusion and exclusion criteria

The inclusion criteria for patients were as follows: (1) Had surgically resectable gastric cancer [clinical T stage of the tumor (cT) 0-3]; (2) had a clinical stage of the tumor determined by at least two imaging examinations; (3) had a diagnostic accuracy test of SLN biopsy guided by ICG combined with optical imaging (near infrared imaging and fluorescence imaging); (4) had prospective studies to predict lymph node metastasis in gastric cancer; (5) had intraoperative or postoperative pathological biopsies performed on all lymph nodes removed during surgery; and (6) had > 10 patients statistically analyzed in the literature.

The exclusion criteria for patients were as follows: (1) Had a history of drug allergy or chemoradiotherapy; (2) had previously undergone endoscopic mucosal resection or endoscopic submucosal dissection; (3) had multiple digestive tract neoplasms; (4) had case reports, conference abstracts, clinical guidelines, editorials, reviews, meta-analyses or letters; (5) had previously undergone in vitro and animal experiments; and (6) had insufficient diagnostic efficiency data.

Literature screening and data extraction

The literature screening was carried out independently by two literature evaluators, and the final inclusion of the literature was decided after discussion by the two scholars. When there was disagreement, a third senior researcher participated in the discussion to make a decision. After the qualified literature was selected, the author, publication year, country, number of patients, age, sex, clinical T stage of the tumor, tumor diameter, ICG concentration, injection site, surgical method, lymph node dissection method, optical imaging equipment type, and pathological staining method were extracted [immunohistochemical (IHC)], hematoxylin-eosin (HE) staining, SLN detection method, sensitivity, specificity, and other information.

Literature quality evaluation

The quality of diagnostic tests was evaluated *via* the QUADAS-2. The evaluation indicators included the following: (1) Case selection: Whether cases were consecutively included and whether case-control design was avoided; (2) test to be evaluated: Whether to interpret the test results to be evaluated without knowing the gold standard test results (blind method); (3) gold standard test: Whether the gold standard test results are interpreted without knowing the test results to be evaluated (blind method) and whether the gold standard test can correctly diagnose the target disease; and (4) trial process and progress: Whether the interval between the trial to be evaluated and the gold standard test is appropriate, whether all subjects receive the same gold standard test, and whether all subjects are included in the statistical analysis.

Statistical methods analysis

Stata 12.0 software was used for the analysis with the "bivariable mixed effect model" combined with the "midas" command. The true positive value, false positive value, false negative value, true negative value, and other information from the included literature were extracted. A literature quality assessment map was drawn to describe the overall quality of the included literature. The heterogeneity of the forest map was analyzed, and $P < 0.01$ was considered to indicate statistical significance. A funnel plot was used to assess publication bias, and $P < 0.1$ was considered to indicate statistical significance. The area under the curve (AUC) calculated by the integrated receiver operating curve method (SROC) describes the diagnostic accuracy. The closer the AUC is to 1, the greater the diagnostic accuracy is; that is, the greater the diagnostic value of SLN biopsy guided by optical imaging combined with ICG is. If there was interstudy

heterogeneity (I^2 > 50%), meta-regression analysis and subgroup analysis were performed, and P < 0.05 was considered to indicate statistical significance. The effect measures used in this meta-analysis included sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, combined AUC value (SROC), and 95%CI.

RESULTS

Included literature and literature quality evaluation

Fifteen studies[6-20] were included in this study, and a total of 1020 patients were included. The literature screening process is shown in Figure 1. Optical imaging equipment includes two methods: Near-infrared (NIR) imaging and fluorescence imaging. The tumor stage included cT1-3. The pathological staining used was IHC + HE or HE alone. The basic characteristics of the included studies are shown in Table 1. A literature quality evaluation revealed that among the 15 included studies, only 3 explicitly stated "continuously included cases"[16,19,20]. Only 2 articles explicitly stated that "interpretation results were interpreted blindly"[6,18], which reduced the overall quality of the included literature and presented a high risk of bias. The literature quality assessment is shown in Figure 2.

Main index results and heterogeneity test

The combined sensitivity of all studies was 0.95 (95%CI: 0.82-0.99), the specificity was 1.00 (95%CI: 0.92-1.00), the positive likelihood ratio was 30.39 (95%CI: 9.14-101.06), and the negative likelihood ratio was 0.05 (95%CI: 0.92-0.99), with a diagnostic odds ratio of 225.54 (95%CI: 88.81-572.77). A heterogeneity test of sensitivity and specificity (Q test) was performed, and the heterogeneity among the included studies was statistically significant (P < 0.001). The sensitivity (I^2) was 89.41%, and the specificity (I^2) was 97.82%, indicating significant heterogeneity (Figure 3).

Diagnostic accuracy and publication bias

The plotted SROC curve did not show an "arm and arm" distribution, indicating that there was no significant threshold effect (actual threshold difference among the included studies). The AUC was 1.00 (95%CI: 0.99-1.00), and the critical values were a sensitivity of 0.95 (95%CI: 0.82-0.99) and a specificity of 1.00 (95%CI: 0.92-1.00). The "diagnostic odds ratio" of SLN biopsy for gastric cancer patients was analyzed with a funnel plot, the asymmetry test of the funnel plot was performed *via* the Deeks method, and the asymmetry of the funnel plot was found to be significant (P = 0.01), indicating significant publication bias (Figure 4).

Meta-regression and subgroup analysis

Surgical techniques for SLN biopsy of gastric cancer: Compared with fluorescence imaging, NIR imaging can achieve greater sensitivity (0.98 *vs* 0.73). Compared with optical imaging immediately after ICG injection, optical imaging after 20 minutes obtained greater sensitivity (0.98 *vs* 0.70). Compared with that of patients with an average SLN detection number < 4, the sensitivity of patients with a SLN detection number ≥ 4 was greater (0.96 *vs* 0.68). Compared with HE staining, IHC + HE staining had greater sensitivity (0.99 *vs* 0.84). Compared with subserous injection of ICG, submucosal injection achieved greater sensitivity (0.98 *vs* 0.40). Compared with 5 g/L ICG, 0.5 and 0.05 g/L ICG had significantly greater sensitivities (0.98 *vs* 0.83) (P < 0.05). However, there was no significant difference in sensitivity between laparotomy and laparoscopy, lymph node regional dissection, or dissection (all P > 0.05).

Patient characteristics: Compared with CT2-3 patients, cT1 patients achieved greater sensitivity (0.96 *vs* 0.72, P = 0.02), while there was no significant difference in sensitivity between patients with a tumor diameter ≤ 30 mm and patients with a tumor diameter > 30 mm (P > 0.05). Number of patients and reference year: Compared with the sample size of ≤ 26 patients, the sensitivity of > 26 patients was greater (0.96 *vs* 0.65). Compared with that in the literature published before 2010, the sensitivity in the literature published after 2010 was greater (0.97 *vs* 0.81), and the differences were statistically significant (all P < 0.05; Table 2).

DISCUSSION

Since the beginning of the 21st century, personalized minimally invasive surgery to preserve the function of the stomach has not only been proposed as a new surgical strategy for gastric cancer but also as an urgent requirement for accurate preoperative staging of gastric cancer[21]. Following the traditional SLN biopsy technique for gastric cancer, optical imaging combined with ICG-guided SLN biopsy of gastric cancer has gradually been included in clinical studies, so it is necessary to objectively evaluate its diagnostic accuracy[22-24]. In this meta-analysis, 1020 patients were included, and a systematic review revealed that the clinical feasibility of this diagnostic technique was good. However, there were differences in several operational technical criteria in the included literature, and the heterogeneity of sensitivity and specificity was significant among the included studies. Therefore, meta-regression and subgroup analysis were used to further explore the factors that may affect diagnostic accuracy.

Optical imaging technology uses near-infrared fluorescence at 700-900 nm, which has the advantages of real-time, low intrinsic fluorescence, and high tissue penetration[25-27]. According to Cabrera *et al*[28], fluorescence imaging may be superior to infrared imaging because the tissue structure image it produces is clearer[28]. It was also mentioned in the included literature that even if individual lymph nodes were not stained, fluorescence technology could be used for

Table 1 Basic characteristics of 15 included literature

Ref.	Year	Country	Cases	Average age (years)	Sex (male/female)	CT staging	Average tumor diameter (mm)	ICC concentration (g/L)	Average number of SLN detections	Sensitivity (%)	Specific (%)
Nimura *et al*[6]	2004	Japan	84	_	_	T1-2	_	5	10.5	100	59.7
Ishikawa *et al*[7]	2007	Japan	16	57.0	8/8	T1-2	21.0	5	2.9	50.0	100
Ohdaira *et al*[8]	2007	Japan	52	59.7	37/15	T1	_	5	_	100	100
Kusano *et al*[9]	2008	Japan	22	67.7	9/13	T1-3	_	5	3.6	40.0	100
Koyama *et al*[10]	2009	Japan	14	56.9	9/5	T1	26.0	5	7.1	100	100
Ohdaira *et al*[11]	2009	Japan	30	62.9	23/7	T1-2	42.6	5	4.8	100	100
Tajima *et al*[12]	2009	Japan	56	68.4	30/26	T1-3		5	7.2	64.7	100
Kelder *et al*[13]	2010	Japan	212	60.0	159/53	T1	30.0	5	6.0	97.0	100
Tajima *et al*[14]	2010	Japan	38	64.3	25/13	T1-2	33.8	5	7.9	75.0	100
Yano *et al*[15]	2012	Japan	130	_	_	T1-2	_	0.5	_	100	86.8
Kinami *et al*[16]	2016	Japan	72	69.3	44/28	T1-3	27.6	0.05	6.0	90.9	100
Takahashi *et al*[17]	2016	Japan	36	_	_	T1-2		5	9.2	100	100
Takahashi *et al*[18]	2017	Japan	44	60.9	3519	T1	24.8	5	7.9	100	100
Kim *et al*[19]	2019	South Korea	28	56.8	16/12	T1	16.0	_	_	100	92.3
Okubo *et al*[20]	2018	Japan	17	_	_	T1-2	19.6	_	4.5	100	100

ICC: Intraclass correlation coefficient; SLN: Sentinel lymph node; ICG: Indocyanine green; CT: Clinical T stage of the tumor.

effective imaging. However, meta-subgroup analysis revealed that NIR imaging has greater sensitivity than fluorescence imaging (0.98 *vs* 0.73). The reason may be the background scattering of fluorescence imaging, leading to a high false negative rate[29]. Therefore, we recommend that NIR imaging be used more in clinical studies[30-32]. However, it is worth noting that with the development of optical imaging technology, fluorescence molecular imaging and intraoperative multimodal imaging technology may be more commonly applied in the clinic in the future. In the included literature, to obtain a good deposition effect, surgeons mostly adopt optical imaging 20 minutes after ICG injection with high sensitivity. Subgroup analysis also revealed that imaging 20 minutes after injection yielded greater sensitivity than imaging immediately after injection[33]. However, if the interval is longer than 20 min, the diagnostic accuracy will be reduced. Therefore, to obtain good diagnostic results, NIR imaging should be performed 20 minutes after ICG injection during surgery[34].

If more SLN is obtained during SLN biopsy, the false negative rate of SLN biopsy for gastric cancer may be reduced. Meta-subgroup analysis suggested that a higher sensitivity could be obtained with an SLN detection number ≥ 4. This result indirectly reflects the complexity of the lymphatic system in gastric cancer; that is, multiple lymphatic drainage events can lead to multiple SLNS[35]. HE and IHC are currently the most widely used histopathological staining reagents. However, HE frequently misses lymph node micrometastasis[36]. Subgroup analysis revealed that IHC (+ HE) had greater sensitivity than HE staining. With increasing attention given to the concept of micrometastasis of isolated tumor cells, the advantages of continuous section technology and molecular diagnostic technology, which may become more reliable methods for intraoperative detection of lymph node metastasis and micrometastasis, are gradually becoming more prominent[37]. Yin *et al*'s study[38] showed that there was no significant difference between submucosal ICG injection and subserosal injection. However, the meta-subgroup analysis in this paper suggested that submucosal injection achieves greater sensitivity[39]. Therefore, this study suggested that submucosal injection may be more advant-

Table 2 Meta-subgroup analysis of the sensitivity-based bivariable mixed effects model

Influencing factor	Number	Sensitivity (95%CI)	*P* value
Optical imaging			< 0.001
Near infrared imaging	10	0.98 (0.96-1.00)	
Fluorescence imaging	7	0.73 (0.56-0.91)	
Image time			< 0.001
20 minutes after injection	10	0.98 (0.96-1.00)	
Immediately after injection	5	0.70 (0.54-0.86)	
Average number of SLNS detected			0.010
≥ 4	12	0.96 (0.90-1.00)	
< 4	3	0.68 (0.20-1.00)	
Pathological staining			< 0.001
IHC + HE	7	0.99 (0.98-1.00)	
HE	10	0.84 (0.70-0.98)	
Injection site			< 0.001
Submucosal injection	14	0.98 (0.95-1.00)	
Subserous injection	2	0.40 (0.18-0.62)	
ICG concentration (g/L)			0.010
5	12	0.83 (0.80-0.89)	
0.5	3	0.98 (0.93-1.00)	
Operation for gastric cancer			0.460
Laparotomy	8	0.95 (0.86-1.00)	
Laparoscopic surgery	9	0.96 (0.88-1.00)	
Cleaning method			0.200
Lymph node regional dissection	14	0.96 (0.89-1.00)	
Lymph node dissection	3	0.96 (0.87-1.00)	
Clinical stage of tumor			0.200
cT1	13	0.96 (0.92-1.00)	
cT2-3	4	0.72 (0.41-1.00)	
Tumor diameter (mm)			0.160
≤ 30	8	0.96 (0.91-1.00)	
> 30	3	0.81 (0.64-0.98)	

SLN: Sentinel lymph node; ICG: Indocyanine green; IHC: Immunohistochemical; HE: Hematoxylin-eosin staining; cT: Clinical T stage of the tumor.

ageous and may be more suitable for early gastric cancer. The recommended concentration for SLN biopsy in breast cancer patients is 0.625 g/L[40]. For gastric cancer, the ICG concentrations used in the included studies were 5 g/L, 0.5 g/L, and 0.05 g/L. Meta-subgroup analysis indicated that higher sensitivity could be obtained at 0.5 or 0.05 g/L ICG than at 5 g/L. These results suggest that high ICG concentrations may reduce optical image recognition. Moreover, excessive concentrations of ICG may have been used in recent SLN biopsy studies of gastric cancer.

In this meta-analysis, there was no statistically significant difference between open and laparoscopic SLN biopsy for gastric cancer ($P = 0.460$). This may be due to the many differences between the application, operation techniques. In this meta-analysis, there was no significant difference between lymph node dissection and lymph node extraction ($P = 0.200$). Therefore, it is not yet possible to determine the optimal gastric cancer surgery and lymph node dissection in an SLN biopsy of gastric cancer patients. The diagnostic accuracy of a reaction-guided SLN biopsy for gastric cancer was negatively correlated with cT. The clinical stages of gastric cancer included in the literature included in this paper were cT1-3, and subgroup analysis also suggested that early gastric cancer can be more sensitive. This may be because advanced gastric cancer cells are more likely to block lymphatic vessels, and new lymphatic vessels also increase the

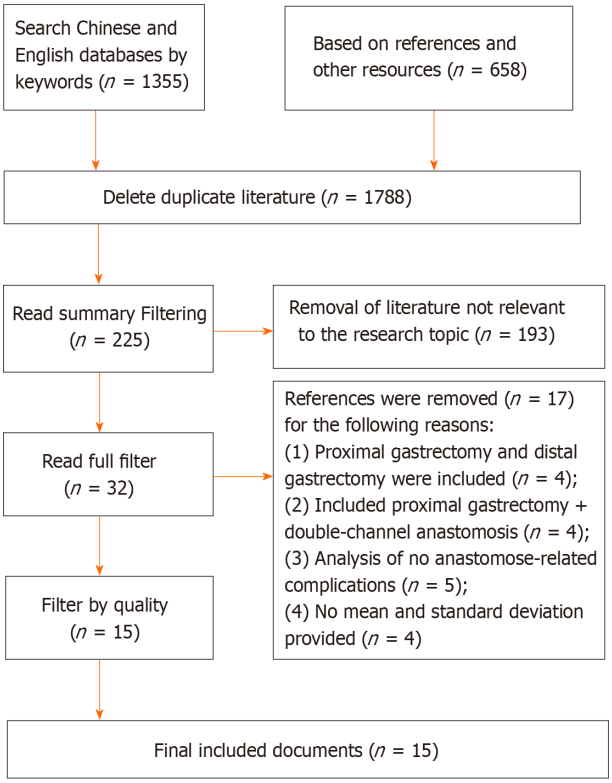


Figure 1 Literature screening flow chart.

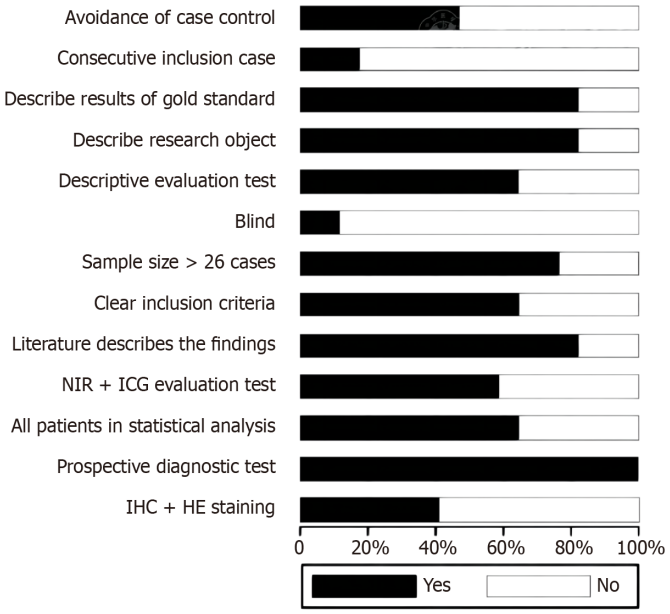


Figure 2 Document quality assessment map. NIR: Near-infrared; ICG: Indocyanine green; IHC: Immunohistochemical; HE: Hematoxylin-eosin staining.

complexity of the lymphatic system. Therefore, the SLN biopsy technique for gastric cancer may be more suitable for early gastric cancer. It is generally believed that the greater the diameter of a gastric cancer tumor is, the greater the degree of invasion and the later the clinical T stage. The average tumor diameter reported in the included literature was mostly < 50 mm, so 30 mm was used as the critical point for grouping in this paper[41]. However, subgroup analysis indicated that there was no statistically significant difference in SLN biopsy sensitivity between the two groups with different tumor diameters. Therefore, it is uncertain whether tumor diameter affects diagnostic accuracy.

There are some limitations to this paper. First, the Deeks funnel plot suggested obvious publication bias. Second, most of the eligible literature was submitted by Japanese scholars, which showed regional bias. Finally, the original data (true positive value, false positive value, false negative value, and true negative value) were mainly presented by the number of patients in the included literature, and the data on the number of lymph nodes could not be effectively extracted, so

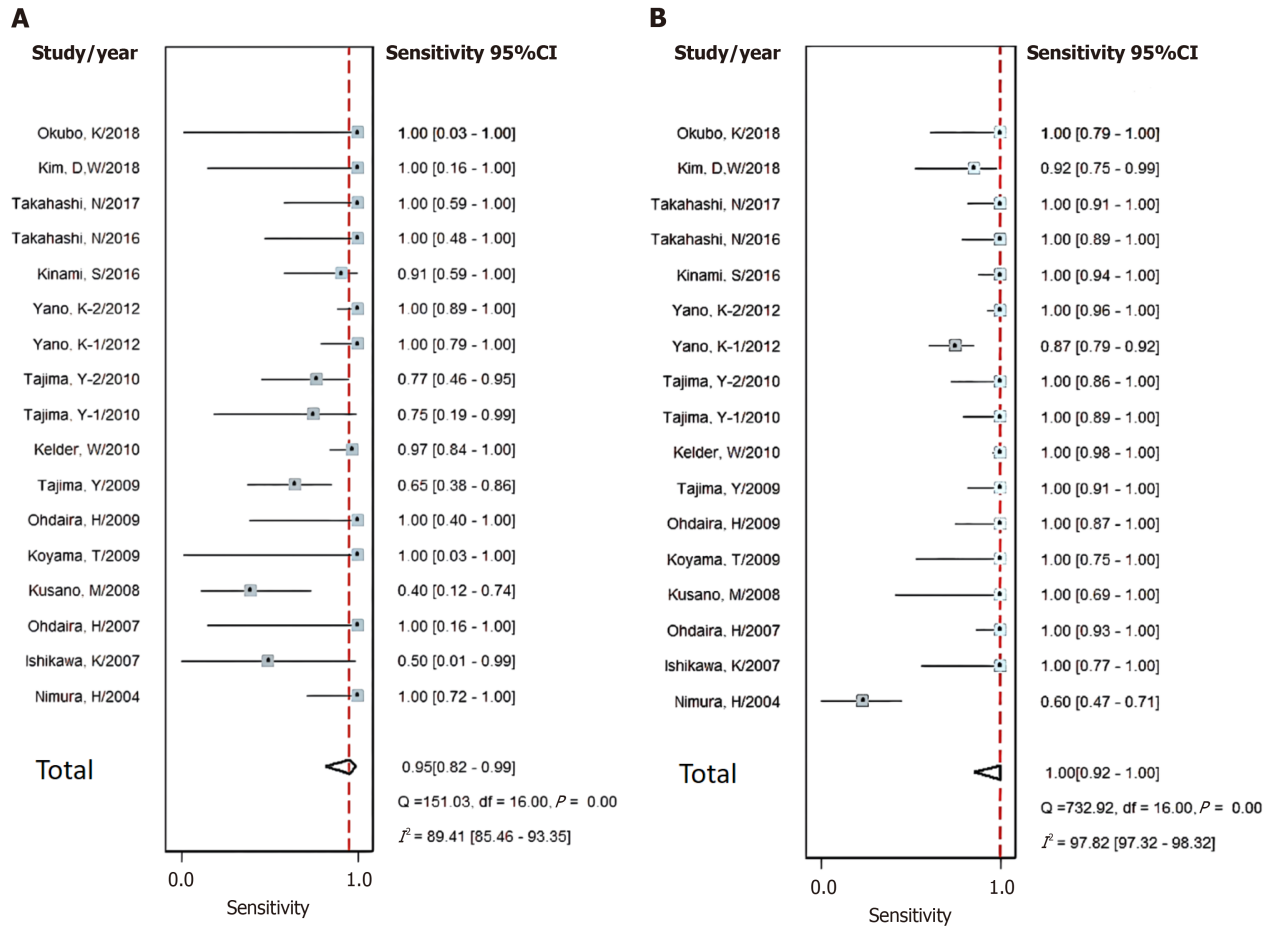


Figure 3 Forest map. A: Included document sensitivity forest map; B: Forest plot with reference specificity.

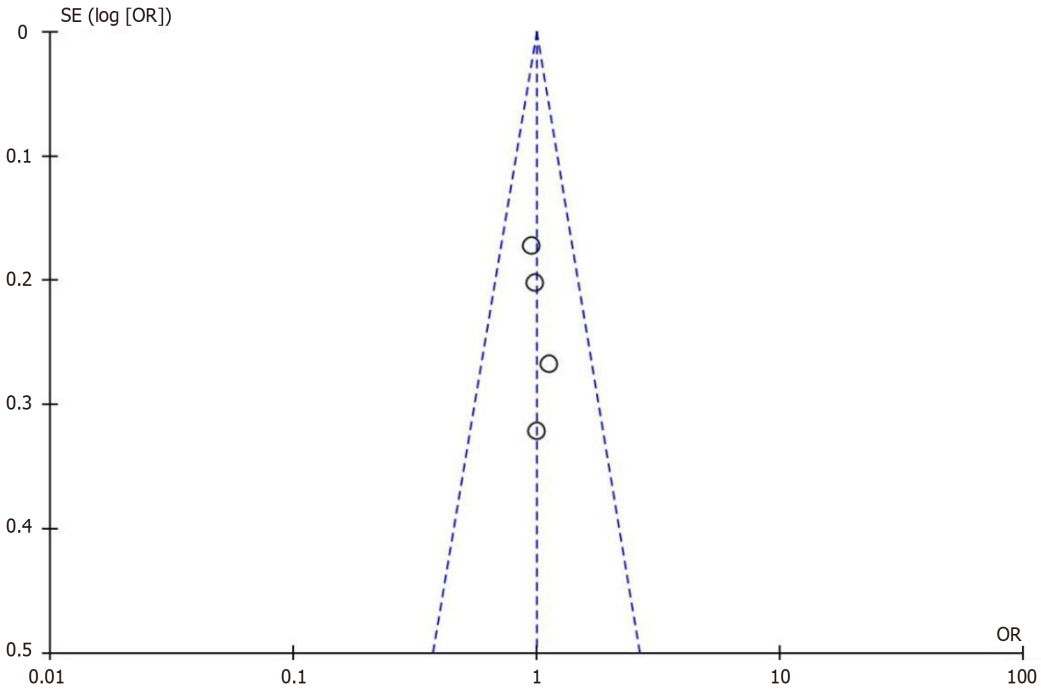


Figure 4 Funnel plot of the diagnostic odds ratio for gastric cancer patients who underwent sentinel lymph node biopsy. OR: Odds ratio.

there was result-reporting bias. In addition, factors such as the small number of included studies and the lack of large-scale multicenter studies may also affect the quality of the evidence in this meta-analysis.

CONCLUSION

In summary, according to the satisfactory results of systematic evaluation of sensitivity and specificity, optical imaging combined with an ICG-guided SLN biopsy of gastric cancer is a feasible clinical diagnostic method, especially for early gastric cancer. Current studies on SLN biopsy in gastric cancer patients may use excessively high concentrations of ICG. Near-infrared imaging may be superior to fluorescence imaging for obtaining higher sensitivity. However, more effective and trustworthy large-scale multicenter studies are still necessary to confirm these findings.

FOOTNOTES

Author contributions: Zhang QJ wrote the manuscript; Cao ZC, Zhu Q, Sun Y and Li RD collected the data; Tong JL and Zheng Q guided the study. Both Tong JL and Zheng Q have played important and indispensable roles in the experimental design, data interpretation and manuscript preparation as the co-corresponding authors. Tong JL applied for and obtained the funds for this research project. Tong JL conceptualized, designed, and supervised the whole process of the project. He searched the literature, revised and submitted the early version of the manuscript. Zheng Q was instrumental and responsible for data re-analysis and re-interpretation, figure plotting, comprehensive literature search, preparation and submission of the current version of the manuscript. This collaboration between Tong JL and Zheng Q is crucial for the publication of this manuscript and other manuscripts still in preparation. All authors reviewed, edited, and approved the final manuscript and revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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REFERENCES

1 **Bargon CA**, Huibers A, Young-Afat DA, Jansen BAM, Borel-Rinkes IHM, Lavalaye J, van Slooten HJ, Verkooijen HM, van Swol CFP, Doeksen A. Sentinel Lymph Node Mapping in Breast Cancer Patients Through Fluorescent Imaging Using Indocyanine Green: The INFLUENCE Trial. *Ann Surg* 2022; **276**: 913-920 [PMID: 35894448 DOI: 10.1097/SLA.0000000000005633]

2 **Zammarrelli WA 3rd**, Afonso AM, Broach V, Sonoda Y, Zivanovic O, Mueller JJ, Leitao MM Jr, Chan A, Abu-Rustum NR. Sentinel lymph node biopsy in patients with endometrial cancer and an indocyanine green or iodinated contrast reaction - A proposed management algorithm. *Gynecol Oncol* 2021; **162**: 262-267 [PMID: 33992449 DOI: 10.1016/j.ygyno.2021.05.009]

3 **Nakamura Y**, Takada M, Imamura M, Higami A, Jiaxi H, Fujino M, Nakagawa R, Inagaki Y, Matsumoto Y, Kawaguchi K, Kawashima M, Suzuki E, Toi M. Usefulness and Prospects of Sentinel Lymph Node Biopsy for Patients With Breast Cancer Using the Medical Imaging Projection System. *Front Oncol* 2021; **11**: 674419 [PMID: 34123842 DOI: 10.3389/fonc.2021.674419]

4 **Wu L**, Li X, Qian X, Wang S, Liu J, Yan J. Lipid Nanoparticle (LNP) Delivery Carrier-Assisted Targeted Controlled Release mRNA Vaccines in Tumor Immunity. *Vaccines (Basel)* 2024; **12** [PMID: 38400169 DOI: 10.3390/vaccines12020186]

5 **Raffone A**, Raimondo D, Raspollini A, Oliviero A, Travaglino A, Renzulli F, Rovero G, Del Forno S, Vullo G, Laganà AS, Chiantera V, Seracchioli R, Casadio P, Mollo A. Comparison between Laparoscopic and Robotic Approach for Sentinel Lymph Node Biopsy in Endometrial Carcinoma Women. *J Pers Med* 2022; **13** [PMID: 36675690 DOI: 10.3390/jpm13010029]

6 **Nimura H**, Narimiya N, Mitsumori N, Yamazaki Y, Yanaga K, Urashima M. Infrared ray electronic endoscopy combined with indocyanine green injection for detection of sentinel nodes of patients with gastric cancer. *Br J Surg* 2004; **91**: 575-579 [PMID: 15122608 DOI: 10.1002/bjs.4470]

7 **Ishikawa K**, Yasuda K, Shiromizu A, Etoh T, Shiraishi N, Kitano S. Laparoscopic sentinel node navigation achieved by infrared ray electronic endoscopy system in patients with gastric cancer. *Surg Endosc* 2007; **21**: 1131-1134 [PMID: 17180275 DOI: 10.1007/s00464-006-9062-2]

8 **Ohdaira H**, Nimura H, Mitsumori N, Takahashi N, Kashiwagi H, Yanaga K. Validity of modified gastrectomy combined with sentinel node navigation surgery for early gastric cancer. *Gastric Cancer* 2007; **10**: 117-122 [PMID: 17577622 DOI: 10.1007/s10120-007-0419-6]

9 **Kusano M**, Tajima Y, Yamazaki K, Kato M, Watanabe M, Miwa M. Sentinel node mapping guided by indocyanine green fluorescence imaging: a new method for sentinel node navigation surgery in gastrointestinal cancer. *Dig Surg* 2008; **25**: 103-108 [PMID: 18379188 DOI:

10.1159/000121905]
10 **Koyama T**, Nimura H, Narimiya N, Mori Y, Ikegami M, Mitsumori N, Yanaga K. Validity of the infrared ray method for sentinel node biopsy in gastric cancer. *Jikeikai Med J* 2009; **56**: 57-62
11 **Ohdaira H**, Nimura H, Takahashi N, Mitsumori N, Kashiwagi H, Narimiya N, Yanaga K. The possibility of performing a limited resection and a lymphadenectomy for proximal gastric carcinoma based on sentinel node navigation. *Surg Today* 2009; **39**: 1026-1031 [PMID: 19997796 DOI: 10.1007/s00595-009-3993-x]
12 **Tajima Y**, Yamazaki K, Masuda Y, Kato M, Yasuda D, Aoki T, Kato T, Murakami M, Miwa M, Kusano M. Sentinel node mapping guided by indocyanine green fluorescence imaging in gastric cancer. *Ann Surg* 2009; **249**: 58-62 [PMID: 19106676 DOI: 10.1097/SLA.0b013e3181927267]
13 **Kelder W**, Nimura H, Takahashi N, Mitsumori N, van Dam GM, Yanaga K. Sentinel node mapping with indocyanine green (ICG) and infrared ray detection in early gastric cancer: an accurate method that enables a limited lymphadenectomy. *Eur J Surg Oncol* 2010; **36**: 552-558 [PMID: 20452171 DOI: 10.1016/j.ejso.2010.04.007]
14 **Tajima Y**, Murakami M, Yamazaki K, Masuda Y, Kato M, Sato A, Goto S, Otsuka K, Kato T, Kusano M. Sentinel node mapping guided by indocyanine green fluorescence imaging during laparoscopic surgery in gastric cancer. *Ann Surg Oncol* 2010; **17**: 1787-1793 [PMID: 20162462 DOI: 10.1245/s10434-010-0944-0]
15 **Yano K**, Nimura H, Mitsumori N, Takahashi N, Kashiwagi H, Yanaga K. The efficiency of micrometastasis by sentinel node navigation surgery using indocyanine green and infrared ray laparoscopy system for gastric cancer. *Gastric Cancer* 2012; **15**: 287-291 [PMID: 22041868 DOI: 10.1007/s10120-011-0105-6]
16 **Kinami S**, Oonishi T, Fujita J, Tomita Y, Funaki H, Fujita H, Nakano Y, Ueda N, Kosaka T. Optimal settings and accuracy of indocyanine green fluorescence imaging for sentinel node biopsy in early gastric cancer. *Oncol Lett* 2016; **11**: 4055-4062 [PMID: 27313740 DOI: 10.3892/ol.2016.4492]
17 **Takahashi N**, Nimura H, Fujita T, Yamashita S, Mitsumori N, Yanaga K. Quantitative assessment of visual estimation of the infrared indocyanine green imaging of lymph nodes retrieved at sentinel node navigation surgery for gastric cancer. *BMC Surg* 2016; **16**: 35 [PMID: 27245664 DOI: 10.1186/s12893-016-0152-3]
18 **Takahashi N**, Nimura H, Fujita T, Mitsumori N, Shiraishi N, Kitano S, Satodate H, Yanaga K. Laparoscopic sentinel node navigation surgery for early gastric cancer: a prospective multicenter trial. *Langenbecks Arch Surg* 2017; **402**: 27-32 [PMID: 27999935 DOI: 10.1007/s00423-016-1540-y]
19 **Kim DW**, Jeong B, Shin IH, Kang U, Lee Y, Park YS, Ahn SH, Park DJ, Kim HH. Sentinel node navigation surgery using near-infrared indocyanine green fluorescence in early gastric cancer. *Surg Endosc* 2019; **33**: 1235-1243 [PMID: 30167947 DOI: 10.1007/s00464-018-6401-z]
20 **Okubo K**, Uenosono Y, Arigami T, Matsushita D, Yanagita S, Kijima T, Amatatsu M, Ishigami S, Maemura K, Natsugoe S. Quantitative assessment of fluorescence intensity of ICG in sentinel nodes in early gastric cancer. *Gastric Cancer* 2018; **21**: 776-781 [PMID: 29516211 DOI: 10.1007/s10120-018-0816-z]
21 **Chen Y**, Xiao Q, Zou W, Xia C, Yin H, Pu Y, Wang Y, Zhang K. Sentinel lymph node biopsy in oral cavity cancer using indocyanine green: A systematic review and meta-analysis. *Clinics (Sao Paulo)* 2021; **76**: e2573 [PMID: 34287476 DOI: 10.6061/clinics/2021/e2573]
22 **Patel N**, Allen M, Arianpour K, Keidan R. The utility of ICG fluorescence for sentinel lymph node identification in head and neck melanoma. *Am J Otolaryngol* 2021; **42**: 103147 [PMID: 34237540 DOI: 10.1016/j.amjoto.2021.103147]
23 **Wu L**, Zheng Y, Liu J, Luo R, Wu D, Xu P, Wu D, Li X. Comprehensive evaluation of the efficacy and safety of LPV/r drugs in the treatment of SARS and MERS to provide potential treatment options for COVID-19. *Aging (Albany NY)* 2021; **13**: 10833-10852 [PMID: 33879634 DOI: 10.18632/aging.202860]
24 **Baldari L**, Boni L, Cassinotti E. Lymph node mapping with ICG near-infrared fluorescence imaging: technique and results. *Minim Invasive Ther Allied Technol* 2023; **32**: 213-221 [PMID: 37261486 DOI: 10.1080/13645706.2023.2217916]
25 **Wang B**, Xue Y, Wang Q, Xu Y, Chen X, Wang C. Sentinel Lymph Node Mapping and Biopsy for Endometrial Cancer at Early Stage with Laparoscopy. *J Vis Exp* 2021 [PMID: 34487124 DOI: 10.3791/63044]
26 **Wu L**, Li H, Liu Y, Fan Z, Xu J, Li N, Qian X, Lin Z, Li X, Yan J. Research progress of 3D-bioprinted functional pancreas and in vitro tumor models. *Int J Bioprint* 2024; **10**: 1256 [DOI: 10.36922/ijb.1256]
27 **Pineda VG**, Zapardiel I, Gracia M, Siegrist J, Diestro MD, Alonso M, Hernández A. Avoiding Full Lymphadenectomies in Intermediate- and High-Risk Endometrial Cancer by Sentinel Lymph Node Biopsy Implementation. *Front Oncol* 2021; **11**: 654285 [PMID: 33937061 DOI: 10.3389/fonc.2021.654285]
28 **Cabrera S**, Barahona-Orpinell M, Almansa-González C, Padilla-Iserte P, Bebia V, Martí L, Tejerizo-García Á, Domingo S, Gil-Moreno A. Combined use of ICG and technetium does not improve sentinel lymph node detection in endometrial cancer: Results of the COMBITEC study. *Gynecol Oncol* 2021; **162**: 32-37 [PMID: 33992451 DOI: 10.1016/j.ygyno.2021.05.002]
29 **Kim JH**, Ku M, Yang J, Byeon HK. Recent Developments of ICG-Guided Sentinel Lymph Node Mapping in Oral Cancer. *Diagnostics (Basel)* 2021; **11** [PMID: 34067713 DOI: 10.3390/diagnostics11050891]
30 **Wu L**, Zhong Y, Wu D, Xu P, Ruan X, Yan J, Liu J, Li X. Immunomodulatory Factor TIM3 of Cytolytic Active Genes Affected the Survival and Prognosis of Lung Adenocarcinoma Patients by Multi-Omics Analysis. *Biomedicines* 2022; **10** [PMID: 36140350 DOI: 10.3390/biomedicines10092248]
31 **Hua B**, Li Y, Yang X, Ren X, Lu X. Short-term and long-term outcomes of indocyanine green for sentinel lymph node biopsy in early-stage breast cancer. *World J Surg Oncol* 2022; **20**: 253 [PMID: 35941602 DOI: 10.1186/s12957-022-02719-7]
32 **Wu L**, Chen X, Zeng Q, Lai Z, Fan Z, Ruan X, Li X, Yan J. NR5A2 gene affects the overall survival of LUAD patients by regulating the activity of CSCs through SNP pathway by OCLR algorithm and immune score. *Heliyon* 2024; **10**: e28282 [PMID: 38601554 DOI: 10.1016/j.heliyon.2024.e28282]
33 **Wang C**, Tong F, Cao Y, Liu P, Zhou B, Liu H, Cheng L, Liu M, Guo J, Xie F, Yang H, Wang S, Peng Y, Wang S. Long-term follow-up results of fluorescence and blue dye guided sentinel lymph node biopsy in early breast cancer. *Breast Cancer Res Treat* 2021; **188**: 361-368 [PMID: 33761081 DOI: 10.1007/s10549-021-06196-6]
34 **Wu L**, Liu Q, Ruan X, Luan X, Zhong Y, Liu J, Yan J, Li X. Multiple Omics Analysis of the Role of RBM10 Gene Instability in Immune Regulation and Drug Sensitivity in Patients with Lung Adenocarcinoma (LUAD). *Biomedicines* 2023; **11** [PMID: 37509501 DOI: 10.3390/biomedicines11071861]
35 **Sánchez-Izquierdo N**, Vidal-Sicart S, Campos F, Torné A, Angeles MA, Migliorelli F, Munmany M, Saco A, Diaz-Feijoo B, Glickman A,

