ISSN 1948-9366 (online)

World Journal of *Gastrointestinal Surgery*

World J Gastrointest Surg 2023 September 27; 15(9): 1841-2097

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 15 Number 9 September 27, 2023

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Cohort Study

Retrospective Study

World Journal of Gastrointestinal Surgery

Monthly Volume 15 Number 9 September 27, 2023

Contents

World Journal of Gastrointestinal Surgery

Monthly Volume 15 Number 9 September 27, 2023

Contents

CASE REPORT

World Journal of Gastrointestinal Surgery

Monthly Volume 15 Number 9 September 27, 2023

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Sung Uk Bae, MD, PhD, Associate Professor, Department of Surgery, Keimyung University Dongsan Hospital, Daegu 42601, South Korea. sabiston0000@hanmail.net

AIMS AND SCOPE

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

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJGS* as 2.0; IF without journal self cites: 1.9; 5-year IF: 2.2; Journal Citation Indicator: 0.52; Ranking: 113 among 212 journals in surgery; Quartile category: Q3; Ranking: 81 among 93 journals in gastroenterology and hepatology; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Rui-Rui Wu*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jia-Ru Fan*.

NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

ISSN
ISSN 1948-9366 (online)

LAUNCH DATE
November 30, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Peter Schemmer

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

PUBLICATION DATE
September 27, 2023

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

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

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 1841-1857

DOI: 10.4240/wjgs.v15.i9.1841

ISSN 1948-9366 (online)

REVIEW

Indocyanine green dye and its application in gastrointestinal surgery: The future is bright green

Zavier Yongxuan Lim, Swetha Mohan, Sunder Balasubramaniam, Saleem Ahmed, Caroline Ching Hsia Siew, Vishal G Shelat

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Bains L, India; Komatsu S, Japan

Received: May 14, 2023
Peer-review started: May 14, 2023
First decision: July 4, 2023
Revised: July 17, 2023
Accepted: July 31, 2023
Article in press: July 31, 2023
Published online: September 27, 2023

Zavier Yongxuan Lim, Swetha Mohan, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore 308232, Singapore

Sunder Balasubramaniam, Saleem Ahmed, Caroline Ching Hsia Siew, Vishal G Shelat, Department of General Surgery, Tan Tock Seng Hospital, Singapore 308433, Singapore

Corresponding author: Zavier Yongxuan Lim, Lee Kong Chian School of Medicine, Nanyang Technological University, 11 Mandalay Road, Singapore 308232, Singapore.
zavi0002@e.ntu.edu.sg

Abstract

Indocyanine green (ICG) is a water-soluble fluorescent dye that is minimally toxic and widely used in gastrointestinal surgery. ICG facilitates anatomical identification of structures (*e.g.*, ureters), assessment of lymph nodes, biliary mapping, organ perfusion and anastomosis assessment, and aids in determining the adequacy of oncological margins. In addition, ICG can be conjugated to artificially created antibodies for tumour markers, such as carcinoembryonic antigen for colorectal, breast, lung, and gastric cancer, prostate-specific antigen for prostate cancer, and cancer antigen 125 for ovarian cancer. Although ICG has shown promising results, the optimization of patient factors, dye factors, equipment, and the method of assessing fluorescence intensity could further enhance its utility. This review summarizes the clinical application of ICG in gastrointestinal surgery and discusses the emergence of novel dyes such as ZW-800 and VM678 that have demonstrated appropriate pharmacokinetic properties and improved target-to-background ratios in animal studies. With the emergence of robotic technology and the increasing reporting of ICG utility, a comprehensive review of clinical application of ICG in gastrointestinal surgery is timely and this review serves that aim.

Key Words: Fluorescence imaging; Gastrointestinal surgery; Indocyanine green

Core Tip: Indocyanine green (ICG) is a safe and widely-used fluorescent dye for anatomy delineation, tumour identification and lymph node mapping. ICG has demonstrated superior results in organ perfusion and anastomosis assessment. However, there is still room for further optimization of patient factors, dye factors, and fluorescence intensity assessment. Other dyes, such as ZW-800 and VM678, have shown better pharmacokinetic properties and target-to-background ratios in animal studies, and novel contrast agents that target unique pathology, such as conjugating ICG to artificially created antibodies, are being developed for disease detection and management.

Citation: Lim ZY, Mohan S, Balasubramaniam S, Ahmed S, Siew CCH, Shelat VG. Indocyanine green dye and its application in gastrointestinal surgery: The future is bright green. *World J Gastrointest Surg* 2023; 15(9): 1841-1857
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/1841.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.1841

INTRODUCTION

Indocyanine green (ICG) was first developed during World War II for colour imaging, and later in the 1950s, used in the medical field to quantify cardiac and renal function. It is a minimally toxic, water-soluble fluorescent dye that is rapidly taken up by the liver and excreted into the bile ducts within minutes after injection, making it ideal for such applications [1,2]. ICG is a favourable contrast agent for *in vivo* application due to its 820 nm near-infrared (NIR) emission wavelength, minimising interference from blood and tissue autofluorescence at 500-600 nm[3]. After intravenous injection, ICG binds to plasma proteins and has a half-life of three minutes. As the lymph is rich in protein content, lymphatics and lymph nodes (LNs) can be easily mapped after ICG injection. In general, ICG is safe at doses below 0.5 mg/kg body weight, however adverse reactions like nausea, pyrexia, and anaphylaxis may occur[1-3].

As early as 1959, ICG quantification was used to assess hepatic function. Given ICG's affinity for the blood, ICG levels in the blood corresponded directly with hepatic function[2]. It was also used to determine cardiac output, and for videoangiography for assessment of choroidal neovascularization[4,5].

Recently, fuelled by the emergence of robotic technology, ICG has gained widespread usage in the identification of tumours, lymphatic mapping, and evaluation of organ perfusion and anastomosis[6]. With its increasing application in general surgery, novel uses for ICG are continuously being uncovered. Therefore, the present review aims to provide a summary and critical analysis of the established applications of ICG in general surgery, as well as emerging avenues for future research and development.

METHODOLOGY

An electronic search of PubMed (MEDLINE), Embase (Ovid), and Google Scholar was performed for the concepts of ("Indocyanine Green" [MeSH Terms]), ("Esophagus" [MeSH Terms]), ("Stomach" [MeSH Terms]), ("Liver" [MeSH Terms]), ("Gallbladder" [MeSH Terms]), ("Pancreas" [MeSH Terms]), ("Adrenal Glands" [MeSH Terms]), ("Spleen" [MeSH Terms]), ("Intestine, Small" [MeSH Terms]), ("Colon" [MeSH Terms]), ("Rectum" [MeSH Terms]), ("Peritoneum" [MeSH Terms]), ("Blood Vessels" [MeSH Terms]), ("Abdomen" [MeSH Terms]), ("General Surgery" [MeSH Terms]) in January 2023. Relevant articles published in English were identified and summarised to produce an up-to-date review on the history, present and future use of ICG in abdominal surgery. We discuss clinical application of ICG in individual organs with a cranial to caudal approach of human anatomy.

RESULTS

Oesophagus

Lymphatic mapping in oesophageal cancer: Oesophageal cancer is a biologically aggressive disease with poor prognosis despite treatment, endoscopic or surgical, with the intent to cure[7]. Lymphadenectomy significantly improves accuracy of tumour staging and impacts long-term survival of patients with oesophageal cancer. However, at present, most lymphadenectomies are performed based on anatomical territory understanding and surgeons' experience and expertise with wide variation in the extent of nodal harvest. Current American Joint Committee on Cancer (AJCC) guidelines recommend the removal of ≥ 20 LNs for T2 disease, or ≥ 30 for T3 and T4 disease, while National Comprehensive Cancer Network guidelines recommend the removal of at least 15 LNs to ensure adequate nodal staging[8,9].

Studies have proposed the use of radiocolloid tracers for sentinel LN (SLN) mapping, but these largely require open procedures with back table dissection of the specimen and radiation exposure[10]. Radioisotope methods are unable to predict locations of primary SLNs perioperatively with high accuracy. This can be attributed to poor spatial resolution and low detail regarding surrounding anatomy, for reasons including the shine-through phenomenon, where the radiation flare of the primary tumour outshines the SLN near to the primary tumour[11,12]. A feasibility study by Yuasa *et al*[12] proposed the use of NIR fluorescence imaging (FI) using ICG, together with preoperative computed tomography

(CT) lymphography for SLN localisation[10]. This involved the injection of ICG in 2 regions around the tumour after thoracotomy, and the oesophagus and LNs that fluoresced were harvested.

A first in human pilot trial by Hachey *et al*[10] demonstrated the feasibility of using NIR guided lymphatic mapping as the sole modality for SLN identification in minimal access oesophagectomy. Regional LNs distinct from the oesophagus specimen were identified in 66.7% (6/9) of the patients where ICG diluted in human serum albumin (HSA) was used, as compared to 40% (2/5) of the patients with ICG only. In both groups, ICG was injected peritumourally *via* 4-corner submucosal injections adjacent to each lesion[10]. The dilution of ICG with HSA increases the quantum yield, which is the efficacy at which fluorescent molecules convert absorbed photons into emitted photons, and also the SLN retention[13, 14]. Furthermore, the combination of ICG with neomannosyl HSA, which targets the macrophage mannose receptor CD206, was trialled by Kim *et al*[15]. This combination was used on porcine models for oesophageal SLN identification and demonstrated higher fluorescence signal, LN retention and allowed for more precise real-time SLN detection in surgery. The use of ICG for lymphatic mapping may allow for targeted lymphadenectomy, decreased operative time, and hence decreased postoperative complications while ensuring the completeness of resection and improving cancer-free survival[16].

Evaluation of oesophago-gastric anastomosis: The evaluation of gastrointestinal-oesophageal anastomosis is the most common application of ICG FI for oesophageal pathologies. There is significant postoperative morbidity and mortality associated with anastomotic leak (AL) post-oesophagectomy. A major factor contributing to oesophago-gastric AL is ischaemia at the tip of the gastric conduit, due to insufficient perfusion from the isolated right gastroepiploic artery[17]. Figure 1 below illustrate this. Therefore, the use of ICG FI intra-operatively to assess perfusion can be valuable as it allows for live monitoring of conduit perfusion, early detection of reversible conduit ischaemia, and hence better selection of the optimal site for anastomosis. Other optical techniques such as optical coherence tomography and NIR spectroscopy have been assessed by authors, but ICG remains the most widely used given the safety, reliability, and ease of use[18].

However, the use of ICG fluoroscopy for assessment of perfusion does not provide surgeons with a quantitative assessment of perfusion but is instead estimated based on the time from initial ICG enhancement at the root of the gastro-epiploic artery until gastric tube tip. Noma *et al*[19] suggested that anastomosis be performed proximal to the point of fluorescence reached in 30 s, or the 90 s rule established by Kumagai *et al*[20]. Noma *et al*[19] reported significant reduction in leakage rate and duration of postoperative intensive care unit (ICU) stay for the ICG group, with no increase in other complications such as pneumonia. In a meta-analysis including 5 studies and 616 patients, Slooter *et al*[21] concluded that ICG reduces the risk of AL and graft necrosis [odds ratio (OR) = 0.30, 95% confidence interval (CI): 0.14-0.63]. Based on this, we computed the number needed to treat (NNT) for ICG to reduce 1 case of AL or graft necrosis as 6.6 oesophagectomies.

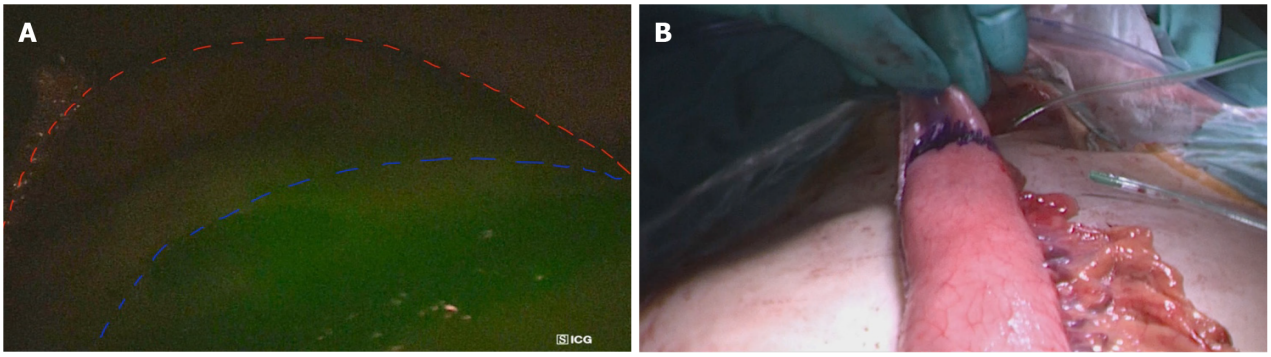
Identification of chylothorax post-oesophagectomy: Besides the use of ICG in oesophageal surgery for assessment of perfusion, a new and upcoming use of ICG is for the detection of chyle leak post-oesophagectomy. The incidence of chylothorax ranges from 1.1%-21% in oesophagectomy patients, with extensive LN dissection and *en bloc* resection of the thoracic duct for oncological reasons as risk factors[22]. Traditionally, the ingestion of milk immediately before surgery, or the intraoperative administration of milk into the duodenum were techniques used to identify the site of chyle leak[23].

Kaburagi *et al*[24] however reported the successful use of intraoperative ICG fluorescence lymphography for the identification of the chyle leak, and to confirm ligation of the thoracic duct transabdominally. Kamiya *et al*[23] similarly achieved this through the injection of 1.5 mL of ICG subcutaneously at the inguinal region bilaterally, and obtained fluorescence images of lymph flow 14 min after injection using a NIR camera. This is in contrast to other techniques such as lymphoscintigraphy, which can identify chyle leak, but cannot delineate the exact site of leak without the use of a single-photon emission computerized tomography scan[25]. Management of the chyle leak reduces the need for postoperative nutritional interventions, infectious morbidity, and reduces the length of hospital stay[22].

Stomach

ICG guided LN dissection: Gastrectomy with D2 lymphadenectomy is a technically demanding surgery requiring experience and expertise to achieve radical lymphadenectomy. With advances in minimal access technology, adoption of training curricula and fellowship programs, laparoscopic gastrectomy is routine in many institutions. ICG can help to improve LN harvest while minimizing complications. Chen *et al*[8] reported a randomized control trial with 266 gastric cancer patients comparing ICG use in gastrectomy with conventional gastrectomy. The ICG group had significantly greater LNs retrieved compared to the non-ICG group (49.6 LNs *vs* 41.7 LNs respectively; $P < 0.001$). In addition, in a matched cohort study of 37 patients who underwent robotic gastrectomy with D2 LN dissection demonstrated higher mean total number of harvested LNs in the ICG group than the control (50.8 *vs* 40.1, $P = 0.03$)[26]. Higher nodal yield aids accurate staging and potentially contributes to improved survival outcomes. The iGreenGO study is a prospective multicentre study which seeks to determine if the use of ICG necessitates a change in surgical conduct, such as performing more extensive dissection after the surgeon has already completed D2 lymphadenectomy without ICG aid [27]. ICG remains a useful surgical adjunct for a surgeon early in their learning curve and for advanced gastric cancers.

Sentinel LN mapping: The stomach has a complex lymphatic drainage system. Gastrectomy with D2 lymphadenectomy remains the gold standard for resectable gastric cancer, however this has higher morbidity than D1 lymphadenectomy therefore may be excessive in clinical T1/T2 N0 gastric cancers where LN metastasis maybe limited. SLN mapping may be a solution to this conundrum where radical lymphadenectomy may be carried out only if SLN is positive. In a prospective multicentre trial by Kitagawa *et al*[28], 397 patients underwent SLN biopsy (SLNB), and the method showed high accuracy in detecting sentinel nodes and metastatic SLNs, with a false negative rate of 1%. Future studies should compare long-term oncologic outcomes of SLN guided surgery *vs* conventional surgery, but this has the potential to



DOI: 10.4240/wjgs.v15.i9.1841

Figure 1 The utility of indocyanine green dye in oesopgago-gastric anastomosis planning. A: The line of demarcation of indocyanine green (ICG (blue line) at the tip of gastric conduit (red line) to assess perfusion in a patient; B: The prepared gastric conduit with the tip of conduit with poor blood supply, as determined by ICG marked with blue marking line.

change surgical management of gastric cancer as what SLNB has done for breast cancer surgery.

Localisation of gastric tumour to guide resection in early gastric cancer: Early gastric cancer may not be visible to the surgeons on the serosal surface. Injection of ICG submucosally around the tumour will emit fluoresce on the serosal surface and aid to ensure adequacy of resection margins when performing subtotal gastrectomy. In a retrospective study including more than 500 patients with early gastric cancers in the body of the stomach, Cho *et al*[29] demonstrated that ICG diffusion area along the gastric wall secured a resection margin of > 28 mm.

Leak tests after sleeve gastrectomy and other anastomosis based bariatric surgeries: ICG has been used by bariatric surgeons for leak test after sleeve gastrectomy and other bariatric surgeries. ICG is instilled *via* nasogastric or orogastric tubes after the sleeve gastrectomy or after anastomosis is completed. Kalmar *et al*[30] reported a sensitivity of 100.0% and specificity of 98.3% for ICG based leak tests. Hagen *et al*[31] reported a series of 95 patients who had Roux-en-Y gastric bypass who had leak tests with air and with a mix of methylene blue and ICG. In their series, no patients had a positive leak test with air, no patients showed methylene blue excretion, and an ICG leak was observed in 4.2% (4/95) patients, suggesting that ICG maybe more sensitive for small ALs. These results need to be validated by others.

ICG in revisional bariatric surgery: ICG has proven it's utility in revisional bariatric surgery. Anatomy of the stomach is distorted in cases of previous gastric surgery especially if complications such as ulcers or perforations have occurred. In addition, in cases where records of previous surgeries are also not available makes deciphering the exact procedure the patient had underdone, vascular pedicles taken *etc*. challenging. This makes the surgery technically challenging with potential for increased morbidity. ICG helps to highlight areas of poor vascularity, identify old staple lines to enable better surgical planning to prevent crossing of staples lines, leaving blind gastric pouches and performing anastomosis in areas of good vascularity[32].

Liver

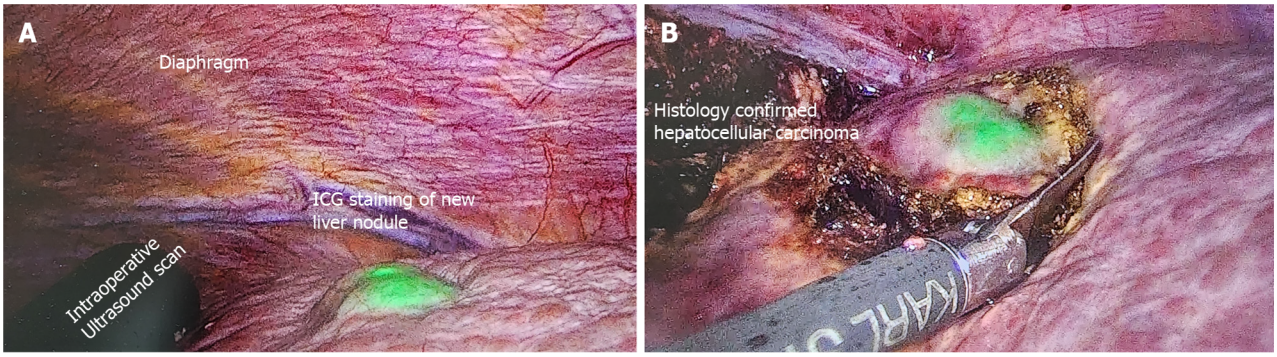
Tumour visualization: Hepatectomy remains the gold standard in treatment of liver malignancies and some benign masses. However, the key to a successful oncological resection is negative margins, which requires clear segment demarcations based on vascular and lymphatic supply[33].

ICG is typically administered intravenously several hours or days before surgery and will be taken up by hepatocytes, which illuminate under an infrared source. ICG is then excreted in the bile and disappears from healthy hepatocytes within a few hours before the surgery begins. However, as the cancerous hepatocytes are underactive and metabolize the ICG slowly, these will be the only areas that illuminate during the operation. Figure 2 shows the use of ICG for the resection in a patient with hepatocellular carcinoma.

In non-hepatocellular cancers, the areas around the tumour will retain the ICG instead. This is termed tumour and peritumoural fluorescence and helps differentiate between hepatocellular and non-hepatocellular cancers intraoperatively[34]. However, since ICG is metabolized by the liver, further studies need to be conducted with regards to dose adjustment for cirrhotic patients, who constitute a large proportion of liver cancer patients[35].

In addition, in a prospective study of 54 patients who underwent robotic assisted liver resections with ICG demonstrated that ICG use decreased operative time and achieved more resections with no histopathologically proven macro- or microscopic tumour residual[36].

Liver function assessment: Proper patient selection is vital for hepatectomies as even healthy patients without underlying liver disease can have severe postoperative liver dysfunction. For patients with pre-existing liver disease, even a minor resection could lead to posthepatectomy liver dysfunction or failure. ICG clearance has been noted as a valuable tool to identify patients that are at risk of developing posthepatectomy liver failure (PHLF)[37,38].



DOI: 10.4240/wjgs.v15.i9.1841 **Copyright** ©The Author(s) 2023.

Figure 2 A 84-year-old patient with imaging showing 7 cm hepatocellular carcinoma was scheduled for elective laparoscopic right posterior sectionectomy. Indocyanine green dye was injected 10 d before the surgery date. A: Cirrhotic liver with a new liver lesion detected by positive indocyanine green (ICG) staining; B: Excision of this nodule with adequate margins as guided by ICG. Postoperative histology confirmed the new nodule to be primary hepatocellular carcinoma. ICG: Indocyanine green.

The ICG retention test after 15 min (ICG-R15) is used conventionally. A single bolus of ICG is administered intravenously, and venous blood samples are drawn and read with a pulse spectrophotometer at 15 min[39]. Literature suggests that ICG-R15 of more than 14% is prognostic of PHLF[38-40]. A study by Schwarz *et al*[37] comprising 698 patients similarly showed that patients with impaired ICG clearance were twice as likely to have postoperative liver dysfunction. A recent retrospective study however highlighted that in patients treated with associating liver partition and portal vein ligation for staged hepatectomy, ICG-R15 overestimated the true liver function increase post-operatively[41]. These results remain to be validated, and are essential in tailoring treatment to prevent PHLF.

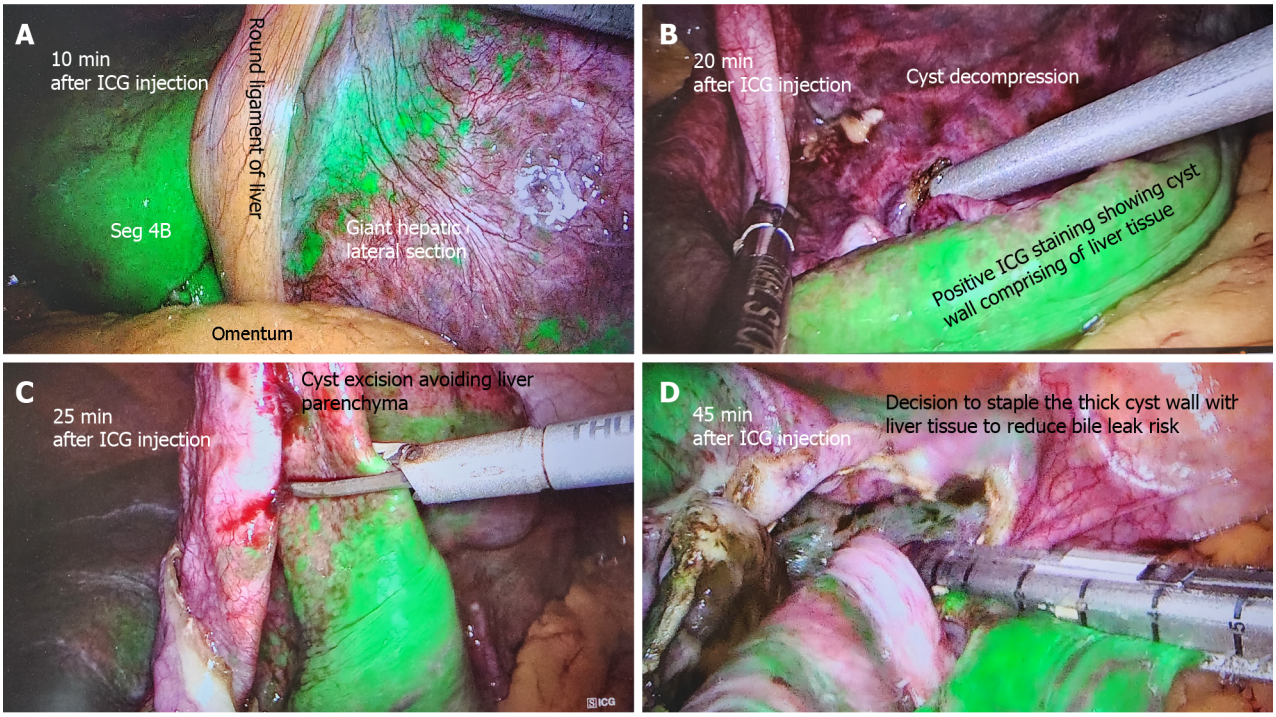
Liver cyst: Several studies have reported the use of ICG FI for liver cyst fenestrations performed laparoscopically. Une *et al*[42] reported the successful implementation of ICG FI to allow for clear distinguishment of cyst from liver parenchyma to guide resection. Hanaki *et al*[43] also reported that ICG FI allowed for visualisation of small bile ducts located within the cyst wall to decrease the risk of bile leaks and prevent iatrogenic bile duct injury (BDI). Authors injected ICG intravenously 1-h prior to surgery. In addition, ICG can be administered *via* endoscopic nasal biliary drain during hepatic cyst deroofing procedures to allow for immediate visualisation, and can also allow for assessment of minor biliary leakage from resection margins or staple lines, preventing postoperative biliary leakage[44]. Figure 3 illustrates the use of ICG FI for liver cyst deroofing.

Gallbladder

Biliary mapping during laparoscopic cholecystectomy: Laparoscopic cholecystectomy is one of the most frequently performed operations worldwide. BDI is an uncommon but significant complication associated with cholecystectomy as it reduces patients' quality of life and exposes surgeon to litigation[45]. The common cause of BDI are misidentification of anatomy, severe scarring and fibrosis due to chronic pathology and surgical experience. In estimated 10%-15% patients, it is not possible to obtain critical view of safety to expose Calot's triangle and a surgeon has to determine the next course of action that may include calling for help[46] and conversion to a bail-out procedure like subtotal cholecystectomy[47]. ICG NIR fluorescence instead provides detailed and real time anatomical mapping of the biliary structures to reduce BDI risk [48]. Yong *et al*[49] highlighted in his case study of a 40-year-old male undergoing laparoscopic cholecystectomy, that the cannabidiol (CBD) and cystic duct were only discernible *via* ICG FI and not at all under white light.

While intraoperative cholangiography remains the gold standard for laparoscopic cholecystectomies, intraoperative ultrasound and ICG NIR FI are often considered as good alternatives. ICG NIR FI has been found to only be useful in discerning the extrahepatic biliary tree, while intraoperative cholangiography is useful for evaluating the intrahepatic biliary tree[50]. However, ICG NIR FI is superior in terms of causing less radiation exposure[49]. Figure 4 below demonstrates the use of ICG in laparoscopic cholecystectomy.

ICG can be administered through either the intravenous or intrabiliary route. For the intravenous route, ICG is administered 30 min before the surgery. Since ICG is metabolized by the liver and excreted in bile, the biliary structures are visualized intraoperatively immediately after dissection of the Calot's triangle[51,52]. For the intrabiliary route, the gallbladder is punctured with cholangiogram or pigtail catheter mid-surgery, and the bile is aspirated and mixed with ICG solution, and then re-injected into the gallbladder[45]. Currently, the intrabiliary route is proven to be more efficacious in mapping the biliary tree. In a retrospective study of 24 patients by Shibata *et al*[53], ICG was administered intravenously in 12 patients and intrabiliary for 12 patients. The biliary tree was well-identified in 100% (12/12) of the patients in the intrabiliary group, as compared to only 83.3% (10/12) of the patients in the intravenous group. Ambe *et al* [52] reported no statistically significant differences in the duration of operation, length of stay in hospital, and risk of BDI when comparing between ICG guided and non-ICG guided laparoscopic cholecystectomy. For this study, the median duration of operation was 53 *vs* 54 min in the group with and without ICG respectively. Median length of stay was 2 d and no BDI occurred for both groups.



DOI: 10.4240/wjgs.v15.i9.1841

Figure 3 A 60-year-old patient undergoing elective liver cyst deroofing for a symptomatic solitary benign epithelial liver cyst was injected with 7 mL of indocyanine green dye after insertion of camera port. A: Liver enhancement at 10 min; B: After 20 min of injection shows the dye enhances the liver and cyst wall remains unenhanced; C: How indocyanine green (ICG) guidance can avoid transecting the liver parenchyma during cyst wall excision; D: The cyst wall with positive ICG staining is excised using stapling technology to reduce bile leak risk. ICG: Indocyanine green.

Additionally, studies have also evaluated the use of ICG cholangiography for use in robotic cholecystectomies. In a retrospective study of 184 robotic cholecystectomies by Esposito *et al*[54] demonstrated this with ICG FI allowing visualization of minimally 1 biliary structure in 99% (182/184) cases, with no laparoscopic or open conversions required.

Gallbladder cancer: Gallbladder cancer (GBC) is associated with high mortality, with a 5-year survival rate of less than 5%[55]. The mainstay of treatment for GBC remains radical resection of the gallbladder, including a central hepatectomy and regional lymphadenectomy. Recent advancements in this area include the increasing use of minimally invasive robotic surgery[56]. Ahmad reported the use of ICG FI in robotic radical resections for GBC in 10 patients, for the purposes of identifying the cystic duct junction with the CBD. This was made easy as NIR FI is a standard feature in daVinciâ surgical robots[56]. In addition, AJCC guidelines recommend removal and evaluation of 6 LNs in GBC resection, however this is rarely achieved[57]. The use of ICG guided regional lymphadenectomies may hence improve our ability to achieve this while reducing the risk of bile duct devascularization, and overcome visualization challenges from scarring and adhesions from previous operations[58,59].

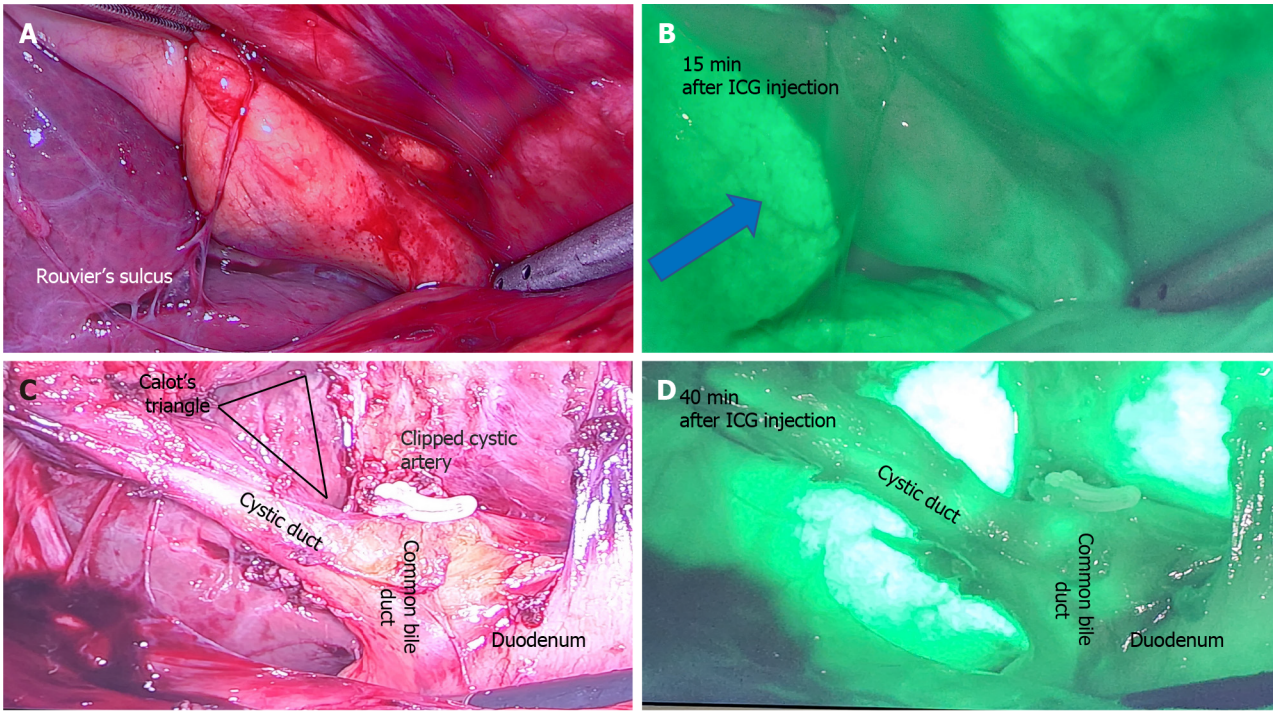
Choledochal cyst excision: The utility of ICG is also explored in identification of pancreatico-biliary junction and distal end of bile duct in a patient with choledochal cyst scheduled for laparoscopic excision[60]. The authors innovated a novel method of exploiting the protein affinity of ICG by mixing ICG with the patient's own bile juice aspirated from the gallbladder during surgery.

Bilio-enteric anastomosis: In patients undergoing hepaticojejunostomy for a variety of indications, ICG is shown to increase the detection of intra-operative bile leak from the anastomosis, thus allowing surgeons to reinforce the suture line and reducing the risk of post-operative biliary fistulas[61].

Pancreas

Tumour detection: During pancreatic tumour surgery, the extent of the tumour is typically evaluated intraoperatively through visual inspection or, in some cases, with the aid of intraoperative ultrasound. However, accurately delineating tumour boundaries can be difficult due to the presence of inflamed surrounding tissue[62]. Insufficient identification of tumour margins can lead to incomplete tumour resection, a predicament that has been shown to contribute to high recurrence rates ranging from 68% to 72%, as reported in a study by Griffin *et al*[63].

Novel NIR fluorescent agents have been developed that target tumour-specific cell surface markers, enzymatic activity, or increased glucose metabolism[64-66]. However, these tumour-specific agents are not yet available for clinical use. ICG on the other hand, can identify tumours based on the enhanced permeability and retention (EPR) effect. This effect refers to the dye's ability to accumulate in tumour spaces for prolonged periods due to the highly porous vessels and poorly developed lymphatics, despite not being tumour specific[67]. However, the EPR effect has been found to be less effective



DOI: 10.4240/wjgs.v15.i9.1841 **Copyright** ©The Author(s) 2023.

Figure 4 A 50-year-old patient undergoing elective laparoscopic cholecystectomy for previous acute cholecystitis was injected with 4 mL of indocyanine green dye after insertion of camera port. A: Rouvier's sulcus and corresponding; B: After 15 min of injection shows the dye enhances the liver (blue arrow) and indocyanine green (ICG) is yet to be excreted in biliary tree; C: Calot's triangle with a critical view of safety and clipped cystic artery; D: At 40 min after ICG injection shows beginning of biliary excretion in cystic duct and common bile duct. ICG: Indocyanine green.

in identifying pancreatic tumours compared to other malignancies such as breast cancer. A study conducted by Hutteman *et al*[62] revealed that only 12.5% (1/8) patients had a clear fluorescence hotspot corresponding to an adenocarcinoma, with no other useful results noted for the remaining patients. This can be attributed to healthy pancreatic cells having almost equal ICG uptake as tumour cells. The COLPAN study concluded that single-bolus intraoperative ICG was effective in delimiting the area of high fluorescence corresponding to functional pancreatic neuroendocrine tumours. Peak tumour fluorescence was obtained 20 min post administration, and ICG also concentrated in peripancreatic LNs[68].

Assessment of pancreatic perfusion post-pancreaticoduodenectomy: ICG dye can be utilised to confirm adequate perfusion of the pancreatic remnant during surgery. Traditional methods for assessing perfusion include clinical inspection of normal bleeding from the cut surface of the pancreas or Doppler ultrasonography for real-time arterial flow [69,70]. However, ultrasonography has limited spatial resolution and is not proficient in identifying concealed arteries, venous perfusion, or microperfusion[71]. In contrast, ICG binds to plasma lipoproteins, remaining within the intravascular space. ICG is administered intravenously during surgery, and its fluorescence in the remnant confirms adequate perfusion, as demonstrated in a case study by Iguchi *et al*[72]. Therefore, it is an effective method for evaluating all vascular supply means of the remnant pancreas.

Adrenals

Use in adrenalectomy: Laparoscopic and robotic techniques are now the gold-standard for adrenalectomies, but it hampers surgeons' ability to receive tactile feedback, which is important for discerning tumour edges and vascular structures[73]. The use of ICG enables differentiation between the hyperfluorescent adrenocortical tissue and hypofluorescent retroperitoneal tissue, facilitating dissection[74]. The best contrast between the adrenal and retroperitoneal fatty tissues was observed 5 min post-injection of ICG[75].

Moreover, ICG guided cortical-sparing adrenalectomy allows for intraoperative visualisation of the boundaries between the normal adrenal cortex and medullary tumour[74]. Phaeochromocytomas were non-fluorescent while healthy cortical tissue was brightly fluorescent, and hence Kahramangil *et al*[76] reported how when the phaeochromocytoma was small and did not penetrate the cortex, the whole adrenal appeared heterogeneously fluorescent and hence ICG usage was not helpful. It was only when the tumour was large, was the non-fluorescence appreciable for guiding resection.

Following the intravenous administration of ICG, the sequence of enhancement was the arterial anatomy, followed by the adrenal parenchyma, and lastly the adrenal vein. The identification of the vasculature is important, particularly for cases with distorted anatomy such as large adrenal neoplasms, and potentially allows for decreased blood loss[77]. Of note however, the identification of the adrenal vein was inconsistent in a larger prospective study of 100 patients[76].

Spleen

Laparoscopic splenectomy, as compared to open, has been shown to improve outcomes including blood loss, length of stay and reduction in wound complications[78]. It is unlikely that routine use of ICG would be indicated in straightforward cases. However, it could be useful in the identification and division of the splenic artery and vein in cases where there is anatomic distortion or adhesions from prior inflammation[79]. This is important as bleeding from these vessels can be substantial, and it is more difficult to obtain control in laparoscopic or robotic surgery compared to open surgery. ICG has been shown to be useful in selected cases during splenic surgery as described below.

Splenic aneurysmectomy: ICG has been reported to be helpful in the treatment of splenic artery aneurysms, an extremely rare disorder[80]. Bertolucci *et al*[81] reported a case where ICG was used in a laparoscopic splenic artery aneurysmectomy to confirm successful clip and resection of aneurysm. The use of ICG FI also enabled assessment of splenic blood supply, allowing for laparoscopic partial splenectomy in 4 patients[79].

Splenic cysts: Dome resection for splenic cysts allows for the preservation of splenic immunological function and has become the primary technique to treat splenic cysts. Masuya *et al*[82] reported the successful use of ICG fluorescence to assess for the thinning area of the cyst to be punctured. This is beneficial to allow preservation of normal parenchyma and avoid unnecessary splenectomy.

Small bowel

Perfusion assessment: There has been growing use of minimally invasive surgery for the treatment of small bowel pathology in recent years, but laparoscopy reduces the ability to discern signs of irreversible vascular insufficiency such as absence of peristaltic movements, mesenteric pulsations, and discolouration of the bowel wall. ICG angiography for assessment of bowel perfusion aids in determining need and extent of bowel resection.

Use in small bowel obstruction: In the setting of small bowel obstruction, Guerra *et al*[83] reported the use of ICG fluorescence in 7 patients for assessment of bowel viability. ICG was administered intravenously and in small 2 mL boluses to assess the intestinal microcirculation. Bowel segments that demonstrated patchy fluorescence or non-fluorescence were then resected. ICG as an adjunct for assessment of bowel perfusion is important, as inability to assess bowel viability is the second most common reason for conversion to open surgery in patients with small bowel obstruction[84]. Likewise, Ganguly *et al*[85] reported the use of ICG FI in 2 patients with incarcerated inguinal hernias containing small bowel. The involved bowel presented dusky areas but ICG administration revealed sufficient fluorescence and bowel resection was avoided.

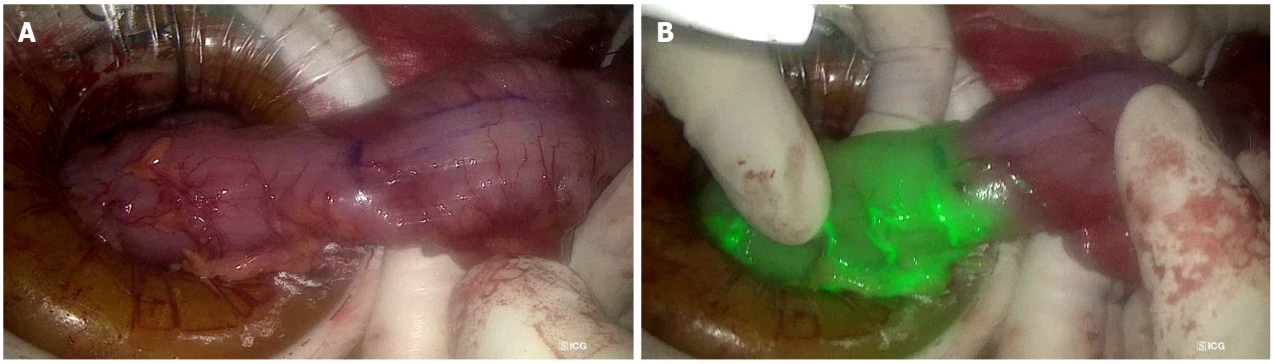
Use in small bowel ischemia: In mesenteric ischemia, it can be challenging to macroscopically differentiate between reversible and irreversible ischaemic bowel. Intraoperative ICG FI makes it possible to detect non-viable intestine that is not apparent to the naked eye. This may reduce the need for repeated laparotomies to reassess bowel viability[86]. In occlusive mesenteric ischemia, it is logical to determine the region of bowel to resect based on the vascular supply as evident on CT angiogram[87]. However, in non-occlusive mesenteric ischemia, hypoperfusion is due to mesenteric vasoconstriction which makes identifying the precise segment of non-viable bowel difficult. ICG plays a crucial role in helping surgeons determine intraoperatively which regions of the bowel are adequately perfused, and hence decide on the need or extent of resection[86].

Colorectal

In colorectal surgery, ICG's applications are varied including fluorescent tumour localisation, LN mapping and intraoperative angiography for anastomosis perfusion assessment[88]. Fluorescence guided visualisation continues to gain popularity amongst colorectal surgeons due to its reliability, safety, and ease of use. A survey of 37 centres in the Italian ColoRectal Anastomotic Leakage study group reported that 78.4% (29/37) of centres used fluorescence in all laparoscopic colorectal resections, and 65.5% of surgeons strongly believed the use of FI will become a minimum requirement in the future[89]. Studies have also demonstrated the use of ICG FI in robotic colorectal surgeries[90].

Assessment of bowel perfusion at site of intended anastomosis: ALs are a known complication of colorectal surgery with incidence between 3%-19%[91]. This is associated with increased morbidity and mortality, prolonged hospital stay, and a potential association with an increased risk of cancer recurrence, translating to worse long-term outcomes[92,93]. Bowel vascularity is a modifiable risk factor for anastomotic healing, hence the utility of ICG fluorescence angiography for intraoperative confirmation of favourable bowel perfusion prior to anastomosis. A retrospective matched-pairs analysis has demonstrated that ICG angiography suggested a change of proximal colonic resection line location in 16.4% and significantly reduced AL rates by 4%[94]. A recent meta-analysis of 4037 patients comparing AL rates between colorectal surgery with and without ICG showed that ICG angiography significantly reduced the AL rate by 4%, which translated to a reduced risk of reoperation and 5.6% reduction in overall complications[95]. This is confirmed by a larger meta-analysis of 25 studies with 7735 patients by Trastulli *et al*[96], which found that ICG angiography led to a reduction in AL rate compared to standard methods of anastomosis perfusion assessment (OR = 0.39, 95%CI: 0.31-0.49, $P < 0.001$). The NNT for ICG to prevent 1 additional AL is 23 patients. Figure 5 illustrates the use of ICG to confirm well vascularised bowel at the site of intended bowel transection and subsequent anastomosis.

Some limitations include the qualitative nature of the assessment for ICG fluorescence in the bowel which can be subjective, with no standard on dose of ICG and observation time. Research has hence been conducted on the quantitative analysis of colonic perfusion, with an evaluation of fluorescence intensity and perfusion time factors. A Korean study has determined that factors related to perfusion time, such as time from first fluorescence increase to maximum fluorescence,



DOI: 10.4240/wjgs.v15.i9.1841

Figure 5 The utility of indocyanine green dye in laparoscopic anterior resection. A: The descending colon prepared for proximal transection during laparoscopic anterior resection, with the purple line indicating intended transection site, 5 cm proximal to tumour; B: The indocyanine green angiography confirms good vascularity at the site of intended transection, prior to creation of colo-rectal anastomosis.

are significant predictors of anastomotic complications[97]. At present there is no consensus on the routine use of ICG for assessment of anastomotic perfusion in colorectal surgery. In spite of this, a recent cost analysis by Liu *et al*[98] on routine ICG use for anastomotic perfusion assessment found it cost-effective.

Perfusion assessment of other structures: Perfusion assessment using ICG has also been performed for pedicled omentoplasty in pelvic surgery, gracilis muscle flaps and anal advancement flaps for perianal fistula[99]. In a study assessing the role of ICG dye in pedicled opemtoplasties, 80% (12/15) of patients had a larger resection than intended as ICG was able to identify areas of malperfused omentum that was not visible under standard white light. While this added an extra median of 8 min (range 3-39 min) to the surgical time, it can be argued that this is a worthwhile limitation[100].

Tumour localisation: Preoperative endoscopic tattooing of colonic lesions using India ink was first described in 1975 by Ponsky and King[101] for the purposes of intraoperative localisation. This is necessary in the setting of minimally invasive surgery in view of the inability to palpate the colorectum intraoperatively to allow identification of lesions. ICG tumour marking has been employed to allow precise intraoperative identification of small lesions without affecting the visibility of the surgical field and tissue planes with colour dye while in conventional viewing mode. The preferred interval between endoscopic submucosal injection of ICG and surgery varies. Lee *et al*[102] endoscopically injected 1-1.5 mL of ICG preoperatively and found that tattoos placed within 2 d of surgery were more often visualised (95%) than if they were placed earlier (40%). In contrast, a Japanese study injecting 0.5 mg of ICG submucosally described 100% intraoperative detection rates within 6 d and significant decrease after 7 d[103]. Furthermore, a prospective case series by Orsi *et al*[104] on 10 patients who underwent robotic colorectal resections also demonstrated the utility of ICG as a preoperative tumour marking dye for robotic surgeries.

Lymphatic mapping: ICG can further be used for LN mapping in colorectal cancer (CRC) patients, similar to that for other gastrointestinal malignancies. ICG spreads through lymphatic drainage from distal perivascular space with slow interstitial fluid reabsorption when ICG is injected into the colonic wall[88]. Concentration and dosing of ICG utilised in the literature varies, with injections performed either subserosal laparoscopically or submucosal endoscopically[105]. In patients with CRC, ICG is useful for two purposes. Firstly, ICG dye injection guides lymphatic mapping to facilitate harvesting of the draining LNs for oncological resection during colorectal resection. Secondly, ICG dye injection helps identify the SLN and provide information to surgeons for resection and is an area of ongoing research initiatives.

A systematic review of 12 studies found the rate of SLN accuracy in T1 CRC to be between 89%-100% when various dyes are used, including ICG and patent blue[106]. However, there is no consensus on the applicability of SLN identification in colorectal cancer. Current practice of complete mesocolic excision and total mesorectal excision ensures enbloc lymphovascular clearance. The role of lymphatic mapping in colorectal cancer could potentially be in early tumour stages to allow for conservative surgical resections but more research is required in this aspect[107].

Lateral pelvic LN dissection: Lateral pelvic LN dissection (LPLD) is recommended for patients diagnosed with mid-to-low advanced rectal cancer, due to the estimated 11%-22% incidence of lateral pelvic LN metastases (LPNM) in patients with T3/4 rectal cancer[108]. LPNM is an important factor for local recurrence, and is treated as a systemic disease due to common occurrence of distant metastasis[109,110]. Zhou *et al*[109] evaluated the use of ICG FI for LPLD, and found significantly reduced blood loss and a greater number of LNs harvested, but no difference in operative time nor postoperative complications. In another longer-term propensity score-matched cohort study, Watanabe *et al*[111] reported decreased 3-year cumulative lateral local recurrence rate in the ICG-FI group. In addition, Yasui *et al*[112] and Noura *et al*[113] proposed the use of ICG FI to identify SLNs in patients without suspected LPNM. However, further prospective studies are required in this regard.

Ureteral visualization: Ureteral injuries, while rare with an incidence of around 0.28% of colorectal surgeries, are associated with increased mortality, morbidity, length of stay, and healthcare costs[114]. Intraureteral ICG administration has been used for intraoperative ureteral identification to reduce iatrogenic injuries, and also allows for the early identi-

fication of any ureteral injury for immediate repair. Administration requires cystoscopy and ureteral catheterisation, and allows for 4 to 12 h of ureteral visualisation[115]. Most studies used 5 mL of 2.5 mg/mL ICG for each ureter. A systematic review of 7 retrospective studies found this safe and effective, although the risks of ureteral catheterisation include ureteral injury itself and infectious complications[116,117].

Urethral identification: Urethral injury is a dreaded complication in transanal total mesorectal excision and abdominoperineal resection, and is increasing in incidence with more minimally invasive transanal surgery being performed[118]. Studies have demonstrated successful visualisation of the urethra with ICG mixed with Instillagel® and ICG-silicon coated Foley catheters, albeit in cadavers[99].

Identification of nerves: The pelvic autonomic nerves are crucial for regulation of anorectal and urogenital function, but may be damaged during colorectal surgery. A pilot study by Jin *et al*[119] demonstrated that intravenous administration of 5 mg/kg ICG 24 h preoperatively allowed for the visualisation of the splanchnic, inferior mesenteric artery and sacral plexus during laparoscopic colorectal resection. This technique still requires further research, but could potentially aid in identification and protection of the pelvic autonomic nerves during laparoscopic colorectal resections.

Peritoneal

Peritoneal metastases occur in up to 30% of colorectal cancer patients (metachronous more than synchronous), and 75% of ovarian cancer patients present with peritoneal disease on diagnosis[120,121]. Conventional imaging modalities such as CT and magnetic resonance imaging have poor sensitivity in detecting small peritoneal nodules, requiring surgical exploration or cytological examination of peritoneal washings for complete evaluation of the peritoneal cavity[122,123]. However, small nodules may remain undetected during the surgeon's visual and tactile assessment. In the context of a diagnostic exploration, this can impact staging and management. In the therapeutic setting, this can affect the completeness of cytoreduction and subsequent long term outcomes. ICG offers a potential solution to this diagnostic challenge, with its theoretical ability to detect micro peritoneal implants using the EPR effect[124]. In a systematic review of 71 patients with 322 peritoneal nodules assessed, ICG demonstrated promising sensitivity and specificity in detecting nodules at 88.2% and 77.8%, respectively[125]. However, there are restrictions to its utility in mucinous colorectal carcinomas, which have poor affinity for ICG. There is a possible role for ICG fluorescence as an adjunct to improve detection of peritoneal metastases in colon and ovarian cancer, but more studies are warranted.

Vascular

Wound healing post-amputation in patients with peripheral artery disease or chronic limb threatening ischaemia is often poor due to the poor vascular status and underlying comorbidities including diabetes mellitus or smoking[126]. ICG NIR FI post-amputation or post-revascularization is one proposed method for assessing regional tissue perfusion in predicting wound healing, determining level of amputation and to assess global limb perfusion. Van Den Hoven *et al*[127] performed a pilot study where ICG NIR FI was performed in 15 patients post-amputation, and noted that impaired wound healing corresponded to regions of low fluorescence in patients, and accurately predicted postoperative skin necrosis in 4 cases.

Bowel ischaemia is a known postoperative complication of abdominal aortic aneurysm (AAA) repair due to malperfusion of the peripheral arteries, with its associated mortality up to 50%[128,129]. ICG angiography provides visualization of peripheral intestinal blood flow, which can be used to determine whether there is sufficient vascular supply to perfuse the bowels. This information can help to guide decisions regarding whether the inferior mesenteric arteries (IMA) and internal iliac arteries (IIA) need to be reconstructed or preserved. In a study conducted by Yamamoto *et al*[129] involving 10 open AAA repairs, the use of ICG angiography resulted in at least 1 IMA or IIA being reconstructed in 8 cases that would not have been done otherwise. This approach helps to ensure that postoperative bowel ischemia, which would require a second surgery, is minimized.

Other abdominal organs

Beyond the organs discussed above, ICG is also used in other abdominal organs beyond the purview of a gastrointestinal surgeon. For example, ICG has been used to define tumour margins from normal kidney, identify branches of the main renal artery in partial nephrectomies, and assess microperfusion to predict early graft function in kidney transplant patients[130-132]. In gynaecological surgery, similar applications were noted in identifying SLNs in endometrial, cervical and vulvar malignancies[133]. It also is used for ureteral identification and localizing endometriosis nodules[134].

DISCUSSION

Current uses

ICG plays a crucial role in the field of gastrointestinal surgery, specifically in the optimization of oncological resections and comprehension of vascular supply. The key factors that contribute to successful cancer resections with low recurrence rates involve precise identification and localisation of the tumour, adequate resection of the tumour with ample margins, and complete removal of the lymphatics[33]. ICG serves as a useful tool in facilitating these steps, enhancing their efficiency and accuracy.

In oncological resections of various organs such as the oesophagus, stomach, hepatobiliary system, and the bowels, lymphatic mapping through ICG is widely employed. This method ensures the precise identification of SLNs and aids in determining the extent of LN dissection[135]. Literature also confirms that ICG can be used to identify tumours intraoperatively, specifically *via* the EPR effect. This helps to assure surgeons that they have resected sufficient tissue to prevent positive margins that may mandate a second operation. This, in turn, enables surgeons to operate with greater confidence that the cancer has been adequately removed, while simultaneously reducing the need for more extensive surgeries when they are not necessary.

ICG also provides surgeons with a better understanding of vascular supply, thereby preventing intraoperative accidental injuries, especially in cases where vessels are difficult to visualize or have aberrant anatomy[135]. Additionally, it facilitates complete vessel anastomoses to prevent leaks. Furthermore, ICG aids in ensuring sufficient perfusion of organs following resections, thereby decreasing the risk of postoperative ischemia. In summary, ICG provides surgeons with valuable insights into the vessels involved in surgery, which significantly reduces surgical morbidity, leading to shorter postoperative complications and ICU stays.

Given these applications of ICG in gastrointestinal surgery, it is only natural that ICG FI is primarily used in minimally invasive surgery or robotic surgery. ICG enables the mitigation of traditional drawbacks such as the lack of tactile feedback and subjective judgment error for tissue perfusion and viability. It remains used in open surgery still in more oncological contexts, such as SLN mapping.

Future direction

ICG has a myriad of clinical applications and many emerging applications. Despite this, the accessibility, availability, affordability, and adoption remain an unmet need that needs to be met by collaborative initiatives of the medico-industrial complex. To begin with, standardized evidence base guidelines need to be developed, disseminated, and implemented for safe adoption in routine clinical practice.

Optimising ICG: Patient factors, dye factors, equipment, and method of assessing fluorescence intensity are factors that implicate and affect the utility of ICG. Patient factors include obesity and inflammation. Eriksson *et al*[136] showed a decreased rate of successful SLN mapping with increased patient body mass index.

Dye factors include the dose and concentration, timing, and route of administration, and increasingly also whether the dye is mixed with any other substances. For the purpose of SLN identification, prolonged accumulation of ICG in the sentinel nodes is crucial. By complexing ICG with HSA in the optimal molar composition, a higher fluorescence can be obtained to aid in this[137].

In addition, other dyes such as ZW-800 and VM678, among many others, have been tested in animal studies, with results showing better pharmacokinetic properties and target-to-background ratio. However, cost remains a barrier for these dyes[138]. ICG coating of the tubes and stents can be made possible with potential future clinical application in surgery. For example, ICG-coated ureteral stents can be useful in colorectal, gynecological, and urological procedures.

Fundamentally, there remains no widely accepted protocols for the use of ICG in most applications, with decisions such as dosing regimens left up to the surgeons' expertise. Further research and study should focus on this area to optimise protocols to ensure the successful use of ICG.

Targeted contrast agents: It would also be useful to look beyond ICG, and develop new contrast agents that better target unique pathologies. This can be done *via* identifying antibodies or ligands for proteins and receptors on cancer cell surfaces, and substrates for cancer specific metabolic pathways. A large proportion of these dyes are ICG-based, as they can be incorporated into hardware that are already in operative rooms. Other cyanine based dyes can also be incorporated with minor modifications in these machinery[139].

There are already several tumour specific dyes produced clinically. LUM015 is a cyanine based dye that targets cathepsin, which is a protease secreted by cancer cells at a higher level than healthy cells. LUM015 targets breast cancer and sarcomas specifically and is not affected by breast density, as compared to ICG, making it more accurate[140].

Studies have also shown that ICG-like fluorescent dyes can be tagged to artificially created antibodies of cell-surface tumour markers. Promising antibodies have been developed for carcinoembryonic antigen (CEA) for colorectal, breast, lung, and gastric cancer, prostate-specific antigen for prostate cancer, and cancer antigen 125 for ovarian cancer[139]. For example, XenoLight CF750 is an anti-CEA antibody conjugated to ICG and NIR probe. It was able to detect peritoneal tumour deposits in all 4 gastric cancer cell lines, including micrometastases < 2 mm in mouse models[141].

The ability to target cancers specifically allows for better cancer detection and surgical margins, and hence this is an area of research that shows great promise. Regardless, further research should be conducted for all applications of ICG to confirm the improvement in outcomes.

CONCLUSION

ICG has wide clinical utility to enhance safety and accuracy of gastrointestinal surgery to improve patient outcomes, both in surgical oncology and in general. With the ongoing advancements in technology and research, the future of FI remains promising and will continue to revolutionize surgery. However, ICG should not be considered as a panacea to guide surgical conduct, and surgeons need to exercise own's informed judgment based on individual skills, experience and training.

FOOTNOTES

Author contributions: Shelat VG contributed to the conceptualization, supervision and project administration of the manuscript; Lim ZY involved in the methodology of this study; Lim ZY and Mohan S curated data; Lim ZY, Mohan S, Balasubramaniam S, Ahmed S, Siew CCH, and Shelat VG wrote the manuscript.

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

Country/Territory of origin: Singapore

ORCID number: Zavier Yongxuan Lim 0000-0001-7639-5123; Swetha Mohan 0000-0001-8463-1579; Sunder Balasubramaniam 0000-0002-4983-7157; Saleem Ahmed 0000-0001-6767-4825; Caroline Ching Hsia Siew 0000-0003-0250-6390; Vishal G Shelat 0000-0003-3988-8142.

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

REFERENCES

1 **Lu CH**, Hsiao JK. Indocyanine green: An old drug with novel applications. *Tzu Chi Med J* 2021; **33**: 317-322 [PMID: 34760625 DOI: 10.4103/tcmj.tcmj_216_20]
2 **Reinhart MB**, Huntington CR, Blair LJ, Heniford BT, Augenstein VA. Indocyanine Green: Historical Context, Current Applications, and Future Considerations. *Surg Innov* 2016; **23**: 166-175 [PMID: 26359355 DOI: 10.1177/1553350615604053]
3 **Kraft JC**, Ho RJ. Interactions of indocyanine green and lipid in enhancing near-infrared fluorescence properties: the basis for near-infrared imaging in vivo. *Biochemistry* 2014; **53**: 1275-1283 [PMID: 24512123 DOI: 10.1021/bi500021j]
4 **Lund-Johansen P**. The dye dilution method for measurement of cardiac output. *Eur Heart J* 1990; **11** Suppl I: 6-12 [PMID: 2092991 DOI: 10.1093/eurheartj/11.suppl_i.6]
5 **Destro M**, Puliafito CA. Indocyanine green videoangiography of choroidal neovascularization. *Ophthalmology* 1989; **96**: 846-853 [PMID: 2472588 DOI: 10.1016/s0161-6420(89)32826-0]
6 **Peltrini R**, Podda M, Castiglioni S, Di Nuzzo MM, D'Ambra M, Lionetti R, Sodo M, Luglio G, Mucilli F, Di Saverio S, Bracale U, Corcione F. Intraoperative use of indocyanine green fluorescence imaging in rectal cancer surgery: The state of the art. *World J Gastroenterol* 2021; **27**: 6374-6386 [PMID: 34720528 DOI: 10.3748/wjg.v27.i38.6374]
7 **Short MW**, Burgers KG, Fry VT. Esophageal Cancer. *Am Fam Physician* 2017; **95**: 22-28 [PMID: 28075104]
8 **Chen QY**, Xie JW, Zhong Q, Wang JB, Lin JX, Lu J, Cao LL, Lin M, Tu RH, Huang ZN, Lin JL, Zheng HL, Li P, Zheng CH, Huang CM. Safety and Efficacy of Indocyanine Green Tracer-Guided Lymph Node Dissection During Laparoscopic Radical Gastrectomy in Patients With Gastric Cancer: A Randomized Clinical Trial. *JAMA Surg* 2020; **155**: 300-311 [PMID: 32101269 DOI: 10.1001/jamasurg.2019.6033]
9 **National Comprehensive Cancer Network**. Guidelines Detail – NCCN Guidelines. [cited 21 Apr 2023]. Available from: https://www.nccn.org/guidelines/guidelines-detail
10 **Hachey KJ**, Gilmore DM, Armstrong KW, Harris SE, Hornick JL, Colson YL, Wee JO. Safety and feasibility of near-infrared image-guided lymphatic mapping of regional lymph nodes in esophageal cancer. *J Thorac Cardiovasc Surg* 2016; **152**: 546-554 [PMID: 27179838 DOI: 10.1016/j.jtcvs.2016.04.025]
11 **den Toom IJ**, Mahieu R, van Rooij R, van Es RJJ, Hobbelink MGG, Krijger GC, Tijink BM, de Keizer B, de Bree R. Sentinel lymph node detection in oral cancer: a within-patient comparison between [(99m)Tc]Tc-tilmanocept and [(99m)Tc]Tc-nanocolloid. *Eur J Nucl Med Mol Imaging* 2021; **48**: 851-858 [PMID: 32839855 DOI: 10.1007/s00259-020-04984-8]
12 **Yuasa Y**, Seike J, Yoshida T, Takechi H, Yamai H, Yamamoto Y, Furukita Y, Goto M, Minato T, Nishino T, Inoue S, Fujiwara S, Tangoku A. Sentinel lymph node biopsy using intraoperative indocyanine green fluorescence imaging navigated with preoperative CT lymphography for superficial esophageal cancer. *Ann Surg Oncol* 2012; **19**: 486-493 [PMID: 21792510 DOI: 10.1245/s10434-011-1922-x]
13 **Ohnishi S**, Lomnes SJ, Laurence RG, Gogbashian A, Mariani G, Frangioni JV. Organic alternatives to quantum dots for intraoperative near-infrared fluorescent sentinel lymph node mapping. *Mol Imaging* 2005; **4**: 172-181 [PMID: 16194449 DOI: 10.1162/15353500200505127]
14 **Wall KP**, Dillon R, Knowles MK. Fluorescence quantum yield measurements of fluorescent proteins: a laboratory experiment for a biochemistry or molecular biophysics laboratory course. *Biochem Mol Biol Educ* 2015; **43**: 52-59 [PMID: 25395254 DOI: 10.1002/bmb.20837]
15 **Kim HK**, Quan YH, Oh Y, Park JY, Park JH, Choi Y, Lee YS, Jeong JM, Choi YH, Kim BM. Macrophage-Targeted Indocyanine Green-Neomannosyl Human Serum Albumin for Intraoperative Sentinel Lymph Node Mapping in Porcine Esophagus. *Ann Thorac Surg* 2016; **102**: 1149-1155 [PMID: 27353484 DOI: 10.1016/j.athoracsur.2016.04.077]
16 **Schlottmann F**, Patti MG. Esophageal Adenocarcinoma Lymphatic Drainage with ICG Fluorescence Imaging. *J Gastrointest Surg* 2019; **23**: 384-385 [PMID: 29713874 DOI: 10.1007/s11605-018-3769-y]
17 **Chandler P**, Wiesel O, Sherwinter DA. Fluorescence-guided surgery of the esophagus. *Ann Transl Med* 2021; **9**: 908 [PMID: 34164542 DOI: 10.21037/atm.2020.03.138]
18 **Fabbi M**, Hagens ERC, van Berge Henegouwen MI, Gisbertz SS. Anastomotic leakage after esophagectomy for esophageal cancer: definitions, diagnostics, and treatment. *Dis Esophagus* 2021; **34** [PMID: 32476017 DOI: 10.1093/dote/doaa039]
19 **Noma K**, Shirakawa Y, Kanaya N, Okada T, Maeda N, Ninomiya T, Tanabe S, Sakurama K, Fujiwara T. Visualized Evaluation of Blood Flow

to the Gastric Conduit and Complications in Esophageal Reconstruction. *J Am Coll Surg* 2018; **226**: 241-251 [PMID: 29174858 DOI: 10.1016/j.jamcollsurg.2017.11.007]

20 **Kumagai Y**, Hatano S, Sobajima J, Ishiguro T, Fukuchi M, Ishibashi KI, Mochiki E, Nakajima Y, Ishida H. Indocyanine green fluorescence angiography of the reconstructed gastric tube during esophagectomy: efficacy of the 90-second rule. *Dis Esophagus* 2018; **31** [PMID: 29897432 DOI: 10.1093/dote/doy052]

21 **Slooter MD**, Eshuis WJ, Cuesta MA, Gisbertz SS, van Berge Henegouwen MI. Fluorescent imaging using indocyanine green during esophagectomy to prevent surgical morbidity: a systematic review and meta-analysis. *J Thorac Dis* 2019; **11**: S755-S765 [PMID: 31080655 DOI: 10.21037/jtd.2019.01.30]

22 **Yang YH**, Park SY, Kim DJ. Chyle Leakage after Esophageal Cancer Surgery. *Korean J Thorac Cardiovasc Surg* 2020; **53**: 191-199 [PMID: 32793451 DOI: 10.5090/kjtcs.2020.53.4.191]

23 **Kamiya K**, Unno N, Konno H. Intraoperative indocyanine green fluorescence lymphography, a novel imaging technique to detect a chyle fistula after an esophagectomy: report of a case. *Surg Today* 2009; **39**: 421-424 [PMID: 19408081 DOI: 10.1007/s00595-008-3852-1]

24 **Kaburagi T**, Takeuchi H, Oyama T, Nakamura R, Takahashi T, Wada N, Saikawa Y, Kamiya S, Tanaka M, Wada T, Kitagawa Y. Intraoperative fluorescence lymphography using indocyanine green in a patient with chylothorax after esophagectomy: report of a case. *Surg Today* 2013; **43**: 206-210 [PMID: 23108512 DOI: 10.1007/s00595-012-0391-6]

25 **Das J**, Thambudorai R, Ray S. Lymphoscintigraphy combined with single-photon emission computed tomography-computed tomography (SPECT-CT): A very effective imaging approach for identification of the site of leak in postoperative chylothorax. *Indian J Nucl Med* 2015; **30**: 177-179 [PMID: 25829744 DOI: 10.4103/0972-3919.152988]

26 **Cianchi F**, Indennitate G, Paoli B, Ortolani M, Lami G, Manetti N, Tarantino O, Messeri S, Foppa C, Badii B, Novelli L, Skalamera I, Nelli T, Coratti F, Perigli G, Staderini F. The Clinical Value of Fluorescent Lymphography with Indocyanine Green During Robotic Surgery for Gastric Cancer: a Matched Cohort Study. *J Gastrointest Surg* 2020; **24**: 2197-2203 [PMID: 31485904 DOI: 10.1007/s11605-019-04382-y]

27 **Lombardi PM**, Mazzola M, Nicastro V, Giacopuzzi S, Baiocchi GL, Castoro C, Rosati R, Fumagalli Romario U, Bonavina L, Staderini F, Gockel I, Gregori D, De Martini P, Gualtierotti M, Danieli M, Beretta S, Mutignani M, Forti E, Ferrari G. The iGreenGO Study: The Clinical Role of Indocyanine Green Imaging Fluorescence in Modifying the Surgeon's Conduct During the Surgical Treatment of Advanced Gastric Cancer-Study Protocol for an International Multicenter Prospective Study. *Front Oncol* 2022; **12**: 854754 [PMID: 35372091 DOI: 10.3389/fonc.2022.854754]

28 **Kitagawa Y**, Takeuchi H, Takagi Y, Natsugoe S, Terashima M, Murakami N, Fujimura T, Tsujimoto H, Hayashi H, Yoshimizu N, Takagane A, Mohri Y, Nabeshima K, Uenosono Y, Kinami S, Sakamoto J, Morita S, Aikou T, Miwa K, Kitajima M. Sentinel node mapping for gastric cancer: a prospective multicenter trial in Japan. *J Clin Oncol* 2013; **31**: 3704-3710 [PMID: 24019550 DOI: 10.1200/JCO.2013.50.3789]

29 **Cho M**, Kim KY, Park SH, Kim YM, Kim HI, Hyung WJ. Securing Resection Margin Using Indocyanine Green Diffusion Range on Gastric Wall during NIR Fluorescence-Guided Surgery in Early Gastric Cancer Patients. *Cancers (Basel)* 2022; **14** [PMID: 36358639 DOI: 10.3390/cancers14215223]

30 **Kalmar CL**, Reed CM, Peery CL, Salzberg AD. Intraluminal indocyanine green for intraoperative staple line leak testing in bariatric surgery. *Surg Endosc* 2020; **34**: 4194-4199 [PMID: 32385707 DOI: 10.1007/s00464-020-07606-4]

31 **Hagen ME**, Diaper J, Douissard J, Jung MK, Buehler L, Aldenkortt F, Barcelos GK, Morel P. Early Experience with Intraoperative Leak Test Using a Blend of Methylene Blue and Indocyanine Green During Robotic Gastric Bypass Surgery. *Obes Surg* 2019; **29**: 949-952 [PMID: 30607685 DOI: 10.1007/s11695-018-03625-2]

32 **Sánchez-Pernaute A**, López-Antoñanzas L, Torres AJ, Dziakova J, Rubio MA, Pérez-Aguirre E. Avoiding Complications During Revisional Bariatric Surgery with Indocyanine Green Fluorescence Imaging. *Obes Surg* 2023; **33**: 972-974 [PMID: 36595146 DOI: 10.1007/s11695-022-06433-x]

33 **Schrembs D**, Rosenberg R. [Principles of modern oncologic surgery]. *Ther Umsch* 2019; **76**: 199-207 [PMID: 31498040 DOI: 10.1024/0040-5930/a001085]

34 **Rossi G**, Tarasconi A, Baiocchi G, De' Angelis GL, Gaiani F, Di Mario F, Catena F, Dalla Valle R. Fluorescence guided surgery in liver tumors: applications and advantages. *Acta Biomed* 2018; **89**: 135-140 [PMID: 30561406 DOI: 10.23750/abm.v89i9-S.7974]

35 **Franz M**, Arend J, Wolff S, Perrakis A, Rahimli M, Negrini VR, Stockheim J, Lorenz E, Croner R. Tumor visualization and fluorescence angiography with indocyanine green (ICG) in laparoscopic and robotic hepatobiliary surgery - valuation of early adopters from Germany. *Innov Surg Sci* 2021; **6**: 59-66 [PMID: 34589573 DOI: 10.1515/iss-2020-0019]

36 **Mehdorn AS**, Richter F, Hess K, Beckmann JH, Egberts JH, Linecker M, Becker T, Braun F. The Role of ICG in Robot-Assisted Liver Resections. *J Clin Med* 2022; **11** [PMID: 35743595 DOI: 10.3390/jcm11123527]

37 **Schwarz C**, Plass I, Fitschek F, Punzengruber A, Mittlböck M, Kampf S, Asenbaum U, Starlinger P, Stremitzer S, Bodingbauer M, Kaczirek K. The value of indocyanine green clearance assessment to predict postoperative liver dysfunction in patients undergoing liver resection. *Sci Rep* 2019; **9**: 8421 [PMID: 31182746 DOI: 10.1038/s41598-019-44815-x]

38 **Sheriff S**, Madhavan S, Lei GY, Chan YH, Junnarkar SP, Huey CW, Low JK, Shelat VG. Predictors of mortality within the first year post-hepatectomy for hepatocellular carcinoma. *J Egypt Natl Canc Inst* 2022; **34**: 14 [PMID: 35368234 DOI: 10.1186/s43046-022-00113-8]

39 **Li M**, Wang J, Song J, Shen F, Song L, Ni X, Suo T, Liu H, Zhong M. Preoperative ICG Test to Predict Posthepatectomy Liver Failure and Postoperative Outcomes in Hilar Cholangiocarcinoma. *Biomed Res Int* 2021; **2021**: 8298737 [PMID: 33681380 DOI: 10.1155/2021/8298737]

40 **Pind ML**, Bendtsen F, Kallemose T, Møller S. Indocyanine green retention test (ICG-r15) as a noninvasive predictor of portal hypertension in patients with different severity of cirrhosis. *Eur J Gastroenterol Hepatol* 2016; **28**: 948-954 [PMID: 27172450 DOI: 10.1097/MEG.0000000000000611]

41 **Chan KS**, Shelat VG, Low HM, Low JK. Is the extent of functional liver remnant increase truly "functional"? A single-institution case series of patients with Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS). *Clin Exp Hepatol* 2023; **9**: 28-36 [PMID: 37064831 DOI: 10.5114/ceh.2023.124476]

42 **Une N**, Fujio A, Mitsugashira H, Kanai N, Saitoh Y, Ohta M, Sasaki K, Miyazawa K, Kashiwadate T, Nakanishi W, Tokodai K, Miyagi S, Unno M, Kamei T. Laparoscopic liver cyst fenestration with real-time indocyanine green fluorescence-guided surgery: a case report. *J Surg Case Rep* 2021; **2021**: rjab196 [PMID: 34025978 DOI: 10.1093/jscr/rjab196]

43 **Hanaki T**, Yagyu T, Uchinaka E, Morimoto M, Watanabe J, Tokuyasu N, Takano S, Sakamoto T, Honjo S, Fujiwara Y. Avoidance of bile duct injury during laparoscopic liver cyst fenestration using indocyanine green: A case report. *Clin Case Rep* 2020; **8**: 1419-1424 [PMID: 32884766 DOI: 10.1002/ccr3.2840]

44 **Umemura A**, Nitta H, Suto T, Fujiwara H, Takahara T, Hasegawa Y, Katagiri H, Kanno S, Ando T, Sasaki A. Indocyanine green fluorescence

imaging *via* endoscopic nasal biliary drainage during laparoscopic deroofing of liver cysts. *J Minim Access Surg* 2021; **17**: 131-134 [PMID: 33353900 DOI: 10.4103/jmas.JMAS_26_20]

45 **Graves C**, Ely S, Idowu O, Newton C, Kim S. Direct Gallbladder Indocyanine Green Injection Fluorescence Cholangiography During Laparoscopic Cholecystectomy. *J Laparoendosc Adv Surg Tech A* 2017; **27**: 1069-1073 [PMID: 28574801 DOI: 10.1089/lap.2017.0070]

46 **Chan KS**, Hwang E, Low JK, Junnarkar SP, Huey CWT, Shelat VG. On-table hepatopancreatobiliary surgical consults for difficult cholecystectomies: A 7-year audit. *Hepatobiliary Pancreat Dis Int* 2022; **21**: 273-278 [PMID: 35367147 DOI: 10.1016/j.hbpd.2022.03.008]

47 **Koo JGA**, Chan YH, Shelat VG. Laparoscopic subtotal cholecystectomy: comparison of reconstituting and fenestrating techniques. *Surg Endosc* 2021; **35**: 1014-1024 [PMID: 33128079 DOI: 10.1007/s00464-020-08096-0]

48 **Polom W**, Markuszewski M, Rho YS, Matuszewski M. Usage of invisible near infrared light (NIR) fluorescence with indocyanine green (ICG) and methylene blue (MB) in urological oncology. Part 1. *Cent European J Urol* 2014; **67**: 142-148 [PMID: 25140227 DOI: 10.5173/ceju.2014.02.art5]

49 **Yong CC**, Yin SM, Sng YP, Chen CL. Prevent bile duct injury by indocyanine green guide fluorescent imaging during laparoscopic cholecystectomy in liver transplantation recipient. *Hepatobiliary Surg Nutr* 2020; **9**: 817-819 [PMID: 33299845 DOI: 10.21037/hbsn-20-342]

50 **Lim SH**, Tan HTA, Shelat VG. Comparison of indocyanine green dye fluorescent cholangiography with intra-operative cholangiography in laparoscopic cholecystectomy: a meta-analysis. *Surg Endosc* 2021; **35**: 1511-1520 [PMID: 33398590 DOI: 10.1007/s00464-020-08164-5]

51 **Bandari M**, Pai MV, Acharya A, Augustine AJ, Murlimanju BV. Anatomical mapping of the biliary tree during laparoscopic cholecystectomy by using indocyanine green dye. *J Minim Access Surg* 2022; **18**: 218-223 [PMID: 35313432 DOI: 10.4103/jmas.JMAS_87_21]

52 **Ambe PC**, Plambeck J, Fernandez-Jesberg V, Zarras K. The role of indocyanine green fluoroscopy for intraoperative bile duct visualization during laparoscopic cholecystectomy: an observational cohort study in 70 patients. *Patient Saf Surg* 2019; **13**: 2 [PMID: 30651756 DOI: 10.1186/s13037-019-0182-8]

53 **Shibata H**, Aoki T, Koizumi T, Kusano T, Yamazaki T, Saito K, Hirai T, Tomioka K, Wada Y, Hakozaki T, Tashiro Y, Nogaki K, Yamada K, Matsuda K, Fujimori A, Enami Y, Murakami M. The Efficacy of Intraoperative Fluorescent Imaging Using Indocyanine Green for Cholangiography During Cholecystectomy and Hepatectomy. *Clin Exp Gastroenterol* 2021; **14**: 145-154 [PMID: 33958888 DOI: 10.2147/CEG.S275985]

54 **Esposito C**, Alberti D, Settimi A, Pecorelli S, Boroni G, Montanaro B, Escolino M. Indocyanine green (ICG) fluorescent cholangiography during laparoscopic cholecystectomy using RUBINA™ technology: preliminary experience in two pediatric surgery centers. *Surg Endosc* 2021; **35**: 6366-6373 [PMID: 34231069 DOI: 10.1007/s00464-021-08596-7]

55 **Rakić M**, Patrlj L, Kopljar M, Kliček R, Kolovrat M, Loncar B, Busic Z. Gallbladder cancer. *Hepatobiliary Surg Nutr* 2014; **3**: 221-226 [PMID: 25392833 DOI: 10.3978/j.issn.2304-3881.2014.09.03]

56 **Ahmad A**. Use of indocyanine green (ICG) augmented near-infrared fluorescence imaging in robotic radical resection of gallbladder adenocarcinomas. *Surg Endosc* 2020; **34**: 2490-2494 [PMID: 31388807 DOI: 10.1007/s00464-019-07053-w]

57 **Papageorge MV**, de Geus SWL, Woods AP, Ng SC, Drake FT, Merrill A, Cassidy MR, McAneny D, Tseng JF, Sachs TE. Lymphadenectomy in gallbladder adenocarcinoma: Are we doing enough? *Am J Surg* 2022; **224**: 423-428 [PMID: 34972539 DOI: 10.1016/j.amjsurg.2021.12.028]

58 **Anselmo A**, Siragusa L, Materazzo M, Sforza D, Bacchiocchi G, Sensi B, Tisone G. ASO Author Reflections: Can Indocyanine Green Increase the Safety of Bile Duct Dissection and Thus Improve Regional Lymphadenectomy in Re-Do Surgery for Incidental Gallbladder Cancer? *Ann Surg Oncol* 2022; **29**: 5554 [PMID: 35739363 DOI: 10.1245/s10434-022-12045-7]

59 **Luján J**, Almeida A, López-Olaondo L, Rotellar F. Laparoscopic radical hepatectomy and lymphadenectomy for incidental gallbladder cancer. Surgical technique with ICG fluorescence enhancement. *Surg Oncol* 2022; **42**: 101756 [PMID: 35429730 DOI: 10.1016/j.suronc.2022.101756]

60 **Onishi S**, Yamada K, Murakami M, Kedoin C, Muto M, Ieiri S. Co-injection of Bile and Indocyanine Green for Detecting Pancreaticobiliary Maljunction of Choledochal Cyst. *European J Pediatr Surg Rep* 2022; **10**: e127-e130 [PMID: 36016648 DOI: 10.1055/s-0042-1747913]

61 **Gijsen A**, Vries RD, Liem M, Lips D. The Use of Indocyanine Green Fluorescence Imaging in Preventing Postoperative Bile Leakage of the Hepaticojejunostomy in Robot-assisted Pancreatic Surgery. *HPB* 2022; **24**: S368-S369 [DOI: 10.1016/j.hpb.2022.05.780]

62 **Hutteman M**, van der Vorst JR, Mieog JS, Bonsing BA, Hartgrink HH, Kuppen PJ, Löwik CW, Frangioni JV, van de Velde CJ, Vahrmeijer AL. Near-infrared fluorescence imaging in patients undergoing pancreaticoduodenectomy. *Eur Surg Res* 2011; **47**: 90-97 [PMID: 21720166 DOI: 10.1159/000329411]

63 **Griffin JF**, Smalley SR, Jewell W, Paradelo JC, Reymond RD, Hassanein RE, Evans RG. Patterns of failure after curative resection of pancreatic carcinoma. *Cancer* 1990; **66**: 56-61 [PMID: 2354408 DOI: 10.1002/1097-0142(19900701)66:1<56::aid-cncr2820660112>3.0.co;2-6]

64 **Lee SB**, Hassan M, Fisher R, Chertov O, Chernomordik V, Kramer-Marek G, Gandjbakhche A, Capala J. Affibody molecules for in vivo characterization of HER2-positive tumors by near-infrared imaging. *Clin Cancer Res* 2008; **14**: 3840-3849 [PMID: 18559604 DOI: 10.1158/1078-0432.CCR-07-4076]

65 **Jiang T**, Olson ES, Nguyen QT, Roy M, Jennings PA, Tsien RY. Tumor imaging by means of proteolytic activation of cell-penetrating peptides. *Proc Natl Acad Sci U S A* 2004; **101**: 17867-17872 [PMID: 15601762 DOI: 10.1073/pnas.0408191101]

66 **Zhou H**, Luby-Phelps K, Mickey BE, Habib AA, Mason RP, Zhao D. Dynamic near-infrared optical imaging of 2-deoxyglucose uptake by intracranial glioma of athymic mice. *PLoS One* 2009; **4**: e8051 [PMID: 19956682 DOI: 10.1371/journal.pone.0008051]

67 **Intes X**, Ripoll J, Chen Y, Nioka S, Yodh AG, Chance B. In vivo continuous-wave optical breast imaging enhanced with Indocyanine Green. *Med Phys* 2003; **30**: 1039-1047 [PMID: 12852527 DOI: 10.1118/1.1573791]

68 **Paiella S**, De Pastena M, Landoni L, Esposito A, Casetti L, Miotto M, Ramera M, Salvia R, Secchettin E, Bonamini D, Manzini G, D'Onofrio M, Marchegiani G, Bassi C. Is there a role for near-infrared technology in laparoscopic resection of pancreatic neuroendocrine tumors? Results of the COLPAN "colour-and-resect the pancreas" study. *Surg Endosc* 2017; **31**: 4478-4484 [PMID: 28374260 DOI: 10.1007/s00464-017-5501-5]

69 **Sperti C**, Polizzi ML, Moro M, Beltrame V, Pedrazzoli S. Middle-preserving pancreatectomy: an interesting procedure for pancreas-sparing resection. *JOP* 2010; **11**: 258-261 [PMID: 20442523]

70 **Ohzato H**, Yamamoto T, Fukunaga M, Imamura H, Furukawa H. Middle-preserving pancreatectomy for multifocal metastatic renal cell carcinoma located in the head, body and tail of the pancreas. A case report. *JOP* 2010; **11**: 633-637 [PMID: 21068502]

71 **Hide T**, Yano S, Shinojima N, Kuratsu J. Usefulness of the indocyanine green fluorescence endoscope in endonasal transsphenoidal surgery. *J Neurosurg* 2015; **122**: 1185-1192 [PMID: 25723307 DOI: 10.3171/2014.9.JNS14599]

72 **Iguchi T**, Iseda N, Hirose K, Ninomiya M, Honboh T, Maeda T, Sawada F, Tachibana YI, Akashi T, Sekiguchi N, Sadanaga N, Matsuura H. Indocyanine green fluorescence to ensure perfusion in middle segment-preserving pancreatectomy: a case report. *Surg Case Rep* 2021; **7**: 262

[PMID: 34928447 DOI: 10.1186/s40792-021-01344-y]
73 **Palomba G**, Dinuzzi VP, Pegoraro F, Troisi RI, Montalti R, De Palma GD, Aprea G. The Role of Intraoperative Indocyanine Green (ICG) and Preoperative 3-Dimensional (3D) Reconstruction in Laparoscopic Adrenalectomy: A Propensity Score-matched Analysis. *Surg Laparosc Endosc Percutan Tech* 2022; **32**: 643-649 [PMID: 36468889 DOI: 10.1097/SLE.0000000000001105]
74 **Moore EC**, Berber E. Fluorescence techniques in adrenal surgery. *Gland Surg* 2019; **8**: S22-S27 [PMID: 31404180 DOI: 10.21037/gs.2019.03.01]
75 **Colvin J**, Zaidi N, Berber E. The utility of indocyanine green fluorescence imaging during robotic adrenalectomy. *J Surg Oncol* 2016; **114**: 153-156 [PMID: 27189336 DOI: 10.1002/jso.24296]
76 **Kahramangil B**, Kose E, Berber E. Characterization of fluorescence patterns exhibited by different adrenal tumors: Determining the indications for indocyanine green use in adrenalectomy. *Surgery* 2018; **164**: 972-977 [PMID: 30087043 DOI: 10.1016/j.surg.2018.06.012]
77 **DeLong JC**, Chakedis JM, Hosseini A, Kelly KJ, Horgan S, Bouvet M. Indocyanine green (ICG) fluorescence-guided laparoscopic adrenalectomy. *J Surg Oncol* 2015; **112**: 650-653 [PMID: 26420733 DOI: 10.1002/jso.24057]
78 **Aloysius TMN**, Shelat VG. Laparoscopic splenectomy for splenic rupture secondary to metastatic choriocarcinoma. *Ann Hepatobiliary Pancreat Surg* 2018; **22**: 79-82 [PMID: 29536060 DOI: 10.14701/ahbps.2018.22.1.79]
79 **Bada-Bosch I**, Mata DP, de la Torre M, Ordóñez J, Blanco MD, de Agustin J. Laparoscopic Partial Splenectomy Assisted by Fluorescence in a 13-Year-Old Girl. *European J Pediatr Surg Rep* 2020; **8**: e81-e85 [PMID: 33101836 DOI: 10.1055/s-0040-1716894]
80 **Chia C**, Pandya GJ, Kamalesh A, Shelat VG. Splenic Artery Pseudoaneurysm Masquerading as a Pancreatic Cyst-A Diagnostic Challenge. *Int Surg* 2015; **100**: 1069-1071 [PMID: 26414829 DOI: 10.9738/INTSURG-D-14-00149.1]
81 **Bertolucci A**, Tartaglia D, Cremonini C, Ginesini M, Cengeli I, Galatioto C, Coccolini F, Chiarugi M. Indocyanine Green (ICG) for the assessment of splenic perfusion during laparoscopic splenic artery aneurysmectomy. A case report. *Ann Ital Chir* 2021; **10** [PMID: 35122425]
82 **Masuya R**, Nakame K, Tahira K, Kai K, Hamada T, Yano K, Imamura N, Hiyoshi M, Nanashima A, Ieiri S. Laparoscopic dome resection for pediatric nonparasitic huge splenic cyst safely performed using indocyanine green fluorescence and percutaneous needle grasper. *Asian J Endosc Surg* 2022; **15**: 693-696 [PMID: 35289491 DOI: 10.1111/ases.13052]
83 **Guerra F**, Coletta D, Greco PA, Eugeni E, Patriti A. The use of indocyanine green fluorescence to define bowel microcirculation during laparoscopic surgery for acute small bowel obstruction. *Colorectal Dis* 2021; **23**: 2189-2194 [PMID: 33876537 DOI: 10.1111/codi.15680]
84 **Quah GS**, Eslick GD, Cox MR. Laparoscopic versus open surgery for adhesional small bowel obstruction: a systematic review and meta-analysis of case-control studies. *Surg Endosc* 2019; **33**: 3209-3217 [PMID: 30460502 DOI: 10.1007/s00464-018-6604-3]
85 **Ganguly A**, Acharya A, Pai MV, Augustine AJ. Assessment of bowel vascularity using indocyanine green fluorescence in incarcerated hernia. *Int Surg J* 2021; **8**: 2834 [DOI: 10.18203/2349-2902.isj20213630]
86 **Karampinis I**, Keese M, Jakob J, Stasiunaitis V, Gerken A, Attenberger U, Post S, Kienle P, Nowak K. Indocyanine Green Tissue Angiography Can Reduce Extended Bowel Resections in Acute Mesenteric Ischemia. *J Gastrointest Surg* 2018; **22**: 2117-2124 [PMID: 29992520 DOI: 10.1007/s11605-018-3855-1]
87 **Shih MC**, Hagspiel KD. CTA and MRA in mesenteric ischemia: part 1, Role in diagnosis and differential diagnosis. *AJR Am J Roentgenol* 2007; **188**: 452-461 [PMID: 17242255 DOI: 10.2214/AJR.05.1167]
88 **Son GM**, Ahn HM, Lee IY, Ha GW. Multifunctional Indocyanine Green Applications for Fluorescence-Guided Laparoscopic Colorectal Surgery. *Ann Coloproctol* 2021; **37**: 133-140 [PMID: 34102813 DOI: 10.3393/ac.2021.05.07]
89 **Baiocchi GL**, Guercioni G, Vettoretto N, Scabini S, Millo P, Muratore A, Clementi M, Sica G, Delrio P, Longo G, Anania G, Barbieri V, Amodio P, Di Marco C, Baldazzi G, Garulli G, Patriti A, Pirozzi F, De Luca R, Mancini S, Pedrazzani C, Scaramuzzi M, Scatizzi M, Taglietti L, Motter M, Ceccarelli G, Totis M, Gennai A, Frazzini D, Di Mauro G, Capolupo GT, Crafa F, Marini P, Ruffo G, Persiani R, Borghi F, de Manzini N, Catarci M. ICG fluorescence imaging in colorectal surgery: a snapshot from the ICRAL study group. *BMC Surg* 2021; **21**: 190 [PMID: 33838677 DOI: 10.1186/s12893-021-01191-6]
90 **Belloni E**, Muttillo EM, Di Saverio S, Gasparrini M, Brescia A, Nigri G. The Role of Indocyanine Green Fluorescence in Rectal Cancer Robotic Surgery: A Narrative Review. *Cancers (Basel)* 2022; **14** [PMID: 35626015 DOI: 10.3390/cancers14102411]
91 **Slieker JC**, Daams F, Mulder IM, Jeekel J, Lange JF. Systematic review of the technique of colorectal anastomosis. *JAMA Surg* 2013; **148**: 190-201 [PMID: 23426599 DOI: 10.1001/2013.jamasurg.33]
92 **Mirnezami A**, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. *Ann Surg* 2011; **253**: 890-899 [PMID: 21394013 DOI: 10.1097/SLA.0b013e3182128929]
93 **Kverneng Hultberg D**, Svensson J, Jutesten H, Rutegård J, Matthiessen P, Lydrup ML, Rutegård M. The Impact of Anastomotic Leakage on Long-term Function After Anterior Resection for Rectal Cancer. *Dis Colon Rectum* 2020; **63**: 619-628 [PMID: 32032197 DOI: 10.1097/DCR.0000000000001613]
94 **Kudszus S**, Roesel C, Schachtrupp A, Höer JJ. Intraoperative laser fluorescence angiography in colorectal surgery: a noninvasive analysis to reduce the rate of anastomotic leakage. *Langenbecks Arch Surg* 2010; **395**: 1025-1030 [PMID: 20700603 DOI: 10.1007/s00423-010-0699-x]
95 **Liu D**, Liang L, Liu L, Zhu Z. Does intraoperative indocyanine green fluorescence angiography decrease the incidence of anastomotic leakage in colorectal surgery? A systematic review and meta-analysis. *Int J Colorectal Dis* 2021; **36**: 57-66 [PMID: 32944782 DOI: 10.1007/s00384-020-03741-5]
96 **Trastulli S**, Munzi G, Desiderio J, Cirocchi R, Rossi M, Parisi A. Indocyanine green fluorescence angiography versus standard intraoperative methods for prevention of anastomotic leak in colorectal surgery: meta-analysis. *Br J Surg* 2021; **108**: 359-372 [PMID: 33778848 DOI: 10.1093/bjs/znaa139]
97 **Son GM**, Kwon MS, Kim Y, Kim J, Kim SH, Lee JW. Quantitative analysis of colon perfusion pattern using indocyanine green (ICG) angiography in laparoscopic colorectal surgery. *Surg Endosc* 2019; **33**: 1640-1649 [PMID: 30203201 DOI: 10.1007/s00464-018-6439-y]
98 **Liu RQ**, Elnahas A, Tang E, Alkhamesi NA, Hawel J, Alnumay A, Schlachta CM. Cost analysis of indocyanine green fluorescence angiography for prevention of anastomotic leakage in colorectal surgery. *Surg Endosc* 2022; **36**: 9281-9287 [PMID: 35290507 DOI: 10.1007/s00464-022-09166-1]
99 **Garoufalia Z**, Wexner SD. Indocyanine Green Fluorescence Guided Surgery in Colorectal Surgery. *J Clin Med* 2023; **12** [PMID: 36675423 DOI: 10.3390/jcm12020494]
100 **Slooter MD**, Blok RD, Wisselink DD, Buskens CJ, Bemelman WA, Tanis PJ, Hompes R. Near-infrared fluorescence angiography for intra-operative assessment of pedicled omentoplasty for filling of a pelvic cavity: a pilot study. *Tech Coloproctol* 2019; **23**: 723-728 [PMID: 31432336 DOI: 10.1007/s10151-019-02048-0]