Ordi J, Perissinotti A, Del Pino M, Paredes P. Detection of the sentinel lymph node with hybrid tracer (ICG-[(99m)Tc]Tc-albumin nanocolloid) in intermediate- and high-risk endometrial cancer: a feasibility study. *EJNMMI Res* 2021; **11**: 123 [PMID: 34905122 DOI: 10.1186/s13550-021-00863-x]

36 **Yang R**, Dong C, Jiang T, Zhang X, Zhang F, Fan Z. Indocyanine Green and Methylene Blue Dye Guided Sentinel Lymph Node Biopsy in Early Breast Cancer: A Single-Center Retrospective Survival Study in 1574 Patients. *Clin Breast Cancer* 2023; **23**: 408-414 [PMID: 36907808 DOI: 10.1016/j.clbc.2023.02.002]

37 **Wu L**, Zhong Y, Yu X, Wu D, Xu P, Lv L, Ruan X, Liu Q, Feng Y, Liu J, Li X. Selective poly adenylation predicts the efficacy of immunotherapy in patients with lung adenocarcinoma by multiple omics research. *Anticancer Drugs* 2022; **33**: 943-959 [PMID: 35946526 DOI: 10.1097/CAD.0000000000001319]

38 **Yin R**, Ding LY, Wei QZ, Zhou Y, Tang GY, Zhu X. Comparisons of ICG-fluorescence with conventional tracers in sentinel lymph node biopsy for patients with early-stage breast cancer: A meta-analysis. *Oncol Lett* 2021; **21**: 114 [PMID: 33376546 DOI: 10.3892/ol.2020.12375]

39 **Kang B**, Lee JH, Lee J, Jung JH, Kim WW, Chu G, Chae Y, Lee SJ, Lee IH, Yang JD, Lee JS, Park HY. Comparative Study Between Radioisotope Uptake and Fluorescence Intensity of Indocyanine Green for Sentinel Lymph Node Biopsy in Breast Cancer. *J Breast Cancer* 2022; **25**: 244-252 [PMID: 35775703 DOI: 10.4048/jbc.2022.25.e27]

40 **Wu L**, Zheng Y, Ruan X, Wu D, Xu P, Liu J, Wu D, Li X. Long-chain noncoding ribonucleic acids affect the survival and prognosis of patients with esophageal adenocarcinoma through the autophagy pathway: construction of a prognostic model. *Anticancer Drugs* 2022; **33**: e590-e603 [PMID: 34338240 DOI: 10.1097/CAD.0000000000001189]

41 **Cwalinski T**, Skokowski J, Polom W, Marano L, Swierblewski M, Drucis K, Roviello G, Cwalina N, Kalinowski L, Roviello F, Polom K. Fluorescence Imaging Using Methylene Blue Sentinel Lymph Node Biopsy in Melanoma. *Surg Innov* 2022; **29**: 503-510 [PMID: 35225083 DOI: 10.1177/15533506221074601]

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SCIENTOMETRICS

Visualizing the landscape of appendiceal tumor research after 2010: A bibliometric study

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Abstract

BACKGROUND

Despite the rarity of appendiceal tumors, research in this field has intensified, resulting in a growing number of studies and published papers. Surprisingly, no comprehensive bibliometric analysis has specifically addressed appendiceal tumors.

AIM

To offer a thorough analysis of the current landscape and future trends in appendiceal tumor research.

METHODS

In our bibliometric analysis studies, we explored the Web of Science Core Collection database. The bibliographic details of the chosen publications were automatically converted and analyzed using the bibliometric package in the R environment. Additionally, we employed VoSviewer to create cooperation network maps for countries, institutions, and authors, as well as clustering maps for keywords. Furthermore, CiteSpace, another software tool, was utilized to build dual-map overlays of journals and analyze references with citation bursts.

RESULTS

Our study included 780 English-language articles published after 2010. The number of related publications and citations has increased in the past decade. The United States leads in this area, but there is a need to improve cooperation and communication among countries and institutions. Co-occurrence analysis also revealed close collaboration among different authors. *Annals of Surgical Oncology* was the most influential journal in this field. Analysis of references with high co-citations and references with citation bursts, consistent with analysis of keywords and hotspots, indicated that current research primarily centers on the classification and management of appendiceal mucinous neoplasms and consequent

pseudomyxoma peritonei. Despite the abundance of clinical studies, a greater number of in-depth basic research studies should be conducted.

CONCLUSION

Current research on appendiceal tumors focuses on classification and management of appendiceal mucinous neoplasms and pseudomyxoma peritonei. Enhanced collaboration and basic research are vital for further advancement.

Key Words: Appendiceal tumor; Appendix; Mucinous neoplasms; Bibliometric analysis; Pseudomyxoma peritonei

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Core Tip: In this bibliometric study, we reviewed both the top 10 most co-cited references and 10 references with citation bursts, which helped us better understand the foundation of research in this area and the revolution of research hotspots and frontiers in the perspective of the timeline. The findings showed that scholars had more interest in the classification and management of appendiceal tumors. We believe that maintaining consistency in their classification is advantageous for more precise management. Therefore, we have visualized the classification and summarized the management of appendiceal tumors based on different classifications.

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INTRODUCTION

Appendiceal tumors are not common, with only 0.12 cases per million people. They are often discovered incidentally during an appendectomy for acute appendicitis[1]. The classification of this tumor has been historically varied and confusing. For instance, Connor *et al*[2] categorized appendiceal tumors as benign, carcinoid, and primary malignant, while Van de Moortele *et al*[3] divided them into the following four subtypes: Colonic-type adenocarcinoma; mucinous neoplasm; goblet cell carcinoma; and neuroendocrine neoplasm. Despite being uncommon, research into this tumor continues to deepen, with an increasing number of studies and published papers from various perspectives. Therefore, establishing a knowledge framework about appendiceal tumors and identifying the research hotspots and trends is necessary to guide future studies.

Bibliometric analysis is a reliable and commonly used method for tracking trends in a specific field over time. This approach employs literature metrics to assess contributions and forecast future developments using tools such as CiteSpace[4], VoSviewer[5], and R package "bibliometrix"[6]. Bibliometric analysis has found extensive application in various fields of medical research, such as in ophthalmology[7], rheumatology[8], oncology[9], and dermatology[10]. However, no bibliometric analysis has yet focused on appendiceal tumors. To provide a comprehensive analysis of the current state of research in this area, we conducted an in-depth investigation using data from the Web of Science Core Collection (WoSCC). Our findings illuminate the development and contributions in appendiceal tumor research as well as potential future focal points in this field.

MATERIALS AND METHODS

Literature search and screening

We searched the WoSCC database to conduct bibliometric analysis studies. All searches were completed on September 25, 2023. The filtering strategy was set to ((((TI = (tumor)) OR TI = (neoplasm)) OR TI = (carcinoma)) OR TI = (cancer)) AND (((TI = (appendiceal)) OR TI = (appendix))). The inclusion criteria were as follows: (1) Language: English; and (2) Publication years: 2010-2023. A total of 1472 publications were included and assessed *via* the exclusion criteria of letters, editorial materials, corrections, books, data sets, proceedings papers, retractions, and retracted publications. Finally, 780 publications were retrieved. Full records and cited references of all the publications that met the inclusion and exclusion criteria were exported and downloaded as plain text files.

Data analyses and visualization

All the available information of these screened publications was downloaded from WoSCC. The bibliographic details of the selected publications were automatically converted and analyzed using the bibliometric package (v3.0.0) in the R environment (v4.3.2). The bibliometric package was used to extract and analyze the following information: Title; author;

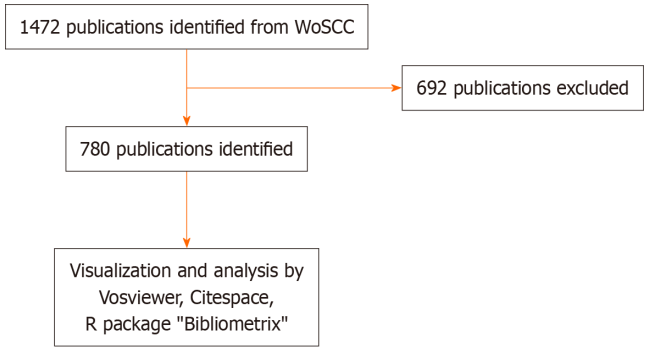


Figure 1 Publications screening flowchart. A total of 1472 publications were included according to the filtering strategy and inclusion criteria. Then, 692 publications were excluded according to exclusion criteria of letters, editorial materials, corrections, books, data sets, proceedings papers, retractions, and retracted publications. In total, 780 publications were retrieved. WoSCC: Web of Science Core Collection.

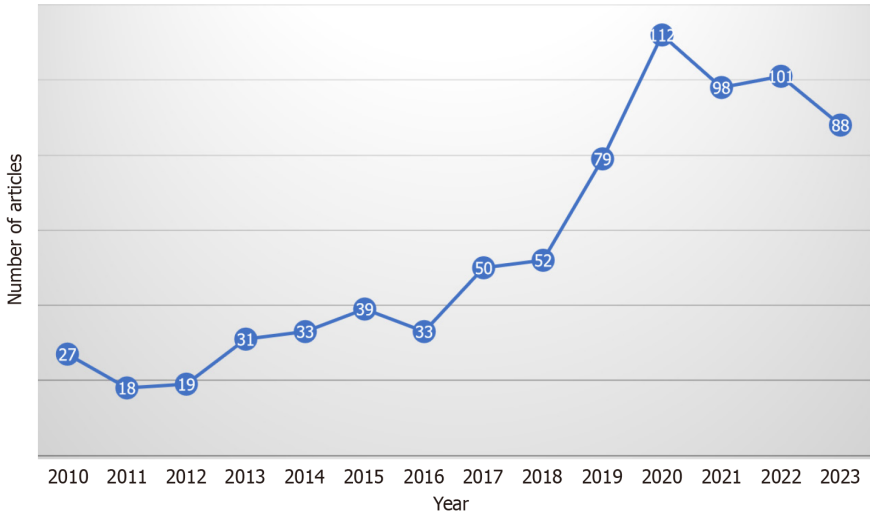


Figure 2 Annual output of appendiceal tumor research. Each point represents the number of papers published in the respective year.

institution; country or region; total number of citations; year of publication; journal; keyword; and impact factor (IF). The IF was represented by the H-index, a high citation index proposed by Hirsch[11] in 2005 as a quantitative evaluation method of academic achievements. VoSviewer (v1.6.19) was utilized to generate the cooperation network map of countries, institution, authors, and keyword clustering[12]. CiteSpace (v6.2.4), a software developed by Synnestvedt *et al* [4] for bibliometric analysis and visualization, was applied to map the dual-map overlay of journals and to analyze references with citation bursts. Additionally, Microsoft Office Excel 2019 was used to conduct quantitative analysis of publication.

RESULTS

Analysis of publication and citations

A total of 780 related publications from January 2010 to September 2023 were finally retrieved (Figure 1), including 670 "articles" and 110 "reviews". Figure 2 presents the annual number of publications. It was evident that literature was limited and grew slowly from 2010 to 2016, while the number of publications increased significantly between 2016 and 2020. After 2020, this number became stable and hovered at around 100 per year.

The total citations from these 780 publications was 10133, and average citations per document was 12.99. The number of citations for 780 manuscripts is 338 (43.33%) for 1-9 citations, 245 (31.41%) for 10-99 citations, and 10 (1.28%) for more than 100 citations (Figure 3). A total of 187 (23.97%) manuscripts never received citations in other publications, with 88 of them being published in 2023. In 2000, *The Pancreas* published the article with the most citations, 352 in total[13]. As a consensus guideline, this paper elaborated the diagnosis and treatment of neuroendocrine tumors (NETs), including those occurring in the appendix. In addition, we filtered out the publications with the most citations and listed them in Table 1.

Table 1 Top 10 publications with the most citations in appendiceal tumor research

Title	Publication year	Total citations
The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the Jejunum, Ileum, Appendix, and Cecum	2010	352
ENETS Consensus Guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas	2012	298
Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma: the 3d English Edition	2019	276
ENETS Consensus Guidelines for Neuroendocrine Neoplasms of the Appendix (Excluding Goblet Cell Carcinomas)	2016	160
The histopathological classification, diagnosis and differential diagnosis of mucinous appendiceal neoplasms, appendiceal adenocarcinomas and pseudomyxoma peritonei	2017	138
ENETS Consensus Guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas	2012	132
Frequent GNAS mutations in low-grade appendiceal mucinous neoplasms	2013	118
Clinicopathologic and molecular analysis of disseminated appendiceal mucinous neoplasms: identification of factors predicting survival and proposed criteria for a three-tiered assessment of tumor grade	2014	108
The rise in appendiceal cancer incidence: 2000-2009	2015	102
Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in 1000 patients with perforated appendiceal epithelial tumours	2016	100

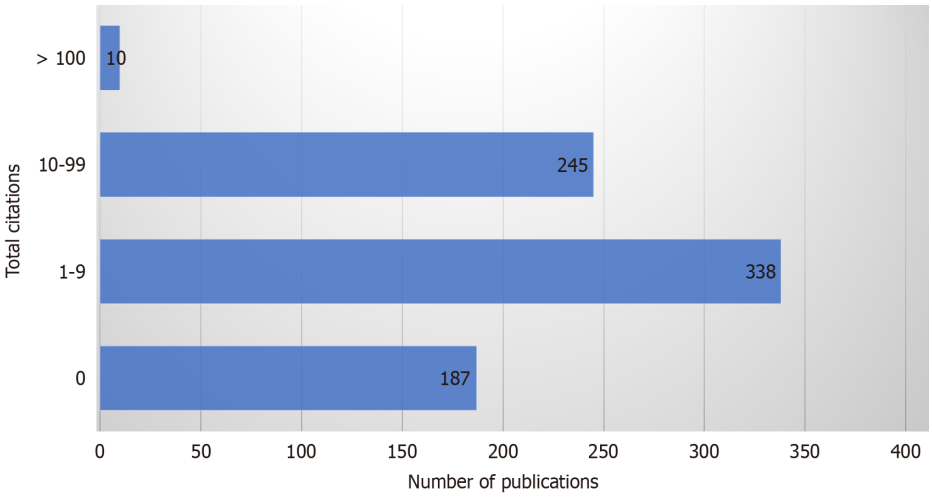


Figure 3 Number of publications by different total citations. The bars of different length correspond to the number of papers in different total citation ranges.

Analysis of countries and institutions

Overall, all these manuscripts came from 67 countries or regions and 1212 institutions. First, we visualized the geographic distribution of countries or regions contributing to this field of research and built a collaborative network based on the number of publications and connections in each country or region (Figure 4). Countries or regions in this visual network contributed at least two relative publications. In this study, nine clusters were created, each colored differently. Larger nodes indicated a higher frequency, while thicker lines indicated a higher degree of collaboration. Notably, there was a lot of active cooperation between different countries. For example, China had active cooperation with Japan and Germany, and Belgium, Denmark, Turkey, and Israel had close cooperation with each other.

We subsequently analyzed the countries or regions and institutions of these manuscripts to identify the high-impact studies. From all 60 countries, the United States contributed both the most publications (n = 427, 36.46%) and the highest number of citations (n = 6975, 49.91%). The top 10 high-yield countries were distributed in Europe (n = 5), North America (n = 2), and Asia (n = 2). Table 2 showed the specific number of articles, total citations, and average article citations of these countries. The United Kingdom published the fourth most articles, but the average number of citations was the second highest. Germany, despite ranked 10th in terms of articles, it ranked 1st in terms of average citations. Therefore, these two countries conduct high-quality research. The top 10 high-yield research institutions are listed in Table 3. Nine of them are located in the United States, proving the country's prominent position in this field. We then screened 58 institutions with at least five publications and created a visualized network according to the collaborative relationships

Table 2 Top 10 countries on research of appendiceal tumors

Country	Articles	Total citations	Average article citations
United States	427	6975	16.3
China	98	460	4.7
Japan	84	556	6.6
United Kingdom	70	1497	21.4
Australia	48	455	9.5
Turkey	46	325	7.1
Italy	42	546	13
Canada	31	448	14.5
France	23	271	11.8
Germany	27	705	26.1

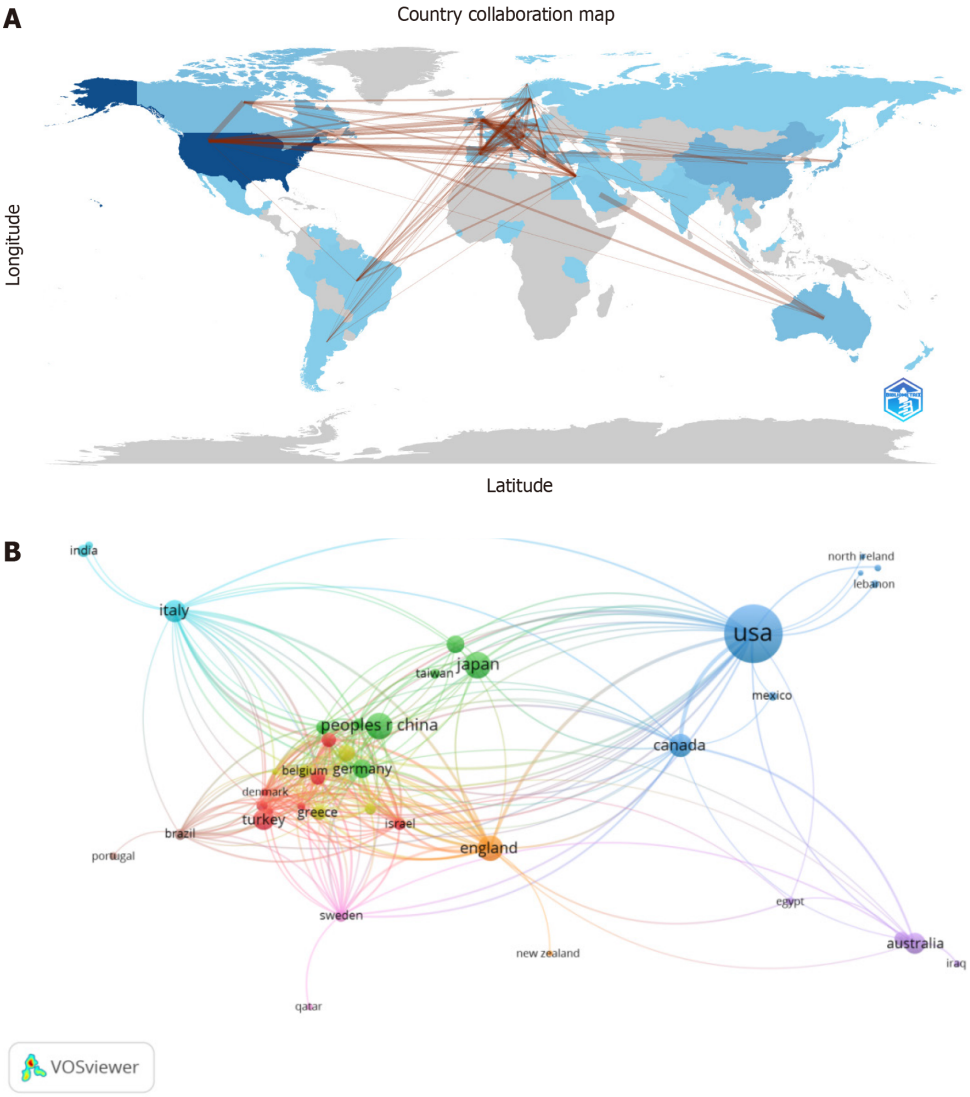


Figure 4 Geographical distribution and visualization of countries/regions. A: Intensity of the blue color represents publication count and thickness of the line represents cooperation intensity; B: Node size represents publication count, and link size indicates cooperation intensity.

Table 3 Top 10 institutions for research of appendiceal tumors

Institution	Articles	Citations
University of Texas MD Anderson Cancer Center	24	925
University of Pittsburgh	23	667
University of California, San Diego	19	342
Ohio State University	18	184
Mercy Medical Center	17	347
University of New South Wales	16	118
Mayo Clinic	13	181
Vanderbilt University	13	158
Emory University	12	191
Memorial Sloan Kettering Cancer Center	12	614

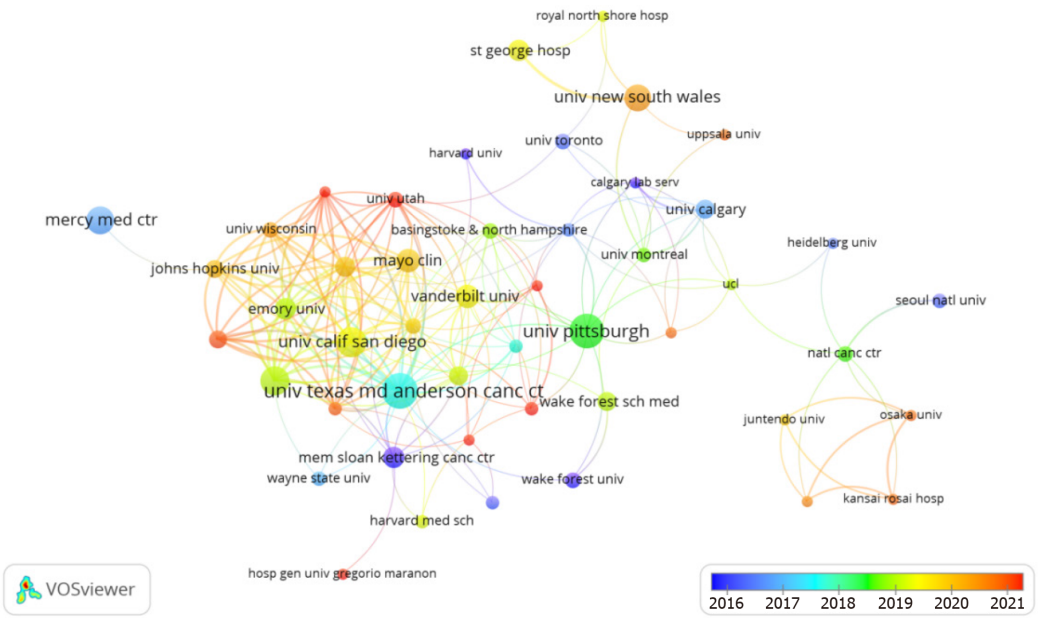


Figure 5 Collaboration network of institutions. Node size represents publication count, and link size indicates cooperation intensity. The time of contributions is presented by the brightness of the color.

among them. Figure 5 shows institutions as dots, with dot size indicating article count and connections showing cooperation. Six clusters were formed based on cooperation closeness. Figure 5 illustrates that the University of Texas MD Anderson Cancer Center served as a hub for collaboration, and the connections between institutions in America were exceptionally strong. In Asia, some institutions such as Osaka University, National Cancer Center (Korea), and Juntendo University also shared links with each other. However, it is evident that cross-continental cooperation remains relatively rare but should be strengthened in the future.

Journals and co-cited journals

In total, 226 journals published the 780 manuscripts. We identified the top 10 high-impact journals according to the H-index (Table 4). It was notable that *Annals of Surgical Oncology*, as the most influential journal, also published the most papers. We then selected 39 journals with at least five relevant publications and created a journal network map (Figure 6A). *Annals of Surgical Oncology* had active citation relationships with *Frontiers in Oncology*, *American Journal of Surgery*, and *Journal of Surgical Oncology*.

We also filtered journals with the minimum co-citation equal to 150 and mapped the co-citation network (Figure 6B). *Diseases of the Colon & Rectum* had positive co-citation relationships with *American Journal of Surgery*, *Annals of Surgical Oncology*, and *Journal of Gastrointestinal Surgery*. Using a dual-map overlay, citation relationships between journals and their co-cited journals were visualized, with citing journals on the left and cited journals on the right (Figure 7). The green path shown in Figure 7 represents the main citation path, indicating that research published in Health/Nursing/Medicine journals was mainly cited by literature in Medicine/Medical/Clinical journals.

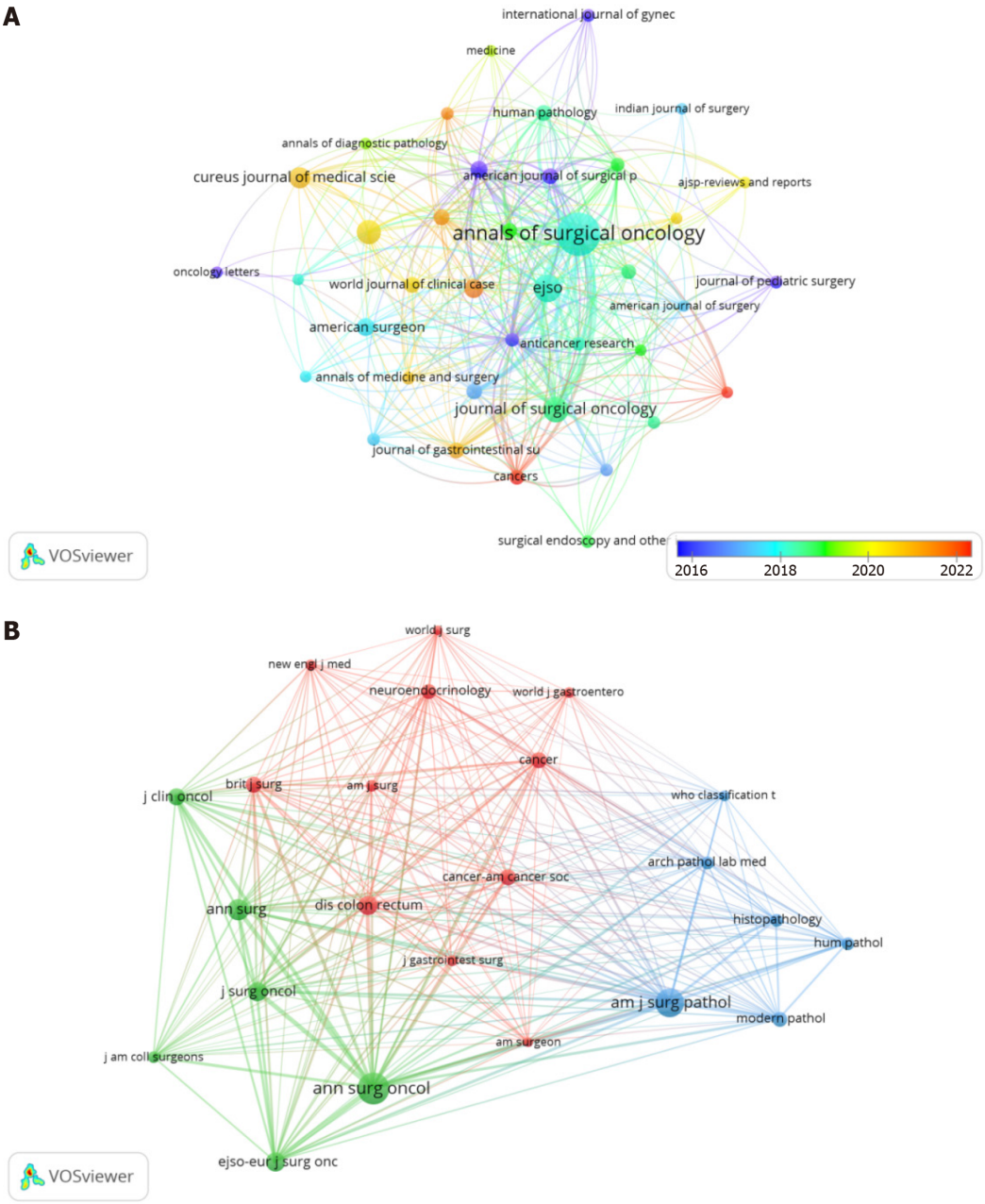


Figure 6 Network of journals and co-cited journals. A: Network of journals; B: Network of co-cited journals. Node size represents frequency of journal, and link size indicates cooperation intensity.

Authors and co-cited authors

In total, 4090 authors dedicated themselves to researching appendiceal tumors. In Table 5, we listed the top 10 high-impact authors according to H-index and the number of papers they have published. We also created a collaborative network based on authors who have published five or more papers (Figure 8A). Edward A Levine, Haroon A Choudry, Perry Shen, and David L Bartlett have the largest nodes due to their extensive publications on the topic. Additionally, we have noted significant collaboration among these authors, such as the close partnership between Edward A Levine and Perry Shen, as well as the active cooperation between Haroon A. Choudry and Reetesh K Pa and David L Bartlett.

Among the 6603 co-cited authors, 39 authors were co-cited more than 50 times. We visualized a co-citation network of these 39 authors. A large node in Figure 8B revealed that Paul H Sugarbaker is the most co-cited author (n = 493), followed by Norman J Carr (n = 481) and Joseph Misdraji (n = 281). Lines in Figure 8B showed that there were also active collaborations among different co-cited authors, such as R M Smeenk, Pierre Jacquet, and Daniel Elias.

Analysis of references

There were 8609 co-cited references on research of appendiceal tumor after 2010. 10 most co-cited references listed in Table 6 were co-cited at least 75 times, with the highest being cited 188 times. Citation bursts refer to references frequently cited by scholars in a specific field over time. In our study, CiteSpace identified 10 references with strong citation bursts (Figure 9). Citation bursts for references were observed from 2010 to 2023. "A Consensus for Classification and Pathologic

Table 4 Top 10 journals for research of appendiceal tumors

Journal	H-index	Articles	IF	Q
Annals of Surgical Oncology	22	67	3.7	2
European Journal of Surgical Oncology	13	28	3.8	2
Journal of Surgical Oncology	9	24	2.5	3
American Journal of Surgical Pathology	8	9	5.6	1
Archives of Pathology & Laboratory Medicine	8	11	4.6	2
Diseases of the Colon & Rectum	7	9	3.9	2
Neuroendocrinology	7	7	4.1	2
Histopathology	6	7	6.4	2
Journal of Pediatric Surgery	6	6	2.4	3
Journal of the American College of Surgeons	6	6	5.2	2

IF: Impact factor; Q: Quartile rankings by *Journal Citation Reports*.

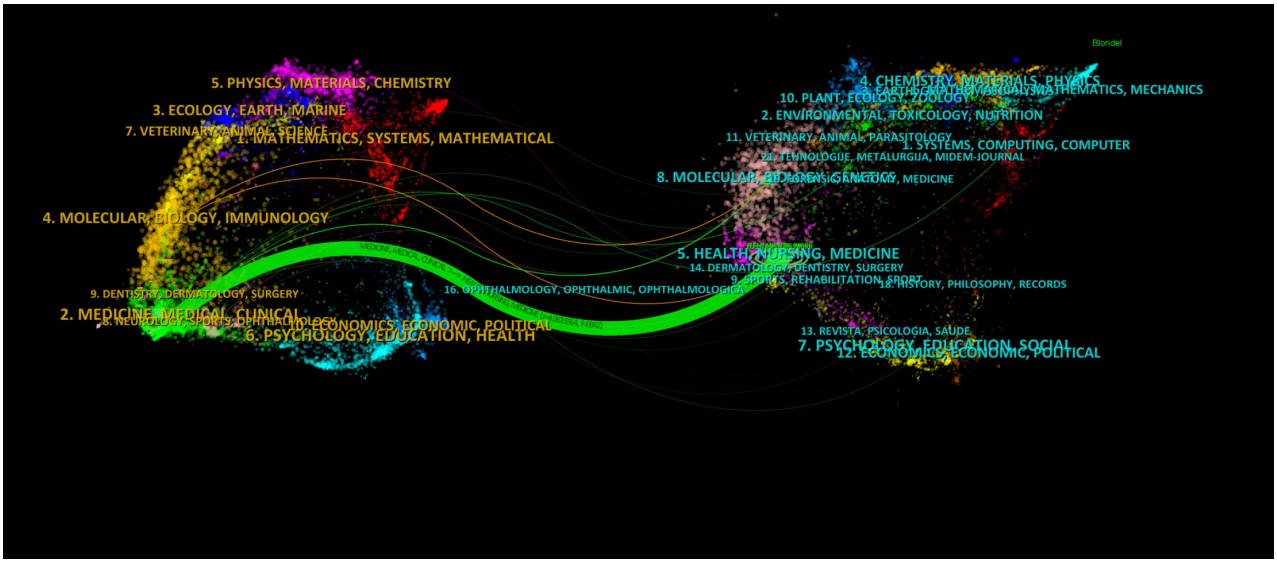


Figure 7 Dual-map overlay of journals. Clusters of citing journals on the left and clusters of cited journals on the right. The lines show relationships between the citing and cited journals. The thickest green curve represents the main citation path.