101 **Ponsky JL**, King JF. Endoscopic marking of colonic lesions. *Gastrointest Endosc* 1975; **22**: 42-43 [PMID: 1205106 DOI: 10.1016/s0016-5107(75)73687-8]

102 **Lee SJ**, Sohn DK, Han KS, Kim BC, Hong CW, Park SC, Kim MJ, Park BK, Oh JH. Preoperative Tattooing Using Indocyanine Green in Laparoscopic Colorectal Surgery. *Ann Coloproctol* 2018; **34**: 206-211 [PMID: 30048996 DOI: 10.3393/ac.2017.09.25]

103 **Satoyoshi T**, Okita K, Ishii M, Hamabe A, Usui A, Akizuki E, Okuya K, Nishidate T, Yamano H, Nakase H, Takemasa I. Timing of indocyanine green injection prior to laparoscopic colorectal surgery for tumor localization: a prospective case series. *Surg Endosc* 2021; **35**: 763-769 [PMID: 32072278 DOI: 10.1007/s00464-020-07443-5]

104 **Orsi AM**, Dias SM, Moreira JE, Camilli JA. [Morphological development of the seminiferous epithelium of the pig at different ages (Sus scrofa of the Landrace strain)]. *Anat Histol Embryol* 1987; **16**: 97-102 [PMID: 3662038 DOI: 10.3389/fsurg.2022.1087889]

105 **Emile SH**, Elfeki H, Shalaby M, Sakr A, Sileri P, Laurberg S, Wexner SD. Sensitivity and specificity of indocyanine green near-infrared fluorescence imaging in detection of metastatic lymph nodes in colorectal cancer: Systematic review and meta-analysis. *J Surg Oncol* 2017; **116**: 730-740 [PMID: 28570748 DOI: 10.1002/jso.24701]

106 **Di Berardino S**, Capolupo GT, Caricato C, Caricato M. Sentinel lymph node mapping procedure in T1 colorectal cancer: A systematic review of published studies. *Medicine (Baltimore)* 2019; **98**: e16310 [PMID: 31305416 DOI: 10.1097/MD.0000000000016310]

107 **Carrara A**, Motter M, Amabile D, Pellecchia L, Moscatelli P, Pertile R, Barbareschi M, Decarli NL, Ferrari M, Tirone G. Predictive value of the sentinel lymph node procedure in the staging of non-metastatic colorectal cancer. *Int J Colorectal Dis* 2020; **35**: 1921-1928 [PMID: 32556650 DOI: 10.1007/s00384-020-03654-3]

108 **Kim MJ**, Oh JH. Lateral Lymph Node Dissection With the Focus on Indications, Functional Outcomes, and Minimally Invasive Surgery. *Ann Coloproctol* 2018; **34**: 229-233 [PMID: 30419720 DOI: 10.3393/ac.2018.10.26]

109 **Zhou SC**, Tian YT, Wang XW, Zhao CD, Ma S, Jiang J, Li EN, Zhou HT, Liu Q, Liang JW, Zhou ZX, Wang XS. Application of indocyanine green-enhanced near-infrared fluorescence-guided imaging in laparoscopic lateral pelvic lymph node dissection for middle-low rectal cancer. *World J Gastroenterol* 2019; **25**: 4502-4511 [PMID: 31496628 DOI: 10.3748/wjg.v25.i31.4502]

110 **Ogawa S**, Itabashi M, Inoue Y, Ohki T, Bamba Y, Koshino K, Nakagawa R, Tani K, Aihara H, Kondo H, Yamaguchi S, Yamamoto M. Lateral pelvic lymph nodes for rectal cancer: A review of diagnosis and management. *World J Gastrointest Oncol* 2021; **13**: 1412-1424 [PMID: 34721774 DOI: 10.4251/wjgo.v13.i10.1412]

111 **Watanabe J**, Ohya H, Sakai J, Suwa Y, Goto K, Nakagawa K, Ozawa M, Ishibe A, Suwa H, Kunisaki C, Endo I. Long-term outcomes of indocyanine green fluorescence imaging-guided laparoscopic lateral pelvic lymph node dissection for clinical stage II/III middle-lower rectal cancer: a propensity score-matched cohort study. *Tech Coloproctol* 2023; **27**: 759-767 [PMID: 36773172 DOI: 10.1007/s10151-023-02761-x]

112 **Yasui M**, Ohue M, Noura S, Miyoshi N, Takahashi Y, Matsuda C, Nishimura J, Haraguchi N, Ushigome H, Nakai N, Fujino S, Sugimura K, Wada H, Takahashi H, Omori T, Miyata H. Exploratory analysis of lateral pelvic sentinel lymph node status for optimal management of laparoscopic lateral lymph node dissection in advanced lower rectal cancer without suspected lateral lymph node metastasis. *BMC Cancer* 2021; **21**: 911 [PMID: 34380428 DOI: 10.1186/s12885-021-08480-6]

113 **Noura S**, Ohue M, Seki Y, Yamamoto T, Idota A, Fujii J, Yamasaki T, Nakajima H, Murata K, Kameyama M, Yamada T, Miyashiro I, Ohigashi H, Yano M, Ishikawa O, Imaoka S. Evaluation of the lateral sentinel node by indocyanine green for rectal cancer based on micrometastasis determined by reverse transcriptase-polymerase chain reaction. *Oncol Rep* 2008; **20**: 745-750 [PMID: 18813813]

114 **Halabi WJ**, Jafari MD, Nguyen VQ, Carmichael JC, Mills S, Pigazzi A, Stamos MJ. Ureteral injuries in colorectal surgery: an analysis of trends, outcomes, and risk factors over a 10-year period in the United States. *Dis Colon Rectum* 2014; **57**: 179-186 [PMID: 24401879 DOI: 10.1097/DCR.0000000000000033]

115 **White LA**, Joseph JP, Yang DY, Kelley SR, Mathis KL, Behm K, Viers BR. Intraureteral indocyanine green augments ureteral identification and avoidance during complex robotic-assisted colorectal surgery. *Colorectal Dis* 2021; **23**: 718-723 [PMID: 33064915 DOI: 10.1111/codi.15407]

116 **Geskin AA**, Westney OL, Graber WJ, Smith Iii TG, Chapin BF, Gregg JR. Complications Of Peri-Operative Ureteral Catheter Placement: Experience at A Major Cancer Center. *Urology* 2022; **164**: 88-93 [PMID: 34280440 DOI: 10.1016/j.urology.2021.04.068]

117 **Rodríguez-Zentner H**, Cukier M, Montagne V, Arrue E. Ureteral identification with indocyanine green in laparoscopic colorectal surgery. *Asian J Endosc Surg* 2023; **16**: 312-316 [PMID: 36562203 DOI: 10.1111/ases.13149]

118 **Ferrara M**, Kann BR. Urological Injuries during Colorectal Surgery. *Clin Colon Rectal Surg* 2019; **32**: 196-203 [PMID: 31061650 DOI: 10.1055/s-0038-1677026]

119 **Jin H**, Zheng L, Lu L, Cui M. Near-infrared intraoperative imaging of pelvic autonomic nerves: a pilot study. *Surg Endosc* 2022; **36**: 2349-2356 [PMID: 33909127 DOI: 10.1007/s00464-021-08512-z]

120 **Liberale G**, Vankerckhove S, Caldon MG, Ahmed B, Moreau M, Nakadi IE, Larsimont D, Donckier V, Bourgeois P; Group R&D for the Clinical Application of Fluorescence Imaging of the Jules Bordet's Institute. Fluorescence Imaging After Indocyanine Green Injection for Detection of Peritoneal Metastases in Patients Undergoing Cytoreductive Surgery for Peritoneal Carcinomatosis From Colorectal Cancer: A Pilot Study. *Ann Surg* 2016; **264**: 1110-1115 [PMID: 27828822 DOI: 10.1097/SLA.0000000000001618]

121 **Veys I**, Pop FC, Vankerckhove S, Barbieux R, Chintinne M, Moreau M, Nogaret JM, Larsimont D, Donckier V, Bourgeois P, Liberale G; Group R&D for the Clinical Application of Fluorescence Imaging of the Jules Bordet Institute. ICG-fluorescence imaging for detection of peritoneal metastases and residual tumoral scars in locally advanced ovarian cancer: A pilot study. *J Surg Oncol* 2018; **117**: 228-235 [PMID: 28787759 DOI: 10.1002/jso.24807]

122 **Low RN**, Barone RM, Lucero J. Comparison of MRI and CT for predicting the Peritoneal Cancer Index (PCI) preoperatively in patients being considered for cytoreductive surgical procedures. *Ann Surg Oncol* 2015; **22**: 1708-1715 [PMID: 25201499 DOI: 10.1245/s10434-014-4041-7]

123 **Ikoma N**, Blum M, Chiang YJ, Estrella JS, Roy-Chowdhuri S, Fournier K, Mansfield P, Ajani JA, Badgwell BD. Yield of Staging Laparoscopy and Lavage Cytology for Radiologically Occult Peritoneal Carcinomatosis of Gastric Cancer. *Ann Surg Oncol* 2016; **23**: 4332-4337 [PMID: 27384751 DOI: 10.1245/s10434-016-5409-7]

124 **Kobayashi H**, Ogawa M, Alford R, Choyke PL, Urano Y. New strategies for fluorescent probe design in medical diagnostic imaging. *Chem Rev* 2010; **110**: 2620-2640 [PMID: 20000749 DOI: 10.1021/cr900263j]

125 **Baiocchi GL**, Gheza F, Molfino S, Arru L, Vaira M, Giacopuzzi S. Indocyanine green fluorescence-guided intraoperative detection of peritoneal carcinomatosis: systematic review. *BMC Surg* 2020; **20**: 158 [PMID: 32680492 DOI: 10.1186/s12893-020-00821-9]

126 **Eneroth M**. Factors affecting wound healing after major amputation for vascular disease: a review. *Prosthet Orthot Int* 1999; **23**: 195-208 [PMID: 10890594 DOI: 10.3109/03093649909071635]

127 **Van Den Hoven P**, Van Den Berg SD, Van Der Valk JP, Van Der Krogt H, Van Doorn LP, Van De Bogt KEA, Van Schaik J, Schepers A,

Vahrmeijer AL, Hamming JF, Van Der Vorst JR. Assessment of Tissue Viability Following Amputation Surgery Using Near-Infrared Fluorescence Imaging With Indocyanine Green. *Ann Vasc Surg* 2022; **78**: 281-287 [PMID: 34182113 DOI: 10.1016/j.avsg.2021.04.030]

128 **Ultee KH**, Zettervall SL, Soden PA, Darling J, Bertges DJ, Verhagen HJ, Schermerhorn ML; Vascular Study Group of New England. Incidence of and risk factors for bowel ischemia after abdominal aortic aneurysm repair. *J Vasc Surg* 2016; **64**: 1384-1391 [PMID: 27475466 DOI: 10.1016/j.jvs.2016.05.045]

129 **Yamamoto M**, Orihashi K, Nishimori H, Wariishi S, Fukutomi T, Kondo N, Kihara K, Sato T, Sasaguri S. Indocyanine green angiography for intra-operative assessment in vascular surgery. *Eur J Vasc Endovasc Surg* 2012; **43**: 426-432 [PMID: 22264591 DOI: 10.1016/j.ejvs.2011.12.030]

130 **Mitsui Y**, Shiina H, Arichi N, Hiraoka T, Inoue S, Sumura M, Honda S, Yasumoto H, Igawa M. Indocyanine green (ICG)-based fluorescence navigation system for discrimination of kidney cancer from normal parenchyma: application during partial nephrectomy. *Int Urol Nephrol* 2012; **44**: 753-759 [PMID: 22215306 DOI: 10.1007/s11255-011-0120-x]

131 **Gadus L**, Kocarek J, Chmelik F, Matejkova M, Heracek J. Robotic Partial Nephrectomy with Indocyanine Green Fluorescence Navigation. *Contrast Media Mol Imaging* 2020; **2020**: 1287530 [PMID: 32410919 DOI: 10.1155/2020/1287530]

132 **Gerken ALH**, Nowak K, Meyer A, Weiss C, Krüger B, Nawroth N, Karampinis I, Heller K, Apel H, Reissfelder C, Schwenke K, Keese M, Lang W, Rother U. Quantitative Assessment of Intraoperative Laser Fluorescence Angiography With Indocyanine Green Predicts Early Graft Function After Kidney Transplantation. *Ann Surg* 2022; **276**: 391-397 [PMID: 33394595 DOI: 10.1097/SLA.0000000000004529]

133 **Ferreira H**, Smith AV, Wattiez A. Application of Indocyanine Green in Gynecology: Review of the Literature. *Surg Technol Int* 2019; **34**: 282-292 [PMID: 31034577]

134 **Bar-Shavit Y**, Jaillet L, Chauvet P, Canis M, Bourdel N. Use of indocyanine green in endometriosis surgery. *Fertil Steril* 2018; **109**: 1136-1137 [PMID: 29885885 DOI: 10.1016/j.fertnstert.2018.02.113]

135 **Schaafsma BE**, Mieog JS, Hutteman M, van der Vorst JR, Kuppen PJ, Löwik CW, Frangioni JV, van de Velde CJ, Vahrmeijer AL. The clinical use of indocyanine green as a near-infrared fluorescent contrast agent for image-guided oncologic surgery. *J Surg Oncol* 2011; **104**: 323-332 [PMID: 21495033 DOI: 10.1002/jso.21943]

136 **Eriksson AG**, Montovano M, Beavis A, Soslow RA, Zhou Q, Abu-Rustum NR, Gardner GJ, Zivanovic O, Barakat RR, Brown CL, Levine DA, Sonoda Y, Leitao MM Jr, Jewell EL. Impact of Obesity on Sentinel Lymph Node Mapping in Patients with Newly Diagnosed Uterine Cancer Undergoing Robotic Surgery. *Ann Surg Oncol* 2016; **23**: 2522-2528 [PMID: 26905542 DOI: 10.1245/s10434-016-5134-2]

137 **Markuszewski M**, Buszewska-Forajta M, Artymowicz M, Połom W, Roslan M, Markuszewski M. Binding indocyanine green to human serum albumin potentially enhances the detection of sentinel lymph nodes. An initial step for facilitating the detection of first-station nodes in penile and other urological cancers. *Arch Med Sci* 2022; **18**: 719-725 [PMID: 35591825 DOI: 10.5114/aoms/113237]

138 **van den Bos J**, Wieringa FP, Bouvy ND, Stassen LPS. Optimizing the image of fluorescence cholangiography using ICG: a systematic review and ex vivo experiments. *Surg Endosc* 2018; **32**: 4820-4832 [PMID: 29777357 DOI: 10.1007/s00464-018-6233-x]

139 **Woo Y**, Chaurasiya S, O'Leary M, Han E, Fong Y. Fluorescent imaging for cancer therapy and cancer gene therapy. *Mol Ther Oncolytics* 2021; **23**: 231-238 [PMID: 34729398 DOI: 10.1016/j.omto.2021.06.007]

140 **Linders DGJ**, Bijlstra OD, Fallert LC, Hilling DE, Walker E, Straight B, March TL, Valentijn ARPM, Pool M, Burggraaf J, Basilion JP, Vahrmeijer AL, Kuppen PJK. Cysteine Cathepsins in Breast Cancer: Promising Targets for Fluorescence-Guided Surgery. *Mol Imaging Biol* 2023; **25**: 58-73 [PMID: 36002710 DOI: 10.1007/s11307-022-01768-4]

141 **Turner MA**, Lwin TM, Amirfakhri S, Nishino H, Hoffman RM, Yazaki PJ, Bouvet M. The Use of Fluorescent Anti-CEA Antibodies to Label, Resect and Treat Cancers: A Review. *Biomolecules* 2021; **11** [PMID: 34944463 DOI: 10.3390/biom11121819]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 1858-1870

DOI: 10.4240/wjgs.v15.i9.1858

ISSN 1948-9366 (online)

REVIEW

Hepatic ischemia-reperfusion syndrome and its effect on the cardiovascular system: The role of treprostinil, a synthetic prostacyclin analog

Christina Mouratidou, Efstathios T Pavlidis, Georgios Katsanos, Serafeim-Chrysovalantis Kotoulas, Eleni Mouloudi, Georgios Tsoulfas, Ioannis N Galanis, Theodoros E Pavlidis

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Shehta A, Egypt; Wu ZJ, China

Received: June 9, 2023
Peer-review started: June 9, 2023
First decision: July 18, 2023
Revised: July 20, 2023
Accepted: July 25, 2023
Article in press: July 25, 2023
Published online: September 27, 2023

Christina Mouratidou, Serafeim-Chrysovalantis Kotoulas, Eleni Mouloudi, Intensive Care Unit, Hippokration General Hospital, Thessaloniki 54642, Greece

Efstathios T Pavlidis, Ioannis N Galanis, Theodoros E Pavlidis, 2nd Propedeutic Department of Surgery, Hippokration General Hospital, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki 54642, Greece

Georgios Katsanos, Georgios Tsoulfas, Department of Transplantation, Hippokration General Hospital, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki 54642, Greece

Corresponding author: Theodoros E Pavlidis, Doctor, PhD, Full Professor, Surgeon, 2nd Propedeutic Department of Surgery, Hippokration General Hospital, School of Medicine, Aristotle University of Thessaloniki, Konstantinoupoleos 49, Thessaloniki 54642, Greece. pavlidth@auth.gr

Abstract

Hepatic ischemia-reperfusion syndrome has been the subject of intensive study and experimentation in recent decades since it is responsible for the outcome of several clinical entities, such as major hepatic resections and liver transplantation. In addition to the organ's post reperfusion injury, this syndrome appears to play a central role in the dysfunction of distant tissues and systems. Thus, continuous research should be directed toward finding effective therapeutic options to improve the outcome and reduce the postoperative morbidity and mortality rates. Treprostinil is a synthetic analog of prostaglandin I2, and its experimental administration has shown encouraging results. It has already been approved by the Food and Drug Administration in the United States for pulmonary arterial hypertension and has been used in liver transplantation, where preliminary encouraging results showed its safety and feasibility by using continuous intravenous administration at a dose of 5 ng/kg/min. Treprostinil improves renal and hepatic function, diminishes hepatic oxidative stress and lipid peroxidation, reduces hepatictoll-like receptor 9 and inflammation, inhibits hepatic apoptosis and restores hepatic adenosine triphosphate (ATP) levels and ATP synthases, which is necessary for functional maintenance of mitochondria. Treprostinil exhibits vasodilatory properties and antiplatelet activity and regulates proinflammatory cytokines; therefore, it can potentially minimize ischemia-reperfusion

injury. Additionally, it may have beneficial effects on cardiovascular parameters, and much current research interest is concentrated on this compound.

Key Words: Hepatic ischemia-reperfusion syndrome; Myocardial damage; Prostaglandins; Treprostinil; Liver transplantation; Hepatectomy

Core Tip: End-stage liver disease is one of the leading causes of morbidity and mortality worldwide. The role of liver transplantation and liver resection in malignant disease has changed over the last decades with the evolution of high-risk surgical techniques and the great improvement in long-term survival. However, hepatic ischemia-reperfusion syndrome remains a significant clinical problem, as it is the main reason for postoperative liver failure and multiple organ dysfunction. Treprostinil is a synthetic analog of prostaglandin I2 with potential protective effects against ischemia-reperfusion injury. We herein discuss the effect of hepatic ischemia-reperfusion syndrome on the cardiovascular system and the role of treprostinil as a new promising therapeutic option.

Citation: Mouratidou C, Pavlidis ET, Katsanos G, Kotoulas SC, Mouloudi E, Tsoulfas G, Galanis IN, Pavlidis TE. Hepatic ischemia-reperfusion syndrome and its effect on the cardiovascular system: The role of treprostinil, a synthetic prostacyclin analog. *World J Gastrointest Surg* 2023; 15(9): 1858-1870
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/1858.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.1858

INTRODUCTION

Hepatic ischemia-reperfusion syndrome has been the subject of intense study and experimentation in recent decades since it is responsible for the outcome of several clinical events, such as hemorrhagic shock, major hepatic resections, Budd-Chiari syndrome and some types of hepatotoxicity[1-3]. Worldwide, end-stage liver disease is a common cause of morbidity and mortality, and liver transplantation remains the gold standard therapy for these patients. Nevertheless, prolonged exposure of the graft to cold and warm ischemia has a direct risk of serious postoperative complications, such as poor early graft function and primary nonfunction[4,5].

The complex blood supply in combination with the increased metabolic activity of the liver and its involvement in homeostasis, detoxification, protein synthesis, energy storage and immunity processes render the organ extremely sensitive to circulatory disorders. Liver ischemia-reperfusion syndrome remains a major cause of worse postoperative clinical outcomes. The pathophysiological changes do not pertain to single organ damage but also to a complex systemic process that affects other structures and tissues, causing a cascade of multiple organ dysfunction[6-9].

The responsible mechanisms are exceedingly complicated and involve numerous factors, including mediators, cytokines, adhesion molecules, vasoactive agents and reactive oxygen species. During an ischemic period, several functional processes take place at the cellular level and stimulate cell injury[9,10]. The exposure of hepatocytes to low oxygen levels results in changes in intracellular pH and a decrease in adenosine triphosphate (ATP) production, thereby attenuating the intrahepatic energy content[11]. Excessive production of reactive oxygen species and reactive nitrogen species in mitochondria and intracellular calcium overload promote organelle destruction and cell death. Innate immunological processes involve the activation of liver Kupffer cells; the accumulation of circulating lymphocytes, neutrophils, platelets and monocytes; and hepatic macrophage polarization and differentiation[12-14]. In this respect, Kupffer cells produce reactive oxygen species, interleukin (IL)-1, and tumor necrosis factor (TNF)-α, thereby triggering the recruitment of CD4+ T lymphocytes. In turn, activated CD4+ T cells can trigger Kupffer cells, leading to aggravation of the inflammatory response. Concurrently, Kupffer cells may have a protective role by producing anti-inflammatory IL-10 and suppressing the expression of proinflammatory factors, such as TNF-α, IL-1β, interferon-γ, and IL-2, and adhesion molecules, such as intercellular adhesion molecule 1[15,16]. Disrupted liver metabolism elicits an endogenous inflammatory cascade, which includes excessive cytokine and chemokine production, the release of adhesive molecules and caspase-1 activation[17,18]. Blood flow restoration and re-exposure of ischemic hepatocytes to high oxygen level conditions contributes to further hepatocellular damage, mediated by reactive oxygen species generation[19]. An inflammatory outbreak of hepatic ischemia-reperfusion has been found to initiate a series of pleiotropic mitogen-activated protein kinase (MAPK) cascades. Among them, the activated P38 and c-Jun N-terminal kinase (JNK) cascades are most involved in the pathways of apoptotic or autophagic hepatic cell death[20,21]. Notably, current evidence suggests that the MAPK, mammalian target of rapamycin and nuclear factor kappa B (NF-κB) inflammatory signals are adjusted by tripartite motif containing protein 37, which plays important role in exacerbation of hepatic ischemia-reperfusion injury by directly interacting with TNF receptor-associated factor 6 (TRAF6)[22]. Cellular damage has been shown to be promoted by the downregulation of microRNAs (miRNAs), which are small, single-stranded, noncoding RNA molecules. Specifically, suppression of miRNA-142-3p, miRNA-146a, miRNA-200c, and miRNA-34a is suggested to worsen the condition of hepatic ischemia-reperfusion injury, while the inhibition of miR-450b-5p has the opposite response[23,24].

On the other hand, miR-125b attenuates hepatic ischemia-reperfusion injury by suppressing TRAF6 and NF-κB signal pathways[25]. In general, long non-coding RNA and miRNAs regulatory networks mediate the pathological progression of hepatic ischemia-reperfusion injury through mutual activation and interference[26].

Hepatic ischemia-reperfusion syndrome mechanisms and its systemic effects

Hepatic ischemia-reperfusion syndrome is associated with several vascular disorders, such as increased vascular permeability, endothelial cell edema and loss of homeostasis between vasoconstricting and vasodilating factors. Accumulated neutrophils form neutrophil extracellular traps (NETs) that have been shown to play a significant role in the interactions with platelets and are involved in pro-coagulation mechanisms in a variety of infectious and sterile inflammatory processes. A recent study demonstrated that hepatic ischemia-reperfusion leads to a NET-mediated hypercoagulable state and subsequent organ injury through microvascular immuno thrombi formation[27]. Further liver microcirculatory milieu obstruction results in deterioration of ischemic hepatocellular damage and cell death. Although hepatic cell injury appears to progress primarily *via* the lytic necrosis pathway, it seems that more complex, often complementary or overlapping mechanisms of programmed cell death occur based on the presence or absence of damage-associated molecular patterns (DAMPs). These mechanisms can be categorized into inflammatory, such as necrosis, necroptosis, pyroptosis, and ferroptosis, and noninflammatory subtypes, such as apoptosis[13,28-30]. In conclusion, the hepatic ischemia-reperfusion mechanisms are summarized in Table 1.

Severe hepatic ischemia-reperfusion injury does not constitute only a local phenomenon. It is characterized by a widespread systemic sterile inflammatory response with the accumulation of inflammatory cells in distant organs. Reactive oxygen radicals that are released following ischemic hepatocyte reperfusion promote systemic oxidative stress, resulting in remote organ damage[31-35]. In addition, platelet aggregation induces a procoagulant state and associated ubiquitous platelet-rich microvascular thrombus formation. Systemic NET-mediated hypercoagulability leads to remote organ injury through platelet toll-like receptor 4 (TLR4)-dependent signaling pathways[36]. These underlying mechanisms are responsible for the dysfunction of other organs, including the lung, kidney, intestine, pancreas, brain, and myocardium (as shown in Figure 1)[1,37,38]. The resulting multiple organ dysfunction syndrome occurs as a progressive, complex and dynamic process with a variable extent of organ failure and a direct deteriorating effect on survivorship[39].

Effect of hepatic ischemia-reperfusion syndrome on the cardiovascular system

Multiple organ dysfunction is a major complication of acute liver failure. The incidence of this particularly severe condition is approximately 1-8 cases per million inhabitants, and it is responsible for 6% of deaths due to liver disease and up to 7%-8% of liver transplants[40]. Although there are several reports of acute liver failure cases followed by myocardial involvement, the direct effects of hepatic ischemia-reperfusion syndrome on the myocardium have not been analyzed completely. Significantly elevated cardiac troponin I and creatine phosphokinase myocardial band (CK-MB) values have been associated with increased mortality, while the incidence of major cardiovascular events is undoubtedly higher in patients with acute liver failure[1,30,41]. Troponin I is a sensitive and myocardium-selective biomarker with both prognostic and diagnostic value. Troponin has become ingrained in the Universal Definition of Acute Myocardial Infarction but may also be detected in stable chronic conditions[42]. However, there is a high prevalence of elevated troponin in noncardiac clinical conditions, such as myocarditis, pulmonary embolism, acute heart failure, septic shock, and drug-induced cardiotoxicity, as well as after interventional procedures such as coronary angioplasty and electrical cardioversions. Thus, measurement of troponin elevation, especially with high-sensitivity assays, allows detection of clinical cases with nonacute coronary syndrome-mediated myocardial injury[43,44]. CK-MB is also preferred in particular situations, specifically in the diagnosis of acute myocardial infarction and cardiac injury evaluation. Although it has limitations in terms of early diagnosis, elevated CK-MB levels reveal myocardial damage secondary to some noncardiac conditions[45,46].

Clinical and pathophysiological variability in the remote organ impairment following acute liver failure is a result of the complicated interactions. Mitochondrial dysfunction and impaired ATP production are characteristic features and lead to energy balance disruption. As a consequence, parenchymal cells are forced to alter their metabolic activity to maintain their energy provision by enhancing proteolysis and lipolysis[47]. Pathogen-associated molecular patterns (PAMPs) and DAMPs released by damaged cells reinforce the systemic immune response and trigger cell death[48,49].

Severe circulatory disturbances are also observed in patients with acute liver failure, regardless of the cause of liver disease. Hyperdynamic circulation is characterized by markedly elevated cardiac output and low systemic vascular resistance due to peripheral vasodilation. These pathophysiological cardiovascular changes are similar to those seen in patients with septic shock[50]. Changes in the microcirculation during acute liver failure have also been described. Intrahepatic and systemic microcirculation abnormalities include vasoconstriction, precapillary shunt formation and reduced blood flow resulting in loss of multiorgan function[51].

In some experimental models, increased cardiac enzyme levels and histopathological myocardial tissue damage were not attributed only to metabolic stress and hemodynamic instability. Other complex mechanisms, such as inflammation, endothelial cell disorders and the production of reactive oxygen and nitrogen species, were also observed[41,47]. The histological examination of animal heart tissue demonstrated wavy fibers, which are consistent with myocardial infarction and the presence of microthrombi in the capillary area of the myocardium, whereas the perivascular lesions were rather unrepresentative, supporting the idea of a mechanism of injury originating from the vascular system[41].

The postischemic phase is characterized by liver parenchymal dysfunction and the secretion of proinflammatory cytokines. Excessive TNF-α and IL-6 production and the systemic inflammatory response contribute to distant organ damage. Reactive oxygen species and cytokines generated during the reperfusion phase flow from the hepatic veins directly to the right atrium. Thus, the heart is the first organ receiving blood flow from postischemic hepatic tissue, which

Table 1 Hepatic ischemia-reperfusion injury mechanisms

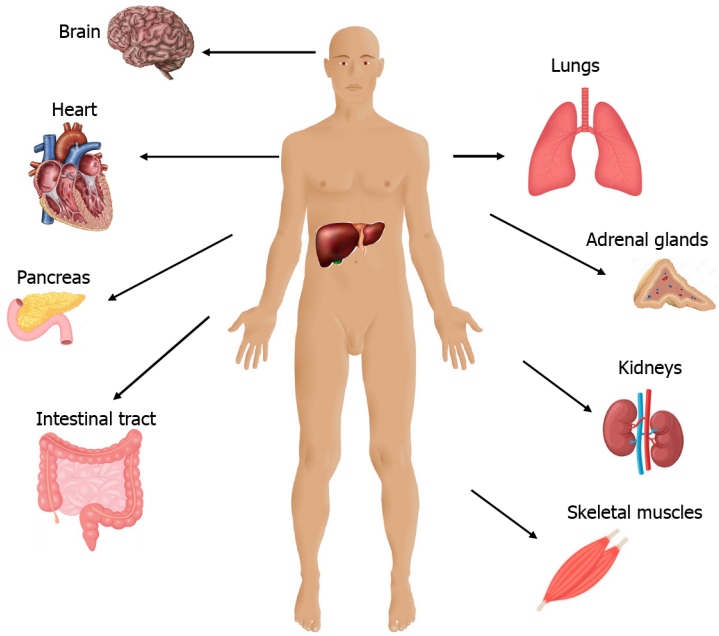
Primary mechanisms	Subsequent reactions	Final outcomes
Metabolism disorders		Systemic inflammatory response syndrome, multiple organ dysfunction syndrome
Anaerobic glycolysis	Mitochondria dysfunction	
ATP production	Cellular immunity	
Lactic acid and toxic acidic metabolites	Cell injury	
Reactive oxygen species	Programmed cell death and apoptosis	
Intracellular calcium overload	Microcirculatory dysfunction	
Microcirculatory system disorders		
Vasoconstriction		
Obstruction	Microcirculatory dysfunction	
Apoptosis of sinusoidal endothelial cells	Vascular permeability	
Expression of adhesion molecules	Endothelial cells oedema	
	Ischemic injury	
	Neutrophil accumulation	
Immune system disorders		
Kupffer cells activation		
Neutrophils activation		
Production of pro- and anti-inflammatory cytokines	Excessive inflammatory process	
Accumulation of circulating lymphocytes, platelets and monocytes	Anti-inflammatory response	
	Recruitment of CD4+ T lymphocytes	
Gene expression		
Imbalance in mRNAs expression	Cell damage	
Programmed cell death	Necrosis, apoptosis, necroptosis, pyroptosis, ferroptosis	

makes it more susceptible to damage[52,53]. The reactive oxygen radicals generated at the onset of reperfusion result in both direct cellular damage (necrosis, membrane disruptions) and indirect damage through cellular signaling pathways [54,55]. In a recent study, a histopathological heart examination of animals subjected to hepatic ischemia-reperfusion demonstrated necrosis, hyperemia, hemorrhage, and edema of myocardial cells[52].

Calcineurin is a calcium- and calmodulin-dependent serine/threonine protein phosphatase that plays an important role in T-cell activation, transcription regulation, cell cycle control and apoptosis[56]. In the heart, calcineurin is primarily present in the context of the hypertrophic growth response and pathological cardiac remodeling due to its role in nuclear factor of activated T cells transcription factor activation[57,58]. The inhibition of the calcineurin signaling pathway by tacrolimus attenuates myocardial damage after total hepatic ischemia-reperfusion. Furthermore, the protective role of tacrolimus in stabilizing the mitochondrial membrane potential, avoiding impairment in mitochondrial respiration and oxidative phosphorylation, improving antioxidant capacity, and reducing calcium overload prevent the myocardium from experiencing cell injury and potentially cell death[59,60]. In general, regulation of calcium homeostasis showed effectiveness on protecting hepatocytes from ischemia-reperfusion injury, such as protection during cardiac arrhythmias. A recently discovered HBF001 heparin fragment acts on sodium-calcium exchanger, by altering peptide structure and accelerating the intracellular calcium output[61].

Hepatic ischemia may induce a series of biochemical reactions, including modifications in the interactions between factors controlling programmed cell death and apoptosis. In a recent experimental study, increased levels of the proapoptotic protein Bax and decreased levels of the antiapoptotic protein Bcl-2 were measured. According to the article, hepatic ischemia-reperfusion injury accelerated apoptosis of myocardial cells and damaged the myocardium. Likewise, based on cardiac function observations, the ventricles of animals were enlarged and thickened, and ventricular systolic function was decreased in the control group[62-64].

Occlusion of the hepatic artery and the portal vein may be necessary to avoid excessive bleeding during major hepatectomy and liver transplantation. However, total hepatic vascular exclusion is associated with profound volume shifts due to preload reduction, resulting in a decrease in cardiac output and hemodynamic instability[65,66]. Chen *et al* [67] showed that decreased left ventricular preload was the primary reason for the reduced cardiac output, stroke volume and ejection fraction during liver ischemia. Along with impaired cardiovascular function, the systemic inflammatory



DOI: 10.4240/wjgs.v15.i9.1858

Figure 1 Remote organ damage after hepatic ischemia-reperfusion injury.

response and activated neutrophil accumulation in the myocardium are simultaneously responsible for remote organ injury induced by hepatic ischemia-reperfusion[56,57].

Myocardial injury appears to be a serious complication of hepatic ischemia-reperfusion syndrome, but the clinical manifestations in humans have not yet been established. Only a small percentage of patients who underwent liver transplantation and presented with mild hepatic ischemia-reperfusion injury (aspartate aminotransferase < 2000 IU/L) developed severe impairment of the left ventricular ejection fraction (< 35%)[68]. Despite being uncommon, post liver transplantation cardiac dysfunction remains a major clinical problem. Although the evidence supporting the idea of a direct association between hepatic ischemia-reperfusion and deterioration of left ventricular systolic function is still inconclusive, it is possible that the systemic inflammatory response and hemodynamic instability can contribute to postoperative cardiomyopathy[69]. Several studies have described an incidence of acute posttransplantation systolic heart failure of 1%-7%, frequently caused by stress-induced cardiomyopathy. However, hepatic ischemia-reperfusion syndrome was not exactly identified as an etiological underlying condition[70,71]. Intraoperative cardiovascular stress negatively affects preexisting cardiac dysfunction. Theoretically, hepatic ischemia-reperfusion syndrome presenting in the surgical postreperfusion phase may be associated with myocardial depression, pulmonary arterial hypertension, a significant reduction in systemic vascular resistance and bradycardia. Reactive oxygen species and multiple inflammatory mediators, such as cytokines and chemokines, are also responsible for the clinical phenotype of postreperfusion syndrome[72-74].

Although the link between hepatic ischemia-reperfusion syndrome and myocardial injury has been made in animal models, the consequences of this effect have yet to be defined. Myocardial damage has been described mostly as histopathological lesions and altered laboratory findings rather than serious clinical manifestations. After all, it must not be forgotten that most experimental and clinical observations are made in relatively healthy individuals and not in those whose heart is already affected by ischemia, cardiomyopathy and systolic/diastolic dysfunction[1,75,76]. Apparently, cardiac impairment following hepatic ischemia-reperfusion syndrome encompasses a large spectrum of subclinical and symptomatic conditions, which are responsible for additional short- and long-term morbidity and low survival[74]. Thus, continuous research should be directed to finding effective therapeutic options to improve the outcome and reduce the postoperative mortality rates.

The therapeutic use of prostaglandins

The therapeutic strategies against hepatic ischemia-reperfusion syndrome mainly include protective intraoperative techniques and an adequate number of pharmacological agents. Prostaglandins are a group of physiologically active lipid compounds called eicosanoids, which consist of oxidized derivatives of 20-carbon polyunsaturated fatty acids, primarily arachidonic acid, formed due to the cyclooxygenase pathway[77-79]. Many studies have shown the liver cytoprotective ability of prostaglandins based on direct or indirect signaling pathways[80]. The effectiveness of prostaglandin analogs has been evaluated in several experimental models along with patients who underwent liver transplantation. Prostaglandin E1 (PGE1) administration has been shown to improve liver microcirculation dysfunction by the expansion of blood vessels and enhancement of perfusion status. PGE1 also downregulates the expression of adhesion molecules and inflammatory mediators, resulting in inhibition of platelet aggregation and leukocyte adherence. Furthermore, suppression of thromboxane A2 in combination with the reduction in protease release and oxygen free radical production leads to attenuation of the inflammatory cascade and minimization of the sinusoidal cell apoptosis rate[81-84]. Prosta-

cyclin (PGI2) is another member of the prostaglandin family with potential vasodilating, antithrombotic and anti-inflammatory effects. Prostacyclin analogs have been established for decades in the treatment of patients with pulmonary arterial hypertension and remain an integral component of the current therapeutic armamentarium[85-87]. Preconditioning with beraprost sodium, a prostacyclin analog, in the experimental hepatic ischemia-reperfusion model led to suppressed production of the inflammatory mediators TNF-α and IL-1β, and attenuation of hepatic cell apoptosis in a dose-dependent manner. Through inhibition of the phosphorylation of P38 and JNK signaling cascades, beraprost sodium could ameliorate the systemic inflammatory response, apoptosis and autophagy processes of hepatic ischemia-reperfusion[21]. Although several studies have shown beneficial effects of prostaglandin therapy in the prevention of liver damage following transplantation, the clinical utility of these agents is rather limited due to their unstable structure, serious adverse reactions and very short half-lives[77,82,88,89].

The protective role of treprostinil

Treprostinil is a relatively new prostaglandin I2 (PGI2, prostacyclin) analog with a stable structure (as shown in Figure 2), longer half-life and improved potency that has been approved by the Food and Drug Administration (FDA) in the United States since 2002 for the treatment of patients with pulmonary arterial hypertension[86]. Treprostinil demonstrated stability for 48 h at 40 °C in different solutions and multiple beneficial effects, promoting its administration in long-term therapy[90-93]. Its binding profile and corresponding biochemical cellular response on human prostanoid receptors have been sufficiently analyzed. Treprostinil has high affinity for the DP_1, EP_2 and IP receptors; low affinity for EP_1 and EP_4 receptors; and even lower affinity for EP_3, FP and TP receptors[94]. The mechanisms of action of treprostinil are summarized in Table 2. In general, the PGI2 signaling pathways are much more complex than anticipated and remain incompletely elucidated. Peroxisome proliferator-activated receptors constitute an important signaling pathway that partially explains the vasodilating effect of prostacyclin, along with its cytoprotective properties[95,96]. The effects of treprostinil on angiogenesis have also been reported, including the vascular endothelial growth factor (VEGF)/NADPH oxidase 4 signaling pathway. *In vitro* treprostinil administration enhanced VEGF-A synthesis by mesenchymal stem cells, resulting in activation of vessel-forming ability[97].

Experimental orthotopic liver transplantation in rats with subcutaneous treprostinil administration at a dose of 100 ng/kg/min showed very encouraging results[98]. Specifically, treprostinil increased liver blood flow during the reperfusion phase while supporting the balance within the vasculature by increasing intracellular cyclic adenosine monophosphate (cAMP) levels. Furthermore, inhibition of platelet aggregation and proinflammatory cytokine production in the early posttransplantation period protected the liver graft against hepatic ischemia-reperfusion injury. Additionally, Hou *et al* [99] demonstrated that treprostinil improves renal and hepatic function, diminishes hepatic oxidative stress and lipid peroxidation and reduces hepatic TLR9, which is located in endosomes and triggers the inflammatory response by recognizing PAMPs and DAMPs[100]. Another recent study suggested that the presence of Gs-coupled prostanoid receptors in liver sinusoidal endothelial cells was responsible for the beneficial effect of prostaglandins. In fact, treprostinil binds and activates EP_2, EP_4, and IP receptors, resulting in attenuation of ischemia-induced hepatic cell injury [101].

Mitochondrial dysfunction during hepatic ischemia-reperfusion leads to increased DNA fragmentation and induction of programmed cell apoptosis. To maintain mitochondrial homeostasis and mediate acute cell injury, a complex fundamental process, named mitochondrial biogenesis, typically occurs in response to postischemic cellular stress. Induction of mitochondrial biogenesis is mediated by upregulation of the transcription factor peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), which is considered to be the master regulator for the process and has been found to be significantly decreased in ischemia-reperfusion injury[99,102-104]. Treprostinil upregulates *Pgc-1α* mRNA expression, thus securing mitochondrial biogenesis and improving mitochondrial dynamics. Additionally, treprostinil inhibits hepatic apoptosis by suppressing the release of mitochondrial cytochrome c and caspase-3 activation. In general, treprostinil restores ATP production, which ameliorates hepatic mitochondrial injury and preserves cellular energy balance[99,105,106].

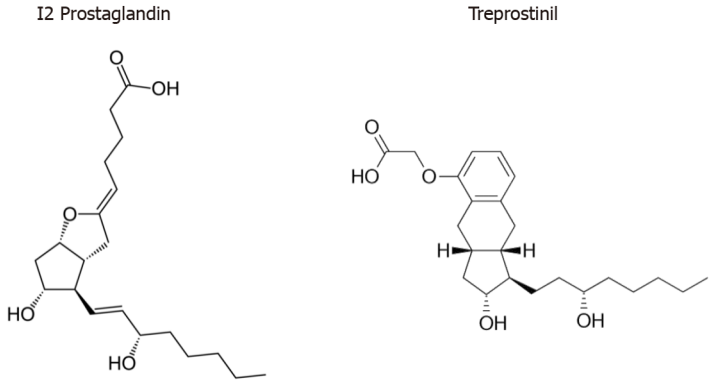
Several studies have shown that hepatic ischemia-reperfusion injury may cause a reduction in hepatic cytochrome P450 (CYP) levels and/or changes in enzyme activity amplitude. CYP has a broad range of functions, including drug metabolism and clearance and detoxification of pharmaceutical substances. The excessive cytokine release and systemic inflammatory response during ischemia-reperfusion injury have been associated with reduced microsomal drug metabolism, which can cause dose-dependent drug toxicity[107-109]. Treprostinil administration improved *CYP* mRNA expression in liver grafts after clinically relevant rat liver transplantation. In addition, treprostinil restored CYP protein expression and improved its activity in liver grafts[110]. The results showed that extended hepatic ischemia-reperfusion injury impaired CYP450 protein expression for at least 48 h post-transplantation, while treprostinil administration improved the protein expression of the three major CYP450 enzymes (CYP3A2, CYP2C11, and CYP2E1) in the liver graft and promoted CYP450-mediated drug metabolism[110].

Isolated rat liver perfusion is a widely performed *ex vivo* experimental model and represents a suitable tool for studying various pathological conditions, such as hepatic ischemia-reperfusion injury[111]. A recent study performed on isolated rat livers demonstrated the effect of postischemic hepatic injury on the expression of basolateral (uptake) and apical (efflux) hepatic drug transporters, which was significantly altered[112]. Importantly, treprostinil administration at a dose of 20 ng/mL during preservation and/or reperfusion reduced the ischemia-reperfusion-mediated effects on the expression of the Slc10a1/Ntcp and Slc22a1/Oct1 drug uptake transporters, similar to the expression of the apical efflux drug transporter P-gp (Mdr1a, Abcb1a). Although these findings illustrated improved liver function due to treprostinil supplementation, deeper knowledge is needed to determine the effect of the particular synthetic prostacyclin on the expression of drug-metabolizing enzymes and the regulation of drug transporters[113].

Table 2 Treprostinil mechanisms of action

Effect	Mechanism of action	Cellular response
Vessel tone	cAMP increased. Endothelin 1 decreased. Potassium decreased	Vasodilation. Improvement of microcirculation dysfunction
Antiproliferative	PPARs increased. cAMP increased. VEGF-A increased	Angiogenesis. Regulation of vascular homeostasis
Antithrombotic	Thromboxane A2 decreased. PDGF decreased	Inhibition of platelets aggregation. Platelets adherence decreased
Anti-inflammatory	P38 and JNK cascades decreased. IL-1, IL-6, TNF-α decreased. IL-10 increased. Reactive oxygen species decreased. TLR 9 decreased	Attenuation of inflammatory cascade. Apoptosis rate increased
Energy balance	Pgc-1α mRNA expression decreased. Cytochrome c decreased. Caspase 3 activation decreased	ATP production increased. Mitochondrial biogenesis increased

cAMP: Cyclic adenosine monophosphate; PPARs: Peroxisome proliferator-activated receptors; VEGF: Vascular endothelial-derived growth factor; JNK: c-Jun N-terminal kinase; IL: Interleukin; TNF: Tumor necrosis factor; TLR: Toll-like-receptor; ATP: Adenosine triphosphate.



DOI: 10.4240/wjgs.v15.i9.1858

Figure 2 The chemical structure of prostaglandin I2 and prostacyclin analogue treprostinil.

Liver graft injury post-transplantation frequently presents with elevated bilirubin and amino-transaminase serum levels during the first 24 h following transplantation. Many studies support the hypothesis of hepatic ischemia-reperfusion syndrome as the leading cause of initial poor graft dysfunction and primary graft nonfunction[114-117]. However, no pharmacological options are currently approved for the prevention of hepatic ischemia-reperfusion injury following transplantation. A prospective, pilot, single-center, open-label, nonrandomized, dose-escalation phase I/II study in liver transplant patients investigated the efficacy of intravenous treprostinil administration in the prevention of hepatic ischemia-reperfusion with some encouraging results[118]. A small group of patients who underwent liver transplantation and received perioperative intravenous treprostinil at a dose of 5 ng/kg/min followed by postoperative contentious infusion at a dose of 2.5-5 ng/kg/min for approximately 5 d showed improved liver function and 100% graft and recipient survival at six months[118]. Preliminary observations indicated a rapid reduction in transaminase plasma levels, improvement in hepatobiliary excretory function and prevention of the occurrence of acute kidney failure. Furthermore, stable hemodynamic parameters in the patients with treprostinil administration during the study period were achieved, since the mean pulmonary arterial pressure, systemic blood pressure, and cardiac index values remained within the normal range.

The initial phase of hepatic injury is characterized by ATP depletion, mitochondrial dysfunction and reactive oxygen species accumulation, followed by a systemic sterile inflammatory response. In general, oxidative and inflammatory pathways have been shown to play an important role in remote organ functional changes in a state of hepatic ischemia-reperfusion injury. Although myocardial impairment is documented mostly as a subclinical event, the general clinical status of remote organ damage in the postreperfusion phase can directly affect overall survival rates. Additionally, while a hypothesis of myocardial injury in the setting of hepatic ischemia-reperfusion has already been reported, the consequences of the particular issue remain unclear[116-118].

Over the last few years, treprostinil has become one of the key therapeutic options for the treatment of patients with pulmonary arterial hypertension[119]. Along with its beneficial influence on pulmonary vascular smooth muscle proliferation, vasoconstriction and pulmonary vascular remodeling, treprostinil also shows a direct favorable effect on cardiac function[120,121]. Experimental treprostinil administration increased stroke volume and cardiac output, leading to a stable hemodynamic state and improved cardiovascular endurance[121-123]. In addition, a broad reduction in reactive oxygen species accumulation and lipid peroxidation and a decrease in cytokine and chemokine mRNA levels during

ischemia-reperfusion may protect the myocardium from postreperfusion injury. However, there are several reports of beneficial effects of prostacyclin analogs on the attenuation of myocardial ischemia-reperfusion injury *via* vasodilation, inhibition of platelet accumulation and anti-inflammation[124,125]. Finally, the acceleration of mitochondrial recovery due to reduced mitochondrial-mediated cell apoptosis supports the hypothesis of treprostinil-mediated organ protection against ischemia-reperfusion injury[104]. Although currently available data are not sufficient, there are several indications of the beneficial effect of treprostinil on remote organ damage in the course of hepatic ischemia-reperfusion syndrome. Recent studies with subcutaneous treprostinil administration in experimental hepatic ischemia-reperfusion models have shown very encouraging results. Furthermore, patients with pulmonary arterial hypertension treated with treprostinil demonstrated an improved hemodynamic state and stable cardiac parameters[123].

CONCLUSION

Hepatic ischemia-reperfusion syndrome is a major complication of liver surgery, including partial liver resection and liver transplantation, liver trauma, resuscitation and other clinical entities. The pathophysiological mechanisms of hepatic ischemia-reperfusion are not responsible for liver damage alone but also occur as a complex systemic process with a direct impact on the function of multiple tissues and organs. Moreover, in some cases, postreperfusion systemic injury can lead to systemic inflammatory response syndrome and/or multiorgan dysfunction syndrome, both of which have a high incidence of mortality and morbidity. Thus, therapeutic strategies, including advanced surgical techniques and pharmacological inhibitors, should be studied intensively to improve the outcome of these patients. Treprostinil is a relatively new, FDA-approved stable prostacyclin analog with potent anti-inflammatory, antifibrotic, vasodilating, antire-modeling and antiapoptotic activities. According to current knowledge, there is a positive correlation between treprostinil supplementation and the attenuation of liver ischemia-reperfusion injury. Such information may be also useful in determining the favorable effect of treprostinil on remote organ damage. Although treprostinil administration holds great promise for attenuating myocardial injury in the course of hepatic ischemia-reperfusion injury, further research is warranted.

FOOTNOTES

Author contributions: Mouratidou C, Pavlidis ET, Katsanos G, and Tsoulfas G designed and performed the research; Mouratidou C, Pavlidis ET, Katsanos G, Kotoulas SC, Mouloudi E, Tsoulfas G, and Galanis IN analyzed data; Kotoulas SC, Mouloudi E, and Galanis IN contributed new analytic tools; Kotoulas SC, Mouloudi E, Tsoulfas G, Galanis IN, and Pavlidis TE reviewed the paper; Pavlidis TE approved the paper.

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

Country/Territory of origin: Greece

ORCID number: Christina Mouratidou 0009-0007-8657-2032; Efstathios T Pavlidis 0000-0002-7282-8101; Georgios Katsanos 0000-0002-5845-8175; Serafeim-Chrysovalantis Kotoulas 0000-0003-6092-1341; Eleni Mouloudi 0000-0003-0079-2012; Georgios Tsoulfas 0000-0001-5043-7962; Ioannis N Galanis 0009-0001-4283-0788; Theodoros E Pavlidis 0000-0002-8141-1412.

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

REFERENCES

1 **Nastos C**, Kalimeris K, Papoutsidakis N, Tasoulis MK, Lykoudis PM, Theodoraki K, Nastou D, Smyrniotis V, Arkadopoulos N. Global consequences of liver ischemia/reperfusion injury. *Oxid Med Cell Longev* 2014; **2014**: 906965 [PMID: 24799983 DOI: 10.1155/2014/906965]

2 **Zhai Y**, Petrowsky H, Hong JC, Busuttil RW, Kupiec-Weglinski JW. Ischaemia-reperfusion injury in liver transplantation--from bench to bedside. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 79-89 [PMID: 23229329 DOI: 10.1038/nrgastro.2012.225]

3 **Konishi T**, Lentsch AB. Hepatic Ischemia/Reperfusion: Mechanisms of Tissue Injury, Repair, and Regeneration. *Gene Expr* 2017; **17**: 277-287 [PMID: 28893351 DOI: 10.3727/105221617X15042750874156]

4 **Huang DQ**, Terrault NA, Tacke F, Gluud LL, Arrese M, Bugianesi E, Loomba R. Global epidemiology of cirrhosis - aetiology, trends and predictions. *Nat Rev Gastroenterol Hepatol* 2023; **20**: 388-398 [PMID: 36977794 DOI: 10.1038/s41575-023-00759-2]

5 **Panconesi R**, Carvalho MF, Muiesan P, Dutkowski P, Schlegel A. Liver perfusion strategies: what is best and do ischemia times still matter? *Curr Opin Organ Transplant* 2022; **27**: 285-299 [PMID: 35438271 DOI: 10.1097/MOT.0000000000000963]

6 **Sookoian S**, Pirola CJ. Liver enzymes, metabolomics and genome-wide association studies: from systems biology to the personalized medicine. *World J Gastroenterol* 2015; **21**: 711-725 [PMID: 25624707 DOI: 10.3748/wjg.v21.i3.711]

7 **Lightsey JM**, Rockey DC. Current concepts in ischemic hepatitis. *Curr Opin Gastroenterol* 2017; **33**: 158-163 [PMID: 28346236 DOI: 10.1097/MOG.0000000000000355]

8 **Cannistrà M**, Ruggiero M, Zullo A, Gallelli G, Serafini S, Maria M, Naso A, Grande R, Serra R, Nardo B. Hepatic ischemia reperfusion injury: A systematic review of literature and the role of current drugs and biomarkers. *Int J Surg* 2016; **33** Suppl 1: S57-S70 [PMID: 27255130 DOI: 10.1016/j.ijsu.2016.05.050]

9 **Montalvo-Jave EE**, Escalante-Tattersfield T, Ortega-Salgado JA, Piña E, Geller DA. Factors in the pathophysiology of the liver ischemia-reperfusion injury. *J Surg Res* 2008; **147**: 153-159 [PMID: 17707862 DOI: 10.1016/j.jss.2007.06.015]

10 **Jiménez-Castro MB**, Cornide-Petronio ME, Gracia-Sancho J, Peralta C. Inflammasome-Mediated Inflammation in Liver Ischemia-Reperfusion Injury. *Cells* 2019; **8** [PMID: 31547621 DOI: 10.3390/cells8101131]

11 **Selzner M**, Selzner N, Jochum W, Graf R, Clavien PA. Increased ischemic injury in old mouse liver: an ATP-dependent mechanism. *Liver Transpl* 2007; **13**: 382-390 [PMID: 17318856 DOI: 10.1002/Lt.21100]

12 **Guan LY**, Fu PY, Li PD, Li ZN, Liu HY, Xin MG, Li W. Mechanisms of hepatic ischemia-reperfusion injury and protective effects of nitric oxide. *World J Gastrointest Surg* 2014; **6**: 122-128 [PMID: 25068009 DOI: 10.4240/wjgs.v6.i7.122]

13 **Hirao H**, Nakamura K, Kupiec-Weglinski JW. Liver ischaemia-reperfusion injury: a new understanding of the role of innate immunity. *Nat Rev Gastroenterol Hepatol* 2022; **19**: 239-256 [PMID: 34837066 DOI: 10.1038/s41575-021-00549-8]

14 **Tacke F**. Targeting hepatic macrophages to treat liver diseases. *J Hepatol* 2017; **66**: 1300-1312 [PMID: 28267621 DOI: 10.1016/j.jhep.2017.02.026]

15 **Hanschen M**, Zahler S, Krombach F, Khandoga A. Reciprocal activation between CD4+ T cells and Kupffer cells during hepatic ischemia-reperfusion. *Transplantation* 2008; **86**: 710-718 [PMID: 18791453 DOI: 10.1097/TP.0b013e3181821aa7]

16 **Ye L**, He S, Mao X, Zhang Y, Cai Y, Li S. Effect of Hepatic Macrophage Polarization and Apoptosis on Liver Ischemia and Reperfusion Injury During Liver Transplantation. *Front Immunol* 2020; **11**: 1193 [PMID: 32676077 DOI: 10.3389/fimmu.2020.01193]

17 **van de Poll MC**, Dejong CH, Fischer MA, Bast A, Koek GH. Decreased hepatosplanchnic antioxidant uptake during hepatic ischaemia/reperfusion in patients undergoing liver resection. *Clin Sci (Lond)* 2008; **114**: 553-560 [PMID: 17995452 DOI: 10.1042/CS20070317]

18 **Li J**, Ke W, Zhou Q, Wu Y, Luo H, Zhou H, Yang B, Guo Y, Zheng Q, Zhang Y. Tumour necrosis factor-α promotes liver ischaemia-reperfusion injury through the PGC-1α/Mfn2 pathway. *J Cell Mol Med* 2014; **18**: 1863-1873 [PMID: 24898700 DOI: 10.1111/jcmm.12320]

19 **Rosser BG**, Gores GJ. Liver cell necrosis: cellular mechanisms and clinical implications. *Gastroenterology* 1995; **108**: 252-275 [PMID: 7806049 DOI: 10.1016/0016-5085(95)90032-2]

20 **Kyriakis JM**, Avruch J. Mammalian MAPK signal transduction pathways activated by stress and inflammation: a 10-year update. *Physiol Rev* 2012; **92**: 689-737 [PMID: 22535895 DOI: 10.1152/physrev.00028.2011]

21 **Deng J**, Feng J, Liu T, Lu X, Wang W, Liu N, Lv Y, Liu Q, Guo C, Zhou Y. Beraprost sodium preconditioning prevents inflammation, apoptosis, and autophagy during hepatic ischemia-reperfusion injury in mice *via* the P38 and JNK pathways. *Drug Des Devel Ther* 2018; **12**: 4067-4082 [PMID: 30568428 DOI: 10.2147/DDDT.S182292]

22 **Yang H**, Huang Z, Luo Y, Lei D, Yan P, Shen A, Liu W, Li D, Wu Z. TRIM37 exacerbates hepatic ischemia/reperfusion injury by facilitating IKKγ translocation. *Mol Med* 2023; **29**: 62 [PMID: 37158850 DOI: 10.1186/s10020-023-00653-2]

23 **Pretzsch E**, Nieß H, Khaled NB, Bösch F, Guba M, Werner J, Angele M, Chaudry IH. Molecular Mechanisms of Ischaemia-Reperfusion Injury and Regeneration in the Liver-Shock and Surgery-Associated Changes. *Int J Mol Sci* 2022; **23** [PMID: 36361725 DOI: 10.3390/ijms232112942]

24 **Huang Z**, Mou T, Luo Y, Pu X, Pu J, Wan L, Gong J, Yang H, Liu Y, Li Z, Shen A, Wu Z. Inhibition of miR-450b-5p ameliorates hepatic ischemia/reperfusion injury *via* targeting CRYAB. *Cell Death Dis* 2020; **11**: 455 [PMID: 32532961 DOI: 10.1038/s41419-020-2648-0]

25 **Huang Z**, Zheng D, Pu J, Dai J, Zhang Y, Zhang W, Wu Z. MicroRNA-125b protects liver from ischemia/reperfusion injury *via* inhibiting TRAF6 and NF-κB pathway. *Biosci Biotechnol Biochem* 2019; **83**: 829-835 [PMID: 30686117 DOI: 10.1080/09168451.2019.1569495]

26 **Zhu SF**, Yuan W, Du YL, Wang BL. Research progress of lncRNA and miRNA in hepatic ischemia-reperfusion injury. *Hepatobiliary Pancreat Dis Int* 2023; **22**: 45-53 [PMID: 35934611 DOI: 10.1016/j.hbpd.2022.07.008]

27 **Eltzschig HK**, Eckle T. Ischemia and reperfusion--from mechanism to translation. *Nat Med* 2011; **17**: 1391-1401 [PMID: 22064429 DOI: 10.1038/nm.2507]

28 **Jaeschke H**, Lemasters JJ. Apoptosis versus oncotic necrosis in hepatic ischemia/reperfusion injury. *Gastroenterology* 2003; **125**: 1246-1257 [PMID: 14517806 DOI: 10.1016/s0016-5085(03)01209-5]

29 **Schwabe RF**, Luedde T. Apoptosis and necroptosis in the liver: a matter of life and death. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 738-752 [PMID: 30250076 DOI: 10.1038/s41575-018-0065-y]

30 **Papoutsidakis N**, Arkadopoulos N, Smyrniotis V, Tzanatos H, Kalimeris K, Nastos K, Defterevos G, Pafiti A, Kostopanagiotou G. Early myocardial injury is an integral component of experimental acute liver failure - a study in two porcine models. *Arch Med Sci* 2011; **7**: 217-223 [PMID: 22291759 DOI: 10.5114/aoms.2011.22070]

31 **Lee HT**, Park SW, Kim M, D'Agati VD. Acute kidney injury after hepatic ischemia and reperfusion injury in mice. *Lab Invest* 2009; **89**: 196-208 [PMID: 19079326 DOI: 10.1038/labinvest.2008.124]

32 **Oguz A**, Kapan M, Kaplan I, Alabalik U, Ulger BV, Uslukaya O, Turkoglu A, Polat Y. The effects of sulforaphane on the liver and remote organ damage in hepatic ischemia-reperfusion model formed with pringle maneuver in rats. *Int J Surg* 2015; **18**: 163-168 [PMID: 25924817 DOI: 10.1016/j.ijsu.2015.04.049]

33 **Kan C**, Ungelenk L, Lupp A, Dirsch O, Dahmen U. Ischemia-Reperfusion Injury in Aged Livers-The Energy Metabolism, Inflammatory Response, and Autophagy. *Transplantation* 2018; **102**: 368-377 [PMID: 29135887 DOI: 10.1097/TP.0000000000001999]

34 **Ma Z**, Xin Z, Di W, Yan X, Li X, Reiter RJ, Yang Y. Melatonin and mitochondrial function during ischemia/reperfusion injury. *Cell Mol Life Sci* 2017; **74**: 3989-3998 [PMID: 28795196 DOI: 10.1007/s00018-017-2618-6]

35 **Wu XY**, Chen YJ, Liu CA, Gong JH, Xu XS. STING Induces Liver Ischemia-Reperfusion Injury by Promoting Calcium-Dependent Caspase 1-GSDMD Processing in Macrophages. *Oxid Med Cell Longev* 2022; **2022**: 8123157 [PMID: 35281468 DOI: 10.1155/2022/8123157]

36 **Zhang H**, Goswami J, Varley P, van der Windt DJ, Ren J, Loughran P, Yazdani H, Neal MD, Simmons RL, Zhang J, Tsung A, Huang H. Hepatic Surgical Stress Promotes Systemic Immunothrombosis That Results in Distant Organ Injury. *Front Immunol* 2020; **11**: 987 [PMID: 32528475 DOI: 10.3389/fimmu.2020.00987]

37 **Xin Y**, Zhang Y, Deng S, Hu X. Vagus Nerve Stimulation Attenuates Acute Skeletal Muscle Injury Induced by Hepatic Ischemia/Reperfusion Injury in Rats. *Front Pharmacol* 2021; **12**: 756997 [PMID: 35046803 DOI: 10.3389/fphar.2021.756997]

38 **Zhu L**, Zhou H, Xu F, Yang H, Li P, Sheng Y, Liu P, Kong W, Liu X, Yang L, Liu L. Hepatic Ischemia-Reperfusion Impairs Blood-Brain Barrier Partly Due to Release of Arginase From Injured Liver. *Front Pharmacol* 2021; **12**: 724471 [PMID: 34721021 DOI: 10.3389/fphar.2021.724471]

39 **Rampes S**, Ma D. Hepatic ischemia-reperfusion injury in liver transplant setting: mechanisms and protective strategies. *J Biomed Res* 2019; **33**: 221-234 [PMID: 32383437 DOI: 10.7555/JBR.32.20180087]

40 **Rovegno M**, Vera M, Ruiz A, Benítez C. Current concepts in acute liver failure. *Ann Hepatol* 2019; **18**: 543-552 [PMID: 31126880 DOI: 10.1016/j.aohep.2019.04.008]

41 **Uhlig M**, Hein M, Habigt MA, Tolba RH, Braunschweig T, Helmedag MJ, Klinge U, Koch A, Trautwein C, Mechelinck M. Acute myocardial injury secondary to severe acute liver failure: A retrospective analysis supported by animal data. *PLoS One* 2021; **16**: e0256790 [PMID: 34460845 DOI: 10.1371/journal.pone.0256790]

42 **Park KC**, Gaze DC, Collinson PO, Marber MS. Cardiac troponins: from myocardial infarction to chronic disease. *Cardiovasc Res* 2017; **113**: 1708-1718 [PMID: 29016754 DOI: 10.1093/cvr/cvx183]

43 **Hamm CW**, Giannitsis E, Katus HA. Cardiac troponin elevations in patients without acute coronary syndrome. *Circulation* 2002; **106**: 2871-2872 [PMID: 12460862 DOI: 10.1161/01.cir.0000044342.50593.63]

44 **Ahmed AN**, Blonde K, Hackam D, Iansavichene A, Mrkobrada M. Prognostic significance of elevated troponin in non-cardiac hospitalized patients: a systematic review and meta-analysis. *Ann Med* 2014; **46**: 653-663 [PMID: 25307362 DOI: 10.3109/07853890.2014.959558]

45 **Aydin S**, Ugur K, Aydin S, Sahin İ, Yardim M. Biomarkers in acute myocardial infarction: current perspectives. *Vasc Health Risk Manag* 2019; **15**: 1-10 [PMID: 30697054 DOI: 10.2147/VHRM.S166157]

46 **Kim S**, Um TH, Cho CR, Jeon JS. False-positive elevation of creatine kinase MB mass concentrations caused by macromolecules in a patient who underwent nephrectomy for renal cell carcinoma. *Ann Lab Med* 2014; **34**: 405-407 [PMID: 25187898 DOI: 10.3343/alm.2014.34.5.405]

47 **Engelmann C**, Clària J, Szabo G, Bosch J, Bernardi M. Pathophysiology of decompensated cirrhosis: Portal hypertension, circulatory dysfunction, inflammation, metabolism and mitochondrial dysfunction. *J Hepatol* 2021; **75** Suppl 1: S49-S66 [PMID: 34039492 DOI: 10.1016/j.jhep.2021.01.002]

48 **Zorov DB**, Juhaszova M, Sollott SJ. Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. *Physiol Rev* 2014; **94**: 909-950 [PMID: 24987008 DOI: 10.1152/physrev.00026.2013]

49 **Idzko M**, Ferrari D, Eltzschig HK. Nucleotide signalling during inflammation. *Nature* 2014; **509**: 310-317 [PMID: 24828189 DOI: 10.1038/nature13085]

50 **Lee J**, Lee S, Zhang H, Hill MA, Zhang C, Park Y. Interaction of IL-6 and TNF-α contributes to endothelial dysfunction in type 2 diabetic mouse hearts. *PLoS One* 2017; **12**: e0187189 [PMID: 29095915 DOI: 10.1371/journal.pone.0187189]

51 **Brito-Azevedo A**, Perez RM, Maranhão PA, Coelho HS, Fernandes ESM, Castiglione RC, de Souza MD, Villela-Nogueira CA, Bouskela E. Organ dysfunction in cirrhosis: a mechanism involving the microcirculation. *Eur J Gastroenterol Hepatol* 2019; **31**: 618-625 [PMID: 30920976 DOI: 10.1097/MEG.0000000000001366]

52 **Zabala V**, Boylan JM, Thevenot P, Frank A, Senthoor D, Iyengar V, Kim H, Cohen A, Gruppuso PA, Sanders JA. Transcriptional changes during hepatic ischemia-reperfusion in the rat. *PLoS One* 2019; **14**: e0227038 [PMID: 31891620 DOI: 10.1371/journal.pone.0227038]

53 **An W**, Kang JS. Effect of Metformin on Myocardial Injury Induced by Hepatic Ischemia-Reperfusion in Rats. *Front Pharmacol* 2022; **13**: 822743 [PMID: 35431970 DOI: 10.3389/fphar.2022.822743]

54 **Espinosa-Diez C**, Miguel V, Mennerich D, Kietzmann T, Sánchez-Pérez P, Cadenas S, Lamas S. Antioxidant responses and cellular adjustments to oxidative stress. *Redox Biol* 2015; **6**: 183-197 [PMID: 26233704 DOI: 10.1016/j.redox.2015.07.008]

55 **Granger DN**, Kvietys PR. Reperfusion injury and reactive oxygen species: The evolution of a concept. *Redox Biol* 2015; **6**: 524-551 [PMID: 26484802 DOI: 10.1016/j.redox.2015.08.020]

56 **Herzog CJ**, Miot S, Mansuy IM, Giros B, Tzavara ET. Chronic valproate normalizes behavior in mice overexpressing calcineurin. *Eur J Pharmacol* 2008; **580**: 153-160 [PMID: 18021766 DOI: 10.1016/j.ejphar.2007.10.050]

57 **Parra V**, Rothermel BA. Calcineurin signaling in the heart: The importance of time and place. *J Mol Cell Cardiol* 2017; **103**: 121-136 [PMID: 28007541 DOI: 10.1016/j.yjmcc.2016.12.006]

58 **Chaklader M**, Rothermel BA. Calcineurin in the heart: New horizons for an old friend. *Cell Signal* 2021; **87**: 110134 [PMID: 34454008 DOI: 10.1016/j.cellsig.2021.110134]

59 **Chen Y**, Xie X. Tacrolimus attenuates myocardium damage to the total hepatic ischemia-reperfusion *via* regulation of the mitochondrial function. *J Surg Res* 2012; **172**: e47-e54 [PMID: 21109259 DOI: 10.1016/j.jss.2010.10.013]

60 **Diotte NM**, Xiong Y, Gao J, Chua BH, Ho YS. Attenuation of doxorubicin-induced cardiac injury by mitochondrial glutaredoxin 2. *Biochim Biophys Acta* 2009; **1793**: 427-438 [PMID: 19038292 DOI: 10.1016/j.bbamcr.2008.10.014]

61 **Vasques ER**, Figueira ER, Rocha-Filho JA, Lanchotte C, Ximenes JL, Nader HB, Tersariol IL, Lima MA, Rodrigues T, Cunha JE, Chaib E, D'Albuquerque LA, Galvão FH. A new heparin fragment decreases liver ischemia-reperfusion injury. *Hepatobiliary Pancreat Dis Int* 2022; **21**: 190-192 [PMID: 34366197 DOI: 10.1016/j.hbpd.2021.07.004]

62 **Megyesi J**, Tarcsafalvi A, Seng N, Hodeify R, Price PM. Cdk2 phosphorylation of Bcl-xL after stress converts it to a pro-apoptotic protein mimicking Bax/Bak. *Cell Death Discov* 2016; **2**: 15066-15066 [PMID: 27226901 DOI: 10.1038/cddiscovery.2015.66]

63 **Ashkenazi A**, Fairbrother WJ, Leverson JD, Souers AJ. From basic apoptosis discoveries to advanced selective BCL-2 family inhibitors. *Nat Rev Drug Discov* 2017; **16**: 273-284 [PMID: 28209992 DOI: 10.1038/nrd.2016.253]

64 **Lv J**, Zou X, Yu C, Ou W, Sun C. Effects of propofol on cardiac function and miR-494 expression in rats with hepatic ischemia/reperfusion injury. *J Int Med Res* 2021; **49**: 300060521990988 [PMID: 33682507 DOI: 10.1177/0300060521990988]

65 **Søreide JA**, Deshpande R. Post hepatectomy liver failure (PHLF) - Recent advances in prevention and clinical management. *Eur J Surg Oncol* 2021; **47**: 216-224 [PMID: 32943278 DOI: 10.1016/j.ejso.2020.09.001]

66 **Chen Y**, Liu Z, Xie X. Hydrogen sulphide attenuates renal and cardiac injury after total hepatic ischemia and reperfusion. *J Surg Res* 2010; **164**: e305-e313 [PMID: 20888584 DOI: 10.1016/j.jss.2010.08.010]

67 **Chen TH**, Chen KH, Wang JJ. Preischemic treatment with melatonin attenuates liver reperfusion-induced impairment of cardiac function. *Transplant Proc* 2012; **44**: 970-973 [PMID: 22564599 DOI: 10.1016/j.transproceed.2012.01.077]

68 **Rokop ZP**, Frick K, Zenisek J, Kroepfl E, Mihaylov P, Patidar KR, Nephew L, Mangus RS, Kubal C. Hepatic Ischemia/Reperfusion Injury

After Liver Transplantation Is Not Associated with Early Impairment of Left Ventricular Ejection Fraction. *Ann Transplant* 2022; **27**: e938105 [PMID: 36510454 DOI: 10.12659/AOT.938105]

69 **Manning MW**, Kumar PA, Maheshwari K, Arora H. Post-Reperfusion Syndrome in Liver Transplantation-An Overview. *J Cardiothorac Vasc Anesth* 2020; **34**: 501-511 [PMID: 31084991 DOI: 10.1053/j.jvca.2019.02.050]

70 **Sonny A**, Govindarajan SR, Jaber WA, Cywinski JB. Systolic heart failure after liver transplantation: Incidence, predictors, and outcome. *Clin Transplant* 2018; **32**: e13199 [PMID: 29323769 DOI: 10.1111/ctr.13199]

71 **Sakr AE**, Fraser GE, Doctorian TP, Kim HB, Narasimha D, Abudayyeh I, Hilliard AD, Shih W, de Vera ME, Baron PW, Volk ML, Stoletniy LN. Predictors of Systolic Heart Failure and Mortality Following Orthotopic Liver Transplantation: a Single-Center Cohort. *Transplant Proc* 2019; **51**: 1950-1955 [PMID: 31303409 DOI: 10.1016/j.transproceed.2019.04.063]

72 **Paugam-Burtz C**, Kavafyan J, Merckx P, Dahmani S, Sommacale D, Ramsay M, Belghiti J, Mantz J. Postreperfusion syndrome during liver transplantation for cirrhosis: outcome and predictors. *Liver Transpl* 2009; **15**: 522-529 [PMID: 19399736 DOI: 10.1002/lt.21730]

73 **Girn HR**, Ahilathirunayagam S, Mavor AI, Homer-Vanniasinkam S. Reperfusion syndrome: cellular mechanisms of microvascular dysfunction and potential therapeutic strategies. *Vasc Endovascular Surg* 2007; **41**: 277-293 [PMID: 17704330 DOI: 10.1177/1538574407304510]

74 **Zaky A**, Bendjelid K. Appraising cardiac dysfunction in liver transplantation: an ongoing challenge. *Liver Int* 2015; **35**: 12-29 [PMID: 24797833 DOI: 10.1111/liv.12582]

75 **Jaber S**, Paugam-Burtz C. Acute liver failure and elevated troponin-I: controversial results and significance? *Crit Care* 2013; **17**: 102 [PMID: 23316924 DOI: 10.1186/cc11897]

76 **Audimooolam VK**, McPhail MJ, Sherwood R, Willars C, Bernal W, Wendon JA, Auzinger G. Elevated troponin I and its prognostic significance in acute liver failure. *Crit Care* 2012; **16**: R228 [PMID: 23190744 DOI: 10.1186/cc11883]

77 **Hossain MA**, Wakabayashi H, Izuishi K, Okano K, Yachida S, Maeta H. The role of prostaglandins in liver ischemia-reperfusion injury. *Curr Pharm Des* 2006; **12**: 2935-2951 [PMID: 16918423 DOI: 10.2174/138161206777947678]

78 **Calder PC**. Eicosanoids. *Essays Biochem* 2020; **64**: 423-441 [PMID: 32808658 DOI: 10.1042/EBC20190083]

79 **Liu H**, Man K. New Insights in Mechanisms and Therapeutics for Short- and Long-Term Impacts of Hepatic Ischemia Reperfusion Injury Post Liver Transplantation. *Int J Mol Sci* 2021; **22** [PMID: 34360975 DOI: 10.3390/ijms22158210]

80 **Yamanaka K**, Houben P, Bruns H, Schultze D, Hatano E, Schemmer P. A systematic review of pharmacological treatment options used to reduce ischemia reperfusion injury in rat liver transplantation. *PLoS One* 2014; **10**: e0122214 [PMID: 25919110 DOI: 10.1371/journal.pone.0122214]

81 **Liu Y**, Ren H, Wang J, Yang F, Li J, Zhou Y, Yuan X, Zhu W, Shi X. Prostaglandin E(2) secreted by mesenchymal stem cells protects against acute liver failure *via* enhancing hepatocyte proliferation. *FASEB J* 2019; **33**: 2514-2525 [PMID: 30260707 DOI: 10.1096/fj.201801349RR]

82 **Hafez T**, Moussa M, Nesim I, Baligh N, Davidson B, Abdul-Hadi A. The effect of intraportal prostaglandin E1 on adhesion molecule expression, inflammatory modulator function, and histology in canine hepatic ischemia/reperfusion injury. *J Surg Res* 2007; **138**: 88-99 [PMID: 17174338 DOI: 10.1016/j.jss.2006.05.009]

83 **Maida K**, Akamatsu Y, Hara Y, Tokodai K, Miyagi S, Kashiwadate T, Miyazawa K, Kawagishi N, Ohuchi N. Short Oxygenated Warm Perfusion With Prostaglandin E1 Administration Before Cold Preservation as a Novel Resuscitation Method for Liver Grafts From Donors After Cardiac Death in a Rat In Vivo Model. *Transplantation* 2016; **100**: 1052-1058 [PMID: 26950723 DOI: 10.1097/TP.0000000000001127]

84 **Hanazaki K**, Kuroda T, Kajikawa S, Amano J. Prostaglandin E1 reduces thromboxane A2 in hepatic ischemia-reperfusion. *Hepatogastroenterology* 2000; **47**: 807-811 [PMID: 10919036]

85 **Misawa H**, Ohashi W, Tomita K, Hattori K, Shimada Y, Hattori Y. Prostacyclin mimetics afford protection against lipopolysaccharide/d-galactosamine-induced acute liver injury in mice. *Toxicol Appl Pharmacol* 2017; **334**: 55-65 [PMID: 28887131 DOI: 10.1016/j.taap.2017.09.003]

86 **Stubbe B**, Opitz CF, Halank M, Habedank D, Ewert R. Intravenous prostacyclin-analogue therapy in pulmonary arterial hypertension - A review of the past, present and future. *Respir Med* 2021; **179**: 106336 [PMID: 33647836 DOI: 10.1016/j.rmed.2021.106336]

87 **Hoeper MM**, McLaughlin VV, Dalaan AM, Satoh T, Galiè N. Treatment of pulmonary hypertension. *Lancet Respir Med* 2016; **4**: 323-336 [PMID: 26975811 DOI: 10.1016/S2213-2600(15)00542-1]

88 **Chen HM**, Chen MF, Shyr MH. Prostacyclin analogue (OP-2507) attenuates hepatic microcirculatory derangement, energy depletion, and lipid peroxidation in a rat model of reperfusion injury. *J Surg Res* 1998; **80**: 333-338 [PMID: 9878334 DOI: 10.1006/jsre.1998.5425]

89 **Cavalcanti AB**, De Vasconcelos CP, Perroni de Oliveira M, Rother ET, Ferraz L Jr. Prostaglandins for adult liver transplanted patients. *Cochrane Database Syst Rev* 2011; CD006006 [PMID: 22071826 DOI: 10.1002/14651858.CD006006.pub2]

90 **Phares KR**, Weiser WE, Miller SP, Myers MA, Wade M. Stability and preservative effectiveness of treprostinil sodium after dilution in common intravenous diluents. *Am J Health Syst Pharm* 2003; **60**: 916-922 [PMID: 12756943 DOI: 10.1093/ajhp/60.9.916]

91 **Kolb M**, Orfanos SE, Lambers C, Flaherty K, Masters A, Lancaster L, Silverstein A, Nathan SD. The Antifibrotic Effects of Inhaled Treprostinil: An Emerging Option for ILD. *Adv Ther* 2022; **39**: 3881-3895 [PMID: 35781186 DOI: 10.1007/s12325-022-02229-8]

92 **Leifer FG**, Konicek DM, Chen KJ, Plaunt AJ, Salvail D, Laurent CE, Corboz MR, Li Z, Chapman RW, Perkins WR, S Malinin V. Inhaled Treprostinil-Prodrug Lipid Nanoparticle Formulations Provide Long-Acting Pulmonary Vasodilation. *Drug Res (Stuttg)* 2018; **68**: 605-614 [PMID: 29791923 DOI: 10.1055/s-0044-100374]

93 **Lambers C**, Kornauth C, Oberndorfer F, Boehm PM, Tamm M, Klepetko W, Roth M. Mechanism of anti-remodelling action of treprostinil in human pulmonary arterial smooth muscle cells. *PLoS One* 2018; **13**: e0205195 [PMID: 30383775 DOI: 10.1371/journal.pone.0205195]

94 **Whittle BJ**, Silverstein AM, Mottola DM, Clapp LH. Binding and activity of the prostacyclin receptor (IP) agonists, treprostinil and iloprost, at human prostanoid receptors: treprostinil is a potent DP1 and EP2 agonist. *Biochem Pharmacol* 2012; **84**: 68-75 [PMID: 22480736 DOI: 10.1016/j.bcp.2012.03.012]

95 **Pluchart H**, Khouri C, Blaise S, Roustit M, Cracowski JL. Targeting the Prostacyclin Pathway: Beyond Pulmonary Arterial Hypertension. *Trends Pharmacol Sci* 2017; **38**: 512-523 [PMID: 28412042 DOI: 10.1016/j.tips.2017.03.003]

96 **Falcetti E**, Flavell DM, Staels B, Tinker A, Haworth SG, Clapp LH. IP receptor-dependent activation of PPARgamma by stable prostacyclin analogues. *Biochem Biophys Res Commun* 2007; **360**: 821-827 [PMID: 17624303 DOI: 10.1016/j.bbrc.2007.06.135]

97 **Smadja DM**, Levy M, Huang L, Rossi E, Blandinières A, Israel-Biet D, Gaussem P, Bischoff J. Treprostinil indirectly regulates endothelial colony forming cell angiogenic properties by increasing VEGF-A produced by mesenchymal stem cells. *Thromb Haemost* 2015; **114**: 735-747 [PMID: 26062754 DOI: 10.1160/TH14-11-0907]

98 **Ghonem N**, Yoshida J, Stolz DB, Humar A, Starzl TE, Murase N, Venkataramanan R. Treprostinil, a prostacyclin analog, ameliorates ischemia-reperfusion injury in rat orthotopic liver transplantation. *Am J Transplant* 2011; **11**: 2508-2516 [PMID: 21668631 DOI: 10.1111/j.1600-6143.2011.03568.x]

99 **Hou J**, Tolbert E, Birkenbach M, Ghonem NS. Treprostinil alleviates hepatic mitochondrial injury during rat renal ischemia-reperfusion injury. *Biomed Pharmacother* 2021; **143**: 112172 [PMID: 34560548 DOI: 10.1016/j.biopha.2021.112172]

100 **Anders HJ**. Toll-like receptors and danger signaling in kidney injury. *J Am Soc Nephrol* 2010; **21**: 1270-1274 [PMID: 20651159 DOI: 10.1681/ASN.2010030233]

101 **Themanns M**, Koban F, Bergmayr C, Chrzan A, Strohmaier W, Haybaeck J, Freissmuth M, Zebedin-Brandl E. Treprostinil reduces endothelial damage in murine sinusoidal obstruction syndrome. *J Mol Med (Berl)* 2019; **97**: 201-213 [PMID: 30535954 DOI: 10.1007/s00109-018-1726-6]

102 **Hasnat M**, Yuan Z, Ullah A, Naveed M, Raza F, Baig MMFA, Khan A, Xu D, Su Y, Sun L, Zhang L, Jiang Z. Mitochondria-dependent apoptosis in triptolide-induced hepatotoxicity is associated with the Drp1 activation. *Toxicol Mech Methods* 2020; **30**: 124-133 [PMID: 31557070 DOI: 10.1080/15376516.2019.1669247]

103 **Ramachandran A**, Umbaugh DS, Jaeschke H. Mitochondrial Dynamics in Drug-Induced Liver Injury. *Livers* 2021; **1**: 102-115 [PMID: 34485975 DOI: 10.3390/livers1030010]

104 **Ding M**, Tolbert E, Birkenbach M, Gohh R, Akhlaghi F, Ghonem NS. Treprostinil reduces mitochondrial injury during rat renal ischemia-reperfusion injury. *Biomed Pharmacother* 2021; **141**: 111912 [PMID: 34328097 DOI: 10.1016/j.biopha.2021.111912]

105 **Ow YP**, Green DR, Hao Z, Mak TW. Cytochrome c: functions beyond respiration. *Nat Rev Mol Cell Biol* 2008; **9**: 532-542 [PMID: 18568041 DOI: 10.1038/nrm2434]

106 **Asadi M**, Taghizadeh S, Kaviani E, Vakili O, Taheri-Anganeh M, Tahamtan M, Savardashtaki A. Caspase-3: Structure, function, and biotechnological aspects. *Biotechnol Appl Biochem* 2022; **69**: 1633-1645 [PMID: 34342377 DOI: 10.1002/bab.2233]

107 **Ogaki S**, Taguchi K, Maeda H, Watanabe H, Ishima Y, Otagiri M, Maruyama T. Kupffer cell inactivation by carbon monoxide bound to red blood cells preserves hepatic cytochrome P450 *via* anti-oxidant and anti-inflammatory effects exerted through the HMGB1/TLR-4 pathway during resuscitation from hemorrhagic shock. *Biochem Pharmacol* 2015; **97**: 310-319 [PMID: 26232728 DOI: 10.1016/j.bcp.2015.07.035]

108 **Iber H**, Sewer MB, Barclay TB, Mitchell SR, Li T, Morgan ET. Modulation of drug metabolism in infectious and inflammatory diseases. *Drug Metab Rev* 1999; **31**: 29-41 [PMID: 10065364 DOI: 10.1081/dmr-100101906]

109 **Zhao M**, Ma J, Li M, Zhang Y, Jiang B, Zhao X, Huai C, Shen L, Zhang N, He L, Qin S. Cytochrome P450 Enzymes and Drug Metabolism in Humans. *Int J Mol Sci* 2021; **22** [PMID: 34884615 DOI: 10.3390/ijms222312808]

110 **Ghonem N**, Yoshida J, Murase N, Strom SC, Venkataramanan R. Treprostinil Improves Hepatic Cytochrome P450 Activity during Rat Liver Transplantation. *J Clin Exp Hepatol* 2012; **2**: 323-332 [PMID: 25755454 DOI: 10.1016/j.jceh.2012.09.002]

111 **Ferrigno A**, Richelmi P, Vairetti M. Troubleshooting and improving the mouse and rat isolated perfused liver preparation. *J Pharmacol Toxicol Methods* 2013; **67**: 107-114 [PMID: 23079697 DOI: 10.1016/j.vascn.2012.10.001]

112 **Almazroo OA**, Shaik IH, Hughes CB, Humar A, Venkataramanan R. Treprostinil Supplementation Ameliorates Hepatic Ischemia Reperfusion Injury and Regulates Expression of Hepatic Drug Transporters: An Isolated Perfused Rat Liver (IPRL) Study. *Pharm Res* 2022; **39**: 2979-2990 [PMID: 36071353 DOI: 10.1007/s11095-022-03384-x]

113 **Hollatz TJ**, Musat A, Westphal S, Decker C, D'Alessandro AM, Keevil J, Zhanhai L, Runo JR. Treatment with sildenafil and treprostinil allows successful liver transplantation of patients with moderate to severe portopulmonary hypertension. *Liver Transpl* 2012; **18**: 686-695 [PMID: 22315210 DOI: 10.1002/lt.23407]

114 **Chen XB**, Xu MQ. Primary graft dysfunction after liver transplantation. *Hepatobiliary Pancreat Dis Int* 2014; **13**: 125-137 [PMID: 24686540 DOI: 10.1016/s1499-3872(14)60023-0]

115 **Goldaracena N**, Cullen JM, Kim DS, Ekser B, Halazun KJ. Expanding the donor pool for liver transplantation with marginal donors. *Int J Surg* 2020; **82S**: 30-35 [PMID: 32422385 DOI: 10.1016/j.ijsu.2020.05.024]

116 **Kok B**, Dong V, Karvellas CJ. Graft Dysfunction and Management in Liver Transplantation. *Crit Care Clin* 2019; **35**: 117-133 [PMID: 30447775 DOI: 10.1016/j.ccc.2018.08.002]

117 **Liu J**, Man K. Mechanistic Insight and Clinical Implications of Ischemia/Reperfusion Injury Post Liver Transplantation. *Cell Mol Gastroenterol Hepatol* 2023; **15**: 1463-1474 [PMID: 36940849 DOI: 10.1016/j.jcmgh.2023.03.003]

118 **Almazroo OA**, Miah MK, Pillai VC, Shaik IH, Xu R, Dharmayan S, Johnson HJ, Ganesh S, Planinsic RM, Demetris AJ, Al-Khafaji A, Lopez R, Molinari M, Tevar AD, Hughes C, Humar A, Venkataramanan R. An evaluation of the safety and preliminary efficacy of peri- and post-operative treprostinil in preventing ischemia and reperfusion injury in adult orthotopic liver transplant recipients. *Clin Transplant* 2021; **35**: e14298 [PMID: 33764591 DOI: 10.1111/ctr.14298]

119 **Feldman J**, Habib N, Fann J, Radosevich JJ. Treprostinil in the treatment of pulmonary arterial hypertension. *Future Cardiol* 2020; **16**: 547-558 [PMID: 32391733 DOI: 10.2217/fca-2020-0021]

120 **Chaudhary KR**, Deng Y, Suen CM, Taha M, Petersen TH, Mei SHJ, Stewart DJ. Efficacy of treprostinil in the SU5416-hypoxia model of severe pulmonary arterial hypertension: haemodynamic benefits are not associated with improvements in arterial remodelling. *Br J Pharmacol* 2018; **175**: 3976-3989 [PMID: 30098019 DOI: 10.1111/bph.14472]

121 **Corboz MR**, Plaunt AJ, Malinin V, Li Z, Gauani H, Chun D, Cipolla D, Perkins WR, Chapman RW. Treprostinil palmitil inhibits the hemodynamic and histopathological changes in the pulmonary vasculature and heart in an animal model of pulmonary arterial hypertension. *Eur J Pharmacol* 2022; **916**: 174484 [PMID: 34508752 DOI: 10.1016/j.ejphar.2021.174484]

122 **Huang ST**, Xu N, Sun KP, Chen Q, Cao H. Effect of Treprostinil on the Early Postoperative Prognosis of Patients with Severe Left Heart Valvular Disease Combined with Severe Pulmonary Hypertension. *Ann Thorac Cardiovasc Surg* 2021; **27**: 18-24 [PMID: 32493870 DOI: 10.5761/atcs.oa.20-00003]

123 **Khan A**, White RJ, Meyer G, Pulido Zamudio TR, Jerjes-Sanchez C, Johnson D, Grover R, Broderick M, Ousmanou A, Holdstock L, Michelakis E. Oral treprostinil improves pulmonary vascular compliance in pulmonary arterial hypertension. *Respir Med* 2022; **193**: 106744 [PMID: 35134631 DOI: 10.1016/j.rmed.2022.106744]

124 **Ding M**, Tolbert E, Birkenbach M, Akhlaghi F, Gohh R, Ghonem NS. Treprostinil, a prostacyclin analog, ameliorates renal ischemia-reperfusion injury: preclinical studies in a rat model of acute kidney injury. *Nephrol Dial Transplant* 2021; **36**: 257-266 [PMID: 33156922 DOI: 10.1093/ndt/gfaa236]

125 **Yajima S**, Miyagawa S, Fukushima S, Sakai Y, Iseoka H, Harada A, Isohashi K, Horitsugi G, Mori Y, Shiozaki M, Ohkawara H, Sakaniwa R,

Hatazawa J, Yoshioka Y, Sawa Y. Prostacyclin Analogue-Loaded Nanoparticles Attenuate Myocardial Ischemia/Reperfusion Injury in Rats. *JACC Basic Transl Sci* 2019; **4**: 318-331 [PMID: 31312756 DOI: 10.1016/j.jacbts.2018.12.006]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 1871-1878

DOI: 10.4240/wjgs.v15.i9.1871

ISSN 1948-9366 (online)

MINIREVIEWS

Advances and challenges of gastrostomy insertion in children

Rana Bitar, Amer Azaz, David Rawat, Mohamed Hobeldin, Mohamad Miqdady, Seifeleslam Abdelsalam

Specialty type: Surgery

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Xiao Y, China

Received: February 6, 2023
Peer-review started: February 6, 2023
First decision: May 9, 2023
Revised: June 13, 2023
Accepted: July 18, 2023
Article in press: July 18, 2023
Published online: September 27, 2023

Rana Bitar, Amer Azaz, Mohamad Miqdady, Pediatric Gastroenterology, Sheikh Khalifa Medical City, Abu Dhabi 767451, United Arab Emirates

Rana Bitar, Amer Azaz, Mohamad Miqdady, Faculty of Medicine, Khalifa University, Abu Dhabi 767451, United Arab Emirates

David Rawat, Pediatric Gastroenterology, Barts Health NHS Trust, London E1 1BB, United Kingdom

Mohamed Hobeldin, Seifeleslam Abdelsalam, Pediatric Surgery, Sheikh Khalifa Medical City, Abu Dhabi 767451, United Arab Emirates

Corresponding author: Rana Bitar, MBBS, Assistant Professor, Pediatric Gastroenterology, Sheikh Khalifa Medical City, Al Karamah Street, Abu Dhabi 767451, United Arab Emirates. drranab@doctors.org.uk

Abstract

When oral feeding cannot provide adequate nutritional support to children, enteral tube feeding becomes a necessity. The overall aim is to ultimately promote appropriate growth, improve the patient's quality of life and increase carer satisfaction. Nasogastric tube feeding is considered appropriate on a short-term basis. Alternatively, gastrostomy feeding offers a more convenient and safer feeding option especially as it does not require frequent replacements, and carries a lower risk of complications. Gastrostomy tube feeding should be considered when nasogastric tube feeding is required for more than 2-3 wk as per the ESPEN guidelines on artificial enteral nutrition. Several techniques can be used to insert gastrostomies in children including endoscopic, image guided and surgical gastrostomy insertion whether open or laparoscopic. Each technique has its own advantages and disadvantages. The timing of gastrostomy insertion, device choice and method of insertion is dependent on the local expertise, patient requirements and family preference, and should be individualized with a multidisciplinary team approach. We aim to review gastrostomy insertion in children including indications, contraindications, history of gastrostomy, insertion techniques and complications.