Reporting of Pseudomyxoma Peritonei and Associated Appendiceal Neoplasia: The Results of the Peritoneal Surface Oncology Group International (PSOGI) Modified Delphi Process" by Carr *et al*[28] received the strongest citation burst (strength = 28.59) which occurred between 2017 and 2021. "Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy" from Chua *et al*[34], hold the second place in citation burst (strength = 16.35) between 2013 and 2017.

Hotspots and frontiers

We identified 20 keywords with the highest co-occurring frequency, accurately capturing the research hotspots in appendiceal tumor research (Table 7). Pseudomyxoma peritonei (PMP) and cytoreductive surgery (CRS) were the most frequently mentioned keywords, indicating the main areas of research interest. Keywords with 50 or more occurrences were filtered and subjected to cluster analysis using VoSviewer (Figure 10A). The thickness of lines connecting nodes indicates the strength of the relationship between keywords. Three distinct clusters were identified, each representing a unique research direction. The green cluster encompassed keywords such as PMP, CRS, hyperthermic intraperitoneal chemotherapy (HIPEC), clinicopathological analysis, *etc*. The keywords in the red cluster included diagnosis, prognosis, management, right hemicolectomy, *etc*. The keyword in the blue cluster only included classification.

The analysis of keyword trends (Figure 10B) indicated that the development of appendiceal research can be roughly divided into three stages. In stage 1 (2014-2018), scholars focused on the origin and clinicopathological analysis of appendiceal tumors. In stage 2 (2018-2020), the focus shifted to the management of appendiceal tumors. In stage 3 (after

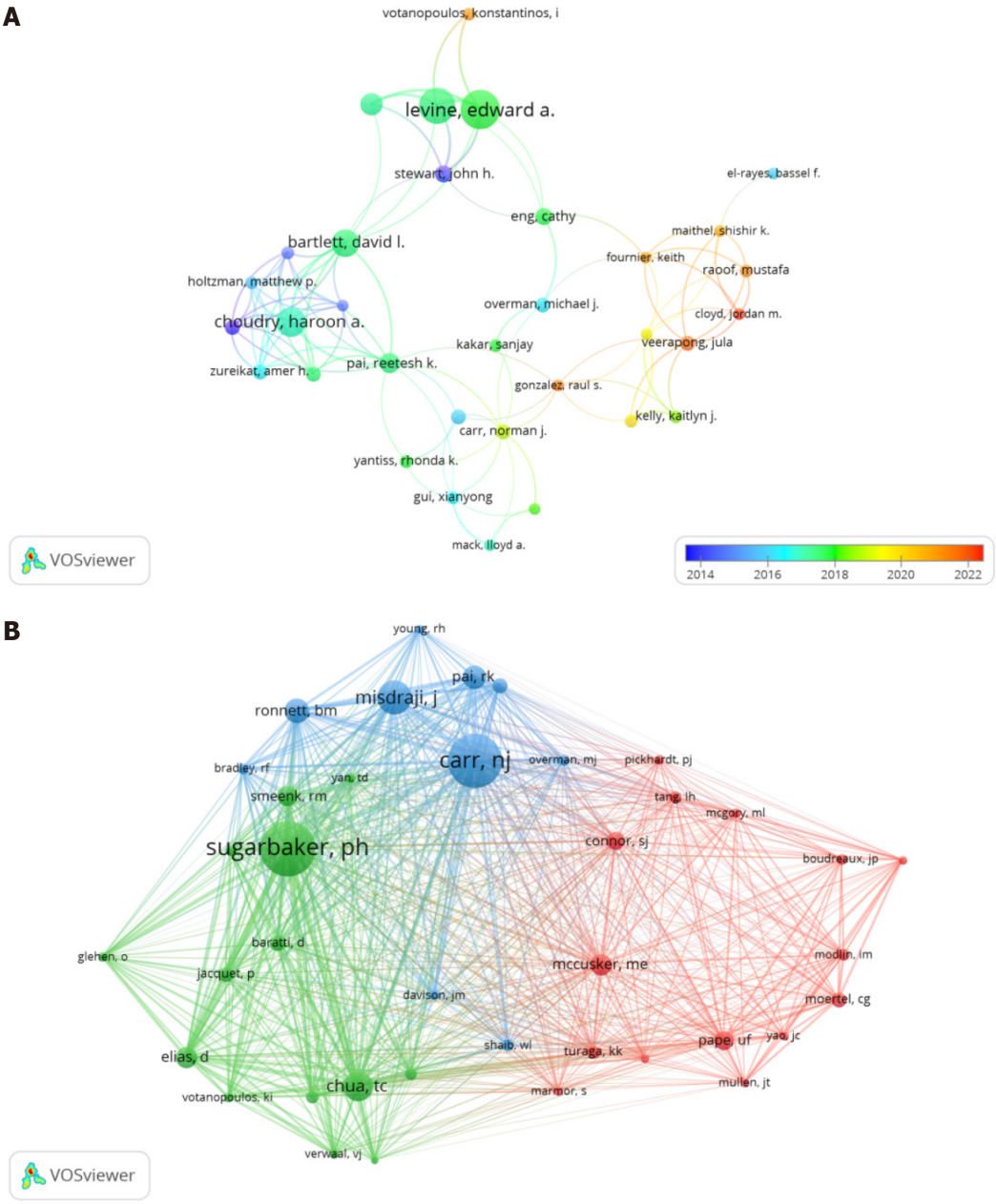


Figure 8 Collaboration network of authors and co-cited authors. A: Collaboration network of authors; B: Collaboration network of co-cited authors. Node size represents frequency of author, and link size indicates cooperation intensity.

2020), scholars turned their attention to the risks and outcomes associated with appendiceal tumors, which revealed the current research hotspots.

DISCUSSION

Our study analyzed 780 publications about appendiceal tumors published after 2010. Quantitative analysis of publications revealed that research on appendiceal tumors has gained increased attention since 2016 and has remained intense, with approximately 100 annual publications in recent years. Upon analyzing the citations, we discovered that most of these publications have been cited more than 10 times, demonstrating significant academic value. Moreover, the majority of the top 10 most cited articles are guidelines, indicating that our understanding of appendiceal tumors is still unclear and constantly evolving.

Combining the analysis of country and institution, we can easily conclude that the United States was the most productive country in this area, as it contributed the most publications and nine of the top ten high-yield institutions are located in the United States. China, despite being ranked second in the number of articles, had an average article citation of only 4.7. In contrast, Germany, ranked 10th in the number of articles, had the highest average number of citations. This comparison highlights the disparity in research quality between the two countries.

Table 5 Top 10 most influential authors according to the H-index

Author	H-index	Articles
Edward A Levine	12	22
David L Bartlett	10	15
Haroon A Choudry	10	15
Vadim Gushchin	10	21
Reetesh K Pai	10	11
Armando Sardi	10	21
Perry Shen	10	19
C Nieroda	9	16
Konstantinos I Votanopoulos	9	18
Brendan John Moran	8	10



Figure 9 Top 10 references with citation burst. The red bar represents the duration of strong citation burstiness. The burst strength represents the scientific value of the article.

Cooperation and communication between countries and institutions can alleviate such imbalances. In fact, cooperative relationships already exist between some countries and institutions, such as the close cooperation among European countries like the United Kingdom, Turkey, Denmark, and Germany. Similarly, there was tight communication among institutions in the United States, such as the University of Texas MD Anderson Cancer Center, Mayo Clinic, and the University of Pittsburgh. However, the breadth and intensity of cooperation is not yet ideal. For instance, there was only limited cooperation between institutions in Europe and Asia, potentially impeding the advancement of this research field over the long term. Consequently, we strongly recommend that institutions across various countries establish broad connections and cooperation to enhance the progress of research on appendiceal tumors.

Most appendiceal tumor research has been published in the *Annals of Surgical Oncology* (IF = 3.7, Q2), making it the most popular journal in this field. Among them, *Histopathology* had the highest IF (IF = 6.4, Q2), followed by the *American Journal of Surgery* (IF = 5.6, Q1). Co-cited journals mostly included high-impact Q1 journals, such as *Annals of Surgery* (IF = 9.0, Q1), *British Journal of Surgery* (IF = 9.6, Q1), and *Journal of Clinical Oncology* (IF = 45.3, Q1). Clearly, these are high-quality international journals that support appendiceal tumor research. Additionally, current appendiceal tumor research was primarily published in clinically related journals focused on Medicine, Medical, and Health, indicating a lack of basic research in the biology and molecular fields.

From our perspective, Edward A Levine appeared to be the most influential figure in this field due to his H-index and overall academic output. His research primarily focuses on the treatment of appendiceal neoplasms with peritoneal dissemination. In 2008, he reported that oxaliplatin could be utilized in intraperitoneal hyperthermic chemoperfusion for treating peritoneal surface dissemination from colorectal and appendiceal cancers[14]. In 2022, he assessed the therapeutic effects of HIPEC with an incomplete cytoreduction[15]. In his basic research, he was the first to employ gene

Table 6 Top 10 co-cited references in appendiceal tumor research

Co-cited reference	Citations
carr nj, 2016, am j surg pathol, v40, p14, doi 10.1097/pas.0000000000000535	188
mccusker me, 2002, cancer, v94, p3307, doi 10.1002/cncr.10589	163
connor sj, 1998, dis colon rectum, v41, p75, doi 10.1007/bf02236899	137
chua tc, 2012, j clin oncol, v30, p2449, doi 10.1200/jco.2011.39.7166	131
misdraji j, 2003, am j surg pathol, v27, p1089, doi 10.1097/00000478-200308000-00006	128
smeenk rm, 2008, ejso-eur j surg onc, v34, p196, doi 10.1016/j.ejso.2007.04.00	98
pai rk, 2009, am j surg pathol, v33, p1425, doi 10.1097/pas.0b013e3181af6067	97
ronnett bm, 1995, am j surg pathol, v19, p1390, doi 10.1097/00000478-199512000-00006	97
sugarbaker ph, 2006, lancet oncol, v7, p69, doi 10.1016/s1470-2045 (05)70539-8	77
carr nj, 2017, histopathology, v71, p847, doi 10.1111/his.13324	76

Table 7 Top 20 high-frequency keywords in appendiceal tumor research

Rank	Keyword	Counts
1	Pseudomyxoma peritonei	289
2	Appendix	192
3	Cytoreductive surgery	150
4	Neoplasms	149
5	Management	138
6	Hyperthermic intraperitoneal chemotherapy	135
7	Tumor	118
8	Origin	117
9	Classification	106
10	Survival	97
11	Clinicopathological analysis	96
12	Diagnosis	90
13	Carcinomatosis	84
14	Cancer	79
15	Adenocarcinoma	74
16	Carcinoid-tumors	65
17	Prognosis	64
18	Appendectomy	61
19	Mucocele	53
20	Systemic chemotherapy	52

expression profiling for appendiceal cancer and demonstrated genomic signatures confirming their unique biology[16].

Reetesh K Pa, in close collaboration with Haroon A Choudry, published several articles on the diagnosis, grading, staging, and histological features of different types of appendiceal cancer, particularly appendiceal mucinous neoplasms [17-19]. In fact, the majority of the articles by these 10 authors were focused on peritoneal dissemination/metastases and PMP, which has been convincingly linked to appendiceal mucinous neoplasms, indicating the hotspots and frontiers in appendiceal tumor research.

Paul H Sugarbaker and Norman J Carr, the most co-cited authors, have different research focuses. Paul H Sugarbaker primarily focuses on peritoneal malignant lesions, such as peritoneal metastases, PMP, and peritoneal mesothelioma[20-23]. Norman J Carr continually updates the classification, diagnosis, and treatment of various types of appendiceal cancer, including mucinous appendiceal neoplasms, appendiceal adenocarcinomas, and neuroendocrine neoplasms of the

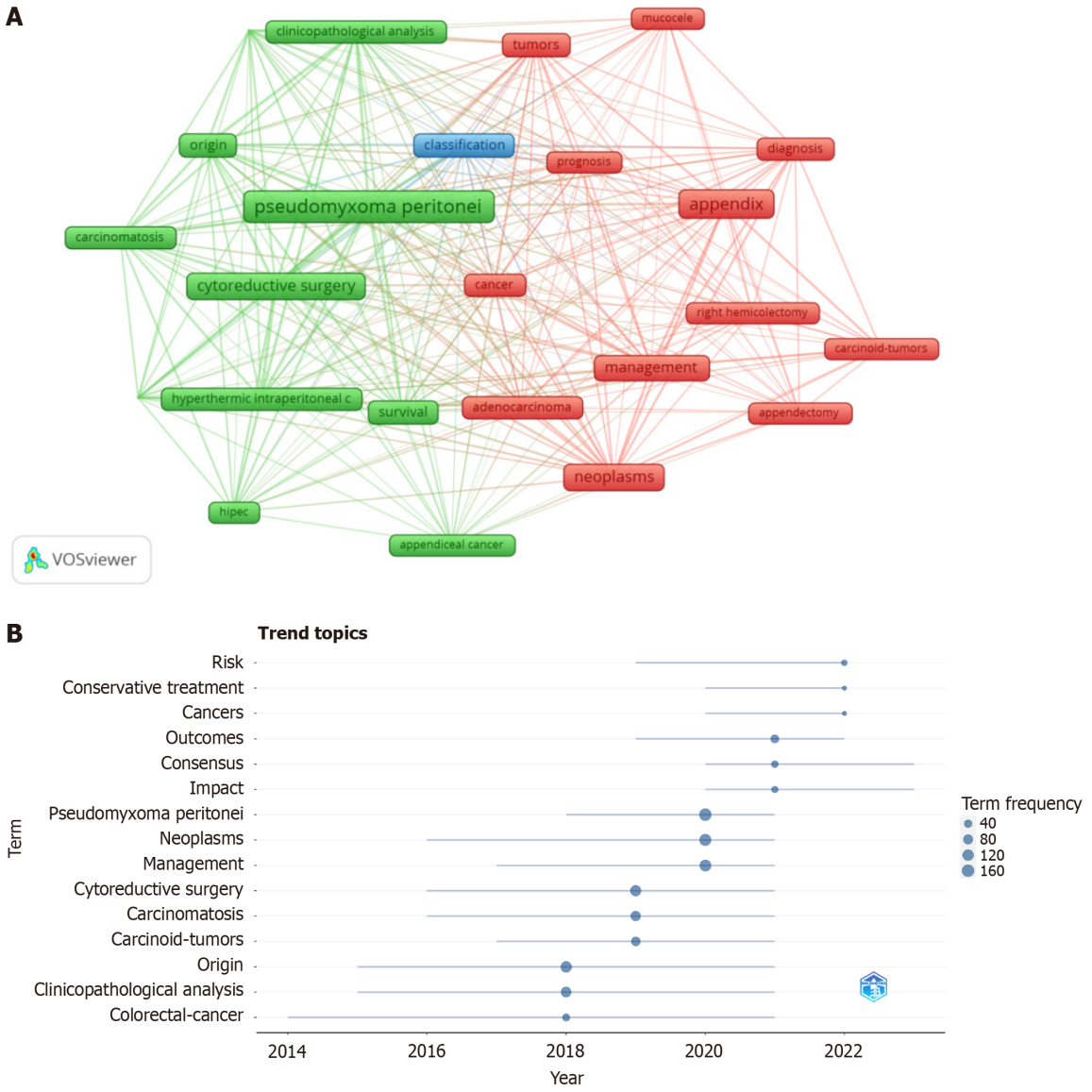


Figure 10 Keyword cluster analysis and trend topic analysis. A: Keyword cluster analysis. Frame size represents frequency of keyword, and each color represents a cluster; B: Trend topic analysis. Node size represents trend frequency, and line length represents the duration.

appendix[24-27]. The work of these two authors established the current consensus that PMP, the primary focus of research on appendiceal tumors, is a complex disease with distinct biological behavior that typically originates from appendiceal mucinous neoplasms[28].

Co-cited references are those that are cited by multiple publications and can be seen as the foundation of research in a particular field. In addition, citation burst references have been heavily cited in a certain time span, reflecting emerging research topics[29]. In this bibliometric study, we reviewed both the top 10 most co-cited references and 10 references with citation bursts, which helped us better understand the foundation of research in this area and the revolution of research hotpots and frontiers.

Early in 1990s, Ronnett *et al*[30] comprehensively described the pathologic features and prognosis of PMP, which was poorly understood at that time. They separated PMP into two diagnostic categories: Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis (PMCA). They identified the relationship with appendiceal mucinous adenoma and appendiceal mucinous adenocarcinoma, respectively. In 1998, Connor *et al*[2] conducted a retrospective clinicopathologic analysis of appendiceal tumors and classified appendiceal tumors into benign (adenoma), carcinoid/adenocarcinoid, and primary malignant (adenocarcinoma). It is interesting that there was very little overlap between these two early studies. This situation changed after entering the 21st century.

The concept of "mucinous" was becoming popular and controversial. McCusker *et al*[31] classified appendiceal tumors into "colonic type" adenocarcinoma, mucinous adenocarcinoma, signet ring cell carcinoma, goblet cell carcinoid, and "malignant carcinoid" in their population-based study in 2002. One year later, appendiceal mucinous neoplasms, one type of appendiceal tumor, was studied by Misdraji *et al*[32] and was divided into low-grade appendiceal mucinous neoplasm (LAMN), mucinous adenocarcinomas. In 2008, the connection between PMP and appendiceal tumors was formally strengthened through the bridge of appendiceal mucinous neoplasm. Smeenk *et al*[33] concluded that one-third of primary epithelial lesions of the appendix lesions are mucinous epithelial neoplasms and may progress into PMP.

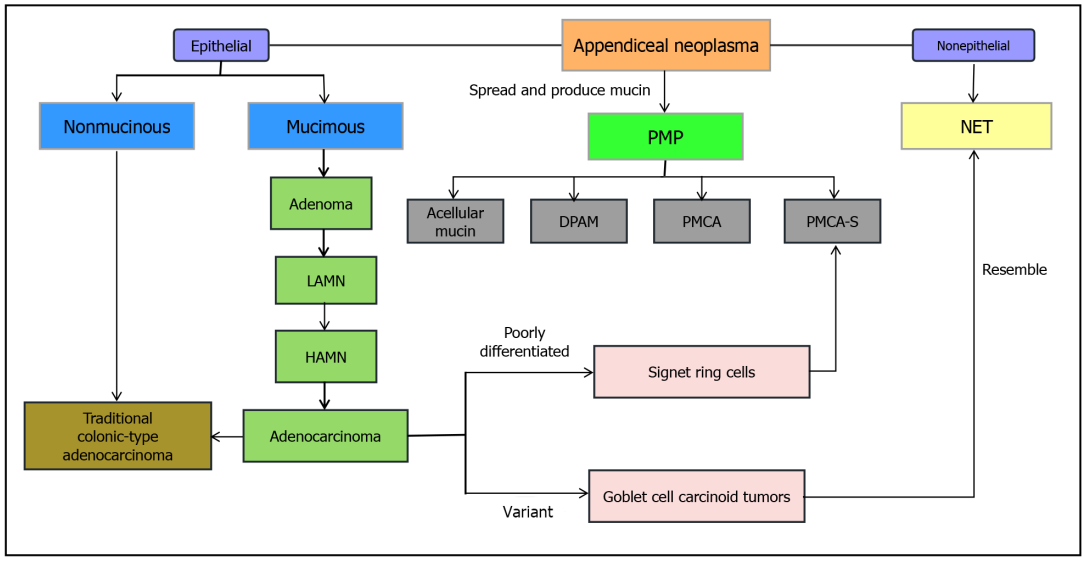


Figure 11 Classification of appendiceal neoplasm. Visualization of classification of appendiceal neoplasm according to influential references. PMP: Pseudomyxoma peritonei; DPAM: Disseminated peritoneal adenomucinosis; PMCA: Peritoneal mucinous carcinomatosis; PMCA-S: Peritoneal mucinous carcinomatosis with signet ring cells; NET: Neuroendocrine tumor; LAMN: Low-grade appendiceal mucinous neoplasm; HAMN: High-grade appendiceal mucinous neoplasm.

Since then, research has focused on PMP and associated appendiceal mucinous neoplasm. Sugarbaker[21] regarded CRS combined with HIPEC as a new standard of care for appendiceal mucinous neoplasms and PMP. The outcome data of this strategy was analyzed by Chua *et al*[34] in 2012. They proved that CRS and HIPEC was acceptable for PMP originating from appendiceal mucinous neoplasm. Furthermore, Fournier *et al*[35] concluded that LAMN have a lower risk for recurrence and clinical surveillance, and expectant management is a viable choice after radical resection.

Despite the evolution of the knowledge of appendiceal tumors and PMP, the classification of PMP and its primary appendiceal neoplasia is still contentious, especially for nomenclature and terminology. Carr *et al*[24] in 2017 and Carr *et al*[28] in 2016 published two consecutive papers attempting to standardize the histopathological classification and diagnosis of appendiceal tumor and PMP. These two papers were both high co-cited references and references with citation bursts, indicating the importance in this research area. In fact, these studies focused on PMP more, while the American Society of Colon and Rectal Surgeons provided clinical practice guidelines stating the classification of appendiceal neoplasms more clearly[36].

The frequent use of popular keywords and the changing trends in topics align with the development of co-cited references and references with citation bursts. Analysis of keywords and topic trends showed a growing scholarly interest in the categorization of appendiceal tumors as well as the risks and outcomes of various treatments like CRS and HIPEC. We believe that maintaining consistency in their classification is advantageous for more precise management. As a result, we have visualized the classification and summarized the management of appendiceal tumors based on different classifications through a literature review of the aforementioned references (Figure 11).

Epithelial appendiceal neoplasms

We hypothesize that the progression from adenoma to LAMN to high-grade appendiceal mucinous neoplasm (HAMN), and ultimately to adenocarcinoma, is a process of increasing invasiveness and cytological atypia. Adenoma is a cytologically bland mucinous neoplasm clearly confined to the appendix without extra-appendiceal mucin or neoplasia[37]. LAMNs are characterized by well-differentiated adenomas that can proliferate outside the appendix in a malignant fashion, and HAMNs share some histological features with LAMNs but exhibit more aggressive cytologic atypia[22]. Adenoma and LAMN without perforation or peritoneal involvement have shown very low recurrence rates after appendectomy[35]. Appendectomy alone is usually enough to treat HAMN, but care should be taken to rule out the presence of associated invasive adenocarcinoma[36]. Adenocarcinoma exhibits infiltrative invasion and poses a high risk, as the rate of metastatic disease to regional lymph nodes ranges from 20% to 67%[38]. Right hemicolectomy is recommended for nonmetastatic adenocarcinoma and goblet cell carcinoid of the appendix, which is considered a variant of adenocarcinoma with some features similar to traditional NETs[39,40].

Nonepithelial appendiceal neoplasms

Nonepithelial appendiceal neoplasms include NETs. Somatostatin receptor scintigraphy can be used to identify the foci of NETs[41]. Somatostatin receptor scintigraphy is also more sensitive for detection of well-differentiated NETs (*e.g.*, those expressing somatostatin receptors), whereas 2-[18F] fluoro-2-deoxy-d-glucose positron emission tomography detects more poorly differentiated NETs[42]. Lesions < 1 cm in diameter and without unfavorable features are adequately treated with appendectomy[43]. Tumors > 2 cm are best treated with formal right hemicolectomy[44]. The largest clinical study found no nodal disease in primary tumors < 2 cm, and some experts suggest appendectomy alone for all lesions under

this size[45].

Peritoneal metastases and PMP

Appendiceal neoplasms with peritoneal metastases are not equal to PMP. PMP refers to the buildup of mucus within the peritoneum due to mucinous neoplasia, often originating from appendiceal tumors. The term PMP is used when appendiceal tumors perforate and spread throughout the peritoneal cavity, leading to the production of significant mucin. Depending on the cellularity within the mucin, PMP is categorized as acellular mucin, low-grade mucinous carcinoma peritonei, or disseminated peritoneal adenomucinosis, high-grade mucinous carcinoma peritonei or PMCA, and high-grade mucinous carcinoma peritonei with signet ring cells or PMCA with signet ring cells[28]. Despite the nuanced differences between these concepts, CRS is recommended for appendiceal tumors with signs of peritoneal spread[46]. Patients treated with combined HIPEC may improve their long-term survival, reduce tumor recurrence, prolong time to disease progression, and reduce the frequency of repeated surgical interventions[34,47,48].

Advantages and shortcomings

In our study, we systematically analyzed publication trends, research evolution, and future research foci on appendiceal tumors using different bibliometric tools. Scholars interested in related research can benefit from this study since bibliometric analysis provides a more complete insight than traditional reviews. However, there are still some shortcomings to consider. First, the study only analyzed publications retrieved from the WoSCC database after 2010, which limits its ability to fully understand the historical development of this field. Second, only English articles were included, potentially underestimating the impact of non-English papers. Publications after October 2023 were not included either. If all these articles were also included, the results would be slightly different.

CONCLUSION

Despite the low incidence, research on appendiceal tumors is highly valued by scholars worldwide, and the number of related publications continues to increase. The United States was the leading country in this field, but cooperation and communication among various countries and institutions need to be strengthened. In recent years, research has mainly focused on appendiceal mucinous neoplasms and their close association with PMP. Scholars have shown more interest in the classification and management of appendiceal tumors, publishing numerous clinical-related articles. It is important to also focus on basic research of appendiceal tumors, such as in biology and molecular fields.

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FOOTNOTES

Author contributions: Ji JN analyzed the data, created figures, and wrote the manuscript; Yin ZB reviewed and revised the manuscript; and all authors read and approved the final manuscript.

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PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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L-Editor: A
P-Editor: Che XX

REFERENCES

1 **Marmor S**, Portschy PR, Tuttle TM, Virnig BA. The rise in appendiceal cancer incidence: 2000-2009. *J Gastrointest Surg* 2015; **19**: 743-750 [PMID: 25560182 DOI: 10.1007/s11605-014-2726-7]

2 **Connor SJ**, Hanna GB, Frizelle FA. Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7,970 appendectomies. *Dis Colon Rectum* 1998; **41**: 75-80 [PMID: 9510314 DOI: 10.1007/bf02236899]

3 **Van de Moortele M**, De Hertogh G, Sagaert X, Van Cutsem E. Appendiceal cancer: a review of the literature. *Acta Gastroenterol Belg* 2020; **83**: 441-448 [PMID: 33094592]

4 **Synnestvedt MB**, Chen C, Holmes JH. CiteSpace II: visualization and knowledge discovery in bibliographic databases. *AMIA Annu Symp Proc* 2005; **2005**: 724-728 [PMID: 16779135]

5 **Yeung AWK**, Tzvetkov NT, Balacheva AA, Georgieva MG, Gan RY, Jozwik A, Pyzel B, Horbańczuk JO, Novellino E, Durazzo A, Lucarini M, Camilli E, Souto EB, Atanasov AG, Santini A. Lignans: Quantitative Analysis of the Research Literature. *Front Pharmacol* 2020; **11**: 37 [PMID: 32116713 DOI: 10.3389/fphar.2020.00037]

6 **Li C**, Ojeda-Thies C, Renz N, Margaryan D, Perka C, Trampuz A. The global state of clinical research and trends in periprosthetic joint infection: A bibliometric analysis. *Int J Infect Dis* 2020; **96**: 696-709 [PMID: 32434084 DOI: 10.1016/j.ijid.2020.05.014]

7 **Boudry C**, Baudouin C, Mouriaux F. International publication trends in dry eye disease research: A bibliometric analysis. *Ocul Surf* 2018; **16**: 173-179 [PMID: 29031646 DOI: 10.1016/j.jtos.2017.10.002]

8 **Wu H**, Cheng K, Guo Q, Yang W, Tong L, Wang Y, Sun Z. Mapping Knowledge Structure and Themes Trends of Osteoporosis in Rheumatoid Arthritis: A Bibliometric Analysis. *Front Med (Lausanne)* 2021; **8**: 787228 [PMID: 34888333 DOI: 10.3389/fmed.2021.787228]

9 **Shi S**, Gao Y, Liu M, Bu Y, Wu J, Tian J, Zhang J. Top 100 most-cited articles on exosomes in the field of cancer: a bibliometric analysis and evidence mapping. *Clin Exp Med* 2021; **21**: 181-194 [PMID: 32266495 DOI: 10.1007/s10238-020-00624-5]

10 **Maymone MBC**, Laughter M, Vashi NA, Jones JD Jr, Hugh J, Dunnick CA, Dellavalle RP. The most cited articles and authors in dermatology: A bibliometric analysis of 1974-2019. *J Am Acad Dermatol* 2020; **83**: 201-205 [PMID: 31279031 DOI: 10.1016/j.jaad.2019.06.1308]

11 **Hirsch JE**. An index to quantify an individual's scientific research output. *Proc Natl Acad Sci U S A* 2005; **102**: 16569-16572 [PMID: 16275915 DOI: 10.1073/pnas.0507655102]

12 **van Eck NJ**, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. *Scientometrics* 2010; **84**: 523-538 [PMID: 20585380 DOI: 10.1007/s11192-009-0146-3]

13 **Boudreaux JP**, Klimstra DS, Hassan MM, Woltering EA, Jensen RT, Goldsmith SJ, Nutting C, Bushnell DL, Caplin ME, Yao JC; North American Neuroendocrine Tumor Society (NANETS). The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the Jejunum, Ileum, Appendix, and Cecum. *Pancreas* 2010; **39**: 753-766 [PMID: 20664473 DOI: 10.1097/MPA.0b013e3181ebb2a5]

14 **Stewart JH 4th**, Shen P, Russell G, Fenstermaker J, McWilliams L, Coldrun FM, Levine KE, Jones BT, Levine EA. A phase I trial of oxaliplatin for intraperitoneal hyperthermic chemoperfusion for the treatment of peritoneal surface dissemination from colorectal and appendiceal cancers. *Ann Surg Oncol* 2008; **15**: 2137-2145 [PMID: 18493824 DOI: 10.1245/s10434-008-9967-1]

15 **Mangieri CW**, Moaven O, Valenzuela CD, Erali RA, Votanopoulos KI, Shen P, Levine EA. Utility of hyperthermic intraperitoneal chemotherapy in cases of incomplete cytoreductive surgery. *J Surg Oncol* 2022; **125**: 703-711 [PMID: 34841542 DOI: 10.1002/jso.26759]

16 **Levine EA**, Blazer DG 3rd, Kim MK, Shen P, Stewart JH 4th, Guy C, Hsu DS. Gene expression profiling of peritoneal metastases from appendiceal and colon cancer demonstrates unique biologic signatures and predicts patient outcomes. *J Am Coll Surg* 2012; **214**: 599-606; discussion 606 [PMID: 22342786 DOI: 10.1016/j.jamcollsurg.2011.12.028]

17 **Choudry HA**, Pai RK. Management of Mucinous Appendiceal Tumors. *Ann Surg Oncol* 2018; **25**: 2135-2144 [PMID: 29717422 DOI: 10.1245/s10434-018-6488-4]

18 **Davison JM**, Choudry HA, Pingpank JF, Ahrendt SA, Holtzman MP, Zureikat AH, Zeh HJ, Ramalingam L, Zhu B, Nikiforova M, Bartlett DL, Pai RK. Clinicopathologic and molecular analysis of disseminated appendiceal mucinous neoplasms: identification of factors predicting survival and proposed criteria for a three-tiered assessment of tumor grade. *Mod Pathol* 2014; **27**: 1521-1539 [PMID: 24633196 DOI: 10.1038/modpathol.2014.37]

19 **Valasek MA**, Pai RK. An Update on the Diagnosis, Grading, and Staging of Appendiceal Mucinous Neoplasms. *Adv Anat Pathol* 2018; **25**: 38-60 [PMID: 29016471 DOI: 10.1097/PAP.0000000000000178]

20 **Mohamed F**, Sugarbaker PH. Peritoneal mesothelioma. *Curr Treat Options Oncol* 2002; **3**: 375-386 [PMID: 12194803 DOI: 10.1007/s11864-002-0003-6]

21 **Sugarbaker PH**. New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome? *Lancet Oncol* 2006; **7**: 69-76 [PMID: 16389186 DOI: 10.1016/S1470-2045(05)70539-8]

22 **Sugarbaker PH**. Update on the prevention of local recurrence and peritoneal metastases in patients with colorectal cancer. *World J Gastroenterol* 2014; **20**: 9286-9291 [PMID: 25071322 DOI: 10.3748/wjg.v20.i28.9286]

23 **Sugarbaker PH**. Prevention and Treatment of Peritoneal Metastases from Gastric Cancer. *J Clin Med* 2021; **10** [PMID: 33924745 DOI: 10.3390/jcm10091899]

24 **Carr NJ**, Bibeau F, Bradley RF, Dartigues P, Feakins RM, Geisinger KR, Gui X, Isaac S, Milione M, Misdraji J, Pai RK, Rodriguez-Justo M, Sobin LH, van Velthuysen MF, Yantiss RK. The histopathological classification, diagnosis and differential diagnosis of mucinous appendiceal neoplasms, appendiceal adenocarcinomas and pseudomyxoma peritonei. *Histopathology* 2017; **71**: 847-858 [PMID: 28746986 DOI: 10.1111/his.13324]

25 **Carr NJ**, Sobin LH. Neuroendocrine tumors of the appendix. *Semin Diagn Pathol* 2004; **21**: 108-119 [PMID: 15807471 DOI: 10.1053/j.semdp.2004.11.004]

26 **Gonzalez RS**, Carr NJ, Liao H, Pai RK, Agostini-Vulaj D, Misdraji J. High-Grade Appendiceal Mucinous Neoplasm: Clinicopathologic Findings in 35 Cases. *Arch Pathol Lab Med* 2022; **146**: 1471-1478 [PMID: 35472721 DOI: 10.5858/arpa.2021-0430-OA]

27 **Tan GHC**, Shamji T, Mehta A, Chandrakumaran K, Dayal S, Mohamed F, Carr NJ, Rowaiye B, Cecil T, Moran BJ. Diagnostic and therapeutic laparoscopy in assessment and management of patients with appendiceal neoplasms. *Int J Hyperthermia* 2018; **34**: 336-340 [PMID: 28605985 DOI: 10.1080/02656736.2017.1338363]

28 **Carr NJ**, Cecil TD, Mohamed F, Sobin LH, Sugarbaker PH, González-Moreno S, Taflampas P, Chapman S, Moran BJ; Peritoneal Surface Oncology Group International. A Consensus for Classification and Pathologic Reporting of Pseudomyxoma Peritonei and Associated

Appendiceal Neoplasia: The Results of the Peritoneal Surface Oncology Group International (PSOGI) Modified Delphi Process. *Am J Surg Pathol* 2016; **40**: 14-26 [PMID: 26492181 DOI: 10.1097/PAS.0000000000000535]

29 **Miao Y**, Zhang Y, Yin L. Trends in hepatocellular carcinoma research from 2008 to 2017: a bibliometric analysis. *PeerJ* 2018; **6**: e5477 [PMID: 30128213 DOI: 10.7717/peerj.5477]

30 **Ronnett BM**, Zahn CM, Kurman RJ, Kass ME, Sugarbaker PH, Shmookler BM. Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. A clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to "pseudomyxoma peritonei". *Am J Surg Pathol* 1995; **19**: 1390-1408 [PMID: 7503361 DOI: 10.1097/00000478-199512000-00006]

31 **McCusker ME**, Coté TR, Clegg LX, Sobin LH. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973-1998. *Cancer* 2002; **94**: 3307-3312 [PMID: 12115365 DOI: 10.1002/cncr.10589]

32 **Misdraji J**, Yantiss RK, Graeme-Cook FM, Balis UJ, Young RH. Appendiceal mucinous neoplasms: a clinicopathologic analysis of 107 cases. *Am J Surg Pathol* 2003; **27**: 1089-1103 [PMID: 12883241 DOI: 10.1097/00000478-200308000-00006]

33 **Smeenk RM**, van Velthuysen ML, Verwaal VJ, Zoetmulder FA. Appendiceal neoplasms and pseudomyxoma peritonei: a population based study. *Eur J Surg Oncol* 2008; **34**: 196-201 [PMID: 17524597 DOI: 10.1016/j.ejso.2007.04.002]

34 **Chua TC**, Moran BJ, Sugarbaker PH, Levine EA, Glehen O, Gilly FN, Baratti D, Deraco M, Elias D, Sardi A, Liauw W, Yan TD, Barrios P, Gómez Portilla A, de Hingh IH, Ceelen WP, Pelz JO, Piso P, González-Moreno S, Van Der Speeten K, Morris DL. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *J Clin Oncol* 2012; **30**: 2449-2456 [PMID: 22614976 DOI: 10.1200/JCO.2011.39.7166]

35 **Fournier K**, Rafeeq S, Taggart M, Kanaby P, Ning J, Chen HC, Overman M, Raghav K, Eng C, Mansfield P, Royal R. Low-grade Appendiceal Mucinous Neoplasm of Uncertain Malignant Potential (LAMN-UMP): Prognostic Factors and Implications for Treatment and Follow-up. *Ann Surg Oncol* 2017; **24**: 187-193 [PMID: 27660258 DOI: 10.1245/s10434-016-5588-2]

36 **Glasgow SC**, Gaertner W, Stewart D, Davids J, Alavi K, Paquette IM, Steele SR, Feingold DL. The American Society of Colon and Rectal Surgeons, Clinical Practice Guidelines for the Management of Appendiceal Neoplasms. *Dis Colon Rectum* 2019; **62**: 1425-1438 [PMID: 31725580 DOI: 10.1097/DCR.0000000000001530]

37 **Pai RK**, Beck AH, Norton JA, Longacre TA. Appendiceal mucinous neoplasms: clinicopathologic study of 116 cases with analysis of factors predicting recurrence. *Am J Surg Pathol* 2009; **33**: 1425-1439 [PMID: 19641451 DOI: 10.1097/PAS.0b013e3181af6067]

38 **Benedix F**, Reimer A, Gastinger I, Mroczkowski P, Lippert H, Kube R; Study Group Colon/Rectum Carcinoma Primary Tumor. Primary appendiceal carcinoma--epidemiology, surgery and survival: results of a German multi-center study. *Eur J Surg Oncol* 2010; **36**: 763-771 [PMID: 20561765 DOI: 10.1016/j.ejso.2010.05.025]

39 **Turaga KK**, Pappas S, Gamblin TC. Right hemicolectomy for mucinous adenocarcinoma of the appendix: just right or too much? *Ann Surg Oncol* 2013; **20**: 1063-1067 [PMID: 23456377 DOI: 10.1245/s10434-012-2783-7]

40 **Rossi RE**, Luong TV, Caplin ME, Thirlwell C, Meyer T, Garcia-Hernandez J, Baneke A, Conte D, Toumpanakis C. Goblet cell appendiceal tumors--management dilemmas and long-term outcomes. *Surg Oncol* 2015; **24**: 47-53 [PMID: 25686643 DOI: 10.1016/j.suronc.2015.01.001]

41 **Bolanowski M**, Bednarczuk T, Bobek-Billewicz B, Handkiewicz-Junak D, Jeziorski A, Nowakowska-Duława E, Steinhof-Radwańska K, Zajęcki W, Zemczak A, Kos-Kudła B; Consensus Conference; Polish Network of Neuroendocrine Tumours. Neuroendocrine neoplasms of the small intestine and the appendix - management guidelines (recommended by the Polish Network of Neuroendocrine Tumours). *Endokrynol Pol* 2013; **64**: 480-493 [PMID: 24431119 DOI: 10.5603/EP.2013.0029]

42 **Squires MH 3rd**, Volkan Adsay N, Schuster DM, Russell MC, Cardona K, Delman KA, Winer JH, Altinel D, Sarmiento JM, El-Rayes B, Hawk N, Staley CA 3rd, Maithel SK, Kooby DA. Octreoscan Versus FDG-PET for Neuroendocrine Tumor Staging: A Biological Approach. *Ann Surg Oncol* 2015; **22**: 2295-2301 [PMID: 25786743 DOI: 10.1245/s10434-015-4471-x]

43 **Shapiro R**, Eldar S, Sadot E, Papa MZ, Zippel DB. Appendiceal carcinoid at a large tertiary center: pathologic findings and long-term follow-up evaluation. *Am J Surg* 2011; **201**: 805-808 [PMID: 21741512 DOI: 10.1016/j.amjsurg.2010.04.016]

44 **Hsu C**, Rashid A, Xing Y, Chiang YJ, Chagpar RB, Fournier KF, Chang GJ, You YN, Feig BW, Cormier JN. Varying malignant potential of appendiceal neuroendocrine tumors: importance of histologic subtype. *J Surg Oncol* 2013; **107**: 136-143 [PMID: 22767417 DOI: 10.1002/jso.23205]

45 **Nussbaum DP**, Speicher PJ, Gulack BC, Keenan JE, Ganapathi AM, Englum BR, Tyler DS, Blazer DG 3rd. Management of 1- to 2-cm Carcinoid Tumors of the Appendix: Using the National Cancer Data Base to Address Controversies in General Surgery. *J Am Coll Surg* 2015; **220**: 894-903 [PMID: 25840530 DOI: 10.1016/j.jamcollsurg.2015.01.005]

46 **Dayal S**, Taflampas P, Riss S, Chandrakumaran K, Cecil TD, Mohamed F, Moran BJ. Complete cytoreduction for pseudomyxoma peritonei is optimal but maximal tumor debulking may be beneficial in patients in whom complete tumor removal cannot be achieved. *Dis Colon Rectum* 2013; **56**: 1366-1372 [PMID: 24201390 DOI: 10.1097/DCR.0b013e3182a62b0d]

47 **Smeenk RM**, Verwaal VJ, Antonini N, Zoetmulder FA. Survival analysis of pseudomyxoma peritonei patients treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg* 2007; **245**: 104-109 [PMID: 17197972 DOI: 10.1097/01.sla.0000231705.40081.1a]

48 **El Halabi H**, Gushchin V, Francis J, Athas N, Macdonald R, Nieroda C, Studeman K, Sardi A. The role of cytoreductive surgery and heated intraperitoneal chemotherapy (CRS/HIPEC) in patients with high-grade appendiceal carcinoma and extensive peritoneal carcinomatosis. *Ann Surg Oncol* 2012; **19**: 110-114 [PMID: 21701929 DOI: 10.1245/s10434-011-1840-y]

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CASE REPORT

No-touch isolation technique in emergency pancreaticoduodenectomy for neoplastic hemorrhage: Two case reports and review of literature

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Abstract

BACKGROUND

Emergency pancreaticoduodenectomy (EPD) is a rare event for complex periampullary etiology. Increased intraoperative blood loss is correlated with poor postoperative outcomes.

CASE SUMMARY

Two patients underwent EPD using a no-touch isolation technique, in which all arteries supplying the pancreatic head region were ligated and divided before manipulation of the pancreatic head and duodenum. The operative times were 220 and 239 min, and the blood loss was 70 and 270 g, respectively. The patients were discharged on the 14th and 10th postoperative day, respectively. Thirty-two patients underwent EPD for the treatment of neoplastic bleeding. The mean operative time was 361.6 min, and the mean blood loss was 747.3 g. The complication rate was 37.5%. The in-hospital mortality rate was 9.38%.

CONCLUSION

The no-touch isolation technique is feasible, safe, and effective for reducing intraoperative blood loss in EPD.

Key Words: No-touch isolation technique; Pancreaticoduodenectomy; Emergency pancreaticoduodenectomy; Neoplastic bleeding; Superior mesenteric artery first approach; Case report

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Core Tip: Emergency pancreaticoduodenectomy (EPD) has been rarely reported as a life-saving procedure. Morbidity and mortality rates remain very high for EPD. Increased intraoperative blood loss has been linked to worse postoperative results. The non-touch isolation technique is feasible, safe, and effective in minimizing intraoperative blood loss in EPD.

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INTRODUCTION

Emergency pancreaticoduodenectomy (EPD) is rarely performed in cases of trauma, endoscopic and/or postoperative complications, perforation, uncontrollable hemorrhage, or progressive multiple-organ failure in severe necrotizing pancreatitis. While the mortality rate of elective PD has shown a significant decrease during the last three decades, it remains higher for EPD[1]. Increased intraoperative blood loss can be correlated with poor postoperative outcomes in PD [2], and there is clearly a higher in-hospital mortality rate for patients with higher intraoperative blood loss in EPD[3]. Therefore, minimizing intraoperative blood loss during EPD is crucial. This report describes a no-touch isolation technique in which all arteries supplying the pancreatic head region are first ligated and divided before manipulation of the pancreatic head and duodenum in the early phase of resection during EPD.

CASE PRESENTATION

Chief complaints

A 67-year-old woman and an 88-year-old woman presented to emergency department with a complaint of melena and dyspnea, respectively.

History of present illness

Symptoms developed just before emergency transport in both patients.

History of past illness

Case 1: The first patient was scheduled to undergo pylorus-preserving PD (PPPD) because of a duodenal gastrointestinal stromal tumor (GIST).

Case 2: The second patient had painless mass that was gradually increasing in size over a period of six months.

Personal and family history

Both two patients denied any family history of malignant tumors.

Physical examination

Case 1: On physical examination, the vital signs were as follows: Body temperature (35.9 °C); blood pressure (75/34 mmHg); heart rate (124 beats per min); respiratory rate (28 breaths per min).

Case 2: On physical examination, the vital signs were as follows: Body temperature (36.4 °C); blood pressure (70/40 mmHg); heart rate (140 beats per min); respiratory rate (36 breaths per min).

Laboratory examinations

Case 1: Levels of serum hemoglobin were 3.7 g/dL.

Case 2: Levels of serum hemoglobin were 5.4 g/dL.

Imaging examinations

Case 1: Contrast-enhanced computed tomography demonstrated a duodenal hyper vascular mass, sized 5.0 cm × 6.0 cm (Figure 1A).

Case 2: A complex, septate cystic mass in the pancreatic head measuring 17 cm, with solid components and adjacent hematoma (Figure 1B).

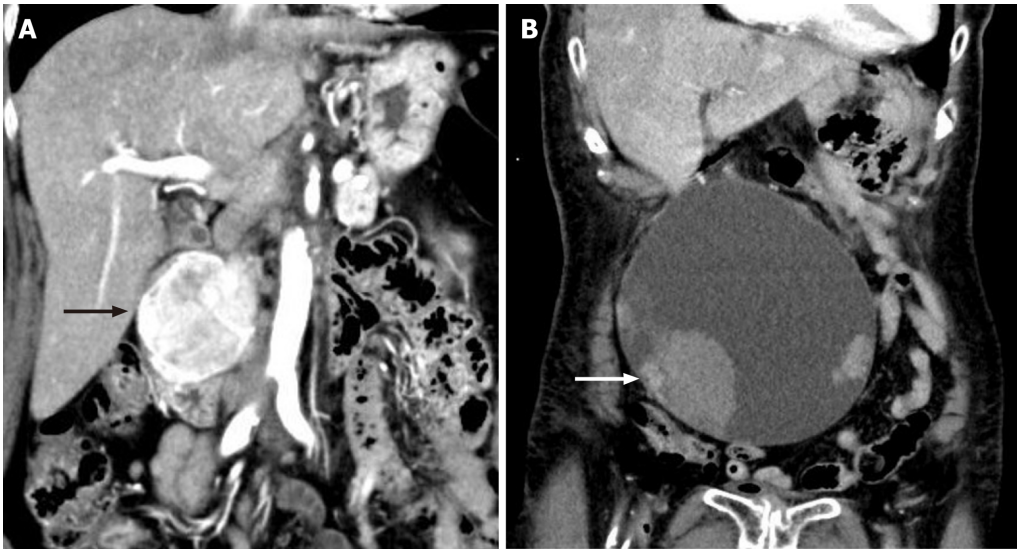


Figure 1 Imaging of the duodenal tumor and pancreatic tumor. A: Imaging of the duodenal tumor and pancreatic tumor. Contrast-enhanced computed tomography showed a well-defined, enhancing masse, sized 5.0 cm × 6.0 cm, with heterogeneous density at the second portion of the duodenum (arrow); B: Imaging of the pancreatic tumor. Contrast-enhanced computed tomography showed a huge cystic mass measuring 17 cm, with some solid components and adjacent hematoma (arrow).

Further diagnostic work-up

A diagnosis of GIST was made in the case 1 by ultrasound-guided fine-needle aspiration.

FINAL DIAGNOSIS

The final diagnosis was a GIST and an intraductal papillary mucinous neoplasm (IPMN).

TREATMENT

Two patients underwent EPD using a no-touch isolation technique as a lifesaving procedure for massive pancreaticoduodenal neoplastic bleeding at our institution between May and June 2023 (Table 1). All procedures were performed in accordance with the ethical guidelines of the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and revised in Tokyo 2004. Appropriate written informed consent was obtained for the publication of these case reports and accompanying images.

Case 1

Eight units of red blood cell concentrate were transfused, and emergency PPPD was performed using a no-touch isolation technique. The operative time was 220 min, and blood loss was 70 g.

Case 2

Ten units of red blood cell concentrate were transfused before surgery. Intraoperative findings showed that the superior mesenteric artery (SMA) and superior mesenteric vein (SMV) and the transverse colon and mesentery firmly adhered to the huge cystic tumor over its entire length, which made dissection difficult, and intraoperative blood loss was increased. Finally, PPPD was performed using a no-touch isolation technique. The operative time was 239 min, and blood loss was 270 g.

Surgical procedure

First, the gastrocolic ligament was divided and the omental bursa was opened to visualize the anterior surface of the pancreas. Dissection along the inferior surface of the pancreatic neck exposed the SMV. The SMA with nerve plexuses surrounding the SMA is taped just to the left side of the SMV. Dissection was performed along the superior surface of the pancreas and between the distal duodenum and the pancreas to isolate the common and proper hepatic arteries and the gastroduodenal artery (GDA), which was ligated and divided. After the pancreatic neck was separated from the SMV, it was taped. The hepatoduodenal ligament was dissected to isolate the portal vein and the common bile duct (CBD). Next, the ligament of Treitz was dissected and opened to visualize the aorta. The taped SMA was visualized immediately superior to the left renal vein. The inferior pancreaticoduodenal artery (IPDA) arises from the first jejunal artery (FJA) or

Table 1 Details of patients who underwent emergency pancreaticoduodenectomy using a no-touch isolation technique

Patients	1	2
Age/sex	67/female	88/female
Pathology	Duodenal-GIST	IPMN
Hb (g/dL) transfusion, U	3.7, 8	5.4, 10
Tumor size (cm)	5	17
Procedure	PPPD	PPPD
Operative time (m)	220	239
Blood loss (g)	70	270
Complication	No	No
Length of stay (d)	14	10

GIST: Gastrointestinal stromal tumor; PPPD: Pylorus-preserving pancreaticoduodenectomy; IPMN: Intraductal papillary mucinous neoplasm; Hb: Hemoglobin.

the SMA. The IPDA usually branches from the left dorsal side of the SMA[4]. The proximal jejunum was pulled to the right and the SMA was rotated counterclockwise. The IPDA was visualized and then ligated and divided. The superior and inferior pancreaticoduodenal arteries were blocked (Figure 2). The inferior pancreatic artery (IPA) forms the arterial arcade between the GDA and the dorsal pancreatic artery (DPA)[5]. Therefore, ligation of the IPA is important. Early ligation of the IPA at the inferior border of the body of the pancreas or the arterial arcade of the DPA can be controlled by stay sutures on both the cranial and caudal sides of the remnant pancreas and amputation of the pancreas if the IPA cannot be isolated.

OUTCOME AND FOLLOW-UP

No patients required intra-or postoperative blood transfusions, and no complications were encountered. Patients were discharged on the 14th and 10th postoperative day, respectively. All lesions had clear surgical margins. The patients were still alive without recurrence.

DISCUSSION

EPD, which has been rarely reported mostly in complex pancreaticoduodenal trauma, perforations, life-threatening hemorrhage, and severe infection is still a very uncommon procedure[1]. Recent rapid developments in technological innovations, improvements in surgical skills, progress in perioperative management, and the extensive experience of surgeons have proven the feasibility and safety of PD[6]. While the mortality rate of elective PD has shown a significant decrease during the last three decades, it remains higher for EPD[7]. EPD has been reported mostly in trauma settings, while non-trauma cases have been also reported, although rarely, which include bleeding, complicated tumors of the pancreaticoduodenal complex, endoscopic complications, and caustic ingestion[1]. Emergent pancreatic resection for neoplastic disease also is associated with significantly higher mortality and morbidity rates compared to elective pancreatic resections[8]. In patients with upper gastrointestinal tract bleeding, including pancreaticoduodenal, endoscopic or radiological procedures can achieve hemostasis in most patients. However, conservative management with interventional radiologic coiling of feeding arteries may momentarily salvage the situation but does not treat the underlying disease, especially in cases of malignancies. Moreover, interventional angiography with embolization of the pancreaticoduodenal arcade might not solve the problem in the presence of erosive tumors. It could also be ineffective because of the notable collateral blood supply of the pancreaticoduodenal area from the celiac and superior mesenteric arterial circulation[5], and the rich extra-blood supply, especially in patients with huge extra-growing tumors[9]. Therefore, in cases of bleeding of neoplastic origin, emergency pancreatoduodenectomy can be a definite therapeutic option. The literature review was performed *via* MEDLINE and PubMed with the key words, "emergency/emergent" and "pancreaticoduodenectomy/pancreatoduodenectomy". In addition, we manually searched the reference lists of all the identified articles to identify further relevant articles. We selected only literature with full texts published between January 2001 and December 2022. All recorded cases of EPD performed for neoplastic bleeding in an emergency setting were extracted. Thirty-two patients[1,10-32] were reported to undergo EPD for neoplastic bleeding causes (Table 2): Seven cases of pancreatic carcinomas, five GISTs, four IPMNs, three duodenal carcinomas, two ampullary carcinomas, two liposarcomas, two lymphomas, and seven others (four cases of metastases from renal cell carcinoma, adrenal cancer, colon cancer, or neuroendocrine tumor, one duodenal sarcoma, one gastric cancer, and one paraganglioma). There were

Table 2 Reported patients that underwent emergency pancreaticoduodenectomy for neoplastic hemorrhage

Characteristic		
Sex, *n* (female/male)		15/17
Age, yr (mean)		20-93 (61.2)
Pre-operative TAE, *n* (%)		2 (6.25)
Operative time, min (mean)		210-553 (361.6)
Blood loss, g (mean)		20-1600 (747.3)
Morbidity, *n* (%)		12 (37.5)
Mortality, *n* (%)		3 (9.38)
Hospital stay, d (mean)		7-63 (25.5)
Underlying diagnosis, *n* (%)	Pancreatic carcinoma	7 (21.8)
	GIST	5 (15.6)
	IPMN	4 (12.5)
	Duodenal carcinoma	3 (9.4)
	Ampullary carcinoma	2 (6.3)
	Liposarcoma	2 (6.3)
	Lymphoma	2 (6.3)
	Others	7 (21.8)

GIST: Gastrointestinal tumor; IPMN: Intraductal papillary mucinous neoplasm; TAE: Transcatheter arterial embolization.

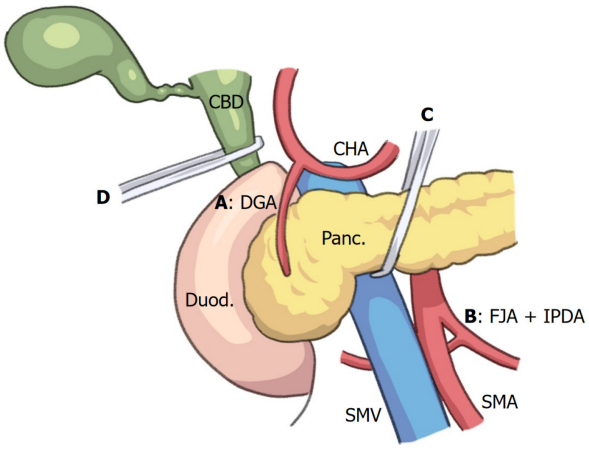


Figure 2 Illustration of no-touch isolation technique in emergency pancreaticoduodenectomy. All arteries (A-D) that supply the pancreatic head region are isolated before manipulation of the pancreatic head and duodenum in the early phase of resection during emergency pancreaticoduodenectomy. A: The gastroduodenal artery; B: First jejunal artery, inferior pancreaticoduodenal artery; C: Intrapancreatic arterial arcade, including the inferior pancreatic artery. D: The para-biliary arterial plexus, including the 3 or 9 o'clock arteries, anastomoses to the posterior superior pancreaticoduodenal artery. Panc: Pancreas; Duod: Duodenum; SMV: Superior mesenteric vein; SMA: Superior mesenteric artery; CHA: Common hepatic artery; CBD: Common bile duct; GDA: Gastroduodenal artery; IPDA: Inferior pancreaticoduodenal artery; FJA: First jejunal artery.

15 females (46.88%) and 17 males (53.12%), with a mean age of 61.2 years. Two of the 32 patients (6.25%) underwent trans-catheter arterial embolization before EPD. Operative time and intraoperative blood loss were described in 11 and 13 patients, respectively. The mean operative time was 361.6 min, and mean blood loss was 747.3 g. The complication rate was 37.5% (n = 12). Pancreatic fistula was the most common complication, occurring in six patients (18.75%). The in-hospital mortality rate was 9.38% (two patients). The mean length of hospitalization was 25.5 d. The overall mortality rate of EPD for tumor bleeding was 9.38%. Blood loss during EPD was 20-1600 g (mean 747.3 g). Increased intraoperative blood loss can be correlated with poor postoperative outcomes in PD[2]. There was a higher in-hospital mortality rate in patients with higher intraoperative blood[3]. Therefore, minimizing intraoperative blood loss during EPD is crucial. A no-touch isolation technique was originally recommended for operations on periampullary cancer to prevent the scattering of cancer cells into the portal blood[33,34]. To the best of our knowledge, this is the first report of a no-touch isolation

technique performed to reduce intraoperative blood loss in EPD. In this procedure, all arteries that supply the pancreatic head region are first ligated and divided before manipulation of the pancreatic head and duodenum[6,33,34]. In conventional PD using Kocher's maneuver, the GDA is usually ligated and divided during surgery; however, IPDA ligation and division are performed in the final stage of resection, which might induce further tumor bleeding. Early ligation of the IPDA is an effective technique for minimizing intraoperative blood loss during PD[33]. Recently, the SMA first approach has been proposed[35]. Using this approach, we identified the origin of the IPDA arising from the posterior aspect of the SMA without mobilization of the duodenum or colon[4,35]. Rotating the SMA counterclockwise facilitates easy identification of the origin of the FJA or IPDA because these arteries arise from the left dorsal aspect of the SMA[4,35]. The arterial supply of the pancreas is marked by numerous anastomoses. Arterial arcades are formed by branches from different main supplying arteries, and between branches from each main artery. Major branches anastomose within the substance of the pancreas[5]. Moreover, the para-biliary arterial plexus, including the 3 or 9 o'clock arteries, anastomoses the posterior superior pancreaticoduodenal artery[36]. Therefore, both the pancreas and CBD should be divided before Kocher's maneuver if bleeding cannot be controlled after ligation of the GDA and IPDA. Duo to our limited experiences, a larger cohort should be evaluated in a prospective, randomized study to elucidate appropriate indications and effects of this novel procedure.

CONCLUSION

Despite our limited experience, and pending future studies to establish appropriate indications, we believe that a non-touch isolation technique is feasible, safe, and effective in minimizing intraoperative blood loss in EPD. The benefits of this approach, however, require further validation, understanding the importance of careful patient selection for successful treatment.

FOOTNOTES

Author contributions: Cho A selected the associated data and edited the article; Cho A, Onizawa S, Sugishita T, Niwa Y, and Kato A participated in the surgery; Higuchi R, Ishita T, Mouri T, and Iwata M contributed to patient treatment; Katagiri S and Ota M revised the manuscript; and all authors have read and approved the final manuscript.

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REFERENCES

1 **Standop J**, Glowka T, Schmitz V, Schaefer N, Hirner A, Kalff JC. Emergency Kausch-Whipple procedure: indications and experiences. *Pancreas* 2010; **39**: 156-159 [PMID: 20182309 DOI: 10.1097/MPA.0b013e3181bb98d2]

2 **Seykora TF**, Ecker BL, McMillan MT, Maggino L, Beane JD, Fong ZV, Hollis RH, Jamieson NB, Javed AA, Kowalsky SJ, Kunstman JW, Malleo G, Poruk KE, Soares K, Valero V 3rd, Velu LKP, Watkins AA, Vollmer CM Jr; Pancreas Fistula Study Group. The Beneficial Effects of Minimizing Blood Loss in Pancreatoduodenectomy. *Ann Surg* 2019; **270**: 147-157 [PMID: 29489483 DOI: 10.1097/SLA.0000000000002714]

3 **Popa C**, Schlanger D, Chirică M, Zaharie F, Al Hajjar N. Emergency pancreaticoduodenectomy for non-traumatic indications-a systematic review. *Langenbecks Arch Surg* 2022; **407**: 3169-3192 [PMID: 36280612 DOI: 10.1007/s00423-022-02702-6]

4 **Kurosaki I**, Minagawa M, Takano K, Takizawa K, Hatakeyama K. Left posterior approach to the superior mesenteric vascular pedicle in pancreaticoduodenectomy for cancer of the pancreatic head. *JOP* 2011; **12**: 220-229 [PMID: 21546696 DOI: 10.6092/1590-8577/3285]

5 **Bertelli E**, Di Gregorio F, Bertelli L, Mosca S. The arterial blood supply of the pancreas: a review. I. The superior pancreaticoduodenal and the anterior superior pancreaticoduodenal arteries. An anatomical and radiological study. *Surg Radiol Anat* 1995; **17**: 97-106, 1 [PMID: 7482159 DOI: 10.1007/BF01627566]

6 **Liu C**, Liu Y, Dong J, Chai Y, Tang H. Laparoscopic pancreaticoduodenectomy versus open pancreaticoduodenectomy for carcinoma of the ampulla of Vater in a medium-volume center: a propensity score matching analysis. *J Int Med Res* 2023; **51**: 3000605231219061 [PMID: 38150553 DOI: 10.1177/03000605231219061]

7 **Krige JE**, Nicol AJ, Navsaria PH. Emergency pancreatoduodenectomy for complex injuries of the pancreas and duodenum. *HPB (Oxford)* 2014; **16**: 1043-1049 [PMID: 24841125 DOI: 10.1111/hpb.12244]

8 **Driedger MR**, Puig CA, Thiels CA, Bergquist JR, Ubl DS, Habermann EB, Grotz TE, Smoot RL, Nagorney DM, Cleary SP, Kendrick ML, Truty MJ. Emergent pancreatectomy for neoplastic disease: outcomes analysis of 534 ACS-NSQIP patients. *BMC Surg* 2020; **20**: 169 [PMID: 32718311 DOI: 10.1186/s12893-020-00822-8]

9 **Cho A**, Ryu M, Ochiai T. Successful resection, using pancreas-sparing duodenectomy, of extrahepatically growing hepatocellular carcinoma associated with direct duodenal invasion. *J Hepatobiliary Pancreat Surg* 2002; **9**: 393-396 [PMID: 12353155 DOI: 10.1007/s005340200048]

10 **Iede K**, Nakao A, Oshima K, Suzuki R, Yamada H, Tashiro M, Oshima Y, Kobayashi H. Controlling the arterial supply into the pancreatic head region as a whole peripancreatic arterial arcade *via* a mesenteric approach during isolated pancreatoduodenectomy. *Surg Today* 2021; **51**: 1819-1827 [PMID: 34014389 DOI: 10.1007/s00595-021-02298-2]

11 **Parray FQ**, Lone IM, Chowdri NA, Wani I, Wani MA, Gulzar GM, Thakur N. Emergency pancreaticoduodenectomy in duodenal paraganglioma: case report. *ISRN Surg* 2011; **2011**: 268674 [PMID: 22084750 DOI: 10.5402/2011/268674]

12 **Sakakima Y**, Inoue S, Fujii T, Hatsuno T, Takeda S, Kaneko T, Nagasaka T, Nakao A. Emergency pylorus-preserving pancreatoduodenectomy followed by second-stage pancreatojejunostomy for a gastrointestinal stromal tumor of the duodenum with an intratumoral gas figure: report of a case. *Surg Today* 2004; **34**: 701-705 [PMID: 15290403 DOI: 10.1007/s00595-004-2771-z]

13 **Maeda H**, Okabayashi T, Kobayashi M, Araki K, Kohsaki T, Nishimori I, Onishi S, Ito S, Ogawa Y, Okuda H, Shuin T. Emergency pancreatoduodenectomy for pancreatic metastasis from renal cell carcinoma in a patient with von Hippel-Lindau disease: a case report. *Dig Dis Sci* 2006; **51**: 1383-1387 [PMID: 16868829 DOI: 10.1007/s10620-005-9032-x]

14 **Stratigos P**, Kouskos E, Kouroglou M, Chrisafis I, Fois L, Mavrogiorgis A, Axiotis E, Zamtrakis S. Emergency pancreatoduodenectomy (whipple procedure) for massive upper gastrointestinal bleeding caused by a diffuse B-cell lymphoma of the duodenum: report of a case. *Surg Today* 2007; **37**: 680-684 [PMID: 17643214 DOI: 10.1007/s00595-007-3465-0]

15 **Hecker A**, Hecker B, Bassaly B, Hirschburger M, Schwandner T, Janssen H, Padberg W. Dramatic regression and bleeding of a duodenal GIST during preoperative imatinib therapy: case report and review. *World J Surg Oncol* 2010; **8**: 47 [PMID: 20515511 DOI: 10.1186/1477-7819-8-47]

16 **Okabayashi T**, Shima Y, Iwata J, Sumiyoshi T, Kozuki A, Tokumaru T, Hata Y, Noda Y, Inagaki T, Morishita S, Morita M. Primary liposarcoma of the duodenum: a first case presentation. *Intern Med* 2013; **52**: 2753-2757 [PMID: 24334580 DOI: 10.2169/internalmedicine.52.1230]

17 **Gulla A**, Tan WP, Pucci MJ, Dambrauskas Z, Rosato EL, Kaulback KR, Pundzius J, Barauskas G, Yeo CJ, Lavu H. Emergent pancreaticoduodenectomy: a dual institution experience and review of the literature. *J Surg Res* 2014; **186**: 1-6 [PMID: 24011528 DOI: 10.1016/j.jss.2013.07.057]

18 **Strobel O**, Schneider L, Philipp S, Fritz S, Büchler MW, Hackert T. Emergency pancreatic surgery--demanding and dangerous. *Langenbecks Arch Surg* 2015; **400**: 837-841 [PMID: 26149078 DOI: 10.1007/s00423-015-1321-z]

19 **Nentwich MF**, Reeh M, Uzunoglu FG, Bachmann K, Bockhorn M, Izbicki JR, Vashist YK. Non-trauma Emergency Pancreatoduodenectomies: A Single-Center Retrospective Analysis. *World J Surg* 2016; **40**: 2261-2266 [PMID: 27138883 DOI: 10.1007/s00268-016-3525-y]

20 **Tsai CY**, Lai BR, Wang SY, Liao CH, Liu YY, Kang SC, Yeh CN, Jan YY, Yeh TS. The impact of preoperative etiology on emergent pancreaticoduodenectomy for non-traumatic patients. *World J Emerg Surg* 2017; **12**: 21 [PMID: 28469698 DOI: 10.1186/s13017-017-0133-6]

21 **Lupascu C**, Trofin A, Zabara M, Vornicu A, Cadar R, Vlad N, Apopei O, Grigorean V, Lupascu-Ursulescu C. Emergency Backwards Whipple for Bleeding: Formidable and Definitive Surgery. *Gastroenterol Res Pract* 2017; **2017**: 2036951 [PMID: 28757865 DOI: 10.1155/2017/2036951]

22 **Mirea CS**, Ciorbagiu MC, Obleagă CV, Moraru E, Mogoantă SŞ, Ciurea RN, Foarfă MC, Vîlcea AM, Vîlcea ID. Stage IV duodenal GIST requiring emergency pancreaticoduodenectomy - diagnosis difficulties and therapeutic options. *Rom J Morphol Embryol* 2018; **59**: 543-548 [PMID: 30173260]

23 **Emiloju O**, Candelario N, Dourado C. Metastatic clear cell endometrial carcinoma: an unusual cause of a common clinical presentation. *BMJ Case Rep* 2020; **13** [PMID: 32532916 DOI: 10.1136/bcr-2020-235051]

24 **Subbarayan R**, Anand S, Selvaraj S. Emergency Pancreaticoduodenectomy for Exsanguinating Ampullary Malignancy. *Indian J Crit Care Med* 2020; **24**: 1279-1280 [PMID: 33446987 DOI: 10.5005/jp-journals-10071-23676]

25 **Miyama A**, Chikaishi Y, Kobayashi D, Matsuo K, Ochi T, Nakamura K, Endo T, Kikuchi K, Katsuno H, Nishijima A, Morise Z. A case of non-ampullary duodenal adenosquamous carcinoma with successful emergency pancreaticoduodenectomy for gastrointestinal hemorrhage. *Surg Case Rep* 2023; **9**: 161 [PMID: 37698671 DOI: 10.1186/s40792-023-01749-x]

26 **Ye N**, Bao X, Zhao X, Wang B. Signet-ring cell carcinoma of the duodenal bulb presenting with gastrointestinal hemorrhage: a case report and literature review. *BMC Gastroenterol* 2022; **22**: 226 [PMID: 35534806 DOI: 10.1186/s12876-022-02267-0]

27 **Aoki Y**, Oshiro H, Yoshida A, Morishima K, Miki A, Sasanuma H, Sakuma Y, Lefor AK, Sata N. Pancreaticoduodenectomy for a primary duodenal capicua transcriptional repressor (CIC) -rearranged sarcoma with severe bleeding: a case report. *BMC Gastroenterol* 2020; **20**: 105 [PMID: 32293288 DOI: 10.1186/s12876-020-01266-3]

28 **Sun M**, Wei Y, Li S, Liu Z, Han X. Emergency laparoscopic pancreatoduodenectomy as treatment for pancreatic head cancer-induced acute gastrointestinal hemorrhage, safe or not? *Hepatobiliary Surg Nutr* 2021; **10**: 146-148 [PMID: 33575309 DOI: 10.21037/hbsn-20-613]

29 **Tokue H**, Morita H, Tokue A, Tsushima Y. Successful management of life-threatening bleeding of intraductal papillary mucinous neoplasms in the pancreatic head. *SAGE Open Med Case Rep* 2017; **5**: 2050313X17741014 [PMID: 29163954 DOI: 10.1177/2050313X17741014]

30 **Cha DE**, Horn C, Passeri M. Triple threat: pancreatic cystic lesion presenting with spontaneous hemorrhage is found to harbor three distinct neoplasms. *World J Surg Oncol* 2021; **19**: 15 [PMID: 33451339 DOI: 10.1186/s12957-021-02119-3]

31 **Long TB**, Binh NT, Dung LV, Linh LT, Luu DT, My TT, Duc NM. Diagnosis and treatment of hemosuccus pancreaticus induced by intraductal papillary mucinous neoplasm: a case report and review of the literature. *Radiol Case Rep* 2021; **16**: 3099-3103 [PMID: 34429811

DOI: 10.1016/j.radcr.2021.07.051]

32 **Azizan N**, Hayati F, Zakaria AD, Shukor NA. Intraductal papillary mucinous neoplasm presenting as bleeding duodenal mass: A surgical rarity. *IIUM Med J Malaysia* 2019; **18**: 123-126 [DOI: 10.31436/imjm.v18i1.221]

33 **Nakao A**, Takagi H. Isolated pancreatectomy for pancreatic head carcinoma using catheter bypass of the portal vein. *Hepatogastroenterology* 1993; **40**: 426-429 [PMID: 8270230]

34 **Hirota M**, Shimada S, Yamamoto K, Tanaka E, Sugita H, Egami H, Ogawa M. Pancreatectomy using the no-touch isolation technique followed by extensive intraoperative peritoneal lavage to prevent cancer cell dissemination: a pilot study. *JOP* 2005; **6**: 143-151 [PMID: 15767730]

35 **Cho A**, Yamamoto H, Kainuma O. Tips of laparoscopic pancreaticoduodenectomy: superior mesenteric artery first approach (with video). *J Hepatobiliary Pancreat Sci* 2014; **21**: E19-E21 [PMID: 24307512 DOI: 10.1002/jhbp.54]

36 **Cho A**, Ryu M. New Liver Anatomy. 1st ed. New York: Springer, 2009

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CASE REPORT

Malignant myopericytoma originating from the colon: A case report

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Abstract

BACKGROUND

Myopericytoma is a benign tumor that typically occurs within subcutaneous tissue and most often involves the distal extremities, followed by the proximal extremities, neck, thoracic vertebrae and oral cavity. Complete resection is often curative. Malignant myopericytoma is extremely rare and has a poor prognosis. Here, we report for the first time a case of malignant myopericytoma originating from the colon.