Key Words: Laparoscopic gastrostomy; Percutaneous endoscopic gastrostomy; Laparoscopic-assisted gastrostomy; Laparoscopic-assisted percutaneous endoscopic gastrostomy; Radiologic gastrostomy; Open gastrostomy

Core Tip: Gastrostomy tubes are inserted to support the long-term nutritional needs of children when oral feeding becomes compromised. Gastrostomy insertion has evolved over the last century to involve multiple feeding devices and various insertion techniques. The insertion technique and device choice need to be selected after careful consideration of patient background medical history, patient needs, available facilities and after adequate counseling in a multi-disciplinary team setting. In this review we will present the indications, contraindications, history, advances, insertion techniques, challenges and complications of gastrostomy insertion in children.

Citation: Bitar R, Azaz A, Rawat D, Hobeldin M, Miqdady M, Abdelsalam S. Advances and challenges of gastrostomy insertion in children. *World J Gastrointest Surg* 2023; 15(9): 1871-1878
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/1871.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.1871

INTRODUCTION

When oral feeding becomes compromised, nasogastric tube feeding is considered appropriate for the support of fluid and nutrition in children on a short-term basis; however, in the long term this type of feeding has many limitations and carries a reduced survival rate[1]. Gastrostomy tubes (GTs) are inserted with the aim to support the long-term nutritional needs of children. Gastrostomy insertion has evolved over the last century to involve multiple feeding devices and various insertion techniques. The device chosen and the insertion technique are selected after careful consideration of patient background medical history, patient and family needs, and available facilities. Prior to insertion, adequate counselling of parents and a multi-disciplinary team (MDT) review is recommended. We aim to present the indications, contraindications, history, advances, insertion techniques, challenges and complications of gastrostomy insertion in children.

INDICATIONS AND CONTRAINDICATIONS

Indications

Gastrostomies should be considered when enteral feeding is required for more than 2-3 wk[2] with the aim of correcting significant nutritional deficiencies, promoting growth in children, and avoiding further body weight loss. Weight per age should be interpreted using disease-specific growth chart centiles when available. The ESPGHAN recommendation on gastrostomy insertion in children recommends consideration of gastrostomy insertion when enteral feeding is required for more than 3-6 wk[3]. Gastrostomies are generally considered in children with underlying chronic nutritional needs such as patients with oncological, metabolic, renal, neurological and gastrointestinal tract disorders in which oral intake is insufficient to sustain growth.

While the specific indications for gastrostomy placement are many and variable, the most frequent indications are related to inadequate oral fluid and nutrition intake and/or impaired swallowing in disorders of the central nervous system, either as a primary cause or in conjunction with chromosomal or metabolic disorders. In addition, renal disorders, congenital cardiac disease, oncological disorders, chronic respiratory diseases such as cystic fibrosis, and gastrointestinal disorders such as Crohn's disease and intestinal failure may require gastrostomy feeding to correct nutritional deficiencies. Gastrostomies are also inserted in congenital or acquired conditions such as esophageal atresia and craniofacial surgery, when oral intake may be anatomically impeded. Moreover, they may be necessary in children who require nutritional restitution to attain recommended weights advisable for certain surgical interventions, for example, in infants with congenital cardiac disorders[4,5]. Gastrostomies are also sometimes indicated in children with unsafe swallowing, at risk of recurrent aspiration from oral feeding and when gastric drainage and decompression is required in cases of foregut dysmotility. Another rare but recognized indication is to deliver therapeutic formulae in patients with certain metabolic disorders, which are usually unpalatable. Finally, it can be offered to patients who require many medications due to other organ diseases to improve compliance and effectiveness of medications[6-8].

Contraindications

Contraindications are relative and can typically be overcome. They include lack of a safe tract for percutaneous insertion due to adhesions, congenital anomalies, severe kyphoscoliosis, distorted anatomy due to multiple abdominal surgery, and interposed organs (liver, colon). In this case, surgical gastrostomy may be the only option whether it is laparoscopic or open. Significant coagulation disorders should be corrected, and placement should be deferred until full recovery if the patients suffer from hemodynamic instability, sepsis, significant ascites, infectious peritonitis, and abdominal wall infection at the placement site. Gastrostomy insertion in patients undergoing peritoneal dialysis is high risk and may be considered a relative contraindication by some centers[9].

HISTORY AND ADVANCES

The initial use of enteral nutrition in the gastrointestinal tract to nourish patients dates back to 1500 BC[10]. Over the centuries, research has evolved and contributed to better understanding of nutritional needs, methods to access the gastrointestinal tract, development of new tubes and equipment, with better understanding of digestion, absorption, and use of macro- and micronutrients.

The very first gastrostomy was used with the purpose of alimentation in obstruction at the gastric cardia or above in adults. It was initially proposed by Egeberg in 1837, and after multiple attempts and failures, it was not performed successfully until 1876 by Verneuil[11]. At that time gastrostomies were inserted by conventional open surgery[12]. In pediatrics, the procedure has been a mainstay in the early stage treatment of esophageal atresia; the first survivors of this condition were reported by Leven[13] and Ladd[14] in the early 1940's, and gastrostomy insertion was part of the therapy. Reports by Martin and Fultzl[15] in 1959, Holder and Gross[16] in 1960, Meeker and Snyder[17] in 1963, and others widened the popularity and indications for gastrostomy to include many pediatric surgical conditions. The less invasive percutaneous endoscopic gastrostomy (PEG) tube placement was introduced in 1980 by Gauderer *et al*[18]. Glow in the stomach of a newborn infant undergoing endoscopy inspired the development of this procedure. The first PEG was inserted in the pediatric operating room on June 12, 1979 in the University Hospital of Cleveland, United States, on a four-month-old with inadequate oral intake[19] under local anesthesia with sedation. Although PEG was originally described in children, it has become a popular method of enteral nutrition in all ages. In 2001, 20 years after it was invented, over 216000 were performed annually in the United States[20].

The application of gastrostomy later extended to cover non-surgical indications, such as supporting the nutritional requirements of patients with severe neurologic impairments and developmental delay. As these two patient groups had a higher risk for general anesthesia, the open operation solely to place a gastrostomy promptly changed to the less invasive approach, the PEG. It was among the first innovations that expanded endoscopy from a diagnostic tool to a therapeutic instrument. It was not until 1991 when laparoscopic gastrostomy application was first cited in the literature [21]. It had the advantage of direct visualization of the peritoneal cavity during placement to protect from inadvertent bowel injury and optimize gastrostomy location while being less invasive than open gastrostomy. Although PEG and laparoscopic-assisted gastrostomy (LAG) are the two most frequently used procedures for gastrostomy placement, to date, there is no agreement as to which procedure, is superior. Many centers prefer to insert a PEG owing to its simplicity and low cost[22]. PEG has since become widely accepted in both the adult and pediatric populations.

Once the concept of a minimally invasive procedure for gastrostomy was introduced, further modifications were introduced to reduce complication rates and facilitate the operative technique. Techniques such as the push gastrostomy technique has the advantage of avoiding the step of pulling the GT through the oropharynx and esophagus and preventing the carriage of microorganisms to the peristomal site[4]. Although the push technique is associated with a lower peristomal infection rate than the pull technique in adults[23], this has not been demonstrated in pediatric patients [24,25]. Another technique modification to avoid the need for frequent general anesthesia with its associated risks, was the one-step gastrostomy device. The one-step gastrostomy device was an appealing, low-profile gastrostomy introduced in pediatric patients which uses a balloon device[26]. The one-step gastrostomy is being increasingly used. As the balloon device does not offer the as secure fixation of the stomach to the abdominal wall as an internal bumper, gastropexy was introduced so that the stomach is fixed to the abdominal wall by sutures or T-fasteners[27], as demonstrated in Figure 1. Gastropexy is performed to ensure adequate apposition of the stomach and the anterior abdominal wall[26,28]. The one-step PEG/LAG placement with the push technique and T-fastener gastropexy[24] gained popularity due to its unique advantages. Regardless of tube insertion technique, GTs are generally changed to a low-profile button after 6 wk to 8 wk to allow for tract maturation[29]. Recently more and more centers have started to insert primary gastrostomy button feeding tubes.

A new technique, combining the use of endoscopy and laparoscopy in gastrostomy insertion was described in 1995 by Stringel *et al*[30], where laparoscopic-assisted PEG (LAPEG) was performed on 2 children when attempts at simple PEG had failed. This technique has been used particularly in difficult cases where PEG was felt to be high risk or impossible. LAPEG combines both endoscopy and laparoscopy for gastrostomy insertion, while using a single umbilical incision to insert the laparoscope to assist in gastrostomy placement. Using the laparoscope permits accuracy in the placement of the PEG, allows identification and subsequent lysis of adhesions, and safe completion of the PEG. In some centers LAPEG is performed routinely[31], in others it is used when PEG is felt to be unsafe or impossible, in other centers it is used if the abdominal wall is > 2 cm, making it technically difficult to perform a laparoscopic gastrostomy[32].

GASTROSTOMY INSERTION OPERATIVE TECHNIQUE

Parents should be given detailed information on the benefits, principles and decision making behind the choice of technique for gastrostomy insertion by the professional undertaking the procedure. Table 1 demonstrates the characteristics of different gastrostomy placement techniques. After MDT involvement, alternative methods of gastrostomy insertion should also be discussed including the pros and cons of each. Procedural as well as intermediate and long-term risks of GT insertion should be discussed with the parents/carers well in advance of the procedure to enable adequate time to process the information, consider any questions and make an effective well-informed decision before giving consent. Regardless of the technique, at the time of gastrostomy insertion, it is recommended that patients are given antibiotics preoperatively[33-35]. Most centers will allow immediate use of the GT for medications, and commencement of feeds may be variable depending on institutional consensus and is no later than one postoperative day.

Table 1 Characteristics of different gastrostomy placement techniques

Parameters compared	PEG	PEG push technique	PIG	LAG	LAPEG	Open Gastrostomy
Operation under general anesthesia	Yes (occasionally under sedation)	Yes	No	Yes	Yes	Yes
Blind puncture through the abdominal cavity	Yes	Yes	Yes	No	No	No
Gastropexy	No	Yes	Yes	Yes	Yes	Yes
Pneumoperitoneum	No	No	No	Yes	Yes	No
Invasiveness, number of transabdominal wall wounds	1	1	1	3	2	Incision, midline or subcoastal
Cosmetics; number of scars on abdominal wall	0	0	0	2	1	1 (incision)
Repeat general anesthesia/sedation for tube change	Yes	No	No	No	No	No

PEG: Percutaneous endoscopic gastrostomy; LAG: Laparoscopic-assisted gastrostomy; LAPEG: Laparoscopic-assisted percutaneous endoscopic gastrostomy; PIG: Percutaneous image guided gastrostomy.

DOI: 10.4240/wjgs.v15.i9.1871

Figure 1 Gastropexy of the stomach to the abdominal wall using three trans-gastric tuckers.

Open gastrostomy

Open gastrostomy has been in use for more than 100 years and has remained the standard until the introduction of less invasive insertion techniques. Nowadays, open gastrostomy is reserved for cases where the anatomy does not allow for a safe LAG or PEG insertion or the child cannot tolerate the pneumoperitoneum; as in cases of scar tissue formation from previous surgery. It should also be considered if the patient requires other surgical procedures at the same time.

There are different techniques described for open gastrotomy tube insertion, the most common technique used includes an incision made in the upper abdomen either midline or left subcostal and the abdominal cavity is entered. The stomach is identified, and an appropriate location for GT insertion selected, on the anterior wall of the body of the stomach, an opening is made on the stomach. The GT is passed through the abdominal wall ideally with the rectus sheath away from the umbilicus and costal margin and then inserted into the stomach. The tube is secured to the stomach with purse string sutures placed around the tube. The stomach is then anchored to the abdominal wall from the inside with sutures. Finally, the surgical incision is closed with sutures.

PEG, pull through technique

Under endoscopic guidance, the stomach is inflated and a position for gastrostomy insertion on the anterior abdominal wall is identified using transabdominal impulse/finger indentation and transillumination. The abdominal wall and skin are injected with local anesthesia. A puncture cannula is inserted through the anterior abdominal wall into the stomach cavity under endoscopic control while the stomach is inflated to allow opposition of the stomach wall to the abdominal wall. The needle is removed from the cannula and an introducer device containing a double thread is inserted through

the cannula. The thread is pushed through the cannula until it is visible endoscopically in the stomach cavity. The thread is then caught and secured through the endoscope with forceps or a snare. The endoscope with the biopsy forceps/snare and adherent thread are pulled out through the mouth as one unit. The thread is then interlocked with the PEG, the PEG is lubricated with lubricant jelly, and the guide thread outside the abdominal wall is pulled through the cannula while the PEG is pulled through the mouth, esophagus and into the stomach. The PEG tube is pulled through the abdominal wall with the inner disk fitting snug along the gastric mucosa. Finally, the PEG is fixed to the anterior abdominal wall by adjusting the external bumpers that are provided with the gastrostomy device used.

Percutaneous image guided gastrostomy

The GT is inserted into the stomach using the Seldinger technique. A nasogastric tube is placed shortly before the procedure to allow air insufflation. Gastric puncture is performed under fluoroscopic guidance with an 18G puncture needle in the left upper abdominal quadrant. To confirm insertion of the needle through the stomach lumen, the radiologist will aspirate air into a syringe or flushes the needle with contrast medium, the gastric and abdominal wall are securely fastened together (gastropexy). Gastropexy is usually performed using introducer needles preloaded with anchors. The abdominal wall and gastric wall are approximated, the gastric wall and stomach wall are punctured near the anchors. The tract is dilated using serial dilators, after adequate dilatation, a balloon type gastrotomy is pushed into the gastric lumen through a peel away sheath. The retention balloon is inflated with water, and the procedure is completed with contrast injection through the GT to confirm correct tube position and to exclude extravasation or other complications.

LAG

Multiple modifications have been described for laparoscopic gastrostomy. In general, the procedure starts with insufflation of the peritoneum. Pressures are maintained between 6 to 12 mmHg based on patient comorbidities and size. A 5-mm telescope is placed through an umbilical port. An extra 5-mm port site is placed in the left upper quadrant below the costal margin. The stomach is then visualized and grasped along the greater curvature.

This small portion of the stomach can be delivered through the abdominal wall, at that time the port is removed and sutures are placed between the stomach and the abdominal wall. A small opening is made in the stomach and the tube is placed into the stomach.

Another technique to perform LAP gastrostomy is to fix the stomach to the abdominal wall by T fasteners or stitches then access the stomach by a needle followed by introduction of a guidewire through the needle. In this case the GT is inserted using the Seldinger technique; serial dilatation of the tract is performed using dilators, after adequate dilatation of the tract, a balloon type gastrotomy is pushed into the gastric lumen through a peel away sheath. Finally, the tube position is checked by infusing and aspirating saline solution under laparoscopic control.

Push one-step PEG

Under endoscopic control, gastropexy is performed using 3 fasteners. At the center of the gastropexy a puncture site is identified and a trocar is inserted into the gastric lumen under direct visualization by the endoscopist. A guidewire is passed through the trocar which is later used to pass a dilator. After serial dilatation of the future gastrostomy track, a feeding tube is inserted into the stomach and the dilator is peeled away. The balloon is inflated

LAPEG

The procedure requires both endoscopic and laparoscopic techniques, and therefore, both an endoscopist, and pediatric surgeon are required.

A 5-mm optical is placed through the umbilicus for the laparoscope. Pneumoperitoneum is recommended at 8-12 mmHg. At the same time, a gastroscopy is performed and the stomach lumen is visualized. After insufflating the stomach, the optimal site for gastrostomy is chosen using external finger indentation and direct visualization. Gastropexy is performed using 3 fasteners, and a needle is inserted into the gastric lumen, a guidewire is passed through the needle which is later used to guide the dilator. After serial dilatation of the track, the GT is inserted and the balloon inflated and the tube is fixed to the skin at an appropriate length. Gastrostomy is inserted under direct laparoscopic and endoscopic visualization.

COMPLICATIONS AND CHALLENGES

GT insertion carries a procedural risk and is also associated with intermediate and long-term post-operative complications. Complications, can be classified as minor or major. Major complications involve failure of GT placement, gastrostomy peritoneal leak causing peritonitis, tube dislodgement, buried bumper syndrome, adjacent bowel injury, major bleeding, esophageal tear, and gastrocolic fistula formation. Minor complications, on the other hand, include minor skin infection, granulation tissue formation, tube leak, and tube occlusion. There is also the possibility of the development or aggravation of gastroesophageal reflux disease[8]. A large meta-analysis looked at complication rates and mortality in association with different gastrostomy insertion operative techniques in children, and data from 18 articles with 4631 patients were analyzed. Techniques compared were that of PEG (pull, single stage, or introducer, percutaneous image guided gastrostomy) and LAG insertion. The overall complications encountered were; minor (33% of patients)-granulation (10.30%), local infection (8.30%) and leakage (6.00%), major (10.00% of patients)-systemic infection (3.50%), cellulitis (1.00%) perforation (< 0.30%) and lethal (0.15%). Interestingly, prematurity or young age did not affect

complication rate[4].

Laparoscopic techniques have been reported to be safer than endoscopic gastrostomy insertion procedures. In a retrospective comparative study between PEG, LAG and open gastrostomy including 236 children; the overall rates of major complications were 9.2% in the endoscopic gastrostomy, 8.9% in the laparoscopic, and 8.1% in open gastrostomy groups[36]. In a larger meta-analysis, which included 8 studies and 1550 pediatric patients; LAG technique was found to be associated with only 1% chance of major complications compared to 5.4% in the PEG technique[37]. Laparoscopic gastrostomy has unique advantages, the surgeon has a better visual intraperitoneal field thereby lowering the risk of perforation of hollow viscous and vascular injury, and particularly the formation of gastrocolic fistula which has been reported in children following PEG. A study examining endoscopic gastrostomy placement in infants less than one year of age found that despite successful placement in a healthier cohort, PEG had more morbid and more costly complications, specifically a 3.8% risk of gastrocolic fistula, compared to laparoscopic gastrostomy[38]. Interestingly, in a systematic review, 8.4% (2.1%-19.4%) of children who underwent PEG and 2.5% (0.0%-8.6%) of children who underwent LAG required re-intervention under general anesthesia with a reported significant difference[39].

Considering the various techniques used to insert GTs in children, the magnitude of the challenges faced with the procedure and the likelihood of complications is highly dependent on the technique used for GT insertion. The higher the blinded components of the technique the more likely are the challenges and major complications. The more the directly visualized components of the technique the less likely are the challenges and major complications. Fixation of the stomach to the abdominal wall is another factor that reduces the likelihood of major complications, it reduces the occurrence of tube dislodgement and possible subsequent intraperitoneal leak. Gastropexy is feasible during laparoscopic, radiologic and push one step endoscopic gastrostomy[26,28]. Based on the above principles, LAPEG in children is associated with a high safety profile due to direct endoscopic and laparoscopic visualization of the entire GT insertion process. In a retrospective review of 76 pediatric patients, LAPEG was performed and completed safely with no recognizable peri-operative complications, despite 26% of the cohort being considered high risk with significant pre-existing comorbidities. The safety and use of LAPEG has also been supported by previous reports[40-48]. A retrospective review comparing LAPEG to LAG demonstrated both procedures to be comparable in reducing the major complication rate but with the added advantage of significantly shorter procedure time in the LAPEG group[48]. In the past, 10 kg of weight was considered the lower limit of body weight for insertion of PEG tubes, below which the procedure was deemed to be more technically challenging[49]. However, PEG insertion is reported to be safe in infants with weight as low as 2.3 kg[50]. Minar *et al*[51] described successful PEG in 39/40 infants with a mean weight of 3.25 kg at the time of procedure. The only major complication reported was esophageal injury. There exists the hypothesis from scholar peers that younger children may be at higher risk of complications at the time of PEG placement as they have thinner tissues which may be easier to transilluminate the gastrocolic omentum or the transverse colon. Thus, resulting in accidental penetration and traversing of the colon, and resultant gastrocolic fistula which can go undetected. Hence, the recommendation by some in using the laparoscopic technique or the LAPEG technique in small patients[52]. In the LAPEG report of 76 patients, one third of the patients were < 7 kg in weight and one third were < 7 mo of age. Therefore, LAPEG is a potential option for this subset of patients.

CONCLUSION

Although gastrostomy insertion has become a common procedure in children, the best method of placement still needs to be determined. The method of placement can vary significantly according to patient age, local expertise, and available healthcare facilities[53]. Therefore, more research is still needed including the best insertion technique for individual patient groups, the timing and type of best enteral feeds to be initiated after placement, and identifying specific risk factors for the development of complications. In our current climate of health economics, reduction in the cost and local availability of resources required for gastrostomy placement in children should be considered. The ideal gastrostomy procedure is a one-step procedure, performed under minimal anesthesia, with no complications, at reduced cost and optimal resources utilization as long as patient safety is considered first and foremost. As technology improves, advanced minimally invasive robotic surgical procedures are likely to expand. This can only succeed if we continue to challenge and improve our current practice by continued collaboration between pediatric surgeons and gastroenterologists with more good quality multi-center research of novel practices and modifications of gastrostomy techniques and perioperative management.

ACKNOWLEDGEMENTS

The authors would like to knowledge Mr. Emad Bashir Sharfi, Retired Medical Librarian in Sheikh Khalifa Medical City for his dedication and support in obtaining all required articles to support the completion of the minireview.

FOOTNOTES

Author contributions: Bitar R made substantial contributions to the conception and design of the work, interpretation of data, drafting, writing and revising the manuscript critically for important intellectual content and approved the final version to be published, and

agrees to be accountable for all aspects of the work; Azaz A, Rawat D, Hobeldin M, Miqdady M, and Abdelsalam S made substantial contributions to the design of the work, acquisition and interpretation of data and revising the manuscript critically for important intellectual content, and approved the final version to be published and agree to be accountable for all aspects of the work.

Conflict-of-interest statement: There is no conflict of interest to declare.

Country/Territory of origin: United Arab Emirates

ORCID number: Rana Bitar 0000-0002-2852-7707; Amer Azaz 0000-0003-2303-0846; David Rawat 0000-0003-1788-8758; Mohamad Miqdady 0000-0001-9089-9424.

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

REFERENCES

1 **Holmes S**. Enteral feeding and percutaneous endoscopic gastrostomy. *Nurs Stand* 2004; **18**: 41-43 [PMID: 14976704 DOI: 10.7748/ns2004.01.18.20.41.c3536]
2 **Löser C**, Aschl G, Hébuterne X, Mathus-Vliegen EM, Muscaritoli M, Niv Y, Rollins H, Singer P, Skelly RH. ESPEN guidelines on artificial enteral nutrition--percutaneous endoscopic gastrostomy (PEG). *Clin Nutr* 2005; **24**: 848-861 [PMID: 16261664 DOI: 10.1016/j.clnu.2005.06.013]
3 **Homan M**, Hauser B, Romano C, Tzivinikos C, Torroni F, Gottrand F, Hojsak I, Dall'Oglio L, Thomson M, Bontems P, Narula P, Furlano R, Oliva S, Amil-Dias J. Percutaneous Endoscopic Gastrostomy in Children: An Update to the ESPGHAN Position Paper. *J Pediatr Gastroenterol Nutr* 2021; **73**: 415-426 [PMID: 34155150 DOI: 10.1097/MPG.0000000000003207]
4 **Balogh B**, Kovács T, Saxena AK. Complications in children with percutaneous endoscopic gastrostomy (PEG) placement. *World J Pediatr* 2019; **15**: 12-16 [PMID: 30456563 DOI: 10.1007/s12519-018-0206-y]
5 **Eger R**, Reif S, Yaron A, Bojanover Y. [Percutaneous endoscopic gastrostomy (PEG) in children: indications, the procedure, outcomes, short and long-term complications]. *Harefuah* 2008; **147**: 21-24, 95 [PMID: 18300618]
6 **Haqqi SAUH**, Farrukh SZUI, Dhedhi AS, Siddiqui AR, Muhammad AJ, Niaz SK. Percutaneous endoscopic gastrostomy; success and outcome of a novel modality for enteral nutrition. *J Pak Med Assoc* 2020; **70**: 1795-1798 [PMID: 33159755 DOI: 10.5455/JPMA.30413]
7 **Ackroyd R**, Saincher M, Cheng S, El-Matary W. Gastrostomy tube insertion in children: the Edmonton experience. *Can J Gastroenterol* 2011; **25**: 265-268 [PMID: 21647461 DOI: 10.1155/2011/821019]
8 **El-Matary W**. Percutaneous endoscopic gastrostomy in children. *Can J Gastroenterol* 2008; **22**: 993-998 [PMID: 19096739 DOI: 10.1155/2008/583470]
9 **Alhaffaf FA**, Alqahtani AS, Alrobyan AA, Alqubaisi SN, Ahmad BA, Almutairi MR, Wali SA, Alhebbi HA. Percutaneous endoscopic gastrostomy in children: A single center experience in Saudi Arabia. *Saudi Med J* 2021; **42**: 205-208 [PMID: 33563740 DOI: 10.15537/smj.2021.2.25692]
10 **Dudrick SJ**, Palesty JA. Historical highlights of the development of enteral nutrition. *Surg Clin North Am* 2011; **91**: 945-964, x [PMID: 21787977 DOI: 10.1016/j.suc.2011.05.002]
11 **Cunha F**. Gastrostomy-Its Inception and Evolution. *Amer J Surg* 1946; **72** [DOI: 10.1016/0002-9610(46)90402-3]
12 **Stamm M**. Gastrostomy: a new method. *Med News* 1894; **65**: 324
13 **Leven NL**. Congenital Atresia of the Esophagus with Tracheoesophageal Fistula: Report of Successful Extrapleural Ligation of Fistulous Communication and Cervical Esophagostomy. *J Thor Surg* 1941; **10**: 648 [DOI: 10.1016/S0096-5588(20)32186-3]
14 **Ladd WE**. The Surgical Treatment of Esophageal Atresia and Tracheoesophageal Fistula. *New Eng J Med* 1944; **230**: 625 [DOI: 10.1056/NEJM194405252302101]
15 **Martin L**, Fultz T. The Use of Gastrostomy in Pediatric Surgery. *Arch Surg* 1959; **78**: 904-7 [DOI: 10.1001/archsurg.1959.04320060092012]
16 **Holder TM**, Gross RE. Temporary gastrostomy in pediatric surgery. Experience with 187 cases. *Pediatrics* 1960; **26**: 36-41 [PMID: 14402573]
17 **Gilchrist RK**. Gastrostomy tubes. *Surg Gynecol Obstet* 1958; **106**: 631-633 [PMID: 13556485]
18 **Gauderer MW**, Ponsky JL, Izant RJ Jr. Gastrostomy without laparotomy: a percutaneous endoscopic technique. *J Pediatr Surg* 1980; **15**: 872-875 [PMID: 6780678 DOI: 10.1016/s0022-3468(80)80296-x]
19 **Gauderer MW**. Percutaneous endoscopic gastrostomy and the evolution of contemporary long-term enteral access. *Clin Nutr* 2002; **21**: 103-110 [PMID: 12056781 DOI: 10.1054/clnu.2001.0533]
20 **Gauderer MW**. Percutaneous endoscopic gastrostomy-20 years later: a historical perspective. *J Pediatr Surg* 2001; **36**: 217-219 [PMID: 11150469 DOI: 10.1053/jpsu.2001.20058]
21 **Humphrey GM**, Najmaldin A. Laparoscopic gastrostomy in children. *Pediatr Surg Int* 1997; **12**: 501-504 [PMID: 9238116 DOI: 10.1007/BF01258711]
22 **Fortunato JE**, Troy AL, Cuffari C, Davis JE, Loza MJ, Oliva-Hemker M, Schwarz KB. Outcome after percutaneous endoscopic gastrostomy in children and young adults. *J Pediatr Gastroenterol Nutr* 2010; **50**: 390-393 [PMID: 20179645 DOI: 10.1097/MPG.0b013e3181aed6f1]
23 **Campoli PM**, de Paula AA, Alves LG, Turchi MD. Effect of the introducer technique compared with the pull technique on the peristomal infection rate in PEG: a meta-analysis. *Gastrointest Endosc* 2012; **75**: 988-996 [PMID: 22365441 DOI: 10.1016/j.gie.2012.01.003]

24 **Göthberg G**, Björnsson S. One-Step Insertion of Low-Profile Gastrostomy in Pediatric Patients vs Pull Percutaneous Endoscopic Gastrostomy: Retrospective Analysis of Outcomes. *JPEN J Parenter Enteral Nutr* 2016; **40**: 423-430 [PMID: 25587008 DOI: 10.1177/0148607114567202]

25 **Jacob A**, Delesalle D, Coopman S, Bridenne M, Guimber D, Turck D, Gottrand F, Michaud L. Safety of the One-Step Percutaneous Endoscopic Gastrostomy Button in Children. *J Pediatr* 2015; **166**: 1526-1528 [PMID: 25868429 DOI: 10.1016/j.jpeds.2015.03.008]

26 **Jeličić Kadić A**, Radošević T, Žitko V, Despot R, Pogorelić Z, Llorente Muñoz CM, Runjić E, Kovačević T, Ćatipović Ardalić T, Polić B, Markić J. Percutaneous Endoscopic Gastrostomy Tubes Can Be Considered Safe in Children: A Single-Center 11-Year Retrospective Analysis. *Medicina (Kaunas)* 2021; **57** [PMID: 34833454 DOI: 10.3390/medicina57111236]

27 **Kvello M**, Knatten CK, Perminow G, Skari H, Engebretsen A, Schistad O, Emblem R, Bjørnland K. Initial experience with percutaneous endoscopic gastrostomy with T-fastener fixation in pediatric patients. *Endosc Int Open* 2018; **6**: E179-E185 [PMID: 29399615 DOI: 10.1055/s-0043-122227]

28 **Seifarth FG**, Dong ML, Guerron AD, Lozada JS, Magnuson DK. Endoscopic gastrostomy button with double-lasso U-stitch in children. *JSLS* 2015; **19**: e2015.00002 [PMID: 25848198 DOI: 10.4293/JSLS.2015.00002]

29 **Akay B**, Capizzani TR, Lee AM, Drongowski RA, Geiger JD, Hirschl RB, Mychaliska GB. Gastrostomy tube placement in infants and children: is there a preferred technique? *J Pediatr Surg* 2010; **45**: 1147-1152 [PMID: 20620310 DOI: 10.1016/j.jpedsurg.2010.02.079]

30 **Stringel G**, Geller ER, Lowenheim MS. Laparoscopic-assisted percutaneous endoscopic gastrostomy. *J Pediatr Surg* 1995; **30**: 1209-1210 [PMID: 7472985 DOI: 10.1016/0022-3468(95)90024-1]

31 **Bitar R**, Azaz A, Alghfeli H, Natour H, Rawat D, Hobeldin M, Miqdady M, Abdelsalam S. Tertiary centre experience of laparoscopic-assisted percutaneous endoscopic gastrostomy in children: a 9-year review. *Curr Pediatr Res* 2021; **25**: 355-360

32 **Yu SC**, Petty JK, Bensard DD, Partrick DA, Bruny JL, Hendrickson RJ. Laparoscopic-assisted percutaneous endoscopic gastrostomy in children and adolescents. *JSLS* 2005; **9**: 302-304 [PMID: 16121876]

33 **Gossner L**, Keymling J, Hahn EG, Ell C. Antibiotic prophylaxis in percutaneous endoscopic gastrostomy (PEG): a prospective randomized clinical trial. *Endoscopy* 1999; **31**: 119-124 [PMID: 10223359 DOI: 10.1055/s-1999-13658]

34 **Jafri NS**, Mahid SS, Minor KS, Idstein SR, Hornung CA, Galandiuk S. Meta-analysis: antibiotic prophylaxis to prevent peristomal infection following percutaneous endoscopic gastrostomy. *Aliment Pharmacol Ther* 2007; **25**: 647-656 [PMID: 17311597 DOI: 10.1111/j.1365-2036.2007.03247.x]

35 **Rajan A**, Wangrattanapranee P, Kessler J, Kidambi TD, Tabibian JH. Gastrostomy tubes: Fundamentals, periprocedural considerations, and best practices. *World J Gastrointest Surg* 2022; **14**: 286-303 [PMID: 35664365 DOI: 10.4240/wjgs.v14.i4.286]

36 **Avitsland TL**, Kristensen C, Emblem R, Veenstra M, Mala T, Bjørnland K. Percutaneous endoscopic gastrostomy in children: a safe technique with major symptom relief and high parental satisfaction. *J Pediatr Gastroenterol Nutr* 2006; **43**: 624-628 [PMID: 17130739 DOI: 10.1097/01.mpg.0000229550.54455.63]

37 **Sandberg F**, Viktorsdóttir MB, Salö M, Stenström P, Arnbjörnsson E. Comparison of major complications in children after laparoscopy-assisted gastrostomy and percutaneous endoscopic gastrostomy placement: a meta-analysis. *Pediatr Surg Int* 2018; **34**: 1321-1327 [PMID: 30291404 DOI: 10.1007/s00383-018-4358-6]

38 **Landisch RM**, Colwell RC, Densmore JC. Infant gastrostomy outcomes: The cost of complications. *J Pediatr Surg* 2016; **51**: 1976-1982 [PMID: 27678507 DOI: 10.1016/j.jpedsurg.2016.09.025]

39 **Suksamanapun N**, Mauritz FA, Franken J, van der Zee DC, van Herwaarden-Lindeboom MY. Laparoscopic versus percutaneous endoscopic gastrostomy placement in children: Results of a systematic review and meta-analysis. *J Minim Access Surg* 2017; **13**: 81-88 [PMID: 27251841 DOI: 10.4103/0972-9941.181776]

40 **Thaker AM**, Sedarat A. Laparoscopic-Assisted Percutaneous Endoscopic Gastrostomy. *Curr Gastroenterol Rep* 2016; **18**: 46 [PMID: 27422123 DOI: 10.1007/s11894-016-0520-2]

41 **Smitherman S**, Pimpalwar A. Laparoendoscopic gastrostomy tube placement: our all-in-one technique. *J Laparoendosc Adv Surg Tech A* 2009; **19**: 119-123 [PMID: 19196093 DOI: 10.1089/Lap.2007.0210]

42 **Raaf JH**, Manney M, Okafor E, Gray L, Chari V. Laparoscopic placement of a percutaneous endoscopic gastrostomy (PEG) feeding tube. *J Laparoendosc Surg* 1993; **3**: 411-414 [PMID: 8268516 DOI: 10.1089/Lps.1993.3.411]

43 **Idowu O**, Driggs XA, Kim S. Laparoscopically assisted antegrade percutaneous endoscopic gastrostomy. *J Pediatr Surg* 2010; **45**: 277-279 [PMID: 20105621 DOI: 10.1016/j.jpedsurg.2009.08.017]

44 **Tomioka K**, Fukoe Y, Lee Y, Lee M, Aoki T, Kato T, Murakami M. Clinical Evaluation of Laparoscopic-Assisted Percutaneous Endoscopic Gastrostomy (LAPEG). *Int Surg* 2015; **100**: 1144-1147 [PMID: 25563858 DOI: 10.9738/INTSURG-D-14-00261.1]

45 **Lodin D**, Gupta AK, Rubay D, Genuit T, Hus N. The Effectiveness of Laparoscopic-assisted Percutaneous Endoscopic Gastrostomy in Patients with Unfavorable Anatomy: A Single-center Retrospective Cohort Study. *Cureus* 2020; **12**: e6647 [PMID: 31976184 DOI: 10.7759/cureus.6647]

46 **Takahashi T**, Okazaki T, Kato Y, Watayo H, Lane GJ, Kobayashi H, Segawa O, Kameoka S, Yamataka A. Laparoscopy-assisted percutaneous endoscopic gastrostomy. *Asian J Surg* 2008; **31**: 204-206 [PMID: 19010764 DOI: 10.1016/S1015-9584(08)60087-1]

47 **Livingston MH**, Pepe D, Jones S, Bütter A, Merritt NH. Laparoscopic-assisted percutaneous endoscopic gastrostomy: insertion of a skin-level device using a tear-away sheath. *Can J Surg* 2015; **58**: 264-268 [PMID: 26204365 DOI: 10.1503/cjs.014814]

48 **Bitar R**, Syed A, Azaz A, Rawat D, Hobeldin M, Miqdady M, Abdelsalam S. Is endoscopy beneficial in pediatric laparoscopic gastrostomy insertion; A 9-year comparative study. *Front Pediatr* 2022; **10**: 950867 [PMID: 36034566 DOI: 10.3389/fped.2022.950867]

49 **Pennington C**. To PEG or not to PEG. *Clin Med (Lond)* 2002; **2**: 250-255 [PMID: 12108477 DOI: 10.7861/clinmedicine.2-3-250]

50 **Wilson L**, Oliva-Hemker M. Percutaneous endoscopic gastrostomy in small medically complex infants. *Endoscopy* 2001; **33**: 433-436 [PMID: 11396762 DOI: 10.1055/s-2001-14268]

51 **Minar P**, Garland J, Martinez A, Werlin S. Safety of percutaneous endoscopic gastrostomy in medically complicated infants. *J Pediatr Gastroenterol Nutr* 2011; **53**: 293-295 [PMID: 21865977 DOI: 10.1097/MPG.0b013e318215c41b]

52 **Backman T**, Arnbjörnsson E, Berglund Y, Larsson LT. Video-assisted gastrostomy in infants less than 1 year. *Pediatr Surg Int* 2006; **22**: 243-246 [PMID: 16402265 DOI: 10.1007/s00383-005-1628-x]

53 **Salazar JH**, Spanbauer C, Sood MR, Densmore JC, Van Arendonk KJ. Variability in the Method of Gastrostomy Placement in Children. *Children (Basel)* 2020; **7** [PMID: 32492791 DOI: 10.3390/children7060053]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 1879-1891

DOI: 10.4240/wjgs.v15.i9.1879

ISSN 1948-9366 (online)

MINIREVIEWS

Surgical decompression for the management of abdominal compartment syndrome with severe acute pancreatitis: A narrative review

Prashant Nasa, Gunjan Chanchalani, Deven Juneja, Manu LNG Malbrain

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Ke L, China; Zhang L, China; Yin Z, China

Received: May 23, 2023
Peer-review started: May 23, 2023
First decision: July 8, 2023
Revised: July 20, 2023
Accepted: August 1, 2023
Article in press: August 1, 2023
Published online: September 27, 2023

Prashant Nasa, Department of Critical Care Medicine, NMC Specialty Hospital, Dubai 7832, United Arab Emirates

Prashant Nasa, Department of Internal Medicine, College of Medicine and Health Sciences, Al Ain 15551, United Arab Emirates

Gunjan Chanchalani, Department of Critical Care Medicine, K.J. Somaiya Hospital and Research Centre, Mumbai 400022, India

Deven Juneja, Institute of Critical Care Medicine, Max Super Specialty Hospital, New Delhi 110017, India

Manu LNG Malbrain, First Department of Anaesthesiology and Intensive Therapy, Medical University of Lublin, Lublin 20-954, Poland

Manu LNG Malbrain, Executive Administration, International Fluid Academy, Lovenjoel 3360, Belgium

Manu LNG Malbrain, Medical Data Management, Medaman, Geel 2440, Belgium

Corresponding author: Prashant Nasa, MD, Chief Physician, Department of Critical Care Medicine, NMC Specialty Hospital, Al Nahda 2, Amman Street, Dubai 7832, United Arab Emirates. dr.prashantnasa@gmail.com

Abstract

Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) play a pivotal role in the pathophysiology of severe acute pancreatitis (SAP) and contribute to new-onset and persistent organ failure. The optimal management of ACS involves a multi-disciplinary approach, from its early recognition to measures aiming at an urgent reduction of intra-abdominal pressure (IAP). A targeted literature search from January 1, 2000, to November 30, 2022, revealed 20 studies and data was analyzed on the type and country of the study, patient demographics, IAP, type and timing of surgical procedure performed, post-operative wound management, and outcomes of patients with ACS. There was no randomized controlled trial published on the topic. Decompressive laparotomy is effective in rapidly reducing IAP (standardized mean difference = 2.68, 95% confidence interval: 1.19-1.47, $P < 0.001$; 4 studies). The

morbidity and complications of an open abdomen after decompressive laparotomy should be weighed against the inadequately treated but, potentially lethal ACS. Disease-specific patient selection and the role of less-invasive decompressive measures, like subcutaneous linea alba fasciotomy or component separation techniques, is lacking in the 2013 consensus management guidelines by the Abdominal Compartment Society on IAH and ACS. This narrative review focuses on the current evidence regarding surgical decompression techniques for managing ACS in patients with SAP. However, there is a lack of high-quality evidence on patient selection, timing, and modality of surgical decompression. Large prospective trials are needed to identify triggers and effective and safe surgical decompression methods in SAP patients with ACS.

Key Words: Intra-abdominal hypertension; Intra-abdominal pressure; Decompression laparotomy; Midline laparotomy; Abdominal compartment syndrome; Acute pancreatitis

Core Tip: Intra-abdominal hypertension (IAH) plays a pivotal role in the pathophysiology of new-onset organ failure in patients with severe acute pancreatitis (SAP). Abdominal compartment syndrome (ACS), a sustained elevation of Intra-abdominal pressure of more than 20 mmHg associated with one or more new organ dysfunction, reflects an unabated progression of IAH. Surgical decompression is an effective core strategic component to manage an overt ACS. However, the morbidity of an open abdomen after decompressive laparotomy should be weighed against the potentially lethal and inadequately treated ACS. Prospective randomized studies are required to evaluate the appropriate timing, technique, and triggers for surgical decompression in ACS associated with SAP.

Citation: Nasa P, Chanchalani G, Juneja D, Malbrain ML. Surgical decompression for the management of abdominal compartment syndrome with severe acute pancreatitis: A narrative review. *World J Gastrointest Surg* 2023; 15(9): 1879-1891
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/1879.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.1879

INTRODUCTION

Acute pancreatitis (AP) is a commonly-diagnosed gastrointestinal emergency that frequently requires hospitalization and admission to the intensive care unit (ICU). Despite a trend of decline in the mortality globally in the last 30 years for AP, the mortality rate of severe AP (SAP) is around 50% and is directly related to both duration as well as severity of persistent organ failure (POF)[1,2].

SAP is a recognized risk factor for intra–abdominal hypertension (IAH). The growing evidence emphasizes the importance of IAH in the pathophysiology of both new-onset as well as POF during the early phase of SAP[3-5]. The pathophysiological mechanisms that underlie IAH among SAP patients is yet to be explored in detail. A possible pathogenesis involves systemic inflammation because of the disease process, which in turn results in capillary leak and fluid sequestration, thus exhibiting retroperitoneal, visceral and bowel edema, ascites, and paralytic ileus. Gastric dilatation, abdominal pain with muscle contraction, and overzealous fluid administration for management of SAP tend to either sustain or exacerbates IAH[5-7]. However, once the IAH gets established, its clinical features overlap with that of SAP and are characterized either by rapid progression or new-onset of organ dysfunction. The incidence rate of IAH, among the patients with AP, varies in different studies and increases with severity, *i.e.*, it reaches up to 50% in patients with SAP[4]. Abdominal compartment syndrome (ACS) is defined as a sustained elevation of intra-abdominal pressure (IAP) of more than 20 mmHg and is associated with new onset organ dysfunction or failure, and also reflects an unabated progression of the IAH[8].

The prevalence rate of ACS among SAP patients is between 15% to 30%. The resultant multi-organ dysfunction observed in ACS, especially the respiratory and renal dysfunction, contributes to high morbidity and mortality rates in SAP[6,9]. On the other hand, the poly-compartment syndrome, characterized by simultaneous elevation of pressure in different compartments, is an extreme association of ACS that causes multi-organ dysfunction and requires immediate intervention[10]. ACS is a potentially-lethal complication with a staggering 50%-75% mortality rate among the patients diagnosed with SAP and ACS[11,12].

The optimal management of ACS involves a multi-disciplinary approach that starts from early recognition of the condition to initiating measures that are aimed at urgent reduction of IAP[13]. The 2013 consensus management guidelines of the Abdominal Compartment Society (www.wsacs.org) on IAH and ACS, recommended 'decompressive laparotomy' as an effective core strategic component in managing the overt ACS. In spite of the recommendation, the guidelines also acknowledged the morbidity risks involved in open abdomen and the associated complications such as the development of frozen abdomen and enterocutaneous fistula[8]. Moreover, the guidelines fail to specify recommendations for optimal timing, disease-specific patient selection and the role of less-invasive decompressive measures such as subcutaneous linea alba fasciotomy or component separation techniques. The morbidity of the open abdomen, after

performing the decompressive laparotomy, should be weighed prior to the procedure against the potentially-lethal inadequately-treated ACS. In this background, the aim of the current paper is to systematically review the evidence on patient selection, optimal techniques and the uncertainties in evidence regarding surgical decompressive technique for the management of ACS and SAP.

LITERATURE REVIEW

For the current review paper, a targeted literature search was conducted through PubMed, Science Direct, *Reference Citation Analysis* (*RCA*), and Google Scholar using the MeSH keywords such as 'Laparotomy' OR 'Intra–Abdominal Hypertension' AND 'Acute Pancreatitis' and the study published between January 1, 2000 and November 30, 2022 was considered and the search revealed 16 results. When broader keywords such as 'Intra-Abdominal Hypertension' AND 'Acute Pancreatitis' were used for the same period, a total of 82 studies were found. Then, a total of 21 studies were analyzed through manual screening by the authors (Nasa P and Chanchalani G), excluding the reviews, non-human studies and non-English literature (Tables 1 and 2)[11,12,14-31]. One study was excluded due to unclear indications for surgical intervention[32]. The data was extracted from the selected studies with regards to type and country of the study, patient demographics, IAP value, type and timing of the surgical procedure performed, post-operative wound management, and the outcomes of patients with ACS.

Statistical analysis

The categorical variables were presented as frequency and percentage. Median [interquartile range (IQR)] or mean ± SD was used for continuous variables. A forest plot was drawn with standardized mean difference (SMD) and 95% confidence interval (CI) to exhibit the changes in IAP after surgical decompression with midline laparotomy. Unless otherwise indicated, all the statistical analyses were performed using SPSS (version 25.0, IBM SPSS Inc., Chicago, IL, United States).

RESULTS

No randomized controlled trial (RCT) was found in this topic. Out of the 20 studies considered for the analysis, 11 were observational and nine (81.8%) were retrospective while four (36.4%) studies were from China which included two large-scale studies (with 94 and 273 patients, respectively). The median of the 20 (IQR = 14) patients with ACS was included in these studies, which ranged from 8 to 273 patients. A male predominance was observed in the results, with a mean age above 40 years; alcohol use and biliary pancreatitis were the most common etiology. Both lungs and kidneys were the two most common organ dysfunctions observed in all the studies (Table 1).

Out of the 225 patients who underwent surgical decompression for ACS in the observational studies, 200 (88.9%) patients underwent midline laparotomy. The rest of the patients also underwent other surgical procedures such as subcutaneous linea alba fasciotomy (17 patients, 7.5%) and subcostal laparostomy (8 patients, 3.6%). There was a considerable decline in IAP rate after the decompression surgery was performed using midline laparotomy (SMD = 2.68, 95%CI: 1.19-1.47, $P < 0.001$; 4 studies) among patients with ACS (Figure 1)[11,12,17,19]. Most of the patients underwent a secondary abdominal closure. The mortality rate, reported in different studies, varied widely from 12.5% to 75%. Further, the studies that included more than 25 patients reported a mortality rate between 25%-75% (Table 3)[11,12,14-22].

For the current review, a total of 17 patients, with a mean age of 45.7 ± 13.8 years from six case reports and three case series with individual patient data, was analyzed separately. Out of the total 17 patients, six (35.2%) were females. Alcohol use (8, 47.1%) and biliary (4, 23.5%) were found to be the common etiologies of AP. The mean cumulative fluid balance of eight patients after 24 h was 5698.7 ± 2638 mL. All the patients required invasive mechanical ventilation whereas eight patients (47.1%) required vasopressors (Table 2). Most patients (14, 82.4%) underwent midline laparotomy and delayed vacuum-assisted closure (VAC) (13, 76.5%). The median number of days of open abdomen was 18 (IQR = 42) while the total time was in the range of 2 to 210 d. The median ICU and hospital length of stay were 30 (IQR = 15) d and 54 (IQR = 41.5) d, respectively, with only one fatal outcome (5.9%). The abdomen was primarily closed in only one patient whereas the rest (16/17, 94.1%) of the patients managed with an open abdomen and delayed primary closure, assisted with VAC, for 10 d to 7 mo. Only one out of the 18 patients died (Table 4).

DISCUSSION

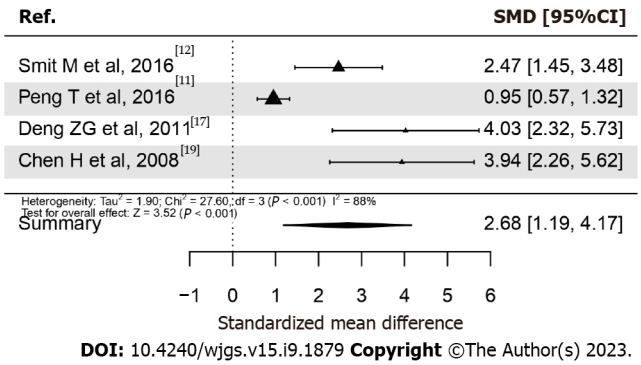
General findings

SAP is a common risk factor of ACS with considerable morbidity and mortality rates, despite the existence of established treatment methods[33,34]. The demography of the patients with ACS was found to be similar like AP patients *i.e.*, a mean age of 40 years and a male predominance. Biliary and alcohol-related factors were found to be the most common etiologies for AP[1]. Elevated IAP, especially ACS are detrimental, not only for the intra-abdominal organs like kidneys, intestines and liver, but it may also impact other organs such as heart, lungs, and brain[10,35,36]. The guidelines recommend an early recognition of ACS using IAP measurement and urgent management in case of positive IAH[8,37].

Table 1 Demographic data of observational studies on abdominal compartment syndrome with acute pancreatitis

Ref.	Country of origin	Type of study	Number of patients with ACS/total studied patients	Etiology of acute pancreatitis, *n* (%)	Age (yr), mean ± SD, median (IQR)	Female, *n* (%)
Husu *et al*[22], 2021	Finland	Retrospective matched-case control	OA: 40/47 (85.1%). CG: 21/47 (44.7%)	Alcohol: 85% (OA), 72% (CG). Biliary: 4.3% (OA), 14.9% (CG). HTG: 4.3% (OA), 2.1% (CG)	OA: 49 (27-82). CG: 50 (18-78)	OA: 10.6%. CG: 12.8%
Smit *et al*[12], 2016	Netherlands	Retrospective	13/29 (44.8%)	Biliary: 40.7%. Alcohol: 22%	55 ± 15	3 (23%)
Peng *et al*[11], 2016	China	Retrospective	273/273 (100%)	Biliary: 41%. Alcohol: 30%. Post ERCP: 10%	46 (17-78)	26 (42.6%)
Davis *et al*[14], 2013	Canada	Retrospective	16/45 (35.6%)	Biliary: 53%. Alcohol: 26.7%	59 ± 13	9 (20%)
Boone *et al*[15], 2013	United States	Retrospective	12/12 (100%)	Biliary: 41.7%. Alcohol: 33.3%	56 ± 13	1 (8.3%)
Leppäniemi *et al*[16], 2011	Finland	Retrospective	10/10 (100%)	Alcohol: 9 (90%). Drug: 1 (10%)	46 (33-61)	1 (10%)
Deng *et al*[17], 2011	China	Retrospective	8/8 (100%)	Alcohol: 8/8	51.5 (35-66)	2 (25%)
Mentula *et al*[18], 2010	Finland	Retrospective	26/26 (100%)	Alcohol: 81%. Drug: 8%. Post ERCP: 4%	42 (35-49)	3 (11.5%)
Chen *et al*[19], 2008	China	Retrospective	20/44 (45.5%)	Biliary: 59.1%. Alcohol: 11.4%. HTG: 15.9%	62.6 ± 11.1	21 (47.7%)
De Waele *et al*[20], 2005	Belgium	Prospective	21/44 (47.7%)	Biliary: 33%. Alcohol: 38%. HTG: 14%	53 (45-68)	16 (45.5%)
Tao *et al*[21], 2003	China	Retrospective	23/23 (100%)	NA	41(31-71)	7 (33%)

ACS: Abdominal compartment syndrome; OA: Open abdomen; CG: Control group; HTG: Hypertriglyceridemia, ERCP: Endoscopic retrograde cholangiopancreatography; NA: Not available; IQR: Interquartile range.



DOI: 10.4240/wjgs.v15.i9.1879

Figure 1 Forest plot of observation studies showing the mean change in intra-abdominal pressure before and after surgical decompression after midline laparotomy. SMD: Standardized mean difference; CI: Confidence interval.

Medical management

SAP treatment is primarily a supportive one, except for acute gallstone pancreatitis. However, the guidelines are controversial in terms of the role played by urgent endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy in managing the acute gallstone pancreatitis[37]. In a recently-conducted multi-center RCT, an urgent ERCP with sphincterotomy was compared with a conservative treatment to treat the acute gallstone pancreatitis without cholangitis. The study found no significant difference in the primary endpoint *i.e.*, a composite outcome of mortality and major complications such as new-onset POF, cholangitis, bacteremia, pneumonia, pancreatic necrosis, or pancreatic insufficiency at six months from the randomization[38]. Hence, ERCP should be considered only for acute severe gallstone pancreatitis associated with cholangitis or persistent cholestasis.

The management of ACS among patients with SAP depends on its severity and the course of the primary disease. The treatment ranges from conservative medical management to surgical decompression laparotomy. The medical

Table 2 Demographic data of case reports or case series on abdominal compartment syndrome with acute pancreatitis

Ref.	Origin of study	Age (yr)/sex	Etiology of acute pancreatitis	Cumulative fluid balance after 24 h (mL)	Cumulative fluid balance after 48 h (mL)	IAP (mmHg) at diagnosis, after decompression	Organ support
Kawasaki *et al*[23], 2022	Japan	42/female	Alcohol-use	10000	NA	52, 30	Mechanical ventilation, RRT
Lee *et al*[27], 2019	Australia	38/male	Alcohol-use	6000		28, NA	Mechanical ventilation, vasopressors
Ikeda *et al*[28], 2019	Japan	65/female	Biliary	NA	NA	22, NA	Mechanical ventilation, vasopressors
McKenzie *et al*[31], 2017	United States	45/male	Biliary	NA	NA	> 20, NA	RRT, mechanical ventilation
Simoneau *et al*[30], 2014	Canada	67/male	Biliary	NA	NA	NA	Mechanical ventilation
Jacob *et al*[29], 2016	Australia	30/male	Alcohol-use	3930	3600	31, NA	RRT, mechanical ventilation, vasopressors
Jacob *et al*[29], 2016	Australia	40/male	Alcohol-use	4400	3600	33, NA	RRT, mechanical ventilation, vasopressors
Jacob *et al*[29], 2016	Australia	32/female	Alcohol-use	4560	3700	28, NA	Mechanical ventilation, vasopressors
Jacob *et al*[29], 2016	Australia	42/male	Alcohol-use	2500	7500	30, NA	RRT, mechanical ventilation, vasopressors
Jacob *et al*[29], 2016	Australia	28/male	Alcohol-use	4200	3650	28, NA	Mechanical ventilation, vasopressors
Siebig *et al*[25], 2008	Germany	56/male	Other	NA	NA	NA	Mechanical ventilation, vasopressors, ECMO
Siebig *et al*[25], 2008	Germany	49/male	Biliary	10000	7000	> 25, NA	Mechanical ventilation
Siebig *et al*[25], 2008	Germany	74/female	Post-surgery	NA	NA	> 20, NA	Mechanical ventilation
De Waele *et al*[26], 2005	Belgium	37/male	Alcohol-use	NA	NA	27, NA	Mechanical ventilation
Hu *et al*[24], 2013	China	27/male	Biliary	NA	NA	26, 15	Mechanical ventilation
Hu *et al*[24], 2013	China	60/female	HTG	NA	NA	25, 17	Mechanical ventilation
Hu *et al*[24], 2013	China	45/female	HTG	NA	NA	22, 14	Mechanical ventilation

IAP: Intraabdominal pressure; RRT: Renal replacement therapy; HTG: Hypertriglyceridemia; ERCP: Endoscopic retrograde cholangiopancreatography; ECMO: Extracorporeal membrane oxygenation; NA: Not available.

management includes hemodynamic support and the optimization of regional and systemic perfusion, improvement of abdominal compliance (*e.g.*, with adequate sedation and analgesia with or without neuromuscular blockade) and reduction of intra-luminal volume (*e.g.*, with nasogastric or colonic decompression) or reduction of intra-abdominal volume (*e.g.*, paracentesis)[7,34,39].

Fluid management

The local and systemic inflammation of the AP results in extravascular fluid accumulation and the depletion of intravascular fluid[7]. Hence, the AP management guidelines recommend early rapid hydration to restore the intravascular volume, improve circulatory dysfunction and ameliorate both tissue and organ dysfunction[37,39].

Table 3 Outcomes data from observational studies on abdominal compartment syndrome with acute pancreatitis

Ref.	IAP (mmHg), mean ± SD (range)		Organ dysfunction	Surgical decompression, including type of surgery	Time to intervention from hospitalization, diagnosis of ACS	Outcome	Post-decompressions complications
	Pre-surgery	Post-surgery					
Husu *et al* [22], 2021	OA: 24 ± 4. CG: 21 ± 5	NA	SOFA: OA: 13 (11-14); CG: 12 (10-15). APACHE II: OA: 23 (17-29); CG: 18 (15-26)	ML in OA: 47/47 (100%)	60 (36-175) h, NA	90 d. mortality: OA: 19/40 (48%); CG: 3/21 (14%)	
Smit *et al* [12], 2016	27 ± 3	18 ± 4	13/13 (100%). AKI: 100%. Respiratory failure: 100%. Shock: 100%	10 (76.9%). ML: 3 (33%). Subcostal full-thickness laparostomy: 7 (67%)	13.4 ± 6.5 d, 12 (2-176) h	Mortality: 7 (53.8%). LOS ICU: 48 d. GI ischemia: 61.5%	Bowel perforation or fistula: 46.2%
Peng *et al* [11], 2016	PCD: 31 (20-44). ML: 34 (20-51)	PCD: 19 (3-40). ML: 15 (2-24)	SOFA: PCD-11(2-23), ML-10 (3-24), decreased to 9 (2-24) and 9 (3-24)	ML: 61/273 (22.3%). PCD: 212/273 (77.7%)	PCD: 61 (2-101) h. ML: 64 (5-95) h	Mortality: PCD: 40 (19%); ML: 32 (52%). LOS hospital: 125 (21-627) d. LOS ICU: PCD: 14 d, ML: 21 d. Subsequent necrosectomy in PCD: 160 (75%), ML: 49 (80%)	Hepatic/portal/superior mesenteric vein/splanchnic vein thrombosis: ML: 3.2%, PCD: 0.9%. Bleeding: ML: 11.4%, PCD: 3.8%. Fistula: ML: 24.6%, PCD:18.4%
Davis *et al* [14], 2013	29.5	NA	AKI: 5 (31.3%). Respiratory failure: 11 (68.8%)	16 (35.6%). ML: 100%	NA, 3.1 h	Mortality: 4 (25%). LOS hospital: 146 d	Fistula: 62.5%. Wound infection: 62.5%. Incisional Hernia: 50%
Boone *et al* [15], 2013	42	NA	Mean APACHE: 23.3. Mean ranson: 9	12 (100%). ML: 12 (100%)	< 7 d in 9 patients, NA	Mortality: 6 (50%). Among survivors: LOS ICU: 37 ± 13 d; LOS hospital: 40.5 ± 25.2 d; IMV: 28 ± 11.4 d	Infection: 16%. Fistula: 16%
Leppäniemi *et al*[16], 2011	31 (23-45)	11 (1-20)	Mean SOFA: 12 (14-17)	Subcutaneous linea alba fasciotomy: 10 (100%). Subsequently, four required completion laparostomy	1-17 d (in 6 cases: < 48 h), NA	Mortality: 4 (40%). LOS hospital: 35 d; LOS ICU: 26 d	Hernia: 30%. Bleeding: 20%. Wound infection: 10%. Fistula: 10%
Deng *et al* [17], 2011	29 (23-38)	7.5 (6-18)	Resp failure: 8 (100%). AKI: 7 (87.5%). Hepatic: 7 (87.5%). Shock-8 (100%)	8 (100%). ML plus continuous regional arterial infusion with protease inhibitors and antibiotics *via* a drug delivery system	3-9 d, NA	Mortality: 1(12.5%), LOS-ICU: 41 d, LOS-hospital- 117 d	Not mentioned
Mentula *et al*[18], 2010	31.5 (27-35)	NA	Resp failure: 24 (92%). AKI: 14 (54%). Shock: 23 (88%). Liver: 2 (8%)	26 (100%). ML: 18 (69.2%). Bilateral subcostal laparostomy: 1 (3.8%). SLAF: 7, 2/7 finally laparostomy	1 (0-29) d, NA	Mortality: 12/26 (46.2%)	Intrabdominal infection: 73%. Fistula: 19%
Chen *et al* [19], 2008	36.7 ± 5.3	18.3 ± 3.3	MODS: 18 (90%). Shock: 14 (70%)	8 (65%). PCD: 5 (25%). ML: 5 (25%). Combined: 3 (15%)	NA, 28.38 ± 2.29 h	Mortality: 15/20 (75%)	No complications reported
De Waele *et al*[20], 2005	> 25	NA	Resp failure: 20 (98%). AKI: 18 (86%). Shock: 19 (94%)	ML: 4/21. Indication for surgery: ACS: 4 (44.4%)	3, < 24 h	Mortality: 3/4 (75%). LOS ICU: 21 (10-37) d. LOS hospital: 42 (20-90) d. IMV: 15 (12.6) d	No complications reported
Tao *et al* [21], 2003	> 20	NA	Resp. failure: 100%. Shock: 100%	18/23 (78.2%). ML with drainage: 100%	NA, 5-22 h	Mortality: 3/18 (16.7%). Definitive closures 3-5 d	Hemorrhage: 42%. Abscess: 19.2%. Perforation/fistula: 3.8%

IAP: Intrabdominal pressure; SOFA: Sequential organ failure assessment; APACHE II: Acute physiology and chronic health evaluation; MODS: Muti-organ dysfunction syndrome; PCD: Percutaneous drainage; ML: Midline laparotomy; ACS: Abdominal compartment syndrome; OA: Open abdomen; CG: Control group; AKI: Acute kidney injury; SD: Standard deviation; SLAF: Subcutaneous line alba fasciotomy; ICU: Intensive care unit; LOS: Length of stay; IMV: Invasive mechanical ventilation; NA: Not available.

Table 4 Demographic data of case reports or case series on abdominal compartment syndrome with acute pancreatitis

Ref.	Type of surgery	Timing of the laparotomy from the diagnosis or admission	Abdomen closed after laparotomy	Management of open abdomen	Duration of open abdomen (d)	Outcome	Duration of ICU stay (d)	Duration of hospital stay (d)	Complications
Kawasaki *et al*[23], 2022	Midline fasciotomy	4 d	No	VAC	7	Alive	29	53	None
Lee *et al* [27], 2019	Midline laparotomy	24 h	No	VAC	75	Alive	44	121	None
Ikeda *et al* [28], 2019	Midline laparotomy	4 h	No	Open with mesh	2	Alive	NA	104	None
McKenzie *et al*[31], 2017	Midline laparotomy	24 h	No	VAC	10	Alive	NA	NA	None
Jacob *et al* [29], 2016	Midline laparotomy	5 h	No	VAC	21	Alive	NA	35	Pancreatic fistula: 4 (80%)
Jacob *et al* [29], 2016	Midline laparotomy	1 d	No	VAC	18	Alive	NA	54	
Jacob *et al* [29], 2016	Midline laparotomy	4 d	No	VAC	15	Alive	22	43	
Jacob *et al* [29], 2016	Midline laparotomy	2 d	No	VAC	18	Alive	30	49	
Jacob *et al* [29], 2016	Midline laparotomy	2 d	No	VAC	10	Alive	32	62	
Simoneau *et al*[30], 2014	Midline laparotomy	12 h	No	VAC and vicryl mesh	210	Alive	210	300	Pancreatic fistula
Hu *et al* [24], 2013	Transverse laparotomy	NA	NA	NA	NA	Alive	NA	71	None
Hu *et al* [24], 2013	Transverse laparotomy	NA	NA	NA	NA	Alive	NA	54	None
Hu *et al* [24], 2013	Transverse laparotomy	NA	NA	NA	NA	Alive	NA	31	None
Siebig *et al* [25], 2008	Midline laparotomy	1 d	Yes	NA	NA	Alive	NA	NA	None
Siebig *et al* [25], 2008	Midline laparotomy	1 d	No	VAC	NA	Death	NA	NA	Lung hemorrhage
Siebig *et al* [25], 2008	Midline laparotomy	< 24 h	No	VAC	90	Alive	NA	NA	None
De Waele *et al*[26], 2005	Midline laparotomy	24 h	No	VAC	29	Alive	NA	NA	Intraabdominal infection

VAC: Vacuum-assisted closure; NA: Not available; ICU: Intensive care unit.

However, injudicious and aggressive fluid resuscitation may propagate fluid accumulation, increase the risk of fluid overload and promote or exacerbate the secondary IAH or ACS. Moreover, the fluid accumulation also impairs the wound healing process which in turn promotes infection[7].

In a recently-published RCT, the incidence of ACS was found to be lower (32.5% *vs* 72.2%, $P < 0.05$) with controlled intravenous fluid administration than the rapid fluid expansion[40]. In another recent RCT, the goal-directed fluid administration was found to be associated with less fluid overload among AP patients than the early aggressive fluid resuscitation method. However, no significant or meaningful difference was found in terms of clinical outcomes[41]. Fluid management in IAH patients is a challenging task that needs to be individualized and titrated to the clinical endpoints[7,42]. Besides, the intravenous fluid administration in patients with IAH may not ameliorate organ dysfunction despite increasing the cardiac output. Functional hemodynamic monitoring such as pulse pressure or stroke volume variation should be considered prior to fluid administration in these patients[43]. On the other hand, fluid removal may be considered for selected IAH patients using diuretics or continuous veno-venous hemofiltration so as to achieve negative fluid balance[44].

Surgical management

Patients with SAP who develop ACS have extremely high chances of mortality and so, early recognition of this condition and timely intervention may help in improving the organs' functions, morbidity and mortality[39,45]. A high incidence of visceral ischemia was found among the patients with SAP and ACS, thus contributing to a high mortality rate of this group of patients[14].

Various surgical interventions have been tried in patients with ACS, who failed the medical management process. Ultrasound or computed tomography scan-guided percutaneous drainage of intra-abdominal collections is a minimally-invasive procedure available to reduce the IAP in selected patients[12,21]. However, urgent surgical decompression is highly effective and potentially, a life–saving treatment for ACS, especially in those patients with refractory ACS. Decompressive laparotomy helps in improving the abdominal compliance by rapidly lowering the IAP[10,39,45]. In this review, the authors found a significant reduction of IAP after surgical decompression in four observational studies that measured pre- and post-decompression IAP levels. However, the impact of surgical decompression on multi-organ dysfunction was found to vary. In porcine model that involved 32 animals with SAP and ACS, the early surgical decompression (within 6 h) was associated with a significant improvement in systemic hemodynamics, alleviation of organ dysfunction and reduced mortality rate compared to the decompression performed at 9 or 12 h[46]. In a retrospective study conducted by Mentula *et al*[18], the surgical decompression procedure improved both respiratory as well as renal functions in nearly half of the patients. A prominent improvement was observed in respiratory function only among those patients with severe hypoxemia[18,20]. Further, early surgical decompression was also found to be associated with reduced mortality[18]. However, high morbidity and the complications associated with open abdomen like ventral hernia, frozen abdomen, pancreatic and enterocutaneous fistula and sepsis result in the recommendation of surgical decompression by the guidelines, only after the failure of medical management to reduce IAP[9,13,41]. Nonetheless, a patient–centric approach and the role of clinical evaluation beyond IAP are lacking in these guidelines[8, 9]. In addition to this, there is a lack of evidence and agreement regarding IAP values, timing, and the techniques that may trigger surgical decompression.

Surgical decompression technique

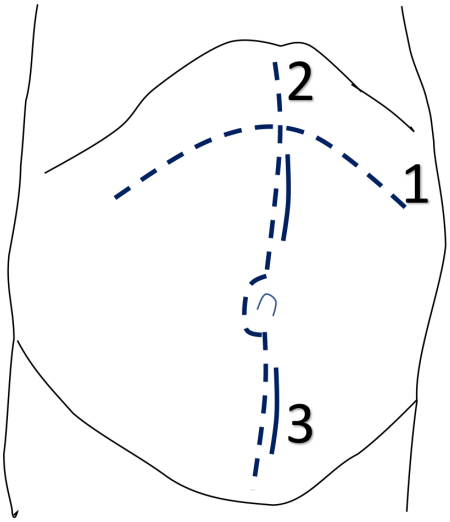
No trials have been conducted so far, comparing the surgical technique for decompression. Often, the choice is individualized as per the available expertise and common sense. The current review found that midline laparotomy is the most common surgical procedure performed for decompression. Midline laparotomy involves a full–thickness (skin, fascia, peritoneum) vertical midline skin incision from xiphoid to pubis.

Midline decompressive laparotomy can rapidly reduce IAP and improve organ dysfunction like hemodynamic, respiratory and renal dysfunctions[18,36]. Other surgical approaches, reported in the literature, include full-thickness bilateral subcostal transverse laparotomy and subcutaneous linea alba fasciotomy (Figure 2). Transverse laparotomy is a quick procedure with a high success rate for fascial closure. However, the incision is done upon the abdominal muscles (rectus and external oblique), which may require a complete reconstruction with temporary mesh in case of loss or retraction of fascia[12,18,24]. On the other hand, subcutaneous linea alba fasciotomy is a less invasive approach that involves 2-3 skin incisions at the linea alba, without opening the peritoneal cavity[47]. It avoids both morbidity and the complications associated with open abdomen. Further, the procedure can also be used as a bridge before committing to perform decompression laparotomy[48]. However, the success rate is only 50%-70%, with a higher risk of incisional hernia[16,49].

Timing of surgery

The timing of surgical decompression is a matter of ongoing debate. The dichotomy of early *vs* late decompression should consider a variety of factors. The meta-analysis of 15 studies (that included both adults and children) by Van Damme *et al* [45], demonstrated the effectiveness of surgical decompression in reducing the IAP and halting the progression of systemic organ failure. However, the overall mortality was 49.7% in adults. In the current review, the authors found the mortality of patients with ACS varied between 25%-75% in spite of undergoing surgical decompression. Higher mortality, observed in these patients, may reveal the higher severity of the disease at the baseline. Another hypothesis is that the delay in the surgical intervention, in the background of progressive multi–organ failure and irreversible visceral ischemia, contributed to higher mortality of these patients[22]. The patients, in most of the studies included, underwent surgical decompression after the failure of medical management whereas the granular data on patients who may benefit from early surgical decompression was missing.

As mentioned earlier, Mentula *et al*[18] found that early surgical decompression (within the first four days of diagnosis) in patients with IAP > 25 mmHg can be associated with low mortality (18% *vs* 46%). Tao *et al*[21] observed the mortality



DOI: 10.4240/wjgs.v15.i9.1879

Figure 2 Techniques of surgical decompression for abdominal compartment syndrome. 1: Bilateral subcostal transverse laparotomy; 2: Midline laparotomy; 3: Subcutaneous linea alba fasciotomy.

rate to be merely 16.7% in 18 patients with surgical decompression for ACS and SAP. For these patients, definitive closure was performed within 3-5 d of surgical decompression. An early intervention (5-22 h after the diagnosis of ACS) and using a lower IAP trigger (> 20 mmHg) could explain about the better outcomes[21]. This outcome aligns with the guidelines that suggest an early closure within the first week, or whenever feasible, to reduce the complications. However, various factors should be considered prior to decision of early closure is made, such as the resolution of cardio-respiratory compromise, no further surgical exploration being considered and no concerns for the recurrence of ACS[50].

In the absence of high–quality evidence, the timing of the surgery should be individualized based on the factors such as the evolution of IAP over time, the severity of organ dysfunction and the response to medical management.

Triggers for surgical decompression

Most of the studies did not identify any cut–off for IAP to guide the surgical decompression whereas intervention was primarily implemented based on the rapid progression of organ dysfunction and medical management failure. The largest retrospective study, conducted on ACS in SAP, found the percutaneous catheter drainage to be superior to open laparotomy with temporary closure, in terms of reducing the need for ICU stay, complications, and mortality. However, open laparotomy was found to be highly effective than the percutaneous drainage procedure in immediate restoration of the physiological variables like hemodynamics or oxygenation (PaO2/FiO2 ratio). The higher mortality in open laparotomy group was linked to increased rate of infections (100% *vs* 55%, $P < 0.001$) and complications (80% *vs* 41%, $P < 0.001$)[11]. However, the patients were recruited in this study only after the failure of medical management whereas those patients with a need for immediate surgery were excluded. There are no studies available so far on prophylactic surgical management to reduce the risk of ACS. The results of the only multi-centric, randomized controlled study (the DECOMPRESS study) comparing decompressive laparotomy and percutaneous drainage are yet to be published[51]. The potential triggers for surgical decompression include compromised oxygenation and/or ventilation, hemodynamic instability and worsening organ dysfunction, despite medical management.

Post-surgical decompression complications

Midline laparotomy with temporary abdominal closure (TAC) is associated with its own complications such as infection, bleeding, fistula, failed fascia closure and incisional hernia. The incidence rate of these complications varied in different studies (Tables 3 and 4). Peng *et al*[11] found a high complication rate in patients with open laparotomy compared to percutaneous drainage (80% *vs* 41%; $P < 0.001$). Fistula (24.6%), especially pancreatic (7.5%), and bleeding (11.4%) were the common complications. Further hepatic, portal, or mesenteric vein thrombosis were also reported in 2 (3.2%) patients.

Open abdomen management

In general, the presence of open abdomen is the consequence after surgical decompression for ACS, because of the need for frequent re-operations and the risk of recurrence. However, it is challenging to manage the open abdomen after surgical decompression as it needs a careful and a dynamic plan. Open abdomen can be managed with TAC techniques like skin-only closure, mesh, bags (*e.g.*, Bogota bag) or the use of a non-adhesive plastic layer (*e.g.*, polyethylene film, opposite dressings), non-absorbable zipper or VAC therapy with close monitoring of IAP for recurrence of IAH[48,51,52]. A common misconception is that open abdomen protects against the recurrence of IAH and ACS, though it is not the case. TAC reduces the complications of an open abdomen like evisceration, contamination, fluid and temperature loss, enterocutaneous fistula, and fascial retraction[53,54].

The current review found that the primary closure got delayed in most of the studies. The least early closure rate in these patients can be explained by the risks involved in recurring IAH after early closure, reported higher rate of intra-abdominal infections, and fistula[11]. Further, a higher proportion of these patients developed infected necrotizing pancreatitis that requires multiple episodes of necrosectomy[18].

In the meta-analysis of randomized and case-controlled studies, the negative pressure wound therapy or VAC for the open abdomen was found to be associated with better outcomes[55]. Negative pressure wound therapy or VAC is also recommended by an international expert panel as the preferred technique for the management of open abdomen[50,56]. VAC has been used in most of the patients in published case reports and case series. When leaving the abdomen open, the most crucial issue is to plan for its closure again. If one fails to plan the closure within the first week after opening, then the possibilities are high for failure with a ventral hernia repair at a later stage.

CONCLUSION

Patients with SAP are prone to develop IAH and ACS and are at risk for worse outcomes. Anticipation and regular monitoring of IAP and organ function are necessary for a timely diagnosis of ACS in patients with SAP. It is challenging to manage ACS in patients with SAP since it needs a multi-modal approach. Surgical decompression is an effective intervention, which can rapidly reduce the IAP and may be considered only in those patients with progressive cardio-respiratory compromise or medical management failure. There is a lack of quality evidence on a few parameters such as the patient selection, timing, and the modality of surgical decompression. Further research is required in this domain in the form of large, prospective controlled trials to identify the triggers and effective and safe modality of surgical decompression in patients with ACS and SAP.

FOOTNOTES

Author contributions: Nasa P conceptualized and designed the article; Nasa P and Chanchalani G performed acquisition of data, analysis and interpretation of data, and drafted the article; Juneja D and Malbrain ML revised the article; and all authors have read and approved the final manuscript.

Conflict-of-interest statement: Nasa P declared to be on the advisory board of Edwards life sciences. Malbrain ML is Professor of Critical Care Research at the 1st Department of Anesthesiology and Intensive Therapy, Medical University of Lublin, Poland. He is co-founder, past-President and current Treasurer of WSACS (The Abdominal Compartment Society, http://www.wsacs.org). He is member of the medical advisory Board of Pulsion Medical Systems (now fully part of Getinge group), Serenno Medical, Potrero Medical, Sentinel Medical and Baxter. He consults for B. Braun, Becton Dickinson, ConvaTec, Spiegelberg, Medtronic, MedCaptain, and Holtech Medical, and received speaker's fees from PeerVoice. He holds stock options for Serenno and Potrero. He is co-founder and President of the International Fluid Academy (IFA). The IFA (http://www.fluidacademy.org) is integrated within the not-for-profit charitable organization iMERiT, International Medical Education and Research Initiative, under Belgian law. Other authors do not declare any conflict of interest in relation to the content of the present paper.

Country/Territory of origin: United Arab Emirates

ORCID number: Prashant Nasa 0000-0003-1948-4060; Gunjan Chanchalani 0000-0001-8429-8526; Deven Juneja 0000-0002-8841-5678; Manu LNG Malbrain 0000-0002-1816-5255.

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

REFERENCES

1 **Li CL**, Jiang M, Pan CQ, Li J, Xu LG. The global, regional, and national burden of acute pancreatitis in 204 countries and territories, 1990-2019. *BMC Gastroenterol* 2021; **21**: 332 [PMID: 34433418 DOI: 10.1186/s12876-021-01906-2]

2 **Shi N**, Liu T, de la Iglesia-Garcia D, Deng L, Jin T, Lan L, Zhu P, Hu W, Zhou Z, Singh V, Dominguez-Munoz JE, Windsor J, Huang W, Xia Q, Sutton R. Duration of organ failure impacts mortality in acute pancreatitis. *Gut* 2020; **69**: 604-605 [PMID: 31233394 DOI: 10.1136/gutjnl-2019-318241]

3 **Jaipuria J**, Bhandari V, Chawla AS, Singh M. Intra-abdominal pressure: Time ripe to revise management guidelines of acute pancreatitis? *World J Gastrointest Pathophysiol* 2016; **7**: 186-198 [PMID: 26909242 DOI: 10.4291/wjgp.v7.i1.186]

4 **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]

5 **De Waele JJ**, Ejike JC, Leppäniemi A, De Keulenaer BL, De Laet I, Kirkpatrick AW, Roberts DJ, Kimball E, Ivatury R, Malbrain ML. Intra-abdominal hypertension and abdominal compartment syndrome in pancreatitis, paediatrics, and trauma. *Anaesthesiol Intensive Ther* 2015; **47**: 219-227 [PMID: 25973660 DOI: 10.5603/AIT.a2015.0027]

6 **Siebert M**, Le Fouler A, Sitbon N, Cohen J, Abba J, Poupardin E. Management of abdominal compartment syndrome in acute pancreatitis. *J Visc Surg* 2021; **158**: 411-419 [PMID: 33516625 DOI: 10.1016/j.jviscsurg.2021.01.001]

7 **Jacobs R**, Wise RD, Myatchin I, Vanhonacker D, Minini A, Mekeirele M, Kirkpatrick AW, Pereira BM, Sugrue M, De Keulenaer B, Bodnar Z, Acosta S, Ejike J, Tayebi S, Stiens J, Cordemans C, Van Regenmortel N, Elbers PWG, Monnet X, Wong A, Dabrowski W, Jorens PG, De Waele JJ, Roberts DJ, Kimball E, Reintam Blaser A, Malbrain MLNG. Fluid Management, Intra-Abdominal Hypertension and the Abdominal Compartment Syndrome: A Narrative Review. *Life (Basel)* 2022; **12** [PMID: 36143427 DOI: 10.3390/life12091390]

8 **Kirkpatrick AW**, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, Duchesne J, Bjorck M, Leppaniemi A, Ejike JC, Sugrue M, Cheatham M, Ivatury R, Ball CG, Reintam Blaser A, Regli A, Balogh ZJ, D'Amours S, Debergh D, Kaplan M, Kimball E, Olvera C; Pediatric Guidelines Sub-Committee for the World Society of the Abdominal Compartment Syndrome. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med* 2013; **39**: 1190-1206 [PMID: 23673399 DOI: 10.1007/s00134-013-2906-z]

9 **De Laet IE**, Malbrain MLNG, De Waele JJ. A Clinician's Guide to Management of Intra-abdominal Hypertension and Abdominal Compartment Syndrome in Critically Ill Patients. *Crit Care* 2020; **24**: 97 [PMID: 32204721 DOI: 10.1186/s13054-020-2782-1]

10 **Malbrain ML**, Peeters Y, Wise R. The neglected role of abdominal compliance in organ-organ interactions. *Crit Care* 2016; **20**: 67 [PMID: 26983963 DOI: 10.1186/s13054-016-1220-x]

11 **Peng T**, Dong LM, Zhao X, Xiong JX, Zhou F, Tao J, Cui J, Yang ZY. Minimally invasive percutaneous catheter drainage versus open laparotomy with temporary closure for treatment of abdominal compartment syndrome in patients with early-stage severe acute pancreatitis. *J Huazhong Univ Sci Technolog Med Sci* 2016; **36**: 99-105 [PMID: 26838748 DOI: 10.1007/s11596-016-1549-z]

12 **Smit M**, Buddingh KT, Bosma B, Nieuwenhuijs VB, Hofker HS, Zijlstra JG. Abdominal Compartment Syndrome and Intra-abdominal Ischemia in Patients with Severe Acute Pancreatitis. *World J Surg* 2016; **40**: 1454-1461 [PMID: 26830909 DOI: 10.1007/s00268-015-3388-7]

13 **Padar M**, Reintam Blaser A, Talving P, Lipping E, Starkopf J. Abdominal Compartment Syndrome: Improving Outcomes With A Multidisciplinary Approach - A Narrative Review. *J Multidiscip Healthc* 2019; **12**: 1061-1074 [PMID: 31908470 DOI: 10.2147/JMDH.S205608]

14 **Davis PJ**, Eltawil KM, Abu-Wasel B, Walsh MJ, Topp T, Molinari M. Effect of obesity and decompressive laparotomy on mortality in acute pancreatitis requiring intensive care unit admission. *World J Surg* 2013; **37**: 318-332 [PMID: 23052814 DOI: 10.1007/s00268-012-1821-8]

15 **Boone B**, Zureikat A, Hughes SJ, Moser AJ, Yadav D, Zeh HJ, Lee KK. Abdominal compartment syndrome is an early, lethal complication of acute pancreatitis. *Am Surg* 2013; **79**: 601-607 [PMID: 23711270 DOI: 10.1177/000313481307900621]

16 **Leppäniemi A**, Hienonen P, Mentula P, Kemppainen E. Subcutaneous linea alba fasciotomy, does it really work? *Am Surg* 2011; **77**: 99-102 [PMID: 21396315 DOI: 10.1177/000313481107700130]

17 **Deng ZG**, Zhou JY, Yin ZY, Peng YY, Wang FQ, Wang XM. Continuous regional arterial infusion and laparotomic decompression for severe acute pancreatitis with abdominal compartment syndrome. *World J Gastroenterol* 2011; **17**: 4911-4916 [PMID: 22171133 DOI: 10.3748/wjg.v17.i44.4911]

18 **Mentula P**, Hienonen P, Kemppainen E, Puolakkainen P, Leppäniemi A. Surgical decompression for abdominal compartment syndrome in severe acute pancreatitis. *Arch Surg* 2010; **145**: 764-769 [PMID: 20713929 DOI: 10.1001/archsurg.2010.132]

19 **Chen H**, Li F, Sun JB, Jia JG. Abdominal compartment syndrome in patients with severe acute pancreatitis in early stage. *World J Gastroenterol* 2008; **14**: 3541-3548 [PMID: 18567084 DOI: 10.3748/wjg.14.3541]

20 **De Waele JJ**, Hoste E, Blot SI, Decruyenaere J, Colardyn F. Intra-abdominal hypertension in patients with severe acute pancreatitis. *Crit Care* 2005; **9**: R452-R457 [PMID: 16137360 DOI: 10.1186/cc3754]

21 **Tao J**, Wang C, Chen L, Yang Z, Xu Y, Xiong J, Zhou F. Diagnosis and management of severe acute pancreatitis complicated with abdominal compartment syndrome. *J Huazhong Univ Sci Technolog Med Sci* 2003; **23**: 399-402 [PMID: 15015646 DOI: 10.1007/BF02829428]

22 **Husu HL**, Leppäniemi AK, Mentula PJ. Who would benefit from open abdomen in severe acute pancreatitis?-a matched case-control study. *World J Emerg Surg* 2021; **16**: 32 [PMID: 34112205 DOI: 10.1186/s13017-021-00376-x]

23 **Kawasaki Y**, Kamidani R, Okada H, Nakashima Y, Yamaji F, Fukuta T, Yoshida T, Yoshida S, Ogura S. Midline fasciotomy for severe acute pancreatitis with abdominal compartment syndrome: Case report. *Ann Med Surg (Lond)* 2022; **79**: 104081 [PMID: 35860170 DOI: 10.1016/j.amsu.2022.104081]

24 **Hu HK**, Du XJ, Li A, Ke NW, Hu WM. A minimally invasive management for abdominal compartment syndrome in severe acute pancreatitis. *Pak J Med Sci* 2013; **29**: 231-233 [PMID: 24353548 DOI: 10.12669/pjms.291.2721]

25 **Siebig S**, Iesalnieks I, Bruennler T, Dierkes C, Langgartner J, Schoelmerich J, Wrede CE. Recovery from respiratory failure after decompression laparotomy for severe acute pancreatitis. *World J Gastroenterol* 2008; **14**: 5467-5470 [PMID: 18803361 DOI: 10.3748/wjg.14.5467]

26 **De Waele JJ**, Hesse UJ. Life saving abdominal decompression in a patient with severe acute pancreatitis. *Acta Chir Belg* 2005; **105**: 96-98 [PMID: 15790212 DOI: 10.1080/00015458.2005.11679675]

27 **Lee AHH**, Lee WS, Anderson D. Severe pancreatitis complicated by abdominal compartment syndrome managed with decompressive laparotomy: a case report. *BMC Surg* 2019; **19**: 113 [PMID: 31419970 DOI: 10.1186/s12893-019-0575-8]

28 **Ikeda S**, Kagami T, Tani S, Uotani T, Yamade M, Hamaya Y, Morita Y, Sakaguchi T, Osawa S, Sugimoto K. Decompressive laparotomy for abdominal compartment syndrome resulting from severe acute pancreatitis: a case report. *BMC Gastroenterol* 2019; **19**: 141 [PMID: 31395017 DOI: 10.1186/s12876-019-1059-0]

29 **Jacob AO**, Stewart P, Jacob O. Early surgical intervention in severe acute pancreatitis: Central Australian experience. *ANZ J Surg* 2016; **86**: 805-810 [PMID: 24890051 DOI: 10.1111/ans.12707]

30 **Simoneau E**, Chughtai T, Razek T, Deckelbaum DL. Pancreaticoatmospheric fistula following severe acute necrotising pancreatitis. *BMJ Case Rep* 2014; **2014** [PMID: 25519860 DOI: 10.1136/bcr-2014-206131]

31 **McKenzie J**, Quinones PM, Mentzer CJ, Kruse EJ. Direct Peritoneal Resuscitation in the Setting of Hemorrhagic Pancreatitis. *Am Surg* 2017;

83: e441-e443 [PMID: 30454231 DOI: 10.1177/000313481708301109]
32 **Al-Bahrani AZ**, Abid GH, Holt A, McCloy RF, Benson J, Eddleston J, Ammori BJ. Clinical relevance of intra-abdominal hypertension in patients with severe acute pancreatitis. *Pancreas* 2008; **36**: 39-43 [PMID: 18192879 DOI: 10.1097/mpa.0b013e318149f5bf]
33 **Sarri G**, Guo Y, Iheanacho I, Puelles J. Moderately severe and severe acute pancreatitis : a systematic review of the outcomes in the USA and European Union-5. *BMJ Open Gastroenterol* 2019; **6**: e000248 [PMID: 30899535 DOI: 10.1136/bmjgast-2018-000248]
34 **Smit M**, Koopman B, Dieperink W, Hulscher JBF, Hofker HS, van Meurs M, Zijlstra JG. Intra-abdominal hypertension and abdominal compartment syndrome in patients admitted to the ICU. *Ann Intensive Care* 2020; **10**: 130 [PMID: 33001288 DOI: 10.1186/s13613-020-00746-9]
35 **Maluso P**, Olson J, Sarani B. Abdominal Compartment Hypertension and Abdominal Compartment Syndrome. *Crit Care Clin* 2016; **32**: 213-222 [PMID: 27016163 DOI: 10.1016/j.ccc.2015.12.001]
36 **De Waele E**, Malbrain MLNG, Spapen HD. How to deal with severe acute pancreatitis in the critically ill. *Curr Opin Crit Care* 2019; **25**: 150-156 [PMID: 30730344 DOI: 10.1097/MCC.0000000000000596]
37 **Leppäniemi A**, Tolonen M, Tarasconi A, Segovia-Lohse H, Gamberini E, Kirkpatrick AW, Ball CG, Parry N, Sartelli M, Wolbrink D, van Goor H, Baiocchi G, Ansaloni L, Biffl W, Coccolini F, Di Saverio S, Kluger Y, Moore E, Catena F. 2019 WSES guidelines for the management of severe acute pancreatitis. *World J Emerg Surg* 2019; **14**: 27 [PMID: 31210778 DOI: 10.1186/s13017-019-0247-0]
38 **Schepers NJ**, Hallensleben NDL, Besselink MG, Anten MGF, Bollen TL, da Costa DW, van Delft F, van Dijk SM, van Dullemen HM, Dijkgraaf MGW, van Eijck CHJ, Erkelens GW, Erler NS, Fockens P, van Geenen EJM, van Grinsven J, Hollemans RA, van Hooft JE, van der Hulst RWM, Jansen JM, Kubben FJGM, Kuiken SD, Laheij RJF, Quispel R, de Ridder RJJ, Rijk MCM, Römkens TEH, Ruigrok CHM, Schoon EJ, Schwartz MP, Smeets XJNM, Spanier BWM, Tan ACITL, Thijs WJ, Timmer R, Venneman NG, Verdonk RC, Vleggaar FP, van de Vrie W, Witteman BJ, van Santvoort HC, Bakker OJ, Bruno MJ; Dutch Pancreatitis Study Group. Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy versus conservative treatment in predicted severe acute gallstone pancreatitis (APEC): a multicentre randomised controlled trial. *Lancet* 2020; **396**: 167-176 [PMID: 32682482 DOI: 10.1016/S0140-6736(20)30539-0]
39 **Smit M**, van Meurs M, Zijlstra JG. Intra-abdominal hypertension and abdominal compartment syndrome in critically ill patients: A narrative review of past, present, and future steps. *Scand J Surg* 2022; **111**: 14574969211030128 [PMID: 34605332 DOI: 10.1177/14574969211030128]
40 **Mao EQ**, Tang YQ, Fei J, Qin S, Wu J, Li L, Min D, Zhang SD. Fluid therapy for severe acute pancreatitis in acute response stage. *Chin Med J (Engl)* 2009; **122**: 169-173 [PMID: 19187641]
41 **de-Madaria E**, Buxbaum JL, Maisonneuve P, García García de Paredes A, Zapater P, Guilabert L, Vaillo-Rocamora A, Rodríguez-Gandía MÁ, Donate-Ortega J, Lozada-Hernández EE, Collazo Moreno AJR, Lira-Aguilar A, Llovet LP, Mehta R, Tandel R, Navarro P, Sánchez-Pardo AM, Sánchez-Marin C, Cobreros M, Fernández-Cabrera I, Casals-Seoane F, Casas Deza D, Lauret-Braña E, Martí-Marqués E, Camacho-Montaño LM, Ubieto V, Ganuza M, Bolado F; ERICA Consortium. Aggressive or Moderate Fluid Resuscitation in Acute Pancreatitis. *N Engl J Med* 2022; **387**: 989-1000 [PMID: 36103415 DOI: 10.1056/NEJMoa2202884]
42 **Crosignani A**, Spina S, Marrazzo F, Cimbanassi S, Malbrain MLNG, Van Regenmortel N, Fumagalli R, Langer T. Intravenous fluid therapy in patients with severe acute pancreatitis admitted to the intensive care unit: a narrative review. *Ann Intensive Care* 2022; **12**: 98 [PMID: 36251136 DOI: 10.1186/s13613-022-01072-y]
43 **Huber W**, Malbrain ML. Goal-directed fluid resuscitation in acute pancreatitis: shedding light on the penumbra by dynamic markers of preload? *Intensive Care Med* 2013; **39**: 784-786 [PMID: 23287874 DOI: 10.1007/s00134-012-2783-x]
44 **Pupelis G**, Plaudis H, Zeiza K, Drozdova N, Mukans M, Kazaka I. Early continuous veno-venous haemofiltration in the management of severe acute pancreatitis complicated with intra-abdominal hypertension: retrospective review of 10 years' experience. *Ann Intensive Care* 2012; **2** Suppl 1: S21 [PMID: 23281603 DOI: 10.1186/2110-5820-2-S1-S21]
45 **Van Damme L**, De Waele JJ. Effect of decompressive laparotomy on organ function in patients with abdominal compartment syndrome: a systematic review and meta-analysis. *Crit Care* 2018; **22**: 179 [PMID: 30045753 DOI: 10.1186/s13054-018-2103-0]
46 **Ke L**, Ni HB, Tong ZH, Li WQ, Li N, Li JS. The importance of timing of decompression in severe acute pancreatitis combined with abdominal compartment syndrome. *J Trauma Acute Care Surg* 2013; **74**: 1060-1066 [PMID: 23511145 DOI: 10.1097/TA.0b013e318283d927]
47 **Cheatham ML**, Fowler J, Pappas P. Subcutaneous linea alba fasciotomy: a less morbid treatment for abdominal compartment syndrome. *Am Surg* 2008; **74**: 746-749 [PMID: 18705579 DOI: 10.1177/000313480807400815]
48 **Duchesne JC**, Howell MP, Eriksen C, Wahl GM, Rennie KV, Hastings PE, McSwain NE Jr, Malbrain ML. Linea alba fasciotomy: a novel alternative in trauma patients with secondary abdominal compartment syndrome. *Am Surg* 2010; **76**: 312-316 [PMID: 20349663 DOI: 10.1177/000313481007600314]
49 **Leppäniemi A**. Surgical management of abdominal compartment syndrome; indications and techniques. *Scand J Trauma Resusc Emerg Med* 2009; **17**: 17 [PMID: 19366442 DOI: 10.1186/1757-7241-17-17]
50 **Coccolini F**, Montori G, Ceresoli M, Catena F, Moore EE, Ivatury R, Biffl W, Peitzman A, Coimbra R, Rizoli S, Kluger Y, Abu-Zidan FM, Sartelli M, De Moya M, Velmahos G, Fraga GP, Pereira BM, Leppaniemi A, Boermeester MA, Kirkpatrick AW, Maier R, Bala M, Sakakushev B, Khokha V, Malbrain M, Agnoletti V, Martin-Loeches I, Sugrue M, Di Saverio S, Griffiths E, Soreide K, Mazuski JE, May AK, Montravers P, Melotti RM, Pisano M, Salvetti F, Marchesi G, Valetti TM, Scalea T, Chiara O, Kashuk JL, Ansaloni L. The role of open abdomen in non-trauma patient: WSES Consensus Paper. *World J Emerg Surg* 2017; **12**: 39 [PMID: 28814969 DOI: 10.1186/s13017-017-0146-1]
51 **Radenkovic DV**, Bajec D, Ivancevic N, Bumbasirevic V, Milic N, Jeremic V, Gregoric P, Karamarkovic A, Karadzic B, Mirkovic D, Bilanovic D, Scepanovic R, Cijan V. Decompressive laparotomy with temporary abdominal closure versus percutaneous puncture with placement of abdominal catheter in patients with abdominal compartment syndrome during acute pancreatitis: background and design of multicenter, randomised, controlled study. *BMC Surg* 2010; **10**: 22 [PMID: 20624281 DOI: 10.1186/1471-2482-10-22]
52 **Montalvo-Jave EE**, Espejel-Deloiza M, Chernitzky-Camaño J, Peña-Pérez CA, Rivero-Sigarroa E, Ortega-León LH. Abdominal compartment syndrome: Current concepts and management. *Rev Gastroenterol Mex (Engl Ed)* 2020; **85**: 443-451 [PMID: 32847726 DOI: 10.1016/j.rgmx.2020.03.003]
53 **Schachtrupp A**, Fackeldey V, Klinge U, Hoer J, Tittel A, Toens C, Schumpelick V. Temporary closure of the abdominal wall (laparostomy). *Hernia* 2002; **6**: 155-162 [PMID: 12424592 DOI: 10.1007/s10029-002-0085-x]
54 **Hecker A**, Hecker B, Hecker M, Riedel JG, Weigand MA, Padberg W. Acute abdominal compartment syndrome: current diagnostic and therapeutic options. *Langenbecks Arch Surg* 2016; **401**: 15-24 [PMID: 26518567 DOI: 10.1007/s00423-015-1353-4]
55 **Roberts DJ**, Zygun DA, Grendar J, Ball CG, Robertson HL, Ouellet JF, Cheatham ML, Kirkpatrick AW. Negative-pressure wound therapy for critically ill adults with open abdominal wounds: a systematic review. *J Trauma Acute Care Surg* 2012; **73**: 629-639 [PMID: 22929494 DOI: 10.1097/TA.0b013e31825c130e]

56 **Bruhin A**, Ferreira F, Chariker M, Smith J, Runkel N. Systematic review and evidence based recommendations for the use of negative pressure wound therapy in the open abdomen. *Int J Surg* 2014; **12**: 1105-1114 [PMID: 25174789 DOI: 10.1016/j.ijsu.2014.08.396]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 1892-1900

DOI: 10.4240/wjgs.v15.i9.1892

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Excision of malignant and pre-malignant rectal lesions by transanal endoscopic microsurgery in patients under 50 years of age

Dafna Shilo Yaacobi, Yael Berger, Tali Shaltiel, Eliahu Y Bekhor, Muhammad Khalifa, Nidal Issa

Specialty type: Surgery

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Liu Z, China; Mishra TS, India; Xiao Y, China

Received: April 5, 2023
Peer-review started: April 5, 2023
First decision: June 14, 2023
Revised: June 24, 2023
Accepted: July 29, 2023
Article in press: July 29, 2023
Published online: September 27, 2023

Dafna Shilo Yaacobi, Department of Plastic Surgery & Burns, Rabin Medical Center, Petah Tikva 4941492, Israel

Yael Berger, Tali Shaltiel, Eliahu Y Bekhor, Muhammad Khalifa, Nidal Issa, Department of Surgery, Rabin Medical Center-Hasharon Hospital, Petah Tikva 4941492, Israel

Corresponding author: Dafna Shilo Yaacobi, MD, Surgeon, Department of Plastic Surgery & Burns, Rabin Medical Center, No. 39 Zabutinsky Street, Petah Tikva 4941492, Israel.
dafna.yaacobi@icloud.com

Abstract

BACKGROUND

The most common technique for treating benign and early malignant rectal lesions is transanal endoscopic microsurgery (TEM). Local excision is an acceptable technique for high-risk and elderly patients, but there are hardly any data regarding young patients.

AIM

To describe TEM outcomes in patients under 50 years of age.

METHODS

We collected demographic, clinical, and pathological data from all patients under the age of 50 years who underwent the TEM procedure at Hasharon Rabin Medical Center from January 2005 to December 2018.

RESULTS

During the study period, a total of 26 patients under the age of 50 years underwent TEM procedures. Their mean age was 43.3 years. Eleven (42.0%) were male. The mean operative time was 67 min, and the mean tumor size was 2.39 cm, with a mean anal verge distance of 8.50 cm. No major intraoperative or postoperative complications were recorded. The median length of stay was 2 d. Seven (26.9%) lesions were adenomas with low-grade dysplasia, four (15.4%) were high-grade dysplasia adenomas, two were T1 carcinomas (7.8%), and three were T2 carcinomas (11.5%). No residual disease was found following endoscopic polypectomy in two patients (7.8%), but four (15.4%) had other pathologies. Surgical margins were negative in all cases. Local recurrence was detected in one patient 33 mo following surgery.

CONCLUSION

Among young adult patients, TEM for benign rectal lesions has excellent outcomes. It may also offer a balance between the efficacy of complete oncologic resection and postoperative quality of life in the treatment of rectal cancer. In some cases, it may be considered an alternative to radical surgery.

Key Words: Transanal endoscopic microsurgery; Young adults; Rectal lesions; Benign lesions; Malignant lesions; Radical surgery alternative

Core Tip: Among young adult patients, transanal endoscopic microsurgery for benign rectal lesions has excellent outcomes. It may also offer the balance between efficacy of complete oncologic resection and postoperative quality of life in the treatment of rectal cancer and in some cases may be considered an alternative to radical surgery.

Citation: Shilo Yaacobi D, Berger Y, Shaltiel T, Bekhor EY, Khalifa M, Issa N. Excision of malignant and pre-malignant rectal lesions by transanal endoscopic microsurgery in patients under 50 years of age. *World J Gastrointest Surg* 2023; 15(9): 1892-1900
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/1892.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.1892

INTRODUCTION

The most common gastrointestinal malignancy is colorectal cancer (CRC), with an incidence rate that is increasing among young adults[1,2]. Mortality has also increased in young adults since 2004 (1.3% per year), along with worse outcomes[3,4], but data regarding this population are still controversial[5]. Some studies have demonstrated similar outcomes in young and elderly patients, while others have suggested poorer outcomes in young patients[6,7]. Not much is known regarding the reason why these patients, without any genetic predispositions, develop CRC[8]. Furthermore, young patients tend to present with more advanced stages of disease compared with elderly patients[5,9]. The American National Comprehensive Cancer Network (NCCN) guidelines for CRC screening have recently been revised, and it is now recommended to begin screening at 45 years of age[10]. In Israel, however, routine screening still begins at the age of 50 years[11].

The extent of surgery may be influenced by the age of the patients, with young patients with colon cancer usually undergoing extended surgery[12]. For rectal cancer, the standard surgical technique is total mesorectal excision (TME), either by anterior resection (AR) or abdominoperineal resection (APR). This procedure is usually curative for early-stage rectal cancer but might have a substantial impact on quality of life due to its high morbidity and mortality rates. In fact, there is a 20%-40% rate of adverse events, including urinary and sexual dysfunction, anastomotic leakage, and permanent colostomy[13,14]. Due to morbidity associated with TME, other less invasive transanal approaches have been explored for the management of rectal cancer, including local excision *via* transanal excision (TAE) or transanal endoscopic microsurgery (TEM).

Surgical treatment of rectal tumors in young patients should help patients achieve a good quality of life and, at the same time, be based on efficient oncologic excision[15]. The TEM technique enables high-quality excision of certain rectal lesions[16]. It has proven its superiority over traditional TAE[17] when treating benign rectal lesions, while for early rectal cancer, it has demonstrated better functional outcomes and has excellent long-term survival rates as a form of radical surgery[18].

TEM may be considered the technique of choice for rectal adenoma[19,20] and an acceptable alternative treatment to radical resection in patients with low-risk T1 rectal adenocarcinoma. In elderly and high-risk patients, local excision is considered an acceptable choice for rectal lesions[21,22], but data are limited regarding its application in young adults [23]. The aim of this study was to explore the outcomes in young patients undergoing TEM for rectal lesions. We set the age cut-off to 50 years due to the above-mentioned minimal age for colonoscopy screening and the rare incidence of CRC before this age[5,11].

MATERIALS AND METHODS

This retrospective cohort study was approved by the Rabin Medical Center Institutional Review Board, with a waiver of informed consent. We reviewed the data on all patients under the age of 50 years who underwent TEM procedures at our medical center between January 2005 and December 2018. All data (demographic, clinical, and pathological) were collected retrospectively from our medical center electronic system. These data included the tumor location, tumor dimensions, tumor histology, indications for surgery, operative findings, postoperative outcomes, and complications.

All patients underwent a preoperative evaluation protocol for TEM before surgery, consisting of a colonoscopy that included a biopsy and a rigid proctoscopy defining the number of lesions, the tumor size, its location within the rectal wall, and its distance from the anal verge. Patients with malignant tumors underwent an endorectal ultrasound examination preoperatively.

Patients who had benign rectal lesions not amenable to endoscopic excision, T1 rectal cancer without the involvement of lymph nodes per radiology, or indeterminate margins following endoscopic polypectomy were routinely offered TEM. TEM was also offered to selected patients with retrorectal and submucosal lesions.

Preparation of the patients for TEM surgery and colon resection was the same, with mechanical bowel preparation performed a day before the procedure and administration of prophylactic antibiotics at the time of anesthesia induction.

The details of the technique were previously described elsewhere[24]. All rectal wall defects were closed transversally with absorbable sutures. All patients had a urinary catheter during surgery, which was removed on postoperative day 1, at which point the intake of oral liquid and a soft diet were resumed. Pain control included oral dipyrone, paracetamol, and narcotics. Patients were discharged when oral intake was well tolerated, and no complications were detected, which meant that no unexpected events had occurred during the procedure or in the postoperative period.

Patients were evaluated 2 wk following surgery and then at 3-mo intervals for the first two postoperative years, and every 6 mo from then on. Each follow-up visits also included a rigid rectoscopy. In cases of rectal wall invasion per final pathology of the TEM specimen or unfavorable histologic findings in T1 tumors indicating SM3 or lymphovascular invasion, patients were referred for rectal resection with TME.

A descriptive data analysis was performed for the categorical variables, and the ranges and means were calculated for the continuous variables.

RESULTS

During the study period, 186 patients underwent TEM procedures. Of these, 26 patients (14%) were under the age of 50 years and therefore included in the study. The patients' demographics and tumor characteristics are shown in Table 1. The mean age was 43.3 years (range 21-49 years). Eleven (42%) of the patients were male, and the remainder were female. Most patients (n = 17, 65.5%) had an American Society of Anesthesiology score of 1. Indications for TEM were low-grade dysplasia adenomas in seven patients (27%), high-grade dysplasia adenomas in five (19.2%), carcinoma diagnosed in preoperative biopsies in four (15.4%), positive margins following endoscopic polypectomy in four (15.4%), and other pathologies (one tailgut cyst, two suspected carcinoid, and three undetermined pathologies) in six (23%). The mean tumor diameter was 2.39 cm (range 1-4 cm), with a mean anal verge distance of 8.5 cm (range 5-13 cm). Eight (30.8%) of the lesions were located in the posterior rectal wall, three (11.5%) in the anterior wall, and 15 (57.7%) in the lateral walls. Four lesions (15.4%) were diagnosed as carcinomas by preoperative biopsies. The stage of all the tumors was T1 SM1, and all had favorable histological features (*i.e.*, no lymphovascular invasion or perineural invasion).

Table 2 presents the perioperative variables. The mean operative time was 67 min (range 46-108 min). No major intraoperative or postoperative complications were documented. The only recorded minor complication was postoperative urinary retention, which occurred in two patients. The estimated blood loss during surgery was minimal. The median length of stay was 2 d (range 1-4 d). One patient was readmitted during the postoperative period (4 d after discharge) due to rectal bleeding; he was treated conservatively with no need for invasive intervention or blood transfusion. No other readmissions were recorded.

Regarding the final pathological results of the specimens (Table 3), adenocarcinoma was found in six patients, T1 carcinoma in four (15.4%), and T2 carcinoma in two (7.8%). Adenomatous polyps were found in 11 patients (42%), high-grade dysplasia in seven (26.9%), and low-grade dysplasia in four (15.4%); there was no residual disease following endoscopic polypectomy in two patients (7.8%). Other pathological findings included a carcinoid tumor, a neuroendocrine tumor, endometriosis, a tailgut cyst, and a solitary rectal ulcer. Surgical margins were free of tumors in all cases.

In two patients with T2 carcinoma on the final pathology, completion of rectal resection was required; therefore, they both underwent laparoscopic AR 10 wk following TEM. There was no residual tumor or lymph node metastasis in the AR specimens in either case.

In the mean follow-up period of 55 mo (range 20-81 mo, median 80 mo), local recurrence of the rectal tumor was detected in one female patient 33 mo after TEM for T1 carcinoma. The patient underwent radiochemotherapy and laparoscopic APR. The final pathology was T3, without the involvement of nodes.

There were no reports of postoperative incontinence in any of the patients.

DISCUSSION

TEM, like other minimally invasive colorectal surgical techniques, offers an effective treatment option with a low morbidity rate. In high-risk and elderly patients, traditional local excision has been found to be more acceptable for rectal lesions[21,22]. Recently, TEM has been considered by several authors[19,20] to be the technique of choice for rectal adenomas and also an acceptable alternative approach for radical resection in patients with T1 rectal carcinoma with favorable features.

Young patients with rectal lesions are being offered more radical resections, which is a reasonable oncological choice due to their longer life expectancy and the advantages of the radical surgery. However, radical resection in the form of AR or APR has considerable postoperative morbidity rates, and it is therefore rational to choose TEM as an alternative

Table 1 Patient demographics and clinical variables

Variable	*n* = 26
Age in yr (range)	43.3 (21-49)
Male/female	45245
BMI (kg/cm^2)	26.8 (20-42)
ASA score (%)	
I	17 (65.5)
II	6 (23.0.)
III	3 (11.5)
Indication for surgery (%)	
Adenoma LGD	7 (27.0)
Adenoma HGD	5 (19.2)
Carcinoma	4 (15.4)
Indeterminate margins after polypectomy	4 (15.4)
Other	6 (23.0)
Tumor diameter, cm (range)	2.39 (1-4)
Distance from anal verge, cm (range)	8.5 (5-13)
Rectal wall location (%)	
Posterior	8 (30.8)
Anterior	3 (11.5)
Right lateral	10 (38.5)
Left lateral	5 (19.2)

ASA: American Society of Anesthesiology; LGD: Low-grade dysplasia; HGD: High-grade dysplasia.

Table 2 Operative variables

Variable	*n* = 24
Operation time, min (range)	67 (46-108)
Hospital stay, d (range)	2 (1-4)
Perioperative complications (%)	
Peritoneal entry	0
Bleeding	0
Urinary retention	2 (8.5)

when taking into consideration the balance between the advantages and disadvantages of the radical resection approach [25,26].

The overall TEM complication rate for all lesions has been reported to range from 6% to 31%[27]. Possible postoperative complications include urinary retention, suture line dehiscence, and bleeding. In the present study, we reported a urinary retention rate of 7.6% (two cases), compared to 10.8% in the study of Tsai *et al*[28]. Neither length of stay nor overall complications were increased in the present study.

As for postoperative incontinence, which is another morbidity to be considered, Cataldo *et al*[29] found no significant deleterious effects of TEM on fecal continence. Morino *et al*[19] noted a temporary decrease in post-procedure anal resting pressure, which returned to preoperative values at a mean time of 4 mo ostoperatively. Our study cohort reported no incidence of incontinence, which is consistent with the reports in other literature[30,31].

The treatment of rectal tumors in young adult patients undoubtedly presents a challenge for the surgeon when seeking to obtain optimal results in terms of both quality of life and oncological outcome. Some studies suggest that the disease is more aggressive in younger adults with rectal carcinoma[32,33]. Others have found no significant differences in oncologic outcomes when comparing young adult patients with rectal tumors adjusted for tumor stage, suggesting that these

Table 3 Final pathological results of the specimens

Pathology (%)	*n* = 24
Adenoma LGD	4 (15.4)
Adenoma HGD	7 (26.9)
Carcinoma T1	4(15.4)
Carcinoma T2	2 (7.8)
Carcinoid	3 (11.5)
NED	1 (3.8)
SRU	1(3.8)
Endometriosis	1(3.8)
Tailgut cyst	1 (3.8)
No residual tumor	2 (7.8)

LGD: Low-grade dysplasia; HGD: High-grade dysplasia; NED: Neuroendocrine tumor; SRU: Solitary rectal ulcer.

patients do not necessarily have a more aggressive disease[34].

Since aggressive management attempts in young patients with colorectal tumors, such as radical resection, have not resulted in improved outcomes, it is suggested that they be handled in the same manner as older patients, considering the increasing incidence of these tumors among this population[35]. Regarding benign lesions, TEM was found to be more effective than transanal local excision in achieving tumor-free margins[17]. In another study, it also resulted in a less fragmented specimen and was therefore associated with lower recurrence rates[27]. TEM represents an alternative to the transabdominal approach, whereby a benign rectal lesion is situated in the upper rectum, which is especially valuable when considering the high morbidity and mortality associated with the latter approach in all age groups[36], with the possibility of a higher impact in young patients. No incontinence was reported in the long-term results among these patients; however, AR syndrome was experienced in 50%-90% of patients undergoing AR[36].

For malignant lesions, TEM is considered effective and safe when treating certain T1 Lesions without adverse pathologic results and with favorable outcomes. It is more strongly associated with lower morbidity and mortality compared to transabdominal radical rectal resection[37,38].

In our cohort, local recurrence of a rectal tumor was detected in one 49-year-old female patient 33 mo after TEM, who had a flat lesion in the lower rectum. The final pathology revealed a T1 carcinoma without vascular or neural invasion, with free margins. She underwent radiochemotherapy treatment followed by a laparoscopic APR. The final pathologic result was T3N0.

In our series, all T1 lesions were SM1. TEM is currently indicated as a curative treatment for malignancies histologically confirmed as pT1 SM1 tumors. Regarding T1 SM2 tumors, the optimal management approach remains unclear, given that they emerge without any unfavorable criteria due to lymph node positivity. In fact, node positivity increases the level of infiltration of the submucosa, with rates of 1%-3% for nodes in T1 SM1 lesions, 8%-10% in T1 SM2, and up to 25% in T1 SM3[39]. Therefore, we suggest that young patients with T1 SM2 lesions be offered radical rectal surgery, with TEM limited to patients participating in prospective trials with neoadjuvant or adjuvant treatment[40].

Two patients in this cohort had a T2 tumor per final pathology and subsequently underwent completion surgery following TEM by radical rectal resection. This approach has been demonstrated to be safe and returned similar oncological outcome to that of primary radical TME surgery. This result was also observed in series where immediate reoperation was performed[41,42]. Laparoscopic rectal surgery following TEM is thus considered safe and has no negative impact on resection completion[43].

For rectal T2 adenocarcinomas, the standard of treatment is TME *via* the transabdominal approach with or without neoadjuvant or adjuvant therapy[44], due to the high recurrence rate with occult lymph node metastases[45]. If an unexpected T2 tumor is excised by TEM, it may be managed safely by salvage radical surgery, with good oncological outcomes.

The rate of local recurrence following TEM ranges from 0%-33% for T1 rectal cancers[46]. Stipa *et al*[47] found that 96% (26/27) of patients with local recurrence following TEM underwent subsequent salvage surgery, nine of whom required repeated TEM, and seventeen of whom underwent radical surgery. In the latter group, the 5-year survival rate was 69%, which is similar to previously reported data[48]. TEM for rectal cancer followed by radical surgery offers an overall good long-term survival rate, which is similar to the rate obtained by initial radical surgery[47]. The risk of recurrence is mitigated by the high repeatability of the procedure, as well as by the satisfactory outcomes seen with salvage radical resection.

In this study, a single case of local recurrence was recorded 33 mo following TEM in a patient with a low rectal T1 lesion who had undergone a subsequent laparoscopic APR with a permanent colostomy. Such patients are more likely to require an APR rather than a low AR, according to some reports, due to secondary scar formation and technical difficulties[49,50]. These technical difficulties, as well as unnecessary APR, can be avoided when choosing the transanal

TME technique[51]. While TEM may offer a better quality of life with long-term oncologic safety, it might require a longer period of postoperative follow-up. However, the exact frequency and required length of the follow-up period have yet to be defined, and it is suggested that these patients be treated as "high risk" until further data become available from larger randomized controlled trials.

The limitations of this study include its small sample size, retrospective nature, and various pathologies. There was also variability in perioperative care, as it evolved over the years due to long accrual periods. Furthermore, diagnostic modalities were not uniform for all patients, which may have impacted the choice of surgical approach and the various pathologies.

Local excision by TEM has indeed been interpreted as a successful and valid alternative to the traditional surgical treatment for adenomas and low risk (T1) rectal tumors[25], but it is still considered a compromise, especially in cases of advanced and high-risk rectal lesions, for which TME is considered the standard of care[24]. At the same time, rectal radical resection carries considerable postoperative morbidity, and it is therefore justifiable to offer TEM instead[26].

This surgical approach is likely not suitable for patients with a polypogenic rectum that has several lesions, but they will benefit from an up-front radical resection of the rectum rather than repeated TEMs due to the increased burden and cost of undergoing several surgical procedures.

CONCLUSION

TEM of benign rectal lesions in young adult patients is safe and leads to excellent outcomes. For early rectal cancer in this group of patients, TEM may offer a balance between postoperative quality of life and the effectiveness of the oncologic resection; therefore, it may be considered in selected cases as an alternative to radical surgery in young adult patients.

ARTICLE HIGHLIGHTS

Research background

Surgical treatment of rectal tumors in young patients should help patients achieve a good quality of life and, at the same time, be based on efficient oncologic excision. The transanal endoscopic microsurgery (TEM) technique enables high-quality excision of certain rectal lesions.

Research motivation

To explore the outcomes in young patients undergoing TEM for rectal lesions.

Research objectives

We set the age cut-off to 50 years due to the above mentioned minimal age for colonoscopy screening and the rare incidence of colorectal cancer before this age.

Research methods

This is a retrospective cohort study on all patients under the age of 50 years who underwent TEM procedures at our medical center between January 2005 and December 2018. Patients were evaluated 2 wk following surgery and then at 3-mo intervals for the first two postoperative years, and every 6 mo from then on. Each follow-up visits also included a rigid rectoscopy. A descriptive data analysis was performed for the categorical variables, and the ranges and means were calculated for the continuous variables.

Research results

During the study period, 186 patients underwent TEM procedures. Of these, 26 patients (14%) were under the age of 50 years and therefore included in the study. The mean age was 43.3 years (range 21-49 years). Eleven (42%) of the patients were male. Indications for TEM were low-grade dysplasia adenomas in seven patients (27%), high-grade dysplasia adenomas in five (19.2%), carcinoma diagnosed in preoperative biopsies in four (15.4%), positive margins following endoscopic polypectomy in four (15.4%), and other pathologies (one tailgut cyst, two suspected carcinoid, and three undetermined pathologies) in six (23%). No major intraoperative or postoperative complications were documented. There was no residual tumor or lymph node metastasis in the AR specimens in either case. In the mean follow-up period of 55 mo (range 20-81 mo, median 80 mo), local recurrence of the rectal tumor was detected in one female patient 33 mo after TEM for T1 carcinoma. The patient underwent radiochemotherapy and laparoscopic abdominoperineal resection. The final pathology was T3, without the involvement of nodes. There were no reports of postoperative incontinence in any of the patients.

Research conclusions

TEM of benign rectal lesions in young adult patients is safe and leads to excellent outcomes. For early rectal cancer in this group of patients, TEM may offer a balance between postoperative quality of life and the effectiveness of the oncologic resection; therefore, it may be considered in selected cases as an alternative to radical surgery in young adult patients.

Research perspectives

The limitations of this study include its small sample size, retrospective nature, and various pathologies. There was also variability in perioperative care, as it evolved over the years due to long accrual periods. Furthermore, diagnostic modalities were not uniform for all patients, which may have impacted the choice of surgical approach and the various pathologies.

FOOTNOTES

Author contributions: Shilo Yaacobi D contributed to methodology, original draft preparation, and manuscript review and editing; Berger Y contributed to investigation and original draft preparation; Shaltiel T contributed to investigation and original draft preparation; Bekhor EY contributed to investigation, statistics, and manuscript review and editing; Khalifa M contributed to original draft preparation and manuscript review and editing; Issa N contributed to project administration, methodology, original draft preparation, and manuscript review and editing.

Institutional review board statement: This retrospective cohort study was approved by the Rabin Medical Center Institutional Review Board (Approval No. RMC-0160-18).

Informed consent statement: This retrospective cohort study was approved by the Rabin Medical Center Institutional Review Board, with a waiver of informed consent.

Conflict-of-interest statement: The authors have no conflicts of interest or financial ties to disclose.

Data sharing statement: The data that support the findings of this study are available from the corresponding author, DSY, upon reasonable request.

Country/Territory of origin: Israel

ORCID number: Dafna Shilo Yaacobi 0000-0003-0553-5664.

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

REFERENCES

1 **Sinicrope FA**. Increasing Incidence of Early-Onset Colorectal Cancer. *N Engl J Med* 2022; **386**: 1547-1558 [PMID: 35443109 DOI: 10.1056/NEJMra2200869]
2 **Chang SH**, Patel N, Du M, Liang PS. Trends in Early-onset vs Late-onset Colorectal Cancer Incidence by Race/Ethnicity in the United States Cancer Statistics Database. *Clin Gastroenterol Hepatol* 2022; **20**: e1365-e1377 [PMID: 34325062 DOI: 10.1016/j.cgh.2021.07.035]
3 **Amri R**, Bordeianou LG, Berger DL. The conundrum of the young colon cancer patient. *Surgery* 2015; **158**: 1696-1703 [PMID: 26298030 DOI: 10.1016/j.surg.2015.07.018]
4 **American Cancer Society**. Colorectal cancer facts & figures 2020-2022. 2020. [cited 3 July 2023]. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/colorectal-cancer-facts-and-figures/colorectal-cancer-facts-and-figures-2020-2022.pdf
5 **O'Connell JB**, Maggard MA, Livingston EH, Yo CK. Colorectal cancer in the young. *Am J Surg* 2004; **187**: 343-348 [PMID: 15006562 DOI: 10.1016/j.amjsurg.2003.12.020]
6 **Lynch PM**. How helpful is age at colorectal cancer onset in finding hereditary nonpolyposis colorectal cancer? *Clin Gastroenterol Hepatol* 2011; **9**: 458-460 [PMID: 21440092 DOI: 10.1016/j.cgh.2011.03.016]
7 **Endreseth BH**, Romundstad P, Myrvold HE, Hestvik UE, Bjerkeset T, Wibe A; Norwegian Rectal Cancer Group. Rectal cancer in the young patient. *Dis Colon Rectum* 2006; **49**: 993-1001 [PMID: 16741599 DOI: 10.1007/s10350-006-0558-6]
8 **McMillan DC**, McArdle CS. The impact of young age on cancer-specific and non-cancer-related survival after surgery for colorectal cancer: 10-year follow-up. *Br J Cancer* 2009; **101**: 557-560 [PMID: 19672260 DOI: 10.1038/sj.bjc.6605222]
9 **O'Connell JB**, Maggard MA, Liu JH, Etzioni DA, Ko CY. Are survival rates different for young and older patients with rectal cancer? *Dis Colon Rectum* 2004; **47**: 2064-2069 [PMID: 15657655 DOI: 10.1007/s10350-004-0738-1]
10 **Abbadessa B**, Early DS, Friedman M. Continue NCCN Guidelines Panel Disclosures NCCN Guidelines Version 2. [cited 3 July 2023]. Available from: https://www.nccn.org/guidelines/guidelines-panels-and-disclosure/disclosure-panels#:~:text=The%20NCCN%20Disclosure%20Policies%20and%20Potential%20Conflicts%20of,Guidelines%20Panel%20and%20NCCN%20staff%20is%20noted%20below.
11 **Ministry of Health Guidelines**. Prevention and early detection of malignant diseases. [cited 3 July 2023]. Available from: https://hq.moh.gov.my/ohd/images/pdf/publication/4.12.2020_Oral%20Cancer%20Guidelines_edaran.pdf

12 **Klos CL**, Montenegro G, Jamal N, Wise PE, Fleshman JW, Safar B, Dharmarajan S. Segmental versus extended resection for sporadic colorectal cancer in young patients. *J Surg Oncol* 2014; **110**: 328-332 [PMID: 24888987 DOI: 10.1002/jso.23649]

13 **Andersson J**, Abis G, Gellerstedt M, Angenete E, Angerås U, Cuesta MA, Jess P, Rosenberg J, Bonjer HJ, Haglind E. Patient-reported genitourinary dysfunction after laparoscopic and open rectal cancer surgery in a randomized trial (COLOR II). *Br J Surg* 2016; **103**: 1746 [PMID: 27801929 DOI: 10.1002/bjs.10279]

14 **Musters GD**, Buskens CJ, Bemelman WA, Tanis PJ. Perineal wound healing after abdominoperineal resection for rectal cancer: a systematic review and meta-analysis. *Dis Colon Rectum* 2014; **57**: 1129-1139 [PMID: 25101610 DOI: 10.1097/DCR.0000000000000182]

15 **Stitzenberg KB**, Sanoff HK, Penn DC, Meyers MO, Tepper JE. Practice patterns and long-term survival for early-stage rectal cancer. *J Clin Oncol* 2013; **31**: 4276-4282 [PMID: 24166526 DOI: 10.1200/JCO.2013.49.1860]

16 **Buess G**. Review: transanal endoscopic microsurgery (TEM). *J R Coll Surg Edinb* 1993; **38**: 239-245 [PMID: 7693935]

17 **Heintz A**, Mörschel M, Junginger T. Comparison of results after transanal endoscopic microsurgery and radical resection for T1 carcinoma of the rectum. *Surg Endosc* 1998; **12**: 1145-1148 [PMID: 9716769 DOI: 10.1007/s004649900802]

18 **Demartines N**, von Flüe MO, Harder FH. Transanal endoscopic microsurgical excision of rectal tumors: indications and results. *World J Surg* 2001; **25**: 870-875 [PMID: 11572026 DOI: 10.1007/s00268-001-0043-2]

19 **Morino M**, Arezzo A, Allaix ME. Transanal endoscopic microsurgery. *Tech Coloproctol* 2013; **17** Suppl 1: S55-S61 [PMID: 23314951 DOI: 10.1007/s10151-012-0936-0]

20 **Heidary B**, Phang TP, Raval MJ, Brown CJ. Transanal endoscopic microsurgery: a review. *Can J Surg* 2014; **57**: 127-138 [PMID: 24666451 DOI: 10.1503/cjs.022412]

21 **Smart CJ**, Korsgen S, Hill J, Speake D, Levy B, Steward M, Geh JI, Robinson J, Sebag-Montefiore D, Bach SP. Multicentre study of short-course radiotherapy and transanal endoscopic microsurgery for early rectal cancer. *Br J Surg* 2016; **103**: 1069-1075 [PMID: 27146472 DOI: 10.1002/bjs.10171]

22 **Serra-Aracil X**, Serra-Pla S, Mora-Lopez L, Pallisera-Lloveras A, Labro-Ciurans M, Navarro-Soto S. Transanal endoscopic micro-surgery in elderly and very elderly patients: a safe option? Observational study with prospective data collection. *Surg Endosc* 2019; **33**: 184-191 [PMID: 29934869 DOI: 10.1007/s00464-018-6292-z]

23 **Cao B**, Min L, Zhu S, Shi H, Zhang S. Long-term oncological outcomes of local excision versus radical resection for early colorectal cancer in young patients without preoperative chemoradiotherapy: a population-based propensity matching study. *Cancer Med* 2018; **7**: 2415-2422 [PMID: 29726125 DOI: 10.1002/cam4.1508]

24 **Issa N**, Fenig Y, Yasin M, Schmilovitz-Weiss H, Khoury W, Powsner E. Laparoscopy following peritoneal entry during transanal endoscopic microsurgery may increase the safety and maximize the benefits of the transanal excision. *Tech Coloproctol* 2016; **20**: 221-226 [PMID: 26908311 DOI: 10.1007/s10151-016-1436-4]

25 **Lee W**, Lee D, Choi S, Chun H. Transanal endoscopic microsurgery and radical surgery for T1 and T2 rectal cancer. *Surg Endosc* 2003; **17**: 1283-1287 [PMID: 12739119 DOI: 10.1007/s00464-002-8814-x]

26 **Middleton PF**, Sutherland LM, Maddern GJ. Transanal endoscopic microsurgery: a systematic review. *Dis Colon Rectum* 2005; **48**: 270-284 [PMID: 15711865 DOI: 10.1007/s10350-004-0804-8]

27 **Moore JS**, Cataldo PA, Osler T, Hyman NH. Transanal endoscopic microsurgery is more effective than traditional transanal excision for resection of rectal masses. *Dis Colon Rectum* 2008; **51**: 1026-30; discussion 1030 [PMID: 18481147 DOI: 10.1007/s10350-008-9337-x]

28 **Tsai BM**, Finne CO, Nordenstam JF, Christoforidis D, Madoff RD, Mellgren A. Transanal endoscopic microsurgery resection of rectal tumors: outcomes and recommendations. *Dis Colon Rectum* 2010; **53**: 16-23 [PMID: 20010345 DOI: 10.1007/DCR.0b013e3181bbd6ee]

29 **Cataldo PA**, O'Brien S, Osler T. Transanal endoscopic microsurgery: a prospective evaluation of functional results. *Dis Colon Rectum* 2005; **48**: 1366-1371 [PMID: 15933798 DOI: 10.1007/s10350-005-0031-y]

30 **Issa N**, Fenig Y, Khatib M, Yasin M, Powsner E, Khoury W. Transanal Endoscopic Microsurgery Combined with Laparoscopic Colectomy for Synchronous Colorectal Tumors: A Word of Caution. *J Laparoendosc Adv Surg Tech A* 2017; **27**: 605-610 [PMID: 27992283 DOI: 10.1089/lap.2016.0420]

31 **Guerrieri M**, Baldarelli M, de Sanctis A, Campagnacci R, Rimini M, Lezoche E. Treatment of rectal adenomas by transanal endoscopic microsurgery: 15 years' experience. *Surg Endosc* 2010; **24**: 445-449 [PMID: 19565297 DOI: 10.1007/s00464-009-0585-1]

32 **Meyer JE**, Cohen SJ, Ruth KJ, Sigurdson ER, Hall MJ. Young Age Increases Risk of Lymph Node Positivity in Early-Stage Rectal Cancer. *J Natl Cancer Inst* 2016; **108** [PMID: 26719881 DOI: 10.1093/jnci/djv284]

33 **You YN**, Xing Y, Feig BW, Chang GJ, Cormier JN. Young-onset colorectal cancer: is it time to pay attention? *Arch Intern Med* 2012; **172**: 287-289 [PMID: 22157065 DOI: 10.1001/archinternmed.2011.602]

34 **Dinaux AM**, Leijssen LGJ, Bordeianou LG, Kunitake H, Berger DL. Rectal Cancer in Patients Under 50 Years of Age. *J Gastrointest Surg* 2017; **21**: 1898-1905 [PMID: 28842810 DOI: 10.1007/s11605-017-3525-8]

35 **Ganapathi S**, Kumar D, Katsoulas N, Melville D, Hodgson S, Finlayson C, Hagger R. Colorectal cancer in the young: trends, characteristics and outcome. *Int J Colorectal Dis* 2011; **26**: 927-934 [PMID: 21424713 DOI: 10.1007/s00384-011-1174-z]

36 **Khoury W**, Igov I, Issa N, Gimelfarb Y, Duek SD. Transanal endoscopic microsurgery for upper rectal tumors. *Surg Endosc* 2014; **28**: 2066-2071 [PMID: 24519026 DOI: 10.1007/s00464-014-3428-7]

37 **De Graaf EJ**, Doornebosch PG, Tollenaar RA, Meershoek-Klein Kranenbarg E, de Boer AC, Bekkering FC, van de Velde CJ. Transanal endoscopic microsurgery versus total mesorectal excision of T1 rectal adenocarcinomas with curative intention. *Eur J Surg Oncol* 2009; **35**: 1280-1285 [PMID: 19487099 DOI: 10.1016/j.ejso.2009.05.001]

38 **Clancy C**, Burke JP, Albert MR, O'Connell PR, Winter DC. Transanal endoscopic microsurgery versus standard transanal excision for the removal of rectal neoplasms: a systematic review and meta-analysis. *Dis Colon Rectum* 2015; **58**: 254-261 [PMID: 25585086 DOI: 10.1097/DCR.0000000000000309]

39 **Carrara A**, Mangiola D, Pertile R, Ricci A, Motter M, Ghezzi G, Zappalà O, Ciaghi G, Tirone G. Analysis of risk factors for lymph nodal involvement in early stages of rectal cancer: when can local excision be considered an appropriate treatment? Systematic review and meta-analysis of the literature. *Int J Surg Oncol* 2012; **2012**: 438450 [PMID: 22778940 DOI: 10.1155/2012/438450]

40 **Lartigau C**, Lebreton G, Alves A. Local resection for small rectal cancer. *J Visc Surg* 2013; **150**: 325-331 [PMID: 24016715 DOI: 10.1016/j.jviscsurg.2013.08.004]

41 **Borschitz T**, Heintz A, Junginger T. The influence of histopathologic criteria on the long-term prognosis of locally excised pT1 rectal carcinomas: results of local excision (transanal endoscopic microsurgery) and immediate reoperation. *Dis Colon Rectum* 2006; **49**: 1492-506;

discussion 1500 [PMID: 16897336 DOI: 10.1007/s10350-006-0587-1]

42 **Wu ZY**, Zhao G, Chen Z, Du JL, Wan J, Lin F, Peng L. Oncological outcomes of transanal local excision for high risk T(1) rectal cancers. *World J Gastrointest Oncol* 2012; **4**: 84-88 [PMID: 22532882 DOI: 10.4251/wjgo.v4.i4.84]

43 **Issa N**, Fenig Y, Gingold-Belfer R, Khatib M, Khoury W, Wolfson L, Schmilovitz-Weiss H. Laparoscopic Total Mesorectal Excision Following Transanal Endoscopic Microsurgery for Rectal Cancer. *J Laparoendosc Adv Surg Tech A* 2018; **28**: 977-982 [PMID: 29668359 DOI: 10.1089/lap.2017.0399]

44 **Benson AB**, Venook AP, Al-Hawary MM, Arain MA, Chen YJ, Ciombor KK, Cohen S, Cooper HS, Deming D, Garrido-Laguna I, Grem JL, Gunn A, Hoffe S, Hubbard J, Hunt S, Kirilcuk N, Krishnamurthi S, Messersmith WA, Meyerhardt J, Miller ED, Mulcahy MF, Nurkin S, Overman MJ, Parikh A, Patel H, Pedersen K, Saltz L, Schneider C, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Johnson-Chilla A, Gurski LA. NCCN Guidelines Insights: Rectal Cancer, Version 6.2020. *J Natl Compr Canc Netw* 2020; **18**: 806-815 [PMID: 32634771 DOI: 10.6004/jnccn.2020.0032]

45 **Landmann RG**, Wong WD, Hoepfl J, Shia J, Guillem JG, Temple LK, Paty PB, Weiser MR. Limitations of early rectal cancer nodal staging may explain failure after local excision. *Dis Colon Rectum* 2007; **50**: 1520-1525 [PMID: 17674104 DOI: 10.1007/s10350-007-9019-0]

46 **Doornebosch PG**, Ferenschild FT, de Wilt JH, Dawson I, Tetteroo GW, de Graaf EJ. Treatment of recurrence after transanal endoscopic microsurgery (TEM) for T1 rectal cancer. *Dis Colon Rectum* 2010; **53**: 1234-1239 [PMID: 20706065 DOI: 10.1007/DCR.0b013e3181e73f33]

47 **Stipa F**, Giaccaglia V, Burza A. Management and outcome of local recurrence following transanal endoscopic microsurgery for rectal cancer. *Dis Colon Rectum* 2012; **55**: 262-269 [PMID: 22469792 DOI: 10.1097/DCR.0b013e318241ef22]

48 **Madbouly KM**, Remzi FH, Erkek BA, Senagore AJ, Baeslach CM, Khandwala F, Fazio VW, Lavery IC. Recurrence after transanal excision of T1 rectal cancer: should we be concerned? *Dis Colon Rectum* 2005; **48**: 711-9; discussion 719 [PMID: 15768186 DOI: 10.1007/s10350-004-0666-0]

49 **van Gijn W**, Brehm V, de Graaf E, Neijenhuis PA, Stassen LP, Leijtens JW, Van De Velde CJ, Doornebosch PG. Unexpected rectal cancer after TEM: outcome of completion surgery compared with primary TME. *Eur J Surg Oncol* 2013; **39**: 1225-1229 [PMID: 23972571 DOI: 10.1016/j.ejso.2013.08.003]

50 **Morino M**, Allaix ME, Arolfo S, Arezzo A. Previous transanal endoscopic microsurgery for rectal cancer represents a risk factor for an increased abdominoperineal resection rate. *Surg Endosc* 2013; **27**: 3315-3321 [PMID: 23479257 DOI: 10.1007/s00464-013-2911-x]

51 **Roodbeen SX**, Penna M, Mackenzie H, Kusters M, Slater A, Jones OM, Lindsey I, Guy RJ, Cunningham C, Hompes R. Transanal total mesorectal excision (TaTME) versus laparoscopic TME for MRI-defined low rectal cancer: a propensity score-matched analysis of oncological outcomes. *Surg Endosc* 2019; **33**: 2459-2467 [PMID: 30350103 DOI: 10.1007/s00464-018-6530-4]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 1901-1909

DOI: 10.4240/wjgs.v15.i9.1901

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Safety and feasibility of modified duct-to-mucosa pancreaticojejunostomy during pancreatoduodenectomy: A retrospective cohort study

Yi Sun, Xiao-Feng Yu, Han Yao, Shi Xu, Yu-Qiao Ma, Chen Chai

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Isaji S, Japan; Shiryajev YN, Russia

Received: May 20, 2023
Peer-review started: May 20, 2023
First decision: July 8, 2023
Revised: July 20, 2023
Accepted: August 4, 2023
Article in press: August 4, 2023
Published online: September 27, 2023

Yi Sun, Xiao-Feng Yu, Han Yao, Shi Xu, Yu-Qiao Ma, Chen Chai, Department of General Surgery, The People's Hospital of Suzhou New District, Suzhou 215000, Jiangsu Province, China

Corresponding author: Chen Chai, MBBS, MD, Chief Doctor, Professor, Surgeon, Department of General Surgery, The People's Hospital of Suzhou New District, No. 95 Huashan Road, High-tech Zone, Suzhou, Suzhou 215000, Jiangsu Province, China. chaich@lzu.edu.cn

Abstract

BACKGROUND

Pancreatoduodenectomy (PD) is the most effective surgical procedure to remove a pancreatic tumor, but the prevalent postoperative complications, including postoperative pancreatic fistula (POPF), can be life-threatening. Thus far, there is no consensus about the prevention of POPF.

AIM

To determine possible prognostic factors and investigate the clinical effects of modified duct-to-mucosa pancreaticojejunostomy (PJ) on POPF development.

METHODS

We retrospectively collected and analyzed the data of 215 patients who underwent PD between January 2017 and February 2022 in our surgery center. The risk factors for POPF were analyzed by univariate analysis and multivariate logistic regression analysis. Then, we stratified patients by anastomotic technique (end-to-side invagination PJ *vs* modified duct-to-mucosa PJ) to conduct a comparative study.

RESULTS

A total of 108 patients received traditional end-to-side invagination PJ, and 107 received modified duct-to-mucosa PJ. Overall, 58.6% of patients had various complications, and 0.9% of patients died after PD. Univariate and multivariate logistic regression analyses showed that anastomotic approaches, main pancreatic duct (MPD) diameter and pancreatic texture were significantly associated with the incidence of POPF. Additionally, the POPF incidence and operation time in patients receiving modified duct-to-mucosa PJ were 11.2% and 283.4 min, respectively, which were significantly lower than those in patients receiving traditional end-to-side invagination PJ (27.8% and 333.2 minutes).

CONCLUSION
Anastomotic approach, MPD diameter and pancreatic texture are major risk factors for POPF development. Compared with traditional end-to-side invagination PJ, modified duct-to-mucosa PJ is a simpler and more efficient technique that results in a lower incidence of POPF. Further studies are needed to validate our findings and explore the clinical applicability of our technique for laparoscopic and robotic PD.

Key Words: Pancreaticojejunostomy; Pancreatoduodenectomy; Suture technique; Pancreatic fistula

Core Tip: We evaluated the safety and feasibility of modified duct-to-mucosa pancreaticojejunostomy (PJ) during pancreatoduodenectomy (PD) by analyzing the data of 215 patients who underwent PD in our surgery center. Compared with traditional end-to-side invagination PJ, modified duct-to-mucosa PJ was a simpler and more efficient technique that resulted in a lower incidence of postoperative pancreatic fistula (11.2%). Meanwhile, we found that anastomotic approach, main pancreatic duct diameter and pancreatic texture were major risk factors for postoperative pancreatic fistula development.

Citation: Sun Y, Yu XF, Yao H, Xu S, Ma YQ, Chai C. Safety and feasibility of modified duct-to-mucosa pancreaticojejunostomy during pancreatoduodenectomy: A retrospective cohort study. *World J Gastrointest Surg* 2023; 15(9): 1901-1909
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/1901.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.1901

INTRODUCTION

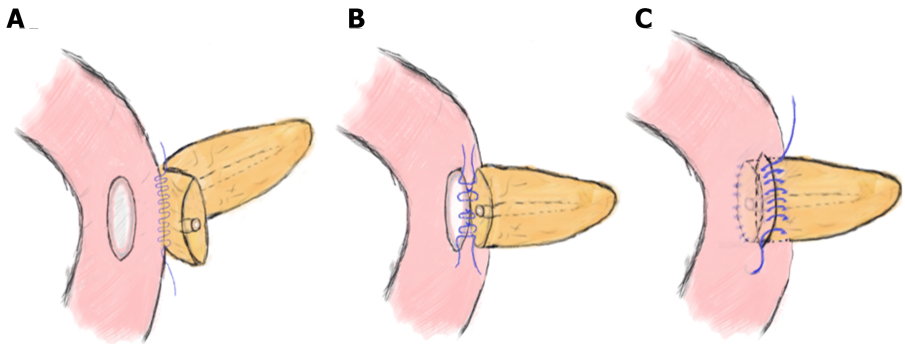
Pancreatoduodenectomy (PD) is widely performed as the standard treatment for resectable tumors in the pancreas and periampullary region. Despite recent advances in surgical techniques and perioperative management, the incidence of postoperative complications and overall mortality remain high[1]. Specifically, a postoperative pancreatic fistula (POPF), the most common and potentially deadly postoperative complication, develops in 5% to 26% of patients[2]. To improve the operation efficacy, effective prevention of POPF can be crucial. Therefore, proper assessment of relevant risk factors for POPF is necessary, and anastomosis has proven to be an effective treatment approach[3]. The intention of this retrospective, single-center study is to explore the risk factors for POPF and further determine the effects of modified duct-to-mucosa pancreaticojejunostomy (PJ) on POPF prevention.

MATERIALS AND METHODS

The data of a series of 215 consecutive patients who underwent elective PD for benign or malignant pathologies in our center between January 2017 and February 2022 were analyzed. Patients were then stratified into two groups according to the anastomotic method for further analysis. Patients with a pathological diagnosis of periampullary lesions, with an American Society of Anesthesiologists score I-III, and who provided informed consent were included in the study. Patients with incomplete medical records, who underwent neoadjuvant treatment preoperatively, who had undergone emergency surgery, or with synchronous cancer were excluded from the study. The primary outcome measure was the POPF rate, and the secondary outcome measures were mortality rates, operative time, blood loss and length of hospital stay. Other outcomes of interest included demographic characteristics (age, sex, anamnesis, concomitant disease, biochemical indices) and intraoperative data (main pancreatic duct (MPD) diameter, pancreas texture, type of anastomosis). According to the International Study Group on Pancreatic Surgery 2016 consensus statement, POPD was strictly defined as “any measurable volume of drained fluid on or after postoperative Day 3 with an amylase level more than 3 times the upper limit of the normal amylase range and having an impact on clinical outcome”[4]. A grade A pancreatic fistula was defined as a "biochemical leak", a grade B fistula required changes in postoperative management, and a grade C fistula needed reoperation or led to organ failure and/or mortality[4]. Mortality specifically referred to the death of inpatients within 3 mo after surgery.

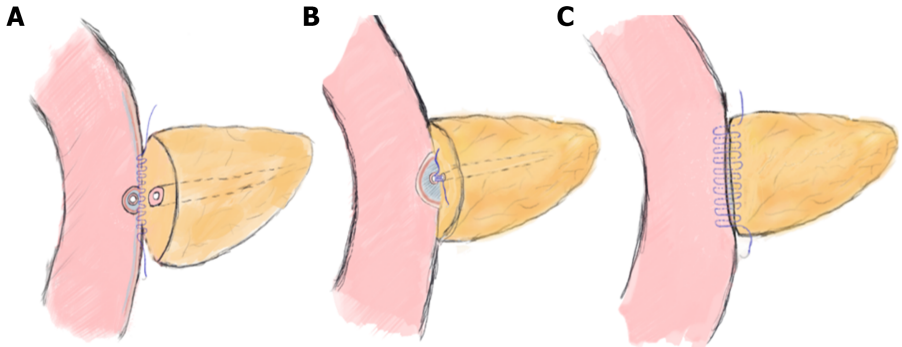
Surgical procedure

Experienced hepato-bilio-pancreatic surgeons performed standard PD (Child's procedure) on all the patients, and there were no differences between the two groups except for the PJ procedure. The routine procedures for placing the pancreatic stent tube were as follows: After suturing the posterior wall of the pancreatic stump, a right-sized stent tube (8-10 cm in length) with side holes was inserted 3-5 cm into the pancreatic duct, and the other end was placed approximately 5 cm into the small intestine. Then, a stitch was placed to suture and fix the stent tube on the posterior side of the pancreas. Classic end-to-side invagination PJ was implemented as previously reported[5], and the key steps are shown in Figure 1. The procedures of modified duct-to-mucosa PJ were as follows: (1) After enterotomy was performed according



DOI: 10.4240/wjgs.v15.i9.1901 **Copyright** ©The Author(s) 2023.

Figure 1 Schematic diagram of end-to-side invagination pancreaticojejunostomy. A: Continuous suturing was performed between the rear side of the pancreatic stump (approximately 1.5 cm from its edge) and the jejunal seromuscular layer with a 3-0 Prolene slip line; B: Suture of the pancreatic margin and seromuscular layer of the jejunum intermittently; C: The pancreatic stump was inserted into the jejunum, and the anterior side of the pancreas and jejunal seromuscular layer were continuously sutured.



DOI: 10.4240/wjgs.v15.i9.1901 **Copyright** ©The Author(s) 2023.

Figure 2 Schematic diagram of modified duct-to-mucosa pancreaticojejunostomy. A: Perform continuous suturing between the rear edge of the pancreatic stump and jejunal seromuscular layer with a 3-0 Prolene suture; B: Sew 3-4 stiches continuously in the posterior wall of the pancreatic duct and the jejunal mucosa with 4-0 Prolene sutures; C: Continuous suturing was performed between the front edge of the pancreatic stump and the whole layer of the jejunum.

to the MPD diameter, the rear edge of the pancreatic stump and the posterior jejunal seromuscular layer were continuously sutured with 3-0 Prolene sutures. The needle was inserted vertically into the pancreas 1.5 cm from the rear edge of the pancreatic stump and passed through the posterior wall of the jejunum after passing through its seromuscular layers. The spacing was approximately 8–10 mm, and the margin was greater than 10 mm (Figure 2A); (2) The posterior wall of the pancreatic duct and the jejunal mucosa were continuously sutured with three to four 4-0 Prolene sutures. The spacing and margin were adjusted according to the MPD diameter (Figure 2B); and (3) After the stent was inserted, the front edges of the pancreatic stump and whole-layer of the jejunum were anastomosed with 3-0 Prolene running sutures. The spacing and margin were similar to those of the first stitch. Although the depth of needle entry was controlled at approximately 1 cm to avoid damaging the MPD on the pancreatic side, it was deeper on the jejunal side to ensure suturing of the whole layer (Figure 2C). In our modified method, tension-free sutures were applied, and no dead space was left between the pancreatic stump and jejunum.

Perioperative management

During the perioperative period, most treatment measures were the same for each patient. The preoperative management included smoking and drinking cessation, weight control, skin preparation and antibiotic prophylaxis. Epidural analgesia and gastrointestinal decompression were administered during the operation. Drain amylase levels were routinely measured on the 1st, 3rd and 5th days after surgery, while octreotide was used simultaneously for 7-10 d. Other postoperative management included thromboprophylaxis, nutritional support and controlled fluid infusion. The patients were followed up for 3 mo after discharge.

Statistical analysis

SPSS 21.0 statistical software was used for data description and analysis. Continuous variables are expressed as the mean ± SD, and Student's t test was used for comparisons where appropriate. Categorical variables were analyzed by using Fisher's exact test and the χ^2 test. Univariate analysis was used to evaluate the factors associated with POPF development, and multivariate regression analysis was performed to determine the independent risk factors.

RESULTS

Of the 215 patients with an average age of 54.5±13.3 years, 112 patients were male and 103 were female. The percentages of patients with diabetes mellitus, smoking history and previous abdominal surgery were 23.7%, 42.8% and 22.3%, respectively. Preoperative blood tests showed that the respective values of total bilirubin and albumin were 186.9 (μmol/L) and 35.4 (g/L). More than half of the patients (57.2%) had undergone biliary drainage preoperatively. According to the pathological results, the most prevalent conditions were ampullary carcinoma, pancreatic head carcinoma and distal cholangiocarcinoma. The average total operative time was 308.4 min, while the average intraoperative blood loss was 555.1 mL. The overall complication rate was 53.5% (115/215), and the mortality rate was 0.9% (2/215). Specifically, POPF was the most common complication (19.5%), followed by peritoneal infection (13%), abdominal bleeding (11.6%) and bile leakage (9.3%). Additionally, the two cases of death were due to abdominal bleeding associated with POPF development (Table 1).

As the most common postoperative complication, POPF can also increase the risks of abdominal infection and hemorrhage[6]. Consequently, we further explored possible factors correlated with POPF development through univariate analysis. As shown in Table 2, POPF development had no significant correlation with the following factors: Age, sex, smoking history, preoperative bilirubin and albumin, preoperative biliary drainage, previous abdominal surgery, blood loss, or operative time. Anastomotic techniques (P = 0.0015), MPD diameter (P = 0.0015) and pancreatic texture (P = 0.0386) were significantly correlated with POPF development in the multivariate logistic regression analysis.

Table 3 shows the differences between traditional end-to-side invagination PJ and modified duct-to-mucosa PJ. Of these patients, 108 received traditional end-to-side invagination PJ, and 107 received modified duct-to-mucosa PJ. The results indicated no difference between the groups in terms of age, sex, pancreatic texture, postoperative hospital stay or mortality. However, patients subjected to modified duct-to-mucosa PJ had a lower incidence of POPF (11.2%) than the other group (27.8%). Further analysis indicated that there were 7 cases of grade A POPFs, 4 cases of grade B POPFs, and 1 case of grade C POPF in the modified PJ group. However, in the traditional group, the number of cases at each grade was 20, 7 and 3, respectively. Obviously, modified PJ might attenuate POPF severity based on the comparison results. Similarly, the modified anastomotic method demonstrated its superiority in terms of operative time (end-to-side invagination PJ: modified duct-to-mucosa PJ: 333.2 min vs. 283.4 min). Contrary to expectations, there were more patients with MPD diameters less than 3 mm in the modified method group, a factor that was previously found to be significantly correlated with POPF development.

DISCUSSION

With the advancements in surgical techniques and perioperative care, the mortality of patients subjected to PD has gradually decreased, while the incidence of POPF remains high[7,8]. As the most frequent lethal complication, POPF has been heavily discussed to reach a consensus on its prevention. Our research preliminarily found that the independent risk factors for POPF included PJ method, MPD diameter and pancreatic texture. Our result was partially consistent with the result of a recent meta-analysis evaluating pancreatic texture and MPD size as risk factors for POPF development[9]. Other factors, including sex, body mass index, anastomotic techniques, intraoperative blood loss, operative time and drain fluid amylase, have also been reported to be related to POPF development[10-12]. Obviously, numerous studies on the risk factors for POPF have indicated seemingly conflicting and perplexing results. Ecker *et al*[13] believed that attempting to create a reliable prediction model based on the risk factors for POPF development seemed to be unrealistic and had limited effectiveness. Nevertheless, we believe that the abovementioned factors are valuable references that can help surgeons improve the therapeutic efficacy during the perioperative period.

In clinical practice, various surgical techniques have been applied to prevent POPF development, such as reconstruction methods [PJ, pancreaticogastrostomy (PG)], anastomotic techniques (Blumgart's method[14], Kakita's method[15], Peng's binding PJ[16] and end-to-side invagination anastomosis) and stent placement. Debates about the pros and cons of the various surgical techniques are ongoing. A multicenter randomized trial conducted between June 2009 and August 2012 showed that PG was more efficient than PJ in reducing the incidence of POPF development[17]. Conversely, in another single-center, phase 3, randomized clinical trial, researchers recommended PJ for patients at high risk for POPF development[18]. In the present study, all the patients were subjected to PJ because surgeons were more skilled and experienced in performing this surgical technique. Two PJ anastomotic techniques were used here: end-to-side invagination anastomosis and modified duct-to-mucosa anastomosis. The operation time (283.4 minutes) and POPF (11.2%) incidence of the modified method group were significantly lower than those of the comparison group. Our results were roughly consistent with some other surgical center reports[19,20]. Classic invagination PJ can completely drain pancreatic juice from the main pancreatic duct and pancreatic stump into the intestinal cavity, but there are risks of pancreatic stump hemorrhage, pancreatic duct obstruction, and pancreatitis[16,21]. Many scholars have conducted comparative studies of various anastomosis methods. Wang *et al*[22] found no significant differences among duct-to-mucosa PJ, invagination PJ and binding PJ in the prevention of postoperative complications and death. While Ratnayake's research favored duct-to-mucosa PG[23], Peng's and Berger's studies indicated that invagination could reduce the incidence of POPF development more significantly[16,21]. Compared with traditional duct-to-mucosa PJ, our technique used double-layer continuous suturing of posterior tissues and single-layer continuous suturing of anterior tissues, namely, "semicontact continuous anastomosis". Our modified method had several advantages: first, the procedure better ensured the continuity between the pancreatic duct and the jejunal mucosa; second, tension-free and continuous anastomosis prevented cutting of the pancreas parenchyma; and third, convenient procedures helped reduce

Table 1 Clinical characteristics of the patients, *n* (%)

Variables	Total patients, *n* = 215
Gender (male/female)	112/103
Age (yr)	54.5 ± 13.3
Diabetes mellitus	51 (23.7)
Smoking history	92 (42.8)
History of abdominal operation	48 (22.3)
Preoperative total bilirubin (μmol/L)	186.9 ± 74.4
Preoperative biliary drainage	123 (57.2)
Albumin (g/L)	35.4 ± 4.8
Pathological types	
Ampullary carcinoma	102 (47.4)
Pancreatic head carcinoma	51 (23.7)
Distal cholangiocarcinoma	35 (16.3)
Duodenal papillary carcinoma	22 (10.2)
Ampullary benign diseases	2 (0.9)
Other rare diseases	3 (1.4)
Anastomotic method	
End-to-side invagination pancreatoduodenectomy	108 (50.2)
Modified duct-to-mucosa pancreatoduodenectomy	107 (47.8)
Main pancreatic duct diameter	
≤ 3 mm	121 (56.3)
> 3 mm	94 (43.7)
Pancreatic texture	
Hard	112 (52.1)
Soft	103 (47.9)
Postoperative complications	
Postoperative pancreatic fistula	42 (19.5)
Grade A	27 (12.6)
Grade B	11 (5.1)
Grade C	4 (1.9)
Operative time (min)	308.4 ± 57.3
Blood loss (mL)	555.1 ± 228.7
Peritoneal infection	28 (13)
Intra-abdominal hemorrhage	25 (11.6)
Biliary fistula	20 (9.3)
Re-operation	4 (1.9)
Mortality	2 (0.9)
Length of stay (d)	15.7 ± 2.7

the difficulty of PD and the surgeon's training time. With the popularity of laparoscopic and robotic PD, the advantages of our modified anastomotic approach might better meet the strict requirements of these operations. Although more high-quality evidence is required to demonstrate the benefits of modified duct-to-mucosa anastomosis, our present study indicated that it was a feasible and effective method for reducing the incidence of POPF development.

Table 2 Univariate and Multivariate logistic regression analysis of risk factors associated with postoperative pancreatic fistula

	Univariate		Multivariate	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Age (≤ 60 *vs* > 60 yr)	1.603 (0.800-3.203)	0.188		
Gender (male *vs* female)	1.143 (0.594-2.266)	0.7		
Diabetes mellitus	0.711 (0.324-1.585)	0.427		
Smoking history	1.275 (0.649-2.470)	0.481		
History of abdominal operation	0.782 (0.355-1.757)	0.57		
Preoperative total bilirubin (≤ 171 *vs* > 171 μmol/L)	1.295 (0.654-2.700)	0.475		
Preoperative biliary drainage (yes *vs* no)	1.444 (0.740-2.894)	0.385		
Serum albumin (≤ 35 *vs* > 35 g/L)	0.665 (0.322-1.359)	0.275		
Anastomotic method (End-to-side invagination pancreaticojejunostomy *vs* Modified duct-to-mucosa pancreaticojejunostomy)	3.045 (1.500-6.248)	0.002[a]	0.288 (0.129-0.606)	0.0015[a]
Main pancreatic duct diameter (≤ 3 *vs* > 3 mm)	2.599 (1.255-5.676)	0.011[a]	3.608 (1.678-8.302)	0.0015[a]
Operative time (≤ 300 *vs* > 300 min)	1.125 (0.583-2.181)	0.735		
Blood loss (≤ 600 *vs* > 600 mL)	0.855 (0.431-1.645)	0.651		
Pancreatic texture (Hard *vs* Soft)	0.494 (0.253-0.956)	0.043[a]	2.171 (1.051-4.602)	0.0386[a]

[a]Statistically significant.

Table 3 Comparison results between End-to-side invagination pancreatoduodenectomy and Modified duct-to-mucosa pancreatoduodenectomy, *n* (%)

	End-to-side invagination pancreatoduodenectomy (*n* = 108)	Modified duct-to-mucosa pancreatoduodenectomy (*n* = 107)	*P* value
Age (yr)	53.6 ± 13.7	55.3 ± 12.8	0.336
Male	50 (46.3)	62 (57.9)	0.088
Pancreatic texture			0.152
Hard	51 (47.2)	61 (57.0)	
Soft	57 (52.8)	46 (43.0)	
Main pancreatic duct diameter			0.033[a]
≤ 3 mm	53 (49.1)	68 (63.6)	
> 3 mm	55 (50.9)	39 (36.4)	
Operative time (min)	333.2 ± 48.9	283.4 ± 54.2	< 0.0001[a]
Blood loss (mL)	571.4 ± 257.3	538.7 ± 195.4	0.295
Postoperative complications			

Postoperative pancreatic fistula	30 (27.8)	12 (11.2)	0.002[a]
Grade A	20 (18.5)	7 (15.9)	
Grade B	7 (6.5)	4 (3.7)	
Grade C	3 (2.8)	1 (0.9)	
Peritoneal infection	13 (12.0)	15 (13.9)	0.38
Intra-abdominal hemorrhage	15 (13.9)	10 (9.3)	0.299
Biliary fistula	11 (10.2)	9 (8.3)	0.654
Re-operation	3 (2.8)	1 (0.9)	0.622
Mortality	2 (1.9)	0 (0)	0.498
Length of stay (d)	16 ± 2.6	15.5 ± 2.8	0.187

[a]Statistically significant.

This study also has some limitations that might weaken the persuasiveness of the evidence. First, our study is a single-center retrospective study with a limited sample size. Second, the limited follow-up time may not accurately reflect the patient's long-term clinical outcome. Therefore, large-scale randomized studies with long-term follow-up are desperately needed.

CONCLUSION

In conclusion, we found that anastomotic approaches, MPD diameter and pancreatic texture were major risk factors for POPF development. In addition, modified duct-to-mucosa PJ had advantages of shorter operation time and lower POPF incidence over classic end-to-side invagination PJ. Although the findings need to be further validated with more high-quality evidence, this modified method could be considered for some patients undergoing PD.

ARTICLE HIGHLIGHTS

Research background

Pancreatoduodenectomy (PD) is widely used as an effective surgical treatment for pancreatic tumors, but there is currently no consensus on how to effectively prevent postoperative complications, especially pancreatic fistula. How to prevent postoperative pancreatic fistula (POPF) is a current research hotspot and our research focuses on how to solve this problem by improving surgical methods

Research motivation

To demonstrate the safety and feasibility of modified duct-to-mucosa pancreaticojejunostomy (PJ) during PD, especially in the terms of preventing POPF.

Research objectives

To identify independent risk factors for POPF and evaluate the clinical outcomes of two anastomotic techniques (end-to-side invagination PJ *versus* modified duct-to-mucosa PJ).

Research methods

This stud was a retrospective cohort study which collected and analyzed the information of patients undergoing PD in our hospital. Univariate analysis and multivariate logistic regression analysis were used to analyze the risk factors of POPF and subgroup analysis were conducted to compare the different outcomes between end-to-side invagination PJ and modified duct-to-mucosa PJ.

Research results

Anastomotic approaches, main pancreatic duct (MPD) diameter and pancreatic texture were proven to be significantly associated with the incidence of POPF. And modified duct-to-mucosa PJ could significantly decrease the POPF incidence (11.2%) and operation time (283.4 min) in patients compared with traditional end-to-side invagination.

Research conclusions

Modified duct-to-mucosa PJ had advantages of shorter operation time and lower POPF incidence over classic end-to-side invagination PJ. Additionally, we found that anastomotic approaches, MPD diameter and pancreatic texture were major risk factors for POPF development.

Research perspectives

Modified duct-to-mucosa PJ is effective and safe according to preliminary outcomes. It is an innovative anastomotic technique with great application prospects in PD and also has broad application prospects in future robotic or minimally invasive operations of pancreatic tumors.

FOOTNOTES

Author contributions: Sun Y and Chai C contributed to conceptualization; Yao H and Yu XF contributed to investigation; Ma YQ and Xu S contributed to data curation; Sun Y contributed to writing – original draft preparation; Sun Y and Chai C contributed to writing – review & editing; All authors read and approved the final manuscript.

Supported by Clinical Medical Science and Technology Development Foundation of Jiangsu University, No. JLY2021118; Science and Technology Project of Suzhou City, No. SKJY2021039.

Institutional review board statement: This retrospective study conformed with the ethical guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board of The People's hospital of Suzhou New District.

Informed consent statement: Written informed consent was obtained from all the subjects involved in this study.

Conflict-of-interest statement: All the Authors have no conflict of interest related to the manuscript.

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

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

Country/Territory of origin: China

ORCID number: Yi Sun 0000-0002-4336-2947; Chen Chai 0000-0002-0258-5650.

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

REFERENCES

1 **Torphy RJ**, Fujiwara Y, Schulick RD. Pancreatic cancer treatment: better, but a long way to go. *Surg Today* 2020; **50**: 1117-1125 [PMID: 32474642 DOI: 10.1007/s00595-020-02028-0]

2 **Marchegiani G**, Bassi C. Prevention, prediction, and mitigation of postoperative pancreatic fistula. *Br J Surg* 2021; **108**: 602-604 [PMID: 33942063 DOI: 10.1093/bjs/znab125]

3 **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]

4 **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]

5 **Bassi C**, Falconi M, Molinari E, Mantovani W, Butturini G, Gumbs AA, Salvia R, Pederzoli P. Duct-to-mucosa *vs* end-to-side pancreaticojejunostomy reconstruction after pancreaticoduodenectomy: results of a prospective randomized trial. *Surgery* 2003; **134**: 766-771 [PMID: 14639354 DOI: 10.1016/s0039-6060(03)00345-3]

6 **Gouillat C**, Gigot JF. Pancreatic surgical complications--the case for prophylaxis. *Gut* 2001; **49** Suppl 4: iv32-iv39 [PMID: 11878792 DOI:

10.1136/gut.49.suppl_4.iv29]
7 **Assifi MM**, Lindenmeyer J, Leiby BE, Grunwald Z, Rosato EL, Kennedy EP, Yeo CJ, Berger AC. Surgical Apgar score predicts perioperative morbidity in patients undergoing pancreaticoduodenectomy at a high-volume center. *J Gastrointest Surg* 2012; **16**: 275-281 [PMID: 22033701 DOI: 10.1007/s11605-011-1733-1]
8 **Fu SJ**, Shen SL, Li SQ, Hu WJ, Hua YP, Kuang M, Liang LJ, Peng BG. Risk factors and outcomes of postoperative pancreatic fistula after pancreatico-duodenectomy: an audit of 532 consecutive cases. *BMC Surg* 2015; **15**: 34 [PMID: 25887526 DOI: 10.1186/s12893-015-0011-7]
9 **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]
10 **Hu BY**, Wan T, Zhang WZ, Dong JH. Risk factors for postoperative pancreatic fistula: Analysis of 539 successive cases of pancreaticoduodenectomy. *World J Gastroenterol* 2016; **22**: 7797-7805 [PMID: 27678363 DOI: 10.3748/wjg.v22.i34.7797]
11 **Yang J**, Huang Q, Wang C. Postoperative drain amylase predicts pancreatic fistula in pancreatic surgery: A systematic review and meta-analysis. *Int J Surg* 2015; **22**: 38-45 [PMID: 26211439 DOI: 10.1016/j.ijsu.2015.07.007]
12 **Peng YP**, Zhu XL, Yin LD, Zhu Y, Wei JS, Wu JL, Miao Y. Risk factors of postoperative pancreatic fistula in patients after distal pancreatectomy: a systematic review and meta-analysis. *Sci Rep* 2017; **7**: 185 [PMID: 28298641 DOI: 10.1038/s41598-017-00311-8]
13 **Ecker BL**, McMillan MT, Allegrini V, Bassi C, Beane JD, Beckman RM, Behrman SW, Dickson EJ, Callery MP, Christein JD, Drebin JA, Hollis RH, House MG, Jamieson NB, Javed AA, Kent TS, Kluger MD, Kowalsky SJ, Maggino L, Malleo G, Valero V 3rd, Velu LKP, Watkins AA, Wolfgang CL, Zureikat AH, Vollmer CM Jr. Risk Factors and Mitigation Strategies for Pancreatic Fistula After Distal Pancreatectomy: Analysis of 2026 Resections From the International, Multi-institutional Distal Pancreatectomy Study Group. *Ann Surg* 2019; **269**: 143-149 [PMID: 28857813 DOI: 10.1097/SLA.0000000000002491]
14 **Grobmyer SR**, Kooby D, Blumgart LH, Hochwald SN. Novel pancreaticojejunostomy with a low rate of anastomotic failure-related complications. *J Am Coll Surg* 2010; **210**: 54-59 [PMID: 20123332 DOI: 10.1016/j.jamcollsurg.2009.09.020]
15 **Fujii T**, Sugimoto H, Yamada S, Kanda M, Suenaga M, Takami H, Hattori M, Inokawa Y, Nomoto S, Fujiwara M, Kodera Y. Modified Blumgart anastomosis for pancreaticojejunostomy: technical improvement in matched historical control study. *J Gastrointest Surg* 2014; **18**: 1108-1115 [PMID: 24733259 DOI: 10.1007/s11605-014-2523-3]
16 **Peng SY**, Wang JW, Lau WY, Cai XJ, Mou YP, Liu YB, Li JT. Conventional *vs* binding pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized trial. *Ann Surg* 2007; **245**: 692-698 [PMID: 17457161 DOI: 10.1097/01.sla.0000255588.50964.5d]
17 **Topal B**, Fieuws S, Aerts R, Weerts J, Feryn T, Roeyen G, Bertrand C, Hubert C, Janssens M, Closset J; Belgian Section of Hepatobiliary and Pancreatic Surgery. Pancreaticojejunostomy *vs* pancreaticogastrostomy reconstruction after pancreaticoduodenectomy for pancreatic or periampullary tumours: a multicentre randomised trial. *Lancet Oncol* 2013; **14**: 655-662 [PMID: 23643139 DOI: 10.1016/S1470-2045(13)70126-8]
18 **Andrianello S**, Marchegiani G, Malleo G, Masini G, Balduzzi A, Paiella S, Esposito A, Landoni L, Casetti L, Tuveri M, Salvia R, Bassi C. Pancreaticojejunostomy With Externalized Stent *vs* Pancreaticogastrostomy With Externalized Stent for Patients With High-Risk Pancreatic Anastomosis: A Single-Center, Phase 3, Randomized Clinical Trial. *JAMA Surg* 2020; **155**: 313-321 [PMID: 32101272 DOI: 10.1001/jamasurg.2019.6035]
19 **Zhang H**, Zhu F, Shen M, Tian R, Shi CJ, Wang X, Jiang JX, Hu J, Wang M, Qin RY. Systematic review and meta-analysis comparing three techniques for pancreatic remnant closure following distal pancreatectomy. *Br J Surg* 2015; **102**: 4-15 [PMID: 25388952 DOI: 10.1002/bjs.9653]
20 **El Nakeeb A**, El Hemaly M, Askr W, Abd Ellatif M, Hamed H, Elghawalby A, Attia M, Abdallah T, Abd ElWahab M. Comparative study between duct to mucosa and invagination pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized study. *Int J Surg* 2015; **16**: 1-6 [PMID: 25682724 DOI: 10.1016/j.ijsu.2015.02.002]
21 **Berger AC**, Howard TJ, Kennedy EP, Sauter PK, Bower-Cherry M, Dutkevitch S, Hyslop T, Schmidt CM, Rosato EL, Lavu H, Nakeeb A, Pitt HA, Lillemoe KD, Yeo CJ. Does type of pancreaticojejunostomy after pancreaticoduodenectomy decrease rate of pancreatic fistula? A randomized, prospective, dual-institution trial. *J Am Coll Surg* 2009; **208**: 738-47; discussion 747 [PMID: 19476827 DOI: 10.1016/j.jamcollsurg.2008.12.031]
22 **Wang W**, Zhang Z, Gu C, Liu Q, Liang Z, He W, Chen J, Lai J. The optimal choice for pancreatic anastomosis after pancreaticoduodenectomy: A network meta-analysis of randomized control trials. *Int J Surg* 2018; **57**: 111-116 [PMID: 29777880 DOI: 10.1016/j.ijsu.2018.04.005]
23 **Ratnayake CBB**, Wells CI, Kamarajah SK, Loveday B, Sen G, French JJ, White S, Pandanaboyana S. Critical appraisal of the techniques of pancreatic anastomosis following pancreaticoduodenectomy: A network meta-analysis. *Int J Surg* 2020; **73**: 72-77 [PMID: 31843679 DOI: 10.1016/j.ijsu.2019.12.003]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 1910-1918

DOI: 10.4240/wjgs.v15.i9.1910

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Application of early enteral nutrition nursing based on enhanced recovery after surgery theory in patients with digestive surgery

Yan-Ru Shao, Xia Ke, Li-Hua Luo, Jin-Dong Xu, Li-Qian Xu

Specialty type: Nursing

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Abu Gazala M, Israel; Vettor R, Italy

Received: May 9, 2023
Peer-review started: May 9, 2023
First decision: May 25, 2023
Revised: June 25, 2023
Accepted: August 2, 2023
Article in press: August 2, 2023
Published online: September 27, 2023

Yan-Ru Shao, Xia Ke, Li-Hua Luo, Jin-Dong Xu, Li-Qian Xu, Department of Anesthesiology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou 510062, Guangdong Province, China

Corresponding author: Li-Qian Xu, BSc, Nurse, Department of Anesthesiology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, No. 106 Zhongshan Second Road, Yuexiu District, Guangzhou 510062, Guangdong Province, China. xu.liqian0706@163.com

Abstract

BACKGROUND

Postoperative nursing can improve the restlessness and gastrointestinal function of patients with tracheal intubation under general anesthesia in digestive surgery. Wide application of various nursing methods and routine nursing in perioperative nursing of patients with general anesthesia in digestive surgery.