CASE SUMMARY

A 69-year-old male was admitted to our hospital with right upper quadrant pain for five days. Imaging suggested a liver mass with hemorrhage. A malignant hepatic tumor was the initial diagnosis. Surgical resection was performed after a complete preoperative work up. Initial postoperative pathology suggested that the mass was a malignant myoblastoma unrelated to the liver. Four months after the first surgery, an enhanced computed tomography (CT) scan revealed a recurrence of the tumor. The diagnosis of malignant myopericytoma derived from the colon was confirmed on histopathological examination of the specimen from the second surgery. The patient did not return to the hospital regularly for surveillance. The first postoperative abdominal CT examination six months after the second surgery demonstrated multiple liver metastases. Survival time between the diagnosis of the tumor to death was approximately one year.

CONCLUSION

Malignant myopericytoma is a rare cancer. Preoperative diagnosis may be difficult. Due to a lack of treatment options, prognosis is poor.

Key Words: Malignant myopericytoma; Liver tumor; Colonic neoplasms; Abdominal pain;

Case report

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Core Tip: The incidence of malignant myopericytoma is very low and prognosis is poor. Presently, there is no ideal intervention. In this case, the patient was initially admitted to hospital with pain secondary to a hemorrhage into a liver tumor. After two surgeries, the patient was definitively diagnosed with a malignant myopericytoma originating in the colon. Due to the lack of comprehensive antitumor therapy and poor patient compliance, the tumor progressed rapidly. The patient's survival was only one year. In view of the lack of diagnostic and treatment guidelines, future clinical and basic science research on myopericytomas is warranted and can hopefully improve prognosis.

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INTRODUCTION

Myopericytoma was formally defined by Granter *et al*[1] in 1998. It is a novel perivascular tumor which shares several histopathologic similarities with angioleiomyoma, myofibromatosis, glomus tumors and infantile haemangiopericytoma, all of which comprise a morphological spectrum of tumours that show differentiation towards perivascular myoid[2,3]. Despite the histological and morphological overlap with these tumors, myopericytomas have distinct characteristics. Microscopically, they are composed of myoid-appearing oval or spindle-shaped cells with a concentric perivascular arrangement, often with diffuse expression of smooth muscle actin (SMA)[4,5].

In the majority of cases, myopericytoma are benign tumors generally arising in the subcutaneous and superficial soft tissues of the extremities. Recurrence is very rare after complete surgical resection[6,7]. Malignant myopericytoma is rare with only a few cases reported in the literature. The rarity and poor prognosis of the disease warranted us to identify more cases in the literature and conduct in-depth research. Herein, we report for the first time a case of malignant myopericytoma originating in the colon, whose imaging results suggested a hepatic neoplasm leading to difficulty in diagnosis and treatment.

CASE PRESENTATION

Chief complaints

A 69-year-old male presented to the emergency department with right upper quadrant pain.

History of present illness

He described the pain as paroxysmal, dull, located in his right upper abdomen and present for five days. He went to the emergency department due to a continued worsening of the pain. He denied nausea, vomiting, melena, change to his bowel habit and weight loss.

History of past illness

The patient reported no past history of specific illness, including jaundice, hepatitis, gallbladder pathology or renal, cardiac, or pulmonary disease.

Personal and family history

The patient was not taking any medication or herbal supplements and had no allergies. Also, he had no significant family history of carcinoma or hepatobiliary pathology. He had not undergone a colonoscopy in the past or during his treatment.

Physical examination

The patient's vital signs were within normal limits. No obvious abnormality was observed on pulmonary or cardiac examination. His abdomen was non-distended and soft. Mild tenderness was found on deep palpation of the right upper quadrant without rebound tenderness.

Laboratory examinations

Routine blood laboratory tests showed no obvious abnormalities in the patient's liver function, kidney function,

coagulation, electrolytes, blood sugar, blood lipids, hepatitis B virus DNA quantification and tumor marker levels.

Imaging examinations

Abdominal computed tomography (CT) scanning with contrast demonstrated an exogenous mass in the lower segment of the right lobe of the liver measuring 4.5 cm × 5.4 cm and moderate ascites. Based on the CT, a rupture and hemorrhage of a hepatoma was the primary diagnosis (Figure 1A and B). The tumor invaded the lower segment of right posterior lobe of liver and the ascending colon. Surgical resection was performed after a complete preoperative work up. Part of the liver and the serosa and mesenteric tissue of the colon were excised during the first surgery (Figure 1C and D). Postoperative CT examination showed no residual mass (Figure 1E and F). Histopathological examination of the resection specimen revealed that the lesion was a malignant myopericytoma without invasion of the surrounding liver tissue. The primary lesion was considered to be in the colon (Figure 2).

FINAL DIAGNOSIS

Four months after the first surgery, a surveillance abdominal CT scan revealed the recurrence of the colonic tumor (Figure 3A and B). A right hemicolectomy with curative intent was performed for the tumor recurrence. During the second surgery, the tumor was found within the mucosal layer of the transverse colon and protrude into the lumen. On examination of the resection specimen, pale tissue was seen on its anatomical surface (Figure 3C). Postoperative imaging indicated complete resection of the tumor (Figure 3D and E). The pathological section obtained in the second operation was correlative with a malignant myopericytoma again. The tumor was eventually diagnosed as a malignant myopericytoma originating in the colon and growing around the liver (Figure 3F-I).

TREATMENT

The patient underwent two open surgeries. During the first surgery, we set the route of excision in liver tissue to about 2 cm from the tumor boundary and the right liver tumor was completely resected along with a 2 cm margin of macroscopically unaffected tissue. The adhesions between the tumor and the colon were carefully separated and part of the serous layer and mesenteric tissue of the colon were concomitantly resected the patient recovered well after the first operation, with no postoperative complications such as bleeding, biliary leakage or hepatic failure. A right hemicolectomy with curative intent was performed for the tumor recurrence. The resection included distal ileum 15 cm away from the ileocecal junction to the proximal third of the transverse colon. The bowel containing the intact mass, and part of mesentery and greater omentum were removed. Finally, an end-to-end ileocoleostomy was performed. One week after the second operation, the patient experienced anastomotic leakage. This was treated with an abdominal drain and antibiotics. The patient recovered smoothly and was discharged from hospital. Due to the lack of effective treatment methods other than surgical resection and the patient's poor treatment compliance, adjuvant therapy such as radiotherapy and/or chemotherapy were not received after surgery.

OUTCOME AND FOLLOW-UP

The patient did not return for early, routine surveillance as requested; however, six months after the second operation, he presented for surveillance. An abdominal CT showed multiple masses in the liver (Figure 4). Due to his past medical history, hepatic metastasis from colonic carcinoma were considered. The patient and his family declined surgery and opted for palliation. The overall survival time from initial tumor diagnosis to death was approximately one year.

DISCUSSION

Requena *et al*[8] suggested the term myopericytoma as an alternative name for some cutaneous adult myofibromas, basing their argument on the myopericytic differentiation seen in these tumors. Later, Granter *et al*[1] described a group of benign tumors showing a distinct histologic pattern characterized by a concentric, perivascular cellular proliferation with myoid differentiation.

Myopericytoma often present as incidental, painless, superficial masses, which have a predilection for subcutaneous sites in the extremities. Histologically, they have clear boundaries and are composed of round or oval cells arranged in the shape of concentric circles and surrounded by blood vessels. Due to the characteristics secondary to the myoid differentiation of tumor cells, they demonstrate a powerful immune response to SMA[9-11]. In recent years, increasing numbers of myopericytoma have been reported. Most cases have a low recurrence rate and a favorable prognosis. Unfortunately, myopericytoma carries a risk of malignant transformation. Malignant myopericytoma, like other malignancies, exhibits increased mitotic activity, nuclear atypia, pleomorphism, necrosis, infiltration, and metastasis[12, 13].

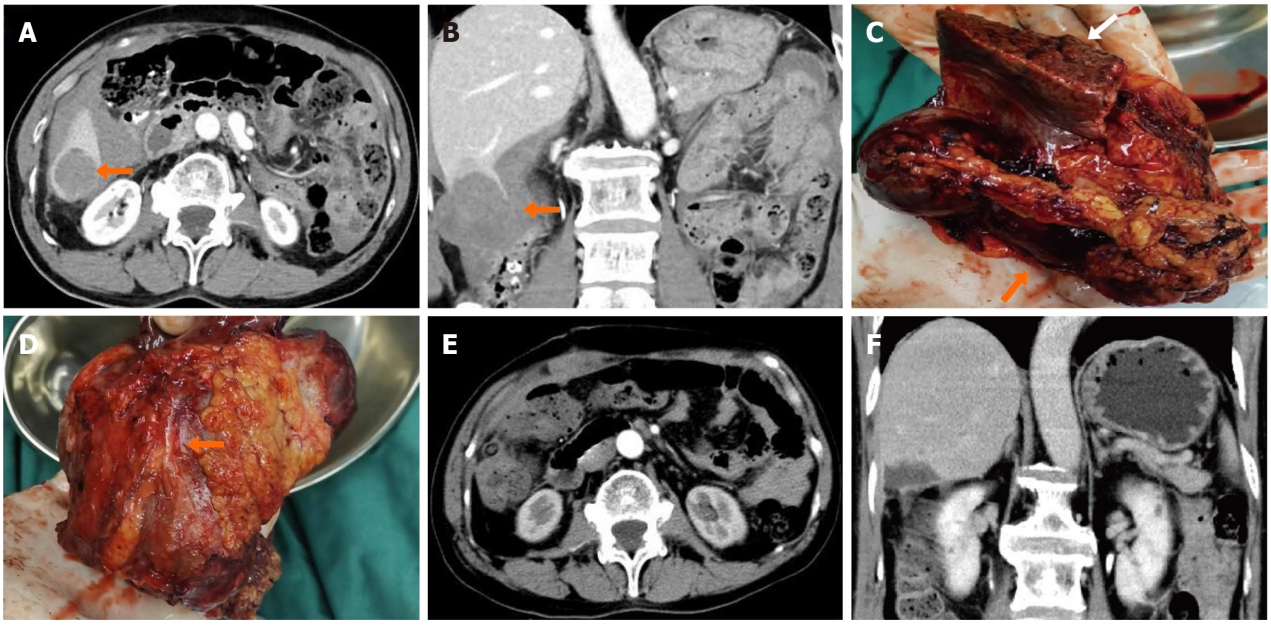


Figure 1 Computed tomography imaging before and after the first surgery. A: Axial view of the tumor prior to surgery; B: Coronal view of the tumor prior to surgery; C: Gross specimen of surgically excised neoplastic lesion. The arrow indicates the margin of the liver and the tumor surrounding the liver; D: The arrow shows the adhesions between the tumor and the colon; E: Axial view after surgery; F: Coronal view after surgery.

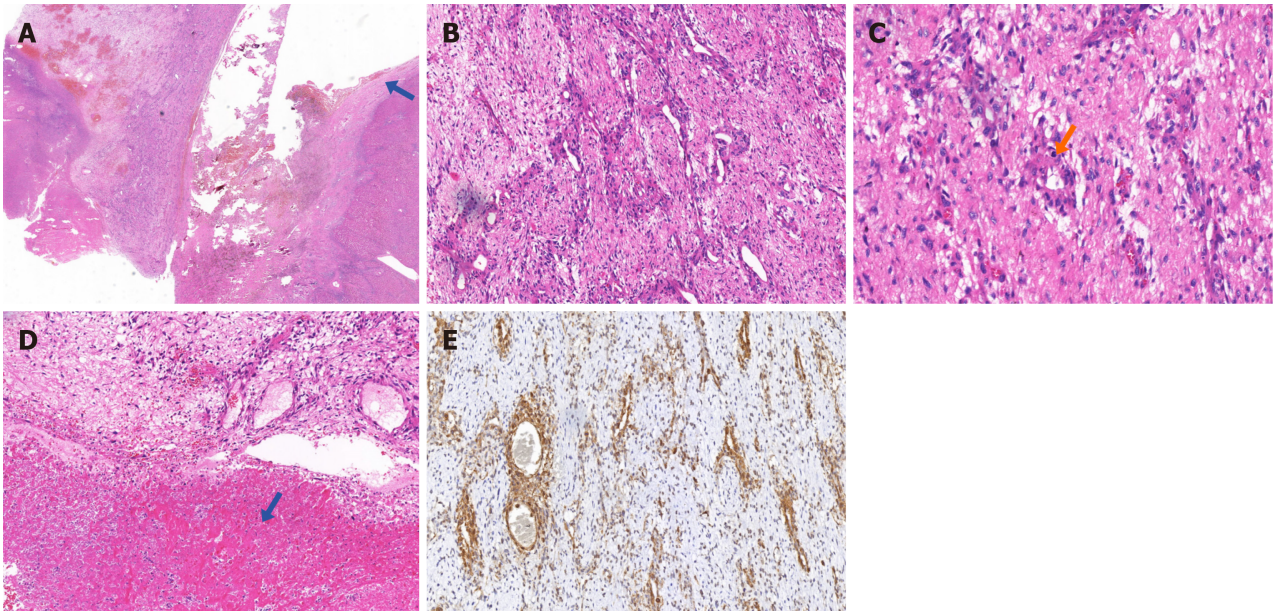


Figure 2 Immunostaining results of the first surgery. A: The left half is tumor tissue and the right half is normal liver tissue. The tumor cells did not significantly invade the normal liver tissue. The arrow indicates a thickened but intact liver capsule (magnification power: 10 ×); B: Tumor cells in a concentric pattern around the blood vessels (magnification power: 100 ×); C: Abnormal mitotic figures appearing in the tumor cells (magnification power: 200 ×); D: Areas of necrosis within the tumor (magnification power: 100 ×); E: Diffuse smooth muscle actin expression in tumor cells (magnification power: 100 ×).

Cases diagnosed as malignant myopericytoma are very rare. The keywords "malignant myopericytoma" were used to search relevant studies in PubMed, Web of Science, GeenMedical, and Google scholar literature databases. Additional literature was identified through hand searches of the references of retrieved literature. After review, we identified fourteen cases of malignant myopericytoma, the characteristics of which are summarized in Table 1[13-19]. By extracting the clinical manifestations, diagnoses and treatment of each case, we noticed that the majority of cases found the lump at first unintentionally or the patient felt mild pain and had symptoms due to the mass pressing on the surrounding organs or nerve tissue. Pathology is the main criterion for the diagnosis of malignant myopericytoma, but the lack of unified diagnostic criteria in imaging and laboratory tests poses a great challenge to the early diagnosis of the disease. In these cases, enhanced magnetic resonance imaging (MRI) and CT are the most commonly used imaging methods. Contrast-enhanced T1-weighted MRI showed that the mass was irregular or lobulated with clear edges, and some cases were accompanied by annular enhancement of the edge of the mass or partial necrosis. The imaging findings of CT are similar

Table 1 Clinical features of reported malignant myopericytomas

Case	Sex/age	Site	Presenting symptoms	Treatment	Follow up	Ref.
1	F/81	Left side of neck	Rapidly growing painless mass	Excision	Liver metastasis 9 months after diagnosis. Alive with disease at 24 months	McMenamin and Fletcher [14], 2002
2	M/46	Left posterior thigh	Painful deep-seated intermuscular mass	Excision, postoperative adjuvant radiotherapy	Metastasis to the heart, brain, liver, and bone after 6 months. Death from the disease at 7 months	McMenamin and Fletcher [14], 2002
3	M/19	Dermis/subcutaneous tissue of the right heel	Painful mass	Below-knee amputation	Metastatic disease and death within 1 yr	McMenamin and Fletcher [14], 2002
4	F/80	Superficial mass of the left upper arm	Superficial painless mass	Marginal excision followed by wide excision	No metastasis. Discharged after 8 months of follow-up	McMenamin and Fletcher [14], 2002
5	F/67	Mass in the superior mediastinum	Short history of superior vena cava obstruction	Excision of cutaneous metastatic deposit	Metastasis disease to the skin and subcutaneous tissue. Died of respiratory failure within 1 month	McMenamin and Fletcher [14], 2002
6	M/61	Lower leg	Subcutaneous painless mass	Marginal excision, recurrence after 12 months treated by wide excision	Disease free a 3 yr	Mentzel *et al* [9], 2006
7	M/30	Lower leg	Obstructive periampullary mass with jaundice	Biopsy and pancreaticoduodenectomy	Liver metastasis 8 months after diagnosis	Ramdial *et al* [15], 2011
8	M/52	Floor of the left atrial wall	Sudden decrease in left vision	Excision of cardiac mass. Excision of metastatic brain tumor followed by γ-knife radiotherapy. Laminectomy and vertebral fixation due to vertebral metastases	Alive with metastatic disease at 8 months	Mainville *et al* [12], 2015
9	M/38	Intradural tumor of the lower spine (L5/S1)	Progressing painful in the right calf during sport	Excision	Disease free after 18 months	Holling *et al* [16], 2015
10	M/65	Dermis/subcutaneous tissue of the right arm	Enlarging painless mass	Excision	Disease free after 5 months	Patrick *et al* [13], 2016
11	F/15	Left shoulder region	Slowly growing mass	Excision, postoperative chemotherapy and radiotherapy	Disease free after 18 months	Binesh *et al* [17], 2016
12	M/56	Subcutaneous tissue left armpit	Pain of left shoulder mass	Preoperative chemotherapy, excision	Disease free after several years	Chen *et al*[18], 2017
13	M/33	Intracranial	New onset seizures	Excision	Disease free after 12 months	Conradie *et al* [19], 2021
14	M/65	Colon	Right upper quadrant pain	Excision	Metastatic disease to the liver and death within 1 yr	This case

to MRI, and the combination of the two may be helpful to diagnosis. Ultrasonography is more commonly used for masses that occur in superficial tissue and present as well-demarcated heterogeneous solid mass. Surgery is currently the only effective intervention. Of the fourteen patients who underwent surgery, seven had varying degrees of recurrence and metastases, and four patients died within one year, indicating a high degree of malignancy and poor prognosis of the tumor. Similar to benign tumors, malignant myopericytomas originating in the extremities are the most common, while the liver appears to be a common site for metastases. Amongst the seven patients with metastasis, four had lesions in the liver. This is likely due to hematogenous spread *via* the abundant blood supply to the liver. All histopathology showed concentric growth of tumor cells around blood vessels, intense expression of SMA, accompanied by increased mitotic activity, nuclear atypia, necrosis and other malignant features.

Here, we report a case of malignant myopericytoma that was indistinguishable on imaging from a liver tumor, which we finally determined actually occurred in the colon. There was a lack of concordance between diagnostic imaging (from both axial and coronal planes) and histopathologic results. Imaging showed that the mass was located within the liver parenchyma and had enhancing edges. Therefore, even if no cirrhosis and/or tumor index anomalies were found, in retrospect, we prefer a hepatic malignancy as the primary diagnosis. During surgery, we found that the mass was grossly

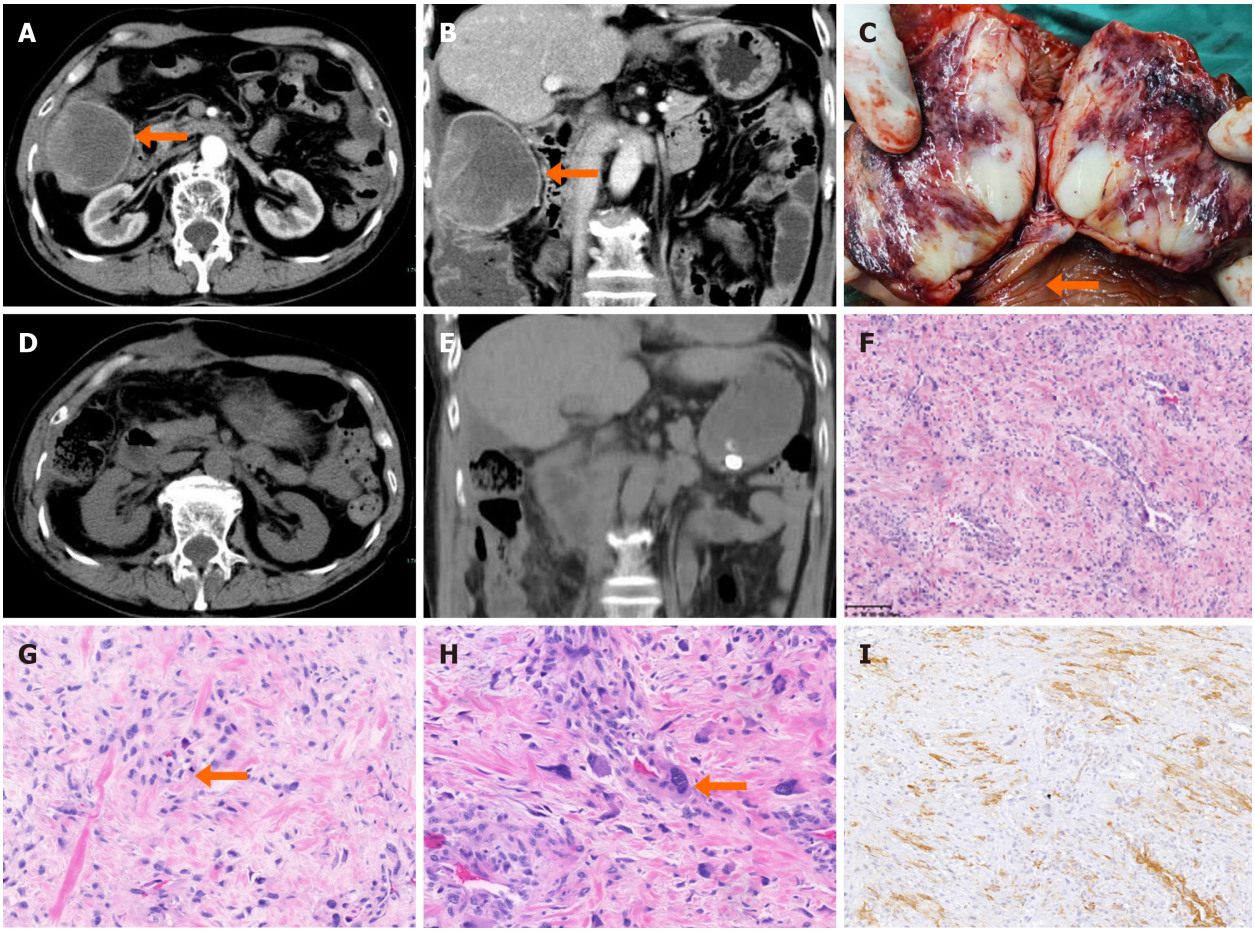


Figure 3 Imaging and immunohistochemical analysis before and after the second operation. A: Axial computed tomography view of the tumor prior to surgery; B: Coronal view of the tumor prior to surgery; C: Gross specimen of tumor tissue. The arrows show the mucosal layer of the colon; D: Axial view after surgery; E: Coronal view after surgery; F: Tumor cells in a concentric pattern around the blood vessels (magnification power: 100 ×); G: Abnormal mitotic figures in the tumor cells (magnification power: 200 ×); H: Hematoxylin and eosin staining revealed tumor giant cells (magnification power: 200 ×); I: Smooth muscle actin was diffusely expressed in tumor cells (magnification power: 100 ×).

adherent to both the liver and colon. We excised portions of liver and colonic tissue *en bloc* to include the intact mass. It was still considered to be an exogenous liver tumor at the end of the operation until histopathology overturned our diagnosis. The pathological report showed that the tumor cells grew around the blood vessels in a typical concentric circle pattern, with increased mitoses, atypia and diffuse expression of SMA. The lesion did not invade the surrounding liver tissue. It was considered as a malignant myopericytoma originating from the colon and surrounding the liver. Due to the rarity of malignant myopericytoma, there is no effective treatment and complete surgical resection is regarded as the best option. Adjuvant therapy is being tried for some patients. One patient received postoperative radiotherapy and six courses of chemotherapy (ifosfamide-etoposide/cyclophosphamide, vincristine-doxorubicin), no recurrence after surgery. But the other patient had no tumor response after receiving two standard courses of theprubicin combined with ifosfamide chemotherapy regimen[14,18]. There are no reports of receiving immunotherapy and targeted therapy at present. As more cases emerge, the possibility of diversified adjuvant therapy will be further explored.

The pathophysiological mechanism of malignant myopericytoma is unclear. This is the main reason for the lack of treatment. Some studies have indicated that BRAF and PDGFRB may be involved in the occurrence and progression of myopericytoma. BRAF is an important component in the regulation of MAPK signaling pathway. Sadow *et al*[20] discovered $BRAF^{V600E}$ mutation in a comprehensive genetic test of myopericytoma. $BRAF^{V600E}$ mutation greatly enhanced the adhesion, migration and angiogenesis of tumor cells by upregulating the expression of some key molecules that influence extracellular matrix remodeling, angiogenesis and tumor microenvironment, which ultimately may lead to invasiveness. PDGFRB is a receptor tyrosine kinase and plays an important role in cell proliferation, migration and vascular development. Its abnormal expression is considered to be a significant cause of various forms of potentially malignant diseases. In a study by Hung *et al*[21], genetic testing found that all myopericytoma cases harbored PDGFRB mutations, strongly suggesting the role of PDGFRB signaling in the pathogenesis of myopericytoma. However, due to their small sample size, these results have not been replicated in other studies[22,23]. The genetic drivers of myopericytoma remain poorly understood. Further basic science and clinical studies of this rare neoplasm are warranted in the future in order to better understand the etiology, improve the diagnosis and determine the optimal clinical management of this rare pathology.

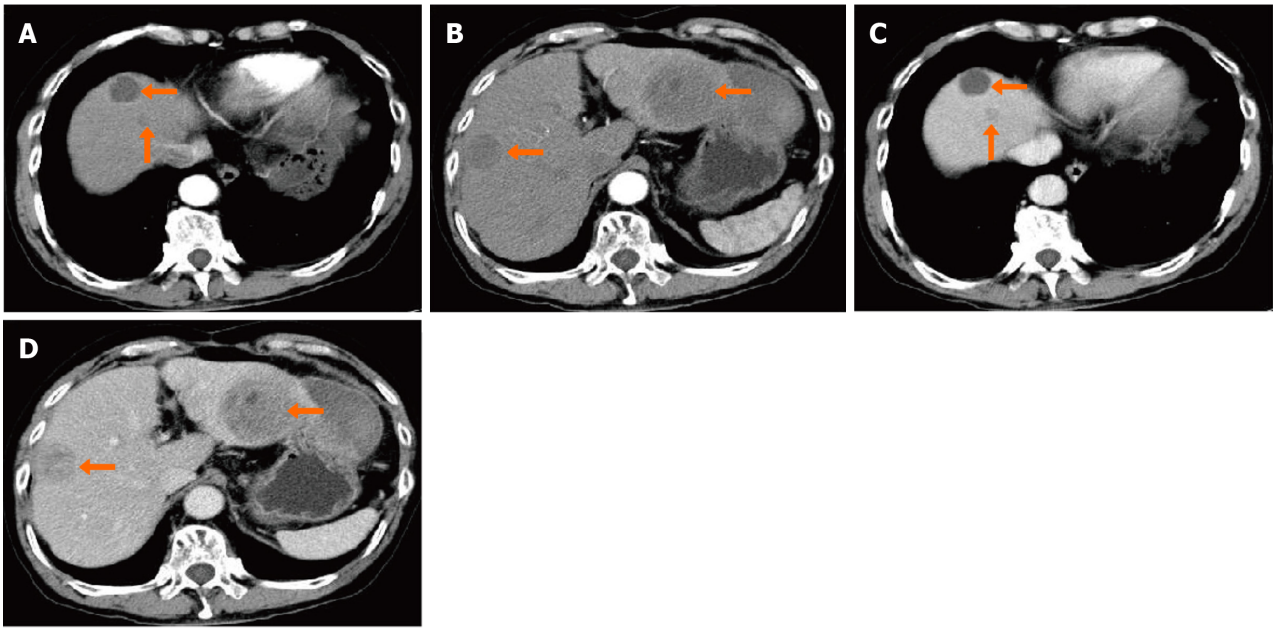


Figure 4 First surveillance enhanced abdominal computer tomography scan. A and B: Axial view of the tumor in the arterial phase; C and D: Axial view of the tumor in the venous phase.

CONCLUSION

We report for the first time a rare case of malignant myopericytoma originating from the colon, which was difficult to differentiate radiographically from a liver neoplasm. The patient had no background of hepatitis or gastrointestinal symptoms and presented only with abdominal pain after hemorrhage into the tumor occurred. Exogenous malignant myopericytomas occurring in deep tissue are asymptomatic or cause only mild symptoms, which are easy to ignore when they are not ruptured. In light of both a lack of established treatment pathways and successful adjuvant treatments, complete surgical excision is the currently preferred treatment. Ongoing molecular studies may uncover key signaling pathways that could provide better diagnostic and therapeutic approaches in the future.

FOOTNOTES

Author contributions: Zhang HL participated in the formulation of clinical diagnosis and treatment plan, collected the clinical data, and wrote the manuscript; Zhang M performed the histopathological diagnosis and contributed to the manuscript drafting; Guo JQ collected the clinical data and performed the follow-up; Wu FN contributed to the manuscript drafting; Zhu JD, Tu CY, and Lv XL supervised the diagnosis and treatment of this patient; Zhang K edited and critically revised the manuscript.

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REFERENCES

1 **Granter SR**, Badizadegan K, Fletcher CD. Myofibromatosis in adults, glomangiopericytoma, and myopericytoma: a spectrum of tumors showing perivascular myoid differentiation. *Am J Surg Pathol* 1998; **22**: 513-525 [PMID: 9591720 DOI: 10.1097/00000478-199805000-00001]

2 **Matsuyama A**, Hisaoka M, Hashimoto H. Angioleiomyoma: a clinicopathologic and immunohistochemical reappraisal with special reference to the correlation with myopericytoma. *Hum Pathol* 2007; **38**: 645-651 [PMID: 17270242 DOI: 10.1016/j.humpath.2006.10.012]

3 **Ide F**, Mishima K, Yamada H, Saito I, Horie N, Shimoyama T, Kusama K. Perivascular myoid tumors of the oral region: a clinicopathologic re-evaluation of 35 cases. *J Oral Pathol Med* 2008; **37**: 43-49 [PMID: 18154577 DOI: 10.1111/j.1600-0714.2007.00594.x]

4 **Inoue T**, Misago N, Asami A, Tokunaga O, Narisawa Y. Myopericytoma proliferating in an unusual anastomosing multinodular fashion. *J Dermatol* 2016; **43**: 557-559 [PMID: 26499100 DOI: 10.1111/1346-8138.13161]

5 **Orenay OM**, Sarifakioglu E, Yildirim U. A perivascular tumour on the wrist; myopericytoma. *J Eur Acad Dermatol Venereol* 2016; **30**: 709-710 [PMID: 25677860 DOI: 10.1111/jdv.13006]

6 **Zhang Z**, Yu D, Shi H, Xie D. Renal myopericytoma: A case report with a literature review. *Oncol Lett* 2014; **7**: 285-287 [PMID: 24348865 DOI: 10.3892/ol.2013.1678]

7 **Agrawal N**, Nag K. Myopericytoma of the thoracic spine: a case report and review of literature. *Spine J* 2013; **13**: e23-e27 [PMID: 24045161 DOI: 10.1016/j.spinee.2013.06.050]

8 **Requena L**, Kutzner H, Hügel H, Rütten A, Furio V. Cutaneous adult myofibroma: a vascular neoplasm. *J Cutan Pathol* 1996; **23**: 445-457 [PMID: 8915853 DOI: 10.1111/j.1600-0560.1996.tb01434.x]

9 **Mentzel T**, Dei Tos AP, Sapi Z, Kutzner H. Myopericytoma of skin and soft tissues: clinicopathologic and immunohistochemical study of 54 cases. *Am J Surg Pathol* 2006; **30**: 104-113 [PMID: 16330949 DOI: 10.1097/01.pas.0000178091.54147.b1]

10 **Agustí J**, Peñas L, Bosch N. Intravascular Myopericytoma of the Plantar Region: Case Report and Discussion of the Probable Origin From a Cutaneous Vascular Malformation. *Am J Dermatopathol* 2016; **38**: 546-548 [PMID: 26959697 DOI: 10.1097/DAD.0000000000000522]

11 **Yang JC**, Venteicher AS, Koch MJ, Stapleton CJ, Friedman GN, Venteicher EM, Shin JH. Myopericytoma at the Craniocervical Junction: Clinicopathological Report and Review of a Rare Perivascular Neoplasm. *Neurosurgery* 2019; **85**: E360-E365 [PMID: 29889275 DOI: 10.1093/neuros/nyy262]

12 **Mainville GN**, Satoskar AA, Iwenofu OH. Primary malignant myopericytoma of the left atrium--a tumor of aggressive biological behavior: report of the first case and review of literature. *Appl Immunohistochem Mol Morphol* 2015; **23**: 464-469 [PMID: 22688352 DOI: 10.1097/PAI.0b013e3182598554]

13 **Patrick A**, Soares-de-Almeida L, Heinz K. Malignant Myopericytoma: Report of a New Case and Review of the Literature. *Am J Dermatopathol* 2016; **38**: 307-311 [PMID: 26863056 DOI: 10.1097/DAD.0000000000000463]

14 **McMenamin ME**, Fletcher CD. Malignant myopericytoma: expanding the spectrum of tumours with myopericytic differentiation. *Histopathology* 2002; **41**: 450-460 [PMID: 12405913 DOI: 10.1046/j.1365-2559.2002.01537.x]

15 **Ramdial PK**, Sing Y, Deonarain J, Singh B, Allopi L, Moodley P. Periampullary Epstein-Barr virus-associated myopericytoma. *Hum Pathol* 2011; **42**: 1348-1354 [PMID: 21411118 DOI: 10.1016/j.humpath.2010.12.001]

16 **Holling M**, Wildförster U, Verheggen R, Müller K, Stummer W, Jeibmann A. Myopericytoma: A Series of 5 Cases Affecting the Nervous System. *World Neurosurg* 2015; **84**: 1493.e5-1493.e8 [PMID: 25931311 DOI: 10.1016/j.wneu.2015.04.041]

17 **Binesh F**, Moghadam RN, Shabani M, Mortazavizadeh MR, Zare S. Malignant Myopericytoma of Shoulder: A Rare Lesion. *APSP J Case Rep* 2016; **7**: 21 [PMID: 27398322 DOI: 10.21699/ajcr.v7i3.421]

18 **Chen W**, Han L, Pang H, Duan L, Zhao Z. Primary malignant myopericytoma with cancer cachexia: Report of the first case and review of literature. *Medicine (Baltimore)* 2017; **96**: e9064 [PMID: 29245316 DOI: 10.1097/MD.0000000000009064]

19 **Conradie JM**, Bonnet EG, Thomas A, Van der Linde G. Intracranial malignant myopericytoma: case report and literature review. *Br J Neurosurg* 2021; 1-5 [PMID: 34259108 DOI: 10.1080/02688697.2021.1950630]

20 **Sadow PM**, Priolo C, Nanni S, Karreth FA, Duquette M, Martinelli R, Husain A, Clohessy J, Kutzner H, Mentzel T, Carman CV, Farsetti A, Henske EP, Palescandolo E, Macconaill LE, Chung S, Fadda G, Lombardi CP, De Angelis AM, Durante O, Parker JA, Pontecorvi A, Dvorak HF, Fletcher C, Pandolfi PP, Lawler J, Nucera C. Role of BRAFV600E in the first preclinical model of multifocal infiltrating myopericytoma development and microenvironment. *J Natl Cancer Inst* 2014; **106** [PMID: 25063326 DOI: 10.1093/jnci/dju182]

21 **Hung YP**, Fletcher CDM. Myopericytomatosis: Clinicopathologic Analysis of 11 Cases With Molecular Identification of Recurrent PDGFRB Alterations in Myopericytomatosis and Myopericytoma. *Am J Surg Pathol* 2017; **41**: 1034-1044 [PMID: 28505006 DOI: 10.1097/PAS.0000000000000862]

22 **Mito JK**, Jo VY. BRAF V600E is not a consistent feature of myopericytoma. *J Cutan Pathol* 2016; **43**: 1248-1249 [PMID: 27870159 DOI: 10.1111/cup.12832]

23 **Agaimy A**, Bieg M, Michal M, Geddert H, Märkl B, Seitz J, Moskalev EA, Schlesner M, Metzler M, Hartmann A, Wiemann S, Mentzel T, Haller F. Recurrent Somatic PDGFRB Mutations in Sporadic Infantile/Solitary Adult Myofibromas But Not in Angioleiomyomas and Myopericytomas. *Am J Surg Pathol* 2017; **41**: 195-203 [PMID: 27776010 DOI: 10.1097/PAS.0000000000000752]

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CASE REPORT

Novel magnetic compression technique for the treatment of postoperative anastomotic stenosis in rectal cancer: A case report

Miao-Miao Zhang, Huan-Chen Sha, Hai-Rong Xue, Yuan-Fa Qin, Xiao-Gang Song, Yun Li, Yu Li, Zheng-Wu Deng, Yu-Lin Gao, Fang-Fang Dong, Yi Lyu, Xiao-Peng Yan

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Abstract

BACKGROUND

The treatment of postoperative anastomotic stenosis after excision of rectal cancer is challenging. Endoscopic balloon dilation and radial incision are not effective in all patients. We present a new endoscopy-assisted magnetic compression technique (MCT) for the treatment of rectal anastomotic stenosis. We successfully applied this MCT to a patient who developed an anastomotic stricture after radical resection of rectal cancer.

CASE SUMMARY

A 50-year-old man had undergone laparoscopic radical rectal cancer surgery at a local hospital 5 months ago. A colonoscopy performed 2 months ago indicated that the rectal anastomosis was narrow due to which ileostomy closure could not be performed. The patient came to the Magnetic Surgery Clinic of the First Affiliated Hospital of Xi'an Jiaotong University after learning that we had successfully treated patients with colorectal stenosis using MCT. We performed endoscopy-assisted magnetic compression surgery for rectal stenosis. The

magnets were removed 16 d later. A follow-up colonoscopy performed after 4 months showed good anastomotic patency, following which, ileostomy closure surgery was performed.

CONCLUSION
MCT is a simple, non-invasive technique for the treatment of anastomotic stricture after radical resection of rectal cancer. The technique can be widely used in clinical settings.

Key Words: Rectal cancer; Magnetic compression technique; Magnetosurgery; Anastomotic stricture; Magnetic surgery clinic; Case report

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Core Tip: Endoscopic balloon dilation and radial incision are commonly used for the treatment of postoperative anastomotic stenosis after surgery for colorectal cancer, but the effect is limited. Magnetic compression technique (MCT) can be used for anastomosis of various parts of the digestive tract. Cases of postoperative anastomotic stricture after colorectal cancer surgery treated by MCT have been rarely reported. We report a patient with low rectal anastomosis who was successfully treated with the MCT. This case report enriches the treatment methods of postoperative anastomotic stenosis of colorectal cancer, which can bring important reference significance for peers.

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INTRODUCTION

The incidence of postoperative anastomotic stenosis following colorectal cancer surgery is relatively low, however, it poses challenges in terms of treatment. Risk factors for anastomotic stenosis include anastomotic leakage, neoadjuvant chemoradiotherapy, gender, postoperative radiotherapy, and anastomotic ischemia[1-5]. The occurrence of anastomotic stenosis precludes the possibility of enterostomy reduction surgery, which adversely affects the quality of life of patients. Endoscopic balloon dilation and radial incision are effective in some patients[6-8], but some patients show poor outcomes. Therefore, the development of effective treatment for postoperative anastomotic stenosis after colorectal cancer surgery is imperative to improve the quality of life of patients. Magnetic compression technique (MCT) is a new surgical technique that can achieve suture-free anastomosis of the digestive tract by leveraging the magnetic force between magnets[9,10]. MCT in combination with endoscopic technique has been used for the treatment of biliary stricture[11-14], ureteral stricture[15,16], and esophageal stricture[17-20]. It has the advantages of simple operation, minimal trauma, and a good therapeutic effect. However, the application of MCT in postoperative anastomotic stenosis after colorectal cancer surgery has rarely been reported. This case report describes the successful use of MCT for the treatment of postoperative anastomotic stricture after radical surgery for rectal cancer.

CASE PRESENTATION

Chief complaints

A 50-year-old man presented with a narrow rectal anastomosis which was discovered 2 months ago during a follow-up colonoscopy following rectal cancer surgery.

History of present illness

The patient had undergone laparoscopic radical resection for rectal cancer 5 months ago. A narrow rectal anastomosis was detected 2 months ago during colonoscopy.

History of past illness

He was diagnosed with type 2 diabetes 5 months ago and his blood sugar has been effectively managed by oral hypoglycemic drugs.

Personal and family history

His family history was unremarkable.

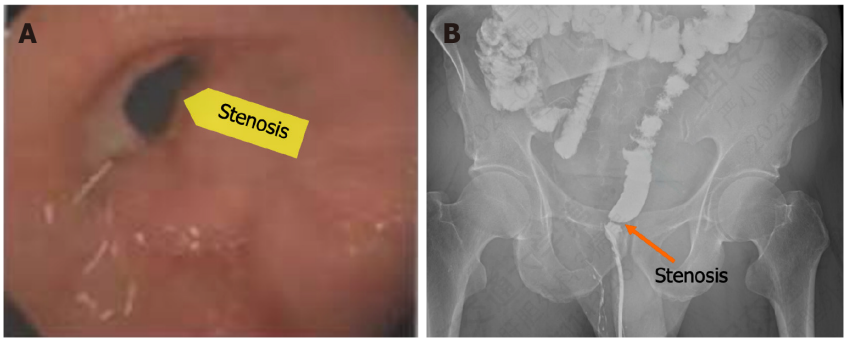


Figure 1 Preoperative examination. A: Colonoscopy image showing the stenosis; B: Colonography.

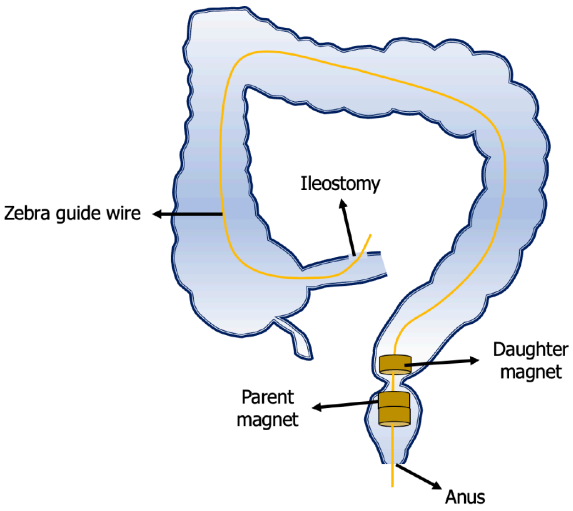


Figure 2 Schematic illustration of the surgical plan. Zebra guide wire was inserted through the ileostomy and pulled out through the anus with the assistance of colonoscopy. The daughter magnet and parent magnets were inserted into the two sides of the rectum stenosis along the zebra guide wire through the ileostomy and the anus, respectively.

Physical examination

Initial physical examination revealed no cardiovascular or respiratory abnormalities. The abdomen was flat and non-tender. An ileostomy was seen on the right side of the abdomen.

Laboratory examinations upon admission

The hematology results were normal.

Imaging examinations

During colonoscopy, a narrow rectal anastomosis located 2 cm above the anus was observed, with a diameter of approximately 5 mm. Anastomotic staples were still present at the site, and the colonoscope could not pass through the narrow rectal anastomosis (Figure 1A). Subsequent, colonography confirmed a stenosis in the lower rectum (Figure 1B).

FINAL DIAGNOSIS

Based on the colonoscopy and colonography, the diagnosis of rectal anastomosis stenosis was established.

TREATMENT

The surgical plan developed by the Multi-disciplinary team of Magnetic Surgery at the First Affiliated Hospital of Xi'an Jiaotong University was shown in Figure 2. The patient and his family members provided written informed consent for the operation. The patient was positioned supine following intravenous anesthesia. Enteroscopy was conducted *via* the ileostomy, reaching the proximal end of the rectal anastomosis. A zebra guide wire was passed through biopsy hole of the colonoscope, and its tip was pulled out through the narrow section of the rectum *via* the anus. The zebra wire was left in

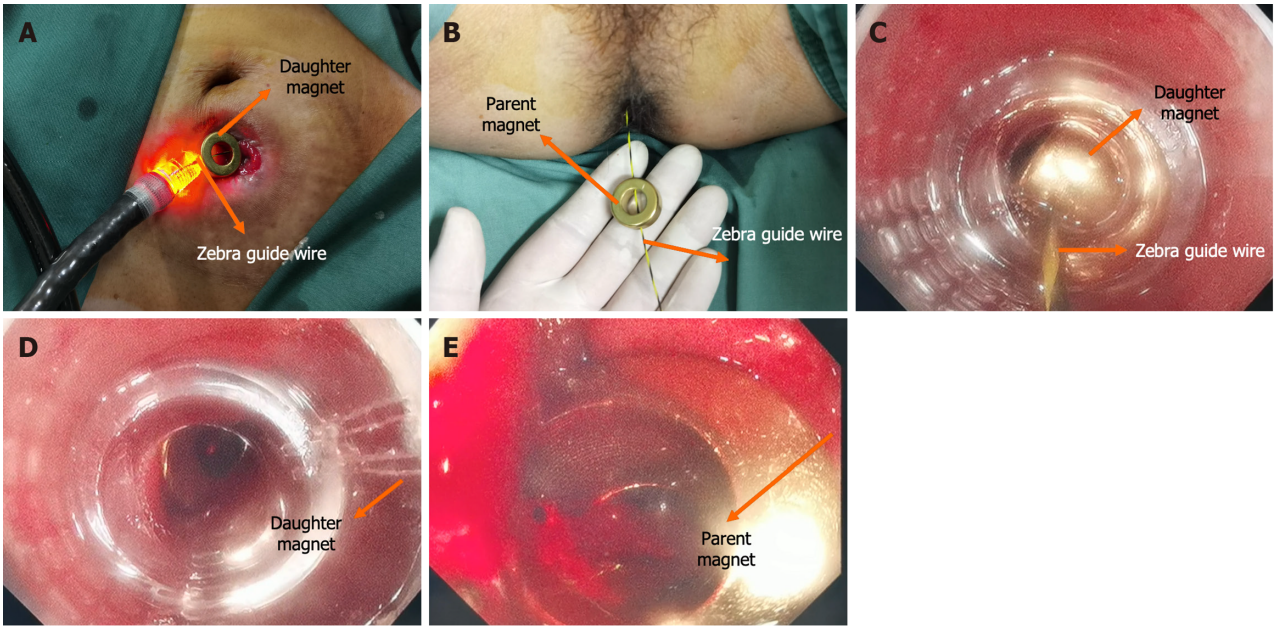


Figure 3 Surgical procedure. A: The daughter magnet was inserted along the zebra guide wire through the ileostomy; B: The parent magnet was inserted along the zebra guide wire through the anus; C: The push process of the daughter magnet; D: The state of the daughter magnet after attraction; E: The state of the parent magnet after attraction.

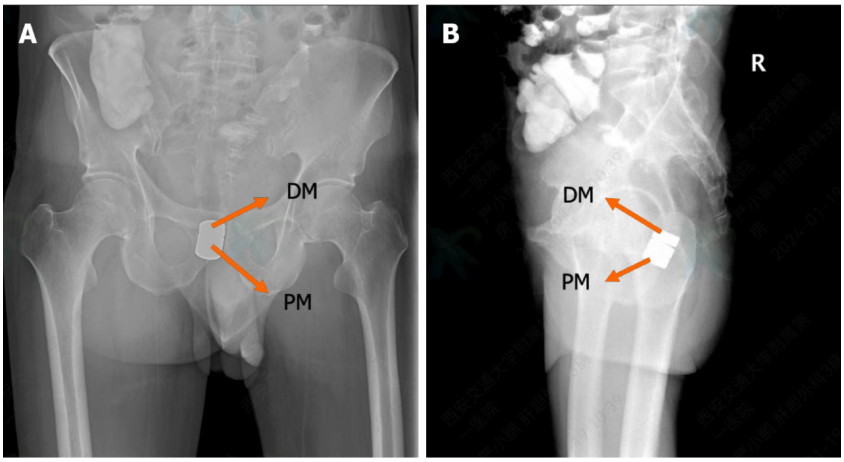


Figure 4 Postoperative x-ray examination. A: Pelvic anteroposterior radiograph showing the attraction state of the daughter and the parent magnets; B: Pelvic lateral radiograph showing the attraction state of the daughter and the parent magnets. DM: Daughter magnet; PM: Parent magnet.

place while the colonoscope was witdrawn. The zebra guide wire located on the side of the ileostomy was passed through the side hole of the daughter magnet and then retrogradely advanced through the biopsy hole of the colonoscope (Figure 3A). The zebra guide wire on the anal side was passed through the side hole of the parent magnet (Figure 3B). The colonoscope was advanced through the ileostomy and pushed the daughter magnet along the zebra guide wire to the proximal end of the rectal anastomosis (Figure 3C). The parent magnet along the zebra guide wire was pushed through the anus. The daughter magnet and the parent magnet were automatically attracted together, following which the zebra guide wire was exited. To increase the magnetic force between the daughter and the parent magnets, another magnet was introduced through the anus. Colonoscopy was performed again through ileostomy and anus to observe the status of daughter magnet and parent magnets (Figures 3D and E). The x-ray examination showed close apposition of the daughter and the parent magnets (Figures 4). Sixteen days after surgery, the daughter and the parent magnets were expelled through the anus (Figure 5A and B). Colonoscopy showed the new anastomosis, and the colonoscope passed smoothly (Figures 5C and D).

OUTCOME AND FOLLOW-UP

Following discharge, the patient insisted on anal dilation treatment using a 20 mm diameter anal dilator. Four months

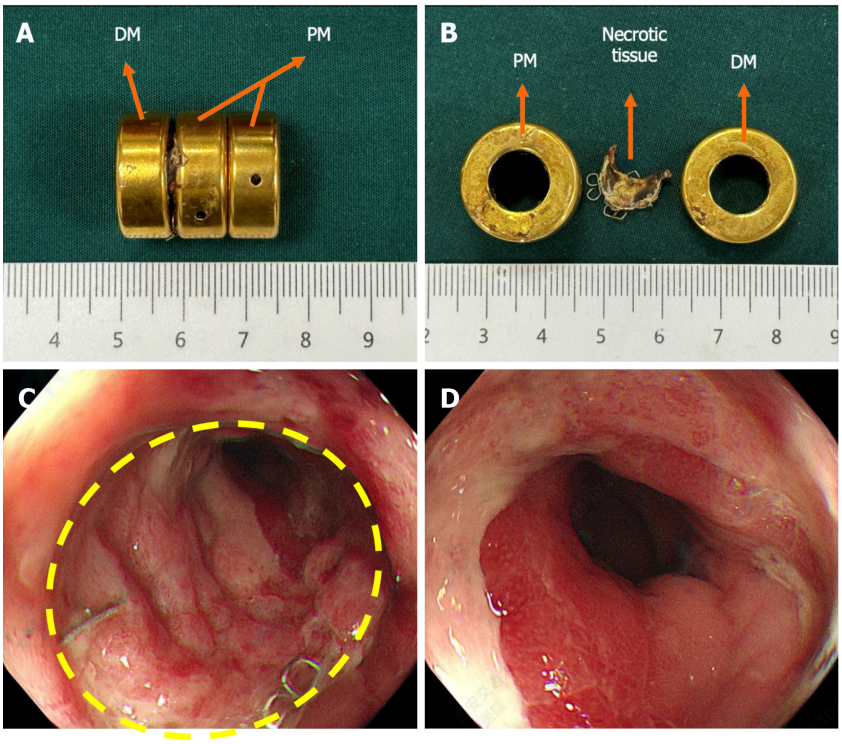


Figure 5 Postoperative colonoscopy. A: The daughter and parent magnets were discharged on the 16th day after surgery; B: The necrotic tissue between the daughter and the parent magnets; C and D: Colonoscopy image showing good patency of magnetic anastomosis. DM: Daughter magnet; PM: Parent magnet.

later, the rectal anastomosis remained good patent, and the ileostomy was successfully closed. The patient experienced normal bowel movements postoperatively.

DISCUSSION

Hyperplasia of the scar tissue is the main pathological cause of anastomotic stenosis after colorectal cancer surgery. Endoscopic balloon dilation and radial incision cannot effectively remove hyperplastic scars, and may even aggravate scar formation. Therefore, there are limited options for the treatment of postoperative anastomotic stenosis of colorectal cancer[6]. The unique anastomotic principle of the MCT makes it effective in treating anastomotic stenosis after operation for colorectal cancer. Firstly, in the treatment of rectal anastomotic stenosis by MCT, the scar of anastomotic hyperplasia is located between the magnets. The continuous magnetic compression induces the pathological change sequence of ischemia-necrosis-shedding[21]. The primary distinction between MCT and other methods like balloon dilation and radial incision lies in the removal of scar tissue. Secondly, MCT does not involve inserting foreign objects into the intestinal wall during the establishment of the anastomosis, reducing the risk of complications such as fistula and infection, further reducing the formation of anastomotic scar. Third, by combining MCT with endoscopic techniques, minimally invasive anastomosis can be achieved, avoiding the trauma and complications associated with traditional surgical procedures.

The present case has some similarities with the previously reported cases where the MCT was used to treat postoperative anastomotic stenosis. However, there are some noteworthy novel aspects of this case. First, the patient had an ileostomy that provided access for the insertion of the daughter magnet. Second, zebra guides wire can pass through the narrow rectal anastomosis, and we chose magnets with holes on the side, which facilitated the placement of magnets. Third, to increase the magnetic force between the daughter magnet and the parent magnet, we inserted two magnets from the anus to act as the parent magnet. Fourth, unlike previous cases, the rectal anastomosis in this patient was near the anus, and there was a risk of anal damage during the magnetic compression process. However, the final results showed that the function of the anus was well maintained. This demonstrated that even if the anastomotic position is very low, the use of MCT does not affect anal function.

CONCLUSION

MCT combined with endoscopic technology can be used for the treatment of postoperative anastomotic stenosis after colorectal cancer surgery. It has the advantages of simple operation, minimal trauma, and good anastomotic patency, making it worthy of widespread clinical application.

FOOTNOTES

Author contributions: Zhang MM, Sha HC, Xue HR, Qin YF, Song XG, Li Y, Li Y, Deng ZW, Gao YL, and Yan XP performed the operation and drafted this manuscript; Dong FF assisted in perioperative care; Yan XP and Lyu Y designed the operation and revised the manuscript; all authors have read and approved the final manuscript.

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REFERENCES

1 **Cong J**, Zhang H, Chen C. Definition and grading of anastomotic stricture/stenosis following low anastomosis after total mesorectal excision: A single-center study. *Asian J Surg* 2023; **46**: 3722-3726 [PMID: 36967350 DOI: 10.1016/j.asjsur.2023.03.027]
2 **Brandt LJ**, Feuerstadt P, Longstreth GF, Boley SJ; American College of Gastroenterology. ACG clinical guideline: epidemiology, risk factors, patterns of presentation, diagnosis, and management of colon ischemia (CI). *Am J Gastroenterol* 2015; **110**: 18-44 [PMID: 25559486 DOI: 10.1038/ajg.2014.395]
3 **Bannura GC**, Cumsille MA, Barrera AE, Contreras JP, Melo CL, Soto DC. Predictive factors of stenosis after stapled colorectal anastomosis: prospective analysis of 179 consecutive patients. *World J Surg* 2004; **28**: 921-925 [PMID: 15593468 DOI: 10.1007/s00268-004-7375-7]
4 **Kirat HT**, Kiran RP, Lian L, Remzi FH, Fazio VW. Influence of stapler size used at ileal pouch-anal anastomosis on anastomotic leak, stricture, long-term functional outcomes, and quality of life. *Am J Surg* 2010; **200**: 68-72 [PMID: 20637338 DOI: 10.1016/j.amjsurg.2009.06.036]
5 **Lee SY**, Kim CH, Kim YJ, Kim HR. Anastomotic stricture after ultralow anterior resection or intersphincteric resection for very low-lying rectal cancer. *Surg Endosc* 2018; **32**: 660-666 [PMID: 28726144 DOI: 10.1007/s00464-017-5718-3]
6 **Kim PH**, Song HY, Park JH, Kim JH, Na HK, Lee YJ. Safe and effective treatment of colorectal anastomotic stricture using a well-defined balloon dilation protocol. *J Vasc Interv Radiol* 2012; **23**: 675-680 [PMID: 22365594 DOI: 10.1016/j.jvir.2011.12.014]
7 **Bravi I**, Ravizza D, Fiori G, Tamayo D, Trovato C, De Roberto G, Genco C, Crosta C. Endoscopic electrocautery dilation of benign anastomotic colonic strictures: a single-center experience. *Surg Endosc* 2016; **30**: 229-232 [PMID: 25835467 DOI: 10.1007/s00464-015-4191-0]
8 **Kawaguti FS**, Martins BC, Nahas CS, Marques CF, Ribeiro U, Nahas SC, Maluf-Filho F. Endoscopic radial incision and cutting procedure for a colorectal anastomotic stricture. *Gastrointest Endosc* 2015; **82**: 408-409 [PMID: 25957477 DOI: 10.1016/j.gie.2015.03.1975]
9 **Wall J**, Diana M, Leroy J, Deruijter V, Gonzales KD, Lindner V, Harrison M, Marescaux J. MAGNAMOSIS IV: magnetic compression anastomosis for minimally invasive colorectal surgery. *Endoscopy* 2013; **45**: 643-648 [PMID: 23807805 DOI: 10.1055/s-0033-1344119]
10 **Gagner M**, Abuladze D, Koiava L, Buchwald JN, Van Sante N, Krinke T. First-in-Human Side-to-Side Magnetic Compression Duodeno-ileostomy with the Magnet Anastomosis System. *Obes Surg* 2023; **33**: 2282-2292 [PMID: 37393568 DOI: 10.1007/s11695-023-06708-x]
11 **Ödemiş B**, Başpınar B, Tola M, Torun S. Magnetic Compression Anastomosis Is a Good Treatment Option for Patients with Completely Obstructed Benign Biliary Strictures: A Case Series Study. *Dig Dis Sci* 2022; **67**: 4906-4918 [PMID: 35050430 DOI: 10.1007/s10620-022-07381-3]
12 **Do MY**, Jang SI, Cho JH, Joo SM, Lee DK. Magnetic compression anastomosis for treatment of biliary stricture after cholecystectomy. *VideoGIE* 2022; **7**: 253-255 [PMID: 35815159 DOI: 10.1016/j.vgie.2022.03.005]
13 **Jang SI**, Cho JH, Lee DK. Magnetic Compression Anastomosis for the Treatment of Post-Transplant Biliary Stricture. *Clin Endosc* 2020; **53**: 266-275 [PMID: 32506893 DOI: 10.5946/ce.2020.095]
14 **Jang SI**, Lee KH, Joo SM, Park H, Choi JH, Lee DK. Maintenance of the fistulous tract after recanalization *via* magnetic compression anastomosis in completely obstructed benign biliary stricture. *Scand J Gastroenterol* 2018; **53**: 1393-1398 [PMID: 30351979 DOI: 10.1080/00365521.2018.1526968]

15 **An Y**, Zhang M, Xu S, Deng B, Shi A, Lyu Y, Yan X. An experimental study of magnetic compression technique for ureterovesical anastomosis in rabbits. *Sci Rep* 2023; **13**: 1708 [PMID: 36720998 DOI: 10.1038/s41598-023-27715-z]

16 **Shlomovitz E**, Copping R, Swanstrom LL. Magnetic Compression Anastomosis for Recanalization of Complete Ureteric Occlusion after Radical Cystoprostatectomy. *J Vasc Interv Radiol* 2023; **34**: 1640-1641 [PMID: 37620060 DOI: 10.1016/j.jvir.2023.04.005]

17 **Krishnan N**, Pakkasjärvi N, Kainth D, Danielson J, Verma A, Yadav DK, Goel P, Anand S. Role of Magnetic Compression Anastomosis in Long-Gap Esophageal Atresia: A Systematic Review. *J Laparoendosc Adv Surg Tech A* 2023; **33**: 1223-1230 [PMID: 37603306 DOI: 10.1089/lap.2023.0295]

18 **Evans LL**, Chen CS, Muensterer OJ, Sahlabadi M, Lovvorn HN, Novotny NM, Upperman JS, Martinez JA, Bruzoni M, Dunn JCY, Harrison MR, Fuchs JR, Zamora IJ. The novel application of an emerging device for salvage of primary repair in high-risk complex esophageal atresia. *J Pediatr Surg* 2022; **57**: 810-818 [PMID: 35760639 DOI: 10.1016/j.jpedsurg.2022.05.018]

19 **Holler AS**, König TT, Chen C, Harrison MR, Muensterer OJ. Esophageal Magnetic Compression Anastomosis in Esophageal Atresia Repair: A PRISMA-Compliant Systematic Review and Comparison with a Novel Approach. *Children (Basel)* 2022; **9** [PMID: 35892616 DOI: 10.3390/children9081113]

20 **Sterlin A**, Evans L, Mahler S, Lindner A, Dickmann J, Heimann A, Sahlabadi M, Aribindi V, Harrison MR, Muensterer OJ. An experimental study on long term outcomes after magnetic esophageal compression anastomosis in piglets. *J Pediatr Surg* 2022; **57**: 34-40 [PMID: 34656308 DOI: 10.1016/j.jpedsurg.2021.09.032]

21 **Zhang M**, Lyu X, Zhao G, An Y, Lyu Y, Yan X. Establishment of Yan-Zhang's staging of digestive tract magnetic compression anastomosis in a rat model. *Sci Rep* 2022; **12**: 12445 [PMID: 35859162 DOI: 10.1038/s41598-022-16794-z]

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CASE REPORT

Magnetic compression anastomosis to restore biliary tract continuity after obstruction following major abdominal trauma: A case report

Miao-Miao Zhang, Jie Tao, Huan-Chen Sha, Yun Li, Xiao-Gang Song, Oliver J Muensterer, Fang-Fang Dong, Li Zhang, Yi Lyu, Xiao-Peng Yan

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Abstract

BACKGROUND

The combination of magnetic compression anastomosis (MCA) and endoscopy has been used to treat biliary stricture after liver transplantation. However, its use for the treatment of complex biliary obstruction after major abdominal trauma has not been reported. This case report describes the successful use of MCA for the treatment of biliary obstruction resulting from major abdominal trauma.

CASE SUMMARY

A 23-year-old man underwent major abdominal surgery (repair of liver rupture, right half colon resection, and ileostomy) following a car accident one year ago. The abdominal drainage tube, positioned at the Winslow foramen, was draining approximately 600-800 mL of bile per day. During the two endoscopic retrograde cholangiopancreatography procedures, the guide wire was unable to enter the common bile duct, which prevented placement of a biliary stent. MCA combined

with endoscopy was used to successfully achieve magnetic anastomosis of the peritoneal sinus tract and duodenum, and then a choledochoduodenal stent was placed. Finally, the external biliary drainage tube was removed. The patient achieved internal biliary drainage leading to the removal of the external biliary drainage tube, which improved the quality of life.

CONCLUSION
Magnetic compression technique can be used for the treatment of complex biliary obstruction with minimal operative trauma.

Key Words: Magnetic compression anastomosis; Magnetosurgery; Endoscopy; Magnetic Surgery Clinic; Biliary obstruction; Case report

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Core Tip: In cases of severe biliary stenosis or occlusion, performing endoscopic balloon dilation or biliary stent implantation *via* endoscopic retrograde cholangiopancreatography is sometimes not possible. There are some research reports on the use of magnetic compression anastomosis (MCA) to treat biliary stricture or occlusion. However, the use of MCA in the treatment of complex biliary obstruction after abdominal trauma has not been reported. This study reports the successful treatment of a patient with complex biliary obstruction after abdominal trauma with MCA.

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INTRODUCTION

Benign biliary strictures are a common occurrence following biliary surgery or liver transplantation[1-3]. These strictures can typically be treated with endoscopic balloon dilation and biliary stent implantation[4,5]. However, in cases with severe stenosis or occlusion, endoscopic retrograde cholangiopancreatography (ERCP) treatment may not be successful [6]. Percutaneous transhepatic biliary drainage is currently the only non-surgical treatment option available for these patients. However, long-term biliary drainage adversely affects the quality of life of these patients. Magnetic compression anastomosis (MCA) has recently emerged as a potential treatment option for severe benign biliary strictures[7-10]. In this report, we present a successful case of abdominal sinus and duodenal MCA in a patient with severe biliary tract injury following abdominal trauma.

CASE PRESENTATION

Chief complaints

One year after undergoing surgery for abdominal trauma, the bile was draining externally for 7 months.

History of present illness

A 23-year-old man underwent surgery for repair of liver rupture, right half colon resection, and ileostomy following a car accident one year ago. Postoperatively, he developed a complex abdominal infection, biliary leakage, abdominal wall incision infection, and intestinal fistula. Following conservative treatment, which included anti-infection measures, nutritional support, and abdominal drainage, his condition remained stable. Seven months later, the abdominal drainage tube, positioned at the Winslow foramen, was draining approximately 600-800 mL of bile per day. A contrast agent was injected *via* the abdominal drainage tube to visualize the middle and upper segments of the common bile duct, hepatic duct, and intrahepatic bile duct. However, the lower segments of the common bile duct were not visualized. During the two ERCP procedures, the guide wire was unable to enter the common bile duct, which prevented the placement of the biliary stent. For further treatment, the patient was admitted to the Magnetic Surgery Clinic of the First Affiliated Hospital of Xi'an Jiaotong University.

History of past illness

The past medical history was unremarkable.

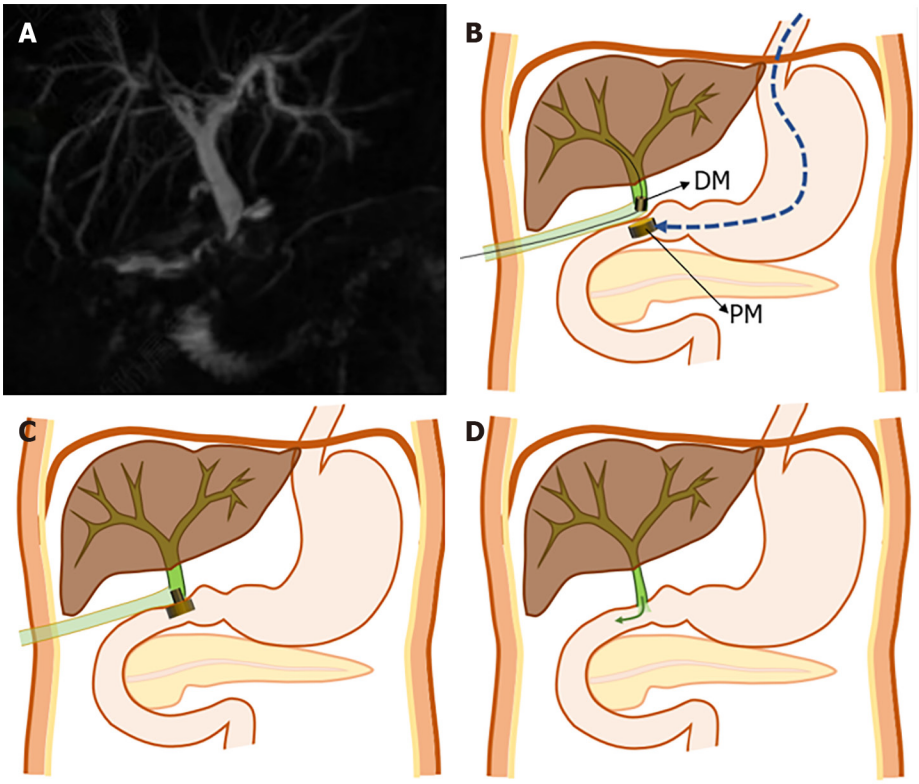


Figure 1 The surgical planning of abdominal sinus-duodenal magnetic compression anastomosis. A: Magnetic resonance cholangiopancreatography; B: Schematic illustration of the placement process of daughter magnet and parent magnet; C: The parent and daughter magnets are in apposition; D: The magnets were expelled and abdominal sinus-duodenal anastomosis was established. DM: Daughter magnet; PM: Parent magnet.

Personal and family history
There was no relevant family history.

Physical examination
The patient's vital signs were stable. Physical examination showed no cardiorespiratory abnormalities. Abdominal examination revealed an old surgical incision scar and a partial abdominal wall defect. An abdominal tube draining brown bile was seen on the right side of the abdomen. The descending ileostomy was visible in the right lower abdomen. The abdomen was flat and soft, with no abdominal tenderness. There was no shifting dullness, and bowel sounds were normal.

Laboratory examinations
Abnormal laboratory parameters included: serum alanine aminotransferase 205 U/L; aspartate aminotransferase 108 U/L; alkaline phosphatase 511 U/L; gamma glutamyl transferase 452 U/L; albumin 34.3 g/L; total bilirubin 91.3 μmol/L; direct bilirubin 70.4 μmol/L; indirect bilirubin 20.9 μmol/L.

Imaging examinations
Magnetic resonance cholangiopancreatography revealed dilation of both the intrahepatic and extrahepatic bile ducts, with an unclear structure of the lower segment of the common bile duct (Figure 1A).

FINAL DIAGNOSIS
The final diagnosis was: Biliary obstruction, biliary fistula, ileostomy status, and right hemicolectomy status.