AIM

To investigate the impact of early postoperative enteral nutrition nursing based on the enhanced recovery after surgery (ERAS) theory on postoperative agitation and gastrointestinal recovery in patients undergoing general anesthesia that experienced tracheal intubation.

METHODS

The data of 126 patients with digestive surgery from May 2019 to February 2022 were retrospectively analyzed. According to different nursing methods, they were divided into control group and observation group, with 63 cases in observation group and 63 cases in control group. The patients in the control group had standard perioperative nursing care, whereas those in the observation group got enteral nourishment as soon as possible after surgery in accordance with ERAS theory. Both the rate and quality of gastrointestinal function recovery were compared between the two groups after treatment ended. Postoperative anesthesia-related adverse events were tallied, patients' nutritional statuses were monitored, and the Riker sedation and agitation score (SAS) was used to measure the incidence of agitation.

RESULTS

When compared to the control group, the awake duration, spontaneous breathing recovery time, extubation time and postoperative eye-opening time were all

considerably shorter ($P < 0.05$). There was no significant difference in the recovery time of orientation force between the two groups ($P > 0.05$); however, the observation group had a lower SAS score than the control group ($P < 0.05$). The recovery time for normal intestinal sounds, the time it took to have the first postoperative exhaust, the time it took to have the first postoperative defecation, and the time it took to have the first postoperative half-fluid feeding were all faster in the observation group than in the control group ($P < 0.05$); Fasting blood glucose was lower in the observation group compared to the control group ($P < 0.05$), while the albumin and hemoglobin levels were higher on the first and third postoperative days; however, there was no statistically significant difference in the incidence of anesthesia-related adverse reactions between the two groups ($P > 0.05$).

CONCLUSION

The extremely early postoperative enteral nutrition nursing based on ERAS theory can reduce the degree of agitation, improve the quality of recovery, promote the recovery of gastrointestinal function, and improve the nutritional status of patients in the recovery period after tracheal intubation under general anesthesia.

Key Words: Enhanced recovery after surgery; Extremely early postoperative enteral nutrition nursing; Gastrointestinal surgery; Tracheal intubation under general anesthesia; Agitation during recovery; Recovery of gastrointestinal function

Core Tip: All the gastrointestinal surgery patients included in this study were gastrointestinal cancer patients. Postoperative enhanced recovery after surgery nursing and postoperative extreme nutritional induction nursing were widely used in gastrointestinal cancer nursing alone. This study integrated the concept of postoperative enhanced recovery after surgery into early enteral nutrition nursing, and integrated and re-innovative previous nursing methods. The purpose of this study is to compare the nursing effect of this nursing method with that of traditional nursing method. This study found that the enhanced recovery after surgery theory based on the very early postoperative enteral nutrition intervention nursing effect is good.

Citation: Shao YR, Ke X, Luo LH, Xu JD, Xu LQ. Application of early enteral nutrition nursing based on enhanced recovery after surgery theory in patients with digestive surgery. *World J Gastrointest Surg* 2023; 15(9): 1910-1918
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/1910.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.1910

INTRODUCTION

Gastrointestinal tumor is a common malignant tumor, which is usually treated by surgery or radiotherapy and chemotherapy, which can effectively reduce the clinical symptoms and improve the prognosis. Relevant studies have pointed out that patients with digestive tract tumors have psychological fluctuations due to long-term illness and worry about surgical risks. In addition, preoperative fasting and water prohibition before surgery reduce the tolerance of the body, which is not conducive to the operation[1]. It has been reported that enhanced recovery after surgery (ERAS) can reduce the stress response after surgery and improve the prognosis of patients[2]. ERAS is a group of surgical models that use a variety of efficient techniques during the perioperative period to lessen the stress and trauma of surgery and hasten the postoperative rehabilitation of patients. These strategies are backed by evidence-based medical data. Early postoperative nutritional support is the core concept of ERAS. Early feeding can not only stimulate gastrointestinal peristalsis and promote the recovery of gastrointestinal function, but also nourish the intestine, maintain the integrity of intestinal mucosa structure and function, reduce the balance of intestinal flora, and thus reduce the incidence of wound infection and other complications[3]. Previous reports also pointed out that the application of ERAS in the perioperative intervention of patients undergoing surgical treatment can promote postoperative recovery[4]. Consequently, the purpose of this research is to notify clinical interventions for patients with this disease by investigating the impact of ERAS-theorized extremely early postoperative enteral nutrition nursing on post-anesthesia agitation and gastrointestinal recovery following tracheal intubation for general anesthesia.

MATERIALS AND METHODS

Clinical data

The data of 126 patients with digestive surgery from May 2019 to February 2022 were retrospectively analyzed. According to different nursing methods, they were divided into control group and observation group, with 63 cases in observation group and 63 cases in control group. As can be shown in Table 1, there was no statistically significant difference in clinical data between the two groups ($P > 0.05$).

Table 1 Comparison of clinical data between the two groups

Item	Observation group (n = 63)	Control group (n = 63)	χ^2/t value	P value
Gender				
Male	36	39	0.297	0.586
Female	27	24		
Age (yr)	51.29 ± 6.31	52.01 ± 6.52	0.630	0.530
Primary disease				
Gastric tumor	24	23	0.548	0.459
Colorectal tumor	39	40		
BMI (kg/m^2)	21.59 ± 1.93	21.86 ± 1.79	0.814	0.417
Operation time (min)	108.14 ± 8.72	110.52 ± 8.13	1.585	0.116
ASA grading				
Grade 1	5	7		
Grade 2	58	56		

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

Inclusion criteria

(1) Patients who fulfilled the diagnostic criteria for colorectal and gastric cancer[5]; and (2) The clinical data was complete.

Exclusion criteria

(1) Patients with contraindications to enteral nutrition; (2) Patients with cognitive dysfunction or mental illness; (3) Patients with severe cardiac, liver and renal dysfunction; (4) Survival time ≤ 3 mo; and (5) Patients with other malignant tumor diseases.

Methods

The patients in the control group underwent standard perioperative nursing care, with venous access established before surgery, vital signs monitored, and standard anesthesia and resuscitation protocols used to keep diastolic and systolic blood pressure at 60-80 mmHg and 90-100 mm Hg, respectively, throughout the procedure. Patients were given infusion of conventional fluids and a routine indwelling catheter. After operation, parenteral nutrition support was performed before anal exhaust. After exhaust, liquid food was taken and analgesic was injected. Patients were instructed to get out of bed according to their wishes.

According to relevant guidelines[6], the observation group was treated with ERAS-based extremely early postoperative enteral nutrition nursing intervention based on the control group: (1) Preoperative nutritional therapy: Patients with NRS2002 score ≥ 5 points were given nutrition treatment 7-10 d before operation. Patients without diabetes history took Ensure Nutrison (enteral nutrition powder) orally, and patients with diabetes history took Glucerna SR orally. Preoperative nutritional requirements were HGB ≥ 80g/L, albumin ≥ 32g/L, and lymphocyte count returned to normal; (2) Preoperative education: Individualized face-to-face education, lectures, wall newspapers, knowledge manuals and other ways were used to publicize ERAS and related knowledge of the perioperative period of gastric cancer, and visceral function reserve. Smokers and alcoholics should quit smoking for at least 2 wk and abstain from alcohol for 4 wk before surgery; (3) Intraoperative treatment: Thermal insulation blanket was used to maintain the patient's central body temperature > 36°C; Restrictive rehydration and prophylactic use of antibiotics to prevent postoperative infection; The indwelling catheter and drainage tube were routinely placed and removed as soon as possible after surgery; (4) Tubes intervention: The patient was placed in an appropriate position. Before the patient was awake, the supine position was taken, the head was tilted to one side. After the patient was awake under general anesthesia and the blood pressure was stable, the patient could be changed to the semi-decumbent position. Explained again the importance of tube retention, strengthened the patrol at night, observed whether the tube was in place and unobstructed, and prevented the tube from being pulled out accidentally during sleep; Removed the gastric tube after the anus exhausts; (5) Extremely early postoperative enteral nutrition nursing: Strictly grasped the "three degree principle" of enteral nutrition, namely, temperature, speed, concentration; Followed the principle of step by step, from less to more, from slow to fast, from thin to thick; The temperature of liquid food should be controlled at 38°C-40°C to prevent spasmodic abdominal pain and diarrhea caused by too low temperature, and damage of digestive tract mucosa caused by too high temperature. After eating, the patient was observed for abdominal distension, abdominal pain, diarrhea, nausea, vomiting and other discomfort. Aspiration pneumonia was the most serious complication in patients with enteral nutrition. Patients should be placed in the semi-decumbent position during feeding, and intestinal sounds should be observed at any time to avoid gastric retention, which was helpful for the prevention of aspiration. If the patient was found to inhale by mistake,

immediately stopped feeding, quickly sucked out the liquid from the trachea, and encouraged the patient to cough hard, and if necessary, performed tracheoscopy to remove foreign matters in the trachea; (6) Postoperative treatment: Postoperative analgesia pump was given to relieve pain. From the first day after operation, massaged bilateral Zusanli acupoints twice a day, 5 min/time, preferably with local feeling of soreness, numbness and swelling, and massaged the opposite side in the same way. Get out of bed (sitting, standing, walking) one day after surgery; Gastric tube was extracted 3-4 d after surgery, catheter was extracted one day after surgery, and abdominal cavity drainage was extracted as soon as possible after surgery. Oral care was performed twice a day, instructing patients to take deep breaths to relieve nausea, vomiting and other discomfort; and (7) Postoperative follow-up: The anesthesia follow-up nurse evaluated patients' consciousness, cognitive impairment and other complications after anesthesia at the bedside on the first day after surgery, and the ward nurse guided patients to change dressing or remove stitches and diet at the time of discharge. Within 3-10 d after discharge, a second follow-up visit was conducted by phone or WeChat, and patients were instructed to seek medical treatment in emergency department in time they felt unwell, and to be readmitted to hospital if necessary.

Observation indicators

(1) Comparing the two groups' waking times, spontaneous respiration recovery times, extubation times, postoperative eye opening times, and directional force recovery times allowed us to identify relevant indices of awakening quality; (2) Agitation: Riker's Sedation-Agitation Scale (SAS)[7] was used to assess agitation in patients, and scores ranged from 1 to 7. 7 points: Hazardous agitation, yanking the endotracheal tube, attempting to remove numerous tubes, scaling the window bar, yelling at the nurses, and wriggling in bed; 6 points: Very agitated, requiring a protective restraint and many verbal warnings to stop, and biting endotracheal intubation, 5 points: Agitation, anxiety or physical restlessness, can be quiet after being dissuaded by verbal prompts; 4 points: Quiet, easy to wake up, obey instructions; 3 points: Calm, drowsy, language stimulation or gentle shaking can wake up, and can obey simple instructions, but quickly fall asleep; 2 points: Very calm, responsive to physical stimulation, unable to communicate and obey instructions, and able to exercise independently; (3) Gastrointestinal function: The two groups' times for the first half-fluid feeding after surgery, the first postoperative exhaust time, the first postoperative defecation time, and the time for intestinal sound recovery were all compared; (4) Nutritional status: D-100™ hemoglobin detector (Bio-Rad company) was used to detect the hemoglobin A1c level on 1st and 3rd day after surgery by high pressure liquid chromatography. Beckman Coulter AU automatic biochemical analyzer and ALB detection kit were used to detect the albumin level of patients on the 1st and 3rd day after operation by bromocresol green method; Beckman Coulter AU automatic biochemical analyzer and GLUC detection kit, provided by Shanghai Kehua Bioengineering Co., LTD., were used to detect fasting blood glucose on 1st and 3rd day after surgery by hexokinase endpoint method; and (5) Adverse reactions: The incidence of anesthetic associated adverse responses such as hypoxemia and chills following surgery was recorded.

Statistical analysis

The data collected was analyzed using SPSS22.0. To facilitate comparisons across groups, the χ^2 test was used to convert the numerical counts to percentages. After determining that the data were normally distributed, the measurements were stated using mean ± SD, and the *t*-test was used to compare the groups. When comparing two groups, a value of $P < 0.05$ was deemed significant.

RESULTS

Comparison of related indexes of recovery period between the two groups

When compared to the control group, the awake duration, spontaneous breathing recovery time, extubation time and postoperative eye-opening time were all considerably shorter ($P < 0.05$). As can be seen in Figure 1, There was no significant difference in the recovery time of orientation force between the two groups ($P > 0.05$).

Comparing the two groups' recovery agitation.

Figure 2 shows the statistical significance ($P < 0.05$) that the lower SAS score of the observation group compared to the control group.

Comparison of gastrointestinal function recovery across groups

The observation group's recovery times for intestinal soundness, first postoperative exhaustion, first postoperative defecation, and first half-fluid eating were all shorter compare to control group ($P < 0.05$), as indicated in Figure 3.

Postoperative nutritional status comparison between groups

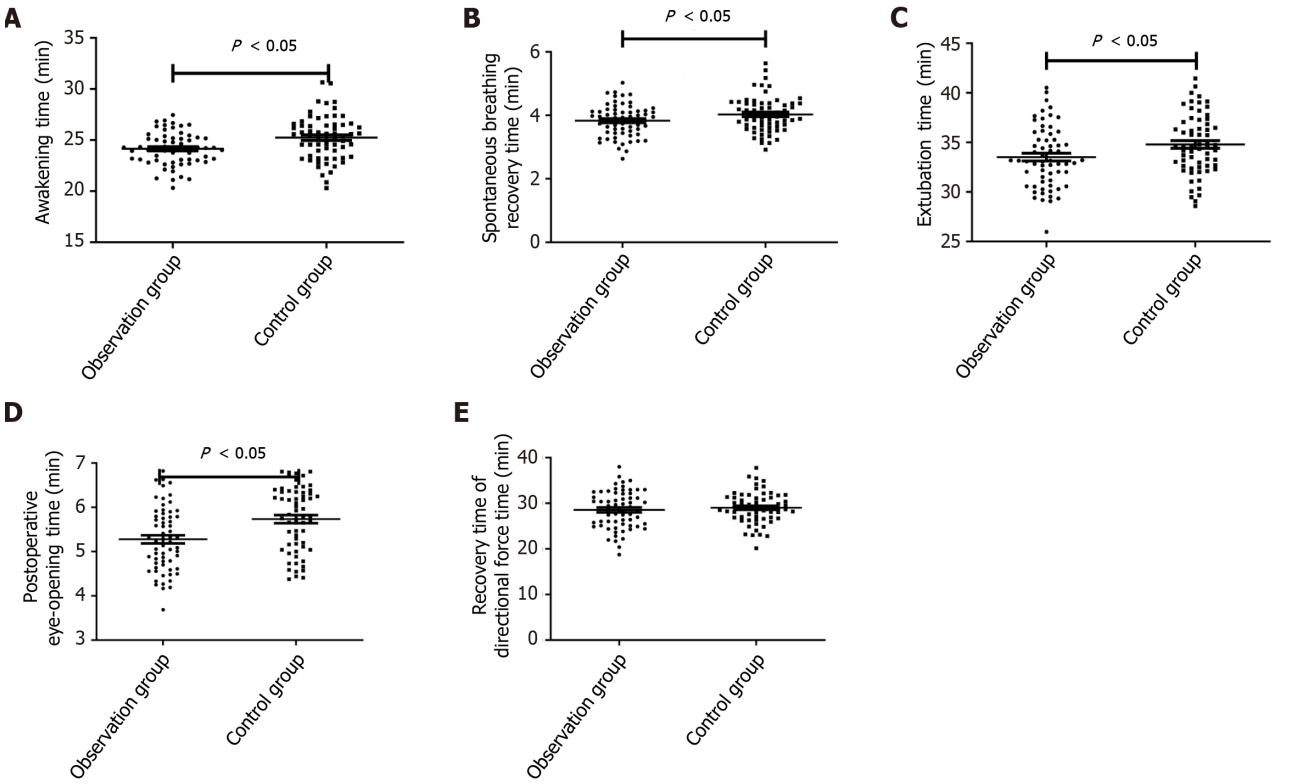
On postoperative days 1 and 3, the observation group had greater albumin and hemoglobin levels, which were higher while the fasting blood glucose value was lower compare to the control group's ($P < 0.05$) (Figure 4).

Comparison of Anesthesia-related adverse responses in both groups

As can be shown in Table 2, there was no statistically significant difference in the occurrence of adverse responses to the anesthesia between the two groups ($P > 0.05$).

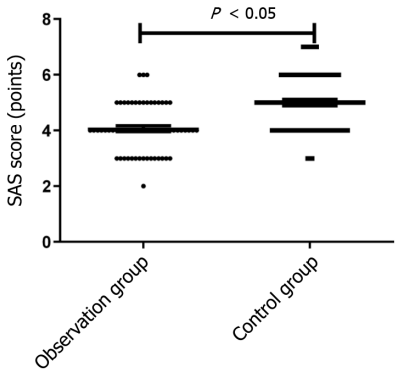
Table 2 Compares the incidence of adverse responses associated to anesthesia in the two groups, *n* (%)

Group	*n*	Hypoxemia	Chills	Nausea and vomiting	Total incidence
Observation group	63	0	4	1	7.94 (5)
Observation group	63	1	5	3	14.29 (9)
χ^2 value					1.286
P value					0.257



DOI: 10.4240/wjgs.v15.i9.1910 **Copyright** ©The Author(s) 2023.

Figure 1 Comparison of relevant recovery duration indices for the two groups. A: Awakening time; B: Spontaneous breathing recovery time; C: Extubation time; D: Postoperative eye-opening time; E: Recovery time of directional force time.



DOI: 10.4240/wjgs.v15.i9.1910 **Copyright** ©The Author(s) 2023.

Figure 2 Incidence of agitation among these two groups throughout the recovery period. SAS: Riker's Sedation-Agitation Scale.

DISCUSSION

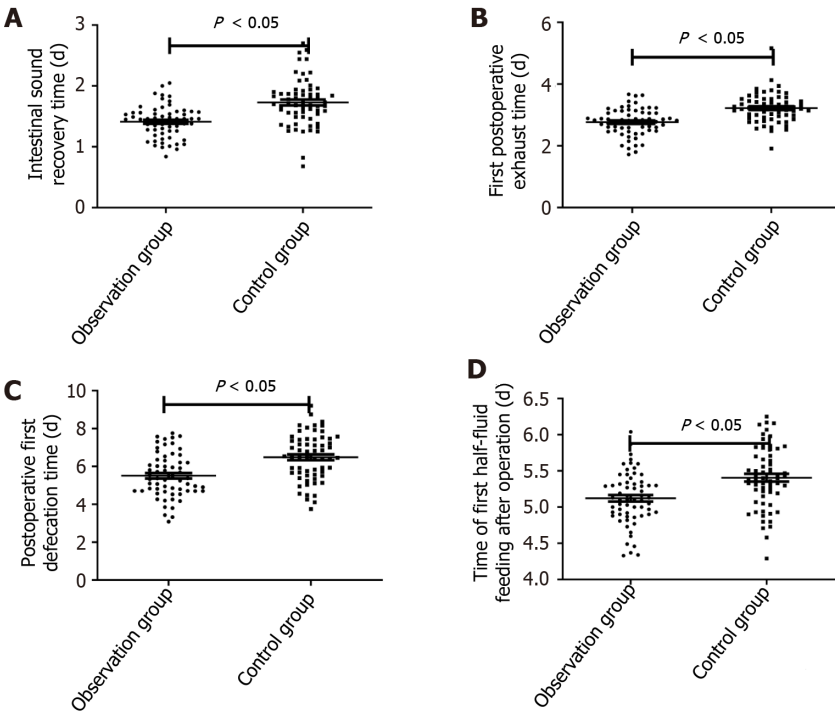
The surgical treatment of digestive tract tumors can bring pain and traumatic stress to patients during anesthesia, invasive operation and other processes, and the stress reaction will destroy the body immune function, increase the release of inflammatory mediators, and interfere with the balance of water and electrolyte, which can delay the recovery, increase postoperative complications, and prolong the hospital stay[8]. According to relevant research, patients' stress responses after surgery have been shown to be significantly enhanced by ERAS intervention[9,10]. Through a coordinated effort of evidence-based perioperative treatment strategies, ERAS may reduce the physiological and psychological impact of surgery on patients, allowing them to recover more quickly. The ERAS idea, according to the aforementioned research, uses multi-mode analgesia, which increases the analgesic impact, prevents the transmission of stress signals, and lessens the stress response[11,12]. This study found that the extremely early postoperative enteral nutrition intervention based on ERAS theory for patients undergoing gastrointestinal surgery can reduce the stress response, which is consistent with the above research results. The reason for this is that the perioperative stress response of patients is reduced and the rehabilitation process is shortened through the integration of nutritional support, anesthesia, and other nursing measures in the extremely early postoperative enteral nutrition intervention based on the ERAS theory[13]. Additionally, this study discovered that the SAS score was lower in the observation group than in the control group and that the awakening time, spontaneous breathing recovery time, extubation time, and postoperative eye-opening time of the observation group were significantly shorter than those of the control group. These findings suggest that the extremely early postoperative enteral nutrition intervention based on ERAS theory can reduce the level of agitation and improve the quality of awakening. This is mainly because ERAS concept, through improving perioperative nursing measures such as pain control and injury control, combines epidural block technology with general anesthesia to reduce patients' perioperative stress response, effectively reduce patients' myocardial oxygen consumption, and thus promote postoperative recovery.

Patients with digestive tract tumors are affected by tumor invasion and various factors secreted by tumor cells, which can affect the nutritional status of the body. In addition, the patients are in a state of high energy consumption due to surgical trauma, which is prone to the risk of malnutrition, resulting in poor prognosis[14,15]. The results of this study showed that the nutritional status of the body for patients in the recovery period after tracheal intubation under general anesthesia could be improved by the extremely early postoperative enteral nutrition intervention based on the ERAS theory, as measured by albumin and hemoglobin levels on the first and third postoperative days and by the fasting blood glucose value than those of the control group. This is mainly because enteral nutrition conforms to normal physiological characteristics and has the characteristics of high nitrogen utilization, which can maintain postoperative nitrogen balance, tissue and organ metabolism and functional integrity of intestinal mucosal barrier, promote gastrointestinal function recovery, reduce abdominal distension, and contribute to the prevention and treatment of anastomotic edema and postoperative delayed gastric functional emptying syndrome[16,17].

Relevant reports have pointed out that patients undergoing surgical treatment often have certain gastrointestinal functional problems or metabolic disorders after surgery, and the treatment of digestive tract tumors often leads to gastrointestinal sympathetic nervous system abnormalities, causing intestinal dysfunction and affecting the postoperative recovery process of patients[18]. The occurrence of this condition will lead to changes in patients' nutritional status, reduced intestinal barrier level, and cause multiple complications. Previous reports have pointed out that surgical treatment is an important factor to aggravate the gastrointestinal dysfunction of patients, and the blood circulation status during gastrointestinal tumor surgery can affect the occurrence of early postoperative gastrointestinal dysfunction of patients[19]. Excessive intraoperative blood loss leads to unstable hemodynamics of blood circulation, and massive blood transfusion and fluid replenishment further lead to disorders of the intravascular coagulation system, affecting the blood supply of the gastrointestinal tract. Operation time makes gastrointestinal congestion time too long, further aggravates gastrointestinal function damage. Relevant research has shown that early enteral nutrition not only has the potential to provide the body with the nutrients it needs; it can also aid in the recovery of gastrointestinal peristalsis function, boost the protective function of the gastrointestinal mucosal barrier, and decrease the occurrence of bacterial flora disorders [20]. To avoid stomach mucosa atrophy and speed up the recovery of gastrointestinal function, enteral nutrition is beneficial. The findings of this research demonstrate that the use of this nursing intervention may shorten the time required for patients in the observation group to regain gastrointestinal function *i.e.*, to regain intestinal sound, experience their first postoperative exhaust, have their first postoperative defecation and begin receiving their first half-fluid feeding after surgery. This is mainly because no drug analgesia is used in ERAS mode intervention, so the inhibition of gastrointestinal peristalsis is less, which is conducive to shortening the time of intestinal peristalsis and anal exhaust. In addition, early enteral nutrition support can promote the repair of intestinal immunity and biological barrier, blood circulation, further accelerate the recovery of gastrointestinal function, reduce complications such as infection, and shorten hospital stay[21].

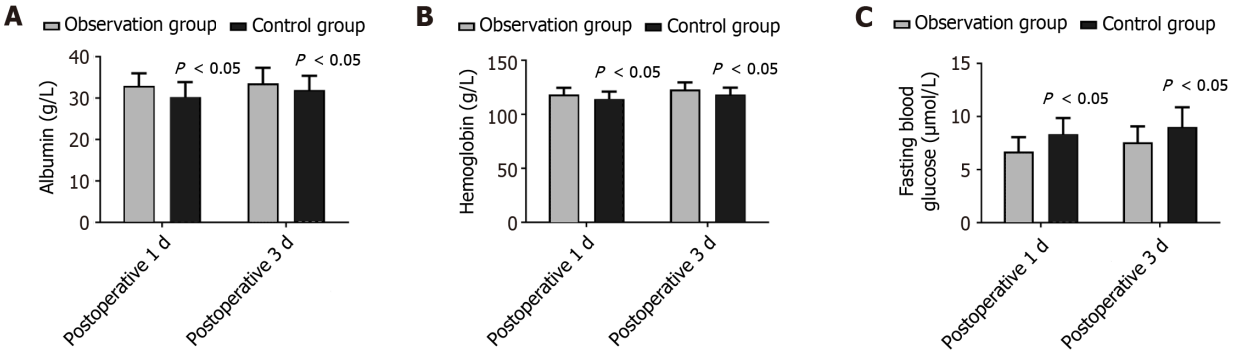
CONCLUSION

In conclusion, extremely early postoperative enteral nutrition intervention based on the ERAS theory has been shown to improve patients' nutritional status during the recovery period, as well as decrease their level of agitation and enhance the reliability with which they regain gastrointestinal function after endotracheal intubation under general anesthesia in digestive surgery.



DOI: 10.4240/wjgs.v15.i9.1910 **Copyright** ©The Author(s) 2023.

Figure 3 Comparison of the two groups' recovery of gastrointestinal function. A: Intestinal sound recovery time; B: First postoperative exhaust time; C: Postoperative first defecation time; D: Time of first half-fluid feeding after operation.



DOI: 10.4240/wjgs.v15.i9.1910 **Copyright** ©The Author(s) 2023.

Figure 4 Comparison of postoperative nutritional condition observed among the two groups. A: Albumin; B: Hemoglobin; C: Fasting blood glucose.

ARTICLE HIGHLIGHTS

Research background

Postoperative nursing can improve the restlessness and gastrointestinal function of patients with tracheal intubation under general anesthesia in digestive surgery. Wide application of various nursing methods and routine nursing in perioperative nursing of patients with general anesthesia in digestive surgery.

Research motivation

The main topics of this study is postoperative nursing of patients with general anesthesia in digestive surgery. Clinical need to explore a more effective nursing method to improve the prognosis of digestive surgery patients with general anesthesia. The significance of this study is that it confirms the effectiveness of new nursing methods for patients with general anesthesia in the department of gastroenterology, encourages the clinical team to continuously explore nursing methods with better nursing effects for patients with general anesthesia in the department of gastroenterology, and promotes the improvement and innovation of nursing programs.

Research objectives

Comparison of nursing effects of different nursing methods, to observe the advantages of very early enteral nutrition based on enhanced recovery after surgery (ERAS) theory over conventional care. The very early enteral nutrition nursing based on ERAS theory showed better improvement in recovery quality, gastrointestinal function, enteral nutrition and immune function in digestive surgery patients with general anesthesia, which confirmed that this nursing method has a good nursing effect. The significance of realizing these objectives for future research is to provide a new reference for perioperative nursing of digestive surgery patients with general anesthesia in the future.

Research methods

Clinical data of patients were retrospectively analyzed and grouped according to nursing methods. Then, independent sample t test, paired sample t test and χ^2 test were used to statistically analyze the general data of the two groups, related indexes of recovery period, restiness during recovery period, gastrointestinal function recovery, postoperative nutritional status, stress indexes before and after surgery, immune function indexes before and after surgery, anesthesia-related adverse reactions. The characteristic of retrospective study is to explore the cause through the results, and case data is more easily obtained.

Research results

The routine nursing of early postoperative enteral nutrition based on ERAS theory has remarkable effects, with good improvements in wake recovery, wake agitation, gastrointestinal function recovery, postoperative nutritional status, stress, immune function and other aspects, which provides a new nursing method for postoperative nursing of patients with general anesthesia in digestive surgery and needs further prospective exploration.

Research conclusions

Post-stress will affect the length of hospital stay in gastrointestinal surgery patients with general anesthesia, so we should pay attention to the influence of nursing methods on post-operative stress. The effect of early postoperative enteral nutrition nursing based on ERAS theory is better, and the nursing plan with better effect should be preferred in clinic.

Research perspectives

Nursing can improve the physiological indicators of patients, and its influence on the psychological state of patients can be further explored.

FOOTNOTES

Author contributions: Shao YR, Ke X and Xu JD designed the research study; Luo LH, Xu JD and Xu LQ performed the research; Xue JZ, Luo LH and Ke X contributed new reagents and analytic tools; Shao YR and Xu LQ analyzed the data and wrote the manuscript; and all authors have read and approve the final manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of the Guangdong Provincial People's Hospital.

Informed consent statement: The informed consent statement was waived by the Ethics Committee.

Conflict-of-interest statement: The author declares no competing interests.

Data sharing statement: The labeled dataset used to support the findings of this study are available from the corresponding author upon request.

Country/Territory of origin: China

ORCID number: Li-Qian Xu 0000-0002-3867-8138.

S-Editor: Wang JL
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Burcharth J**, Falkenberg A, Schack A, Ekeloef S, Gögenur I. The effects of early enteral nutrition on mortality after major emergency abdominal surgery: A systematic review and meta-analysis with Trial Sequential Analysis. *Clin Nutr* 2021; **40**: 1604-1612 [PMID: 33744604

DOI: 10.1016/j.clnu.2021.02.050]
2 **Chen R**, Yin W, Gao H, Zhang H, Huang Y. The effects of early enteral nutrition on the nutritional statuses, gastrointestinal functions, and inflammatory responses of gastrointestinal tumor patients. *Am J Transl Res* 2021; **13**: 6260-6269 [PMID: 34306365]
3 **Besson AJ**, Kei C, Djordjevic A, Carter V, Deftereos I, Yeung J. Does implementation of and adherence to enhanced recovery after surgery improve perioperative nutritional management in colorectal cancer surgery? *ANZ J Surg* 2022; **92**: 1382-1387 [PMID: 35302700 DOI: 10.1111/ans.17599]
4 **Sun YB**, Li YL, Li WM, Sun DL, Li SM, Xu QW, Li YJ, Lin YY, Cen YY, Xu PY. Effect of appetite-conditioned reflex stimulation on early enteral nutrition tolerance after surgery. *Acta Gastroenterol Belg* 2020; **83**: 527-531 [PMID: 33321007]
5 **Pagano D**, Ricotta C, Barbàra M, Cintorino D, di Francesco F, Tropea A, Calamia S, Lomaglio L, Terzo D, Gruttadauria S. ERAS Protocol for Perioperative Care of Patients Treated with Laparoscopic Nonanatomic Liver Resection for Hepatocellular Carcinoma: The ISMETT Experience. *J Laparoendosc Adv Surg Tech A* 2020; **30**: 1066-1071 [PMID: 32716674 DOI: 10.1089/lap.2020.0445]
6 **Jiang ZW**, Li N. [Chinese Expert Consensus on Accelerating Rehabilitation Surgery in Colorectal Surgery (2015 Edition)]. *Zhonghua Weichang Waike Zazhi* 2015; **35**: 785-787 [DOI: 10.3760/cma.j.issn.1671-0274.2015.08.018]
7 **Xiang Q**, Yuan H, Cai W, Qie S. Effect of early enteral nutrition on laparoscopic common bile duct exploration with enhanced recovery after surgery protocols. *Eur J Clin Nutr* 2019; **73**: 1244-1249 [PMID: 30967640 DOI: 10.1038/s41430-019-0425-x]
8 **Vigorita V**, Cano-Valderrama O, Celentano V, Vinci D, Millán M, Spinelli A, Pellino G. Inflammatory Bowel Diseases Benefit from Enhanced Recovery After Surgery [ERAS] Protocol: A Systematic Review with Practical Implications. *J Crohns Colitis* 2022; **16**: 845-851 [PMID: 34935916 DOI: 10.1093/ecco-jcc/jjab209]
9 **Gürcan M**, Atay Turan S. Examining the expectations of healing care environment of hospitalized children with cancer based on Watson's theory of human caring. *J Adv Nurs* 2021; **77**: 3472-3482 [PMID: 34142737 DOI: 10.1111/jan.14934]
10 **Gu LL**, Zhang XJ, Li J, Zhou G. [Practice and application of enhanced recovery after surgery in perioperative period of liver operation]. *Zhonghua Yixue Zazhi* 2019; **99**: 2052-2056 [DOI: 10.3760/cma.j.issn.0376-2491.2019.26.010]
11 **Wang JJ**, Wu ZM, Wang H. [The role of enhanced recovery after surgery model in postoperative care of patients with ovarian cancer]. *Chongqing Yixue* 2020; **49**: 2334-2337 [DOI: 10.3969/j.issn.1671-8348.2020.14.020]
12 **Ohbe H**, Jo T, Matsui H, Fushimi K, Yasunaga H. Differences in effect of early enteral nutrition on mortality among ventilated adults with shock requiring low-, medium-, and high-dose noradrenaline: A propensity-matched analysis. *Clin Nutr* 2020; **39**: 460-467 [PMID: 30808573 DOI: 10.1016/j.clnu.2019.02.020]
13 **Iranmanesh P**, Delaune V, Meyer J, Liot E, Konrad B, Ris F, Toso C, Buchs NC. Comparison of Outcomes between Obese and Non-Obese Patients in a Colorectal Enhanced Recovery After Surgery (ERAS) Program: A Single-Center Cohort Study. *Dig Surg* 2020; **37**: 420-427 [PMID: 32434182 DOI: 10.1159/000507545]
14 **Yu XL**, Yang Q. [The effect of very early postoperative enteral nutrition nursing on the recovery of gastrointestinal function in elderly patients with colon cancer]. *Chongqing Yixue* 2021; **50**: 434-436
15 **Vlad O**, Catalin B, Mihai H, Adrian P, Manuela O, Gener I, Ioanel S. Enhanced recovery after surgery (ERAS) protocols in patients undergoing radical cystectomy with ileal urinary diversions: A randomized controlled trial. *Medicine (Baltimore)* 2020; **99**: e20902 [PMID: 32629682 DOI: 10.1097/MD.0000000000020902]
16 **Lowen DJ**, Hodgson R, Tacey M, Barclay KL. Does deep neuromuscular blockade provide improved outcomes in low pressure laparoscopic colorectal surgery? A single blinded randomized pilot study. *ANZ J Surg* 2022; **92**: 1447-1453 [PMID: 35014162 DOI: 10.1111/ans.17458]
17 **Cheng KW**, Wang GH, Shu KS, Zheng M, Liu HX, Tang AP, Zuo BH, Wang ZX, Wang YJ, Hu WJ, Ma DH. [Application of enhanced recovery after surgery in laparoscopic assisted radical resection for gastric cancer and its influence on postoperative recovery, nutrition status and stress of the patients]. *Zhongguo Putong Waike Zazhi* 2019; **28**: 1228-1236 [DOI: 10.7659/j.issn.1005-6947.2019.10.010]
18 **Bai SS**, Yuan X, Li XD, Liang Y, Bai MJ, Li S, Liu GL. [Application of rapid postoperative rehabilitation in perioperative nursing of cesarean section]. *Zhongguo Fuchanke Linchuang Zazhi* 2022; **23**: 406-408
19 **Hecht S**, Halstead NV, Boxley P, Brockel MA, Rove KO. Opioid prescribing patterns following implementation of Enhanced Recovery After Surgery (ERAS) protocol in pediatric patients undergoing lower tract urologic reconstruction. *J Pediatr Urol* 2021; **17**: 84.e1-84.e8 [PMID: 33229228 DOI: 10.1016/j.jpurol.2020.10.029]
20 **Yu MM**, Gong XL, Xu Z. [Effects of enhanced recovery after surgery on postoperative recovery, psychological state of patients with laparoscopic gastrointestinal surgery]. *Zhongguo Zhongxiyi Jiehe Jijiu Zazhi* 2019; **26**: 218-222 [DOI: 10.3969/j.issn.1008-9691.2019.02.020]
21 **Kennedy GT**, Hill CM, Huang Y, So A, Fosnot J, Wu L, Farrar JT, Tchou J. Enhanced recovery after surgery (ERAS) protocol reduces perioperative narcotic requirement and length of stay in patients undergoing mastectomy with implant-based reconstruction. *Am J Surg* 2020; **220**: 147-152 [PMID: 31627839 DOI: 10.1016/j.amjsurg.2019.10.007]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 1919-1931

DOI: 10.4240/wjgs.v15.i9.1919

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Autologous bone marrow infusion *via* portal vein combined with splenectomy for decompensated liver cirrhosis: A retrospective study

Bao-Chi Liu, Ming-Rong Cheng, Lin Lang, Lei Li, Yan-Hui Si, Ai-Jun Li, Qing Xu, Hui Zhang

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Kumar R, India; Kupeli S, Turkey

Received: April 6, 2023
Peer-review started: April 6, 2023
First decision: May 30, 2023
Revised: June 8, 2023
Accepted: July 11, 2023
Article in press: July 11, 2023
Published online: September 27, 2023

Bao-Chi Liu, Lei Li, Yan-Hui Si, Department of Surgery, Shanghai Public Health Clinical Center, Fudan University, Shanghai 201508, China

Bao-Chi Liu, Lin Lang, He Nuo Medical Clinic, Shanghai New Hongqiao International Medical Center, Shanghai 201100, China

Ming-Rong Cheng, Department of Anorectal Surgery, The Third Affiliated Hospital of Guizhou Medical University, Duyun 558000, Guizhou Province, China

Ai-Jun Li, Department of Hepatobiliary Surgery, Oriental Hepatobiliary Surgery Hospital, Shanghai 200433, China

Qing Xu, Department of Hepatobiliary Surgery, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200127, China

Hui Zhang, Department of Hepatobiliary Surgery, Shanghai Oriental Hospital Affiliated to Tongji University, Shanghai 200120, China

Corresponding author: Bao-Chi Liu, Doctor, MD, Chief Physician, Department of Surgery, Shanghai Public Health Clinical Center, Fudan University, No. 2901 Caolang Road, Jinshan District, Shanghai 201508, China. liubaochi200227@aliyun.com

Abstract

BACKGROUND

In a previous study, autologous bone marrow infusion (ABMI) was performed in patients with decompensated liver cirrhosis (DLC) and acquired immunodeficiency syndrome and achieved good results, but whether splenectomy affected outcome was unclear.

AIM

To investigate the efficacy of ABMI combined with splenectomy for treatment of DLC.

METHODS

Eighty-three patients with DLC were divided into an intervention group (43 cases) and control group (40 cases) according to whether splenectomy was performed. The control group was treated with ABMI through the right omental

vein, and the intervention group was additionally treated with splenectomy.

RESULTS

After ABMI, the prothrombin time, serum total bilirubin levels, ascites volume and model for end-stage liver disease score in both groups were significantly lower, while the albumin levels were significantly higher than before ABMI ($P < 0.01$), but there were no significant differences between the groups ($P > 0.05$). After ABMI, the white blood cell and platelets counts in both groups were significantly higher than before ABMI ($P < 0.01$), and the counts in the intervention group were significantly higher than in the control group ($P < 0.01$). After ABMI the $CD4^+$ and $CD8^+$ T cell counts in both groups were significantly higher than before ABMI ($P < 0.01$). The $CD8^+$ T cell counts in the intervention group increased continuously and the increase had a shorter duration compared with control group.

CONCLUSION

ABMI through the portal vein in patients with DLC can significantly improve liver synthetic and secretory functions, and splenectomy promotes improvement of bone marrow hematopoietic and cellular immune functions.

Key Words: Autologous bone marrow; Splenectomy; Cell therapy; Cirrhosis; Cellular immunity

Core Tip: In this study, autologous bone marrow infusion (ABMI) through the portal vein in patients with decompensated liver cirrhosis (DLC) can significantly improve liver synthetic and secretory functions and is effective in patients with DLC. And it is the first attempt to investigate the impact of splenectomy on bone marrow hematopoietic function and cellular immune function after ABMI in patients with DLC.

Citation: Liu BC, Cheng MR, Lang L, Li L, Si YH, Li AJ, Xu Q, Zhang H. Autologous bone marrow infusion *via* portal vein combined with splenectomy for decompensated liver cirrhosis: A retrospective study. *World J Gastrointest Surg* 2023; 15(9): 1919-1931

URL: https://www.wjgnet.com/1948-9366/full/v15/i9/1919.htm

DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.1919

INTRODUCTION

Cirrhosis is the end stage of liver fibrosis and has several causes. In the global ranking of causes of death in 2012, cirrhosis ranked 14th[1], and drug treatment was not effective. At present, liver transplantation is still the most effective treatment for advanced liver disease. However, due to the lack of donor livers and high costs, there is an urgent need to find a safe and effective alternative that can be widely used[2]. Cell therapy has achieved outstanding results in basic and clinical research and is a promising new treatment. In animal experiments, bone marrow stem cells (BMSCs) can be transformed into hepatic oval cells, hepatocytes and bile duct cells in the liver, which play an important role in the repair of liver damage[3]. In a clinical experiment, it was found that after transplantation of male bone marrow cells (BMCs) to female patients, Y-chromosome-positive hepatocytes were detected in the liver, and it was confirmed that BMSCs can be transformed into hepatocytes[4]. Liver-derived liver stem cells have a positive contribution to hepatocyte regeneration. Lu *et al*[5] induced hepatocyte apoptosis by targeted deletion of *Mdm2*, and then transplanted liver progenitor cells into mouse liver. The transplanted liver progenitor cells differentiated into hepatocytes and bile duct cells, significantly improving the structure and function of the damaged liver.

Several studies have reported positive effects of BMCs transplantation for treatment of decompensated liver cirrhosis (DLC). Most studies used BMCs, peripheral blood hematopoietic stem cells and umbilical cord blood stem cells. BMCs were separated by gradient centrifugation, and the suspension of BMCs was injected into the liver through the hepatic artery by interventional methods. Liver function was repaired, but the specific mechanism is still not clear[6]. The anti-DLC effect of autologous BMSCs has been established in animal models[7]. In addition, clinical trials have shown that autologous BMSC transplantation can quickly improve liver function without obvious side effects. However, there are not many clinical trials about autologous BMSCs for cirrhosis, and there is no unified treatment plan[8,9]. In a previous study, BMSCs were used to treat human immunodeficiency virus (HIV) patients with DLC, and achieved good results. This treatment method has the following advantages: BMSCs do not need to be centrifuged, and are reproducible, nonimmunogenic, and free of graft-versus-host disease[10]. Therefore, autologous BMSCs have received much attention in basic and clinical research, and are increasingly used in clinical treatment of various diseases[11-13]. BMSCs are transplanted to the liver mainly through the hepatic artery, portal vein and peripheral vein. This has a significant effect on DLC, is safe and feasible, and can significantly improve the clinical symptoms and liver function[14-16]. It is readily accepted by DLC patients. Other transplantation routes such as intrasplenic transplantation, intraperitoneal and peripheral vein transplantation are commonly used clinically. In a study of four patients with DLC who were treated with

peripheral intravenous injection of autologous mesenchymal stem cells, after 2 years of follow-up, it was found that the scores of the end-stage liver disease model in two patients were significantly improved[17], but the number of cases was too small. The mechanism by which stem cells repair liver cells through systemic blood circulation is still unclear, and no effective induction method has been found to orient stem cells to migrate and home to the target organ. This transplantation method is the most applied method in liver cirrhosis.

Due to the rich blood supply and nutrients in the portal vein, stem cells stay in the liver sinusoids for a long time, with good selectivity distribution, and the portal system contains high concentrations of hepatotropic cytokines, which are important for the survival and growth of BMCs that are returned to the liver. In previous clinical trials surgery was performed to insert an infusion port into the right omental vein (ROV), autologous BMCs were returned through the infusion port, and good results were observed in the treatment of HIV patients with DLC[18]. However, it remains unclear whether splenectomy has an effect on patient outcomes. In this study, the efficacy of autologous bone marrow infusion (ABMI) combined with splenectomy was observed in the treatment of patients with DLC.

MATERIALS AND METHODS

Patients

This was a retrospective analysis of 83 patients with DLC who received ABMI, including 52 males and 31 females, aged 27-75 years, with an average age of 47.53 ± 8.82 years from January 2016 to December 2018 from Shanghai Public Health Clinical Center Affiliated to Fudan University, Shanghai Dongfang Hospital Affiliated to Tongji University, Shanghai Dongfang Hepatobiliary Surgery Hospital Affiliated to Naval Medical University, and Renji Hospital Affiliated to Shanghai Jiao Tong University. There were 60 cases of hepatitis B cirrhosis, four of alcoholic cirrhosis, 11 of hepatitis C cirrhosis and eight cases of schistosomiasis cirrhosis. Child–Pugh classification was grade B in 77 cases and grade C in six.

Inclusion was in accordance with the diagnostic criteria for DLC[19]: (1) Computed tomography (CT), color Doppler ultrasound, or liver biopsy suggested the formation of liver cirrhosis; (2) liver cirrhosis was diagnosed by liver hardness scan; (3) albumin level < 35 g in liver function; (4) gastroscopy showed signs of esophageal and gastric varices; (5) platelet count < 10^{11}/L; (6) esophageal and gastric varices; (7) prothrombin time was longer than normal for 3 s; and (8) ascites formation. If any three items in (1)-(5) were met and any item in (6)-(8), it was possible to diagnose DLC. Exclusion criteria were: (1) Age < 18 years; (2) pregnant and breastfeeding women; (3) malignant tumors of the liver or other organs; (4) spontaneous peritonitis or active gastrointestinal bleeding; (5) patients who could not tolerate the treatment, such as severe those with heart disease and pulmonary insufficiency; (6) hormone therapy; and (7) intellectual disability or mental illness.

Informed consent was signed by all patients and the study was approved by the Ethics Committee of the Shanghai Public Health Clinical Center (2013-030).

Treatment

Conventional liver protection and diuresis were used for all patients. In addition, viral liver cirrhosis was treated with anti-hepatitis B or C drugs.

According to whether splenectomy was performed during the operation, the patients were divided into an intervention group (43 cases) and control group (40 cases). The control group was treated with ABMI through the ROV, and the intervention group underwent splenectomy in addition to ABMI.

Under general anesthesia, a midline incision was made in the upper abdomen, the ascites was removed after entering the abdominal cavity, the spleen was fully exposed and then the spleen was removed (in the intervention group). The infusion port was embedded in the ROV. During the operation, 40 mL of bone marrow was extracted from the anterior superior iliac spine by puncture, and 40 mL of ABM (without washing, filtration and concentration) was slowly injected with a syringe through the puncture window of the infusion port, and entered the portal vein through the ROV. Saline (5 mL) was injected into the infusion port to prevent coagulation. At 1 and 3 mo after the operation, 40 mL of ABM was infused once again through the infusion port. Five milliliters of cubital venous blood were drawn before surgery, at 1, 3, 6 and 12 mo after ABMI, placed in an anticoagulation tube, and allowed to stand at room temperature for 30 min. The samples were centrifuged centrifugal radius was 9 cm, centrifugal speed was 3000 rpm, 15 min (Tengying Machinery Manufacturing Co., Ltd., Zhangjiagang, China), and supernatants were collected and stored at -80 °C.

Biochemical analysis

Serum total bilirubin (TB), serum albumin and creatinine levels were detected using an AU5800 automatic biochemical analyzer (Beckman Coulter Co. Ltd., CA, United States). Prothrombin time (PT) and international normalized ratio (INR) were measured by CA-500 automatic coagulation analyzer (Sysmex Corporation, Kobe, Japan) using the coagulation index detection kit. The white blood cell (WBC) and platelet counts and hemoglobin level were detected by automatic blood analyzer (Mindray BC-5000, Shenzhen, China).

Flow cytometry

FACS Calibur flow cytometer, CD4-FITC/CD8-PE, TruCOUNT absolute counting tube, four-color fluorescent standard microspheres, and FACS hemolysin (10 ×) were the products of BD Company in the United States. Multiset tri-color reagent (20 μL) and 50 μL whole blood were added to a TruCOUNT absolute counting tube, mixed thoroughly, and placed in the dark for 15 min. Then, 450 μL of FACS hemolysin (10 ×) was added, mixed well, and placed in the dark for

15 min. After sample preparation, the Multiset program was run on the computer immediately for detection, and the absolute counts of $CD4^+$ and $CD8^+$ T cells in the total T cells were analyzed.

Determination of ascites

Inadomi *et al*[20] reported a method of measuring the volume of ascites with ultrasound in 1996. Two variables were observed: Abdominal circumference and maximum ascites depth. Specific operation: Instruct the patient to lie on his back and lie on the stomach, and we measured the abdominal circumference (C) around the umbilicus, and then the patient changed to the prone position. The ultrasonic probe probed the maximum depth of ascites at the umbilical circumference (d), that is, the maximum vertical distance from the interface of the floating intestinal loop to the probe. We used the following formula to calculate the amount of ascites: $r = C/2\pi$; V (volume of ascites) = $1/3\ [\pi d^2\ (3r-d)]$ (Note: r is radius, π is constant).

Model for end-stage liver disease

Model for end-stage liver disease (MELD) score is often used as an indicator of liver function. The formula was MELD score[21] = 3.78 × ln[TB (μmol/L)] + 11.2 × ln(INR) + 9.6 × ln[creatinine (mmol/L)] + 6.4 × (etiology: Biliary or alcoholic was 0, and other diseases were 1).

Statistical analysis

SPSS 19.0 was used for statistical analysis. The normal distribution was tested using the Shapiro-Wilk test. The measurement data conforming to the normal distribution were expressed as mean ± SD. Before and after treatment, the paired *t* test was used for comparison of the intervention group and control group. The data with non-normal distribution were expressed in M (P25, P75), using the Mann-Whitney test. Numerical data were used to describe the percent, using the χ^2 test. $P < 0.05$ was considered statistically significant. The test standard was $\alpha = 0.05$.

RESULTS

Comparison of general baseline data between control and intervention groups

There was no significant difference in gender, age, etiology of liver cirrhosis and Child–Pugh grading between the intervention group and control group ($P > 0.05$), and the baseline data of the two groups were comparable (Table 1).

Comparison of postoperative complications

In the intervention group, 43 patients underwent splenectomy and had an infusion port placed in the right gastroepiploic vein. Three patients (all Child-Pugh grade B before surgery) had liver failure due to oozing blood in the splenectomy wound, and died within 3 d after surgery. The surgery-related fatality rate was 6.98%. In the control group, 40 patients had an infusion port placed in the right gastroepiploic vein, and two patients (1 Child-Pugh grade B and 1 grade C before surgery) died of liver failure caused by gastrointestinal bleeding after surgery, and the fatality rate was 5.0%. There was no significant difference in the fatality rate between the two groups after surgery ($\chi^2 = 0.007$, $P > 0.05$). In the intervention group, two cases were Child-Pugh grade C. Due to emergency surgery for gastrointestinal bleeding, the portal vein pressure was high. If splenectomy is not performed, it may recur to bleed after surgery, so splenectomy was performed. After 1-year follow-up, both patients showed good improvement in liver function, similar to that in the Child–Pugh grade B patients.

Liver synthetic and secretory functions after surgery

Figure 1A and Table 2 show that there was no significant difference in serum PT levels between the control and intervention groups before ABMI ($P > 0.05$). After ABMI, serum PT in both groups was significantly lower than before ABMI ($P < 0.01$), but there was no significant difference between the two groups at each time point ($P > 0.05$).

Figure 1B and Table 3 show that there was no significant difference in serum albumin levels between the two groups before ABMI ($P > 0.05$). After ABMI, albumin level in both groups was significantly higher than before ABMI ($P < 0.01$), but there was no significant difference between the two groups at each time point ($P > 0.05$).

Figure 1C and Table 4 show that there was no significant difference in serum TB level between the two groups before ABMI ($P > 0.05$). After ABMI, serum TB level in both groups was significantly lower than before ABMI ($P < 0.01$), but there was no significant difference between the two groups at each time point ($P > 0.05$).

Figure 1D and Table 5 showed that there was no significant difference in ascites volume before ABMI between the two groups ($P > 0.05$). After ABMI, ascites volume in both groups was significantly lower than before ABMI ($P < 0.01$), but there was no significant difference between the two groups at each time point ($P > 0.05$).

Figure 1E and Table 6 showed that there was no significant difference in MELD score before ABMI between the two groups ($P > 0.05$). After ABMI, MELD score in both groups was significantly lower than before ABMI ($P < 0.01$), but there was no significant difference between the two groups at each time point ($P > 0.05$).

Hematopoietic function before and after ABMI

Figure 2A and Table 7 show that there was no significant difference in WBC count between the control and intervention groups before ABMI ($P > 0.05$). After ABMI, WBC count in both groups was significantly higher than before ABMI ($P < 0.01$). The increase in the intervention group at each time point was significantly higher than in the control group ($P <$

Table 1 Comparison of general baseline data between control and intervention groups

Group	Sex (M/F)	Age (yr)	Etiology				Child-Pugh grade	
			Hepatitis B cirrhosis	Alcoholic cirrhosis	Hepatitis C cirrhosis	Schistosomiasis cirrhosis	B	C
Control	27/13	47.53 ± 9.21	30	1	6	3	36	4
Intervention	25/18	47.53 ± 8.51	30	3	5	5	41	2
χ^2/t	0.428	0.000	1.484				0.266	
P value	0.513	0.999	0.686				0.606	

M: Male; F: Female.

Table 2 Serum prothrombin time levels in control and intervention groups before and after autologous bone marrow infusion

Group	Before	1 mo	*t/P* value	3 mo	*t/P* value	6 mo	*t/P* value	12 mo	*t/P* value
Control	19.42 ± 3.95	17.55 ± 2.42	5.603/0.000	16.16 ± 1.82	5.811/0.000	15.26 ± 1.81	8.008/0.000	14.42 ± 1.80	9.909/0.000
Intervention	19.50 ± 3.89	17.55 ± 2.39	6.053/0.000	16.15 ± 2.13	8.780/0.000	15.13 ± 2.03	10.528/0.000	14.43 ± 2.10	11.755/0.000
t	0.089	0.005		0.018		0.317		0.009	
P value	0.929	0.996		0.986		0.752		0.993	

Results are expressed as s mean ± SD.

Table 3 Serum albumin levels in control and intervention groups before and after autologous bone marrow infusion (mean ± SD, g/L)

Group	Before	1 mo	*t/P* value	3 mo	*t/P* value	6 mo	*t/P* value	12 mo	*t/P* value
Control	29.45 ± 4.26	35.05 ± 3.45	16.560/0.000	37.13 ± 3.20	12.024/0.000	39.55 ± 2.33	14.535/0.000	40.24 ± 2.24	18.460/0.000
Intervention	29.38 ± 4.16	34.83 ± 3.54	17.465/0.000	36.85 ± 3.70	18.241/0.000	38.25 ± 3.97	17.519/0.000	39.53 ± 3.28	19.131/0.000
t	0.076	0.287		0.359		0.980		1.114	
P value	0.940	0.775		0.721		0.330		0.369	

Results expressed as mean ± SD (g/L).

Table 4 The serum total bilirubin levels in control and intervention groups before and after autologous bone marrow infusion

Group	Before	1 mo	*t/P* value	3 mo	*t/P* value	6 mo	*t/P* value	12 mo	*t/P* value
Control	44.89 ± 20.56	35.11 ± 15.20	6.536/0.000	29.95 ± 12.69	7.379/0.000	27.26 ± 11.77	7.896/0.000	24.29 ± 8.57	8.255/0.000
Intervention	42.90 ± 19.77	31.48 ± 14.12	7.534/0.000	27.58 ± 12.55	9.014/0.000	26.05 ± 11.02	9.021/0.000	23.65 ± 8.44	9.120/0.000
t	0.437	1.093		0.830		0.470		0.332	
P value	0.663	0.278		0.409		0.640		0.741	

Results expressed as mean ± SD (μmol/L).

0.01).

Figure 2B and Table 8 show that there was no significant difference in serum platelet count between the two groups before ABMI ($P > 0.05$). After ABMI, platelet count in both groups was significantly higher than before ABMI ($P < 0.01$). The increase in the intervention group at each time point was significantly higher than in the control group ($P < 0.01$).

Table 5 Ascites volume in control and intervention groups before and after autologous bone marrow infusion

Group	Before	1 mo	*Z/P* value	3 mo	*Z/P* value	6 mo	*Z/P* value	12 mo	*Z/P* value
Control	3000 (1500-4125)	1000 (0-2000)	5.386/0.000	500 (0-1500)	5.388/0.000	250 (0-1125)	5.392/0.000	0 (0-1000)	5.394/0.000
Intervention	3000 (1500-4000)	750 (0-1875)	5.519/0.000	0 (0-500)	5.519/0.000	0 (0-500)	5.525/0.000	0 (0-500)	5.457/0.000
Z	0.226	0.780		1.379		1.353		1.374	
P value	0.790	0.436		0.168		0.176		0.170	

Results expressed as M (P_{25}-P_{75}) (mL).

Table 6 Comparison of model for end-stage liver disease scores in two groups before and after autologous bone marrow infusion

Group	Before	1 mo	*t/P* value	3 mo	*t/P* value	6 mo	*t/P* value	12 mo	*t/P* value
Control	21.53 ± 6.17	18.87 ± 5.09	2.050/0.044	17.73 ± 6.42	2.631/0.010	13.76 ± 5.51	5.790/0.000	12.58 ± 4.64	7.147/0.000
Intervention	22.61 ± 5.61	18.92 ± 4.85	3.147/0.002	16.67 ± 5.75	4.677/0.000	15.42 ± 5.61	5.732/0.000	11.94 ± 5.00	8.980/0.000
t	0.804	0.044		0.770		1.325		0.577	
P value	0.424	0.965		0.443		0.189		0.566	

Results are expressed as mean ± SD.

Table 7 Comparison of white blood cell in control and intervention groups before and after autologous bone marrow infusion

Group	Before	1 mo	*t/P* value	3 mo	*t/P* value	6 mo	*t/P* value	12 mo	*t/P* value
Control	3.14 ± 0.76	5.17 ± 1.32	12.975/0.000	3.42 ± 0.98	3.363/0.002	3.27 ± 0.93	2.311/0.026	3.33 ± 0.82	3.505/0.001
Intervention	3.20 ± 1.17	8.00 ± 1.28	23.457/0.000	6.44 ± 1.54	11.474/0.000	6.15 ± 1.37	13.409/0.000	5.89 ± 0.97	13.776/0.000
t	0.258	9.625		10.211		10.768		12.531	
P value	0.797	0.000		0.000		0.000		0.000	

Results expressed as mean ± SD (cell count × 10^9/L).

Table 8 Comparison of platelet counts in control and intervention groups before and after autologous bone marrow infusion

Group	Before	1 mo	*t/P* value	3 mo	*t/P* value	6 mo	*t/P* value	12 mo	*t/P* value
Control	42.82 ± 12.66	44.64 ± 13.08	2.776/0.009	45.79 ± 12.67	3.433/0.001	47.45 ± 12.02	5.037/0.000	49.26 ± 13.37	5.093/0.0000
Intervention	44.30 ± 13.51	231.63 ± 57.78	22.601/0.000	226.50 ± 47.92	27.006/0.000	226.68 ± 41.32	31.942/0.000	222.90 ± 39.36	32.647/0.000
t	0.500	19.475		22.503		25.719		25.812	
P value	0.618	0.000		0.000		0.000		0.000	

Results expressed as mean ± SD (cell count × 10^9/L).

Figure 2C and Table 9 showed that there was no significant difference in serum hemoglobin level between the two groups before ABMI ($P > 0.05$). Serum hemoglobin level in both groups at 3, 6 and 12 mo after ABMI was significantly higher than before ABMI ($P < 0.01$). The increase at 6 and 12 mo in the intervention group was significantly higher than in the control group ($P < 0.05$ and $P < 0.01$).

Comparison of CD4⁺ and CD8⁺ T cell counts before and after ABMI

Figure 3A and Table 10 show that there was no significant difference in $CD4^+$ T cell count before ABMI between the control and intervention groups ($P > 0.05$). After ABMI, $CD4^+$ T cell count in the intervention group at 1, 3, 6 and 12 mo, and in the control group at 3, 6 and 12 mo was significantly higher than before ABMI ($P < 0.01$), but there was not significant difference between the two groups at each time point ($P > 0.05$).

Table 9 Comparison of hemoglobin levels in control and intervention groups before and after autologous bone marrow infusion

Group	Before	1 mo	*t/P* value	3 mo	*t/P* value	6 mo	*t/P* value	12 mo	*t/P* value
Control	94.74 ± 20.86	95.03 ± 19.39	0.387/0.701	99.47 ± 19.12	4.211/0.000	102.84 ± 18.11	6.286/0.000	104.13 ± 17.19	7.498/0.000
Intervention	97.48 ± 23.20	97.03 ± 20.19	0.394/0.696	106.70 ± 18.97	6.716/0.000	113.08 ± 16.69	9.445/0.000	117.33 ± 11.70	8.318/0.000
t	0.547	0.446		1.675		2.596		3.980	
P value	0.586	0.657		0.098		0.011		0.000	

Results expressed as mean ± SD (g/L).

Table 10 Comparison of $CD4^+$ T cell count in control and intervention groups before and after autologous bone marrow infusion

Group	Before	1 mo	*t/P* value	3 mo	*t/P* value	6 mo	*t/P* value	12 mo	*t/P* value
Control	432 ± 190	432 ± 183	0.384/0.703	440 ± 184	2.805/0.008	445 ± 189	5.259/0.000	447 ± 186	4.796/0.000
Intervention	436 ± 243	487 ± 227	9.029/0.000	492 ± 219	8.140/0.000	507 ± 223	10.150/0.000	510 ± 213	8.566/0.000
t	0.106	1.177		1.148		1.329		1.400	
P value	0.916	0.243		0.255		0.188		0.166	

Results expressed as mean ± SD (cells/μL).

Figure 3B and Table 11 showed that there was no significant difference in $CD8^+$ T cell count before ABMI between the two groups ($P > 0.05$). After ABMI, $CD8^+$ T cell count in the intervention group at 1, 3, 6 and 12 mo, and in the control group at 1, 3 and 6 mo were significantly higher than before ABMI ($P < 0.01$), but there was no significant difference between the two groups at each time point ($P > 0.05$).

DISCUSSION

Stem cells are not highly differentiated and have the potential to regenerate various tissues and organs in the human body. They are called universal cells in the medical field. Under certain conditions, they can differentiate into multiple functional cells. According to different differentiation potentials, they can be divided into four categories[22]: (1) Totipotent stem cells that can develop into independent individuals; (2) multipotent stem cells that are the descendants of universal stem cells; they cannot develop into individuals, but they can develop into multiple tissues; (3) pluripotent stem cells that can only differentiate into cells of specific groups, such as specific tissues or organs; and (4) unipotent stem cells that can only produce one cell type and have a self-updating property. BMSCs are a type of stem cells with multidirectional differentiation potential and self-renewal. They can differentiate into specific tissues under special circumstances, including liver cells and cardiomyocytes. BMSC transplantation, as a new technology for repairing regenerated damaged organs, has become a research hotspot for stem cell transplantation due to the advantages of convenient collection, low rejection, safety and reliability, and low cost[23,24]. BMSCs can replace damaged hepatocytes by inducing differentiation into hepatocytes in severe liver disease, improve function of the damaged liver, and bring new hope for the treatment of cirrhosis[25,26]. In our previous study, ABMI for patients with DLC and acquired immunodeficiency syndrome significantly prolonged survival. ABMI has the following advantages over traditional treatment: (1) It is simple and easy to collect autologous bone marrow, and there is no shortage of donors; (2) there is usually no immune rejection; (3) it is safe, with almost no adverse reactions, exogenous pollution, and disease transmission; and (4) it has remarkable efficacy at a low cost. Whether splenectomy has an impact on the efficacy of patients with DLC remains unclear. In this study, regardless of whether the spleen was removed, serum PT, TB, and ascites volume after ABMI were significantly lower than before ABMI, and albumin levels were significantly higher. TB is an index for evaluating liver reserve function, albumin is an important index for evaluating liver synthetic function, and PT is an index for evaluating the degree of liver cell necrosis. If these indexes increase or decrease, it indicates that liver function is damaged. The possible mechanism is that after ABMI through the ROV, BMSCs can secrete a large number of different growth factors themselves, stimulate damaged liver cells, promote production of hepatocyte growth factors, promote BMSC differentiation, and exert anti-apoptosis, so that the fibrotic liver regenerates and repairs liver function[27,28]. Liver function improvement also improves coagulation function and reduces the risk of spontaneous bleeding. Most DLC patients still have bleeding in the digestive tract after endoscopic ligation and compression of the three-lumen two-balloon tube in other hospitals, and it is often difficult to undergo further treatment. For patients with gastrointestinal bleeding, conservative treatment such as blood transfusion, hemostasis, and hepatoprotective diuresis can alleviate the condition. We adopt elective splenectomy + infusion port placement. For patients who fail conservative treatment, emergency surgery is required. If the liver function is above Child-Pugh grade B, splenectomy and infusion port placement can be selected. Child-Pugh grade C increases the

Table 11 Comparison of CD8⁺ T cell count in control and intervention groups before and after autologous bone marrow infusion

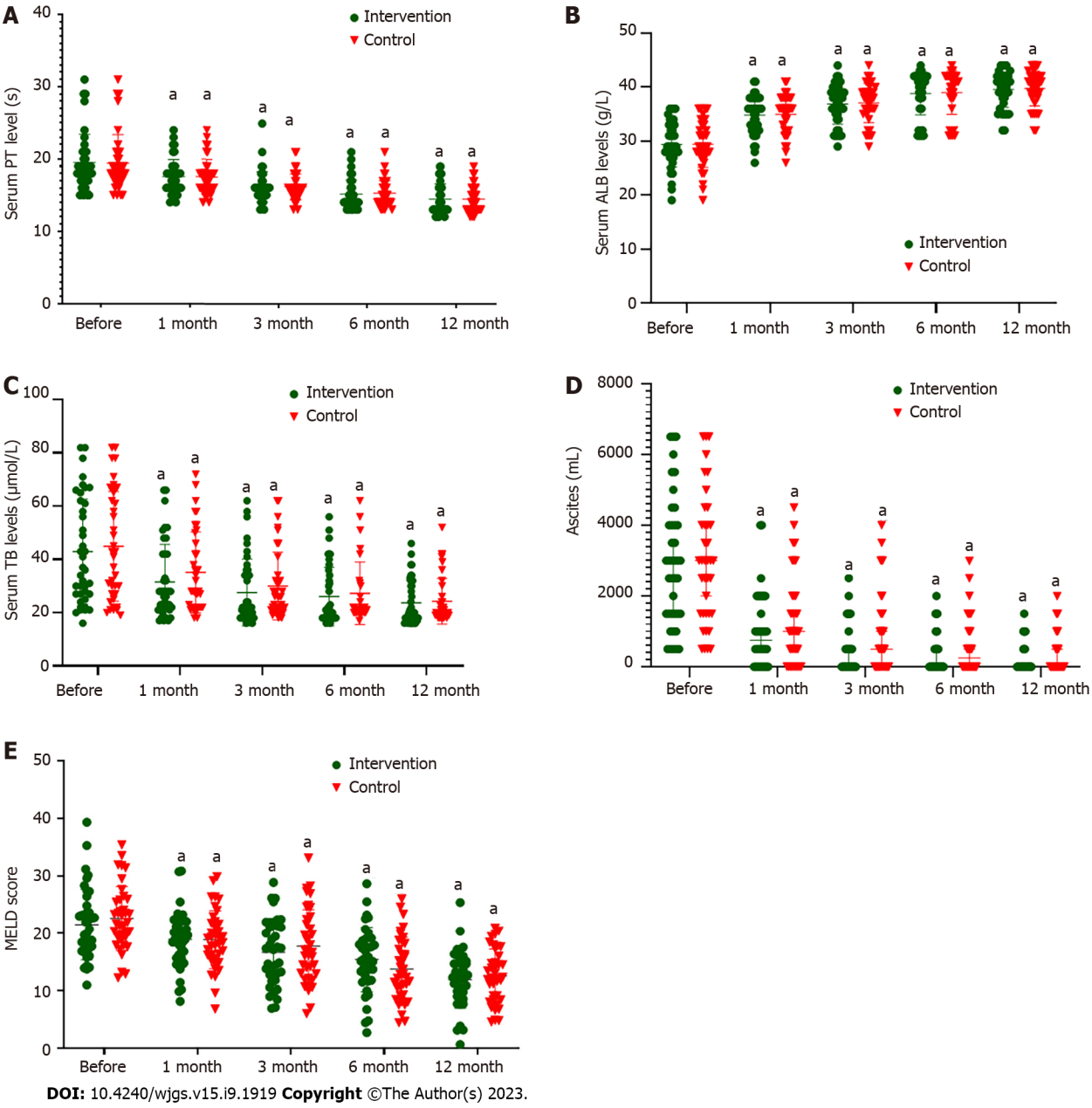
Group	Before	1 mo	*t/P* value	3 mo	*t/P* value	6 mo	*t/P* value	12 mo	*t/P* value
Control	338 ± 210	349 ± 215	2.961/0.000	361 ± 211	4.917/0.000	363 ± 213	3.432/0.001	356 ± 204	1.092/0.282
Intervention	328 ± 210	357 ± 211	9.594/0.000	376 ± 210	10.948/0.000	396 ± 212	12.880/0.000	408 ± 207	12.709/0.000
t	0.206	0.169		0.328		0.684		1.119	
P value	0.837	0.866		0.744		0.496		0.267	

Results expressed as mean ± SD (cells/μL).

risk of postoperative complications. It is necessary to consider the comprehensive conditions and the pros and cons of splenectomy in patients with DLC. If conditions permit, splenectomy can be considered. In the intervention group, there were two DLC patients with acute gastrointestinal hemorrhage with Child-Pugh grade C. If splenectomy is not performed, postoperative bleeding may occur. Therefore, splenectomy was still selected during the operation. After 1-year follow-up, the Child-Pugh grade C patients achieved the same curative effect as the patients with grade B, so liver function classification is not a barrier for choosing splenectomy, and we will expand the number of DLC patients in our future clinical work. In DLC patients, splenectomy can be selected if one of the following three indications was met: (1) Giant spleen, which affects the daily life of the patient; (2) the hypersplenism is serious; and (3) preventing bleeding caused by portal vein pressure. This study showed that splenectomy does not increase the complications caused by surgery, and can improve the symptoms caused by hypersplenism. We found that there was no significant difference between the surgical mortality of the intervention and control groups. The intervention group mainly suffered from bleeding on the wound surface due to splenectomy, while the control group mainly suffered from gastrointestinal bleeding after surgery. There was no obvious relationship between gastrointestinal bleeding and ABMI. The infusion volume in this group was approximately 40 mL, the infusion speed was slow, and the possibility of gastrointestinal bleeding was small. So the bleeding is mainly related to the stress of surgical trauma.

In this study, the surgical complications in both groups had some relationship with coagulation dysfunction, and after ABMI, the coagulation function gradually improved. Ascites is an important indicator of liver dysfunction. After ABMI, the levels of ascites in both groups were significantly less than before ABMI, indicating that both treatments had a significant effect on improving liver function. There was no significant difference in PT, albumin, ascites and MELD score between the two groups at each time point after ABMI, indicating that ABMI improved liver synthetic and secretory functions and this was not related to splenectomy. The MELD score estimated liver disease severity according to the three parameters of INR, TB and creatinine reflecting not only liver injury but also kidney function. Fung *et al*[21] studied patients with acute onset of chronic hepatitis B and found that MELD score accurately predicted short-term mortality of patients. When MELD score was ≥ 10.51, the risk of death increased 3.057 times, which has clinical significance for guiding assessment of later follow-up and prognosis.

There are multiple reasons for anemia in patients with liver cirrhosis. The deposition of fibrous tissue in the liver leads to impaired portal vein blood flow, thereby limiting liver hyperplasia[29,30]. Long-term anorexia leads to malnutrition, which makes the intake of iron inadequate, and patients generally have portal hypertension gastrointestinal disease, which reduces iron absorption. Chronic blood loss in turn causes the loss of iron to exceed the amount of iron supplementation, and the stored iron decreases. The possible mechanisms are: (1) Hepatitis B virus causes bone marrow hematopoietic stem cells and hematopoietic regulatory factors to fail to function normally[31]; (2) hematopoietic stem cells proliferate, maintain stemness, or are blocked for differentiated into myeloid stem cells and lymphoid stem cells[32]; (3) hepatitis B virus infection causes immune damage, resulting in hematopoietic stem cell apoptosis, leading to bone marrow hematopoietic failure[33]; and (4) virus-mediated autoimmune abnormalities cause liver dysfunction, reduce degradation of toxic metabolites, resulting in ischemia and necrosis of pluripotent stem cells, proliferation of hematopoietic stem cells is inhibited, and peripheral blood cell production is reduced from the source[34]. Cirrhosis causes portal hypertension, increased splenic vein pressure, splenic congestion and hypersplenism, leading to increased destruction of peripheral blood cells. In this study, after ABMI through the ROV in two groups, liver function was improved, and the levels of WBC count, hemoglobin, and platelet count were higher than before ABMI, but the increases in the intervention group were more obvious than in the control group, indicating that splenectomy can relieve hypersplenism caused by liver cirrhosis. Peripheral blood T cell subsets mediate the adaptive cellular immune response, which is often regarded as an indicator of immune function in clinical practice. In particular, the immune response of virus-specific T cells has an important effect and regulation in liver pathology and virus clearance[35]. CD4⁺ T cells are helper T cells, CD8⁺ T cells are cytotoxic T cells, and they secrete different cytokines to exert immune effects[36]. In a previous study, after ABMI through the ROV in the treatment of HIV patients with DLC[18], the CD8⁺ and CD4⁺ T cells showed obvious changes, and we found that CD8⁺ and CD4⁺ also changed in non-HIV patients with DLC, so we found that ABMI had an impact on immune function, so we retained these two indicators in the present study. We found that after ABMI, the CD4⁺ T cell count at each time point in the control and intervention groups was significantly higher than before ABMI, but there was no significant difference between the two groups. The CD8⁺ T cell count in the control group showed a significant increase after ABMI at 1 and 6 mo, but decreased at 12 mo, which was not significantly different from that before ABMI. In the intervention group, the CD8⁺ T cell count continued to increase after ABMI at 3, 6 and 12 mo, and there was no obvious decrease in CD8⁺ T cell count, indicating that splenectomy can promote continuous



DOI: 10.4240/wjgs.v15.i9.1919

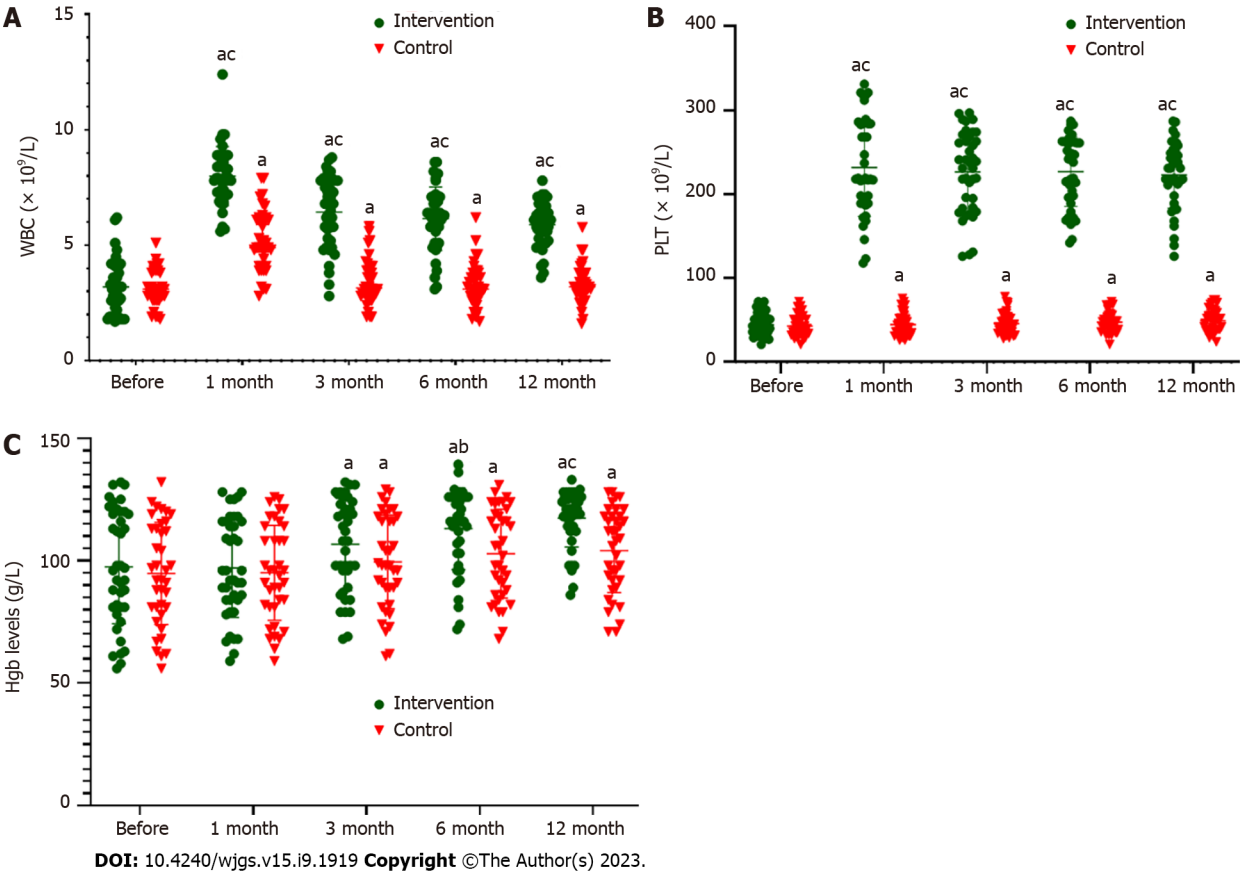
Figure 1 Scatter plots of serum prothrombin time, albumin, total bilirubin, ascites volume and model for end-stage liver disease score before and after autologous bone marrow infusion in control and intervention groups. A: Scatter plot of serum prothrombin time levels before and after autologous bone marrow infusion (ABMI) in both groups; B: Scatter plot of serum albumin levels before and after ABMI in both groups; C: Scatter plot of serum total bilirubin levels before and after ABMI in both groups; D: Scatter plot of ascites volume before and after ABMI in both groups; E: Scatter plot of model for end-stage liver disease score before and after ABMI in both groups. Compared with before ABMI, $^{a}P < 0.01$. PT: Prothrombin time; TB: Total bilirubin; MELD: Model for end-stage liver disease; ALB: Albumin.

increase of $CD8^+$ T cell count. Without removing the spleen, there was a transient increase in $CD8^+$ T cell count, and after 12 mo of ABMI the $CD8^+$ T cell count was continuously decreased in the spleen because of hypersplenism.

This study had some limitations. The follow-up time was too short to analyze the 5-year survival of patients. The specific mechanism of nucleated cells in treatment of DLC is still unclear. In order to address the above shortcomings, we will further follow up the patients, extend the follow-up time to > 5 years. We will also carry out animal experiments to further explore the mechanism of nucleated cells in treatment of DLC.

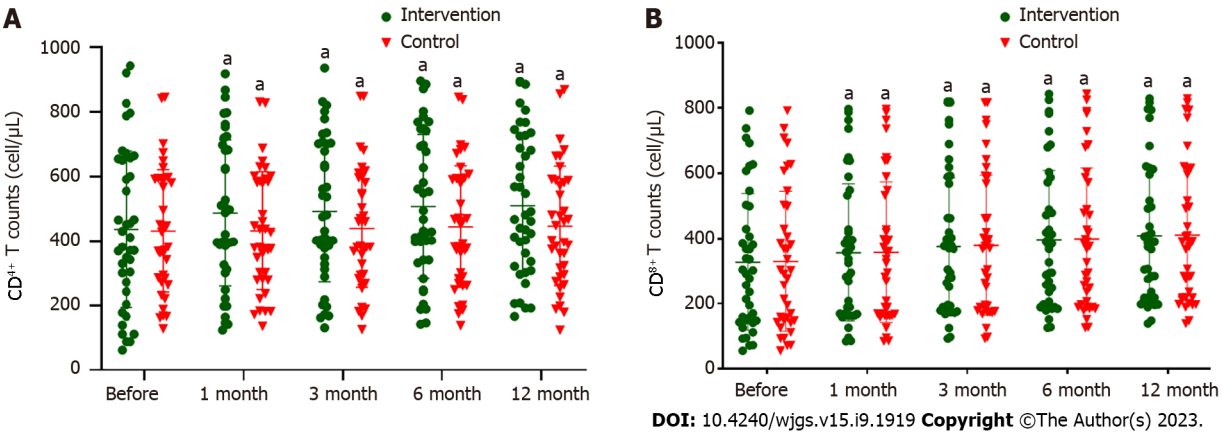
CONCLUSION

ABMI through the ROV in patients with DLC can significantly improve liver synthetic and secretory functions but cannot relieve hypersplenism. ABMI combined with splenectomy can improve liver function and alleviate hypersplenism. However, splenectomy in patients with DLC has a higher risk of surgery-related complications.



DOI: 10.4240/wjgs.v15.i9.1919 **Copyright** ©The Author(s) 2023.

Figure 2 Scatter plots of white blood cell, platelet and hemoglobin levels before and after autologous bone marrow infusion in control and intervention groups. A: Scatter plot of white blood cell count before and after autologous bone marrow infusion (ABMI) in both groups; B: Scatter plot of platelet count before and after ABMI in both groups; C: Scatter plot of hemoglobin level before and after ABMI in both groups. Compared with before ABMI, $^{a}P < 0.01$; compared with control group, $^{b}P < 0.05$, $^{c}P < 0.01$. WBC: White blood cell; PLT: Platelet; Hgb: Hemoglobin.



DOI: 10.4240/wjgs.v15.i9.1919 **Copyright** ©The Author(s) 2023.

Figure 3 Scatter plot of CD4⁺ T and CD8⁺ T counts in control and intervention groups before and after autologous bone marrow infusion**.** A: Scatter plot of CD4⁺ T cell count in both groups before and after autologous bone marrow infusion (ABMI); B: Scatter plot of CD8⁺ T cell count in both groups before and after ABMI. Compared with before ABMI, $^{a}P < 0.01$.

ARTICLE HIGHLIGHTS

Research background

Autologous bone marrow infusion (ABMI) was performed in patients with decompensated liver cirrhosis (DLC), with good results, but whether splenectomy affects outcome is still unclear.

Research motivation

The main purpose of this study was to determine the efficacy of ABMI combined with splenectomy in the treatment of DLC, to clarify the impact of splenectomy on liver and bone marrow function, and to provide a basis for routine splenectomy in patients with DLC.

Research objectives

To clarify the efficacy of ABMI combined with splenectomy in the treatment of DLC, and the impact of splenectomy on liver and bone marrow function, so as to provide basis for rational treatment of DLC.

Research methods

In this study, ABMI combined with splenectomy was used to treat DLC, and the impact of splenectomy on liver and bone marrow function was observed. These common clinical indicators (such as the prothrombin time, serum total bilirubin, ascites volume, white blood cell and platelets counts and so on.) were used to evaluate liver and bone marrow function, which were easy to be popularized in clinic.

Research results

This study shows that ABMI combined with splenectomy is effective in the treatment of DLC, which can help to recover liver and bone marrow function, and alleviate hypersplenism. However, the sample size of this study is small and the follow-up time is short, which needs to be further improved in future studies.

Research conclusions

ABMI combined with splenectomy is a new method for the treatment of DLC, which provides a theoretical basis for the treatment of other chronic diseases.

Research perspectives

Whether ABMI is suitable for other diseases such as osteoarthropathy, cerebral infarction sequelae, diabetes and other chronic diseases, they still need further study.

ACKNOWLEDGEMENTS

We would like to thank Chinese Academy of Sciences Experimental Platform for providing technological support.

FOOTNOTES

Author contributions: Liu BC outlined the content and reviewed the manuscript; Cheng MR reviewed the literature and wrote the manuscript; Lang L, Li L and Si YH performed this experimental work and analyzed the data; Li AJ, Xu Q and Zhang H participated in the experiments; Liu BC and Cheng MR contributed equally as joint first authors.

Supported by Shenkang Hospital Development Center of Shanghai, China, No. SHDC12016129.

Institutional review board statement: This study was approved by the Ethics Committee of the Shanghai Public Health Clinical Center (2013-030).

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

Conflict-of-interest statement: The authors declare that they have no competing interests.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Bao-Chi Liu 0000-0001-9051-1223; Lin Lang 0000-0002-2891-408X; Ai-Jun Li 0000-0002-2891-4079; Qing Xu 0000-0012-2891-407X; Hui Zhang 0000-0092-2891-407X.

S-Editor: Yan JP
L-Editor: A
P-Editor: Yu HG

REFERENCES

1 **Lozano R**, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, De Leo D, Degenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorsey ER, Driscoll T, Duber H, Ebel B, Erwin PJ, Espindola P, Ezzati M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabriel SE, Gakidou E, Gaspari F, Gillum RF, Gonzalez-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassebaum N, Keren A, Khoo JP, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabweijano J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mock C, Mocumbi AO, Mokdad AA, Moran A, Mulholland K, Nair MN, Naldi L, Narayan KM, Nasseri K, Norman P, O'Donnell M, Omer SB, Ortblad K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivero AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope CA 3rd, Porrini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De León FR, Rosenfeld LC, Rushton L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Sliwa K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Towbin JA, Truelsen T, Undurraga EA, Venketasubramanian N, Vijayakumar L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh PH, Yip P, Zabetian A, Zheng ZJ, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2095-2128 [PMID: 23245604 DOI: 10.1016/S0140-6736(12)61728-0]

2 **Marques HP**, Barros I, Li J, Murad SD, di Benedetto F. Current update in domino liver transplantation. *Int J Surg* 2020; **82S**: 163-168 [PMID: 32244002 DOI: 10.1016/j.ijsu.2020.03.017]

3 **Sun T**, Li H, Bai Y, Bai M, Gao F, Yu J, Wu R, Du L, Li F. Ultrasound-targeted microbubble destruction optimized HGF-overexpressing bone marrow stem cells to repair fibrotic liver in rats. *Stem Cell Res Ther* 2020; **11**: 145 [PMID: 32245503 DOI: 10.1186/s13287-020-01655-1]

4 **Alison MR**, Poulsom R, Jeffery R, Dhillon AP, Quaglia A, Jacob J, Novelli M, Prentice G, Williamson J, Wright NA. Hepatocytes from non-hepatic adult stem cells. *Nature* 2000; **406**: 257 [PMID: 10917519 DOI: 10.1038/35018642]

5 **Lu WY**, Bird TG, Boulter L, Tsuchiya A, Cole AM, Hay T, Guest RV, Wojtacha D, Man TY, Mackinnon A, Ridgway RA, Kendall T, Williams MJ, Jamieson T, Raven A, Hay DC, Iredale JP, Clarke AR, Sansom OJ, Forbes SJ. Hepatic progenitor cells of biliary origin with liver repopulation capacity. *Nat Cell Biol* 2015; **17**: 971-983 [PMID: 26192438 DOI: 10.1038/ncb3203]

6 **Pai M**, Spalding D, Xi F, Habib N. Autologous bone marrow stem cells in the treatment of chronic liver disease. *Int J Hepatol* 2012; **2012**: 307165 [PMID: 22121493 DOI: 10.1155/2012/307165]

7 **Takami T**, Terai S, Sakaida I. Novel findings for the development of drug therapy for various liver diseases: Current state and future prospects for our liver regeneration therapy using autologous bone marrow cells for decompensated liver cirrhosis patients. *J Pharmacol Sci* 2011; **115**: 274-278 [PMID: 21350310 DOI: 10.1254/jphs.10r13fm]

8 **Amer ME**, El-Sayed SZ, El-Kheir WA, Gabr H, Gomaa AA, El-Noomani N, Hegazy M. Clinical and laboratory evaluation of patients with end-stage liver cell failure injected with bone marrow-derived hepatocyte-like cells. *Eur J Gastroenterol Hepatol* 2011; **23**: 936-941 [PMID: 21900788 DOI: 10.1097/MEG.0b013e3283488b00]

9 **Peng L**, Xie DY, Lin BL, Liu J, Zhu HP, Xie C, Zheng YB, Gao ZL. Autologous bone marrow mesenchymal stem cell transplantation in liver failure patients caused by hepatitis B: short-term and long-term outcomes. *Hepatology* 2011; **54**: 820-828 [PMID: 21608000 DOI: 10.1002/hep.24434]

10 **Liu B**, Chen X, Wang Y, Shi Y. Curative effect of hepatic portal venous administration of autologous bone marrow in AIDS patients with decompensated liver cirrhosis. *Cell Death Dis* 2013; **4**: e739 [PMID: 23887630 DOI: 10.1038/cddis.2013.261]

11 **Giannotti S**, Parchi PD, Colasanti GB, Agostini G, Moreschini F, Cataldi C, Ferrata P, Capanna R. Use of autologous bone marrow cells concentrate enriched with platelet-fibrin on extensor mechanism allograft reconstruction for extensor mechanism failure following total knee arthroplasty. *J Biol Regul Homeost Agents* 2017; **31**: 107-111 [PMID: 29186946]

12 **Lamirault G**, de Bock E, Sébille V, Delasalle B, Roncalli J, Susen S, Piot C, Trochu JN, Teiger E, Neuder Y, Le Tourneau T, Manrique A, Hardouin JB, Lemarchand P. Sustained quality of life improvement after intracoronary injection of autologous bone marrow cells in the setting of acute myocardial infarction: results from the BONAMI trial. *Qual Life Res* 2017; **26**: 121-125 [PMID: 27439601 DOI: 10.1007/s11136-016-1366-7]

13 **Rice CM**, Marks DI, Walsh P, Kane NM, Guttridge MG, Redondo J, Sarkar P, Owen D, Wilkins A, Scolding NJ. Repeat infusion of autologous bone marrow cells in multiple sclerosis: protocol for a phase I extension study (SIAMMS-II). *BMJ Open* 2015; **5**: e009090 [PMID: 26363342 DOI: 10.1136/bmjopen-2015-009090]

14 **Abdel Aziz M**, Atta H, Roshdy N, Rashed L, Sabry D, Hassouna A, Aboul Fotouh G, Hasan N, Younis R, Chowdhury J. Amelioration of Murine Schistosoma mansoni Induced Liver Fibrosis by Mesenchymal Stem Cells. *J Stem Cells Regen Med* 2012; **8**: 28-34 [PMID: 24693190 DOI: 10.46582/jsrm.0801005]

15 **Matsumoto T**, Takami T, Sakaida I. Cell transplantation as a non-invasive strategy for treating liver fibrosis. *Expert Rev Gastroenterol Hepatol* 2016; **10**: 639-648 [PMID: 26691057 DOI: 10.1586/17474124.2016.1134313]

16 **Takami T**, Terai S, Sakaida I. Stem cell therapy in chronic liver disease. *Curr Opin Gastroenterol* 2012; **28**: 203-208 [PMID: 22395569 DOI: 10.1097/MOG.0b013e3283521d6a]

17 **Mohamadnejad M**, Alimoghaddam K, Mohyeddin-Bonab M, Bagheri M, Bashtar M, Ghanaati H, Baharvand H, Ghavamzadeh A, Malekzadeh R. Phase 1 trial of autologous bone marrow mesenchymal stem cell transplantation in patients with decompensated liver cirrhosis. *Arch Iran Med* 2007; **10**: 459-466 [PMID: 17903050]

18 **Liu B**, Cheng M, Chen X, Li L, Si Y, Wang S, Wang Y, Shi Y. Autologous bone marrow cell transplantation in the treatment of HIV patients with compensated cirrhosis. *Biosci Rep* 2020; **40** [PMID: 32520354 DOI: 10.1042/BSR20191316]

19 **Yoshiji H**, Nagoshi S, Akahane T, Asaoka Y, Ueno Y, Ogawa K, Kawaguchi T, Kurosaki M, Sakaida I, Shimizu M, Taniai M, Terai S, Nishikawa H, Hiasa Y, Hidaka H, Miwa H, Chayama K, Enomoto N, Shimosegawa T, Takehara T, Koike K. Evidence-based clinical practice guidelines for Liver Cirrhosis 2020. *J Gastroenterol* 2021; **56**: 593-619 [PMID: 34231046 DOI: 10.1007/s00535-021-01788-x]

20 **Inadomi J**, Cello JP, Koch J. Ultrasonographic determination of ascitic volume. *Hepatology* 1996; **24**: 549-551 [PMID: 8781322 DOI:

10.1002/hep.510240314]
21 **Fung J**, Mak LY, Chan AC, Chok KS, Wong TC, Cheung TT, Dai WC, Sin SL, She WH, Ma KW, Seto WK, Lai CL, Lo CM, Yuen MF. Model for End-Stage Liver Disease With Additional Criteria to Predict Short-Term Mortality in Severe Flares of Chronic Hepatitis B. *Hepatology* 2020; **72**: 818-828 [PMID: 31872444 DOI: 10.1002/hep.31086]
22 **Poliwoda S**, Noor N, Downs E, Schaaf A, Cantwell A, Ganti L, Kaye AD, Mosel LI, Carroll CB, Viswanath O, Urits I. Stem cells: a comprehensive review of origins and emerging clinical roles in medical practice. *Orthop Rev (Pavia)* 2022; **14**: 37498 [PMID: 36034728 DOI: 10.52965/001c.37498]
23 **Philips CA**, Augustine P, Rajesh S, Ahamed R, George T, Padsalgi G, Paramaguru R, Valiathan G, John SK. Granulocyte Colony-Stimulating Factor Use in Decompensated Cirrhosis: Lack of Survival Benefit. *J Clin Exp Hepatol* 2020; **10**: 124-134 [PMID: 32189927 DOI: 10.1016/j.jceh.2019.05.003]
24 **Anand L**, Bihari C, Kedarisetty CK, Rooge SB, Kumar D, Shubham S, Kumar G, Sahney A, Sharma MK, Maiwall R, Kumar A, Sarin SK. Early cirrhosis and a preserved bone marrow niche favour regenerative response to growth factors in decompensated cirrhosis. *Liver Int* 2019; **39**: 115-126 [PMID: 29962032 DOI: 10.1111/liv.13923]
25 **Latorre R**, Vaquero J, Rincón D, Puerto M, Ponce MD, Sarnago F, Matamoros JA, Ramón E, Elizaga J, Bañares R, Ripoll C. Determinants of platelet count are different in patients with compensated and decompensated cirrhosis. *Liver Int* 2016; **36**: 232-239 [PMID: 26134264 DOI: 10.1111/liv.12908]
26 **Mohamadnejad M**, Vosough M, Moossavi S, Nikfam S, Mardpour S, Akhlaghpoor S, Ashrafi M, Azimian V, Jarughi N, Hosseini SE, Moeininia F, Bagheri M, Sharafkhah M, Aghdami N, Malekzadeh R, Baharvand H. Intraportal Infusion of Bone Marrow Mononuclear or CD133+ Cells in Patients With Decompensated Cirrhosis: A Double-Blind Randomized Controlled Trial. *Stem Cells Transl Med* 2016; **5**: 87-94 [PMID: 26659833 DOI: 10.5966/sctm.2015-0004]
27 **Chen B**, Pang L, Cao H, Wu D, Wang Y, Tao Y, Wang M, Chen E. Autologous stem cell transplantation for patients with viral hepatitis-induced liver cirrhosis: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2019; **31**: 1283-1291 [PMID: 31206409 DOI: 10.1097/MEG.0000000000001455]
28 **Wu CX**, Wang D, Cai Y, Luo AR, Sun H. Effect of Autologous Bone Marrow Stem Cell Therapy in Patients with Liver Cirrhosis: A Meta-analysis. *J Clin Transl Hepatol* 2019; **7**: 238-248 [PMID: 31608216 DOI: 10.14218/JCTH.2019.00008]
29 **Paternostro R**, Kapzan L, Mandorfer M, Schwarzer R, Benedikt S, Viveiros A, Bauer D, Ferlitsch M, Zoller H, Trauner M, Ferlitsch A. Anemia and iron deficiency in compensated and decompensated cirrhosis: Prevalence and impact on clinical outcomes. *J Gastroenterol Hepatol* 2020; **35**: 1619-1627 [PMID: 31972057 DOI: 10.1111/jgh.14988]
30 **Yang J**, Yan B, Yang L, Li H, Fan Y, Zhu F, Zheng J, Ma X. Macrocytic anemia is associated with the severity of liver impairment in patients with hepatitis B virus-related decompensated cirrhosis: a retrospective cross-sectional study. *BMC Gastroenterol* 2018; **18**: 161 [PMID: 30384828 DOI: 10.1186/s12876-018-0893-9]
31 **Lin BL**, Chen JF, Qiu WH, Wang KW, Xie DY, Chen XY, Liu QL, Peng L, Li JG, Mei YY, Weng WZ, Peng YW, Cao HJ, Xie JQ, Xie SB, Xiang AP, Gao ZL. Allogeneic bone marrow-derived mesenchymal stromal cells for hepatitis B virus-related acute-on-chronic liver failure: A randomized controlled trial. *Hepatology* 2017; **66**: 209-219 [PMID: 28370357 DOI: 10.1002/hep.29189]
32 **Sun A**, Gao W, Xiao T. Autologous bone marrow stem cell transplantation *via* the hepatic artery for the treatment of hepatitis B virus-related cirrhosis: a PRISMA-compliant meta-analysis based on the Chinese population. *Stem Cell Res Ther* 2020; **11**: 104 [PMID: 32138750 DOI: 10.1186/s13287-020-01627-5]
33 **Nadelson J**, Satapathy SK, Nair S. Glycated Hemoglobin Levels in Patients with Decompensated Cirrhosis. *Int J Endocrinol* 2016; **2016**: 8390210 [PMID: 27882051 DOI: 10.1155/2016/8390210]
34 **Wang Z**, Sheng L, Yang Y, Yang F, Xiao X, Hua J, Guo C, Wei Y, Tang R, Miao Q, Zhang J, Li Y, Fang J, Qiu D, Krawitt EL, Bowlus CL, Gershwin ME, Wang Q, Ma X. The Management of Autoimmune Hepatitis Patients with Decompensated Cirrhosis: Real-World Experience and a Comprehensive Review. *Clin Rev Allergy Immunol* 2017; **52**: 424-435 [PMID: 27515672 DOI: 10.1007/s12016-016-8583-2]
35 **Shi Y**, Wu W, Yang Y, Yang Q, Song G, Wu Y, Wei L, Chen Z. Decreased Tim-3 expression is associated with functional abnormalities of monocytes in decompensated cirrhosis without overt bacterial infection. *J Hepatol* 2015; **63**: 60-67 [PMID: 25701694 DOI: 10.1016/j.jhep.2015.02.020]
36 **Chen CH**, Chang CL, Chen KH, Cheng BC, Chen HH, Chiang JY, Sung PH, Yip HK. Level and Value of T Cell-derived Circulating Microparticles in Liver Cirrhosis Patients. *In Vivo* 2019; **33**: 2265-2272 [PMID: 31662566 DOI: 10.21873/invivo.11732]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 1932-1940

DOI: 10.4240/wjgs.v15.i9.1932

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Application of multidisciplinary collaborative nursing with family care for enhanced recovery after surgery in children with inguinal hernia

Xiu-Mei Wang, Qiang Hou

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Lehrskov LL, Denmark; Nomden M, Netherlands

Received: May 9, 2023
Peer-review started: May 9, 2023
First decision: May 25, 2023
Revised: June 30, 2023
Accepted: July 19, 2023
Article in press: July 19, 2023
Published online: September 27, 2023

Xiu-Mei Wang, Department of Pediatric Surgery, The Second Affiliated Hospital of Shandong First Medical University, Taian 271000, Shandong Province, China

Qiang Hou, Department of Burns, The Second Affiliated Hospital of Shandong First Medical University, Taian 271000, Shandong Province, China

Corresponding author: Qiang Hou, MM, Doctor, Department of Burns, The Second Affiliated Hospital of Shandong First Medical University, No. 366 Taishan Street, Taian 271000, Shandong Province, China. hqtyfy@163.com

Abstract

BACKGROUND

Perioperative nursing can reduce the stress reaction and improve the prognosis of children.

AIM

To elucidate the influence of multidisciplinary collaborative nursing for enhanced recovery after surgery (ERAS) with family care in perioperative nursing children with an inguinal hernia and its impact on the prognosis.

METHODS

The data of 100 children with inguinal hernia were retrospectively analyzed. The participants were divided into three groups according to different nursing methods: Groups A (n = 38), B (n = 32), and C (n = 30). Group A received multidisciplinary collaborative ERAS nursing combined with family care nursing; Group B received multidisciplinary collaborative nursing for ERAS; and Group C received routine nursing. The postoperative recovery results of the three groups were compared, including intraoperative blood loss and postoperative feeding time, time of getting out of bed, hospitalization time, and defecation time. Furthermore, the incidence of common complications was also compared between the three groups.

RESULTS

There was less intraoperative blood loss in Groups A and B than in Group C (P < 0.05), and the time of getting out of bed and postoperative hospitalization and defecation times were also decreased in Group C (P < 0.05). There was no

significant difference in postoperative feeding time among the three groups ($P > 0.05$). Each index had no statistical significance between Groups A and B ($P > 0.05$). The incidence of urinary retention, infection, hematoma, and hernia recurrence in Group A was less than that in Group C ($P < 0.05$). No significant difference was observed in the overall complication rate between Groups A and B and between Groups B and C ($P > 0.05$).

CONCLUSION

The application of multidisciplinary collaborative nursing combined with family care in the perioperative care of children with an inguinal hernia for ERAS may promote postoperative rehabilitation for children and reduce the incidence of complications.

Key Words: Multidisciplinary collaborative; Enhanced recovery after surgery; Family care; Perioperative nursing; Prognosis; Postoperative complications

Core Tip: This study integrates the concept of multidisciplinary collaborative enhanced recovery after surgery, and integrates and re-innovates the previous application of rapid rehabilitation surgical nursing. In view of the special status of children, kinship care is very necessary. The purpose of this study was to compare the effects of routine perioperative nursing, multidisciplinary collaborative rapid rehabilitation surgical nursing, and multidisciplinary collaborative rapid rehabilitation surgical nursing combined with kinship care nursing. The results showed that multidisciplinary collaborative rapid rehabilitation surgical nursing combined with kinship care nursing has good nursing effects.

Citation: Wang XM, Hou Q. Application of multidisciplinary collaborative nursing with family care for enhanced recovery after surgery in children with inguinal hernia. *World J Gastrointest Surg* 2023; 15(9): 1932-1940
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/1932.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.1932

INTRODUCTION

Inguinal hernia in children is a common pediatric disease that requires surgery, with an incidence rate of 1% to 4%. In these children, congenital development of the abdominal wall is imperfect and can form direct and oblique hernias. The oblique hernia and the incidence of hernia (in general) in male children is higher. After the male is born, the testis descends to the scrotum along the inguinal canal, and the peritoneum that descends with the testis forms a sheath process [1,2]. In children with an open sheath process, the abdominal pressure increases with constipation, cough, ascites, abdominal tumor, or long-term crying, causing abdominal organs such as the small intestine and omentum majus to protrude from the body surface through the internal ring outside the inferior abdominal artery and the subcutaneous ring. The clinical manifestation is a circular elastic mass on one side of the groin that can be recovered into the abdominal cavity. Currently, surgery is the only clinical treatment for oblique inguinal hernia in children. Children under 6 mo old easily self-heal, and those who do not self-heal require surgery. However, surgery may cause psychological and physical trauma, significantly affecting the postoperative rehabilitation of children; therefore, effective nursing is required during the perioperative period. Enhanced recovery after surgery (ERAS) refers to nursing protocols that relieve patients' pain, reduce the stress response and complications, and promote postoperative rehabilitation by optimizing nursing measures during the perioperative period according to evidence-based medicine. Multidisciplinary collaboration is the medical strategy that integrates experts' opinions in nursing, anesthesia, nutrition, surgery, and other disciplines for effective perioperative care. Currently, multidisciplinary collaborations are primarily applied to cancer treatment and nursing. With the continuous development of modern medical technology, interdisciplinary cooperation has become an inevitable trend in medical care. This strategy mainly targets medical care behaviors during the perioperative period of patients undergoing elective surgery, aiming to accelerate patients' rehabilitation from the physiological, psychological, and social medical care modes[3,4]. Integrating multidisciplinary care into enhanced recovery will break down the barriers between disciplines and focus on coordinating the entire care process. Some domestic studies have explored the effects of multidisciplinary collaboration on ERAS. Lan *et al*[5] applied multidisciplinary collaborative nursing for ERAS to perioperative colorectal cancer patients and observed a significant shortening of the hospital stay. Zhou *et al*[6] also implemented ERAS nursing under multidisciplinary collaboration for patients undergoing a whole joint replacement surgery and observed effective postoperative recovery. Children with insufficient cognitive ability are more likely to have postoperative manifestations such as fear and nightmares. Family care emphasizes humanistic care in nursing to eliminate children's negative emotions. Multidisciplinary collaborative nursing for ERAS has been widely used in clinical practice, with significant results[7,8]. Family care is also widely recommended for pediatric diseases[9,10].

This study explored the effects of multidisciplinary collaborative nursing combined with family care nursing for ERAS in the perioperative care of children with inguinal hernia.

MATERIALS AND METHODS

General data

This retrospective study analyzed the data of 100 children with an inguinal hernia from May 2020 to August 2022 and categorized them into Groups A (n = 38), B (n = 32), and C (n = 30) according to different nursing methods. In Group A, there were 35 males and 3 females, aged 17-24 mo (average = 20.89 ± 1.45 mo); there were 29 cases of right and 9 of left indirect hernias. Group B comprised 30 males and 2 females, aged 18-25 mo (average = 20.91 ± 1.94 mo), with 25 right and 7 left indirect hernia cases. Group C included 25 males and 5 females, aged 18-24 mo (average = 20.90 ± 1.37 mo), with 22 right and 8 cases of left indirect hernias. The general data of the three groups were comparable (P > 0.05).

Inclusion criteria

(1) Children diagnosed with an inguinal hernia by clinical symptoms, signs, and imaging data; (2) 6 mo ≤ age ≤ 6 years; (3) Children with unilateral indirect inguinal hernia; and (4) Children treated with internal ring high-ligation *via* transumbilical single-site laparoscopy under general anesthesia.

Exclusion criteria

(1) Children with an external incarcerated and huge inguinal hernias (internal ring diameter ≥ 1.5 cm); (2) Children with severe organ dysfunction such as heart, liver, kidney, and lung; (3) Children with severe immune diseases; (4) Children with blood diseases; and (5) Children with contraindications to surgery.

Methods

Group C: Group C received routine perioperative nursing, including preoperative health education, postoperative water deprivation and fasting, intraoperative fluid replenishment, and routine warming.

Group B: Group B was given multidisciplinary collaborative ERAS nursing. (1) A multidisciplinary collaborative nursing team comprised of professionals from the pediatrics, anesthesiology, general surgery, nutrition, and psychology departments. The head nurse of pediatrics was the team leader for coordinating team affairs, and nurses from all departments were team members responsible for implementing the nursing plan. The team members jointly analyzed the condition of the children and formulated the anesthesia and perioperative management plans; (2) Preoperative nursing. Health education: The medical staff educated the patients about inguinal hernia by distributing a knowledge manual, informed children's families of the possible perioperative conditions and provided relevant solutions, and encouraged the children with appropriate psychological care and preoperative contact to help them establish confidence to overcome the disease. Preoperative preparation: 6 h before the operation, fasting and water deprivation were performed, and a normal diet was resumed after anesthesia recovery. After a multidisciplinary discussion, an appropriate anesthesia plan was determined; (3) Intraoperative nursing. Intraoperative warming: The operating room temperature was controlled at 24-26 ℃, and the disinfection and towel-laying processes were closely connected. Strict liquid intake control: Liquid intake was maintained at 6-10 mL/kg/h to avoid bladder swelling at the end of the surgery, causing restfulness in children. Intraoperative analgesia: Appropriate lidocaine cream was applied after endotracheal incubation, and local infiltration anesthesia was administered with bupivacaine for umbilicus abdominal access after the operation. Bladder emptying: Before surgery, after successful anesthesia, the bladder area was squeezed to empty to avoid the surgical vision field; and (4) Postoperative nursing. Pain management: Children were distracted from pain and discomfort by distracting their attention, instructing their families to provide toys they love, playing music or cartoons they like, and with pacifiers or licking lollipops. During the operation, children with tracheal intubation failure were given methylprednisolone (1-2 mg/kg) prophylactically and budesonide (0.5-1 mg/time) by intravenous drip or aerosol inhalation per doctors' advice. Children with incision pain were given intravenous tramadol 1-2 mg/kg (≤ 100 mg) and oral ibuprofen 10 mg/kg (≤ 200 mg). Diet management: Children were allowed lollipops after anesthesia to reduce hunger and for a pacifying role. This fake feeding behavior also promotes the recovery of gastrointestinal function and reduces postoperative complications. Children were allowed to drink a small amount of water 4 h postoperatively with 15 min of observation. If the child did not appear nauseous, vomit, or show any other symptoms, they were allowed liquid food, followed by multiple small meals, to gradually transition from semi-liquid to general food. Oxygen inhalation: After surgery, the children's face and lips were observed for an anoxic state, the blood oxygen saturation changes were measured, and low-flow oxygen was given according to the children's needs. Fluid supplement: After the operation, a small amount of fluid was given, and the amount and infusion speed were adjusted according to the age and the children's body mass. The fluid amount was < 500 mL/d and the infusion stopped the next day after the operation. Early activity: Activity was recommended at the earliest after the operation. After awakening, the child was put in a knee flexion supine position to reduce the abdominal incisions' tension and the incision pain. After anesthesia, children could move properly in bed when they woke up and left the bed after 6 h; intense activities were avoided.

Group A: For ERAS, Group A received multidisciplinary collaborative nursing and family care nursing. Multidisciplinary collaborative ERAS nursing protocols were similar to Group B. Family care operating room: The head nurse of the department of pediatrics carefully analyzed the children's medical records, inquired about their condition in detail, and developed a perioperative family care nursing protocol. (1) Admission: The receiving nurse dressed properly and introduced herself to family members and children with a kind attitude and etiquette; (2) Hospitalization: During hospitalization, "smile" communication was performed to understand a child's needs. During communication, gentle children's heads touch comforted them through physical contact, gave them a sense of intimacy, and eliminated their fear. Every day, a thoughtful greeting and a caring action were exhibited to the child to make him feel warm. If a child asked

questions, patient and gentle answers were given and were actively communicated with to ensure comfort to the child and family; and (3) Discharge: Nurses organized children to hold hands and wish each other a happy life. This "handshake" activity sends family affection to the children and eliminates their fear and inferiority complex. Nurses were guided to pay more attention to the children and their families, greet and explain, and give them more preoperative and postoperative comfort.

Indicator analysis

(1) Postoperative rehabilitation process. The changes in postoperative rehabilitation indexes, such as blood loss, feeding time, the time of getting out of bed, hospitalization time, and defecation time, were compared among the three groups; (2) The postoperative pain at 4, 12, and 24 h was assessed and compared among the three groups. With the help of facial expression scoring (FLACC)[11], the pain at 4, 12, and 24 h after surgery was evaluated in the three groups. The scale is applied to children aged 0 to 7 years and comprises five items with a total score of 10 points, where 0 = painless, 1-3 = mild pain, 4-6 = moderate pain, and 7-10 = severe pain; (3) Comparison of postoperative stress indexes among the three groups. The heart rate (HR), systolic blood pressure (SBP), and diastolic BP (DBP) were assessed in the three groups before and 1 h after the operation. Furthermore, 3 mL fasting venous blood was collected from the three groups before and 1 h after the operation. After serum separation, the three groups' noradrenaline (NE) and cortisol (Cor) levels were determined by the enzyme-linked immunosorbent assay; (4) Comparison of complications among the three groups; and (5) Family satisfaction. A questionnaire was established to evaluate the satisfaction of patients' family members with nursing, including health education, nursing attitude, nursing quality, and psychological nursing. The full score of each content was 0-100 points; the higher the score, the higher the satisfaction.

Statistical methods

Two persons independently entered all data into excel tables, analyzed it, and then processed it using SPSS 24.0. The data are expressed as the mean ± SD. For normally distributed and homogeneous variance data, a *t*-test was performed, and single-factor analysis of variance was performed for the intergroup comparison. Counting data were described by *n* and %, and not normally distributed data were compared by χ^2 test or the Fisher's exact test. $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of postoperative rehabilitation progress of the three groups

There was less intraoperative blood loss in Groups A and B than in Group C ($P < 0.05$), and the postoperative time of getting out of bed, hospitalization time, and defecation were also lower than in Group C ($P < 0.05$). There was no significant difference in postoperative feeding time among the three groups ($P > 0.05$). There was no statistically significant difference in each index between Groups A and B ($P > 0.05$) (Table 1).

Comparison of postoperative FLACC scores at 4, 12, and 24 h in the three groups

There was no significant difference in postoperative FLACC scores among the three groups at 4 h ($P > 0.05$). At 12 and 24 h after surgery, the FLACC score of the three groups was decreased ($P < 0.05$). The FLACC scores were lower in Groups A and B than in Group C ($P < 0.05$), and lower in Group A than in Group B ($P < 0.05$) (Table 2).

Comparison of stress indexes among the three groups

No significant differences were observed in the preoperative HR, SBP, DBP, NE, and Cor levels among the three groups ($P > 0.05$). At 1 h after surgery, the HR, SBP, DBP, NE, and Cor levels in the three groups were increased ($P < 0.05$). The HR, SBP, DBP, NE, and Cor changes before and after surgery in Groups A and B were less than those in Group C ($P < 0.05$). The HR, NE, and Cor changes in Group A pre- and post-surgery were less than those in Group B ($P < 0.05$) (Table 3).

Comparison of complications among the three groups

There was a lower incidence of urinary retention, infection, hematoma, hernia recurrence, and other complications in Group A than in Group C ($P < 0.05$). No significant differences were identified in the overall complication rate between Groups A and B and between Groups B and C ($P > 0.05$) (Table 4).

Comparison of satisfaction among three groups

Groups A and B scores for health education, nursing attitude, nursing quality, and psychological nursing satisfaction were higher than those in Group C ($P < 0.05$), and each satisfaction score in Group A was higher than that in Group B ($P < 0.05$) (Table 5).

Table 1 Comparison of postoperative rehabilitation progress of the three groups

Group	Intraoperative blood loss in mL	Postoperative feeding time in h	Time of getting out of bed after the operation in d	Postoperative hospitalization time in d	Postoperative defecation time in h
A, *n* = 38	7.55 ± 1.02[c]	4.87 ± 1.80	0.94 ± 0.29[c]	1.86 ± 0.29[c]	17.55 ± 7.28[c]
B, *n* = 32	7.59 ± 0.79[c]	4.31 ± 1.38	0.97 ± 0.29[c]	1.92 ± 0.33[c]	18.25 ± 7.31[c]
C, *n* = 30	11.51 ± 3.16	5.07 ± 1.48	1.31 ± 0.24	2.58 ± 0.47	39.13 ± 13.56
F value	45.641	1.929	17.340	27.637	51.482
P value	< 0.001	0.151	< 0.001	< 0.001	< 0.001

Data are presented as mean ± SD.
[c]*P* < 0.05 *vs* Group C.

Table 2 Comparison of facial expression scoring scores at 4, 12, and 24 h after surgery in the three groups

Group	4 h after surgery	12 h after surgery	24 h after surgery
A, *n* = 38	7.16 ± 1.60	4.05 ± 1.41[b,c]	2.45 ± 0.98[b,c]
B, *n* = 32	7.22 ± 1.26	4.97 ± 0.90[c]	3.56 ± 0.84[c]
C, *n* = 30	7.60 ± 1.25	5.77 ± 1.14	4.20 ± 1.00
F value	0.938	17.733	30.452
P value	0.395	< 0.001	< 0.001

Data are presented as mean ± SD.
[b]*P* < 0.05 *vs* Group B.
[c]*P* < 0.05 *vs* Group C.

Table 3 Comparison of stress indexes among the three groups

Group	HR in beats/min		SBP in mmHg		DBP in mmHg		NE in ng/L		Cor in mg/L	
	Before surgery	1 h after surgery	Before surgery	1 h after surgery	Before surgery	1 h after surgery	Before surgery	1 h after surgery	Before surgery	1 h after surgery
A, *n* = 38	102.01 ± 6.34	118.93 ± 11.48[a,b,c]	95.87 ± 6.47	106.86 ± 7.66[a,c]	84.25 ± 6.70	96.83 ± 6.65[a,b,c]	139.64 ± 7.84	159.95 ± 12.07[a,b,c]	133.78 ± 4.30	151.07 ± 12.27[a,b,c]
B, *n* = 32	98.96 ± 6.68	125.27 ± 11.91[a,c]	95.88 ± 6.28	110.99 ± 8.60[a,c]	83.91 ± 7.23	109.73 ± 8.20[a,c]	139.29 ± 9.45	171.00 ± 11.23[a,c]	134.14 ± 6.41	159.80 ± 13.35[a,c]
C, *n* = 30	101.63 ± 7.53	132.69 ± 11.89[a]	98.15 ± 7.81	119.39 ± 10.27[a]	85.17 ± 7.16	114.20 ± 10.11[a]	143.40 ± 6.97	182.86 ± 16.30[a]	135.42 ± 7.92	180.74 ± 18.69[a]
F value	1.963	11.529	1.161	17.241	0.268	41.032	2.438	25.158	0.619	34.682
P value	0.146	< 0.001	0.318	< 0.001	0.766	< 0.001	0.093	< 0.001	0.54	< 0.001

Data are presented as mean ± SD.
[a]*P* < 0.05 *vs* before operation.
[b]*P* < 0.05 *vs* Group B.
[c]*P* < 0.05 *vs* Group C. Cor: Cortisol; DBP: Diastolic blood pressure; HR: Heart rate; NE: Noradrenaline; SBP: Systolic blood pressure.

DISCUSSION

The ERAS is a novel protocol with many advantages over traditional perioperative management. It has been widely used in orthopedics, obstetrics and gynecology, oncology, and other departments[12-14], achieving good outcomes. The multidisciplinary collaborative mode is the clinical treatment/nursing strategy developed by professionals from different disciplines for a certain disease. In the multidisciplinary collaborative nursing for ERAS, multidisciplinary clinical

Table 4 Comparison of complications among the three groups

Group	Urinary retention	Infection	Hematoma	Hernia recurrence	Overall complication rate
A, n = 38	0 (0.00)	1 (2.63)	0 (0.00)	1 (2.63)	2 (5.26)[c]
B, n = 32	1 (3.13)	0 (0.00)	1 (3.13)	1 (3.13)	3 (9.38)
C, n = 30	2 (6.67)	3 (10.00)	1 (3.33)	2 (6.67)	8 (26.67)
Fisher's exact probability value					0.032

Data are presented as n (%).
[c]$P < 0.05$ *vs* Group C.

Table 5 Comparison of satisfaction among the three groups

Group	Health education	Nursing attitude	Nursing quality	Psychological nursing
A, n = 38	91.37 ± 5.58[b,c]	93.21 ± 4.13[b,c]	87.53 ± 7.12[b,c]	92.37 ± 7.12[b,c]
B, n = 32	85.66 ± 5.68[c]	86.91 ± 7.15[c]	79.53 ± 8.53[c]	86.22 ± 7.25[c]
C, n = 30	77.87 ± 9.84	82.43 ± 6.91	71.60 ± 9.19	80.10 ± 6.05
F value	29.911	26.934	31.491	26.899
P value	< 0.001	< 0.001	< 0.001	< 0.001

Data are presented as mean ± SD.
[b]$P < 0.05$ *vs* Group B.
[c]$P < 0.05$ *vs* Group C.

knowledge is integrated into nursing. This is a challenge for professionals of different departments such as pediatrics, anesthesiology, comprehensive surgery, nutrition, and psychology[15,16]. In nursing, family care refers to treating children as relatives and providing them with comprehensive, considerate, and safe services, embodying humanized nursing mode. Family care has also been widely used for patients' breast cancer and other diseases, with significant effects[9,10].

In this study, Group A was given multidisciplinary collaborative nursing combined with family care for ERAS, Group B was given multidisciplinary collaborative nursing for ERAS, and Group C was only given routine nursing. The results showed that the intraoperative blood loss and postoperative time of getting out of bed, hospitalization, and defecation in Groups A and B were significantly better than in Group C. There was no significant difference in postoperative rehabilitation indexes between Groups A and B, suggesting that multidisciplinary collaborative nursing for ERAS can significantly improve postoperative recovery and the prognosis of children with inguinal hernia surgery. The multidisciplinary collaborative nursing for ERAS, a multidisciplinary collaborative team for nursing management, was established. The personnel from the pediatrics, anesthesia, general surgery, nutrition, and psychology departments analyzed the physiological and psychological conditions of the children. The anesthesia and perioperative nursing plans were formulated. Intraoperative fluid control, anesthesia (per anesthesiologist advice), and intraoperative heat preservation were important for a smooth operation and reduced postsurgical outcomes. Furthermore, postoperative pain management, early exercise, and diet management also reduce pain and shorten the postoperative time of hospital stay, getting out of bed, and defecation[17,18]. Multiple previous studies[19,20] have shown that multidisciplinary collaborative ERAS nursing effectively promotes postoperative rehabilitation of patients, consistent with the results of this study. In terms of pain, improved FLACC scores were observed in Groups A and B than in Group C, and that of Group A was better than Group B. Both Groups A and B received multidisciplinary collaborative nursing for ERAS; pain management programs were developed through multidisciplinary discussion; therefore, paint improvement was better than Group C receiving routine nursing. Stressful invasive surgery can cause trauma to the children's body. Additionally, the fear of an unfamiliar environment can cause anxiety, depression, and other negative emotions. According to the literature[21], postoperative pain is closely related to anxiety and depression, and other adverse emotions. Therefore, the family care nursing in Group A improved children's bad mood and relieved their incision pain with care and love similar to their relatives, indicating improved pain in Group A than in Group B.

According to related reports[22], traumatic surgical stimulation can lead to the excitation of the sympathetic nervous system, increased adrenaline secretion, and hemodynamic changes in patients, manifested as increased HR and BP. Due to cognitive insufficiency, children show strong psychological stress when facing traumatic surgery. Here, the stress indexes, including HR, SBP, DBP, NE, and Cor levels in Groups A and B one hour before and after surgery, were less than in Group C, and that of Group A was decreased than in Group B. The results showed that multidisciplinary collaborative nursing combined with family care nursing positively relieved children's physiological stress, indicating that in Groups A and B, attention was paid to environmental management during surgery, the appropriate temperature was adjusted,

physiological discomfort was reduced, and psychological intervention was given to children before and after surgery. Since Group A was treated with family care nursing, the nursing staff actively encouraged and comforted the children like their relatives, increased communication to divert their attention, and managed their pain. The combined action of various measures effectively relieved their stress response. Furthermore, the incidence of urinary retention, infection, hematoma, hernia recurrence, and other complications in Group A was lower than in Group C ($P < 0.05$). No significant difference was observed in the overall complication rate between Groups A and B and between B and C ($P > 0.05$). The satisfaction scores of health education, nursing attitude, nursing quality, and psychological nursing in Groups A and B were higher than Group C ($P < 0.05$), and each satisfaction score of Group A was higher than Group B ($P < 0.05$). It was indicated that multidisciplinary collaborative nursing with family care effectively alleviated the complications in children and improved the nursing satisfaction of their families by providing high-quality nursing care with multidisciplinary opinions such as nursing, nutrition, and psychological intervention. Family care can also improve nursing compliance and reduce the incidence of complications to a certain extent through encouragement. Combined nursing integrates multidisciplinary collaboration, ERAS, and family care models. It is highly professional in health education, nursing attitude, nursing quality, and psychological intervention, so the family members of children are more satisfied.

The limitation of this retrospective study was its small size. Therefore, for additional perspectives, a large sample size and multicenter study are required to explore the influence of multidisciplinary collaborative nursing with family care for ERAS in children with inguinal hernia.

CONCLUSION

In conclusion, the application of multidisciplinary collaborative nursing with family care for ERAS in perioperative children with an inguinal hernia can effectively improve their postoperative recovery, relieve their pain, reduce their postoperative stress and incidence of complications, and improve the satisfaction of their families, which has clinical application value.

ARTICLE HIGHLIGHTS

Research background

Perioperative nursing can reduce the stress reaction and improve the prognosis of children. Various nursing methods and routine nursing are widely used in perioperative nursing of children. Research significance is to explore the more effective nursing plan of children with inguinal hernia during perioperative nursing.

Research motivation

Perioperative nursing of children with inguinal hernia operation. Clinical need to explore more effective nursing methods to improve the prognosis of children with inguinal hernia surgery. The significance of this study was to affirm the effectiveness of new nursing methods for children with inguinal hernia, encourage clinical teams to continue to explore better nursing methods for children with inguinal hernia, and promote the improvement and innovation of nursing programs.

Research objectives

The main objective was to compare the nursing effect of different nursing methods and observe the advantages of multidisciplinary collaborative enhanced recovery after surgery (ERAS) nursing combined with family care in perioperative nursing of children. The combination of multidisciplinary collaborative ERAS nursing combined with family care can improve the rehabilitation process, pain, stress and nursing satisfaction of children with inguinal hernia, which proves that this nursing method has good nursing effect. It provides a new reference for perioperative nursing of inguinal hernia in children.

Research methods

The clinical data of the children were analyzed retrospectively and grouped according to nursing methods. Then, one-way analysis of variance, paired sample *t*-test and χ^2 test were used to statistically analyze the general data, postoperative rehabilitation indicators, pain scores, stress indicators, occurrence of symptoms and nursing satisfaction of the three groups of patients. The feature of retrospective study is to explore the cause through the results, and it is easier to obtain the case data.

Research results

Multidisciplinary collaborative ERAS nursing combined with family care has a remarkable nursing effect, and has a good improvement in postoperative rehabilitation, pain, post-operative stress and other aspects, providing a new nursing method for perioperative nursing of children with inguinal hernia, which needs further prospective exploration. The effectiveness of the nursing method was further verified.

Research conclusions

Children are prone to bad mood after traumatic surgery, which aggravates postoperative pain. Therefore, attention

should be paid to the influence of nursing methods on children's mood. The nursing effect of multidisciplinary collaborative ERAS nursing combined with family care is better, and the nursing scheme with better effect should be preferred in clinic.

Research perspectives

Nursing can improve the physiological indicators of children, and the specific influence on the psychological state of children needs to be further explored.

FOOTNOTES

Author contributions: Wang XM were responsible for the research design, conducting the experiments, and data acquisition; Hou Q were responsible for the investigation, data analysis, writing, and revising the manuscript; Both authors contributed to the completion of this paper.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Shandong First Medical University.

Informed consent statement: As the study used anonymous and pre-existing data, the requirement for the informed consent from patients was waived.

Conflict-of-interest statement: The authors have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Qiang Hou 0009-0002-3787-7554.

S-Editor: Qu XL
L-Editor: Filipodia
P-Editor: Cai YX

REFERENCES

1 **Morini F**, Dreuning KMA, Janssen Lok MJH, Wester T, Derikx JPM, Friedmacher F, Miyake H, Zhu H, Pio L, Lacher M, Sgró S, Zani A, Eaton S, van Heurn LWE, Pierro A. Surgical Management of Pediatric Inguinal Hernia: A Systematic Review and Guideline from the European Pediatric Surgeons' Association Evidence and Guideline Committee. *Eur J Pediatr Surg* 2022; **32**: 219-232 [PMID: 33567466 DOI: 10.1055/s-0040-1721420]

2 **Johnson KN**, Criss CN, Hirschl RB, Ladino-Torres M, Yang D, Jarboe MD. Ultrasound-guided pediatric inguinal hernia repair. *J Pediatr Surg* 2021; **56**: 1240-1245 [PMID: 33812656 DOI: 10.1016/j.jpedsurg.2021.02.053]

3 **Xiang S**, Tang W, Shang X, Ni H. Practice of Multidisciplinary Collaborative Chain Management Model in Constructing Nursing Path for Acute Trauma Treatment. *Emerg Med Int* 2022; **2022**: 1342773 [PMID: 35941963 DOI: 10.1155/2022/1342773]

4 **Ma W**, Zhang L, Wang C, Xu X. Effect of Multidisciplinary Team Collaborative Nursing Model Combined with Mind Mapping Teaching Method on Postoperative Complications and Mental Health of Patients with Advanced Pancreatic Cancer. *Iran J Public Health* 2022; **51**: 535-543 [PMID: 35865063 DOI: 10.18502/ijph.v51i3.8929]

5 **Lan WX**, Li YP, Wu LJ. Application of enhanced recovery after surgery nursing model based on multidisciplinary collaboration in perioperative management of patients with colorectal cancer. *Zhonghua Xiandai Huli Zazhi* 2022; **28**: 370-373 [DOI: 10.3760/cma.j.cn115682-20210707-02993]

6 **Zhou HY**, Zhang LL, Chen JJ, Guan TJ. Analysis of the effectiveness of multidisciplinary collaboration in accelerated rehabilitation surgery in total knee arthroplasty. *Zhongguo Shiyong Huli Zazhi* 2022; **38**: 192-197 [DOI: 10.3760/cma.j.cn211501-20210105-00028]

7 **Wang D**, Liu Z, Zhou J, Yang J, Chen X, Chang C, Liu C, Li K, Hu J. Barriers to implementation of enhanced recovery after surgery (ERAS) by a multidisciplinary team in China: a multicentre qualitative study. *BMJ Open* 2022; **12**: e053687 [PMID: 35288383 DOI: 10.1136/bmjopen-2021-053687]

8 **Gramlich LM**, Surgeoner B, Baldini G, Ballah E, Baum M, Carli F, Karimuddin AA, Nelson G, Richebé P, Watson D, Williams C, LaFlamme C; Enhanced Recovery Canada. Development of a clinical pathway for enhanced recovery in colorectal surgery: a Canadian collaboration. *Can J Surg* 2020; **63**: E19-E20 [PMID: 31944637 DOI: 10.1503/cjs.006819]

9 **Li YF**. The application of cognitive behavior intervention combined with family care in perioperative nursing of breast cancer patients undergoing surgery. *Shiyong Linchuang Yiyao Zazhi* 2018; **22**: 93-96

10 **Yang SD**, Feng HJ. Discussion on the combination of critical nursing and family care for breast cancer patients. *Shiyong Linchuang Yiyao Zazhi* 2018; **22**: 133-135

11 **Malviya S**, Voepel-Lewis T, Burke C, Merkel S, Tait AR. The revised FLACC observational pain tool: improved reliability and validity for pain assessment in children with cognitive impairment. *Paediatr Anaesth* 2006; **16**: 258-265 [PMID: 16490089 DOI: 10.1111/j.1460-9592.2005.01773.x]

12 **Wainwright TW**, Gill M, McDonald DA, Middleton RG, Reed M, Sahota O, Yates P, Ljungqvist O. Consensus statement for perioperative care in total hip replacement and total knee replacement surgery: Enhanced Recovery After Surgery (ERAS(®)) Society recommendations. *Acta Orthop* 2020; **91**: 3-19 [PMID: 31663402 DOI: 10.1080/17453674.2019.1683790]

13 **Sorabella LL**, Bauchat JR. Enhanced Recovery after Surgery: Cesarean Delivery. *Anesthesiol Clin* 2021; **39**: 743-760 [PMID: 34776107 DOI: 10.1016/j.anclin.2021.08.012]

14 **Ashok A**, Niyogi D, Ranganathan P, Tandon S, Bhaskar M, Karimundackal G, Jiwnani S, Shetmahajan M, Pramesh CS. The enhanced recovery after surgery (ERAS) protocol to promote recovery following esophageal cancer resection. *Surg Today* 2020; **50**: 323-334 [PMID: 32048046 DOI: 10.1007/s00595-020-01956-1]

15 **Wesson H**, Lazo MCJ, Shyu YW, You C, Yutuc E. Enhanced recovery after surgery at howard couty general hospital: A multidisciplinnary and collaborative initiative. *Journal of PeriAnesthesia Nursing* 2021; **36**: e14-e15 [DOI: 10.1016/j.jopan.2021.06.047]

16 **Pickens RC**, Cochran AR, Lyman WB, King L, Iannitti DA, Martinie JB, Baker EH, Ocuin LM, Riggs SB, Davis BR, Matthews BD, Vrochides D. Impact of Multidisciplinary Audit of Enhanced Recovery After Surgery (ERAS)® Programs at a Single Institution. *World J Surg* 2021; **45**: 23-32 [PMID: 32886166 DOI: 10.1007/s00268-020-05765-y]

17 **Liu D**. Application of Enhanced Recovery after Surgery in Gastrointestinal Surgery based on Multidisciplinary Team. *International Journal of Sciences* 2019; **8**: 112-115 [DOI: 10.18483/ijSci.1920]

18 **Han HQ**, Xu Y, Fu T. The application of fast-track surgery combined with multidisciplinary model in nursing perioperative colon cancer patients. *Zhonghua Jiezhichang Jibing Dianzi Zazhi* 2018; **7**: 92-94

19 **Ouyang JB**, Huang GW, He W, Yang JY, Wei W, Ji LD, Gao HM, Peng SP. Application of multidisciplinary enhanced recovery after surgery in perioperative period of laparoscopic inguinal hernia repair. *Zhongguo Putong Waike Zazhi* 2017; **26**: 506-513

20 **Wang BQ**, LI HY, Jiang XH. Application on rapid rehabilitation mode of multidisciplinary cooperation in patients with cerebral arteriovenous malformation. *Huli Shijian Yu Yanjiu* 2019; **16**: 69-71

21 **Wang Y**, Zhang YK, Gui WH, Zhang XD, Li H, Zhao ZB, Feng JY. Research progress on the effect of preoperative anxiety on postoperative pain. *Xinxiang Yixueyuan Xuebao* 2022; **39**: 996-1000

22 **Hirose M**, Okutani H, Hashimoto K, Ueki R, Shimode N, Kariya N, Takao Y, Tatara T. Intraoperative Assessment of Surgical Stress Response Using Nociception Monitor under General Anesthesia and Postoperative Complications: A Narrative Review. *J Clin Med* 2022; **11** [PMID: 36294399 DOI: 10.3390/jcm11206080]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 1941-1949

DOI: 10.4240/wjgs.v15.i9.1941

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Preoperative and postoperative complications as risk factors for delayed gastric emptying following pancreaticoduodenectomy: A single-center retrospective study

Fang-Liang Xie, Li-Jun Ren, Wei-Dong Xu, Tong-Lei Xu, Xia-Qing Ge, Wei Li, Xu-Ming Ge, Wen-Kai Zhou, Kai Li, Yun-Hai Zhang, Zhong Wang

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Rastogi A, India; Yoshikawa K, Japan

Received: May 19, 2023
Peer-review started: May 19, 2023
First decision: June 1, 2023
Revised: June 21, 2023
Accepted: July 18, 2023
Article in press: July 18, 2023
Published online: September 27, 2023

Fang-Liang Xie, Wei-Dong Xu, Tong-Lei Xu, Xia-Qing Ge, Wei Li, Xu-Ming Ge, Wen-Kai Zhou, Kai Li, Zhong Wang, Department of Hepatobiliary Surgery, Xuzhou Medical University Affiliated Hospital of Lianyungang (The First People's Hospital of Lianyungang), Lianyungang 222061, Jiangsu Province, China

Li-Jun Ren, Operating Theatre, Xuzhou Medical University Affiliated Hospital of Lianyungang (The First People's Hospital of Lianyungang), Lianyungang 222061, Jiangsu Province, China

Yun-Hai Zhang, Department of Pain, Xuzhou Medical University Affiliated Hospital of Lianyungang (The First People's Hospital of Lianyungang), Lianyungang 222061, Jiangsu Province, China

Corresponding author: Zhong Wang, Doctor, Doctor, Department of Hepatobiliary Surgery, Xuzhou Medical University Affiliated Hospital of Lianyungang (The First People's Hospital of Lianyungang), No. 6 Zhenhua East Road, Haizhou District, Lianyungang 222061, Jiangsu Province, China. wanglyggdwk@126.com

Abstract

BACKGROUND

Mortality rates after pancreaticoduodenectomy (PD) have significantly decreased in specialized centers. However, postoperative morbidity, particularly delayed gastric emptying (DGE), remains the most frequent complication following PD.

AIM

To identify risk factors associated with DGE after the PD procedure.

METHODS

In this retrospective, cross-sectional study, clinical data were collected from 114 patients who underwent PD between January 2015 and June 2018. Demographic factors, pre- and perioperative characteristics, and surgical complications were assessed. Univariate and multivariate analyses were performed to identify risk factors for post-PD DGE.

RESULTS

The study included 66 males (57.9%) and 48 females (42.1%), aged 33-83 years

(mean: 62.5), with a male-to-female ratio of approximately 1.4:1. There were 63 cases (55.3%) of PD and 51 cases (44.7%) of pylorus-preserving pancreatoduodenectomy. Among the 114 patients who underwent PD, 33 (28.9%) developed postoperative DGE. Univariate analysis revealed significant differences in four of the 14 clinical indexes observed: pylorus preservation, retrocolonic anastomosis, postoperative abdominal complications, and early postoperative albumin (ALB). Logistic regression analysis further identified postoperative abdominal complications [odds ratio (OR) = 4.768, P = 0.002], preoperative systemic diseases (OR = 2.516, P = 0.049), and early postoperative ALB (OR = 1.195, P = 0.003) as significant risk factors.

CONCLUSION

Postoperative severe abdominal complications, preoperative systemic diseases, and early postoperative ALB are identified as risk factors for post-PD DGE.

Key Words: Delayed gastric emptying; Postoperation; Pancreaticoduodenectomy; Treatment

Core Tip: This study enrolled 114 patients with pancreaticoduodenectomy (PD) over a recent 5-year period at a single center with a short time span and detailed and reliable data. To investigate the risk factors for delayed gastric emptying after PD. We have draw the conclusion that postoperative severe abdominal complications, preoperative systemic diseases and early postoperative albumin are risk factors for post-PD delayed gastric emptying.

Citation: Xie FL, Ren LJ, Xu WD, Xu TL, Ge XQ, Li W, Ge XM, Zhou WK, Li K, Zhang YH, Wang Z. Preoperative and postoperative complications as risk factors for delayed gastric emptying following pancreaticoduodenectomy: A single-center retrospective study. *World J Gastrointest Surg* 2023; 15(9): 1941-1949

URL: https://www.wjgnet.com/1948-9366/full/v15/i9/1941.htm

DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.1941

INTRODUCTION

Pancreaticoduodenectomy (PD) is a commonly performed surgical procedure for treating tumors in the head of the pancreas, the lower part of the common bile duct, and the ampullary region of the duodenum. It involves the resection of the pancreatic head, lower portion of the common bile duct, gallbladder, distal stomach, duodenum, and part of the jejunum[1]. With medico-technological advancements, PD has become a standardized surgical approach for treating pancreatic head cancer and periampullary benign and malignant tumors[2], decreasing serious postoperative complications such as severe pancreatic leakage, bile leakage, and massive hemorrhage[3]. However, the underlying mechanism of delayed gastric emptying (DGE), one of its complications, remains unknown, presenting a challenge for clinicians in its treatment[4]. Despite advancements in surgical techniques and perioperative management, which have reduced the occurrence of severe postoperative complications such as severe pancreatic leakage, bile leakage, and massive hemorrhage, some complications, particularly DGE, continue to be prevalent among those who underwent PD, with no known cause or effective treatment[5].

DGE is a syndrome characterized by a gastric motility disorder and gastric emptying disturbances, primarily caused by non-mechanical obstruction factors resulting from abdominal surgery[6]. The cause of DGE has remained unknown, resulting in poor treatment outcomes and prolonged hospital stays, posing challenges for clinicians. Evidence indicates that DGE is a functional gastric emptying disorder without organic lesions[7]. The incidence of DGE has been consistently high for many decades, with a study conducted by the International Study Group of Pancreatic Surgery (ISGPS) in 2007 reporting an incidence ranging from 19% to 57% following pancreatic surgery[5]. A recent foreign research review discovered that the incidence of DGE ranges from 3.2% to 59%, with 3234 (27.7%) out of 11669 patients experiencing post-PD DGE[8]. In recent years, numerous pancreas centers worldwide have conducted extensive studies and discussions on the factors inducing DGE after PD[9]; however, a definite and convincing conclusion is yet to be reached. Determining whether the cause lies in surgical techniques, perioperative management issues, or other factors is crucial in guiding treatment decisions.

Regarding treatment, the specific pathogenesis of DGE remains uncharacterized[5] without an established treatment plan for DGE, resulting in undesirable effects with various treatment approaches. Consequently, comprehensive measures have been generically adopted. For patients with postoperative DGE, the routine treatment plan of our team is to correct hypoproteinemia (HP) and electrolyte imbalances, maintain stable blood sugar levels, and utilize methods such as intramuscular metoclopramide, acupuncture, gastroscope-guided jejunal nutrition tube placement, and occasional intravenous erythromycin infusions[10-12]. However, past treatment attempts using these approaches have failed to improve gastric motility significantly or indicate the exact timing at which gastric function recovers in patients.

Therefore, this study aims to thoroughly investigate the risk factors associated with DGE and introduce a novel treatment approach, as detailed below.

MATERIALS AND METHODS

Baseline data

The clinical data of 114 patients who underwent PD between January 2015 and June 2018 at The First People's Hospital of Lianyungang were collected. Inclusion criteria: (1) Patients who underwent PD; (2) Patients who met the diagnostic criteria for DGE following PD; (3) Patients without cerebrovascular diseases who could tolerate surgery; (4) Patients with no history of abdominal surgery; and (5) Patients with complete clinical data. Exclusion criteria: (1) Patients with incomplete clinical data; (2) Patients with pre-existing gastrointestinal obstructive diseases; (3) Patients with Grade A DGE; (4) Patients with postoperative pulmonary infection; and (5) Patients undergoing re-operation due to postoperative complications.

Surgical methods

All the included patients underwent either PD or pylorus-preserving pancreatoduodenectomy (PPPD) under general anesthesia. The tumor was resected through a median abdominal incision, and lymph nodes were dissected from the pancreatic head, the lower part of the common bile duct, the gallbladder, the upper jejunum, the duodenum, and portions of the distal stomach. All digestive tract reconstructions were performed using the Child procedure. Anastomosis was performed as follows: Firstly, pancreaticojejunostomy was performed using a modified pancreatic duct-jejunal mucosa-to-mucosa one-layer anastomosis or pancreas-jejunal invagination anastomosis; secondly, the gastrointestinal anastomosis was performed by a full-thickness continuous absorbable suture with absorbable threads; finally, end-to-side gastrojejunostomy (for PD) or duodenal-jejunal end-to-side anastomosis (for PPPD) was adopted for gastrointestinal anastomosis. The gastrointestinal anastomosis stoma was located either in the anterior or posterior colon. The stomach and some jejunal feeding tubes were routinely placed during the operation, and two abdominal drainage tubes were inserted postoperatively.

Diagnostic criteria for DGE

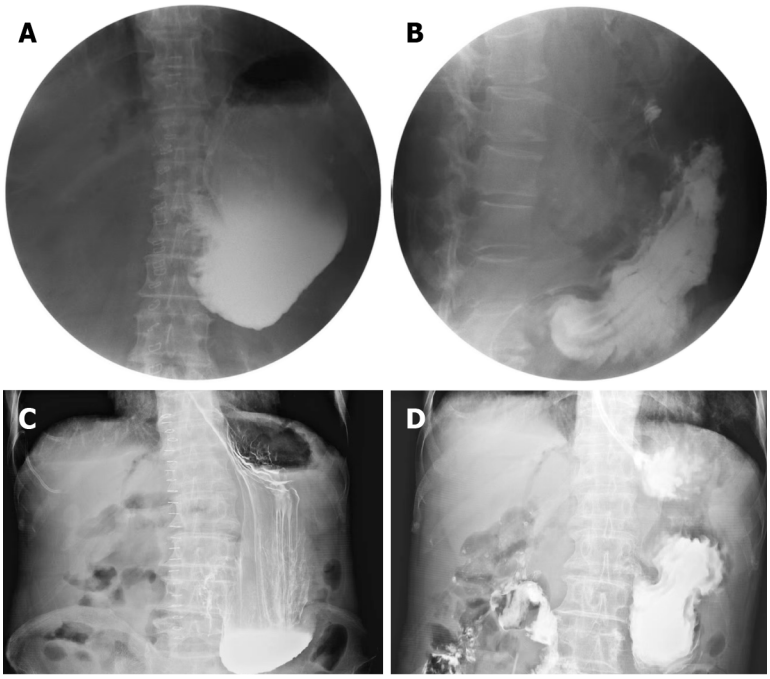
The current diagnosis of DGE after pancreatic surgery follows the requirements recommended by the ISGPS in 2007. Gastroparesis (GP) can be diagnosed if the following conditions are met: (1) Continuous gastrointestinal decompression with a daily drainage volume of > 500 mL for > 3 d after pancreatic surgery; (2) Inability to consume solid food within 7 days after the operation; (3) Vomiting or bloating; and (4) Requirement for gastrointestinal excitomotors. When considering these symptoms, it is essential to rule out mechanical obstruction of the gastrointestinal outflow tract. ISGPS classifies DGE after pancreatic surgery into grades A, B, and C based on the severity. Grade A refers to the retention of the gastric tube for 4-7 d after the operation or the inability to consume solid food on the 7th postoperative day; grade B refers to the retention of gastric tubes for 8-14 d after the operation, or the inability to consume a solid diet on the 14th postoperative day; grade C corresponds to the postoperative gastric tube retention for > 14 d, significantly impacting patient recovery, or the inability to consume a solid diet even after 21 postoperative days. Patients with grades B and C, which have a significant impact on postoperative recovery, were included in the study[5].

Diagnostic criteria for complications

According to the Consensus on the Diagnosis, Treatment, and Prevention of Common Complications in Pancreatic Surgery (2017)[13], formulated by the Pancreatic Surgery Group of the Chinese Medical Association, postoperative complications such as pancreatic fistula, biliary fistula, postoperative bleeding, and chylous fistula were assessed. A pancreatic fistula is an abnormal channel between the pancreatic ductal epithelium and other epithelial surfaces, resulting in the flow of enzyme-rich fluid from the pancreas. The diagnostic criteria for pancreatic fistula are as follows: The amylase concentration in the drainage fluid, measured at least 3 d after the operation, exceeds three times the upper limit of the normal serum amylase concentration, alongside corresponding clinical manifestations. A biliary fistula is an abnormal passage through which bile flows out of the biliary system into the abdominal cavity or outside the body through a breach (or the cholangio-jejunal anastomotic stoma) of the biliary system. Postoperative bleeding is defined as bleeding that occurs after pancreatic surgery, typically indicated by bloody fluid in the abdominal drainage or gastrointestinal decompression tube or hematochezia. Simultaneous changes in vital signs, such as the heart rate and decreased hemoglobin (Hb) concentration, were observed. Chylous fistula is diagnosed when chylous fluid is drained from a drainage tube, orifice, or wound at ≥ 3 d after the operation, regardless of the amount of drainage, provided the concentration of triglycerides is > 1100 mg/L. Intra-abdominal infection is defined by symptoms such as chills, high fever, abdominal distension, and intestinal paralysis, occurring 3 d after the operation and persisting for > 24 h. Laboratory tests showing significantly elevated white blood cell count, with or without HP and anemia, and imaging evidence of intra-abdominal fluid accumulation contribute to the diagnosis of intra-abdominal infection. The diagnosis can be confirmed if the puncture extract is purulent or if bacteria are detected.

Observation indicators selected

Postoperative indicators were considered primary outcome measures, while general information and surgical factors were secondary.



DOI: 10.4240/wjgs.v15.i9.1941

Figure 1 Gastrointestinal series showing the effect of different medications on gastrointestinal motility. Angiography was performed in patients A and B after oral administration of meglumine diatrizoate. A: On postoperative day 9, patient A showed no peristalsis and high tension in the stomach; B: On postoperative day 13, 24 h following the injection of neostigmine through the transdermal receptor pathway, peristaltic waves were observed in patient A; C: On postoperative day 11, patient B showed no peristalsis in the stomach; D: On postoperative day 13, 24 h after the injection of neostigmine through the transdermal receptor pathway, peristaltic waves were observed in patient B.

General information: Gender, age, preoperative systemic diseases, preoperative nutritional status.

Surgical factors: Pylorus preservation status, lymph node dissection, operation time (min), intraoperative blood loss (mL).

Postoperative indicators: Pancreatic fistula, abdominal complications, early enteral nutrition treatment (within 4 d), and Hb and albumin (ALB) levels on postoperative days 1, 4, and 7.

Statistics analysis

All data were statistically analyzed using SPSS 23.0. Enumeration data were expressed as proportions and compared using the Chi-square test or Fisher exact probability method. Measurement data were expressed as medians ± SD and analyzed using the *t*-test. Variables with a test value of $P < 0.10$ in the univariate analysis were included in the multivariate analysis to identify independent risk factors associated with DGE using logistic regression. The estimated odds ratio with 95% confidence intervals was used to describe the relative risk. Statistical significance was indicated by $P < 0.05$.

RESULTS

Occurrence of DGE after PD

The study included 66 males (57.9%) and 48 females (42.1%) (male-to-female ratio is approximately 1.4:1), with a mean age of 62.5 years (range: 33-83 years). Sixty-three cases (55.3%) underwent PD, while 51 (44.7%) received PPPD. The primary diseases diagnosed were pancreatic cancer, cholangiocarcinoma, ampullary carcinoma, solid pseudopapillary tumor of the pancreas, intraductal papillary mucinous neoplasms, chronic pancreatitis, duodenal stromal tumor, and duodenal papillary adenomyoma, with 46, 32, 23, 3, 3, 3, 2, and 2 cases, respectively. DGE occurred in 33 patients, with an incidence of 28.9%. The angiography results are shown in Figure 1.

Analysis of risk factors for post-PD DGE

Univariate analysis of postoperative DGE showed that pylorus preservation, gastrointestinal anastomosis mode, postoperative abdominal complications, and ALB on a postoperative day 4 were significant risk factors for post-PD DGE ($P < 0.05$), as shown in Table 1.

Table 1 Univariate analysis of delayed gastric emptying in 114 cases after pancreaticoduodenectomy

Clinical indexes	*n*	Postoperative delayed gastric emptying		χ^2/t	*P* value
		Yes	No		
Sex				0.002	0.965
Male	66	19	47		
Female	48	14	34		
Age (yr)		62.00 ± 9.47	62.63 ± 9.72	0.316	0.752
Preoperative systemic disease				3.271	0.071
With	44	17	27		
Without	70	16	54		
Preoperative nutritional status				0.729	0.393
Good	92	25	67		
Poor	22	8	14		
Pylorus preservation				4.731	0.03
Yes	51	20	31		
No	63	13	50		
Lymph node dissection				2.451	0.117
Yes	58	13	45		
No	56	20	36		
Operation time (min)		216.54 ± 63.23	233.56 ± 66.35	1.259	0.211
Gastrointestinal anastomosis mode				4.731	0.03
Antecolic anastomosis	63	13	50		
Retrocolic anastomosis	51	20	31		
Intraoperative hemorrhage (mL)		327.27 ± 185.86	367.28 ± 273.54	0.77	0.443
Postoperative pancreatic fistula				0.277	0.871
Without	61	17	44		
Mild	41	13	28		
Severe	12	3	9		
Postoperative abdominal complications				8.551	0.003
With	62	25	37		
Without	52	8	44		
Early enteral nutrition				0.215	0.643
With	9	2	7		
Without	105	31	74		
Hb on postoperative day 1		117.23 ± 16.21	115.45 ± 18.23	0.488	0.627
Hb on postoperative day 4		113.12 ± 13.45	108.23 ± 14.32	1.682	0.095
Hb on postoperative day 7		109.64 ± 14.42	109.87 ± 14.23	0.078	0.938
ALB on postoperative day 1		30.93 ± 4.05	30.52 ± 3.73	0.519	0.605
ALB on postoperative day 4		34.85 ± 4.01	32.20 ± 5.22	2.616	0.01
ALB on postoperative day 7		34.52 ± 5.16	33.62 ± 4.27	0.959	0.339

Hb: Hemoglobin; ALB: Albumin.

The six observation indexes (preoperative systemic disease, pylorus preservation, gastrointestinal anastomosis mode, postoperative abdominal complications, Hb and ALB on postoperative day 4), which were identified with $P < 0.10$ in the univariate analysis, were subjected to logistic regression analysis. The results are presented in Table 2.

Finally, the regression equation included postoperative abdominal complications, preoperative systemic diseases, and ALB on postoperative day 4 as factors influencing the occurrence of DGE after PD, as shown in Table 3.

DISCUSSION

This study enrolled 114 patients who underwent PD within a recent 5-year period at a single center, ensuring a brief timeframe and providing comprehensive and reliable data. Severe DGE grades of B and C were observed in 33 of the 114 patients after PD, resulting in an incidence rate of 28.9%, consistent with findings from other reports. We further investigated the potential impact of pyloric preservation on the risk of DGE, which has been controversial. A randomized controlled trial (RCT) study conducted by Japanese scholars[14] on 130 patients who underwent PD reported a significantly higher incidence of DGE in patients with pylorus preservation compared to those without pylorus preservation (17.2% *vs* 4.5%, $P = 0.02$). However, another RCT study conducted by German scholars on 188 patients undergoing PD by German scholars[15] found no significant difference in the incidence of DGE in 95 patients with pylorus preservation and 93 patients without pylorus preservation (25.3% *vs* 31.2%, $P = 0.208$). In the clinical setting, we have consistently observed patients undergoing PPPD to have a higher possibility of developing DGE. The univariate analysis of this study also showed a higher incidence of DGE in patients who underwent PPPD ($P = 0.03$), with 20 (39.2%) among the 51 patients developing DGE, compared to 13 (20.6%) among the 63 patients who underwent PD, which suggesting that PPPD patients have a high incidence of DGE in patients who have undergone PPPD. However, the multivariate analysis did not reveal a significant correlation between pylorus preservation and DGE. A further in-depth study found that patients with pylorus preservation experienced earlier and milder cases of DGE. If there were no other associated risk factors, the faster patient recovery would not compromise the safety of the procedure or the occurrence of postoperative abdominal complications.

Many studies have indicated postoperative abdominal complications as risk factors for DGE[14,16]. In this research, the univariate analysis revealed that postoperative abdominal complications are independent risk factors ($P = 0.003$) for DGE. Multivariate analysis identified postoperative abdominal complications as the most significant risk factors for DGE (OR = 4.768). Serious postoperative abdominal complications, such as abdominal infection, hemorrhage, chylous fistula, and anastomotic leakage, primarily occur due to pancreatic fistula and biliary fistula with infection. Although postoperative pancreatic leakage was considered an observation index in this study, both univariate and multivariate analyses showed no significant association with postoperative DGE. This finding could be attributed to the adequate abdominal drainage of a simple pancreatic fistula and the absence of local infection in the abdominal cavity, reducing the likelihood of developing postoperative DGE.

Some scholars have suggested[16] that local inflammation or infection foci caused by pancreatic fistula may contribute to DGE. Therefore, measures such as improving the operation quality and implementing early postoperative interventions to promote intestinal peristalsis could lower the incidence of postoperative pancreatic fistula; this ensures unobstructed drainage after the occurrence of pancreatic fistula. The prompt puncture and drainage of the fistula could prevent the accumulation of corrosive fluids, thereby lowering the risk of postoperative DGE. Furthermore, this study identified two other significant risk factors: early postoperative ALB and preoperative systemic diseases. Postoperative ALB, in the presence of systemic diseases, leads to anastomotic edema; suture cutting causes a significant increase in the incidence of anastomotic leakage, which can easily result in abdominal infection, bleeding, and other complications, resulting in postoperative DGE.

A study has investigated the use of neostigmine in treating GP following abdominal surgery[17]; it has shown encouraging results, particularly in the treatment of post-PD DGE. In this study, neostigmine was administered to a 73-year-old male patient with refractory GP after distal gastrectomy, demonstrating a certain degree of safety and clinical efficacy, suggesting that neostigmine is a safe and effective treatment in GP. Previous studies have reported[18-20] the presence of receptor pathways for spinal and sympathetic nerves in the skin and the clinical effectiveness of intradermal administration in treating conditions such as herpes zoster neuralgia and visceral pain[21,22]. Our study demonstrated the unique effects of neostigmine administered *via* the transdermal receptor pathway, which cannot be replicated through other routes of administration. Investigating the target of neostigmine in the receptor pathway is also a future research direction for our team.

CONCLUSION

Based on the results of this study, the following recommendations can be made for the prevention of DGE after PD: (1) Effective communication with patients and their families before the operation is crucial; this allows them to fully comprehend the potential postoperative complications, management strategies, and past experiences in handling complications, helping alleviate their anxiety; (2) Patients with systemic diseases such as hypertension and diabetes should receive careful perioperative treatment to maintain hemodynamic stability and a stable internal environment; (3) Standardizing and improving the procedure is essential to minimize postoperative pancreatic and bile leakage; and (4) Timely initiation of preoperative nutritional support therapy and postoperative ALB supplementation is essential to prevent tissue edema and maintain water-electrolyte balance. Continuous postoperative gastrointestinal decompression,

Table 2 Observational indexes included in multivariate analysis ($P < 0.10$)

Clinical indexes	*n*	Postoperative delayed gastric emptying		χ^2/t	*P* value
		Yes	No		
Preoperative systemic diseases				3.271	0.071
With	44	17	27		
Without	70	16	54		
Pylorus preservation				4.731	0.03
Yes	51	20	31		
No	63	13	50		
Gastrointestinal anastomosis mode				4.731	0.03
Antecolic anastomosis	63	13	50		
Retrocolic anastomosis	51	20	31		
Postoperative abdominal complications				8.551	0.003
With	62	25	37		
Without	52	8	44		
Hb on postoperative day 4		113.12 ± 13.45	109.43 ± 14.32	1.269	0.207
ALB on postoperative day 4		34.85 ± 4.01	32.20 ± 5.07	2.616	0.01

Hb: Hemoglobin; ALB: Albumin.

Table 3 Multivariate analysis of delayed gastric emptying in 114 cases after pancreaticoduodenectomy

Related factors	Regression coefficients	OR	OR (95%CI)	*P* value
Postoperative abdominal complications	1.562	4.768	1.748-13.005	0.002
Preoperative systemic diseases	0.923	2.516	1.004-6.304	0.049
ALB on postoperative day 4	0.178	1.195	1.062-1.344	0.003

Constant: Regression coefficient - 8.241. Regression equation: Logit (*P*) = 1.562 × postoperative abdominal complications + 0.923 × preoperative medical complications + 0.178 × early postoperative hypoproteinemia - 8.241. ALB: Albumin; OR: Odds ratio.

and using patent gastric and abdominal cavity drainage tubes could help reduce the likelihood of abdominal complications.

However, this study has some limitations. As a single-center retrospective study, the potential biases in the data collection and analysis processes could have moderately influenced the final study results. Moreover, no specific analysis was performed during DGE treatment, and a larger sample size with more extensive data is needed to verify the therapeutic effect of neostigmine. Therefore, well-designed, multi-center studies with larger sample sizes are necessary for validation.

ARTICLE HIGHLIGHTS

Research background

Mortality after pancreaticoduodenectomy (PD) has decreased to very low levels in specialized centers. However, postoperative morbidity remains high. Delayed gastric emptying (DGE) still remains the most frequent complication following pancreatoduodenectomy (PD).

Research motivation

When it comes to treatment, the specific pathogenesis of DGE remains uncharacterized, nor is there a specific treatment plan for DGE, resulting in unsatisfactory effects of various treatment approaches. The purpose of this study is to thoroughly explore the risk factors of the disease and introduce a new treatment method.

Research objectives
This study aims to identify related risk factors for DGE after the PD procedure.

Research methods
In this retrospective, cross-sectional study, clinical data were collected from 114 patients who underwent PD from January 2015 to June 2018. They were analyzed regarding demographic factors, pre- and perioperative characteristics, and surgical complications. Univariate and multivariate analyses were performed to identify the risk factors for post-PD DGE.

Research results
The study included 66 males (57.9%) and 48 females (42.1%), aged 33-83 years (mean: 62.5), with a male-to-female ratio of approximately 1.4:1. There were 63 cases (55.3%) of PD and 51 cases (44.7%) of pylorus-preserving pancreatoduodenectomy (PPPD). Among the 114 patients who underwent PD, 33 (28.9%) developed postoperative DGE. Univariate analysis revealed significant differences in four of the 14 clinical indexes observed: Pylorus preservation, retrocolonic anastomosis, postoperative abdominal complications, and early postoperative albumin (ALB). Logistic regression analysis further identified postoperative abdominal complications [odds ratio (OR) = 4.768, P = 0.002], preoperative systemic diseases (OR = 2.516, P = 0.049), and early postoperative ALB (OR = 1.195, P = 0.003) as significant risk factors.

Research conclusions
Postoperative severe abdominal complications, preoperative systemic disease and early postoperative ALB are risk factors for post-PD DGE.

Research perspectives
The research perspective of this study is to thoroughly explore the risk factors for post-PD DGE.

FOOTNOTES

Author contributions: Xie FL and Ren LJ contributed equally to this work and are co-first authors; Xie FL and Ren LJ designed the research and wrote the first manuscript; Wang Z, Xu WD, Xu TL, Ge XQ, LW, Ge XM and Zhou WK contributed to conceiving the research and analyzing data; Wang Z, Li K and Zhang YH conducted the analysis and provided guidance for the research; all authors reviewed and approved the final manuscript.

Institutional review board statement: This study was approved by the Ethic Committee of Xuzhou Medical University Affiliated Hospital of Lianyungang (The First People's Hospital of Lianyungang) (Approval No. LW-20230411001-01).

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: There is no conflict of interest.

Data sharing statement: All data and materials are available from the corresponding author.

Country/Territory of origin: China

ORCID number: Zhong Wang 0009-0000-9467-8880.

S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP

REFERENCES

1 **Xiang Y**, Wu J, Lin C, Yang Y, Zhang D, Xie Y, Yao X, Zhang X. Pancreatic reconstruction techniques after pancreaticoduodenectomy: a review of the literature. *Expert Rev Gastroenterol Hepatol* 2019; **13**: 797-806 [PMID: 31282769 DOI: 10.1080/17474124.2019.1640601]

2 **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]

3 **Schorn S**, Demir IE, Vogel T, Schirren R, Reim D, Wilhelm D, Friess H, Ceyhan GO. Mortality and postoperative complications after different types of surgical reconstruction following pancreaticoduodenectomy-a systematic review with meta-analysis. *Langenbecks Arch Surg* 2019; **404**: 141-157 [PMID: 30820662 DOI: 10.1007/s00423-019-01762-5]

4 **Wang TH**, Lin AY, Mentor K, O'Grady G, Pandanaboyana S. Delayed Gastric Emptying and Gastric Remnant Function After Pancreaticoduodenectomy: A Systematic Review of Objective Assessment Modalities. *World J Surg* 2023; **47**: 236-259 [PMID: 36274094 DOI: 10.1007/s00268-022-06784-7]

5 **Simon R**. Complications After Pancreaticoduodenectomy. *Surg Clin North Am* 2021; **101**: 865-874 [PMID: 34537148 DOI: 10.1016/j.suc.2021.06.011]

6 **Kurahara H**, Shinchi H, Maemura K, Mataki Y, Iino S, Sakoda M, Ueno S, Takao S, Natsugoe S. Delayed gastric emptying after pancreatoduodenectomy. *J Surg Res* 2011; **171**: e187-e192 [PMID: 22001182 DOI: 10.1016/j.jss.2011.08.002]

7 **Cogliandro RF**, Rizzoli G, Bellacosa L, De Giorgio R, Cremon C, Barbara G, Stanghellini V. Is gastroparesis a gastric disease? *Neurogastroenterol Motil* 2019; **31**: e13562 [PMID: 30773743 DOI: 10.1111/nmo.13562]

8 **Panwar R**, Pal S. The International Study Group of Pancreatic Surgery definition of delayed gastric emptying and the effects of various surgical modifications on the occurrence of delayed gastric emptying after pancreatoduodenectomy. *Hepatobiliary Pancreat Dis Int* 2017; **16**: 353-363 [PMID: 28823364 DOI: 10.1016/S1499-3872(17)60037-7]

9 **Mao SH**, Shyr BS, Chen SC, Wang SE, Shyr YM, Shyr BU. Risk factors for delayed gastric emptying in pancreaticoduodenectomy. *Sci Rep* 2022; **12**: 22270 [PMID: 36564517 DOI: 10.1038/s41598-022-26814-7]

10 **Navas CM**, Wadas ED, Zbib NH, Crowell MD, Lacy BE. Gastroparesis and Severity of Delayed Gastric Emptying: Comparison of Patient Characteristics, Treatments and Medication Adverse Events. *Dig Dis Sci* 2021; **66**: 526-534 [PMID: 32306190 DOI: 10.1007/s10620-020-06258-7]

11 **Tewari M**, Mahendran R, Kiran T, Verma A, Dixit VK, Shukla S, Shukla HS. Outcome of 150 Consecutive Blumgart's Pancreaticojejunostomy After Pancreaticoduodenectomy. *Indian J Surg Oncol* 2019; **10**: 65-71 [PMID: 30948875 DOI: 10.1007/s13193-018-0821-z]

12 **Luttikhold J**, de Ruijter FM, van Norren K, Diamant M, Witkamp RF, van Leeuwen PA, Vermeulen MA. Review article: the role of gastrointestinal hormones in the treatment of delayed gastric emptying in critically ill patients. *Aliment Pharmacol Ther* 2013; **38**: 573-583 [PMID: 23879699 DOI: 10.1111/apt.12421]

13 **Study Group of Pancreatic Surgery in Chinese Society of Surgery of Chinese Medical Association**; Pancreatic Disease Committee of Chinese Research Hospital Association; Editorial Board of Chinese Journal of Surgery. [A consensus statement on the diagnosis, treatment, and prevention of common complications after pancreatic surgery (2017)]. *Zhonghua Wai Ke Za Zhi* 2017; **55**: 328-334 [PMID: 28464570 DOI: 10.3760/cma.j.issn.0529-5815.2017.05.003]

14 **Kawai M**, Tani M, Hirono S, Miyazawa M, Shimizu A, Uchiyama K, Yamaue H. Pylorus ring resection reduces delayed gastric emptying in patients undergoing pancreatoduodenectomy: a prospective, randomized, controlled trial of pylorus-resecting versus pylorus-preserving pancreatoduodenectomy. *Ann Surg* 2011; **253**: 495-501 [PMID: 21248633 DOI: 10.1097/SLA.0b013e31820d98f1]

15 **Matsumoto I**, Shinzeki M, Asari S, Goto T, Shirakawa S, Ajiki T, Fukumoto T, Suzuki Y, Ku Y. A prospective randomized comparison between pylorus- and subtotal stomach-preserving pancreatoduodenectomy on postoperative delayed gastric emptying occurrence and long-term nutritional status. *J Surg Oncol* 2014; **109**: 690-696 [PMID: 24619624 DOI: 10.1002/jso.23566]

16 **Qu H**, Sun GR, Zhou SQ, He QS. Clinical risk factors of delayed gastric emptying in patients after pancreaticoduodenectomy: a systematic review and meta-analysis. *Eur J Surg Oncol* 2013; **39**: 213-223 [PMID: 23294533 DOI: 10.1016/j.ejso.2012.12.010]

17 **Jayarajah U**, Yapa K, Ranaweera K, Rahuman A, Perera P, Weerasekara D. Successful use of neostigmine for resistant gastroparesis following distal gastrectomy: A case report. *Int J Surg Case Rep* 2023; **106**: 108166 [PMID: 37068456 DOI: 10.1016/j.ijscr.2023.108166]

18 **Orihara M**, Takazawa T, Horiuchi T, Sakamoto S, Nagumo K, Tomita Y, Tomioka A, Yoshida N, Yokohama A, Saito S. Comparison of incidence of anaphylaxis between sugammadex and neostigmine: a retrospective multicentre observational study. *Br J Anaesth* 2020; **124**: 154-163 [PMID: 31791621 DOI: 10.1016/j.bja.2019.10.016]

19 **Dagnino APA**, Campos MM. Chronic Pain in the Elderly: Mechanisms and Perspectives. *Front Hum Neurosci* 2022; **16**: 736688 [PMID: 35308613 DOI: 10.3389/fnhum.2022.736688]

20 **Rzhevskiy A**, Popov A, Pavlov C, Anissimov Y, Zvyagin A, Levin Y, Kochba E. Intradermal injection of lidocaine with a microneedle device to provide rapid local anaesthesia for peripheral intravenous cannulation: A randomised open-label placebo-controlled clinical trial. *PLoS One* 2022; **17**: e0261641 [PMID: 35100279 DOI: 10.1371/journal.pone.0261641]

21 **Wang YL**, Zhu HY, Lv XQ, Ren XY, Peng YC, Qu JY, Shen XF, Sun R, Xiao ML, Zhang H, Chen ZH, Cong P. Electroacupuncture Zusanli (ST36) Relieves Somatic Pain in Colitis Rats by Inhibiting Dorsal Root Ganglion Sympathetic-Sensory Coupling and Neurogenic Inflammation. *Neural Plast* 2023; **2023**: 9303419 [PMID: 36910013 DOI: 10.1155/2023/9303419]

22 **Yang XN**, Geng ZS, Zhang XL, Zhang YH, Wang XL, Zhang XB, Cui JZ. Single intracutaneous injection of local anesthetics and steroids alleviates acute nonspecific neck pain: A CONSORT-perspective, randomized, controlled clinical trial. *Medicine (Baltimore)* 2018; **97**: e11285 [PMID: 29995761 DOI: 10.1097/MD.0000000000011285]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 1950-1958

DOI: 10.4240/wjgs.v15.i9.1950

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Efficacy of ileus tube combined with meglumine diatrizoate in treating postoperative inflammatory bowel obstruction after surgery

Wen Yang, Jing Pu

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Elkan H, Turkey; Kaya BC, Turkey

Received: May 21, 2023
Peer-review started: May 21, 2023
First decision: June 1, 2023
Revised: July 3, 2023
Accepted: July 29, 2023
Article in press: July 29, 2023
Published online: September 27, 2023

Wen Yang, Jing Pu, Department of Third General Surgery, Lanzhou Second People's Hospital, Lanzhou 730046, Gansu Province, China

Corresponding author: Jing Pu, MD, Doctor, Department of Third General Surgery, Lanzhou Second People's Hospital, No. 388 Jingyuan Road, Lanzhou 730046, Gansu Province, China. 18119373828@163.com

Abstract

BACKGROUND

Early postoperative inflammatory small bowel obstruction (EPISBO) is easy to be complicated after colorectal cancer surgery. Both intestinal obstruction catheter and meglumine can treat EPISBO.

AIM

To investigate the efficacy of an intestinal obstruction tube combined with meglumine diazo in treating EPISBO of colorectal cancer.

METHODS

Data from 60 patients with colorectal cancer and intestinal obstruction admitted to the Proctology Department of our hospital from April 2018 to May 2022 were collected and analyzed and divided into three cohorts according to different treatment regimens. Cohort A (n = 20) received a transnasal intestinal obstruction catheter with panumglumine, and cohort B (n = 20) received a transnasal intestinal obstruction catheter with liquid paraffin. Cohort C (n = 20) received oral treatment with meglumine. The clinical efficacy, first exhaust/defecation time, length of hospital stay, gastrointestinal decompression time, relief time of abdominal pain, and relief time of abdominal distension were compared among the three cohorts. The levels of C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), monocyte chemotactic protein-1 (MCP-1), serum albumin, and transferrin were compared among the three cohorts before and after treatment. The occurrence of adverse reactions in the three cohorts was compared.

RESULTS

Compared with cohort C, the successful treatment rate of cohort A was significantly higher. There were statistically significant variations in the time of first exhaust/defecation, length of hospital stays, gastrointestinal decompression time, relief time of abdominal pain, and relief time of abdominal distention among the three cohorts. Compared with cohort C, cohort A's first exhaust/defecation time,

hospitalization time, gastrointestinal decompression time, abdominal pain relief time, and abdominal distension relief time was reduced ($P < 0.05$). After treatment, serum CRP, TNF-α, IL-6, and MCP-1 expression levels increased, and serum albumin and serum transferrin levels increased in the three cohorts. The serum albumin level in cohort A was higher than in cohort C. Compared with cohort B and cohort C, the serum transferrin level in cohort A increased ($P < 0.05$). Compared with cohort C, the total incidence of adverse reactions in cohorts A and B was significantly higher ($P < 0.05$). The incidence of adverse reactions was similar between cohort A and cohort B.

CONCLUSION

Using an ileus tube combined with meglumine diatrizoate can effectively treat postoperative inflammatory ileus obstructions after surgery colorectal cancer and improve prognosis, inflammatory response, and nutritional status.

Key Words: Ileus tube; Meglumine diatrizoate; Colorectal cancer; Inflammatory bowel obstruction; Early postoperative inflammatory small bowel obstruction

Core Tip: Early postoperative inflammatory small bowel obstruction (EPISBO) patients with colorectal cancer that were difficult to re-operate were mostly treated with conservative therapy. Transnasal ileus catheter has better hypotensive effect and has been widely used in the treatment of EPISBO. However, the effect of combined ileus catheter and meglumine in the treatment of EPISBO has not been discussed in detail. The objective of this study was to compare the efficacy of oral meglumine for EPISBO, ileus catheter alone and ileus catheter combined with meglumine for EPISBO. The effect of intestinal obstruction catheter combined with meglumine in the treatment of EPISBO is better than that of treatment alone.

Citation: Yang W, Pu J. Efficacy of ileus tube combined with meglumine diatrizoate in treating postoperative inflammatory bowel obstruction after surgery. *World J Gastrointest Surg* 2023; 15(9): 1950-1958
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/1950.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.1950

INTRODUCTION

Early postoperative inflammatory small bowel obstruction (EPISBO) is a common postoperative complication following treatment for colorectal cancer. EPISBO is an adhesive intestinal obstruction caused by intestinal wall edema and inflammatory exudation caused by abdominal surgery, intestinal tube injury, and leakage of contents. In patients with colorectal cancer undergoing radical surgery, the intestinal canal is exposed for a long time, and abdominal bleeding and foreign bodies can lead to inflammation. Many inflammatory cells accumulate, eventually leading to inflammation and adhesion [1,2].

If not treated in time, this enhanced inflammatory state can lead to short bowel syndrome, intestinal fistula, infection, and other serious complications. Several studies have shown that EPISBO mainly occurs within two weeks after surgery, and the main clinical manifestations include abdominal distention, cessation of anal exhaust, and defecation.

Clinical-based EPISBO therapy remains conservative, including fasting/water restriction, parenteral nutrition support, and reoperation that can damage the intestine. Traditional nasogastric tube decompression can only remove gastric juice. Additionally, it is difficult to drain the contents of the small intestine, resulting in a long conservative treatment time for early postoperative inflammatory ileus. While semi-effective, some patients have a poor curative effect.

The transnasal ileus tube could drain fluid in the small intestine, reducing edema and intestinal pressure. Meglumine diatrizoate has the characteristics of hypertonicity and has been shown to induce no apparent adverse reactions. After decompression through the intestinal obstruction catheter, angiography can significantly reduce the dilution of contrast medium by intestinal effusion and improve the effectiveness of diagnosis and treatment[3-5]. In addition to being used as a contrast agent, oral administration of meglumine diatrizoate can reduce intestinal wall edema, dilate the small intestine at the distal end of obstruction, stimulate gastrointestinal peristalsis, and relieve intestinal obstruction. This study aimed to probe the therapeutic efficacy of ileus tubes and meglumine diatrizoate for treating EPISBO after surgery for colorectal cancer.

MATERIALS AND METHODS

Ethics

This study was approved by the Ethics Committee of Lanzhou Second People's Hospital. Due to the retrospective design, patient consent was not required.

General information

Data from 60 patients with colorectal cancer and intestinal obstruction admitted to the Proctology Department of our hospital from April 2018 to May 2022 were collected and analyzed. The patients were divided into three cohorts, namely A (n = 20), B (n = 20), and C (n = 20), according to different treatment regimens. Cohort A comprised 14 males and 6 females, with a mean age of 57.95 ± 3.10 years (50-64 years). Within this cohort, these patients presented with the following obstruction locations: Four cases of obstruction in the rectum, six in the descending colon, and 10 in the sigmoid colon. Regarding TNM staging, 10 cases were identified as stage II and 10 as stage III. Cohort B comprised 12 males and 8 females, with a mean age of 59.10 ± 3.46 years (53-65 years). Within this cohort, the patients presented with the following obstruction locations: Two cases of obstruction in the rectum, seven cases in the descending colon, and 11 cases in the sigmoid colon. Regarding TNM staging: Seven cases were identified as stage II and 13 as stage III. Lastly, cohort C comprised 16 males and four females, with a mean age of 60.20 ± 4.29 years (51-68 years). Within this cohort, the patients presented with the following obstruction locations: Six rectum cases, five descending colon cases, and nine sigmoid colon cases. Regarding TNM staging: 11 cases were identified as stage II and nine as stage III.

Inclusion and exclusion criteria

Patients with complete case data that presented with symptoms including abdominal distension, abdominal pain, vomiting, stop of exhaustion, and defecation, had a palpable mass in the right lower abdomen, had no signs of peritonitis, and weakened or absent bowel sounds were included. Furthermore, only patients whose X-ray examination showed intestinal effusion, abdominal computed tomography examination showed intestinal wall edema, thickening, and extensive exudation were included.

Patients with intestinal obstruction caused by intestinal hernia or intussusception, intestinal obstruction or cancerous obstruction caused by mesenteric disease or intestinal paralysis, or patients with hematological diseases, severe infections, and immune diseases were excluded. Furthermore, pregnant and nursing women, patients with neurological diseases, and patients allergic to drugs used in this study were excluded.

Treatment

Cohort A was administered a transnasal ileus tube combined with meglumine diatrizoate, cohort B was administered a transnasal ileus tube combined with liquid paraffin, and cohort C was administered oral meglumine diatrizoate. All three cohorts were given primary treatment, which consisted of fasting and gastrointestinal decompression, early deep vein nutrition treatment to maintain water, electrolyte, and acid-base balance, the correction of hypoalbuminemia and anemia, administration of omeprazole and octreotide to inhibit the secretion of digestive juices. Lastly, a broad-spectrum antibiotic was administered as an anti-infection treatment.

Cohort A: The ileus tube was placed and connected to an external negative pressure suction device, and 100-150 mL of 76% meglumine was injected into the lesion through the ileus tube for intestinal angiography. The ileus tube was retained for continuous negative pressure suction for patients with extensive weakened intestinal peristalsis and apparent pleural effusion. For patients with segmental intestinal peristalsis caused by local adhesion, and if distal intestinal peristalsis was expected, the tube provided enteral nutrition through the obstruction site, and negative pressure drainage was performed through the lateral hole. Parenteral nutrition support was given during treatment.