TREATMENT
After the patient declined further abdominal surgery, a MCA was scheduled upon obtaining his informed consent. The surgical plan for the abdominal sinus-duodenal MCA is illustrated in Figure 1B-D. The parent magnet (PM) and daughter magnet (DM) were designed by the authors (Yan XP and Zhang MM) and manufactured by Jinshan Electronic Appliances Ltd. (Xi'an, China). The magnetic force test showed that the magnetic force of the DM and the PM at zero

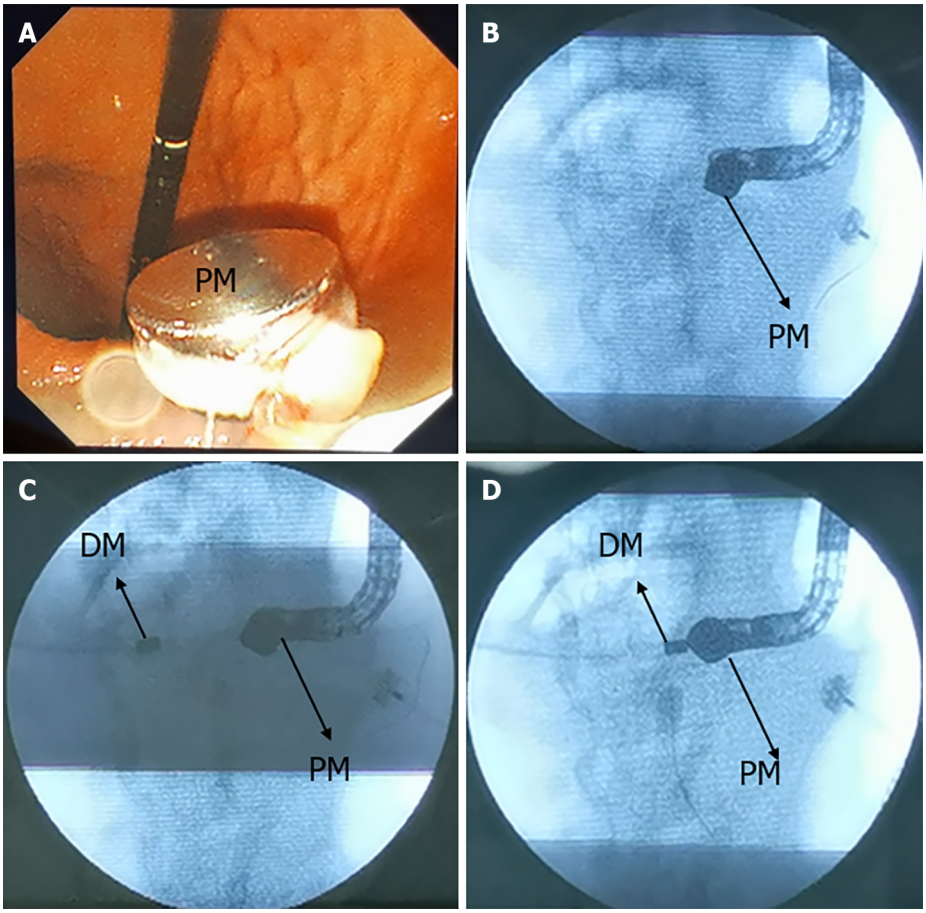


Figure 2 Endoscopic procedure. A: The parent magnet (PM) enters the duodenum; B: The PM is shown in X-ray; C: The daughter magnet (DM) is inserted through the abdominal sinus; D: X-ray shows that the DM is attracted to the PM. DM: Daughter magnet; PM: Parent magnet.

distance is 7.57 N, and the magnetic force at 5 mm is 2.81 N. The PM was guided into the duodenum using a gastroscope while being monitored by X-ray (Figure 2A and B). The DM was then inserted into the lower part of the common bile duct through the abdominal sinus (Figure 2C). The daughter magnet and parent magnet were observed to be in close apposition due to magnetism (Figures 2D and 3A). Subsequently, an indwelling external biliary drainage tube was placed *via* the abdominal sinus. Three days after the operation, the parent and daughter magnets were discharged from the body through the ileostomy (Figure 3B and C). Subsequently, a choledochoduodenal stent was inserted through the magnetic anastomosis channel during an ERCP procedure (Figure 3D). The external biliary drainage tube was removed after three days, and internal biliary drainage was established.

OUTCOME AND FOLLOW-UP

The patient's bilirubin level returned to normal after two weeks, and the serum transaminase level returned to normal after one month. The biliary stent was replaced after three months and was finally removed after 6 months. As of 18-month follow-up, the patient is in a good condition with normal liver function.

DISCUSSION

Several reports have documented the use of MCA in conjunction with ERCP for treating severe benign biliary strictures [6-8]. The magnet placement process is easier when the guide wire can pass through the stenosis. However, the surgical approach becomes more complicated when the guide wire cannot pass through the stenosis. In contrast to previously reported cases, this special case was highly complex due to the absence of the lower biliary duct structure. The patient's only means of clearing bile was through the abdominal sinus. In this case, we used MCA to create a new channel between the abdominal sinus and duodenum instead of abdominal drainage. The establishment of this channel is facilitated using magnetic compression anastomosis, and its unique features. The patient's abdominal drainage tube was removed to allow for internal bile drainage. Follow-up assessments indicated that the patient's overall condition was stable. To the best of our knowledge, MCA between the abdominal sinus and the duodenum has not been reported. The development of flexible magnet designs and placement methods has enabled the successful use of the MCA technique for the treatment of

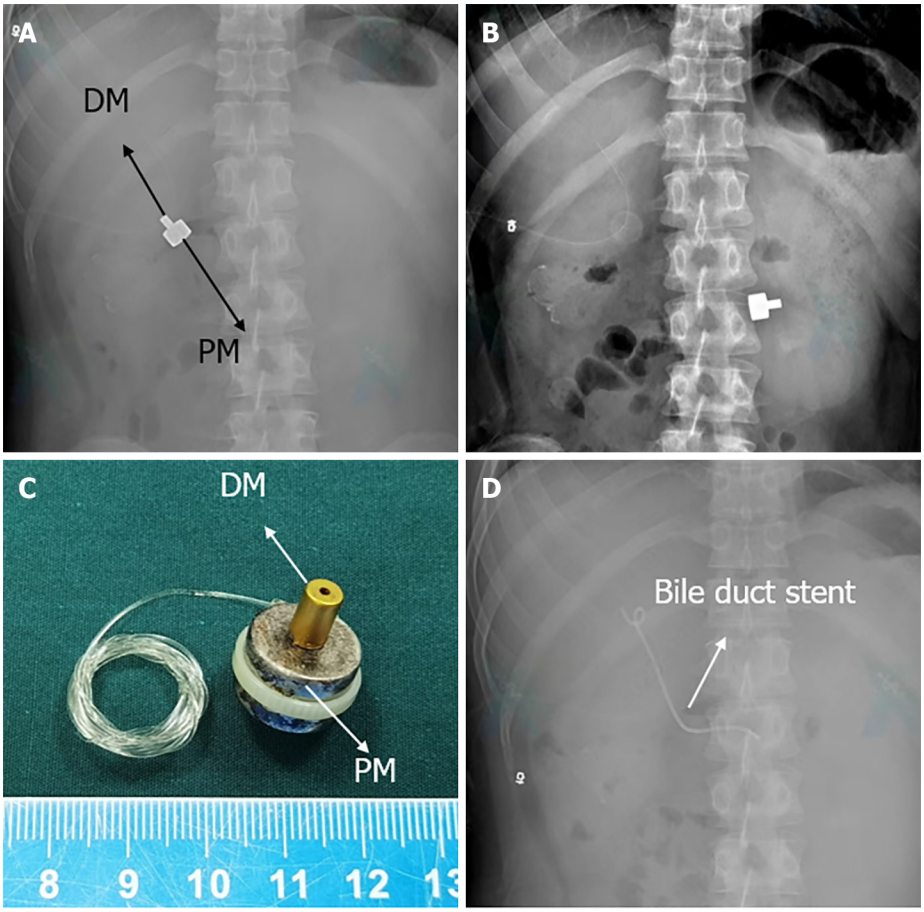


Figure 3 Postoperative abdominal imaging data. A: The state of the magnets one day after the operation; B: The state of the magnets three days after the operation; C: The magnets expelled from the body; D: Biliary stent has been placed at the abdominal sinus-duodenal magnetic anastomosis. DM: Daughter magnet; PM: Parent magnet.

some complex digestive tract stenosis[11].

CONCLUSION

The successful outcome of MCA in the treatment of biliary stenosis in this patient shows the benefits of the technique. Our experience may serve as a valuable reference for treating patients with complex biliary obstruction in the future.

FOOTNOTES

Author contributions: Zhang MM and Tao J contributed equally to this work and are the co-first author; Muensterer OJ, Lyu Y and Yan XP designed the operational plan; Zhang MM, Tao J, Sha HC, Li Y, Song XG and Yan XP performed the endoscopic magnetic compression anastomosis; Dong FF and Zhang L assisted in patient care; Zhang MM and Tao J wrote the manuscript; Zhang MM, Li Y, and Song XG assisted in data collection; Muensterer OJ, Lyu Y and Yan XP contributed to manuscript revision; all authors have read and approved the final manuscript. The reasons for designating Yan XP and Lyu Y as co-corresponding authors are as follows: Yan XP and Lyu Y have equal contributions in study design and making critical revisions to the manuscript. The two co-corresponding authors ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Yan XP and Lyu Y contributed efforts of equal substance throughout the research process. Therefore, Yan XP and Lyu Y are designated as co-corresponding authors in this manuscript.

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REFERENCES

1 **Mascarenhas A**, Marques HP, Coutinho J, Martins A, Nolasco F. Liver cirrhosis requiring transplantation in the context of hepaticojejunostomy stricture after a traumatic bile duct injury. *Radiol Case Rep* 2024; **19**: 835-838 [PMID: 38188946 DOI: 10.1016/j.radcr.2023.11.045]

2 **Yan Q**, Liu Y, Deng FW, Wang FJ, Chen HW. Effects of Preservation of Donor Liver Gastroduodenal Artery on Post-Transplant Biliary Complications in 187 Liver Transplant Recipients: A Retrospective Study. *Ann Transplant* 2023; **28**: e941699 [PMID: 38146150 DOI: 10.12659/AOT.941699]

3 **Ly M**, Lau NS, McKenzie C, Kench JG, Seyfi D, Majumdar A, Liu K, McCaughan G, Crawford M, Pulitano C. Histological Assessment of the Bile Duct before Liver Transplantation: Does the Bile Duct Injury Score Predict Biliary Strictures? *J Clin Med* 2023; **12** [PMID: 37959258 DOI: 10.3390/jcm12216793]

4 **Bofill A**, Cárdenas A. A practical approach to the endoscopic management of biliary strictures after liver transplantation. *Ann Hepatol* 2024; **29**: 101186 [PMID: 38035999 DOI: 10.1016/j.aohep.2023.101186]

5 **Colombo M**, Forcignanò E, Da Rio L, Spadaccini M, Andreozzi M, Giacchetto CM, Carrara S, Maselli R, Galtieri PA, Pellegatta G, Capogreco A, Massimi D, Khalaf K, Hassan C, Anderloni A, Repici A, Fugazza A. Endoscopic management of benign biliary strictures: Looking for the best stent to place. *World J Clin Cases* 2023; **11**: 7521-7529 [PMID: 38078147 DOI: 10.12998/wjcc.v11.i31.7521]

6 **Tan N**, Lubel J, Kemp W, Roberts S, Majeed A. Current Therapeutics in Primary Sclerosing Cholangitis. *J Clin Transl Hepatol* 2023; **11**: 1267-1281 [PMID: 37577219 DOI: 10.14218/JCTH.2022.00068S]

7 **Do MY**, Jang SI, Cho JH, Joo SM, Lee DK. Magnetic compression anastomosis for treatment of biliary stricture after cholecystectomy. *VideoGIE* 2022; **7**: 253-255 [PMID: 35815159 DOI: 10.1016/j.vgie.2022.03.005]

8 **Ödemiş B**, Başpınar B, Tola M, Torun S. Magnetic Compression Anastomosis Is a Good Treatment Option for Patients with Completely Obstructed Benign Biliary Strictures: A Case Series Study. *Dig Dis Sci* 2022; **67**: 4906-4918 [PMID: 35050430 DOI: 10.1007/s10620-022-07381-3]

9 **Jang SI**, Cho JH, Lee DK. Magnetic Compression Anastomosis for the Treatment of Post-Transplant Biliary Stricture. *Clin Endosc* 2020; **53**: 266-275 [PMID: 32506893 DOI: 10.5946/ce.2020.095]

10 **Nakaseko Y**, Shiba H, Yamanouchi E, Takano Y, Sakamoto T, Imazu H, Ashida H, Yanaga K. Successful Treatment of Stricture of Duct-to-Duct Biliary Anastomosis After Living-Donor Liver Transplantation of the Left Lobe: A Case Report. *Transplant Proc* 2017; **49**: 1644-1648 [PMID: 28838456 DOI: 10.1016/j.transproceed.2017.06.008]

11 **Zhang M**, He S, Sha H, Xue H, Lv Y, Yan X. A novel self-shaping magnetic compression anastomosis ring for treatment of colonic stenosis. *Endoscopy* 2023; **55**: E1132-E1134 [PMID: 37875150 DOI: 10.1055/a-2183-8942]

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CASE REPORT

Colo-colonic intussusception as a rare complication of colonoscopy with polypectomy: Two case reports

Sai-Heng Xiang, Guo-Qiang Xu

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Abstract

BACKGROUND

Colonoscopy is the most frequently used diagnostic and therapeutic tool for the treatment of colorectal diseases. Although the complication rate is low, it can be potentially serious. Intussusception is a rare and severe complication often associated with polypectomy. Only a handful of post-colonoscopy intussusception cases have been reported, making this study a valuable addition to the medical literature.

CASE SUMMARY

Case 1: A 61-year-old man underwent colonoscopy with polypectomy for chronic abdominal pain. The patient experienced abdominal pain 11 hours later but was still discharged after pain management. He was readmitted due to recurring pain. Computed tomography (CT) showed colo-colonic intussusception. Initial conservative management and attempts at endoscopic reduction failed; therefore, laparoscopic right hemicolectomy was performed. Histopathological examination revealed tubular adenomas in the polyps and inflammation in the resected specimens. Case 2: A 59-year-old woman underwent colonoscopy with polypectomy for a polyp in the transverse colon. She experienced upper abdominal pain, fever, nausea, and vomiting 9 hours after the procedure. Emergency CT and blood tests revealed a colo-colonic intussusception near the hepatic flexure and an elevated white blood cell count. Initial attempts at endoscopic reduction failed and conservative treatment showed no improvement. She underwent successful laparoscopic reduction and recovered uneventfully. Histopathological examination of the resected polyp revealed hyperplasia.

CONCLUSION

Post-colonoscopy intussusception in adults is rare, and polypectomy may contribute to its occurrence. Early diagnosis is crucial, with prompt CT examination serving as key. After excluding malignancies, conservative management and reduction of intussusception should be considered before surgical bowel

resection.

Key Words: Intussusception; Colonoscopy; Polypectomy; Complication; Case report

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Core Tip: This study discusses two rare cases of colo-colonic intussusception as a complication of colonoscopy with polypectomy in adults. A 61-year-old man and 59-year-old woman developed intussusception after polyp removal during colonoscopy. Both patients underwent unsuccessful conservative and endoscopic reduction interventions, leading to surgical procedures. These findings highlight the importance of early detection using computed tomography and suggest that polypectomy may increase the risk of intussusception. Conservative management should be attempted before surgical resection, assuming that malignancy has been ruled out. This study highlights the importance of awareness and prompt management of this rare complication.

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INTRODUCTION

Colonoscopy is the most frequently used diagnostic and therapeutic tool for colorectal diseases including colorectal tumors, inflammatory bowel disease, and lower gastrointestinal bleeding. The incidence of complications associated with colonoscopy is very low at < 1%[1]. Polypectomy performed during colonoscopy is generally considered safe. However, multiple colonoscopy-related complications may still occur, with the most common being gastrointestinal bleeding, perforation, and cardiopulmonary events, and over 85% of serious complications are reported in patients undergoing colonoscopy with polypectomy[1,2]. Intussusception after colonoscopy in adults is extremely rare and often associated with polypectomy. To the best of our knowledge, only 15 cases of post-colonoscopy intussusception have been reported since the first description by Yamazaki *et al*[3] in 2000.

To raise awareness and provide more information for better management of this unusual condition, we present two cases of intussusception after colonoscopy with polypectomy in adults, followed by a short review of the literature on this condition.

CASE PRESENTATION

Chief complaints

Case 1: A 61-year-old man experienced colicky abdominal pain in the right lower quadrant 11 hours after colonoscopy with polypectomy. Abdominal computed tomography (CT) revealed colo-colonic intussusception.

Case 2: A 59-year-old woman presented with upper abdominal pain and distention 9 hours after colonoscopy with polypectomy. Abdominal CT revealed a colo-colonic intussusception.

History of present illness

Case 1: The patient presented to our hospital with a 10-month history of abdominal pain in the lower right quadrant. Abdominal CT performed 1 month previously showed no positive findings, and colonoscopy performed 7 months previously showed multiple polyps. To further investigate the cause of abdominal pain and remove the polyps, we performed CT enterography (CTE), followed by colonoscopy and polypectomy. The CTE revealed no anomalies.

Colonoscopy was performed under intravenous anesthesia. The quality of bowel preparation was adequate, and no technical difficulties were encountered during colonoscopy. The colonoscopy took 25 minutes, including 11 minutes for intubation and 14 minutes for withdrawal. The terminal ileum was intubated. Three polyps in the sigmoid colon, sized 4-6 mm, were discovered during intubation and removed from the spot by cold snare polypectomy (CSP). Two polyps in the ascending colon near the hepatic flexure, sized 4-5 mm, were discovered during withdrawal and removed by CSP (Figure 1). No other abnormalities were found during colonoscopy. The patient regained consciousness approximately 6 minutes after the procedure and felt well without obvious abdominal discomfort.

Eleven hours later, the patient started to experience colicky abdominal pain in the right lower quadrant with tenderness, but no rebound tenderness. The patient rated the pain as 3 on a scale of 1–10. The pain lasted for 1 hour and was still not relieved; therefore, the doctor on duty administered 10 mg of anisodamine intramuscularly. The patient's pain was relieved. However, only 4 hours later, the pain recurred without tenderness or rebound tenderness. The patient

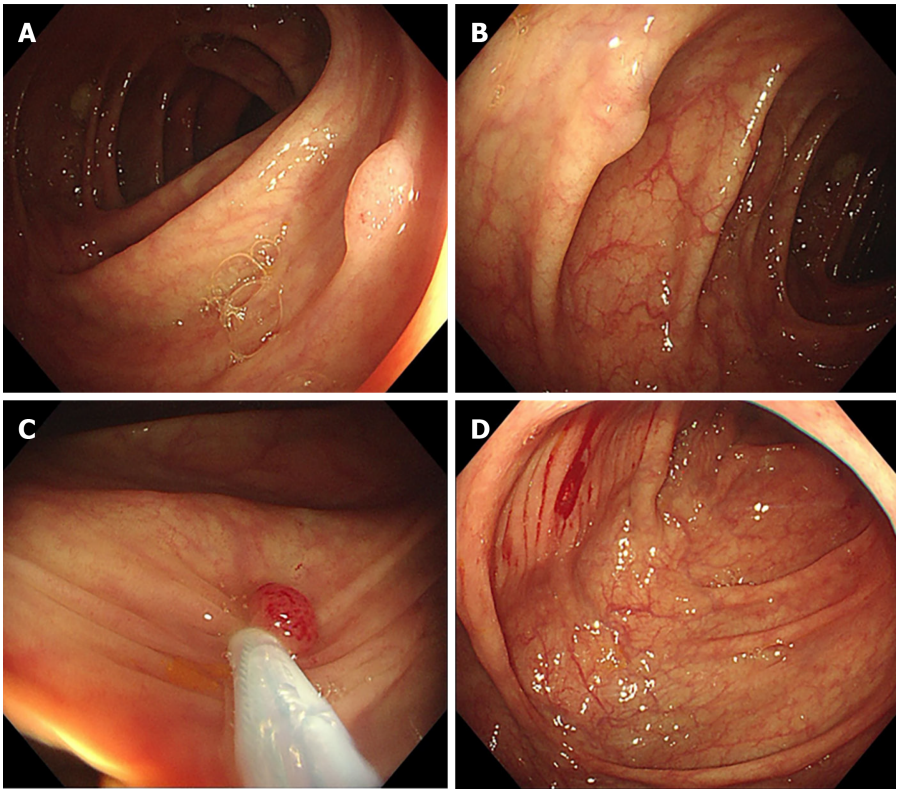


Figure 1 Images of initial colonoscopy of case 1. A and B: Two polyps measuring 4-5 mm in the ascending colon near the hepatic flexure discovered during withdrawal; C: Polyp in Figure 1A removed by cold snare polypectomy (CSP); D: Post-polypectomy wound after CSP of the polyp in Figure 1B.

was administered a second intravenous dose of anisodamine (10 mg). The pain was relieved, and the patient was discharged 2 hours later. However, 8 hours after the patient was sent home, he returned to the emergency room because of recurring colicky abdominal pain in the right lower quadrant.

Case 2: The patient visited our hospital because a polyp was found in the transverse colon during routine colonoscopy three months prior to presentation.

Colonoscopy and endoscopic polypectomy were performed under intravenous anesthesia. The quality of bowel preparation was adequate, and no technical difficulties were encountered during colonoscopy. The terminal ileum was not intubated. Colonoscopy took 36 minutes, including 10 minutes for intubation of the cecum and 26 minutes for withdrawal and polypectomy. A flat polyp measuring 12 mm in the transverse colon near the hepatic flexure was discovered and removed using endoscopic mucosal resection. The mucosal defect was closed using five metal clips (Figure 2). No other abnormalities were found during colonoscopy. Histopathological examination of the resected polyp revealed hyperplasia.

Nine hours after colonoscopy, the patient began to experience pain and distention in the upper abdomen. The pain worsened in the next 2 hours, and the patient rated it 7 on a scale of 1–10. A glycerin enema and antispasmodics (anisodamine and magnesium sulfate) were administered. The pain was briefly alleviated and then intensified again, accompanied by fever, nausea, and vomiting.

History of past illness

Case 1: Past medical history included chronic hepatitis B for 5 years and hepatocellular carcinoma surgery 4 years previously.

Case 2: The patient had a history of cesarean section surgery 30 years previously, and ectopic pregnancy surgery 22 years previously.

Personal and family history

Both patients' personal and family history was unremarkable.

Physical examination

Case 1: Upon returning to the emergency room, an abdominal physical examination revealed moderate tenderness with peritoneal signs in the right lower quadrant. The patient's body temperature was 38 °C, heart rate 93 beats/minute (bpm), respiratory rate 20 breaths/minute, and blood pressure was 101/63 mmHg.

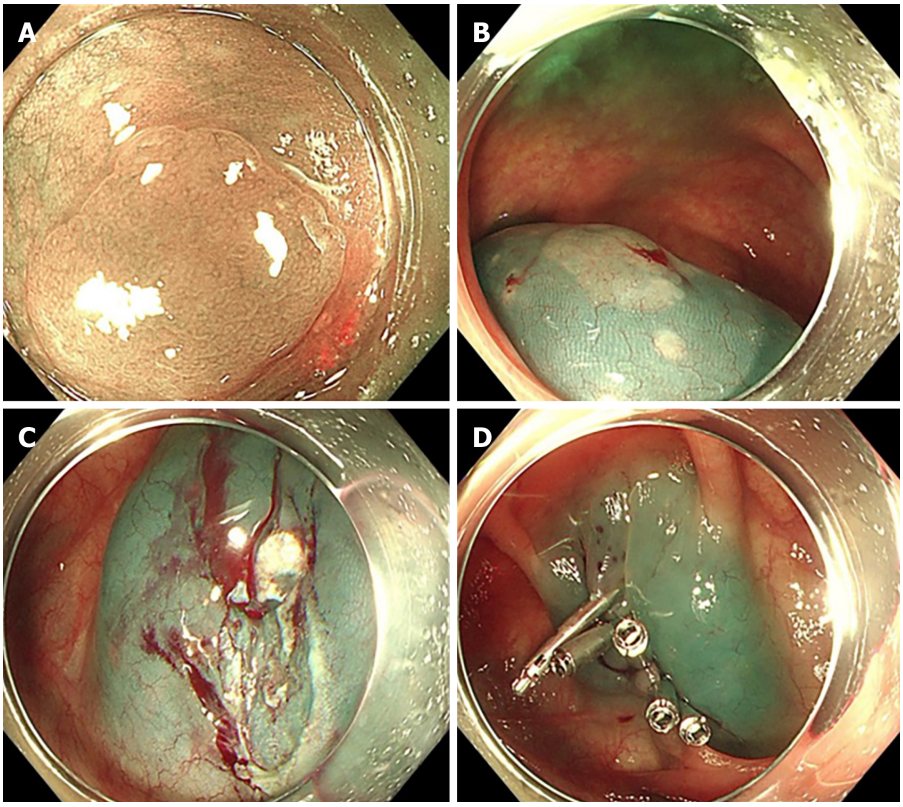


Figure 2 Images of initial colonoscopy of case 2. A-C: A flat polyp measuring 12 mm discovered in the transverse colon near the hepatic flexure, and removed by endoscopic mucosal resection; D: The mucosal defect closed using five metal clips.

Case 2: Initially, the patient exhibited moderate upper abdominal tenderness. After the pain intensified and the patient became febrile, with accompanying nausea and vomiting, the vital signs were recorded as follows: Temperature, 38 °C; heart rate, 106 bpm; respiratory rate, 22 breaths/minute; and blood pressure, 169/91 mmHg. Further examination revealed tenderness and rebound tenderness of the upper abdomen.

Laboratory examinations

Case 1: Laboratory examinations demonstrated an elevated white blood cell count of 14.9 × 10^9/L (normal 4.0-10.0 × 10^9/L), with a predominance of neutrophils (90.9%). The C-reactive protein level was normal (5.07 mg/L; normal 0-8 mg/L).

Case 2: Laboratory examinations demonstrated an elevated white blood cell count of 12.5 × 10^9/L (normal 4.0-10.0 × 10^9/L), with a predominance of neutrophils (77.9%). The C-reactive protein level was normal (1.21 mg/L; normal 0-8 mg/L) at that point and was found to be significantly elevated to 76.92 mg/L 13 hours later, while the complete blood cell count remained similar.

Imaging examinations

Case 1: Urgent abdominal CT revealed a colo-colonic intussusception near the hepatic flexure: The bowel near the hepatic flexure was dilated and the proximal colon was invaginated into it, which appeared as a target-like lesion (Figure 3A). There were no signs of bowel obstruction, perforation, or masses.

Case 2: Emergency abdominal CT revealed metal clips near the hepatic flexure and a target-like lesion with thickened intestinal walls in the distal colon near the clips, indicative of colo-colonic intussusception (Figure 3B).

FINAL DIAGNOSIS

Both patients were diagnosed with colo-colonic intussusception.

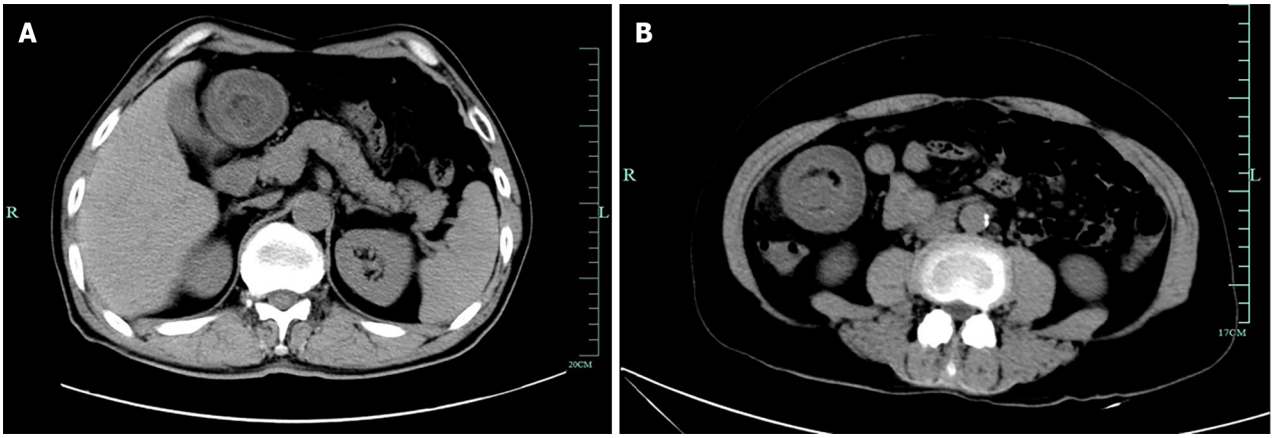


Figure 3 Urgent abdominal computed tomography. A: Urgent abdominal computed tomography (CT) revealing a colo-colonic intussusception near the hepatic flexure; B: Emergency abdominal CT revealing a target-like lesion with thickened intestinal walls.

TREATMENT

Case 1

The patient was readmitted and initially managed conservatively with fasting and the maintenance of intravenous fluids, analgesics (pethidine), antispasmodics (anisodamine), antibiotics (meropenem), antipyretics (indomethacin), and parenteral nutrition. However, the abdominal pain persisted, and the patient passed approximately 20 mL of dark red bloody stool 4 hours after readmittance.

Emergency colonoscopy was performed to attempt endoscopic reduction. Colonoscopy revealed a congested, swollen, purple-red-colored mucosa in the ascending colon near the hepatic flexure invaginating the distal bowel (Figure 4). Repeated attempts to reduce the colo-colonic intussusception by pumping water and air failed.

The patient was then transferred to the operating room for laparoscopic surgery. Intraoperative findings included colo-colonic intussusception in the ascending colon near the hepatic flexure, with significant inflammation and exudation. Due to concerns about possible intestinal necrosis, a laparoscopic right hemicolectomy with intracorporeal anastomosis was performed.

Case 2

Emergency colonoscopy was performed to reduce endoscopic intussusception. Colonoscopy revealed a congested, swollen, and purple-red-colored mucosa in the transverse colon that invaginated the distal bowel. The post-polypectomy wound with metal clips was located approximately 5 cm above the inflamed mucosa and was unaffected by intussusception (Figure 5). Repeated attempts to reduce colo-colonic intussusception by changing the position and pumping water and air failed.

Owing to the patient's unwillingness to undergo surgery, conservative treatment was administered. However, the patient's condition did not improve, and a repeat abdominal CT showed no signs of improvement. Twelve hours after the emergency colonoscopy, the patient was transferred to the operating room for laparoscopic surgery. The intraoperative findings included colo-colonic intussusception in the transverse colon near the hepatic flexure with edema and inflammation. The intussusception was laparoscopically reduced.

OUTCOME AND FOLLOW-UP

Case 1

The patient's postoperative recovery was uneventful, and was discharged 11 days later. No complications occurred.

Histopathological examination of the polyps resected during the initial endoscopy revealed tubular adenomas, whereas the specimen resected laparoscopically showed inflammatory changes with no evidence of malignancy or mass.

Case 2

Postoperative recovery was uneventful, and the patient was discharged 8 days later. No complications occurred.

Both patients shared their perspective that complications are best avoided, and if unavoidable, successful conservative treatment is preferred over surgery; if surgery is necessary, reduction is preferred over resection.

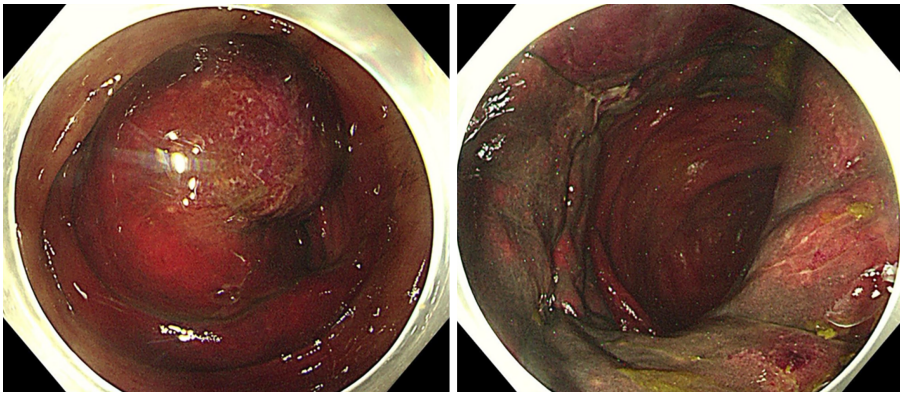


Figure 4 Images of emergency colonoscopy of case 1. Colonoscopy revealing congested, swollen, purple-red-colored mucosa in the ascending colon near hepatic flexure, invaginating into the distal bowel.

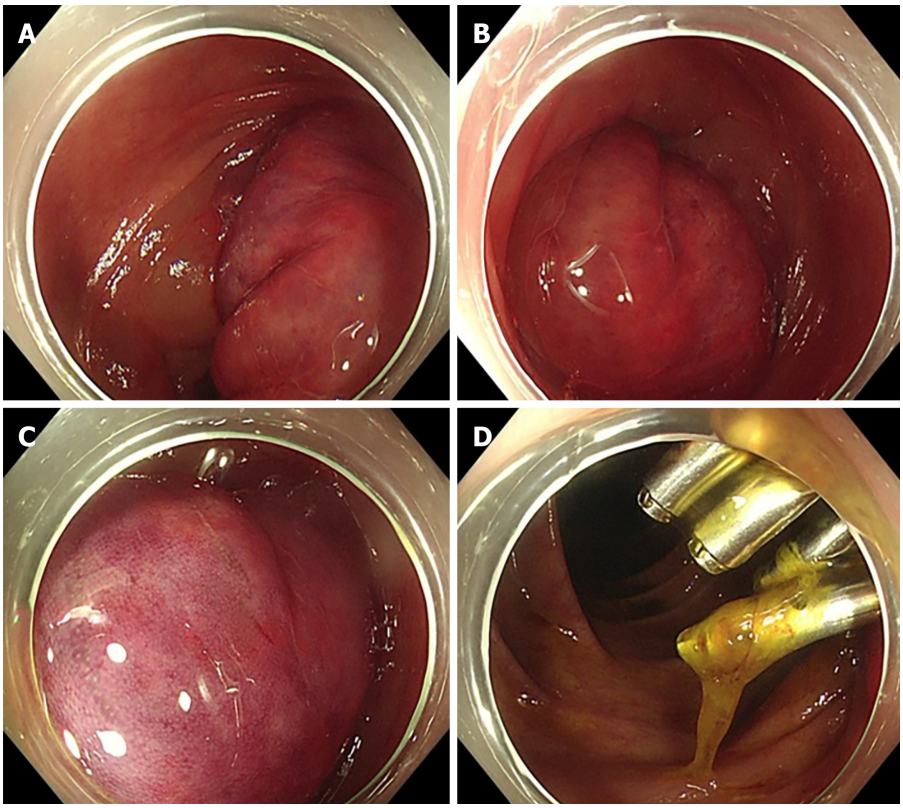


Figure 5 Images of emergency colonoscopy of case 2. A-C: Colonoscopy revealing congested, swollen, and purple-red-colored mucosa in the transverse colon, invaginating into the distal bowel; D: Post-polypectomy wound with metal clips located approximately 5 cm above the inflamed mucosa and not affected by the intussusception.

DISCUSSION

Intussusception after a colonoscopy is exceedingly rare in adults. To date, only 17 cases, including our two cases, have been reported (Table 1)[3-17]. In these cases, the age of patients ranged from 19 to 73 years (average 47.6 years), and the sex ratio was roughly equal (8 males to 9 females). All patients experienced abdominal pain that occurred several hours after colonoscopy as the main clinical symptom, with tenderness as the main abdominal sign. Other less documented symptoms include fever, bloody stools, nausea, and vomiting. Laboratory examination results were documented in 12 cases, all showing elevated white blood cell counts ranging from 10.8 to 22 × 10^9/L (average 14.1 × 10^9/L). All diagnoses of intussusception were made by using abdominal CT. The majority (13 cases, 76.5%) were colo-colic intussusceptions, and only four cases (23.5%) were ileocolic. Almost all lesions occurred in the right colon, except in one case where it was located in the splenic flexure. Endoscopic interventions (biopsies or polypectomies) were performed during the initial colonoscopy in 14 (82.4%) of the 17 cases. Of the remaining three cases, one had a large polyp in the terminal ileum[7], which may serve as a potential cause, whereas the other two seemed normal. Regarding the treatments, four cases were successfully treated conservatively, four underwent laparoscopic reduction, one underwent successful endoscopic

Table 1 Summary of the reported cases of intussusception after colonoscopy

Ref.	Age (years)/sex	Endoscopic intervention	Type of intussusception	Treatment
Yamazaki *et al*[3], 2000	48/male	Biopsy	Cecal colo-colonic	Open resection
Theodoropoulou *et al*[4], 2009	19/male	No	Ileocecal	Open resection
Ho *et al*[5], 2010	32/male	Polypectomy	Cecal colo-colonic	Laparoscopic reduction
Nachnani *et al*[6], 2012	73/female	Biopsy	Ascending colo-colonic	Laparoscopic reduction
Lasithiotakis *et al*[7], 2012	58/male	No	Ileocecal	Open resection
Lee *et al*[8], 2013	47/male	Polypectomy	Cecal colo-colonic	Laparoscopic resection
Min *et al*[9], 2017	31/female	Biopsy	Cecal colo-colonic	Laparoscopic resection
Araki *et al*[10], 2018	28/male	Polypectomy	Cecal colo-colonic	Endoscopic reduction
Hassan *et al*[11], 2018	43/female	Biopsy	Ascending colo-colonic	Conservative management
He *et al*[12], 2020	54/female	Polypectomy and biopsy	Transverse colo-colonic	Conservative management
Ahmed *et al*[13], 2020	42/female	Polypectomy and biopsy	Transverse colo-colonic	Conservative management
Moon *et al*[14], 2022	58/female	Polypectomy	Hepatic flexure colo-colonic	Conservative management
Lee *et al*[15], 2022	69/male	Polypectomy	Ileocecal	Laparoscopic resection
Vadakkenchery *et al*[16], 2022	36/female	No	Splenic flexure colo-colonic	Laparoscopic reduction
Jastaniah *et al*[17], 2023	51/female	Polypectomy	Ileocecal	Laparoscopic resection
Current case 1	61/male	Polypectomy	Ascending colo-colonic	Laparoscopic resection
Current case 2	59/female	Polypectomy	Transverse colo-colonic	Laparoscopic reduction

reduction, five underwent laparoscopic segmental bowel resection, and three underwent open segmental bowel resection. No malignant histopathological findings were observed.

Intestinal intussusception mostly occurs in the small intestine, with only 20% of cases involving solely the large bowel [18]. Less than 5% of intussusceptions occur in adults[19]. Intussusception in adults is usually related to definable causes, with only 10%-20% of all cases being idiopathic[20]. Common causes of adult colonic intussusception include adherence, inflammatory lesions, polyps, and benign or malignant tumors[19]. The most prevalent cause is a pathological lead point in the bowel, which is malignant in half of the cases[17]. However, these causes are not usually present in post-colonoscopy intussusception.

The etiology of intussusception after colonoscopy remains unclear. Several hypotheses have been proposed to explain the phenomenon. Some scholars have suggested that edema or hematoma caused by endoscopic interventions, including biopsy and polypectomy, may serve as a lead point[14,15,17]. The metal clips used after polypectomy may also act as a lead point. This may explain the occurrence of intussusception in our first case, as the location of intussusception observed during emergent colonoscopy was consistent with the site of the prior polypectomy. As mentioned previously, biopsies or polypectomies were performed during the initial colonoscopy in 14 (82.4%) of the 17 cases. However, in our second case, the post-polypectomy wound with metal clips was located approximately 5 cm above the inflamed mucosa and was not affected by intussusception, which implies that the post-polypectomy wound and metal clips were not the lead points. Additionally, no endoscopic interventions were applied in two of the previously reported cases. This finding implies the involvement of other mechanisms. Yamazaki *et al*[3] speculated that the intussusception was induced by hyperperistalsis, which vents gas and empties the insufflated colon after colonoscopy[3]. Hassan *et al*[11] proposed that gas aspiration during colonoscope withdrawal creates a vacuum effect, leading to the collapse and invagination of the proximal colon into the distal colon, which is primarily observed in the right colon because of the mobility and freedom of movement of the cecum within the abdomen[11]. In addition, a history of abdominal surgery may predispose patients to intussusception[9]. Both of our patients underwent abdominal surgery. Another hypothesis suggests that complex bowel loops may form during colonoscopy, potentially leading to transient intussusception[6].

Because its etiology is unclear, it is challenging to determine effective preventive measures. We speculate that measures such as avoiding excessive insufflation during colonoscopy, gentle suction maneuvers, and administration of antispasmodic drugs, such as anisodamine, when hyperperistalsis is observed may potentially reduce the incidence of post-colonoscopy intussusception.

Compared to prevention, early diagnosis may be more practical. Early diagnosis of intussusception improves the prognosis. Prompt CT examination is the key to early diagnosis. In our two cases, the severity of the situation was not initially recognized, resulting in delays in performing abdominal CT scans and instead administering pain management, which led to a delayed diagnosis of intussusception. In our first case, laparoscopic resection was performed instead of reduction because of the potential ischemic necrosis, which could have been avoided if the intussusception had been identified earlier. This served as an important cautionary measure. If abdominal pain accompanied by tenderness occurs within hours to days after colonoscopy, particularly after a polypectomy, abdominal CT should be performed promptly.

Additional manifestations, including elevated white blood cell count, fever, and bloody stools, further indicate the need for urgent CT evaluation.

Traditionally, laparoscopic or open bowel resection has been the standard approach for treating bowel intussusception in adults to allow the examination of specimens for any potential malignancy[18,19]. However, in cases of post-colonoscopy intussusception in which the colon has already been examined and malignancy has been ruled out, we believe that conservative management should be considered prior to surgery. If surgical treatment is necessary, after the exclusion of bowel ischemic necrosis or perforation, reduction should be prioritized over resection. Multiple reports have suggested that intussusceptions with a short-affected segment and no lead-point mass can be managed using a 'wait and see' strategy with regular clinical and imaging evaluations to monitor spontaneous resolution[19]. Endoscopic reduction is seldom performed to treat adult intussusception[19,20]. Only 1 of the 17 patients underwent successful endoscopic reduction, whereas this failed in our two cases. We look forward to the future development of endoscopic reduction techniques with high efficacy, which would be the ideal treatment approach for post-colonoscopy intussusception.

This study has several limitations. First, there have been multiple reports on this condition prior to our report. Second, images obtained during surgery were not preserved. Third, we were unable to identify the exact etiology in the two cases. Finally, we failed to provide preventive measures with definite efficacy. Nevertheless, our report of the two cases provides more detailed information, including details of the initial colonoscopies, abundant original images, and the entire process of disease development, diagnosis, and treatment. This study adds to our knowledge of this rare condition and emphasizes the importance of early recognition. Patient perspectives were also reported in our study. Additionally, we conducted a short review of previous reports on this entity.

CONCLUSION

Intussusception after colonoscopy is rare in adults. The etiology of this condition remains unclear. An edema or hematoma caused by a biopsy or polypectomy may serve as the lead point. No preventive measures have been established. Early diagnosis plays a crucial role in the management of this condition, and prompt CT examination is crucial for early diagnosis. If malignancy is ruled out by the initial colonoscopy, conservative management should be considered before surgery. If surgery is necessary, reduction should be prioritized over resection after excluding bowel ischemic necrosis or perforation.

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FOOTNOTES

Author contributions: Xiang SH contributed to manuscript writing and editing, data collection, and data analysis; Xu GQ guided the treatment and contributed to conceptualization and supervision; All authors have read and approved the final manuscript.

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REFERENCES

1 **Fisher DA**, Maple JT, Ben-Menachem T, Cash BD, Decker GA, Early DS, Evans JA, Fanelli RD, Fukami N, Hwang JH, Jain R, Jue TL, Khan KM, Malpas PM, Sharaf RN, Shergill AK, Dominitz JA; ASGE Standards of Practice Committee. Complications of colonoscopy. *Gastrointest Endosc* 2011; **74**: 745-752 [PMID: 21951473 DOI: 10.1016/j.gie.2011.07.025]

2 **Church J**. Complications of colonoscopy. *Gastroenterol Clin North Am* 2013; **42**: 639-657 [PMID: 23931864 DOI: 10.1016/j.gtc.2013.05.003]

3 **Yamazaki T**, Okamoto H, Suda T, Sakai Y, Hatakeyama K, Hokari I, Toyoda S, Souma T. Intussusception in an adult after colonoscopy. *Gastrointest Endosc* 2000; **51**: 356-357 [PMID: 10699791 DOI: 10.1016/s0016-5107(00)70371-3]

4 **Theodoropoulou A**, Konstantinidis K, Kteniadakis S, Tribonias G, Tzanoudakis G, Vardas E, Karmiris K, Psillakis K, Zois E, Tzortzakakis E, Paspatis GA. Intussusception following enteroscopy and ileo-colonoscopy in an adult with acquired immune deficiency syndrome. *Endoscopy* 2009; **41** Suppl 2: E162-E163 [PMID: 19544281 DOI: 10.1055/s-0029-1214688]

5 **Ho MM**, Park JJ, Prasad LM. Post Colonoscopy Colonic Intussusception Reduced *via* a Laparoscopic Approach. *JSLS* 2010; **14**: 596-599 [PMID: 21605531 DOI: 10.4293/108680810X12924466008727]

6 **Nachnani J**, Burns E, Margolin D, Clarkston WK. Colocolonic intussusception after colonoscopy. *Gastrointest Endosc* 2012; **75**: 223-225 [PMID: 21481863 DOI: 10.1016/j.gie.2011.01.046]

7 **Lasithiotakis K**, Grisbolaki E, Filis D, Athanasakis I, Zoras O, Chalkiadakis G. Ileocolic intussusception precipitated by diagnostic colonoscopy: a case report. *Surg Laparosc Endosc Percutan Tech* 2012; **22**: e161-e163 [PMID: 22678343 DOI: 10.1097/SLE.0b013e31824b230f]

8 **Lee CK**, Shim JJ, Jang JY. Ceco-colic intussusception with subsequent bowel infarction as a rare complication of colonoscopic polypectomy. *Endoscopy* 2013; **45** Suppl 2 UCTN: E106-E107 [PMID: 23526500 DOI: 10.1055/s-0032-1326345]

9 **Min MX**, Sklow B, Vaughn BP. Intussusception after Routine Colonoscopy: A Rare Complication. *ACG Case Rep J* 2017; **4**: e63 [PMID: 28462240 DOI: 10.14309/crj.2017.63]

10 **Araki O**, Fukuda A, Kusaka T, Seno H. A case of cecocolonic intussusception after endoscopic submucosal dissection of a cecal adenoma. *Gastrointest Endosc* 2018; **87**: 1589-1590 [PMID: 29223381 DOI: 10.1016/j.gie.2017.12.002]

11 **Hassan WAW**, Teoh W. Intussusception after Colonoscopy: A Case Report and Review of Literature. *Clin Endosc* 2018; **51**: 591-595 [PMID: 30300987 DOI: 10.5946/ce.2018.056]

12 **He H**, Rambhujun V, DeMaria M, Ali M, Vrabie R. Early Postendoscopic Transverse Colo-Colonic Intussusception. *Case Rep Gastroenterol* 2020; **14**: 1-6 [PMID: 32009867 DOI: 10.1159/000505228]

13 **Ahmed A**, Zhang J, Anas K. Intussusception in a Routine Colonoscopy. *ACG Case Rep J* 2020; **7**: e00422 [PMID: 32766364 DOI: 10.14309/crj.0000000000000422]

14 **Moon JY**, Lee MR, Yim SK, Ha GW. Colo-colonic intussusception with post-polypectomy electrocoagulation syndrome: A case report. *World J Clin Cases* 2022; **10**: 8939-8944 [PMID: 36157670 DOI: 10.12998/wjcc.v10.i25.8939]

15 **Lee GH**, Noh CK. Ileocolonic Intussusception Due to Hematoma After Snare Polypectomy. *Am J Gastroenterol* 2022; **117**: 1554 [PMID: 35545819 DOI: 10.14309/ajg.0000000000001830]

16 **Vadakkenchery Varghese E**, Steen C, Juszczyk K, An V. Splenic flexure intussusception: a rare complication post colonoscopy. *ANZ J Surg* 2022; **92**: 1545-1546 [PMID: 34694677 DOI: 10.1111/ans.17325]

17 **Jastaniah A**, AlBusaidi N, Bandegi P, Grushka J. Intussusception after colonoscopic polypectomy: a rare complication. *BMJ Case Rep* 2023; **16** [PMID: 37270178 DOI: 10.1136/bcr-2023-255048]

18 **Hong KD**, Kim J, Ji W, Wexner SD. Adult intussusception: a systematic review and meta-analysis. *Tech Coloproctol* 2019; **23**: 315-324 [PMID: 31011846 DOI: 10.1007/s10151-019-01980-5]

19 **Panzera F**, Di Venere B, Rizzi M, Biscaglia A, Praticò CA, Nasti G, Mardighian A, Nunes TF, Inchingolo R. Bowel intussusception in adult: Prevalence, diagnostic tools and therapy. *World J Methodol* 2021; **11**: 81-87 [PMID: 34026581 DOI: 10.5662/wjm.v11.i3.81]

20 **Marsicovetere P**, Ivatury SJ, White B, Holubar SD. Intestinal Intussusception: Etiology, Diagnosis, and Treatment. *Clin Colon Rectal Surg* 2017; **30**: 30-39 [PMID: 28144210 DOI: 10.1055/s-0036-1593429]

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CASE REPORT

Resection of polyps involving the appendiceal orifice by combined endo-laparoscopic surgery: Two case reports

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Abstract

BACKGROUND

The management of polyps involving the appendiceal orifice (AO) presents notable challenges. Endoscopic resection is frequently hindered by operational complexities, a heightened risk of incomplete removal, and an elevated risk of procedural complications, including appendicitis. Conversely, surgical resection may entail unnecessary excision of intestinal segments, leading to potential morbidity.

CASE SUMMARY

Here, we reported two patients who presented with polyps deeply situated within the AO, with indistinct boundaries making it challenging to ensure completeness using traditional endoscopic resection. To overcome these challenges, we employed combined endo-laparoscopic surgery (CELS), achieving curative resection without postoperative complications.

CONCLUSION

The application of CELS in managing polyps involving the AO is emerging as a safe and effective treatment modality.

Key Words: Polyps; Laterally spreading tumor; Appendiceal orifice; Endoscopic resection; Combined endo-laparoscopic surgery; Case report

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Core Tip: Resecting polyps involving the appendiceal orifice (AO) poses a significant challenge. Endoscopic treatment risks incomplete resection and high postoperative complications, while surgery may entail excessive removal of normal intestinal segments, leading to additional damage. Here, we present two cases of deeply extended polypoid lesions in AO, where vague boundaries hindered complete resection with traditional endoscopy. Hence, we adopted a combined endo-laparoscopic surgery (CELS) approach, achieving curative resection without postoperative complications. Our experience confirms that CELS is a safe and effective method for AO polyp removal, meriting further exploration.

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INTRODUCTION

Resecting polyps involving the appendiceal orifice (AO) poses a significant challenge. Endoscopic resection is hindered by a confined working space and the limited maneuverability of the endoscope. Simultaneously, this approach carries a heightened risk of incomplete resection, perforation, and post-resection appendicitis. Surgical resection faces challenges in accurately delineating the lesion border under a laparoscope. This difficulty may lead to extended surgery, potentially necessitating the removal of the right hemi-colon, resulting in excessive damage for a benign lesion.

In this context, we present two cases involving polyps extending to the AO, successfully treated with combined endo-laparoscopic surgery (CELS), which provide an effective and safe method for the resection of lesion involving the AO.

CASE PRESENTATION

Chief complaints

Case 1: A 71-year-old female underwent colonoscopy as part of a routine physical examination, reporting no discomfort.

Case 2: A 49-year-old male underwent colonoscopy as part of a routine health screening.

History of present illness

Case 1: During the examination, a 20-mm laterally spreading tumor encircling the AO was identified in the cecum, and the edge of the lesion remained invisible (Figure 1).

Case 2: Colonoscopy revealed multiple polyps in the AO, with the largest measuring 6mm, and the root of the polyp could not be exposed (Figure 2A and B).

History of past illness

Case 1: The patient had a history of hypertension and hyperlipidemia, with no reported instances of abdominal pain, rectal bleeding, or weight loss.

Case 2: The patient had a history of diabetes. He had no history of abdominal pain or weight loss.

Personal and family history

Case 1: The patient was not aware of any family history of malignant tumors.

Case 2: The patient denied any family history of malignant tumors.

Physical examination

Case 1: During the physical examination, the patient had a body temperature of 36.5 °C, blood pressure of 127/73 mmHg, heart rate of 78 beats per minute, and respiratory rate of 18 breaths per minute. Abdominal examination revealed no signs of pressure or rebound pain, and no palpable abdominal masses were noted.

Case 2: During the physical examination, the patient had a body temperature of 36.2 °C, blood pressure of 118/72 mmHg, heart rate of 72 beats per minute, and respiratory rate of 19 breaths per minute. He showed no signs of pressure or rebound pain during abdominal examination. No masses were palpable.

Laboratory examinations

Case 1: Histopathological examination of the lesion confirmed tubular adenoma. Other laboratory examinations yielded normal results.

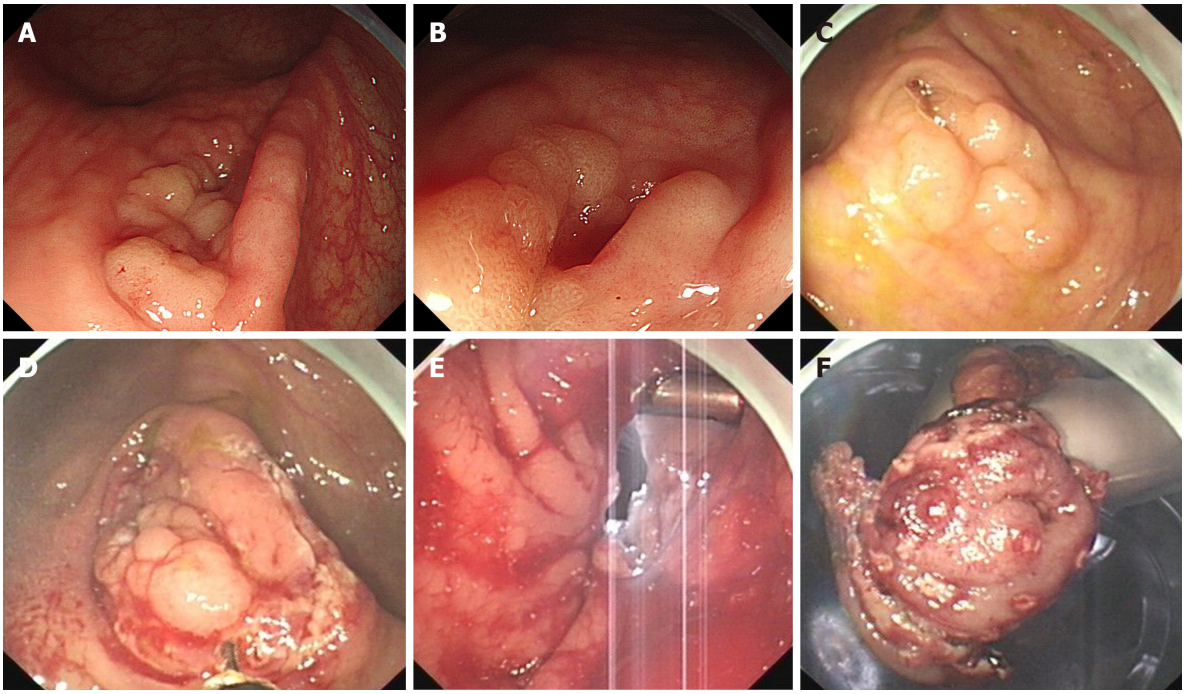


Figure 1 Endoscopic findings of the laterally spreading tumor encircling the appendiceal orifice and procedure of combined endo-laparoscopic surgery to remove the lesion encircling the appendiceal orifice of the first patient. A: Distant view of the polyp at the appendiceal orifice; B: Close-up view of the polyp at the appendiceal orifice; C: Exploration and localization of the lesion; D: A near-full-thickness incision was made around the lesion; E: Incisions were made through the layers of the cecal wall under laparoscopy; F: The gross specimen revealed markers around the outer edge of the lesion.

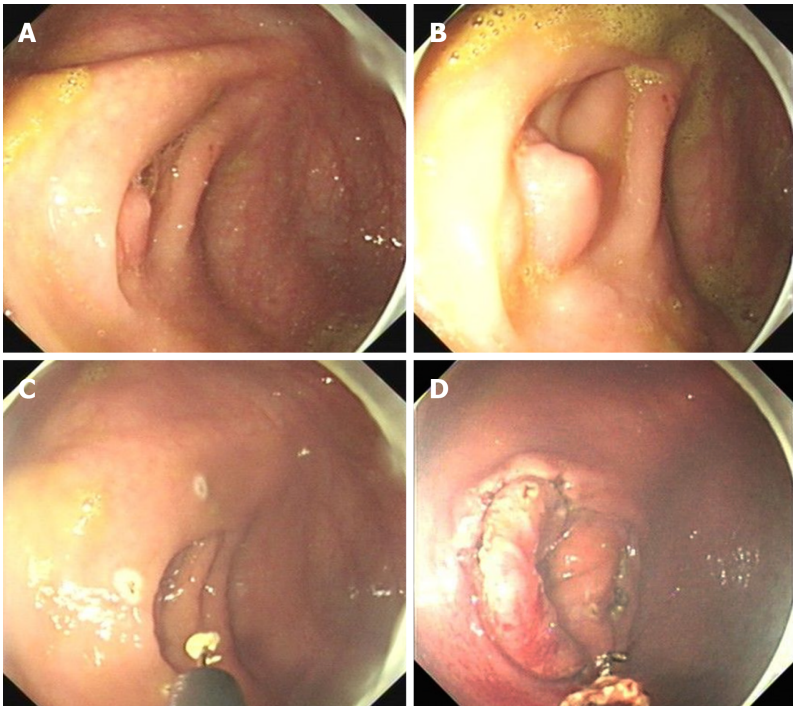


Figure 2 Endoscopic findings and endoscopic resection procedure of the second patient. A: Distant view of the polyp at the appendiceal orifice; B: Close-up view of the polyp at the appendiceal orifice; C: Marking of the lesion; D: Near-full-thickness incision of the bowel wall.

Case 2: Biopsy pathology of the lesion revealed tubular adenoma.

Imaging examinations

Case 1: Aside from the endoscopic abnormality, no other abnormalities were detected on imaging examinations.

Case 2: Aside from the endoscopic abnormality, the patient had no other abnormalities on imaging examinations.

FINAL DIAGNOSIS

Both cases were diagnosed as tubular adenoma extending into the AO.

TREATMENT

Given the risk of incomplete resection and subsequent appendicitis associated with traditional endoscopic submucosal dissection (ESD) due to the lesions' obscured margins, the CELS technique was chosen for polyp removal in both patients.

Pre-operative bowel preparation was conducted for both patients a day prior to the procedure, consistent with colonoscopy requirements. The surgeries were performed under general anesthesia. After the insertion of a nasogastric tube and urinary catheter, the patient was placed in lithotomy position to facilitate colonoscopy, which was carried out with carbon dioxide insufflation.

The approach to polyp removal was largely consistent between the two patients. The endoscopist began by exploring and identifying the lesion (Figure 1C). The lesion's borders were then marked circumferentially using a hook knife set to soft coagulation ERBE mode (Figure 2C). Then, a near-full-thickness incision was executed around the lesion using the hook knife in endocut mode (Figures 1D and 2D), aiming to visualize the lesion's boundaries from the serosal surface during laparoscopy. Pneumoperitoneum was established to inspect the abdominal cavity, and three trocars were introduced. The marked lesion boundaries from the endoscopy were clearly visible on the serosal surface. Using an ultrasonic knife guided by the colonoscope's cutting line, incisions were made through the layers of the cecal wall (Figure 1E). The appendix, together with a portion of the cecum, was excised to ensure complete removal of the cecal mass. The incision in the cecum was then meticulously closed using 3-0 V-lock sutures. The specimen, enclosed in a specimen bag, was extracted through the primary operating port and sent for pathological evaluation.

OUTCOME AND FOLLOW-UP

The gross examination of the specimen revealed markers around the lesion's outer edge, confirming the completeness of the resection (Figure 1F). Furthermore, both pathological examinations confirmed the presence of tubular adenomas, which were completely excised with clear margins. The distance from the edge of the lesions to the resection margin was 7 mm in both cases.

Both patients abstained from oral intake for two days post-surgery, gradually resuming under close supervision thereafter. Encouragingly, neither patient encountered any postoperative complications, such as bleeding or perforation. They were both discharged from the hospital five days after the surgical procedure, indicating a smooth recovery process.

DISCUSSION

In this report, we present two cases of polyps extending into the AO, with the lesion border extending into the appendix, posing challenges in recognition. The polyp was resected using CELS, achieving R0 resection without postoperative complications. This procedure offers several advantages.

Firstly, it ensures *en bloc* resection and improves the R0 resection rate. The primary technical challenge in endoscopic resection of AO lesions is achieving an R0 resection due to difficulties in recognizing the lesion border, particularly for those lesions extending into the appendiceal lumen. In traditional ESD, the rate of complete histological resection was only 76.7%[1]. Traction techniques can help expose the lesion border[2], but if the lesion extends deep into the appendiceal lumen, exposing the lesion boundaries can remain challenging even with traction. By contrast, we confirmed the lesion boundary outside the appendix using colonoscopy and marked the border with a near-full-thickness resection. This enabled precise recognition of the boundary during laparoscopy, reducing the extent of surgical resection while ensuring complete lesion removal. Both gross appearance and microscopic examination confirmed the *en bloc* R0 resection of the lesion in both patients.

Secondly, the procedure exhibits a high level of safety. Endoscopic resection of AO lesions with complete appendix preservation poses a high risk of postoperative appendicitis. This may result from inadequate drainage of the AO post-procedure. The postoperative appendicitis rate for endoscopic full-thickness resection (EFTR) can reach as high as 17%[3]. Despite EFTR achieving a high R0 resection rate of up to 93%[3], its widespread application is severely limited by the excessively high rate of postoperative appendicitis. Since the CELS procedure removes the appendix completely, the risk of post-operative appendicitis is eliminated.

Lastly, the procedure exhibits high accessibility and reliability. Both endoscopic circumferential near-full-thickness resection of the appendix and laparoscopic appendectomy are fundamental procedures for endoscopists and surgeons. This ensures that the procedure is easily learned and can be widely adopted. There are some emerging technologies, such as endoscopic transcecal appendectomy (ETA), offering a balance between a high R0 resection rate and low complication

rate[4]. ETA involves a near-circumferential full-thickness resection of the appendix, introduction of the endoscope into the abdominal cavity, dissection of the appendiceal mesentery, and ultimately complete appendectomy[5]. However, this procedure demands a high level of technical skill and a thorough understanding of abdominal anatomy from endoscopists, limiting its widespread adoption.

CONCLUSION

We present a novel procedure for treating polys involving the AO, demonstrating a high level of efficacy, safety and accessibility. We believe that CELS can be widely employed for the treatment of appendiceal polyps. However, more case reports are required to more robustly determine its efficacy and safety in the future.

FOOTNOTES

Author contributions: Zhang YY contributed to manuscript writing and editing, and data collection; Lu JY and Wang Q contributed to data analysis; Wang Q and Yang AM contributed to conceptualization and supervision; and all authors have read and approved the final manuscript.

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REFERENCES

1 **Song EM**, Yang HJ, Lee HJ, Lee HS, Cha JM, Kim HG, Jung Y, Moon CM, Kim BC, Byeon JS. Endoscopic Resection of Cecal Polyps Involving the Appendiceal Orifice: A KASID Multicenter Study. *Dig Dis Sci* 2017; **62**: 3138-3148 [PMID: 28936593 DOI: 10.1007/s10620-017-4760-2]

2 **Cignoli D**, Fallara G, Aleotti F, Larcher A, Rosiello G, Rowe I, Basile G, Colandrea G, Martini A, De Cobelli F, Brembilla G, Lucianò R, Colecchia M, Lena MS, Partelli S, Tamburrino D, Zamboni G, Rubini C, Falconi M, Montorsi F, Salonia A, Capitanio U. Pancreatic metastases after surgery for renal cell carcinoma: survival and pathways of progression. *World J Urol* 2022; **40**: 2481-2488 [PMID: 35904571 DOI: 10.1007/s00345-022-04106-z]

3 **Ichkhanian Y**, Barawi M, Seoud T, Thakkar S, Kothari TH, Halabi ME, Ullah A, Edris W, Aepli P, Kowalski T, Shinn B, Shariaha RZ, Mahadev S, Mosko JD, Andrisani G, Di Matteo FM, Albrecht H, Giap AQ, Tang SJ, Naga YM, van Geenen E, Friedland S, Tharian B, Irani S, Ross AS, Jamil LH, Lew D, Nett AS, Farha J, Runge TM, Jovani M, Khashab MA. Endoscopic full-thickness resection of polyps involving the appendiceal orifice: a multicenter international experience. *Endoscopy* 2022; **54**: 16-24 [PMID: 33395714 DOI: 10.1055/a-1345-0044]

4 **Guo L**, Ye L, Feng Y, Bethge J, Yang J, Schreiber S, Hu B. Endoscopic transcecal appendectomy: a new endotherapy for appendiceal orifice lesions. *Endoscopy* 2022; **54**: 585-590 [PMID: 34905794 DOI: 10.1055/a-1675-2625]

5 **Yuan XL**, Cheung O, Du J, Ye LS, Hu B. Endoscopic transcecal appendectomy. *Endoscopy* 2019; **51**: 994-995 [PMID: 31096274 DOI: 10.1055/a-0889-7289]

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LETTER TO THE EDITOR

Evaluating bacterial contamination and surgical site infection risks in intracorporeal anastomosis: Role of bowel preparation

Junho Lee

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Abstract

We recently read the study by Kayano *et al* on intracorporeal anastomosis (IA) for colon cancer, which assessed bacterial contamination and medium-term oncological outcomes and affirmed that IA is analogous to extracorporeal anastomosis in reducing intraperitoneal bacterial risk and achieving similar oncological results. Our commentary addresses gaps, particularly concerning bowel preparation and surgical site infections (SSIs), and highlights the need for comprehensive details on the bowel preparation methods that are currently employed, including mechanical bowel preparation, oral antibiotics (OA), their combination, and specific OA types. We emphasize the necessity for further analyses that investigate these methods and their correlation with SSI rates, to enhance clinical protocol guidance and optimize surgical outcomes. Such meticulous analyses are essential for refining strategies to effectively mitigate SSI risk in colorectal surgeries.

Key Words: Intracorporeal anastomosis; Surgical site infection; Mechanical bowel preparation; Oral antibiotics; Bacterial contamination; Colon cancer

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Core Tip: We examined the study by Kayano *et al* on intracorporeal anastomosis for colon cancer, with a focus on its equivalence to extracorporeal anastomosis in managing bacterial risk and achieving oncological outcomes. A detailed examination of current bowel preparation methodologies that distinguishes between mechanical bowel preparation, oral antibiotics, or their combination and specific impact on surgical site infections (SSIs) is needed. Further research that precisely links bowel preparation methods with SSI rates are required to enhance patient outcomes and surgical safety during colorectal procedures. This critical insight urges a reevaluation of current practices and paves the way for substantial procedural improvements.

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TO THE EDITOR

We read the recent paper "Evaluation of bacterial contamination and medium-term oncological outcomes of intracorporeal anastomosis for colon cancer: A propensity score matching analysis" by Kayano *et al*[1] with great interest. We thank the authors for their extensive work and their contributions to the field of intracorporeal anastomosis (IA) in colon cancer treatment.

This study evaluated bacterial contamination and medium-term oncological outcomes of IA for colon cancer and revealed that IA is comparable to extracorporeal anastomosis in terms of intraperitoneal bacterial contamination risk and medium-term oncological results. However, here, we address certain aspects of the methodology and findings, particularly with regards to bowel preparation and surgical site infections (SSIs).

Despite ongoing efforts to reduce SSIs in colorectal surgery using various bowel preparation methods, SSIs persist and are of particular concern in IA. Recent guidelines recommend the use of oral antibiotics (OA) alone for right colon surgery, while a combination of mechanical bowel preparation (MBP) and OA is advised for IA procedures for the right colon[2]. This difference can be attributed to the characteristics of IA procedures, which can affect SSI.

Given these considerations, a detailed description of the bowel preparation methods used in this study is essential for a thorough SSI risk assessment. Information should include whether MBP alone, OA alone, or a combination of MBP and OA was employed, and the specific types of OA that were administered. This detailed preparation methodology information is crucial for evaluating the effectiveness of different strategies that aim to minimize the incidence of SSIs in colorectal surgery.

Additional analyses that examine SSIs that occur in relation to bowel preparation methods are required. Notably, studies that compared MBP with OA and OA alone for bowel preparation have attracted recent attention[3]. However, there is a paucity of data that compares the effectiveness of MBP with OA *vs* OA alone, particularly in the context of IA [4]. This gap is particularly critical, as the choice of bowel preparation could significantly affect the rates of SSIs and other postoperative complications. In this study, additional analyses that examine SSI relative to bowel preparation methods could provide invaluable insights and potentially guide future clinical protocols.

Additionally, the pioneering discussion on bacterial contamination in IA can be expanded by correlating culture-positive rates with specific bowel preparation methods. Notably, the incorporation of a detailed analysis of culture-positive rates that correlates with specific bowel preparation methods would enhance our understanding of the procedural implications of bacterial contamination risks. Such data are pivotal in determining the most effective bowel preparation regimens to minimize the bacterial load and reduce SSI risk.

We believe that addressing these points would not only clarify the methodologies of this impactful study but also enhance the utility of the investigators' findings for diverse clinical applications. Furthermore, detailed and specific data on bowel preparation methods can guide more accurate clinical decisions and optimize patient outcomes and procedural efficacy around the world.

FOOTNOTES

Author contributions: Lee J designed and conducted the study and wrote the manuscript; the author has read and approved the final manuscript.

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REFERENCES

1 **Kayano H**, Mamuro N, Kamei Y, Ogimi T, Miyakita H, Nakagohri T, Koyanagi K, Mori M, Yamamoto S. Evaluation of bacterial contamination and medium-term oncological outcomes of intracorporeal anastomosis for colon cancer: A propensity score matching analysis. *World J Gastrointest Surg* 2024; **16**: 670-680 [PMID: 38577098 DOI: 10.4240/wjgs.v16.i3.670]

2 **Antoniou SA**, Huo B, Tzanis AA, Koutsiouroumpa O, Mavridis D, Balla A, Dore S, Kaiser AM, Koraki E, Massey L, Pellino G, Psichogiou M, Sayers AE, Smart NJ, Sylla P, Tschudin-Sutter S, Woodfield JC, Carrano FM, Ortenzi M, Morales-Conde S. EAES, SAGES, and ESCP rapid guideline: bowel preparation for minimally invasive colorectal resection. *Surg Endosc* 2023; **37**: 9001-9012 [PMID: 37903883 DOI: 10.1007/s00464-023-10477-0]

3 **Catarci M**, Guadagni S, Masedu F, Sartelli M, Montemurro LA, Baiocchi GL, Tebala GD, Borghi F, Marini P, Scatizzi M; The Italian ColoRectal Anastomotic Leakage iCral Study Group. Oral Antibiotics Alone *versus* Oral Antibiotics Combined with Mechanical Bowel Preparation for Elective Colorectal Surgery: A Propensity Score-Matching Re-Analysis of the iCral 2 and 3 Prospective Cohorts. *Antibiotics (Basel)* 2024; **13** [PMID: 38534670 DOI: 10.3390/antibiotics13030235]

4 **Willis MA**, Toews I, Soltau SL, Kalff JC, Meerpohl JJ, Vilz TO. Preoperative combined mechanical and oral antibiotic bowel preparation for preventing complications in elective colorectal surgery. *Cochrane Database Syst Rev* 2023; **2**: CD014909 [PMID: 36748942 DOI: 10.1002/14651858.CD014909.pub2]



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