Cohort B: The transnasal ileus tube was inserted into the stomach under gastroscopy and delivered to the distal descending part of the duodenum with the help of a guide wire or foreign body forceps. Approximately 15 mL of sterilized water was injected into the front balloon and relaxed the tube; the external nasal edge was not fixed. The tube was connected to a negative pressure suction device, and 50-80 mL of liquid paraffin was injected through the negative pressure suction port of the tube. The patient was told to move around more, turn over on the bed, and the tube was sent to the obstruction position through intestinal peristalsis.

Cohort C: Patients were administered 100 mL of meglumine orally, and abdominal signs and disease changes were strictly monitored. All three cohorts were treated twice a day, and the conditions of the three cohorts were monitored following seven days of therapy.

Treatment outcomes to be assessed

Baseline data, clinical efficacy, the time of first exhaust/defecation, length of hospital stays, gastrointestinal decompression time, abdominal pain relief time, abdominal distension relief time, laboratory indicators, nutritional indicators, and the occurrence of adverse reactions were collected and assessed. The clinical efficacy, the time of first exhaust/defecation, length of hospital stays, gastrointestinal decompression time, abdominal pain relief time, and abdominal distension relief time were compared among the three cohorts. The levels of C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), monocyte chemotactic protein-1 (MCP-1), serum albumin, and transferrin were compared among the three cohorts before and after treatment and the occurrence of adverse reactions in the three cohorts was compared.

Efficacy evaluation criteria

Cases where the clinical symptoms and signs of the patient disappeared, and the abdominal vertical position plain film showed normal were defined as "cured" following treatment. Cases where the clinical symptoms and signs disappeared, and the abdominal vertical position plain film showed that the intestinal tube was slightly inflated or had a small amount of liquid level were defined as receiving "effective" treatment. Finally, cases whose clinical symptoms, signs, and

abdominal vertical position plain film did not meet the above criteria were defined as responding "ineffectively" to treatment. Totally effective treatment = cure + effective[6].

Statistical methods

SPSS 20.0 was employed for analyzing/processing datasets, with measurement data reflecting mean ± SD. The independent sample *t*-test was used for comparisons across cohorts, and the paired *t*-test was used for comparison pre-/post-therapy within cohorts. Counting datasets reflected frequency/composition ratio. The comparison of disordered classification data used the chi^2 test or Fisher's exact probability method, and the rank sum test compared rank data. A P value < 0.05 was deemed to confer statistical significance.

RESULTS

Comparative analyses for clinical efficacy among all cohorts

The effectiveness rate of cohort A was significantly elevated compared to cohort C. The effective rates across cohorts "A and B" and "B and C" were similar (Table 1).

Comparative analyses for prognosis among all cohorts

There were statistically significant differences in the time of first exhaust/defecation, length of hospital stays, gastrointestinal decompression time, relief time of abdominal pain, and relief time of abdominal distention among all cohorts (Table 2). Compared to cohort C, the time of first exhaust/defecation, length of hospital stays, gastrointestinal decompression time, relief time of abdominal pain, and relief time of abdominal distention in cohort A were significantly reduced (Table 2).

Comparative analyses for inflammatory factor expression pre-/post-therapy in all cohorts

Pre-therapy, all cohorts had a similar secretion of serum biomarkers, including CRP, TNF-α, IL-6, and MCP-1 expression. Post-therapy, serum CRP, TNF-α, IL-6, and MCP-1 expression in all cohorts were increased, and the indexes in cohort A were significantly elevated compared to cohort B and C, while cohort B expression profiles were significantly upregulated compared to cohort A (Table 3).

Comparative analyses for nutritional status of all cohorts pre-/post-therapy

Pre-therapy, serum albumin, and serum transferrin levels were similar among all cohorts. However, post-therapy, serum albumin and serum transferrin levels in all cohorts were increased. Specifically, the serum albumin level in cohort A was significantly elevated compared to cohort C, and the serum transferrin level in cohort A was significantly elevated compared to cohort B and C (Table 4).

Comparative analyses for the incidence of adverse reactions among all cohorts

The widespread occurrence of adverse events within cohorts A and B was significantly elevated compared to cohort C. Additionally, the occurrence of adverse events between cohorts A and B was similar (Table 5).

DISCUSSION

EPISBO pathogenesis after colorectal cancer surgery is mainly related to neuroinhibitory effects, hormones, hypoalbuminemia, inflammatory response, and anesthesia. Intestinal wall tissue damage during surgery can lead to infiltration of a high quantity of macrophages/neutrophils, combined with the release of increased levels of IL-6 and CRP, forming aseptic inflammation. Such inflammatory substances inhibit the inhibition of gastrointestinal vagal nerve and gastrointestinal peristalsis disorder[7-9]. Additionally, inflammatory factors can excite gastrointestinal sympathetic nerves, leading to intestinal wall congestion and mechanical obstruction[10-12]. The rise of intestinal canal pressure can result in intestinal blood circulation disorder, eventually leading to intestinal perforation, necrosis, and abdominal infection. Reoperation can further damage the intestinal canal, leading to postoperative infection and bleeding. Therefore, conservative therapy is often used in clinical therapy of the disease.

Conservative EPISBO therapy includes fasting, gastrointestinal decompression, spasmolysis and analgesia, and correction of water, electrolyte, and acid-base balance disorders. A traditional nasogastric tube decompression can only aspirate gastric juice but cannot drain the contents of the small intestine, the therapeutic cycle is long, and the therapeutic effect is poor. A transnasal ileus tube can be delivered into the duodenum under the guidance of a gastroscope. Peristalsis and water sac can promote the tube to move to the distal part of the small intestine and reach the proximal part of the obstruction site for decompression. The transnasal ileus tube can quickly play the role of intestinal hypotension, relieve intestinal edema, and promote gastrointestinal function recovery. Water injection by the posterior airbag and water pumping by the anterior airbag can ensure the unidirectional movement of the contrast agent, promote further determination of obstruction location and nature, and promote intestinal decompression. Meglumine diatrizoate was initially used as a contrast agent and, recently, was employed within therapy for intestinal obstruction in several studies with sound therapeutic effects[13-15]. The hypertonic 76% meglumine diatrizoate solution assists in transferring interstitial

Table 1 Comparative analyses for clinical efficacy among all cohorts [cases (%)]

Cohort	Cure	Effective	Ineffective	Total effective rate
Cohort A (n=20)	11 (55.00)	8 (40.00)	1 (5.00)	19 (95.00)[a]
Cohort B (n=20)	9 (45.00)	7 (35.00)	4 (20.00)	16 (80.00)
Cohort C (n=20)	7 (35.00)	5 (25.00)	8 (40.00)	12 (60.00)
χ^2 values				7.267
P value				0.026

[a]Indicated $P < 0.05$ compared to cohort C.
There is no significant difference between group A and group B.

Table 2 Comparative analyses for prognosis among all cohorts ($x \pm s$)

Cohort	Time of first exhaust/defecation (d)	Length of hospital stay (d)	Gastrointestinal decompression time (d)	Relief time of abdominal pain (d)	Relief time of abdominal distention (d)
Cohort A (n = 20)	7.85 ± 1.53[a,b]	15.30 ± 1.95[c]	11.30 ± 1.84[a,b]	2.05 ± 0.51[a,b]	5.55 ± 1.79[a,b]
Cohort B (n = 20)	10.75 ± 2.86[c]	17.10 ± 2.57[c]	14.40 ± 2.74[c]	3.00 ± 1.12	3.85 ± 1.09
Cohort C (n = 20)	13.05 ± 1.90	20.25 ± 2.53	16.35 ± 1.60	3.60 ± 1.35	3.55 ± 1.10
F value	28.749	22.381	28.933	10.923	12.458
P value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

[a]Indicated $P < 0.05$ when compared to cohort B.
[b]Indicated $P < 0.05$ when compared to cohort C.

Table 3 Comparative analyses for inflammatory factors levels pre-/post-therapy in all cohorts ($x \pm s$)

Cohort	CRP (mg/L)		TNF-α (ng/L)		IL-6 (ng/L)		MCP-1 (ng/L)	
	Pre-therapy	Post-therapy	Pre-therapy	Post-therapy	Pre-therapy	Post-therapy	Pre- therapy	Post-therapy
Cohort A (n = 20)	32.84 ± 3.90	17.14 ± 2.27[a,b,c]	10.11 ± 1.74	2.62 ± 0.83[a,b,c]	34.92 ± 2.31	15.27 ± 1.15[a,b,c]	213.33 ± 14.91	122.91 ± 19.00[a,b,c]
Cohort B (n = 20)	34.40 ± 4.67	19.99 ± 3.51[a,c]	11.03 ± 1.99	3.79 ± 1.06[a,c]	35.59 ± 1.59	18.88 ± 1.58[a,c]	215.24 ± 19.15	150.74 ± 19.76[a,c]
Cohort C (n = 20)	32.27 ± 2.78	25.16 ± 2.41[a]	10.80 ± 2.06	5.35 ± 0.95[a]	34.92 ± 3.09	23.43 ± 2.26[a]	211.07 ± 16.46	167.83 ± 15.10[a]
F value	1.636	42.566	1.227	41.469	0.526	112.506	0.303	31.482
P value	0.204	< 0.001	0.301	< 0.001	0.594	< 0.001	0.740	< 0.001

[a]Indicated $P < 0.05$ when compared with the same cohort pre-therapy.
[b]Indicated $P < 0.05$ when compared with cohort B.
[c]Indicated $P < 0.05$ when compared with cohort C.
CRP: C-reactive protein; TNF-α: Tumor necrosis factor-alpha; IL-6: Interleukin-6; MCP-1: Monocyte chemoattractant protein-1.

fluid to the intestinal lumen, relieving intestinal wall edema. In addition, meglumine diatrizoate helps determine the size and shape of intestinal filling. According to relevant studies, meglumine diatrizoate can improve local microcirculation, protect intestinal mucosal barrier function, and relieve inflammation. Furthermore, the body can quickly metabolize an appropriate amount of meglumine diatrizoate in a short period with reasonable safety, leading to high clinical tolerance.

This investigation's dataset outcomes demonstrated that cohort A's effective rate was significantly elevated compared to cohort C. Furthermore, the effective rate across cohorts "A and B" and "B and C" were similar. Compared to cohort C, the time of first exhaust/defecation, length of hospital stays, gastrointestinal decompression time, relief time of abdominal pain, and relief time of abdominal distension in cohort A were significantly reduced. Together, these results indicate that combined therapy has a better effect on EPISBO after colorectal cancer surgery and can more effectively

Table 4 Comparative analyses for nutritional status of all cohorts pre- and post-therapy ($x \pm s$)

Cohort	Serum albumin (g/L)		Serum transferrin (g/L)	
	Pre-therapy	Post-therapy	Pre-therapy	Post-therapy
Cohort A (n = 20)	43.46 ± 3.33	49.88 ± 3.60[a,c]	2.24 ± 0.53	3.55 ± 0.42[a,b,c]
Cohort B (n = 20)	42.79 ± 4.36	47.90 ± 3.90[a]	2.02 ± 0.55	3.16 ± 0.23[a]
Cohort C (n = 20)	43.58 ± 2.14	46.68 ± 2.41[a]	2.27 ± 0.49	2.13 ± 0.51[a]
F value	0.306	4.596	1.377	7.000
P value	0.737	0.014	0.261	0.002

[a]Indicated $P < 0.05$ when compared with the same cohort pre-therapy.
[b]Indicated $P < 0.05$ when compared with cohort B.
[c]Indicated $P < 0.05$ when compared with cohort C.

Table 5 Comparative analyses for adverse event occurrence among all cohorts [cases (%)]

Cohort	Anorexia	Vomiting	Tube obstruction	Rash	The total incidence of adverse reactions
Cohort A (n = 20)	1 (5.00)	4 (20.00)	0 (0.00)	0 (0.00)	5 (25.00)
Cohort B (n = 20)	1 (5.00)	3 (15.00)	1 (5.00)	1 (5.00)	6 (30.00)
Cohort C (n = 20)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Fisher's exact probability value					0.029

promote the recovery of gastrointestinal function and shorten the therapy time.

The therapy plan of the ileus tube combined with meglumine diatrizoate injection combines the therapeutic advantages of the ileus tube and meglumine diatrizoate. Using an ileus tube, meglumine diatrizoate can quickly reach the site of intestinal obstruction, dilute intestinal obstruction contents, relieve intestinal stenosis, recover gastrointestinal function, and avoid further aggravation of intestinal obstruction. Thus, this method can effectively shorten the hospital stay and reduce clinical manifestations in patients. Cohort B was administered an ileus tube combined with liquid paraffin, which also took advantage of the dual advantages of an ileus tube and liquid paraffin. Therefore, cohorts A and B's clinical efficacy and prognosis were better than cohort C, who were administered oral meglumine diatrizoate alone.

CRP is synthesized by stem cells, and its expression level can be abnormally elevated when the body is subjected to inflammatory stimulation or stress response[16,17]. Lymphocytes and fibroblasts produce TNF-α, and endothelial cells, which can enhance the chemotaxis of neutrophils, release inflammatory factors, aggravate the body's inflammatory response, and exacerbate tumor cellular proliferative rate, leading to patient condition deterioration. IL-6 is an inflammatory cytokine produced by endothelial cells, lymphoid cells, and mononuclear macrophages, which can regulate inflammatory response and induce stem cells to synthesize CRP. MCP-1 can reduce the speed of gastrointestinal motility through inhibitory adrenergic nerve pathway activity and is abnormally expressed in various inflammatory responses, affecting gastrointestinal neuromuscular movement. Additionally, several studies have shown that MCP-1 expression level is intimately linked with the severity of intestinal obstruction[18-20]. This investigation revealed that serum CRP, TNF-α, IL-6, and MCP-1 levels in all cohorts were significantly increased post-therapy. In contrast, the levels of each index in cohort A were elevated compared to cohort B and C, and the levels of each index in cohort B were significantly elevated compared to cohort A. These data indicate that an ileus tube combined with meglumine diatrizoate for treating EPISBO after colorectal cancer surgery could effectively relieve the inflammatory response of patients and that the effect is better than instances where an ileus tube combined with liquid paraffin therapy and meglumine diatrizoate is used alone. This observation may be because, compared with liquid paraffin, meglumine diatrizoate can play a particular therapeutic effect in addition to the contrast effect in the therapy of EPISBO; thus, the combination of ileus tube and meglumine diatrizoate has a better therapeutic effect. We hypothesize that the mechanism underlying this effect may be because the ileus tube combined with meglumine diatrizoate relieves the body's inflammatory response, improving clinical symptoms.

EPISBO patients, after colorectal cancer surgery, are prone to malnutrition. Parenteral nutrition can provide adequate nutritional support to patients and reduce the incidence of complications. However, long-term enteral nutrition can damage the intestinal microbial barrier function, cause entheogenic infection, and affect the postoperative recovery of patients. Therefore, enteral nutrition is generally given to patients with intestinal obstruction to improve their nutritional status and promote the recovery of gastrointestinal function. In this study, serum albumin and serum transferrin levels in all cohorts increased post-therapy. Specifically, the serum albumin level in cohort A was significantly elevated compared to cohort C and the serum transferrin level in cohort A was significantly elevated compared to cohort B and C. These results suggest that an ileus tube combined with meglumine diatrizoate in the therapy of EPISBO after colorectal cancer surgery can effectively improve the nutritional status of patients. Because the transnasal ileus tube can effectively shorten

the recovery time of the gastrointestinal function and provide enteral nutrition as soon as possible, the nutritional status of patients in cohort A was better than in cohort B and C. The incidence of total adverse reactions in cohorts A and B was significantly elevated compared to cohort C. The incidence of adverse reactions was similar across cohort A and cohort B. The higher incidence of adverse reactions observed in cohorts A and B could be attributed to using the ileus tube in these groups.

This study has several limitations. First, this is a retrospective study with a small sample size; unintentional biases may have been introduced. Further large-scale, multi-center prospective studies are expected to explore the effect of ileus tubes combined with meglumine diatrizoate in the therapy of EPISBO after colorectal cancer surgery and provide references for clinical treatment.

CONCLUSION

In conclusion, the use of an ileus tube combined with meglumine diatrizoate in the therapy of EPISBO after colorectal cancer surgery can effectively shorten the length of hospital stay, promote the recovery of gastrointestinal function, and relieve the inflammatory response of the body, with good therapeutic effect and clinical application value.

ARTICLE HIGHLIGHTS

Research background

Early postoperative inflammatory small bowel obstruction (EPISBO) is easy to be complicated after colorectal cancer surgery. Both intestinal obstruction catheter and meglumine can treat EPISBO. Extensive application of parenteral nutrition support, traditional nasogastric tube, intestinal obstruction catheter and meglumine in EPISBO treatment. Research significance is to explore a new method for the treatment of EPISBO after colorectal cancer surgery.

Research motivation

The main topics is treatment of EPISBO after colorectal cancer surgery. There is a clinical need to explore more effective therapies to treat EPISBO after colorectal cancer surgery. The significance of this study is to confirm the effectiveness of the new method of ileus catheter combined with meglumine for the treatment of EPISBO after colorectal cancer surgery, encourage clinical teams to continue to explore more effective treatment methods for EPISBO after colorectal cancer surgery, and promote the continuous progress of medical technology.

Research objectives

To compare the effects of different treatment methods for EPISBO, and to observe the advantages of intestinal obstruction catheter combined with meglumine in the treatment of EPISBO. The combination of intestinal obstruction catheter and meglumine in the treatment of EPISBO after colorectal cancer surgery can significantly improve the short-term prognosis, inflammatory status and nutritional status of patients, which confirms that this treatment method has a good therapeutic effect, and provide a new reference for future clinical treatment of EPISBO after colorectal cancer surgery.

Research methods

Clinical data of patients were retrospectively analyzed and divided into three groups according to different treatment methods. One-way analysis of variance, paired sample *t*-test and Chi-square test were used to statistically analyze the general data, clinical efficacy, short-term prognostic indicators, inflammatory factors, nutritional status indicators and incidence of adverse reactions of patients in the three groups. The feature of retrospective study is to explore the cause through the results, and it is easier to obtain the case data.

Research results

Intestinal obstruction catheter combined with meglumine has a significant effect in the treatment of EPISBO after colorectal cancer surgery, showing good improvement in clinical efficacy, short-term prognosis, inflammatory status and nutritional status, providing a new treatment method for EPISBO after colorectal cancer surgery, and further prospective studies are needed to verify the effectiveness of this treatment method.

Research conclusions

Malnutrition in EPISBO patients can lead to a variety of complications and affect the prognosis of patients. Therefore, attention should be paid to the influence of treatment methods on the nutritional status of patients after treatment. Intestinal obstruction catheter combined with meglumine is effective in the treatment of EPISBO after colorectal cancer surgery, and the clinical treatment plan with better effect should be preferred.

Research perspectives

Clinical treatment plan should not only consider the therapeutic effect, but also consider the impact on the patient's prognosis. Future research is aimed at further exploring the impact of medicine on quality of life.

FOOTNOTES

Author contributions: Yang W initiated the project, designed the experiment, performed postoperative follow-up and recorded data, and wrote the original manuscript; Pu J conducted collated data, assisted with the statistical analysis, and revised the paper; all authors reviewed and approved the paper; and all authors have read and approved the final manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of Lanzhou Second People's Hospital.

Informed consent statement: Due to the retrospective design, patient consent was not required.

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

Data sharing statement: All data generated or analyzed during this study are included in this published article.

Country/Territory of origin: China

ORCID number: Jing Pu 0000-0001-8925-3060.

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

REFERENCES

1 **Wu Z**, Wang S, Yuan S, Lin M. Clinical efficacy and safety of somatostatin in the treatment of early postoperative inflammatory small bowel obstruction: A protocol for systematic review and meta analysis. *Medicine (Baltimore)* 2020; **99**: e20288 [PMID: 32443374 DOI: 10.1097/MD.0000000000020288]
2 **Haumann A**, Ongaro S, Detry O, Meunier P, Meurisse M. Acute pelvic inflammatory disease as a rare cause of acute small bowel obstruction. *Acta Chir Belg* 2019; **119**: 328-330 [PMID: 29560794 DOI: 10.1080/00015458.2018.1453438]
3 **Chen YH**, Qian O, Guan JH, Wang JX, Pan YF, Zhuang ZH. Removal of magnetic beads retained in small intestine by endoscopy combined with transnasal ileus catheter. *J Dig Dis* 2020; **21**: 529-531 [PMID: 32621363 DOI: 10.1111/1751-2980.12920]
4 **Zuo L**, Cao L, Ding C, Tu H, Wei C, Yuan L, Wang H, Zhang B. Strategy to small intestine obstruction caused by Crohn's disease on the basis of transnasal ileus tube insertion. *BMC Surg* 2022; **22**: 183 [PMID: 35568851 DOI: 10.1186/s12893-022-01632-w]
5 **Li XF**. [Study on the effect of gastroscopic transnasal obstruction catheter in the therapy of acute intestinal obstruction]. *Chin Remed Clin* 2018; **18**: 589-590 [DOI: 10.11655/zgywylc2018.04.041]
6 **Zhu WM**, Li N. [Diagnosis and therapy of early postoperative inflammatory bowel obstruction]. *Chin J Pract Surg* 2000; **22**: 219-220 [DOI: 10.3321/j.issn:1005-2208.2000.08.005]
7 **Nakamura Y**, Matsuda K, Yokoyama S, Hotta T, Takifuji K, Yamamoto M, Iwahashi M, Tominaga T, Horiuchi T, Kinoshita H, Tsubakihara H, Noguchi K, Yamaguchi K, Shimada K, Oku Y, Yamaue H. Intraoperative maneuvers may affect the development of early postoperative small bowel obstruction after laparoscopic colorectal cancer surgery: Multicenter prospective cohort study. *Int J Surg* 2021; **86**: 52-56 [PMID: 33508470 DOI: 10.1016/j.ijsu.2021.01.007]
8 **Fukami Y**, Kobayashi S, Sekoguchi E, Kurumiya Y. Randomized controlled trial of hyperbaric oxygen therapy in adhesive postoperative small bowel obstruction. *Langenbecks Arch Surg* 2018; **403**: 555-559 [PMID: 29808324 DOI: 10.1007/s00423-018-1682-1]
9 **Guo Y**, Zhu Q, Chen S, Li Y, Fu D, Qiao D, Wang Y, Yang Y. Effect of sodium hyaluronate-arboxycellulose membrane (Seprafilm®) on postoperative small bowel obstruction: A meta-analysis. *Surgery* 2021; **169**: 1333-1339 [PMID: 33461779 DOI: 10.1016/j.surg.2020.12.004]
10 **Mege D**, Colombo F, Stellingwerf ME, Germain A, Maggiori L, Foschi D, Buskens CJ, de Buck van Overstraeten A, Sampietro G, D'Hoore A, Bemelman W, Panis Y. Risk Factors for Small Bowel Obstruction After Laparoscopic Ileal Pouch-Anal Anastomosis for Inflammatory Bowel Disease: A Multivariate Analysis in Four Expert Centres in Europe. *J Crohns Colitis* 2019; **13**: 294-301 [PMID: 30312385 DOI: 10.1093/ecco-jcc/jjy160]
11 **Stenberg E**, Chen R, Hildén K, Fall K. Pregnancy As a Risk Factor for Small Bowel Obstruction After Laparoscopic Gastric Bypass Surgery. *Ann Surg* 2020; **272**: 125-129 [PMID: 30601250 DOI: 10.1097/SLA.0000000000003163]
12 **Heng S**, Hardy J, Good P. A retrospective audit on usage of Diatrizoate Meglumine (Gastrografin(®)) for intestinal obstruction or constipation in patients with advanced neoplasms. *Palliat Med* 2018; **32**: 294-298 [PMID: 28805119 DOI: 10.1177/0269216317726430]
13 **Miao X**, Tao L, Huang L, Li J, Pan S. Application of Laparoscopy Combined with Enhanced Recovery after Surgery (ERAS) in Acute Intestinal Obstruction and Analysis of Prognostic Factors: A Retrospective Cohort Study. *Biomed Res Int* 2022; **2022**: 5771526 [PMID: 36105936 DOI: 10.1155/2022/5771526]
14 **Shen Y**, Qi L, Li Y, Zhang Y, Gao X, Zhu Y, Wang K. The Downregulation of lncRNA pgm5-as1 Inhibits the Proliferation and Metastasis Via Increasing miR-484 Expression in Colorectal Cancer. *Cancer Biother Radiopharm* 2021; **36**: 220-229 [PMID: 32354224 DOI: 10.1089/cbr.2019.3059]
15 **Wang L**, Zhai L, Xie Z, Zhang B. [The value of meglumine meglumine in the dietary care of patients with acute pancreatitis]. *Shanxi Med J* 2019; **48**: 867-869
16 **Calvo-Rodríguez R**, Montero-Pérez FJ, García-Olid A, Baena-Delgado E, Gallardo-Valverde JM, Calderón de la Barca-Gázquez JM,

Jiménez-Murillo LM. [Value of plasma C-reactive protein and lactate dehydrogenase levels in the diagnosis of intestinal obstruction in an emergency department]. *An Sist Sanit Navar* 2016; **39**: 115-122 [PMID: 27125616 DOI: 10.4321/S1137-6627/2016000100013]

17 **Chen W**, Yu X. Diagnostic Value of Color Doppler Flow Imaging Combined with Serum CRP, PCT, and IL-6 Levels for Neonatal Pneumonia. *Evid Based Complement Alternat Med* 2022; **2022**: 2113856 [PMID: 35990828 DOI: 10.1155/2022/2113856]

18 **Xu X**. [Effects of laparoscopic surgery on inflammatory factors, surgical indicators and postoperative recovery in patients with colorectal cancer intestinal obstruction]. *J Colorect Anal Sur* 2020; 8-9

19 **Hong GS**, Zillekens A, Schneiker B, Pantelis D, de Jonge WJ, Schaefer N, Kalff JC, Wehner S. Non-invasive transcutaneous auricular vagus nerve stimulation prevents postoperative ileus and endotoxemia in mice. *Neurogastroenterol Motil* 2019; **31**: e13501 [PMID: 30406957 DOI: 10.1111/nmo.13501]

20 **Zuo X**, Shi X, Zhang X, Chen Z, Yang Z, Pan X, Lai R, Zhao Z. Postoperative Ileus with the Topical Application of Tongfu Decoction Based on Network Pharmacology and Experimental Validation. *Evid Based Complement Alternat Med* 2022; **2022**: 2347419 [PMID: 35388311 DOI: 10.1155/2022/2347419]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 1959-1968

DOI: 10.4240/wjgs.v15.i9.1959

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Effect of internet multiple linkage mode-based extended care combined with in-hospital comfort care on colorectal cancer patients undergoing colostomy

Li Xu, Mei-Zhen Zhou

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Cornish AJ, United Kingdom; Elkord E, Qatar

Received: May 31, 2023
Peer-review started: May 31, 2023
First decision: June 14, 2023
Revised: July 7, 2023
Accepted: August 2, 2023
Article in press: August 2, 2023
Published online: September 27, 2023

Li Xu, Department of Public Health, Dongtai Hospital Affiliated to Jiangsu Vocational College of Medicine, Yancheng 224200, Jiangsu Province, China

Li Xu, Department of Public Health, People's Hospital of Dongtai City, Yancheng 224200, Jiangsu Province, China

Mei-Zhen Zhou, Department of Gynaecology and Obstetrics, Dongtai Hospital Affiliated to Jiangsu Vocational College of Medicine, Yancheng 224200, Jiangsu Province, China

Mei-Zhen Zhou, Department of Gynaecology and Obstetrics, People's Hospital of Dongtai City, Yancheng 224200, Jiangsu Province, China

Corresponding author: Mei-Zhen Zhou, MM, Doctor, Department of Gynaecology and Obstetrics, Dongtai Hospital Affiliated to Jiangsu Vocational College of Medicine, No. 2 Kangfu West Road, Yancheng 224200, Jiangsu Province, China. zhengzhi152@163.com

Abstract

BACKGROUND

Patients with colorectal cancer may need postoperative nursing to improve prognosis, and conventional nursing is not effective. Clinical research is needed to explore nursing methods that can more effectively improve postoperative conditions on colorectal cancer patients undergoing colostomy.

AIM

To explore the effect of internet multiple linkage mode-based extended care combined with in-hospital comfort care on colorectal cancer patients undergoing colostomy.

METHODS

Data from 187 patients with colostomy treated in our hospital from May 2019 to March 2022 were collected and divided into three groups, A (n = 62), B (n = 62) and C (n = 63), according to different intervention methods. Group A received internet multiple linkage mode-based extended care combined with in-hospital comfort care. Group B received internet multiple linkage mode-based extended care. Group C received usual care intervention. Complications were compared among the three groups. The stoma self-efficacy scale, Hamilton Anxiety Scale,

Hamilton Depression Scale, Brief Fatigue Inventory and City of Hope-quality of Life-ostomy Questionnaire before and after intervention were compared among the three groups.

RESULTS

The complication rate of group A, B and C (16.13%, 20.97% and 60.32%, respectively) was significantly different (all $P < 0.05$). The incidence of complications in groups A and B was lower than that in group C, and there was no significant difference between groups A and B ($P > 0.05$). After intervention, the scores of ostomy care, social contact, diet choice, confidence in maintaining vitality, confidence in self-care of ostomy, confidence in sexual life, confidence in sexual satisfaction and confidence in physical labor in the three groups were all higher than before intervention, and the scores of groups A and B were higher than those of group C, with statistical significance ($P < 0.05$). The Hamilton Anxiety Scale and Hamilton Depression Scale scores of the three groups after intervention were lower than those before intervention. The scores of groups A and B were lower than those of group C, and the score of group A was lower than that of group B, all with statistical significance (all $P < 0.05$). There was a statistically significant difference in cancer-induced fatigue among the three groups ($P < 0.05$). After intervention, the scores of physical health, psychological health, social health and mental health of the three groups were lower than before the intervention. The scores of group A and B were lower than that of group C; and the score of group A was lower than that of group B, all with statistical significance (all $P < 0.05$).

CONCLUSION

Internet multiple linkage mode-based extended care combined with in-hospital comfort care can effectively improve self-efficacy, bad mood, cancer-related fatigue and life quality of colorectal cancer patients undergoing colostomy.

Key Words: Internet multiple linkage mode; Extended care; In-hospital comfort care; Colorectal cancer patients; Patients undergoing colostomy

Core Tip: Comfort care and continuous care are widely used in patients with colorectal cancer. The internet multiple linkage model was introduced into the continuous nursing of patients with colorectal cancer ostomy, and the traditional nursing methods were integrated into the internet multiple linkage model. The purpose of this study was to compare the nursing effect of the combined comfort nursing in the hospital based on the internet multiple linkage model, the traditional conventional nursing and the internet multiple linkage model of the extended nursing. The internet multiple linkage mode-based extended care combined with in-hospital comfort care had a good effect.

Citation: Xu L, Zhou MZ. Effect of internet multiple linkage mode-based extended care combined with in-hospital comfort care on colorectal cancer patients undergoing colostomy. *World J Gastrointest Surg* 2023; 15(9): 1959-1968
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/1959.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.1959

INTRODUCTION

Colorectal cancer refers to the malignancy occurring at the junction of the rectum and sigmoid colon and is the second most common gastrointestinal malignancy after gastric cancer. The main clinical manifestations of patients are mucousy and bloody stool, constipation and diarrhea. The incidence of colorectal cancer is related to diet, environment, genetics and other factors[1-3]. The 2018 Chinese cancer statistics showed that the incidence and mortality of colorectal cancer in China ranks fifth among all malignant tumors, including 376000 new cases and 191000 deaths[4].

At present, laparoscopic-assisted transabdominal perineal combined radical rectal resection (Miles operation) has the same indications as traditional laparotomy. Generally, tumors less than 5 cm away from the anal verge are surgically removed. This procedure requires a permanent colostomy in the left lower abdomen[5]. In China there are about 100000 new colostomy patients every year, and the cumulative number of colostomy patients has exceeded 1 million. It is expected that this number will continuously increase[6]. Permanent colostomy is required in 50%-60% of colorectal cancer patients[7]. The incidence of enterostomy complications abroad is 11%-60%, and the domestic literature reports 16.3%-53.8%[8]. Patients will lose their normal defecation ability and be unable to defecate independently. Additionally, the installation of an ostomy bag brings severe psychological pressure to patients, which causes anxiety, depression and other adverse emotions, affecting the prognosis of patients. Thus, it is of great significance to give scientific and effective care to patients with colorectal cancer[9].

Routine nursing refers to the normative regulations of nursing prevention and control measures formulated under the guidance of basic theory and combined with long-term clinical nursing practice experience[10]. For patients undergoing

colostomy, routine care only meets basic needs. Comfort care is a new mode of nursing, which refers to a nursing method that encourages patients to the happiest mental, physical and socio-spirit state[11]. Due to the special situation of patients undergoing colostomy, sufficient nursing guidance should be paid not only during hospitalization but also after discharge to extend the nursing of patients from the clinic to the family and further improve the nursing effect[12-14].

Multiple linkage mode refers to the integration of hospital, community and family to avoid disjointed nursing intervention after discharge[15-17]. Internet-based continuous care has also been widely used in clinical practice. Recent studies have applied it to the care of adrenal tumor patients, and the nursing effect was good[18]. The present study explored the application effect of the internet-based continuous care mode hospital guidance-community participation-family cooperation combined with in-hospital comfort care in patients undergoing colorectal cancer colostomy.

MATERIALS AND METHODS

General data

Data from 187 patients with colostomy who were treated in our hospital from May 2019 to March 2022 were collected and divided into three groups, A (n = 62), B (n = 62) and C (n = 63), according to different intervention methods. In group A, there were 39 males and 23 females. The ages ranged from 32 years to 68 years, with an average of 47.82 ± 5.42 years; 29 cases completed junior middle school or below, 27 cases completed technical secondary school/senior high school, and 6 cases completed junior college or higher. Patients were divided by Dukes stage as follows: 30 cases were in stage I; 24 cases were in stage II; and 8 cases were in stage III. Thirty-five cases were in ostomy stage II, and 27 cases were in ostomy stage III. In group B, there were 44 males and 18 females. The ages ranged from 30 years to 70 years, with an average of 48.15 ± 5.37 years; 26 cases completed junior middle school or below, 25 cases completed technical secondary school/senior high school, and 11 cases completed junior college or above. Patients were divided by Dukes stage as follows: 33 cases were in stage I; 21 cases were in stage II; and 8 cases were in stage III. Twenty-three cases were in ostomy stage II, and 39 cases were in ostomy stage III. In group C, there were 39 males and 24 females. The ages ranged from 28 years to 66 years, with an average of 47.36 ± 4.59 years; 32 cases completed junior middle school or below, 22 cases completed technical secondary school/senior high school, and 9 cases completed junior college or above. Patients were divided by Dukes stage as follows: 33 cases were in stage I; 23 cases were in stage II; and 7 cases were in stage III. Twenty-five cases were in ostomy stage II, and 38 cases were in ostomy stage III. The general data of the two groups were comparable (all P > 0.05). This study was approved by the ethics committee of the hospital.

Inclusion criteria

(1) Diagnosed with colorectal cancer by clinicopathological diagnosis; (2) Older than 18-years-old; and (3) Complete clinical case data.

Exclusion criteria

(1) Patients with severe physical dysfunction; (2) Patients with severe hearing impairment and visual impairment; (3) Patients with consciousness dysfunction; (4) Patients with palliative surgical resection; and (5) Patients with vascular dementia, mental disorders and disturbance of consciousness caused by stroke.

Methods

Group A received internet multiple linkage mode-based extended care combined with in-hospital comfort care. Group B received internet multiple linkage mode-based extended care. Group C received usual care intervention.

Group A: Group A was given internet multiple linkage mode-based extended care combined with in-hospital comfort care. Internet multiple linkage mode-based extended care was the same as group B and is described below. The details of in-hospital comfort care were as follows: (1) Creation of comfortable sickroom environment. Comfortable ward environment was created for patients to ensure adequate light and cleanliness in the ward, to ensure indoor quiet and to ensure that patients get comfortable sleep; (2) Psychological comfort care. Colorectal cancer patients with colostomy have great psychological pressure and emotional instability and are prone to irritability, fear and other adverse emotions. Nursing staff can take the initiative to provide psychological support for patients, chat with patients more and alleviate patients' adverse emotions so patients can reach a comfortable state psychologically; (3) Pain care. Medical staff can explain the law of postoperative pain to patients, guide patients to distract themselves from the pain by listening to music and chatting with their families, evaluate the degree of pain and give painkillers appropriately; (4) Dietary care. The nursing staff should instruct the patients to avoid eating greasy, flatulent and crude fiber-rich foods, minimize the number and amount of defecation, protect the artificial anus, eat more foods with high protein, high vitamins and low fiber, eat on time and to not overeat; (5) Stoma comfort care. The patients were required to expose the stoma and clean the excrement from the stoma 2-3 d after the operation. Physiological saline was used to clean the skin around the stoma, and relevant skin care solution was used to protect the skin around the stoma and reduce fecal pollution; and (6) Rehabilitation comfort care. Medical staff should tell patients to wear loose and comfortable clothes and prevent friction stomatology. Patients should avoid water wetting their stomatology bags when bathing. They can cover the stomatology bags and replace the stomatology bags after bathing. They should regularly clean up excreta and make bags and put deodorant in the stoma bag to remove the smell.

Group B: Group B was given internet multiple linkage mode-based extended care. An intervention group for colorectal cancer patients with colostomy based on internet + multiple linkage mode was established. One network engineer with more than 5 years of working experience and 15 medical oncology staff were selected to form the intervention group. The 15 medical staff included 2 attending doctors and 13 nurses. The 13 nurses included 1 chief superintendent nurse, 1 deputy chief superintendent nurse, 5 supervisor nurses and 6 nurses, all of whom had more than 6 years of ostomy nursing experience. The chief superintendent nurse was responsible for the overall guidance of the nursing process. The deputy chief superintendent nurse was responsible for the data-push and training of nursing knowledge. The supervisor nurses were responsible for the training and guidance of the nurses in the community hospital. They also cooperated with the network engineer to adequately design the network platform and update the push content, check and reply to the messages of patients and their families and collect background feedback. Among the 6 nurses, 4 were responsible for nursing training of family members and patients themselves, and the other 2 were responsible for collecting intervention data and sorting data.

The network engineer built a WeChat applet called "colorectal microplatform" and created patient communication groups. The applet included the medical side and the patient side. The medical side had three sections: information verification; health knowledge; and physician-patient interaction. Information verification was used to audit and verify the registration information of patients and their families. The health knowledge section aimed to collect videos, pictures and texts about colostomy nursing knowledge of colorectal cancer and push it three times a week for 1 mo. The content of the 1st week included psychological counseling and ostomy bag replacement method. Physical needs included exercise, bathing, clothing, diet and sexual life and social interaction (traveling, working and gathering). The content of the 2nd week included observation and prevention of the occurrence of ostomy complications, ostomy defecation and abdominal conditions, observation of local and surrounding skin conditions of ostomy, guidance of enterostomy methods and the time and method of the appointment of ostomy clinic review. After 1 mo, the above content can be sent repeatedly. In the physician-patient interaction section, daily observation records, message response and online follow-up can be viewed.

The patient side included the patient's personal data, information platform and interaction. The personal data included the patient's sex, age and other basic information as well as ostomy information. The information platform provided psychological and physiological knowledge of colorectal cancer ostomy. The interactive section provided the function of leaving messages in the background. Patients and their families can leave messages in the interaction section for consultation if they have any questions. Intervention group members checked background messages every day and answered them in time. Patients could also express their questions through WeChat group chat. The interaction section also included a service evaluation content, which enabled patients and their families to put forward opinions and suggestions to the interventionists and the platform, which was conducive to continuous improvement of the platform.

Group C: Group C was given usual care intervention. During the period of hospitalization, patients were instructed in routine daily behavior, and usual care was carried out according to the nursing method of enterostomy. The patient was instructed in a series of daily activities such as diet, exercise, washing, rest and defecation and was told to clean the enterostomy and surrounding skin. The emergency treatment measures for possible abnormalities after the completion of the enterostomy were explained. Appropriate psychological intervention was performed for patients with colostomy of colorectal cancer.

Observation targets

Baseline data, the occurrence of complications, the stoma self-efficacy scale (SSES)[19] rating, Hamilton Anxiety Scale (HAMA)[20], Hamilton Depression Scale (HAMD)[21], Brief Fatigue Inventory[22], City of Hope-Quality of life-Ostomy Questionnaire (COH-QOL-OQ)[23] were collected from all patients. Complications were compared among the three groups. The SSES, HAMA, HAMD and COH-QOL-OQ scores of the three groups were compared before and after intervention. SSES included two dimensions and six individual items, with a total of 28 items and a total score of 28-140 points calculated with a 5-point scoring system. The score of ostomy care efficacy was 13-65 points, and the score of social efficacy was 9-45 points. HAMA had 14 items in total, and the score was 0-4 with 5 grades. The total score was 0-56. The higher the score, the worse the anxiety symptoms. HAMD had 17 items in total, and the score was 0-4 with 5 grades. The total score was 0-68. The higher the score, the worse the depression symptoms. The Brief Fatigue Inventory consisted of nine items, which were scored on a scale of 0 to 10, including no fatigue (0), mild fatigue (1 to 3), moderate fatigue (4 to 6) and severe fatigue (7 to 10). COH-QOL-OQ included four dimensions with a total of 32 items: physical health (11 items); psychological health (9 items); social health (7 items); and mental health (5 items) It adopted the scoring method of 0-10 points, and the total score was 0-320 points. The higher the score, the worse the quality of life.

Statistical methods

SPSS 11.0 statistical software was used to analyze and process the obtained data, and the measurement data was expressed as ($x \pm s$). Independent sample t test was used for inter-group comparison, and paired t test was used for intra-group comparison before and after intervention. Counting data were expressed as frequency and constituent ratio. χ^2 test or Fisher exact probability method was used to compare disordered classification data, and rank sum test was for ranked data. $P < 0.05$ indicated that the difference was statistically significant.

RESULTS

Comparison of complication rate among the three groups

The complication rate in group A, B and C (16.13%, 20.97% and 60.32%) was significantly different (all $P < 0.05$). The complication rate in groups A and B was lower than that in group C, and there was no significant difference between groups A and B (all $P > 0.05$, Table 1).

Comparison of self-efficacy among the three groups

Before intervention, there were no significant differences in stoma care, social contact, diet choice, confidence in maintaining vitality, confidence in stoma self-care, confidence in sexual life, confidence in sexual satisfaction and confidence in physical labor among the three groups (all $P > 0.05$). After intervention, the scores of stoma care, social contact, diet choice, confidence in maintaining vitality, confidence in stoma self-care, confidence in sexual life, confidence in sexual satisfaction and confidence in physical labor in the three groups were all higher than before intervention. The scores of groups A and B were higher than those of group C (all $P > 0.05$, Table 2).

Comparison of anxiety and depression among the three groups

Before intervention, there were no significant differences in HAMA and HAMD scores among the three groups (all $P > 0.05$). After intervention, the HAMA and HAMD scores of the three groups were lower than before intervention. The scores of groups A and B were lower than that of group C. The scores of group A were lower than that of group B (all $P < 0.05$, Table 3).

Comparison of cancer-induced fatigue among the three groups

There were significant differences in cancer-induced fatigue among the three groups (all $P < 0.05$, Table 4).

Comparison of quality of life among the three groups

Before the intervention, there were no significant differences in the scores of physical health, psychological health, social health and mental health among the three groups (all $P > 0.05$). After the intervention, the scores of physical health, psychological health, social health and mental health of the three groups were lower than before the intervention. The scores of group A and B were lower than group C. The scores of group A were lower than group B (all $P < 0.05$, Table 5).

DISCUSSION

The main clinical treatment for colorectal cancer is surgical resection, but patients often need to perform ostomy after resection to promote the discharge of intestinal contents to protect the distal intestinal anastomosis and promote the recovery of intestinal diseases. Although ostomy can save the lives of patients, it violates the objective laws of the human body and can lead to the abnormal excretion pathway of patients, increase the psychological burden of patients and cause anxiety and depression in patients. Therefore, it is very important to provide long-term care in and out of the hospital for patients with colorectal cancer after ostomy[24-26].

Internet + mode is a new nursing mode that has emerged in the era of big data. The multiple linkage mode of the internet breaks the limitation of conventional nursing time and space, expands the scope of nursing services and can meet the health needs of patients at multiple levels. The use of information can encourage a close relationship between the hospital and patients, timely monitoring of the patients' conditions and promotion of patient recovery. This study integrated the multiple linkage cooperation mode into nursing work. Information sharing and maintenance reminders were carried out through an internet platform, and hospital-community-home nursing was linked to provide comprehensive extended care for patients with colorectal cancer colostomy[27,28]. In-hospital comfort care is a humanized nursing measure, whose intervention aims to reduce patient discomfort, promote patient physical and mental comfort and ultimately promote patient postoperative recovery[29].

In this study, group A adopted the internet-based multiple linkage mode combined with in-hospital comfort care intervention, group B adopted the internet-based multiple linkage mode intervention, and group C adopted routine intervention. The results showed that the incidence of complications in groups A and B was lower than that in group C, and that no significant difference was seen between groups A and B. Intervention based on the multiple linkage mode of internet could effectively reduce the incidence of complications in colorectal cancer patients with colostomy. Complications of enterostomy patients may lead to the inability of the stoma bag to effectively collect excreta, seriously affecting patient emotions. In the intervention scheme based on internet multiple linkage mode, patients with abnormal conditions when dealing with the stoma can contact the medical staff through the WeChat platform, and the nursing staff can provide intervention support as soon as possible, effectively reducing the incidence of complications.

After intervention, scores of self-efficacy in groups A and B were significantly higher than those in group C, indicating that intervention based on internet multiple linkage mode can effectively improve self-efficacy in colorectal cancer patients with colostomy. This scheme pushed colostomy knowledge through the WeChat applet and provided colostomy patients and their families with colostomy-related medical knowledge by means of pictures and texts, which promoted colostomy patient understanding of their own state. By applying the knowledge learned in the WeChat applet to daily life, patients also further deepened their impression of colorectal cancer ostomy knowledge. Related psychological counseling pictures and texts in the information section were also conducive to improve patient confidence in treatment,

Table 1 Comparison of complication rate among the three groups

Item	Group A, *n* = 62	Group B, *n* = 62	Group C, *n* = 63	χ^2 value	*P* value
Stomal necrosis	0 (0.00)	1 (1.61)	1 (1.59)	N/A	N/A
Stomal bleeding	1 (1.61)	0 (0.00)	1 (1.59)	N/A	N/A
Stomal edema	1 (1.61)	0 (0.00)	9 (14.29)	N/A	N/A
Parastomal hernia	1 (1.61)	1 (1.61)	5 (7.94)	N/A	N/A
Stomal infection	3 (4.84)	3 (4.84)	8 (12.70)	N/A	N/A
Stomal stenosis	3 (4.84)	5 (8.06)	11 (17.46)	N/A	N/A
Stomal prolapse	1 (1.61)	3 (4.84)	3 (4.76)	N/A	N/A
Total complication rate	10 (16.13)	13 (20.97)	38 (60.32)	33.490	< 0.001

Data are presented as *n* (%). Group A received internet multiple linkage mode-based extended care combined with in-hospital comfort care; Group B received internet multiple linkage mode-based extended care; Group C received usual care intervention. N/A: Not applicable.

Table 2 Comparison of self-efficacy among the three groups

Item	Intervention timing status	Group A, *n* = 62	Group B, *n* = 62	Group C, *n* = 63	*t* value	*P* value
Stoma care	Before	37.97 ± 6.58	37.39 ± 5.47	37.41 ± 4.85	0.209	0.811
	After	48.47 ± 7.48[a]	46.21 ± 6.63[a]	40.67 ± 5.18[a,b,c]	23.918	< 0.001
Social contact	Before	24.19 ± 6.59	24.40 ± 5.72	23.83 ± 6.05	0.138	0.871
	After	35.63 ± 5.27[a]	31.66 ± 3.96[a,b]	27.94 ± 6.68[a,b,c]	31.388	< 0.001
Diet choice	Before	2.06 ± 0.70	2.02 ± 0.78	1.92 ± 0.77	0.577	0.562
	After	3.74 ± 0.79[a]	3.40 ± 0.93[a,b]	2.92 ± 0.77[a,b,c]	15.311	< 0.001
Confidence in maintaining vitality	Before	1.82 ± 0.80	1.65 ± 0.75	1.62 ± 0.63	1.360	0.259
	After	3.65 ± 0.79[a]	3.34 ± 0.87[a,b]	2.63 ± 0.66[a,b,c]	28.313	< 0.001
Confidence in stoma self-care	Before	1.97 ± 0.79	2.05 ± 0.88	1.95 ± 0.81	0.255	0.775
	After	3.90 ± 0.78[a]	3.55 ± 0.88[a,b]	2.95 ± 0.81[a,b,c]	21.257	< 0.001
Confidence in sexual life	Before	1.95 ± 0.84	1.90 ± 0.69	1.75 ± 0.76	1.157	0.317
	After	3.32 ± 0.85[a]	3.24 ± 0.80[a]	2.75 ± 0.76[a,b,c]	9.232	< 0.001
Confidence in sexual satisfaction	Before	1.56 ± 0.59	1.45 ± 0.59	1.43 ± 0.59	0.876	0.418
	After	3.05 ± 0.58[a]	2.79 ± 0.68[a,b]	2.42 ± 0.59[a,b,c]	16.408	< 0.001
Confidence in physical labor	Before	1.18 ± 0.43	1.15 ± 0.36	1.21 ± 0.48	0.309	0.734
	After	3.66 ± 0.85[a]	3.37 ± 1.00[a,b]	2.57 ± 0.86[a,b,c]	24.330	< 0.001

Data are presented as mean ± SD.

[a]*P* < 0.05, compared with the same group before intervention.

[b]*P* < 0.05, compared with group A.

[c]*P* < 0.05, compared with group B.

Group A received internet multiple linkage mode-based extended care combined with in-hospital comfort care; Group B received internet multiple linkage mode-based extended care; Group C received usual care intervention.

and patient self-efficacy was significantly improved.

The HAMA and HAMD scores after intervention of the three groups were lower than before intervention. After intervention, the scores of groups A and B were lower than that of group C, and the score of group A was lower than that of group B. This showed that internet multiple linkage mode-based care combined with in-hospital comfort care can effectively improve anxiety and depression conditions in colorectal cancer patients with colostomy. Internet-based multimode intervention enabled patients to feel the support and care from medical staff all the time, shortened the distance between doctors and patients and nurses and patients and helped patients correctly face anxiety and depression. The WeChat public platform had message function, and medical staff encouraged patients through this board to relieve

Table 3 Comparison of anxiety and depression among the three groups

Item	Intervention timing status	Group A, *n* = 62	Group B, *n* = 62	Group C, *n* = 63	*t* value	*P* value
HAMA score	Before	43.15 ± 3.97	43.58 ± 4.63	43.51 ± 4.91	0.162	0.851
	After	23.42 ± 4.44	29.45 ± 4.44[a,b]	35.38 ± 6.48[a,b,c]	82.105	< 0.001
HAMD score	Before	52.74 ± 5.32	52.05 ± 7.90	52.08 ± 5.98	0.224	0.799
	After	30.06 ± 2.22	34.68 ± 5.73[a,b]	38.60 ± 3.46[a,b,c]	68.965	< 0.001

Data are presented as mean ± SD.
[a]*P* < 0.05, compared with the same group before intervention.
[b]*P* < 0.05, compared with group A.
[c]*P* < 0.05, compared with group B.
Group A received internet multiple linkage mode-based extended care combined with in-hospital comfort care; Group B received internet multiple linkage mode-based extended care; Group C received usual care intervention. HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Scale.

Table 4 Comparison of cancer-induced fatigue among the three groups

Item	Group A, *n* = 62	Group B, *n* = 62	Group C, *n* = 63	*z* value	*P* value
No fatigue	18 (29.03)	12 (19.35)	8 (12.70)[b]	N/A	N/A
Mild fatigue	30 (48.39)	24 (38.71)	17 (26.98)[b]	N/A	N/A
Moderate fatigue	11 (17.74)	18 (29.03)	25 (39.68)[b]	N/A	N/A
Severe fatigue	3 (4.84)	8 (12.90)	13 (20.63)[b]	17.510	< 0.001

Data are presented as *n* (%).
[b]*P* < 0.05, compared with group A.
Group A received internet multiple linkage mode-based extended care combined with in-hospital comfort care; Group B received internet multiple linkage mode-based extended care; Group C received usual care intervention.

Table 5 Comparison of quality of life among the three groups

Group	Intervention timing status	Group A, *n* = 62	Group B, *n* = 62	Group C, *n* = 63	*t* value	*P* value
Physical health	Before	47.61 ± 4.61	48.21 ± 3.46	47.54 ± 4.04	0.511	0.601
	After	32.19 ± 1.80	37.37 ± 2.79[a,b]	42.76 ± 4.86[a,b,c]	150.346	< 0.001
Psychological health	Before	61.89 ± 5.31	62.44 ± 5.22	62.62 ± 5.27	0.325	0.723
	After	47.23 ± 5.04	52.35 ± 5.64[a,b]	57.16 ± 4.69[a,b,c]	58.414	< 0.001
Social health	Before	51.60 ± 6.08	51.21 ± 5.20	52.37 ± 5.05	0.732	0.483
	After	38.18 ± 2.56	43.22 ± 4.44[a,b]	47.38 ± 6.10[a,b,c]	62.401	< 0.001
Mental health	Before	25.03 ± 2.30	25.18 ± 2.22	25.87 ± 2.74	2.125	0.122
	After	14.13 ± 3.36	18.10 ± 2.06[a,b]	21.02 ± 3.29[a,b,c]	84.898	< 0.001

Data are presented as mean ± SD.
[a]*P* < 0.05, compared with the same group before intervention.
[b]*P* < 0.05, compared with group A.
[c]*P* < 0.05, compared with group B.
Group A received internet multiple linkage mode-based extended care combined with in-hospital comfort care; Group B received internet multiple linkage mode-based extended care; Group C received usual care intervention.

patient anxiety and depression symptoms. In-hospital comfort care enables patients to feel the care from medical staff through the creation of a comfortable ward environment, psychological comfort nursing, pain nursing, diet nursing and stoma comfort nursing. Thus, patient anxiety and depression were significantly improved, and the improvement of group A was better than group B and C.

After intervention, the cancer-induced fatigue condition in group A was better than that in group B and group C, the scores of quality of life in groups A and B were lower than that in group C, and the scores of quality of life in group A were lower than that in group B. These results showed that internet-based multi-linkage model intervention combined with in-hospital comfort care can effectively relieve the cancer-induced fatigue and improve the quality of life of colorectal cancer patients with colostomy. The multiple linkage mode of the internet provided extended care through the WeChat platform, which not only provides health information but also includes communication with medical staff to answer questions, which allows patients to receive professional guidance more conveniently. In-hospital comfort care pays more attention to the physical and mental comfort of the patient and adopts a variety of measures to promote physical and mental comfort. The combined application of the two schemes further improved the cancer-related fatigue state and quality of life.

This study also had certain shortcomings. The sample size of this study was small, and it was a single-center study. In the future, a multi-center study will be undertaken to expand the sample size to ensure the accuracy of this study.

CONCLUSION

The application of extended care based on internet multiple interaction mode combined with in-hospital comfort care in patients with colorectal cancer colostomy can effectively reduce the occurrence of complications, improve their self-efficacy, relieve their cancer-induced fatigue and improve their quality of life, showing clinical application value.

ARTICLE HIGHLIGHTS

Research background

The occurrence of postoperative complications in patients with colorectal cancer stomy can affect patient emotions and self-efficacy. Therefore, attention should be given to the improvement of nursing methods on postoperative complications in patients with colorectal cancer stomy. The extensive application of various nursing methods and traditional routine nursing in patients with colorectal cancer stomostomy is currently being studied. Exploring new nursing methods that can more effectively improve the postoperative recovery of patients with colorectal cancer stomostomy will be beneficial.

Research motivation

The purpose of this study was to explore more effective nursing methods to improve patient quality of life and self-efficacy in postoperative colorectal cancer patients. The significance of this study was to affirm the effectiveness of new nursing methods for patients with colorectal cancer ostomy, encourage clinical nursing teams to continue to introduce more effective and humanized nursing methods for patients with colorectal cancer ostomy and promote the improvement and progress of clinical nursing work.

Research objectives

This study compared the effects of three nursing methods and observed the advantages of internet multiple linkage mode-based extended care combined with in-hospital comfort care compared with internet multiple linkage mode-based extended care and conventional nursing.

Research methods

The clinical data of patients were analyzed retrospectively and grouped according to different nursing methods. Paired t test and χ^2 test were used to analyze the general data, complication rate, self-efficacy, anxiety and depression, cancer-related fatigue, quality of life and other clinical data of the three groups of patients.

Research results

The results of this study showed that the internet multiple linkage mode-based extended care combined with in-hospital comfort care had a good nursing effect and significantly improved the occurrence of complications, self-efficacy, anxiety and depression, cancer-related fatigue and quality of life, providing a new nursing method for postoperative nursing of colorectal cancer.

Research conclusions

This study confirmed that the internet multiple linkage mode-based extended care combined with in-hospital comfort care has a better effect on patients.

Research perspectives

In the future, a multi-center study should be undertaken to expand the sample size to ensure the accuracy of this study.

FOOTNOTES

Author contributions: Xu L initiated the project and designed the experiment, conducted clinical data collection and performed postoperative follow-up and recorded data; Zhou MZ conducted a number of collation and statistical analysis, wrote the original manuscript and revised the paper; Both authors reviewed and approved the paper; All authors read and approved the final manuscript.

Supported by Clinical Teaching Base of Jiangsu Medical Vocational College, No. 20219141.

Institutional review board statement: This study was approved by the Ethics Committee of People's Hospital of Dongtai City.

Informed consent statement: The study was approved by the institutional review board at each participating site. The data are anonymous, and the requirement for informed consent was therefore waived.

Conflict-of-interest statement: The authors declare having no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Data sharing statement: All data generated or analyzed during this study are included in this published article.

Country/Territory of origin: China

ORCID number: Mei-Zhen Zhou 0000-0001-8178-5070.

S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Cai YX

REFERENCES

1 **Mauri G**, Sartore-Bianchi A, Russo AG, Marsoni S, Bardelli A, Siena S. Early-onset colorectal cancer in young individuals. *Mol Oncol* 2019; **13**: 109-131 [PMID: 30520562 DOI: 10.1002/1878-0261.12417]
2 **Heinimann K**. [Hereditary Colorectal Cancer: Clinics, Diagnostics and Management]. *Ther Umsch* 2018; **75**: 601-606 [PMID: 31232663 DOI: 10.1024/0040-5930/a001046]
3 **Thanikachalam K**, Khan G. Colorectal Cancer and Nutrition. *Nutrients* 2019; **11** [PMID: 30646512 DOI: 10.3390/nu11010164]
4 **Cheng S**, Chen M, Cai J, Sun J, Guo R, Bi X, Lau WY, Wu M. Chinese Expert Consensus on Multidisciplinary Diagnosis and Treatment of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus (2018 Edition). *Liver Cancer* 2020; **9**: 28-40 [PMID: 32071907 DOI: 10.1159/000503685]
5 **Zheng HH**, Zhao EH. Thinking and prospect of laparoscopic sphinctectomy for low rectal cancer. *Yazhou Linchuang Yixue Zazhi* **3**: 32 [DOI: 10.26549/yzlcyxzz.v3i5.5253]
6 **Yu DH**. Status and prospect of enterostomy treatment in my country. *Zhonghua Huli Zazhi* 2005; **40**: 415-417 [DOI: 10.1088/0031-9120/40/5/f10]
7 **Koshiyama A**, Ichibangase T, Imai K. Comprehensive fluorogenic derivatization-liquid chromatography/tandem mass spectrometry proteomic analysis of colorectal cancer cell to identify biomarker candidate. *Biomed Chromatogr* 2013; **27**: 440-450 [PMID: 22991145 DOI: 10.1002/bmc.2811]
8 **Lu ZH**, Wan DS. Complications and management of enterostomy surgery. *Guangdong Yixue* 2009; **30**: 1029-1030 [DOI: 10.3969/j.issn.1001-9448.2009.08.003]
9 **Yang XX**, Fu JF, Li Q, Duan JB, Liu Y. Study on the quality of life of patients with permanent. *Huli Yanjiu* 2011; **(10)**: 3 [DOI: 10.3969/j.issn.1009-6493.2011.29.012]
10 **Dong JH**, Dong XF, Cardiology DO. Comparison of the Effects of Case Management and Routine Nursing on Cardiovascular Risk Factors in Diabetic Patients. *Tangniaobing Xinshijie* 2019; **22**: 3 [DOI: 10.4093/jkd.2019.20.3.157]
11 **Umar A**, Chang EY, Odebunmi I. Ambiguities in Comfort Care Discussions. *JAMA Intern Med* 2019; **179**: 273-274 [PMID: 30715108 DOI: 10.1001/jamainternmed.2018.7489]
12 **Ping H**, Ling X, Xue Y, Dong F. Effect of ERAS Combined with Comfortable Nursing on Quality of Life and Complications in Femoral Neck Fractures of the Aged People. *Evid Based Complement Alternat Med* 2021; **2021**: 8753076 [PMID: 34777537 DOI: 10.1155/2021/8753076]
13 **Ye Y**, Ge J. Clinical application of comfort nursing in elderly patients with advanced lung cancer. *Am J Transl Res* 2021; **13**: 9750-9756 [PMID: 34540105]
14 **Qian H**, Zhou J, Huang T, Cao X, Zhou C, Yang M, Chen Y. Comfort nursing can alleviate pain and negative emotion of patients after surgery for LVCFs and improve their living ability. *Am J Transl Res* 2021; **13**: 2939-2946 [PMID: 34017459]
15 **Ross P**, Cross R. Rise of the e-Nurse: the power of social media in nursing. *Contemp Nurse* 2019; **55**: 211-220 [PMID: 31280696 DOI: 10.1080/10376178.2019.1641419]
16 **Wang J**, Tong Y, Jiang Y, Zhu H, Gao H, Wei R, Que X, Gao L. The effectiveness of extended care based on Internet and home care platform for orthopaedics after hip replacement surgery in China. *J Clin Nurs* 2018; **27**: 4077-4088 [PMID: 29851157 DOI: 10.1111/jocn.14545]
17 **Feng L**, Wang W, Wu M, Ma H. Effect of WeChat-Based Health Education Combined with Satir Model on Self-Management Behaviors and

Social Adaptation in Colorectal Cancer Patients during the Perioperative Period. *J Healthc Eng* 2021; **2021**: 2701039 [PMID: 34925730 DOI: 10.1155/2021/2701039]

18 **Yao J**, He W, Chen H, Qi Y. Nursing effect of continuous nursing intervention based on "Internet Plus" on patients with severe adrenal tumor. *Medicine (Baltimore)* 2023; **102**: e33187 [PMID: 36897676 DOI: 10.1097/MD.0000000000033187]

19 **Karaçay P**, Toğluk Yigitoglu E, Karadağ A. The validity and reliability of the Stoma Self-Efficacy Scale: A methodological study. *Int J Nurs Pract* 2020; **26**: e12840 [PMID: 32301580 DOI: 10.1111/ijn.12840]

20 **Thompson E**. Hamilton Rating Scale for Anxiety (HAM-A). *Occup Med (Lond)* 2015; **65**: 601 [PMID: 26370845 DOI: 10.1093/occmed/kqv054]

21 **Fenton C**, McLoughlin DM. Usefulness of Hamilton rating scale for depression subset scales and full versions for electroconvulsive therapy. *PLoS One* 2021; **16**: e0259861 [PMID: 34752484 DOI: 10.1371/journal.pone.0259861]

22 **Nunes AF**, Bezerra CO, Custódio JDS, Friedrich CF, Oliveira IS, Lunardi AC. Clinimetric Properties of the Brief Fatigue Inventory Applied to Oncological Patients Hospitalized for Chemotherapy. *J Pain Symptom Manage* 2019; **57**: 297-303 [PMID: 30391653 DOI: 10.1016/j.jpainsymman.2018.10.508]

23 **Konjevoda V**, Zelić M, Munjas Samarin R, Petek D. City of Hope Quality of Life-Ostomy Questionnaire Validity and Reliability Assessment on a Croatian Sample. *Int J Environ Res Public Health* 2020; **17** [PMID: 31991817 DOI: 10.3390/ijerph17030768]

24 **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]

25 **van Rooijen S**, Carli F, Dalton S, Thomas G, Bojesen R, Le Guen M, Barizien N, Awasthi R, Minnella E, Beijer S, Martínez-Palli G, van Lieshout R, Gögenur I, Feo C, Johansen C, Scheede-Bergdahl C, Roumen R, Schep G, Slooter G. Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications: the first international randomized controlled trial for multimodal prehabilitation. *BMC Cancer* 2019; **19**: 98 [PMID: 30670009 DOI: 10.1186/s12885-018-5232-6]

26 **Ni X**, Jia D, Chen Y, Wang L, Suo J. Is the Enhanced Recovery After Surgery (ERAS) Program Effective and Safe in Laparoscopic Colorectal Cancer Surgery? A Meta-Analysis of Randomized Controlled Trials. *J Gastrointest Surg* 2019; **23**: 1502-1512 [PMID: 30859422 DOI: 10.1007/s11605-019-04170-8]

27 **Guo R**, Wang H. Analysis of Lung Imaging Intelligent Diagnosis System for Nursing Intervention of Lung Cancer Patients' Quality of Life. *Contrast Media Mol Imaging* 2021; **2021**: 6750934 [PMID: 34867113 DOI: 10.1155/2021/6750934]

28 **Koivunen M**, Saranto K. Nursing professionals' experiences of the facilitators and barriers to the use of telehealth applications: a systematic review of qualitative studies. *Scand J Caring Sci* 2018; **32**: 24-44 [PMID: 28771752 DOI: 10.1111/scs.12445]

29 **Cui M**, Sun M, Bu L. The effect of comfort nursing on liver function and nursing satisfaction of patients with liver cirrhosis. *Am J Transl Res* 2021; **13**: 6973-6979 [PMID: 34306451]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 1969-1977

DOI: 10.4240/wjgs.v15.i9.1969

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Short- and long-term results of open *vs* laparoscopic multisegmental resection and anastomosis for synchronous colorectal cancer located in separate segments

Ji-Chuan Quan, Xin-Jun Zhou, Shi-Wen Mei, Jun-Guang Liu, Wen-Long Qiu, Jin-Zhu Zhang, Bo Li, Yue-Gang Li, Xi-Shan Wang, Hu Chang, Jian-Qiang Tang

Specialty type: Oncology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Diez-Alonso M, Spain; Gad EH, Egypt

Received: May 3, 2023
Peer-review started: May 3, 2023
First decision: June 13, 2023
Revised: June 29, 2023
Accepted: July 27, 2023
Article in press: July 27, 2023
Published online: September 27, 2023

Ji-Chuan Quan, Shi-Wen Mei, Wen-Long Qiu, Jin-Zhu Zhang, Bo Li, Yue-Gang Li, Xi-Shan Wang, Jian-Qiang Tang, Department of Colorectal Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Xin-Jun Zhou, Department of Colorectal Anorectal Surgery, Shengli Oilfield Central Hospital, Dongying 257000, Shandong Province, China

Jun-Guang Liu, Department of General Surgery, Peking University First Hospital, Beijing 100034, China

Hu Chang, Department of Hospital Administration Office, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Corresponding author: Jian-Qiang Tang, MD, Surgeon, Department of Colorectal Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17 Panjiayuan Nanli, Chaoyang District, Beijing 100021, China. doc_tjq@hotmail.com

Abstract

BACKGROUND

It remains unclear whether laparoscopic multisegmental resection and anastomosis (LMRA) is safe and advantageous over traditional open multisegmental resection and anastomosis (OMRA) for treating synchronous colorectal cancer (SCRC) located in separate segments.

AIM

To compare the short-term efficacy and long-term prognosis of OMRA as well as LMRA for SCRC located in separate segments.

METHODS

Patients with SCRC who underwent surgery between January 2010 and December 2021 at the Cancer Hospital, Chinese Academy of Medical Sciences and the Peking University First Hospital were retrospectively recruited. In accordance with the

inclusion and exclusion criteria, 109 patients who received right hemicolectomy together with anterior resection of the rectum or right hemicolectomy and sigmoid colectomy were finally included in the study. Patients were divided into the LMRA and OMRA groups (n = 68 and 41, respectively) according to the surgical method used. The groups were compared regarding the surgical procedure's short-term efficacy and its effect on long-term patient survival.

RESULTS

LMRA patients showed markedly less intraoperative blood loss than OMRA patients (100 *vs* 200 mL, P = 0.006). Compared to OMRA patients, LMRA patients exhibited markedly shorter postoperative first exhaust time (2 *vs* 3 d, P = 0.001), postoperative first fluid intake time (3 *vs* 4 d, P = 0.012), and postoperative hospital stay (9 *vs* 12 d, P = 0.002). The incidence of total postoperative complications (Clavien-Dindo grade: ≥ II) was 2.9% and 17.1% (P = 0.025) in the LMRA and OMRA groups, respectively, while the incidence of anastomotic leakage was 2.9% and 7.3% (P = 0.558) in the LMRA and OMRA groups, respectively. Furthermore, the LMRA group had a higher mean number of lymph nodes dissected than the OMRA group (45.2 *vs* 37.3, P = 0.020). The 5-year overall survival (OS) and disease-free survival (DFS) rates in OMRA patients were 82.9% and 78.3%, respectively, while these rates in LMRA patients were 78.2% and 72.8%, respectively. Multivariate prognostic analysis revealed that N stage [OS: HR hazard ratio (HR) = 10.161, P = 0.026; DFS: HR = 13.017, P = 0.013], but not the surgical method (LMRA/OMRA) (OS: HR = 0.834, P = 0.749; DFS: HR = 0.812, P = 0.712), was the independent influencing factor in the OS and DFS of patients with SCRC.

CONCLUSION

LMRA is safe and feasible for patients with SCRC located in separate segments. Compared to OMRA, the LMRA approach has more advantages related to short-term efficacy.

Key Words: Synchronous colorectal cancer; Separate segments; Laparoscopic surgery; Multisegmental resection; Short-term efficacy; Prognosis

Core Tip: The efficacy and safety of laparoscopic multisegmental resection and anastomosis (LMRA) in patients with synchronous colorectal cancer involving separate segments has not been fully evaluated. We compared the short-term efficacy and long-term prognosis between LMRA and open multisegmental resection and anastomosis, and found that the LMRA approach has more advantages related to faster postoperative recovery, less intraoperative blood loss, reduced postoperative hospital stay, fewer postoperative complications, and a greater total number of lymph nodes dissected.

Citation: Quan JC, Zhou XJ, Mei SW, Liu JG, Qiu WL, Zhang JZ, Li B, Li YG, Wang XS, Chang H, Tang JQ. Short- and long-term results of open *vs* laparoscopic multisegmental resection and anastomosis for synchronous colorectal cancer located in separate segments. *World J Gastrointest Surg* 2023; 15(9): 1969-1977
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/1969.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.1969

INTRODUCTION

Synchronous colorectal cancer (SCRC), a colorectal malignancy, refers to the simultaneous presence of multiple primary colorectal cancers (CRCs) in one patient. SCRC lesions can be located in the same segments, adjacent segments, or different segments of the colorectum. For patients with SCRC localized in separate segments, multisegmental resection and anastomosis are often selected for treatment. Compared to conventional surgery, multisegmental resection is less common and more difficult. Selection of the optimal surgical method to promote rapid recovery in patients with SCRC involving separate segments still requires further study.

Previous studies have shown the safety and advantages of laparoscopic surgery in treating solitary CRC[1-5]. However, to date, there are few comparisons of the application of laparoscopic multisegmental resection and anastomosis (LMRA) and open multisegmental resection and anastomosis (OMRA) for SCRC. Therefore, the safety and efficacy of LMRA are not adequately understood and require further evaluation.

To determine the efficacy and safety of LMRA in patients with SCRC involving separate segments, a retrospective two-institution investigation was performed to compare the short-term surgical results, 5-year overall survival (OS) rate, as well as the 5-year disease-free survival (DFS) rate of patients receiving LMRA and OMRA.

MATERIALS AND METHODS

Selection of patients

Patients with SCRC who underwent surgery between January 2010 and December 2021 at the Cancer Hospital, Chinese Academy of Medical Sciences and the Peking University First Hospital were included. Multiple CRC lesions were diagnosed following published guidelines[6].

The following types of patients were included: (1) SCRC patients with pathological confirmation of lesions as primary adenocarcinoma; (2) SCRC patients with one lesion in the right hemicolon and the others located in the sigmoid colon or rectum; and (3) patients receiving right hemicolectomy as well as anterior resection of the rectum or right hemicolectomy and sigmoid colectomy. The following categories of patients were excluded: (1) Those with familial adenomatous polyposis, ulcerative colitis, hereditary nonpolyposis CRC, or Lynch syndrome; (2) patients with SCRC involving the same segment; (3) patients with SCRC involving adjacent segments; (4) those receiving Hartmann's procedure or abdominal perineal resection; (5) those receiving subtotal colectomy, total colectomy, or proctocolectomy with ileoanal anastomosis; and (6) SCRC patients with distant metastasis. The selected patients were included in the LMRA and OMRA groups based on the surgical method. The study was approved by the Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences.

Data collection

The following clinicopathological data were collected: Age, gender, abdominal surgery history, concomitant diseases, preoperative chemotherapy, carbohydrate antigen 19-9 (CA19-9) level, carcinoembryonic antigen (CEA) level, American Society of Anesthesiologists (ASA) physical status level, surgical approach (laparoscopic or open), operative time, volume of blood loss (mL), postoperative first exhaust time (d), time to first liquid diet (d), postoperative hospital stay (d), postoperative complications, classification of complications, tumor size (cm), tumor differentiation status, N stage, T stage and TNM stage, total number of positive lymph nodes (LNs), and number of LNs dissected. Pathological staging was evaluated using the American Joint Committee on Cancer (8^{th} ed.) staging system. The Clavien-Dindo (CD) system[7] was employed to grade postoperative complications.

Follow-up

Patients were followed up through telephone calls or outpatient examination. The following time frame was chosen: every 3 mo in the first 2 years following surgery, every 6 mo at 3–5 years following surgery, and then yearly 5 years after surgery. Follow-up assessment included physical examination, determination of serum tumor marker levels, CT scans of the abdomen, chest, and pelvic area, and colonoscopy.

Statistical analysis

The Mann-Whitney *U* test or Student's *t*-test was used to compare continuous variables; Fisher's exact test or the chi-square test was used to compare categorical variables. The Kaplan-Meier analysis was employed to create survival curves. Survival differences were compared between the groups by the log-rank test. The Cox proportional hazards model was used to conduct univariate and multivariate prognostic analyses. A value of $P < 0.05$ was considered statistically significant. Statistical Product and Service Solutions (SPSS) version 26.0 from IBM (Armonk, NY, United States) was used for statistical determinations.

RESULTS

Clinicopathological characteristics

From January 2010 to December 2021, 605 SCRC patients underwent surgical treatment at the above-mentioned institutions. Of these 605 patients, 496 patients were excluded according to the aforementioned criteria. Finally, 109 patients with SCRC located in separate segments were included, with 41 and 68 patients placed in the OMRA and LMRA groups, respectively.

Clinicopathological characteristics of the patients are shown in Table 1. As noted in this table, the groups did not differ significantly in age, gender, abdominal surgery history, concomitant diseases, preoperative chemotherapy, CA19-9 and CEA levels, ASA class, postoperative chemotherapy, tumor size, tumor differentiation status, N stage, T stage, and TNM stage.

Surgical results

Table 2 presents the surgical outcomes of both groups. LMRA patients showed markedly less intraoperative blood loss than OMRA patients (100 *vs* 200 mL, $P = 0.006$). The LMRA group showed a significantly shorter postoperative first exhaust time (2 *vs* 3 d, $P = 0.001$), postoperative first fluid intake time (3 *vs* 4 d, $P = 0.012$), and postoperative hospital stay (9 *vs* 12 d, $P = 0.002$) than the OMRA group. The incidence of total postoperative complications (CD grade ≥ II) was 2.9% in the LMRA group; this percentage was markedly lower than the value (17.1%) recorded for the OMRA group ($P = 0.025$). Furthermore, LMRA patients had a lower incidence of anastomotic leakage than OMRA patients; however, the difference was nonsignificant (2.9% *vs* 7.3%, $P = 0.558$). The mean number of LNs dissected was significantly greater in LMRA patients as compared to OMRA patients (45.2 *vs* 37.3, $P = 0.020$). However, there were no significant differences in operating time, mortality rate, and number of positive LNs between the two groups.

Table 1 Basic characteristics between laparoscopic group and open group, *n* (%)

Variable	OMRA group, *n* = 41	LMRA group, *n* = 68	*P* value
Age (yr)			
≤ 65	24 (58.5)	31 (45.6)	0.190
> 65	17 (41.5)	37 (54.4)	
Gender			
Female	14 (34.1)	26 (38.2)	0.668
Male	27 (65.9)	42 (61.8)	
ASA physical status			0.058
I-II	33 (80.5)	63 (92.6)	
III	8 (19.5)	5 (7.4)	
Concomitant diseases			
No	19 (46.3)	29 (42.6)	0.707
Yes	22 (53.7)	39 (57.4)	
History of abdominal surgery			
No	30 (73.2)	56 (82.4)	0.255
Yes	11 (26.8)	12 (17.6)	
Preoperative chemotherapy			
No	39 (95.1)	68 (100)	0.139
Yes	2 (4.9)	0 (0)	
Tumor size[1], cm			
≤ 5	20 (50.0)	40 (58.8)	0.373
> 5	20 (50.0)	28 (41.2)	
Tumor differentiation			
Well-moderate	24 (58.5)	32 (47.1)	0.245
Poor	17 (41.5)	36 (52.9)	
pT stage			
T1-T2	2 (4.9)	7 (10.3)	0.525
T3-T4	39 (95.1)	61 (89.7)	
pN stage			
N0	16 (39.0)	25 (36.8)	0.915
N1	19 (46.3)	31 (45.6)	
N2	6 (14.6)	12 (17.6)	
Stage			
I	1 (2.4)	6 (8.8)	0.338
II	15 (36.6)	19 (27.9)	
III	25 (61.0)	43 (63.2)	
CEA			
≤ 5	19 (46.3)	31 (45.6)	0.929
> 5	13 (31.7)	20 (29.4)	
Unknown	9 (22.0)	17 (25.0)	
CA199			
≤ 37	28 (68.3)	42 (61.8)	0.696

> 37	3 (7.3)	9 (13.2)	
Unknown	10 (24.4)	17 (25.0)	
Postoperative chemotherapy			
No	20 (48.8)	30 (44.1)	0.636
Yes	21 (51.2)	38 (55.9)	

[1]Unknown for one patient.
OMRA: Open multisegmental resection and anastomosis; LMRA: Laparoscopic multisegmental resection and anastomosis; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; ASA: American Society of Anesthesiologists.

Table 2 Surgical results between laparoscopic group and open group

Variable	OMRA group, *n* = 41	LMRA group, *n* = 68	*P* value
Operative time (min)	253.0 ± 101.9	274.0 ± 83.4	0.244
Blood loss (mL)	200 (30-600)	100 (20-600)	0.006
Time to first exhaust (d)	3 (1-6)	2 (1-4)	0.001
Time to first liquid diets (d)	4 (2-9)	3 (2-6)	0.012
Postoperative complications (Grade II-V)	7 (17.1)	2 (2.9)	0.025
Ileus	2 (4.9)	0 (0.0)	0.139
Anastomotic leakage	3 (7.3)	2 (2.9)	0.558
Cerebral infarction	1 (2.4)	0 (0.0)	0.376
Abdominal incision infection	1 (2.4)	0 (0.0)	0.376
No. of retrieved lymph nodes	37.3 ± 17.1	45.2 ± 16.8	0.020
No. of positive lymph nodes	1 (0-13)	1 (0-15)	0.542
Mortality	0 (0)	0 (0)	1.000
Postoperative hospital stay, median, range, days	12 (7-34)	9 (3-30)	0.002

OMRA: Open multisegmental resection and anastomosis; LMRA: Laparoscopic multisegmental resection and anastomosis.

Long-term oncological consequences

The median follow-up period was 53.5 mo for all patients. OMRA patients had 3-year and 5-year OS rates of 87.5% and 82.9%, respectively; these rates for LMRA patients were 84% and 78.2%, respectively. Additionally, the 3-year and 5-year DFS rates for OMRA patients were 82.6% and 78.3%, respectively; these rates for LMRA patients were 79.3% and 72.8%, respectively. Both groups showed no significant differences in OS (P = 0.690) and DFS (P = 0.694) rates (Figure 1). According to the multivariate prognostic analysis, N stage was an independent prognostic factor for OS [hazard ratio (HR) = 10.161, P = 0.026] and DFS (HR = 13.017, P = 0.013) (Table 3).

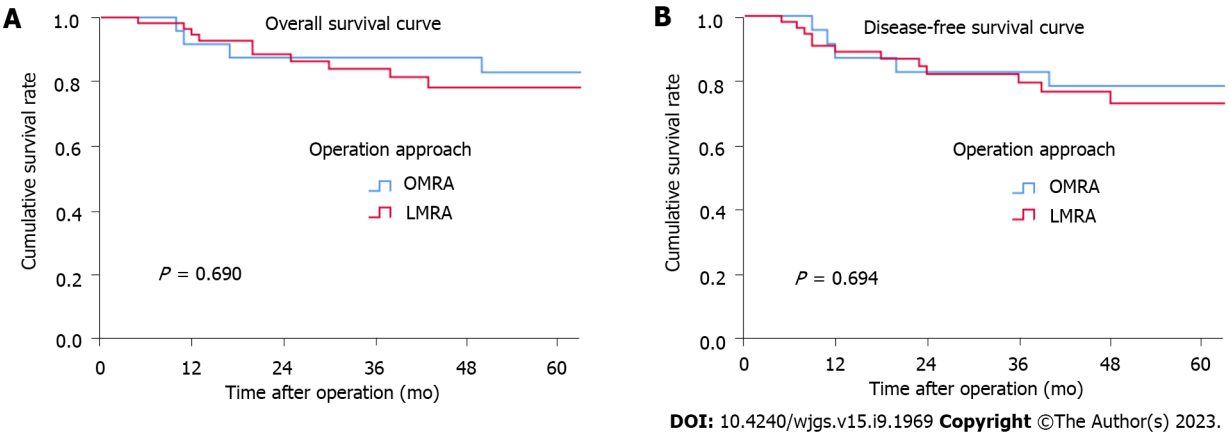
DISCUSSION

SCRC involving separate segments is a relatively rare type of CRC. Surgeons can choose two regional resections and anastomoses for preserving the left hemicolon or extensive resection, for example, total colectomy, subtotal colectomy, or proctocolectomy with ileoanal anastomosis. Which is the best treatment option is still unresolved. Lee *et al*[8] retrospectively analyzed the postoperative bowel movements in SCRC, and found that the mean number of bowel movements in a two regional resections group and an extensive resection group was 1.9 times and 4.3 times, respectively, with a significant difference between the two groups. You *et al*[9] compared the bowel function and quality of life between patients with extended resections and segmental colonic resections. The results showed that median daily stool frequency after segmental resections, ileosigmoid anastomosis and ileorectal anastomosis was 2, 4 and 5, respectively, and the overall quality of life was 98.5, 94.9, and 91.2, respectively. As multisegmental resection provides better postoperative defecation function and quality of life[8,9] and does not increase complications such as anastomotic leakage[9], this technique is recommended by some researchers.

Table 3 Univariate and multivariate analysis of overall survival and disease-free survival

Variable	Overall survival				Disease-free survival			
	Univariable analysis		Multivariate analysis		Univariable analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age (> 65/≤ 65 yr)	2.830 (0.983-8.150)	0.054	2.378 (0.793-7.128)	0.122	2.048 (0.779-5.384)	0.146	1.869 (0.674-5.188)	0.230
Gender (male/female)	1.051 (0.382-2.894)	0.923			1.180 (0.436-3.191)	0.744		
CEA level (> 5/≤ 5)	1.278 (0.389-4.198)	0.686			1.098 (0.348-3.465)	0.873		
CA19-9 level (> 37/≤ 37)	1.951 (0.506-7.521)	0.332			1.304 (0.285-5.958)	0.732		
ASA physical status (III/I-II)	2.565 (0.817-8.050)	0.106			2.280 (0.655-7.940)	0.195		
Tumor differentiation (poor/well- moderate)	0.918 (0.340-2.478)	0.866			1.119 (0.431-2.906)	0.817		
Tumor size (> 5/≤ 5 cm)	1.058 (0.383-2.920)	0.913			0.863 (0.328-2.269)	0.764		
T stage (T3-T4/T1-T2)	0.994 (0.130-7.627)	0.994			1.302 (0.172-9.854)	0.798		
N stage (N1-N2/N0)	11.266 (1.487-85.384)	0.019	10.161 (1.327-77.790)	0.026	13.414 (1.775-101.359)	0.012	13.107 (1.719-99.925)	0.013
Operative approach (LMRA/OMRA)	1.240 (0.426-3.611)	0.693	0.834 (0.274-2.534)	0.749	1.233 (0.432-3.516)	0.695	0.812 (0.269-2.454)	0.712

OMRA: Open multisegmental resection and anastomosis; LMRA: Laparoscopic multisegmental resection and anastomosis; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; ASA: American Society of Anesthesiologists; HR: Hazard ratio; CI: Confidence interval.



DOI: 10.4240/wjgs.v15.i9.1969

Figure 1 Kaplan-Meier survival analysis. A: Overall survival curves for patients with different operative methods; B: Diseases-free survival curves for patients with different operative methods. OMRA: Open multisegmental resection and anastomosis; LMRA: Laparoscopic multisegmental resection and anastomosis.

Following advances in laparoscopic techniques, several studies have confirmed that laparoscopic radical resection of CRC is safe and reliable; moreover, it can achieve the same curative effect as open surgery[10-14] and offers the advantages of minimally invasive surgery, such as small incision, mild postoperative pain, and rapid recovery[15,16]. However, unlike conventional CRC surgery, surgical treatment of SCRC with multisegmental resection is more difficult as more anastomoses are required. Presently, there are limited reports on the differences between laparoscopic and open surgical approach for SCRC involving separate segments. These studies are limited to single-center investigations with few patients and are mainly focused on the analysis of short-term efficacy; consequently, they lack a comparison of long-term prognosis[17,18]. Here, we studied patients from two institutions with SCRC located in separate segments. These patients underwent either LMRA or OMRA as curative surgery. We found that intraoperative blood loss together with postoperative parameters such as postoperative first exhaust time, postoperative first fluid intake time, the incidence of postoperative complications, and postoperative hospital stay were less in LMRA patients when compared with those in

OMRA patients. Furthermore, LMRA patients had more LNs dissected than OMRA patients, while the prognosis for both groups was similar. To our knowledge, this study includes the largest sample size for comparing LMRA and OMRA approaches with regard to short-term efficacy as well as long-term results.

Intraoperative blood loss and the incidence of postoperative complications are critical parameters for evaluating whether a surgical procedure is safe. Previous studies have confirmed that laparoscopic surgery has more advantages than open surgery for solitary CRC in terms of less intraoperative blood loss[19-22], reduced postoperative oral intake time[21,22], and shorter postoperative hospital stay[21-25]. Moreover, previous single-center, small-sample studies have reached the same conclusion for patients with SCRC involving different segments. Takatsu *et al*[17] compared the short-term efficacy of LMRA and OMRA in 42 patients with SCRC located in different segments; the authors noted that postoperative hospital stay and intraoperative blood loss were significantly decreased in the laparoscopic group as compared to the open surgery group. Nozawa *et al*[18] performed a single-center study of 25 patients with SCRC; the authors found that the laparoscopic group showed less intraoperative blood loss than the open surgery group. Here, we analyzed the surgical results of 109 patients with SCRC located in separate segments and found significantly less intraoperative blood loss in LMRA patients than in OMRA patients. Moreover, the total postoperative complication as well as hospital stay were remarkably better in LMRA patients. Furthermore, the operating time was not significantly increased in LMRA patients.

The number of dissected LNs is another crucial factor in evaluating radical surgery of CRC. In accordance with the guidelines of the National Comprehensive Cancer Network, the number of dissected LNs should be 12 or more after radical surgery of CRC. If the number of dissected LNs is small, the final staging will be affected. For SCRC located in separate segments, the number of dissected LNs is another vital indicator in evaluating surgical quality. Laparoscopy enables magnification of the operative field; hence, the dissection of LNs by laparoscopy is more precise than that by open surgery. A significantly higher number of LNs have been dissected by laparoscopy than by traditional open surgery [17]. The present study revealed that the average number of LNs dissected in LMRA patients was significantly more than that in OMRA patients; this finding was in agreement with the result of Takatsu *et al*[17]. However, both groups did not significantly differ in the number of positive LNs.

According to several studies, both laparoscopic and open surgeries have similar oncological results[26-30]. However, for SCRC located in separate segments, comparative studies on the long-term efficacy of LMRA and OMRA are presently inadequate. In our study, the 5-year OS rates of LMRA and OMRA patients were 78.2% and 82.9%, respectively, while the 5-year DFS rates of LMRA and OMRA patients were 72.8% and 78.3%, respectively. Both groups did not markedly differ in long-term prognosis. We further performed a multivariate prognostic analysis and found that the N stage was the sole independent prognostic factor that affected DFS and OS.

There are a few limitations in this research. First, selection bias probably existed due to the study's retrospective nature. Second, some patients' clinical data were incomplete, such as the time of first ambulation and postoperative pain score; thus, we could not compare and analyze the differences between open and laparoscopic approaches with regard to these aspects. Third, as the incidence of SCRC located in separate segments is low, although the sample size in this study is the largest thus far, the number of patients included in the analysis is still small. Therefore, multicenter prospective studies are needed in the future to confirm the advantages of LMRA.

CONCLUSION

LMRA is safe and feasible for SCRC located in separate segments; moreover, it has the benefits of less bleeding, rapid recovery, shorter postoperative hospital stay, reduced complications, a greater total number of LNs dissected and achieves the same long-term oncological outcomes as OMRA.

ARTICLE HIGHLIGHTS

Research background

Limited studies have focused on the differences between laparoscopic multisegmental resection and anastomosis (LMRA) and open multisegmental resection and anastomosis (OMRA) for synchronous colorectal cancer (SCRC) involving separate segments. Therefore, more studies on the safety and efficacy of LMRA are needed.

Research motivation

To assess the efficacy and safety of LMRA in patients with SCRC involving separate segments.

Research objectives

The objectives of this study were to compare the short-term efficacy and long-term oncological consequences of OMRA as well as LMRA for SCRC located in separate segments.

Research methods

A retrospective two-institution investigation was performed in 109 patients who received right hemicolectomy together with anterior resection of the rectum or right hemicolectomy and sigmoid colectomy. The OMRA and LMRA groups

included 41 and 68 patients, respectively. The clinicopathological characteristics and surgical results were compared between the groups, and the Cox proportional hazards model was used to conduct univariate and multivariate prognostic analyses.

Research results

LMRA patients showed significantly shorter postoperative first exhaust time, postoperative first fluid intake time, and postoperative hospital stay than OMRA patients. Intraoperative blood loss, and the incidence of total postoperative complications (Clavien-Dindo grade: ≥ II) were markedly less in the LMRA group. The mean number of lymph nodes dissected was significantly higher in the LMRA group. Prognostic analysis showed that N stage was the independent prognostic factor for overall survival and disease-free survival.

Research conclusions

On the basis of this study, we conclude that LMRA has some short-term advantages compared with OMRA, and is safe and feasible for patients with SCRC located in separate segments.

Research perspectives

Future multicenter prospective studies are needed to further confirm the advantages of LMRA.

FOOTNOTES

Author contributions: Quan JC and Zhou XJ contributed equally to this work; Quan JC and Chang H wrote the manuscript; Tang JQ, Zhou XJ and Wang XS conceived and designed the study; Quan JC, Liu JG, Chang H, Mei SW and Zhou XJ collected the data; Zhang JZ, Qiu WL, Li B and Li YG analyzed the data; all authors made critical revisions for the manuscript and approved the final manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences.

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: The authors declare no conflict of interest.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Ji-Chuan Quan 0000-0002-4250-3699; Xin-Jun Zhou 0009-0003-5479-1733; Shi-Wen Mei 0000-0002-9735-3261; Jun-Guang Liu 0000-0001-5230-4565; Wen-Long Qiu 0000-0002-6938-7878; Jin-Zhu Zhang 0000-0001-6979-0539; Bo Li 0000-0001-6763-230X; Yue-Gang Li 0000-0001-9115-3448; Xi-Shan Wang 0000-0002-1675-5083; Hu Chang 0009-0009-8157-1182; Jian-Qiang Tang 0000-0003-3933-8060.

S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP

REFERENCES

1 **Yang X**, Zhong ME, Xiao Y, Zhang GN, Xu L, Lu J, Lin G, Qiu H, Wu B. Laparoscopic vs open resection of pT4 colon cancer: a propensity score analysis of 94 patients. *Colorectal Dis* 2018; **20**: O316-O325 [PMID: 30240536 DOI: 10.1111/codi.14428]
2 **Moon SY**, Kim S, Lee SY, Han EC, Kang SB, Jeong SY, Park KJ, Oh JH; SEoul COlorectal Group (SECOG). Laparoscopic surgery for patients with colorectal cancer produces better short-term outcomes with similar survival outcomes in elderly patients compared to open surgery. *Cancer Med* 2016; **5**: 1047-1054 [PMID: 26923309 DOI: 10.1002/cam4.671]
3 **Tan KL**, Deng HJ, Chen ZQ, Mou TY, Liu H, Xie RS, Liang XM, Fan XH, Li GX. Survival outcomes following laparoscopic vs open surgery for non-metastatic rectal cancer: a two-center cohort study with propensity score matching. *Gastroenterol Rep (Oxf)* 2020; **8**: 319-325 [PMID: 32843980 DOI: 10.1093/gastro/goaa046]
4 **Li Z**, Zou Z, Lang Z, Sun Y, Zhang X, Dai M, Mao S, Han Z. Laparoscopic versus open radical resection for transverse colon cancer: evidence from multi-center databases. *Surg Endosc* 2021; **35**: 1435-1441 [PMID: 33507386 DOI: 10.1007/s00464-021-08285-5]
5 **Yang ZF**, Wu DQ, Wang JJ, Lv ZJ, Li Y. Short- and long-term outcomes following laparoscopic vs open surgery for pathological T4 colorectal cancer: 10 years of experience in a single center. *World J Gastroenterol* 2018; **24**: 76-86 [PMID: 29358884 DOI: 10.3748/wjg.v24.i1.76]

6 **Warren S**, Gates O. Multiple primary malignant tumors: a survey of the literature and a statistical study. *Am J Cancer* 1932; **16**: 1358-1414

7 **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]

8 **Lee BC**, Yu CS, Kim J, Lee JL, Kim CW, Yoon YS, Park IJ, Lim SB, Kim JC. Clinicopathological features and surgical options for synchronous colorectal cancer. *Medicine (Baltimore)* 2017; **96**: e6224 [PMID: 28248880 DOI: 10.1097/MD.0000000000006224]

9 **You YN**, Chua HK, Nelson H, Hassan I, Barnes SA, Harrington J. Segmental vs. extended colectomy: measurable differences in morbidity, function, and quality of life. *Dis Colon Rectum* 2008; **51**: 1036-1043 [PMID: 18470560 DOI: 10.1007/s10350-008-9325-1]

10 **Völkel V**, Draeger T, Schnitzbauer V, Gerken M, Benz S, Klinkhammer-Schalke M, Fürst A. Surgical treatment of rectal cancer patients aged 80 years and older-a German nationwide analysis comparing short- and long-term survival after laparoscopic and open tumor resection. *Eur J Surg Oncol* 2019; **45**: 1607-1612 [PMID: 31092363 DOI: 10.1016/j.ejso.2019.05.005]

11 **Hida K**, Okamura R, Sakai Y, Konishi T, Akagi T, Yamaguchi T, Akiyoshi T, Fukuda M, Yamamoto S, Yamamoto M, Nishigori T, Kawada K, Hasegawa S, Morita S, Watanabe M; Japan Society of Laparoscopic Colorectal Surgery. Open versus Laparoscopic Surgery for Advanced Low Rectal Cancer: A Large, Multicenter, Propensity Score Matched Cohort Study in Japan. *Ann Surg* 2018; **268**: 318-324 [PMID: 28628565 DOI: 10.1097/SLA.0000000000002329]

12 **Fujii S**, Ishibe A, Ota M, Yamagishi S, Watanabe J, Suwa Y, Kunisaki C, Endo I. Long-term results of a randomized study comparing open surgery and laparoscopic surgery in elderly colorectal cancer patients (Eld Lap study). *Surg Endosc* 2021; **35**: 5686-5697 [PMID: 32989541 DOI: 10.1007/s00464-020-08026-0]

13 **Quintana JM**, Antón-Ladisla A, González N, Lázaro S, Baré M, Fernández de Larrea N, Redondo M, Briones E, Escobar A, Sarasqueta C, García-Gutierrez S; REDISSEC-CARESS/CCR group. Outcomes of open versus laparoscopic surgery in patients with colon cancer. *Eur J Surg Oncol* 2018; **44**: 1344-1353 [PMID: 29921557 DOI: 10.1016/j.ejso.2018.05.030]

14 **Creavin B**, Kelly ME, Ryan ÉJ, Ryan OK, Winter DC. Oncological outcomes of laparoscopic versus open rectal cancer resections: meta-analysis of randomized clinical trials. *Br J Surg* 2021; **108**: 469-476 [PMID: 33748848 DOI: 10.1093/bjs/znaa154]

15 **Sun JL**, Xing SY. Short-term outcome of laparoscopic surgery versus open surgery on colon carcinoma: A meta-analysis. *Math Biosci Eng* 2019; **16**: 4645-4659 [PMID: 31499682 DOI: 10.3934/mbe.2019233]

16 **Huang YM**, Lee YW, Huang YJ, Wei PL. Comparison of clinical outcomes between laparoscopic and open surgery for left-sided colon cancer: a nationwide population-based study. *Sci Rep* 2020; **10**: 75 [PMID: 31919417 DOI: 10.1038/s41598-019-57059-6]

17 **Takatsu Y**, Akiyoshi T, Nagata J, Nagasaki T, Konishi T, Fujimoto Y, Nagayama S, Fukunaga Y, Ueno M. Surgery for synchronous colorectal cancers with double colonic anastomoses: A comparison of laparoscopic and open approaches. *Asian J Endosc Surg* 2015; **8**: 429-433 [PMID: 26245358 DOI: 10.1111/ases.12216]

18 **Nozawa H**, Ishihara S, Murono K, Yasuda K, Otani K, Nishikawa T, Tanaka T, Kiyomatsu T, Hata K, Kawai K, Yamaguchi H, Watanabe T. Laparoscopy-assisted versus open surgery for multiple colorectal cancers with two anastomoses: a cohort study. *Springerplus* 2016; **5**: 287 [PMID: 27066324 DOI: 10.1186/s40064-016-1948-4]

19 **Sasi S**, Kammar P, Masillamany S, De' Souza A, Engineer R, Ostwal V, Saklani A. Laparoscopic versus open resection in locally advanced rectal cancers: a propensity matched analysis of oncological and short-term outcomes. *Colorectal Dis* 2021; **23**: 2894-2903 [PMID: 34379866 DOI: 10.1111/codi.15870]

20 **Zhou S**, Wang X, Zhao C, Liu Q, Zhou H, Zheng Z, Zhou Z, Liang J. Laparoscopic vs open colorectal cancer surgery in elderly patients: short- and long-term outcomes and predictors for overall and disease-free survival. *BMC Surg* 2019; **19**: 137 [PMID: 31521147 DOI: 10.1186/s12893-019-0596-3]

21 **Nishikawa T**, Ishihara S, Hata K, Murono K, Yasuda K, Otani K, Tanaka T, Kiyomatsu T, Kawai K, Nozawa H, Yamaguchi H, Watanabe T. Short-term outcomes of open versus laparoscopic surgery in elderly patients with colorectal cancer. *Surg Endosc* 2016; **30**: 5550-5557 [PMID: 27752818 DOI: 10.1007/s00464-016-4921-y]

22 **Dai J**, Yu Z. Comparison of Clinical Efficacy and Complications Between Laparoscopic Versus Open Surgery for Low Rectal Cancer. *Comb Chem High Throughput Screen* 2019; **22**: 179-186 [PMID: 30973104 DOI: 10.2174/1386207322666190411113252]

23 **Goto K**, Watanabe J, Suwa Y, Nakagawa K, Suwa H, Ozawa M, Ishibe A, Ota M, Kunisaki C, Endo I. A multicenter, propensity score-matched cohort study about short-term and long-term outcomes after laparoscopic versus open surgery for locally advanced rectal cancer. *Int J Colorectal Dis* 2021; **36**: 1287-1295 [PMID: 33575889 DOI: 10.1007/s00384-021-03871-4]

24 **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]

25 **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]

26 **Pedrazzani C**, Turri G, Park SY, Hida K, Fukui Y, Crippa J, Ferrari G, Origi M, Spolverato G, Zuin M, Bae SU, Baek SK, Costanzi A, Maggioni D, Son GM, Scala A, Rockall T, Larson DW, Guglielmi A, Choi GS. Laparoscopic versus open surgery for left flexure colon cancer: A propensity score matched analysis from an international cohort. *Colorectal Dis* 2022; **24**: 177-187 [PMID: 34706130 DOI: 10.1111/codi.15962]

27 **Son IT**, Kim JY, Kim MJ, Kim BC, Kang BM, Kim JW. Clinical and oncologic outcomes of laparoscopic versus open surgery in elderly patients with colorectal cancer: a retrospective multicenter study. *Int J Clin Oncol* 2021; **26**: 2237-2245 [PMID: 34453641 DOI: 10.1007/s10147-021-02009-4]

28 **Liu ZH**, Wang N, Wang FQ, Dong Q, Ding J. Oncological outcomes of laparoscopic versus open surgery in pT4 colon cancers: A systematic review and meta-analysis. *Int J Surg* 2018; **56**: 221-233 [PMID: 29940259 DOI: 10.1016/j.ijsu.2018.06.032]

29 **Matsumoto A**, Shinohara H, Suzuki H. Laparoscopic and open surgery in patients with transverse colon cancer: short-term and oncological outcomes. *BJS Open* 2021; **5** [PMID: 34518870 DOI: 10.1093/bjsopen/zrab078]

30 **Pla-Martí V**, Martín-Arévalo J, Moro-Valdezate D, García-Botello S, Pérez-Santiago L, Lapeña-Rodríguez M, Bauzá-Collado M, Huerta M, Roselló-Keränen S, Espí-Macías A. Prognostic implications of surgical specimen quality on the oncological outcomes of open and laparoscopic surgery in mid and low rectal cancer. *Langenbecks Arch Surg* 2021; **406**: 2759-2767 [PMID: 34716825 DOI: 10.1007/s00423-021-02351-1]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 1978-1985

DOI: 10.4240/wjgs.v15.i9.1978

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Prediction model of stress ulcer after laparoscopic surgery for colorectal cancer established by machine learning algorithm

Dong-Mei Yu, Chun-Xiao Wu, Jun-Yi Sun, Hui Xue, Zhe Yuwen, Jiang-Xue Feng

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Fielding GA, United States; Surve A, United States

Received: May 31, 2023
Peer-review started: May 31, 2023
First decision: June 14, 2023
Revised: June 25, 2023
Accepted: July 19, 2023
Article in press: July 19, 2023
Published online: September 27, 2023

Dong-Mei Yu, Hui Xue, School of Nursing, Hebei University of Traditional Chinese Medicine, Shijiazhuang 050000, Hebei Province, China

Chun-Xiao Wu, Jiang-Xue Feng, Department I of Anorectal, Hebei Traditional Chinese Medicine Hospital, Shijiazhuang 050000, Hebei Province, China

Jun-Yi Sun, Department of Inspection Center, Hebei Traditional Chinese Medicine Hospital, Shijiazhuang 050000, Hebei Province, China

Zhe Yuwen, Department of Perivascular, Hebei Traditional Chinese Medicine Hospital, Shijiazhuang 050000, Hebei Province, China

Corresponding author: Jiang-Xue Feng, BSc, Associate Chief Nurse, Department I of Anorectal, Hebei Traditional Chinese Medicine Hospital, No. 389 Zhongshan East Road, Chang'an District, Shijiazhuang 050000, Hebei Province, China. fengjiangxue0330@163.com

Abstract

BACKGROUND

Patients with colorectal cancer (CRC) are prone to stress ulcer after laparoscopic surgery. The analysis of risk factors for stress ulcer (SU) in patients with CRC is important to reduce mortality and improve patient prognosis.

AIM

To identify risk factors for SU after laparoscopic surgery for CRC, and develop a nomogram model to predict the risk of SU in these patients.

METHODS

The clinical data of 135 patients with CRC who underwent laparoscopic surgery between November 2021 and June 2022 were reviewed retrospectively. They were divided into two categories depending on the presence of SUs: The SU group (n = 23) and the non-SU group (n = 112). Univariate analysis and multivariate logistic regression analysis were used to screen for factors associated with postoperative SU in patients undergoing laparoscopic surgery, and a risk factor-based nomogram model was built based on these risk factors. By plotting the model's receiver operating characteristic (ROC) curve and calibration curve, a Hosmer-Lemeshow goodness of fit test was performed.

RESULTS

Among the 135 patients with CRC, 23 patients had postoperative SU, with an incidence of 17.04%. The SU group had higher levels of heat shock protein (HSP) 70, HSP90, and gastrin (GAS) than the non-SU group. Age, lymph node metastasis, HSP70, HSP90, and GAS levels were statistically different between the two groups, but other indicators were not statistically different. Logistic regression analysis showed that age ≥ 65 years, lymph node metastasis, and increased levels of HSP70, HSP90 and GAS were all risk factors for postoperative SU in patients with CRC ($P < 0.05$). According to these five risk factors, the area under the ROC curve for the nomogram model was 0.988 (95%CI: 0.971-1.0); the calibration curve demonstrated excellent agreement between predicted and actual probabilities, and the Hosmer-Lemeshow goodness of fit test revealed that the difference was not statistically significant ($\chi^2 = 0.753$, $P = 0.999$), suggesting that the nomogram model had good discrimination, calibration, and stability.

CONCLUSION

Patients with CRC aged ≥ 65 years, with lymph node metastasis and elevated HSP70, HSP90, GAS levels, are prone to post-laparoscopic surgery SU. Our nomogram model shows good predictive value.

Key Words: Colorectal cancer; Laparoscope; Stress ulcer; Risk factors; Nomogram

Core Tip: Colorectal cancer (CRC) can cause hematochezia, dizziness, abdominal pain, diarrhea, constipation and other symptoms. We evaluated 135 patients who underwent laparoscopic surgery for CRC, identified 17 risk factors for post-surgery stress ulcer (SU), and established a nomogram model to predict the risk of SU in these patients. This model is useful for clinical prevention of postoperative SU in patients with CRC.

Citation: Yu DM, Wu CX, Sun JY, Xue H, Yuwen Z, Feng JX. Prediction model of stress ulcer after laparoscopic surgery for colorectal cancer established by machine learning algorithm. *World J Gastrointest Surg* 2023; 15(9): 1978-1985
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/1978.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.1978

INTRODUCTION

Colorectal cancer (CRC) is a common malignant tumor with an increasing incidence, which seriously threatens people's health[1]. It is easily overlooked by patients as the early symptoms are not obvious. As the cancer progresses, patients may experience abdominal pain, constipation and diarrhea, and in the advanced stage, they may experience general symptoms such as anemia and weight loss[2]. CRC kills over 900000 individuals worldwide each year, which makes it the fourth most lethal cancer[3]. Due to the advantages of low trauma, aesthetic criteria, and rapid postoperative recovery, laparoscopic radical dissection of CRC has emerged as the primary treatment for this disease[4,5]. However, CO_2 pneumoperitoneum, hemodynamic changes, local immune dysfunction and other reasons may lead to changes in neuroendocrine metabolism in patients, causing a significant stress response[6,7]. Stress ulcer (SU) is one of the more typical postoperative complications in patients with CRC. The main clinical manifestations are acute mucosal erosion and ulceration, which eventually progress to hemorrhage and intestinal perforation, leading to a major physiological and psychological impact on the patient[8]. Severe bleeding from a SU can result in longer hospital stays and an elevated risk of death. Therefore, analyzing and preventing SU risk factors in CRC patients can effectively reduce mortality, accurately forecast CRC predisposition, and provide targeted treatment for high-risk groups. In the present study, we examined the clinical information of 135 CRC patients admitted to Hebei Traditional Chinese Medicine Hospital, examined the risk factors for the growth of SU after CRC surgery, and built a nomogram model to provide a foundation for the early prevention and risk reduction of SU after CRC surgery.

MATERIALS AND METHODS

Data source and inclusion criteria

All 135 patients with CRC who underwent laparoscopic surgery at the Hebei Traditional Chinese Medicine Hospital between November 2021 and June 2022 were chosen for this retrospective study. The patients consisted of 80 males and 55 females, ranging in age from 22 to 85 years, with a mean age of (55.16 ± 13.18) years. Inclusion criteria were: (1) Meet the diagnostic criteria for CRC in the "Chinese protocol of diagnosis and treatment of colorectal cancer (2020 edition)"[9] and confirmed by pathology; (2) All patients underwent laparoscopic surgery; and (3) Complete clinical data. Exclusion criteria were: (1) Presence of hematological diseases; (2) Recent peptic ulcer; (3) Recent gastrointestinal surgery or invasive gastrointestinal examination; and (4) Other trauma, bleeding, *etc*. leading to blood in the digestive tract.

Research methods

The patients were divided into the SU (23 cases) and non-SU (112 cases) group according to whether they developed a SU after surgery, with an SU incidence of 17.04%. SU was diagnosed if the patient met one of the following parameters: (1) Spitting or gastric extract showed visible bright red or coffee colored liquid; (2) Tar colored stool, black stool or fecal occult blood test was positive; and (3) Microscopic examination revealed that the patient's gastric mucosa showed patchy or punctate bloody lesions, ulceration or erosion[10].

Observed indices

Clinical data collected included gender, age, smoking history, drinking history, liver and kidney function, lymph node status, *etc*. Laboratory examinations included routine blood and biochemical blood indicators including C-reactive protein, tumor necrosis factor α, interleukin (IL)-6, IL-8, heat shock protein (HSP) 70, HSP90, gastrin (GAS), hemoglobin, albumin, fasting blood glucose at admission, serum potassium, *etc*.

Statistical analysis

SPSS26.0 statistical software was used for data processing and analysis. The χ^2 test was applied to compare the two groups. Data on counts are presented as [*n* (%)]. The Shapiro-Wilk test was used to determine normalcy. The two independent samples *t*-test was used to analyze measurement data with a normal distribution. The non-normal distribution measurement data were reported as the median and interquartile range [M (P25, P75)], and the Mann-Whitney *U* test was employed. The risk factors for SU after CRC surgery were evaluated using univariate and multivariate logistic regression analysis, and the risk factors were imported into R software to develop a nomogram model to predict the risk of SU following CRC surgery. To assess the model's discrimination, a receiver operating characteristic (ROC) curve was created and the area under the curve (AUC) was determined. An AUC ≥ 90% was excellent, 70%-89% was good, 50%-69% was moderate, and 0.05 indicated good stability. $P \leq 0.05$ was regarded as statistically significant.

RESULTS

Clinical data of the SU group and non-SU group

The differences in age, lymph node metastases, HSP70, HSP90, and GAS levels between the two groups were statistically significant, while the other indicators were not. The SU group had higher levels of HSP70, HSP90, and GAS than the non-SU group (Table 1).

Multivariate logistic regression analysis

Univariate analysis was employed to identify statistically significant variables among the 17 factors related to CRC, including gender, age, drinking history, smoking history, abnormal liver and kidney function, lymph node metastasis, postoperative albumin decline and other laboratory indicators, to assign them (Age: < 65 years = 1, ≥ 65 years = 2; lymph node metastasis: yes = 1, no = 0), and regression analysis was carried out using a multivariate model. The results indicated that age ≥ 65 years, lymph node metastasis, and increased levels of HSP70, HSP90 and GAS were all independent risk factors for the development of SU in CRC patients after surgery ($P < 0.05$) (Table 2).

Construction and validation of the nomogram

Based on the independent risk factors for postoperative SU in CRC patients screened out in multivariate analysis, the risk prediction model of postoperative SU in patients was established by R statistical software. The individual scores for each risk factor were obtained from the scale at the top of the nomogram for that factor, and the scores for all risk factors were added together to obtain a total score to obtain the incidence of SU in the corresponding patient. A higher total score indicated a greater likelihood of developing a SU (Figure 1). The AUC of the ROC was 0.988 (95%CI: 0.971-1.0), indicating that this nomogram model discriminated well (Figure 2). When the Youden index was 0.908, the related sensitivity and specificity were 93.3% and 97.5%, respectively. The training and validation set calibration curves suggested that the simulated and actual curves essentially followed the same trend (Figure 3), suggesting that prediction of the probability of postoperative SU in patients with CRC obtained by the nomogram model had good consistency with the actual probability. The Hosmer-Lemeshow goodness of fit test revealed no statistically significant change ($\chi^2 = 0.753$, $P = 0.999$), indicating that the model was well calibrated and stable. The decision curve analysis (DCA) is based on continuous potential risk thresholds, and the net benefit of risk-stratifying patients illustrates the model's clinical value. The prediction model's decision curves revealed that the model trended away from extreme curves with a high net benefit and clinical practicability (Figure 4).

DISCUSSION

SU is one of the postoperative complications of CRC. It occurs when the human body is subjected to various major injuries or psychological diseases, causing acute gastrointestinal mucosal erosion, ulcer and other lesions. Severe cases can be complicated by gastrointestinal bleeding or even perforation, leading to aggravation and deterioration of the original disease and increased mortality[11]. Analyzing the risk factors for SU in patients with CRC is of great significance

Table 1 Clinical data of the two groups of patients

Variables	Non-SU group (*n* = 112)	SU group (*n* = 23)	χ^2/t	*P* value
Sex, *n* (%)			0.086	0.769
Male	67 (59.82)	13 (56.52)		
Female	45 (40.18)	10 (43.48)		
Age (yr), *n* (%)			15.062	< 0.001
< 65	80 (71.43)	6 (26.09)		
≥ 65	32 (28.57)	17 (73.91)		
Drinking history, *n* (%)			2.280	0.131
Yes	46 (41.07)	14 (60.87)		
No	66 (58.93)	9 (39.13)		
Smoking history, *n* (%)			0.513	0.474
Yes	61 (54.46)	15 (65.23)		
No	51 (45.54)	8 (34.78)		
Liver and kidney dysfunction, *n* (%)			2.035	0.088
Yes	21 (18.75)	8 (34.78)		
No	91 (81.25)	15 (65.22)		
Lymph node metastasis, *n* (%)			14.316	< 0.001
Yes	33 (29.46)	17 (73.91)		
No	79 (70.54)	6 (26.09)		
Postoperative albumin decreased, *n* (%)			0.263	0.608
< 50	28 (25.00)	4 (17.39)		
≥ 50	84 (75.00)	19 (82.61)		
Serum potassium (mmol/L)	3.71 ± 0.58	3.73 ± 0.61	-0.154	0.878
Hemoglobin (g/L)	121.28 ± 16.39	115.20 ± 18.52	0.115	0.115
Fasting blood glucose (mmol/L)	10.03 ± 4.54	8.15 ± 3.62	1.866	0.064
CRP (mg/L)	72.37 ± 12.09	75.32 ± 13.47	1.045	0.298
TNF-α (pg/mL)	149.00 ± 18.37	151.75 ± 21.41	0.635	0.526
IL-6 (pg/mL)	14.46 ± 2.28	15.02 ± 3.27	0.990	0.324
IL-8 (pg/mL)	18.43 ± 3.45	19.82 ± 3.04	1.793	0.075
HSP70	2.32 ± 0.56	3.37 ± 0.81	-5.876	< 0.001
HSP90	119.42 ± 17.81	159.35 ± 27.37	-6.712	< 0.001
GAS	121.92 ± 29.39	146.82 ± 35.36	-3.571	< 0.001

CRP: C-reactive protein; TNF-α: Tumor necrosis factor α; IL-6: Interleukin 6; IL-8: Interleukin 8; HSP70: Heat shock protein 70; HSP90: Heat shock protein 90; GAS: Gastrin; SU: Stress ulcer.

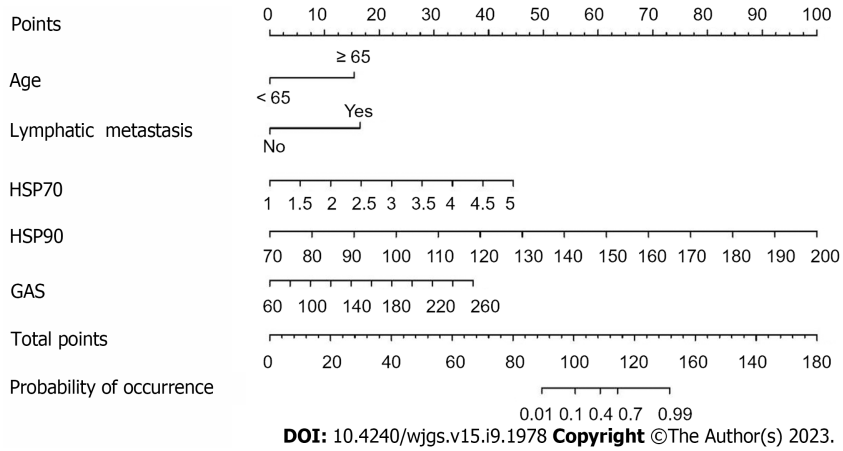
for the prevention and prognosis of SU after CRC surgery.

Serum HSP70 and HSP90 are highly conserved stress proteins in the heat shock protein family. They have anti-inflammatory and anti-oxidation effects and can affect cell stability and the stress response[12]. Studies have found that HSP70 and HSP90 Levels are closely linked to SU risk[13,14]. When gastric mucosal cells are stimulated by trauma factors, the cell protein configuration changes, which can induce cell inflammatory response and activate HSP70 and HSP90. With the increase in HSP70 and HSP90 content, this promotes the synthesis and folding of proteins in gastric mucosal cells, thereby reducing the damage caused by the stress response to mucosal cells and exerting a role in gastric mucosal protection[15]. According to our findings, patients in the SU group had greater serum levels of HSP70 and HSP90 than patients in the non-SU group. It is suggested that the higher the levels of HSP70 and HSP90, the more severe the postoperative stress response in patients with CRC, the greater the compensatory increase in HSP70 and HSP90, the more serious the damage caused by stress response to gastric mucosal cells, and the higher the risk of SU. Therefore, serum levels of HSP70 and

Table 2 Multivariate logistic regression analysis of factors affecting postoperative stress ulcer in patients with colorectal cancer

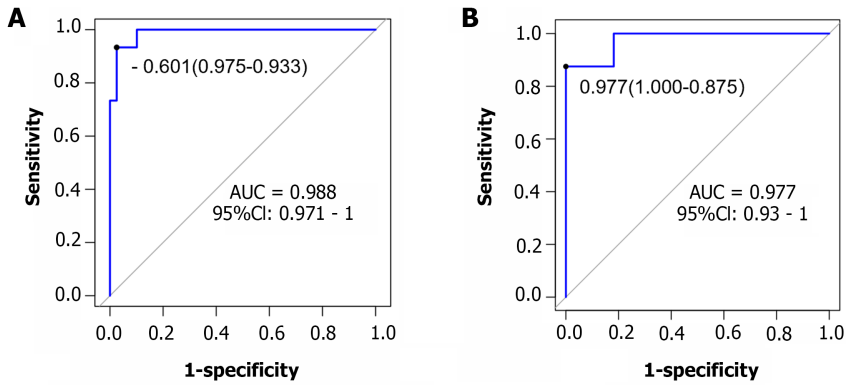
Variables	β	SE	Wald	*P* value	OR	95%CI
Age	3.301	1.505	4.811	0.028	27.146	1.421-518.593
Lymph node metastasis	3.462	1.721	4.048	0.044	31.869	1.093-928.858
HSP70	2.496	1.132	4.857	0.028	12.129	1.318-928.858
HSP90	0.169	0.061	7.758	0.005	1.184	1.051-1.333
GAS	0.041	0.018	5.510	0.019	1.042	1.007-1.079

HSP70: Heat shock protein 70; HSP90: Heat shock protein 90; GAS: Gastrin.



DOI: 10.4240/wjgs.v15.i9.1978 **Copyright** ©The Author(s) 2023.

Figure 1 Nomogram for predicting postoperative stress ulcer in colorectal cancer patients. HSP70: Heat shock protein 70; HSP90: Heat shock protein 90; GAS: Gastrin.

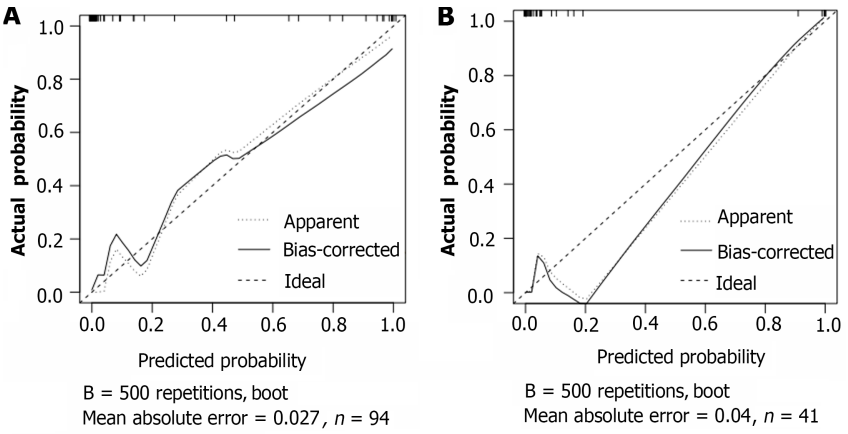


DOI: 10.4240/wjgs.v15.i9.1978 **Copyright** ©The Author(s) 2023.

Figure 2 Validation of the nomogram by the receiver operating characteristic curve. A: The training cohort; B: The validation cohort. AUC: Area under the curve.

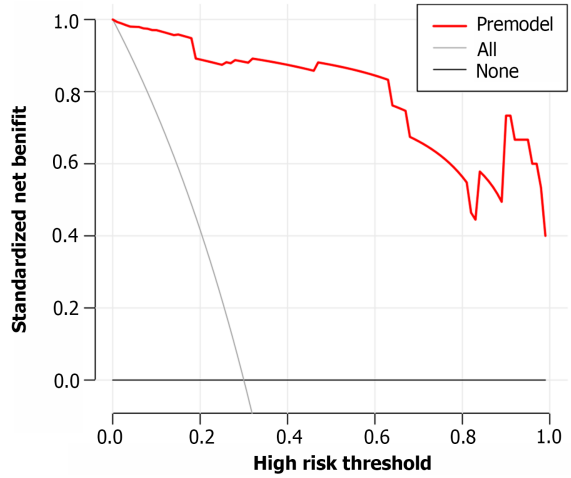
HSP90 are indicators of the likelihood of developing a SU in individuals who undergo laparoscopic surgery for CRC.

GAS is a potent hormone that promotes gastric acid secretion. The increase in GAS level may be related to sympathetic nerve excitation caused by trauma, continuous contraction of gastric mucosal blood vessels, vagus nerve choline fiber excitation caused by increased intracranial pressure, use of a strong dose of dehydrating agent and catabolic disorder[16]. Studies have found that when the level of serum GAS in critically ill patients increases, it will increase gastric acid secretion, resulting in transient small intestinal dysfunction and decreased gastric emptying capacity and gastric pyloric sphincter tension. Food reflux from the small intestine stimulates GAS secretion[17]. According to the study findings, patients with SUs had higher serum GAS levels than patients without SUs. The results of regression analysis showed that GAS level was a risk factor for SU, which was consistent with the results reported in the literature[12]. In this study, it was concluded that the increase in serum GAS level correlated with disease severity, and that the severity of the patient's condition was correlated with the intensity of the stress response and stomach mucosal damage, which could be utilized



DOI: 10.4240/wjgs.v15.i9.1978 **Copyright** ©The Author(s) 2023.

Figure 3 Calibration plot of the nomogram for the probability of metastasis. A: The training cohort; B: The validation cohort.



DOI: 10.4240/wjgs.v15.i9.1978 **Copyright** ©The Author(s) 2023.

Figure 4 Prediction model decision curve analysis diagram.

as a predictor of the likelihood of developing a SU.

The results of this study suggest that age ≥ 65 years and lymph node metastasis are risk factors for the development of SU following CRC surgery. This may be the reason why elderly patients are prone to SU, and may be related to stress changes such as relatively low physical resistance and decreased postoperative self-regulation ability. Lymphatic metastasis is a common feature of advanced cancer. Surgical treatment of advanced rectal cancer often involves a long operation time and complicated procedures. Lymph node dissection leads to increased surgical trauma, stress response, acid-base imbalance and further acidosis. At the same time, the increase in oxygen free radicals increases the risk of SU bleeding[18].

In this study, 17 factors that may affect postoperative SU in patients with CRC were investigated by univariate analysis combined with multivariate logistic regression analysis. To construct a nomogram model, five independent risk factors identified in the logistic analysis were entered into R software. The nomogram model performed well in terms of discrimination, as indicated by the AUC of 0.988 (95%CI: 0.971-1.0), and this performance was further confirmed in the validation set. In addition, the calibration curves also demonstrated the good consistency of the nomogram model. No significant difference was found by the Hosmer-Lemeshow goodness of fit test (χ^2 = 0.753, P = 0.999), indicating a stable and well-calibrated model. However, these results do not fully explain whether the nomogram model can be applied in clinical practice. Therefore, further analysis by DCA was carried out and the results of the prediction model DCA showed that the model was far from the extreme curve and the net benefit rate was high, showing that the nomogram had good clinical applicability. In this retrospective study with a small number of affecting factors, the findings may be biased as it was not a multi-center, large-sample epidemiological survey. In the future, a more reasonable and larger-sample prospective randomized controlled clinical trial will be designed to further improve the model's predictive value.

CONCLUSION

Age ≥ 65 years, lymph node metastasis, and elevated HSP70, HSP90, and GAS are independent risk factors for postoperative SU in patients with CRC. The nomogram model constructed accordingly had high clinical application value, calibration, and stability. It is helpful for clinicians to take targeted measures to reduce the incidence of postoperative SU in patients with CRC.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) is a complex multifactorial disease, usually manifested as hematochezia, abdominal pain, diarrhea, and constipation.

Research motivation

Patients with rectal cancer are prone to stress ulcer (SU) after laparoscopic surgery.

Research objectives

This study aimed to investigate the risk factors for SU in patients with CRC after laparoscopic surgery, and construct a risk prediction nomogram model with clinical value based on these risk factors.

Research methods

This study was a retrospective analysis of the clinical data of 135 patients with CRC who underwent laparoscopic surgery from November 2021 to June 2022. Risk factors for the development of postoperative SU were screened by univariate and multivariate regression analyses, and nomogram models were constructed based on these risk factors.

Research results

Among the 135 patients with CRC, 23 patients had postoperative SU, with an incidence of 17.04%.

Research conclusions

By comparing other studies, we found that most scholars emphasize the advantages of laparoscopic treatment of CRC, but there is a lack of research on its disadvantages. This study proposes that laparoscopic treatment of CRC is prone to SU, further analyzes its influencing factors, and establishes a predictive model with clinical value. This study proposed a new prediction model of SU after laparoscopic surgery in patients with CRC.

Research perspectives

Future research should be based on clinical observation, incorporating more possible influencing factors, and establishing a more practical predictive model.

FOOTNOTES

Author contributions: Yu DM designed and performed the research and wrote the paper; Feng JX designed the research and supervised the report; Yu DM and Feng JX designed the research and contributed to the analysis; Sun JY, Wu CX, Xue H and Yuwen Z provided clinical advice; Sun JY, Wu CX, Xue H and Yuwen Z supervised the report; all authors have read and approved the final version to be published.

Institutional review board statement: The study was reviewed and approved by the Hebei Traditional Chinese Medicine Hospital.

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

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

Data sharing statement: The data set for this study can be obtained from the corresponding author.

Country/Territory of origin: China

ORCID number: Dong-Mei Yu 0009-0008-2990-7358; Chun-Xiao Wu 0000-0002-9883-2141; Jun-Yi Sun 0009-0008-5390-6478; Hui Xue 0009-

0007-6296-5245; Zhe Yuwen 0009-0001-4459-6833; Jiang-Xue Feng 0009-0007-0826-2995.

S-Editor: Yan JP
L-Editor: A
P-Editor: Cai YX

REFERENCES

1 **Alçın G**, Şanlı Y, Yeğen G, Kaytan Sağlam E, Çermik TF. The Impact of Primary Tumor and Locoregional Metastatic Lymph Node SUV(max) on Predicting Survival in Patients with Rectal Cancer. *Mol Imaging Radionucl Ther* 2020; **29**: 65-71 [PMID: 32368877 DOI: 10.4274/mirt.galenos.2020.40316]
2 **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]
3 **Keum N**, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 713-732 [PMID: 31455888 DOI: 10.1038/s41575-019-0189-8]
4 **Chen Y**, Xi D, Zhang Q. Laparoscopic Radical Resection versus Routine Surgery for Colorectal Cancer. *Comput Math Methods Med* 2022; **2022**: 4899555 [PMID: 36238486 DOI: 10.1155/2022/4899555]
5 **Nakagawa K**, Watanabe J, Ota M, Suwa Y, Suzuki S, Suwa H, Momiyama M, Ishibe A, Saigusa Y, Yamanaka T, Kunisaki C, Endo I. Efficacy and safety of enoxaparin for preventing venous thromboembolic events after laparoscopic colorectal cancer surgery: a randomized-controlled trial (YCOG 1404). *Surg Today* 2020; **50**: 68-75 [PMID: 31385041 DOI: 10.1007/s00595-019-01859-w]
6 **Liu R**, Qin H, Wang M, Li K, Zhao G. Transversus abdominis plane block with general anesthesia blunts the perioperative stress response in patients undergoing radical gastrectomy. *BMC Anesthesiol* 2019; **19**: 205 [PMID: 31699052 DOI: 10.1186/s12871-019-0861-0]
7 **Balagué Ponz C**, Trias M. Laparoscopic surgery and surgical infection. *J Chemother* 2001; **13** Spec No 1: 17-22 [PMID: 11936362 DOI: 10.1179/joc.2001.13.Supplement-2.17]
8 **Mohamed WA**, Schaalan MF, Ramadan B. The expression profiling of circulating miR-204, miR-182, and lncRNA H19 as novel potential biomarkers for the progression of peptic ulcer to gastric cancer. *J Cell Biochem* 2019; **120**: 13464-13477 [PMID: 30945348 DOI: 10.1002/jcb.28620]
9 **National Health Commission of the People's Republic of China**. [Chinese Protocol of Diagnosis and Treatment of Colorectal Cancer (2020 edition)]. *Zhonghua Wai Ke Za Zhi* 2020; **58**: 561-585 [PMID: 32727186 DOI: 10.3760/cma.j.cn112139-20200518-00390]
10 **Siddiqui AH**, Farooq U, Siddiqui F. Curling Ulcer. 2023 Apr 16. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan- [PMID: 29493972]
11 **Pallan A**, Dedelaite M, Mirajkar N, Newman PA, Plowright J, Ashraf S. Postoperative complications of colorectal cancer. *Clin Radiol* 2021; **76**: 896-907 [PMID: 34281707 DOI: 10.1016/j.crad.2021.06.002]
12 **Szyller J**, Kozakiewicz M, Siermontowski P, Kaczerska D. Oxidative Stress, HSP70/HSP90 and eNOS/iNOS Serum Levels in Professional Divers during Hyperbaric Exposition. *Antioxidants (Basel)* 2022; **11** [PMID: 35624872 DOI: 10.3390/antiox11051008]
13 **Khotib J**, Rahmadi M, Ardianto C, Nisak K, Oktavia R, Ratnasari A, Dinintia Y, Shinta DW, Aryani T; Suharjono. Selective serotonin reuptake inhibitor fluvoxamine ameliorates stress- and NSAID-induced peptic ulcer possibly by involving Hsp70. *J Basic Clin Physiol Pharmacol* 2019; **30**: 195-203 [PMID: 30730837 DOI: 10.1515/jbcpp-2018-0067]
14 **Hoter A**, Naim HY. The Functions and Therapeutic Potential of Heat Shock Proteins in Inflammatory Bowel Disease-An Update. *Int J Mol Sci* 2019; **20** [PMID: 31717769 DOI: 10.3390/ijms20215331]
15 **Schulze A**, Beliu G, Helmerich DA, Schubert J, Pearl LH, Prodromou C, Neuweiler H. Cooperation of local motions in the Hsp90 molecular chaperone ATPase mechanism. *Nat Chem Biol* 2016; **12**: 628-635 [PMID: 27322067 DOI: 10.1038/nchembio.2111]
16 **Ren X**, Wang Y, He Z, Liu H, Xue K. Effects of cefuroxime axetil combined with Xingpi Yanger granules on the serum gastrin, motilin, and somatostatin levels in children with upper respiratory tract infection accompanied by diarrhea: results of a randomized trial. *Transl Pediatr* 2021; **10**: 2106-2113 [PMID: 34584881 DOI: 10.21037/tp-21-314]
17 **Zhou X**, Fang H, Xu J, Chen P, Hu X, Chen B, Wang H, Hu C, Xu Z. Stress ulcer prophylaxis with proton pump inhibitors or histamine 2 receptor antagonists in critically ill adults - a meta-analysis of randomized controlled trials with trial sequential analysis. *BMC Gastroenterol* 2019; **19**: 193 [PMID: 31752703 DOI: 10.1186/s12876-019-1105-y]
18 **Jin M**, Frankel WL. Lymph Node Metastasis in Colorectal Cancer. *Surg Oncol Clin N Am* 2018; **27**: 401-412 [PMID: 29496097 DOI: 10.1016/j.soc.2017.11.011]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 1986-1994

DOI: 10.4240/wjgs.v15.i9.1986

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Effect of two surgical approaches on the lung function and prognosis of patients with combined esophagogastric cancer

Chong-Bing Sun, Xiao-Qing Han, Hao Wang, Yi-Xuan Zhang, Meng-Chun Wang, Yong-Ning Liu

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Terashima M, Japan; Wei W, China

Received: May 24, 2023
Peer-review started: May 24, 2023
First decision: June 13, 2023
Revised: July 4, 2023
Accepted: July 31, 2023
Article in press: July 31, 2023
Published online: September 27, 2023

Chong-Bing Sun, Hao Wang, Meng-Chun Wang, Yong-Ning Liu, Department of General Surgery, Weifang People's Hospital, Weifang 261041, Shandong Province, China

Xiao-Qing Han, Department of Spinal Surgery, Weifang People's Hospital, Weifang 261041, Shandong Province, China

Yi-Xuan Zhang, Department of Medical, Weifang People's Hospital, Weifang 261041, Shandong Province, China

Corresponding author: Yong-Ning Liu, MSc, Attending Doctor, Department of General Surgery, Weifang People's Hospital, No. 151 Kuiwen District, Weifang 261041, Shandong Province, China. rmyyliuyn@wfmc.edu.cn

Abstract

BACKGROUND

Adenocarcinoma of the esophagogastric junction has a center of origin within 5 cm of the esophagogastric junction. Surgical resection remains the main treatment. A transthoracic approach is recommended for Siewert I adenocarcinoma of the esophagogastric junction and a transabdominal approach is recommended for Siewert III adenocarcinoma of the esophagogastric junction. However, there is a need to determine the optimal surgical approach for Siewert II adenocarcinoma of the esophagogastric junction to improve lung function and the prognosis of patients.

AIM

To investigate and compare the surgical effects, postoperative changes in pulmonary function, and prognoses of two approaches to treating combined esophagogastric cancer.

METHODS

One hundred and thirty-eight patients with combined esophagogastric cancer treated by general and thoracic surgeries in our hospital were selected. They were divided into group A comprising 70 patients (transabdominal approach) and group B comprising 68 patients (transthoracic approach) based on the surgical approach. The indexes related to surgical trauma, number of removed lymph nodes, indexes of lung function before and after surgery, survival rate, and survival duration of the two groups were compared 3 years after surgery.

RESULTS

The duration of surgery, length of hospital stay, and postoperative drainage duration of the patients in group A were shorter than those of the patients in group B, and the volume of blood loss caused by surgery was lower for group A than for group B ($P < 0.05$). At the one-month postoperative review, the first second, maximum ventilation volume, forceful lung volume, and lung volume values were higher for group A than for group B ($P < 0.05$). Preoperatively, the QLQ-OES18 scale scores of the patients in group A were higher than those in group B on re-evaluation at 3 mo postoperatively ($P < 0.05$). The surgical complication rate of the patients in group A was 10.00%, which was lower than that of patients in group B, which was 23.53% ($P < 0.05$).

CONCLUSION

Transabdominal and transthoracic surgical approaches are comparable in treating combined esophagogastric cancer; however, the former results in lesser surgical trauma, milder changes in pulmonary function, and fewer complications.

Key Words: Transabdominal approach; Transthoracic approach; Esophagogastric Junction cancer; Pulmonary function; Prognosis; Adenocarcinoma

Core Tip: Surgical resection remains the main treatment for adenocarcinoma of the esophagogastric junction. The transthoracic approach is recommended for Siewert I, and the transabdominal approach for Siewert III adenocarcinomas of the esophagogastric junction. However, the optimal surgical approach for Siewert II adenocarcinoma of the esophagogastric junction remains inconclusive. We found that the transabdominal approach has the advantage of lesser surgical trauma, lesser impact on patients' pulmonary function, and fewer complications.

Citation: Sun CB, Han XQ, Wang H, Zhang YX, Wang MC, Liu YN. Effect of two surgical approaches on the lung function and prognosis of patients with combined esophagogastric cancer. *World J Gastrointest Surg* 2023; 15(9): 1986-1994
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/1986.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.1986

INTRODUCTION

Adenocarcinoma of the esophagogastric junction has a center of origin within 5 cm of the esophagogastric junction. It is classified as a separate disease because of its anatomical location and biological characteristics, and its incidence is increasing significantly globally[1]. Surgical resection remains the main treatment. The transthoracic and transabdominal approaches are recommended for Siewert I and III adenocarcinomas of the esophagogastric junction, respectively, for complete resection[2]. However, the optimal surgical approach for Siewert II adenocarcinoma of the esophagogastric junction has not been established[3]. The three common approaches for the surgical treatment of Siewert II adenocarcinoma of the esophagogastric junction are transthoracic, transabdominal, and combined transthoracic and abdominal[4]. However, the transthoracic and transabdominal approaches are more commonly used. This study aimed to investigate and compare the surgical effects, changes in postoperative pulmonary function, and differences in prognosis associated with the transthoracic and transabdominal epigastric approaches for the treatment of adenocarcinoma of the esophagogastric junction.

MATERIALS AND METHODS

Information

One hundred and thirty-eight patients with combined esophagogastric cancer surgically treated by general and thoracic surgeries in our hospital were recruited between July 2015 and June 2017 for this study. Based on the surgical approach, they were divided into group A comprising 70 patients (transabdominal approach) and group B comprising 68 patients (transthoracic approach). The inclusion criteria were as follows: (1) Esophageal cancer diagnosed according to the criteria in the NCCN Esophageal Cancer Guidelines 2015 V3 edition[5]; (2) age of 19 to 75 years; (3) esophageal cancer confirmed by biopsies taken by fiberoptic esophagoscopy before surgery and Siewert type II adenocarcinoma confirmed by pathology; and (4) absence of distant metastasis during preoperative examination. The exclusion criteria were as follows: (1) Patients requiring surgery due to emergencies, such as obstruction, perforation, or bleeding; (2) coagulation disorders; (3) palliative tumor resection; (4) previous history of open-heart or open abdominal surgery; (5) preoperative history of radiotherapy; and (6) missing data. The study protocol did not violate the relevant medical ethics requirements.

The characteristics of group A were as follows: Age range of 42–75 years with an average of 58.3 ± 7.0 years; gender distribution: 40 males and 30 females; TNM tumor stages: 13 cases of stage I, 30 cases of stage II, and 27 cases of stage III; tumor lesion diameter of 5.27 ± 1.40 cm; and Lauren's staging: 50 cases of intestinal type, 6 cases of diffuse type, 14 cases of mixed type.

The characteristics of group B were as follows: Age range of 40-75 years with an average of 56.8 ± 6.9 years; gender distribution: 34 males and 34 females; tumor TNM stages: 16 cases of stage I, 30 cases of stage II, and 22 cases of stage III; tumor lesion diameter of 5.10 ± 1.35 cm; Lauren typing: 52 cases of intestinal type, 4 cases of diffuse type, and 12 cases of mixed type. The baseline information of the two patient groups was above that of the baseline comparison, and the difference was not statistically significant ($P > 0.05$).

Surgical method

All patients were diagnosed preoperatively using gastroscopy and underwent cardiac color Doppler ultrasonography, pulmonary function test, chest computed tomography (CT), abdominal CT, routine electrocardiogram, routine biochemical tests, and coagulation function tests (Figure 1).

Group A: Transabdominal approach to surgical treatment (Figure 2). After the successful induction of general anesthesia, the patient was placed on his back and disinfected routinely. An incision was made in the middle of the upper abdomen, the abdomen was opened in layers, and the transverse colon was elevated. The gastrocolic ligament was opened along its upper edge, on the left near the splenic flexure of the colon, and on the right at the hepatic flexure of the colon, exposing the greater omentum and the anterior lobe of the transverse mesocolon. There was an upward separation along the greater curvature of the stomach. The left vessel of the gastric omentum was ligated, and the lymph nodes were swept. The primordial band of the liver and stomach was cut along the lesser curvature of the stomach on the right side of the cardia, the stomach was turned upward, and the gastric artery and vein were severed. The right and left diaphragmatic angles were opened, the anterior and posterior vagus nerve trunks were separated, and the lower end of the esophagus was freed and cut 3-5 cm from the cardia. The anastomotic stapler was placed in the esophagus, and the anastomosis was fixed in a purse string. The closing apparatus was placed close to the gastric body and sutured, and the esophagogastric anastomosis was strengthened intermittently. After the abdominal cavity was irrigated to stop bleeding, an abdominal drain was placed, and the abdomen was closed layer-by-layer. The abdominal and lower mediastinal lymph nodes were dissected.

Group B: Transthoracic approach to surgical treatment. After the successful induction of general anesthesia for transthoracic surgical access, the patient was placed in the supine position and routinely disinfected. An incision was made in the middle of the upper abdomen, and the abdomen was opened in layers. The transverse colon was elevated. The gastrocolic ligament was opened along its upper edge, on the left near the splenic flexure of the colon, and on the right to the hepatic flexure of the colon, exposing the greater omentum and the anterior lobe of the transverse mesocolon. There was an upward separation along the greater curvature of the stomach, the left vessel of the gastric omentum was ligated, and the lymph nodes were swept. The primordial band of the liver and stomach was separated along the lesser curvature of the stomach on the right side of the cardia, the stomach was turned upward, and the gastric artery and vein were severed. The right and left diaphragmatic angles were opened, the anterior and posterior vagus nerve trunks were separated, and the lower end of the esophagus was freed and cut 3-5 cm from the cardia. The anastomotic stapler was placed in the esophagus, and the anastomosis was secured in a purse string. The closing apparatus was placed close to the gastric body and sutured, and the esophagogastric anastomosis was strengthened intermittently. After the abdominal cavity was irrigated to stop bleeding, an abdominal drain was placed, and the abdomen was closed layer-by-layer. The mediastinal and perigastric lymph nodes were dissected.

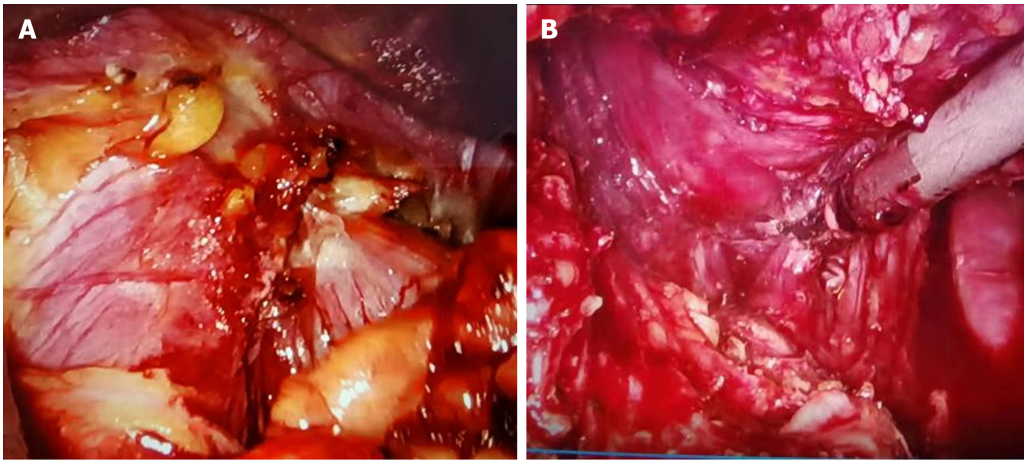
The tumor center, number of lymph nodes, and positive status were confirmed based on the postoperative pathological findings of the specimen. R staging of the residual disease was used to determine the rate of radical resection: r0 indicated no signs of a residual tumor to the naked eye and under the microscope; r1 indicated a residual tumor that was not visible to the naked eye but was visible at the margin under the microscope; and r2 indicated a tumor visible to the naked eye at the cut edge.

Indices for observation and detection methods

We compared the duration of surgery, bleeding volume, number of cleared lymph nodes, number of positive lymph nodes, positive margin rate, and length of hospital stay. We also compared the two groups based on the four indicators of forced expiratory volume within the first second (FEV1), maximum ventilation volume (MVV), forceful lung volume (FVC), and lung volume (VC) as percentages of their expected values; surgical complications; and 3-year survival rates and durations before and after surgery.

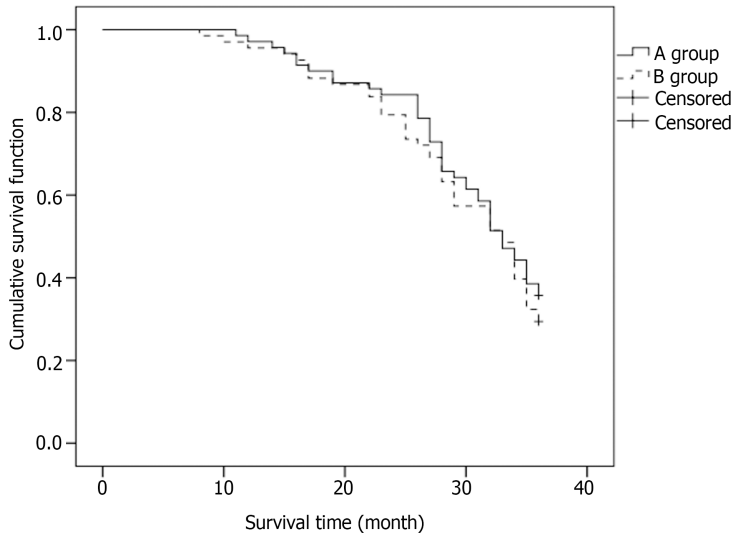
Pulmonary function was measured preoperatively and 1 mo postoperatively. A JAEGER Flowscreen pulmonary function tester (Jaeger, Germany) was used to examine the patients while fully awake and in the sitting position[6]. The main indices included VC, FVC, FEV, and MVV, and the data are expressed as percentages of the actual value to the desired value.

The quality of survival was assessed preoperatively and at 3 mo postoperatively. The QLQ-OES18 scale for esophageal cancer[7] was used to evaluate the quality of survival; it contains 19 questionnaire items, 18 of which have a score range of 0-3, and one which has a score range of 0-4, with a total score of 58. Higher scores indicated higher quality of survival for the patient.



DOI: 10.4240/wjgs.v15.i9.1986 **Copyright** ©The Author(s) 2023.

Figure 1 The approaches. A: Transabdominal approach; B: Transthoracic approach.



DOI: 10.4240/wjgs.v15.i9.1986 **Copyright** ©The Author(s) 2023.

Figure 2 Survival function diagram of the two patient groups.

Statistical analysis

Statistical analysis was performed using SPSS 21.0 software. Measurement data such as duration of surgery, length of hospital stay, and bleeding volume were expressed as mean and standard deviation (x ± s) for both groups. The *t*-test was used to compare the two groups. The χ^2 test was used to compare the counting data of the groups. The Kaplan-Meier method was used for survival analysis. Statistical significance was set at $P < 0.05$.

RESULTS

Comparison of the durations of surgery of the patient groups

The durations of surgery, lengths of hospital stay, and postoperative drainage durations of patients in group A were shorter than those in group B. Bleeding caused by surgery was lower in group A than in group B ($P < 0.05$), and there was no statistically significant difference in the positive incision margin rate between the patients in groups A and B ($P > 0.05$) (Table 1).

Comparison of lymph node dissection in the two groups

There were no statistically significant differences in the number of cleared lymph nodes, positive lymph nodes, lower mediastinal lymph nodes, subdiaphragmatic lymph nodes, or abdominal lymph nodes between groups A and B ($P > 0.05$) (Table 2).

Table 1 Comparison of operation time between two groups of patients

Group	*n*	Operation time (min)	Bleeding volume (mL)	Positive rate of cutting edge (%)	Postoperative drainage time (d)	Postoperative landing time (h)	Length of stay (d)
A group	70	168.1 ± 15.7	136.8 ± 36.1	1 (1.43)	3.71 ± 0.84	27.81 ± 7.51	12.30 ± 2.13
B group	68	188.0 ± 19.3	188.2 ± 43.7	3 (4.41)	4.40 ± 1.22	29.40 ± 7.82	13.54 ± 2.35
t/χ^2		-6.653	-7.542	1.091	-3.879	-1.218	-3.250
P value		0.000	0.000	0.296	0.000	0.225	0.001

Table 2 Comparison of lymph node dissection effect between two groups of patients (mean ± SD, number)

Group	*n*	Number of lymph nodes cleaned	Number of positive lymph nodes	Inferior mediastinal lymph nodes	Subphrenic lymph node	Number of abdominal lymph nodes
A group	70	33.87 ± 3.82	3.65 ± 1.20	3.81 ± 1.20	2.56 ± 0.72	27.50 ± 2.95
B group	68	34.33 ± 2.90	3.92 ± 1.53	4.03 ± 1.15	2.74 ± 0.75	27.56 ± 3.02
t value		-0.795	-1.155	-1.099	-1.438	-0.118
P value		0.428	0.250	0.274	0.153	0.906

Comparison of changes in pulmonary function in the two groups

The preoperative values of FEV1, MVV, FVC, and VC for the patients in groups A and B were not significantly different ($P > 0.05$). However, the values obtained during the review conducted one month after surgery showed higher percentages of FEV1, MVV, FVC, and VC relative to their expected values for group A than for group B ($P < 0.05$) (Table 3).

Comparison of the quality of the survival scores for the two groups

Before surgery, the QLQ-OES18 scores of patients in groups A and B were compared, and the difference was not statistically significant ($P > 0.05$). When re-evaluated 3 mo after surgery, the QLQ-OES18 scores for the patients in group A were higher than those for the patients in group B ($P < 0.05$) (Table 4).

Comparison of the complication rates of the two groups

The surgical complication rate of 10.00% for group A was lower than that of 23.53% for group B ($P < 0.05$; Table 5).

Comparison of the prognoses of the two groups of patients

After 3 years of postoperative follow-up, there was no statistically significant difference in the survival rate of 35.71% for group A relative to 29.41% for group B ($P > 0.05$) (Table 6).

The median duration of survival was 30.0 mo for the patients in group A and 29.0 mo for those in group B. The difference between the two groups was not statistically significant ($P > 0.05$) (Figure 2).

DISCUSSION

Adenocarcinoma of the esophagogastric junction is considered a special type of tumor because of its anatomical location and physiological function. It is independent of esophageal and gastric cancers and is more common in patients with Siewert II and III types[8]. Surgery for adenocarcinoma of the esophagogastric junction is usually performed by a gastrointestinal or thoracic surgeon or both. However, the choice of surgical approach for the Siewert II type has not been established. The advantage of combined thoracoabdominal therapy for adenocarcinoma of the esophagogastric junction is that it allows for complete dissection of the abdominal and mediastinal lymph nodes. However, this surgical approach is more invasive, increases the risk of surgery, and does not significantly improve the long-term survival of patients; therefore, most scholars recommend the transthoracic or transabdominal approach[9]. The advantage of the transthoracic approach is that it can completely expose the structures and tissues of the esophagus and cardia; however, exposure of the tissues near the distal stomach and spleen is poor. The transabdominal approach can fully expose the abdomen and facilitate the dissection of the abdominal lymph node; however, exposure to the distal esophagus is poor[9-11].

The duration of surgery and the severity of intraoperative blood loss are lateral reflections of surgical trauma and are interrelated[12]. Less intraoperative bleeding ensures less obstruction of the surgical field and a shorter duration of

Table 3 Comparison of pulmonary function parameters between two groups of patients (mean ± SD)

Group	*n*	Preoperative	1 mo after operation	*t* value	*P* value	Preoperative	1 mo after operation	*t* value	*P* value
		FEV1 (%)				MVV (%)			
A group	70	95.66 ± 8.64	90.21 ± 8.50	3.734	0.000	98.16 ± 9.26	93.48 ± 9.11	2.992	0.003
B group	68	97.03 ± 8.11	86.30 ± 7.76	7.937	0.000	96.32 ± 8.58	88.75 ± 8.36	5.248	0.000
t value		-0.960	2.820			1.210	3.175		
P value		0.339	0.006			0.228	0.002		
		FVC (%)				VC (%)			
A group	70	97.34 ± 8.14	92.36 ± 6.06	4.067	0.000	93.06 ± 4.85	90.01 ± 4.43	3.854	0.000
B group	68	99.03 ± 7.93	89.51 ± 7.24	7.359	0.000	94.41 ± 5.00	88.26 ± 5.25	7.048	0.000
t value		-1.235	2.510			-1.610	2.119		
P value		0.219	0.013			0.11	0.036		

FEV1: First second; MVV: Maximum ventilation volume; FVC: Forceful lung volume; VC: Lung volume.

Table 4 Comparison of quality of life scores between the two groups (mean ± SD, scores)

Group	*n*	Preoperative	3 mo after operation	*t* value	*P* value
A group	70	31.83 ± 6.60	43.09 ± 5.57	-10.816	0.000
B group	68	30.50 ± 5.78	40.14 ± 5.42	-10.100	0.000
t value		1.258	3.152		
P value		0.211	0.002		

Table 5 Comparison of complication rates between the two groups

Group	*n*	Pulmonary infection	Abdominal infection	Anastomotic fistula	Pyothorax	Incision infection	Pleural effusion	Complication rate (%)
A group	70	1	2	1	0	1	2	7 (10.00)
B group	68	7	0	3	2	1	3	16 (23.53)
χ^2								4.546
P value								0.033

Table 6 Survival comparison

Group	*n*	Subsist	Die
A group	70	25 (35.71)	45 (64.29)
B group	68	20 (29.41)	48 (70.59)
χ^2		0.623	
P value		0.430	

bleeding. The results of this study showed that the duration of surgery, length of hospital stay, and postoperative drainage of the patients in group A were shorter than those of the patients in group B. The blood loss during surgery was significantly lower for Group A than for Group B. This indicates that the transabdominal is less traumatic than the transthoracic approach. The pectoral muscle or the rib cage of the patient needs to be severed to expose the left side of the chest cavity, which is rich in intercostal vessels, and bleeding can easily occur when opening the chest. The transabdominal approach, which involves entering the abdominal cavity through the white line of the abdomen, results in less severe blood loss and a shorter duration of surgery. However, it is difficult to expose the organs and lymph nodes in the

abdominal cavity, the scope of surgery is relatively small, the duration of surgery is prolonged, and intraoperative bleeding and duration of surgery may be further prolonged if adhesions and anatomical abnormalities are present in the abdominal cavity during exposure. The results of this study showed no statistically significant difference in the positive margin rate between the two groups, indicating that the outcomes of the two surgical approaches were comparable. Complete removal of regional lymph nodes is a key factor for the long-term survival of patients with Siewert type II adenocarcinoma of the esophagogastric junction and helps improve the long-term survival of patients during the progressive stage[13]. Studies have shown[14-18] that lymph node metastases are more likely to metastasize to the abdominal cavity than to the thoracic cavity in patients with type II esophagogastric junction cancer. Therefore, more attention should be paid to the removal of abdominal lymph nodes during surgery for type II esophagogastric junction cancer. In this study, there were no statistically significant differences in the number of removed lymph nodes, positive lymph nodes, lower mediastinal lymph nodes, subdiaphragmatic lymph nodes, or abdominal lymph nodes between the two groups. Increased attention of the surgeon combined with the use of laparoscopy and other techniques has resulted in no significant difference in the number of positive lymph node dissections associated with the current transabdominal and transthoracic approaches.

FEV1, MVV, FVC, and VC, expressed as percentages of the expected values, were higher for group A than for group B. Both groups showed different degrees of decline. Owing to the residual effects of general anesthesia, early postoperative pain, and the use of a chest strap, chest compliance decreased, and respiratory function decreased. The differences in postoperative pulmonary function associated with the two surgical approaches in this study were mainly attributed to the transabdominal approach through the right anterolateral incision, which maintained the integrity of the diaphragm during open thoracotomy with relatively little damage to the chest wall muscles. In addition, a shorter duration of surgery of the thoracic cavity resulted in less interference with the lung tissue. The transthoracic approach caused more severe damage to the chest wall muscles, impairment of the diaphragmatic integrity, greater interference with the lung tissue, and a greater deterioration of lung function. Group A had a significantly lower rate of surgical complications than group B. The transthoracic approach may have disrupted the normal muscles of the chest during the left thoracic incision, requiring incision and re-suturing of the diaphragm and damaging the respiratory muscles; this was detrimental to postoperative sputum expulsion and affected respiratory function. The intraoperative collapse of the left lung; ventilation of the right lung; intra-thoracic surgical involvement and compression of the lung tissue, heart, and blood vessels; and postoperative chest tube placement increase the inflammatory response in the thoracic cavity. Transthoracic surgery destroys the intercostal nerves of the patient, results in more severe postoperative pain than abdominal surgery, and is more likely to result in sputum accumulation. As a result, the incidence of pulmonary complications was higher for group B, which may have led to longer postoperative hospital stays. Patients in group A had higher QLQ-OES18 scores than those in group B when re-evaluated 3 mo postoperatively. Patients who underwent surgery with the transabdominal approach had a better prognosis. The 3-year postoperative follow-up evaluation revealed no statistically significant differences between the survival rates and median durations of survival of the two groups. The results of this study are consistent with those of previous studies[3,19-23], showing that the treatment of Siewert II esophagogastric junction cancer through the left thorax and abdomen is equally reliable.

Current clinical studies on the treatment of combined esophagogastric cancer mainly compare the efficacies and adverse effects of the different approaches[24-27]; they less frequently focus on the changes in the parameters of pulmonary function. In this study, the clinical outcomes, lymph node removal, and lung function recovery of patients with combined oesophagogastric cancer treated using transabdominal and transthoracic surgical approaches were studied comprehensively. This was more conducive to finding a more advantageous surgical approach. There were some limitations and shortcomings in the design of this study. It was a single-center retrospective study with a short duration of follow-up. Therefore, the results need to be confirmed by prospective, multicenter, randomized controlled clinical studies.

CONCLUSION

Transabdominal and transthoracic surgical approaches for the treatment of combined esophagogastric cancer are comparable. However, the former has the advantages of milder surgical trauma, less impact on pulmonary function, and fewer complications. Thus, it is suitable for older patients with frailty, cardiopulmonary insufficiency, or more complicated diseases.

ARTICLE HIGHLIGHTS

Research background

Different types of esophagogastric junction adenocarcinoma have different operation methods.

Research motivation

We need to determine the optimal surgical approach for Siewert II adenocarcinoma of the esophagogastric junction to improve lung function and the prognosis of patients.

Research objectives
To investigate and compare the surgical effects, postoperative changes in pulmonary function, and prognoses of two approaches to treating combined esophagogastric cancer.

Research methods
Patients with esophageal gastric cancer who received combined treatment in our hospital were selected, and the relevant indicators were compared after grouping.

Research results
The transabdominal approach has the advantages of less trauma, less impact on lung function and fewer complications.

Research conclusions
Transabdominal surgical approaches is suitable for older patients with frailty, cardiopulmonary insufficiency, or more complicated diseases.

Research perspectives
It was a single-center retrospective study with a short duration of follow-up. Therefore, the results need to be confirmed by prospective, multicenter, randomized controlled clinical studies.

FOOTNOTES

Author contributions: Sun CB and Liu YN designed the research study; Sun CB, Han XQ and Wang H performed the research; Zhang YX contributed new reagents and analytic tools; Wang MC and Sun CB analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Weifang People's Hospital Institutional Review Board, No. AF/SQ-01/01.0.

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

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

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Chong-Bing Sun 0009-0008-5472-1168; Xiao-Qing Han 0009-0003-9739-8317; Hao Wang 0009-0006-3007-9516; Yi-Xuan Zhang 0009-0002-5501-965X; Meng-Chun Wang 0009-0009-9127-8318; Yong-Ning Liu 0009-0000-7926-3265.

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

REFERENCES

1 **Chevallay M**, Bollschweiler E, Chandramohan SM, Schmidt T, Koch O, Demanzoni G, Mönig S, Allum W. Cancer of the gastroesophageal junction: a diagnosis, classification, and management review. *Ann N Y Acad Sci* 2018; **1434**: 132-138 [PMID: 30138540 DOI: 10.1111/nyas.13954]

2 **Türeci O**, Sahin U, Schulze-Bergkamen H, Zvirbule Z, Lordick F, Koeberle D, Thuss-Patience P, Ettrich T, Arnold D, Bassermann F, Al-Batran SE, Wiechen K, Dhaene K, Maurus D, Gold M, Huber C, Krivoshik A, Arozullah A, Park JW, Schuler M. A multicentre, phase IIa study of zolbetuximab as a single agent in patients with recurrent or refractory advanced adenocarcinoma of the stomach or lower oesophagus: the MONO study. *Ann Oncol* 2019; **30**: 1487-1495 [PMID: 31240302 DOI: 10.1093/annonc/mdz199]

3 **Kumamoto T**, Kurahashi Y, Niwa H, Nakanishi Y, Okumura K, Ozawa R, Ishida Y, Shinohara H. True esophagogastric junction adenocarcinoma: background of its definition and current surgical trends. *Surg Today* 2020; **50**: 809-814 [PMID: 31278583 DOI: 10.1007/s00595-019-01843-4]

4 **Urabe M**, Matsusaka K, Ushiku T, Fukuyo M, Rahmutulla B, Yamashita H, Seto Y, Fukayama M, Kaneda A. Adenocarcinoma of the stomach and esophagogastric junction with low DNA methylation show poor prognoses. *Gastric Cancer* 2023; **26**: 95-107 [PMID: 36224483 DOI:

10.1007/s10120-022-01344-3]
5 **Manabe N**, Matsueda K, Haruma K. Epidemiological Review of Gastroesophageal Junction Adenocarcinoma in Asian Countries. *Digestion* 2022; **103**: 29-36 [PMID: 34718236 DOI: 10.1159/000519602]
6 **Treese C**, Hartl K, Pötzsch M, Dahlmann M, von Winterfeld M, Berg E, Hummel M, Timm L, Rau B, Walther W, Daum S, Kobelt D, Stein U. S100A4 Is a Strong Negative Prognostic Marker and Potential Therapeutic Target in Adenocarcinoma of the Stomach and Esophagus. *Cells* 2022; **11** [PMID: 35326507 DOI: 10.3390/cells11061056]
7 **Zhang CD**, Takeshima H, Sekine S, Yamashita S, Liu YY, Hattori N, Abe H, Yamashita H, Fukuda M, Imamura Y, Ushiku T, Katai H, Makino H, Watanabe M, Seto Y, Ushijima T. Prediction of tissue origin of adenocarcinomas in the esophagogastric junction by DNA methylation. *Gastric Cancer* 2022; **25**: 336-345 [PMID: 34557982 DOI: 10.1007/s10120-021-01252-y]
8 **Jung MK**, Schmidt T, Chon SH, Chevallay M, Berlth F, Akiyama J, Gutschow CA, Mönig SP. Current surgical treatment standards for esophageal and esophagogastric junction cancer. *Ann N Y Acad Sci* 2020; **1482**: 77-84 [PMID: 32798235 DOI: 10.1111/nyas.14454]
9 **Suhara H**, Hirooka Y, Kawashima H, Ohno E, Ishikawa T, Nakamura M, Miyahara R, Ishigami M, Hashimoto S, Goto H. Transabdominal ultrasound elastography of the esophagogastric junction predicts reflux esophagitis. *J Med Ultrason (2001)* 2019; **46**: 99-104 [PMID: 30043241 DOI: 10.1007/s10396-018-0890-1]
10 **Dai Z**, Lang W, Yang H, Tian J, Sun W, Pekbay B, Lin Y, Wang M, Cui B, Yang S, Li H, Luo L, Guo H, Zhang L. Validation of EORTC QLQ-OES18 for Chinese patients with esophageal cancer. *Dis Esophagus* 2017; **30**: 1-7 [PMID: 28859386 DOI: 10.1093/dote/dox046]
11 **DeCarlo C**, Manxhari C, Boitano LT, Mohebali J, Schwartz SI, Eagleton MJ, Conrad MF. Transabdominal approach associated with increased long-term laparotomy complications after open abdominal aortic aneurysm repair. *J Vasc Surg* 2021; **73**: 1603-1610 [PMID: 33080323 DOI: 10.1016/j.jvs.2020.08.154]
12 **Trevellin E**, Pirozzolo G, Fassan M, Vettor R. Prognostic value of stem cell markers in esophageal and esophagogastric junction cancer: a meta-analysis. *J Cancer* 2020; **11**: 4240-4249 [PMID: 32368307 DOI: 10.7150/jca.33699]
13 **Ajani JA**, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P, Denlinger CS, Enzinger PC, Fanta P, Farjah F, Gerdes H, Gibson M, Glasgow RE, Hayman JA, Hochwald S, Hofstetter WL, Ilson DH, Jaroszewski D, Johung KL, Keswani RN, Kleinberg LR, Leong S, Ly QP, Matkowskyj KA, McNamara M, Mulcahy MF, Paluri RK, Park H, Perry KA, Pimiento J, Poultsides GA, Roses R, Strong VE, Wiesner G, Willett CG, Wright CD, McMillian NR, Pluchino LA. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2019; **17**: 855-883 [PMID: 31319389 DOI: 10.6004/jnccn.2019.0033]
14 **van Workum F**, Verstegen MHP, Klarenbeek BR, Bouwense SAW, van Berge Henegouwen MI, Daams F, Gisbertz SS, Hannink G, Haveman JW, Heisterkamp J, Jansen W, Kouwenhoven EA, van Lanschot JJB, Nieuwenhuijzen GAP, van der Peet DL, Polat F, Ubels S, Wijnhoven BPL, Rovers MM, Rosman C; ICAN collaborative research group. Intrathoracic *vs* Cervical Anastomosis After Totally or Hybrid Minimally Invasive Esophagectomy for Esophageal Cancer: A Randomized Clinical Trial. *JAMA Surg* 2021; **156**: 601-610 [PMID: 33978698 DOI: 10.1001/jamasurg.2021.1555]
15 **Lee Y**, Min SH, Park KB, Park YS, Ahn SH, Park DJ, Kim HH. Long-term Outcomes of Laparoscopic Versus Open Transhiatal Approach for the Treatment of Esophagogastric Junction Cancer. *J Gastric Cancer* 2019; **19**: 62-71 [PMID: 30944759 DOI: 10.5230/jgc.2019.19.e1]
16 **Berlth F**, Hoelscher AH. History of Esophagogastric Junction Cancer Treatment and Current Surgical Management in Western Countries. *J Gastric Cancer* 2019; **19**: 139-147 [PMID: 31245158 DOI: 10.5230/jgc.2019.19.e18]
17 **Hoshino I**, Gunji H, Ishige F, Iwatate Y, Takiguchi N, Ikeda A, Soda H, Tonooka T, Sato N, Kawahara K, Nabeya Y. Surgical treatment strategy for esophagogastric junction cancers based on the tumor diameter. *BMC Surg* 2019; **19**: 152 [PMID: 31651313 DOI: 10.1186/s12893-019-0614-5]
18 **Shinohara H**, Haruki S, Ohata Y, Ueda H, Arita K, Ito K, Matsumoto A, Takiguchi N. [A Case of Advanced Esophagogastric Junction Cancer Responding to Combined Modality Therapy]. *Gan To Kagaku Ryoho* 2020; **47**: 466-468 [PMID: 32381917]
19 **Pericay C**, Macías-Declara I, Arrazubi V, Vilà L, Marín M. Treatment in esophagogastric junction cancer: Past, present and future. *Cir Esp (Engl Ed)* 2019; **97**: 459-464 [PMID: 31155142 DOI: 10.1016/j.ciresp.2019.03.016]
20 **Hosoda K**, Yamashita K, Tsuruta H, Moriya H, Mieno H, Ema A, Washio M, Watanabe M. Prognoses of advanced esophago-gastric junction cancer may be modified by thoracotomy and splenectomy. *Oncol Lett* 2018; **15**: 1200-1210 [PMID: 29399174 DOI: 10.3892/ol.2017.7441]
21 **Takada K**, Yabuuchi Y, Yamamoto Y, Yoshida M, Kawata N, Takizawa K, Kishida Y, Ito S, Imai K, Hotta K, Ishiwatari H, Matsubayashi H, Kawabata T, Ono H. Predicting the depth of superficial adenocarcinoma of the esophagogastric junction. *J Gastroenterol Hepatol* 2022; **37**: 363-370 [PMID: 34820917 DOI: 10.1111/jgh.15741]
22 **Thompson ED**, Zahurak M, Murphy A, Cornish T, Cuka N, Abdelfatah E, Yang S, Duncan M, Ahuja N, Taube JM, Anders RA, Kelly RJ. Patterns of PD-L1 expression and CD8 T cell infiltration in gastric adenocarcinomas and associated immune stroma. *Gut* 2017; **66**: 794-801 [PMID: 26801886 DOI: 10.1136/gutjnl-2015-310839]
23 **Chen Y**, Hu L, Lin H, Yu H, You J. Serum metabolomic profiling for patients with adenocarcinoma of the esophagogastric junction. *Metabolomics* 2022; **18**: 26 [PMID: 35441991 DOI: 10.1007/s11306-022-01883-x]
24 **Zheng YH**, Zhao EH. Recent advances in multidisciplinary therapy for adenocarcinoma of the esophagus and esophagogastric junction. *World J Gastroenterol* 2022; **28**: 4299-4309 [PMID: 36159003 DOI: 10.3748/wjg.v28.i31.4299]
25 **Tang Z**, Wang Y, Liu D, Wang X, Xu C, Yu Y, Cui Y, Tang C, Li Q, Sun J, Zhang Q, Ji Y, Ma G, Li H, Shen Z, Shen K, Zheng R, Hou Z, Liu T, Wang J, Sun Y. The Neo-PLANET phase II trial of neoadjuvant camrelizumab plus concurrent chemoradiotherapy in locally advanced adenocarcinoma of stomach or gastroesophageal junction. *Nat Commun* 2022; **13**: 6807 [PMID: 36357415 DOI: 10.1038/s41467-022-34403-5]
26 **Rice TW**, Lu M, Ishwaran H, Blackstone EH; Worldwide Esophageal Cancer Collaboration Investigators. Precision Surgical Therapy for Adenocarcinoma of the Esophagus and Esophagogastric Junction. *J Thorac Oncol* 2019; **14**: 2164-2175 [PMID: 31442498 DOI: 10.1016/j.jtho.2019.08.004]
27 **Kumar NA**, Desouza A, Bhandare MS, Murugan JR, Khandelwal G, Chaudhari V, Ostwal V, Shrikhande SV. Curative resection for adenocarcinoma of the gastro-esophageal junction following neo-adjuvant chemotherapy-thoraco-abdominal vs. trans-abdominal approach. *Langenbecks Arch Surg* 2021; **406**: 613-621 [PMID: 33242137 DOI: 10.1007/s00423-020-02020-9]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 1995-2002

DOI: 10.4240/wjgs.v15.i9.1995

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Clinical significance of serum oxidative stress and serum uric acid levels before surgery for hepatitis B-related liver cancer

Jin-Xia Hou, Yu-Bin Wang, Jing Wu, Guo-sheng Ding, Yang Wu, Lian-Hua Wei, Fang Wang, Zhe-Mei Zhang

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Napolitano M, Italy; Thakur U, India

Received: June 6, 2023
Peer-review started: June 6, 2023
First decision: June 21, 2023
Revised: June 30, 2023
Accepted: July 26, 2023
Article in press: July 26, 2023
Published online: September 27, 2023

Jin-Xia Hou, Yu-Bin Wang, Jing Wu, Guo-sheng Ding, Yang Wu, Lian-Hua Wei, Fang Wang, Zhe-Mei Zhang, Department of Clinical Laboratory, Gansu Provincial Hospital, Gansu Provincial Clinical Research Center for Laboratory Medicine, Lanzhou 730000, Gansu Province, China

Corresponding author: Zhe-Mei Zhang, MBBS, Associate Chief Physician, Department of Clinical Laboratory, Gansu Provincial Hospital, Gansu Provincial Clinical Research Center for Laboratory Medicine, No. 204 Donggang West Road, Chengguan District, Lanzhou 730000, Gansu Province, China. zhangzm1122@126.com

Abstract

BACKGROUND

The incidence and mortality of liver cancer are among the highest of all malignant tumors in China. The high recurrence rate after conventional hepatectomy is worrying. There is a lack of effective prognostic indicators for liver cancer.

AIM

To explore the clinical significance of preoperative serum oxidative stress and serum uric acid (UA) levels in hepatitis B-related liver cancer.

METHODS

The medical records of 110 hepatitis B-related liver cancer patients who underwent hepatectomy in Gansu Provincial Hospital were retrospectively analyzed. Recurrence in patients within 3 years after surgery was determined. The logistic regression model and Pearson or Spearman correlation were used to analyze the correlation between oxidative stress level and UA, and the recurrence of hepatitis B-related liver cancer.

RESULTS

Compared with the non-recurrence group, the levels of superoxide dismutase (SOD) and glutathione (GSH) in the recurrence group were lower and the levels of malondialdehyde (MDA) and UA were higher (all $P < 0.05$). UA, SOD, MDA, and GSH were risk factors for postoperative recurrence in hepatitis B-related liver cancer patients ($P < 0.05$). UA was positively correlated with MDA ($r = 0.395$, $P < 0.001$) and negatively correlated with GSH ($r = -0.204$, $P = 0.032$). The area under the receiver operating characteristic curve (AUC) of SOD, MDA, GSH, and UA in predicting the prognosis was 0.276, 0.910, 0.199, and 0.784, respectively (all $P < 0.001$).

CONCLUSION
The preoperative serum SOD, GSH, MDA, and UA levels had significant predictive effects on postoperative recurrence of hepatitis B-related liver cancer.

Key Words: Hepatitis B; Liver cancer; Serum oxidative stress; Serum uric acid; Recurrence; Correlation

Core Tip: Hepatitis B-related liver cancer is characterized by high morbidity and mortality. Conventional surgery results in a poor prognosis and a high recurrence rate of liver cancer. In this study, we analyzed the clinical data of 110 patients with hepatitis B-related liver cancer who underwent hepatectomy and determined recurrence within three years after surgery. The correlation between preoperative serum oxidative stress level and serum uric acid, and recurrence of hepatitis B-related liver cancer was assessed. These findings provide a breakthrough in prognostic evaluation indicators of liver cancer.

Citation: Hou JX, Wang YB, Wu J, Ding GS, Wu Y, Wei LH, Wang F, Zhang ZM. Clinical significance of serum oxidative stress and serum uric acid levels before surgery for hepatitis B-related liver cancer. *World J Gastrointest Surg* 2023; 15(9): 1995-2002
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/1995.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.1995

INTRODUCTION

The incidence and mortality rate of liver cancer, also known as primary liver cancer, are among the highest of all malignant tumors in China, and is a serious threat to the health and life of our residents[1]. Hepatitis B virus (HBV) is the leading cause of hepatocellular carcinoma (HCC), which accounts for 90% of all liver cancers[2]. According to the data, more than 50% of HCCs worldwide are caused by HBV infection[3]. The HBV can change the genes in liver cells and cause liver lesions, thus inducing cirrhosis and even liver cancer (hepatitis B-related liver cancer)[4]. At present, hepatectomy is an important treatment for liver cancer, but the prognosis of patients after surgery is not ideal. The recurrence rate of HCC after surgery is as high as 70%[5]. Therefore, early improvement of the condition and prognosis of liver cancer is a hot research topic. Oxidative stress injury is involved in the process of liver fibrosis, thereby promoting disease progression[6]. Serum uric acid (UA) in critically ill patients is closely related to oxidative stress[7]. Thus, we speculate that there may be a relationship between preoperative oxidative stress and UA, and liver cancer prognosis, and could be used to assess the patient's condition and prognosis to guide clinical intervention. In addition, following a literature review, we found that there are few studies on the effects of oxidative stress and UA on the prognosis of HCC. Both these parameters may provide a breakthrough in the study of liver cancer prognosis evaluation indicators. Therefore, we analyzed oxidative stress, UA, and recurrence in hepatitis B-related liver cancer patients who underwent hepatectomy, to identify a simple and effective index for evaluation of the condition and recurrence of the disease, to improve the level of treatment.

MATERIALS AND METHODS

Materials

Hepatitis B-related liver cancer patients who underwent hepatectomy in Gansu Provincial Hospital from January 2016 to March 2019 were retrospectively analyzed. The inclusion criteria were: (1) Postoperative pathology confirmed HCC[8]; (2) Liver cancer in patients was caused by hepatitis B; and (3) The medical records, related indicators and follow-up data were complete. The exclusion criteria were: (1) Liver cancer combined with other tumors; (2) Patients who had received radiofrequency ablation, transcatheter arterial chemoembolization, molecularly targeted drugs, immune checkpoint inhibitors, and other anti-tumor treatment; and (3) Combined systemic infection.

Data collection

The clinicopathological features included age, gender, hepatitis B surface antigen, TNM stage, tumor diameter, tumor differentiation, lymph node metastasis, tumor number, and alpha-fetoprotein. Serum oxidative stress indices, superoxide dismutase (SOD), malondialdehyde (MDA), and glutathione (GSH) were determined in addition to UA level.

Surgery and detection methods

The patients were treated with hepatectomy under general anesthesia. The size and volume of the liver were determined according to preoperative imaging data. According to the primary site of HCC, the tumor, and the surrounding blood vessels, the patients were reasonably selected for local hepatectomy, segmental hepatectomy, lobectomy, hemihepatectomy, and other surgical treatment. According to the intraoperative situation, the Pringle method was used to block

the hepatic portal system, 5 min each time.

SOD, MDA, and GSH levels were detected by chemical colorimetry, and UA level was detected by the uricase method.

Follow-up indicators

The recurrence data in the outpatient or inpatient system were reviewed. The last visit record or telephone follow-up record was used as the follow-up result to collect information on tumor recurrence within 3 years after surgery. Patients lost to follow-up or death were defined as censored.

Statistical analysis

SPSS 17.0 was used to process the data. The data were described by mean ± SD, cases or percentages (%), and the differences between groups were tested by the *t*-test or chi-square test. Multiple factors were analyzed with a logistic regression model, and Pearson or Spearman correlation analysis was used for bivariate correlation analysis. The predictive ability was analyzed by the receiver operating characteristic (ROC) curve. A P value > 0.05 was considered statistically significant.

RESULTS

Clinicopathological features of the recurrence group and non-recurrence group

In total, 110 patients were enrolled, including 69 recurrent patients (recurrence group) and 41 non-recurrent patients (non-recurrence group). In comparison with the non-recurrence group, the proportion of patients with TNM stage III-IV (59.42% *vs* 26.83%), high tumor differentiation (56.52% *vs* 31.71%), and lymph node metastasis (43.48% *vs* 21.95%) was high in the recurrence group ($P < 0.05$) (Table 1).

Oxidative stress level and UA level between the two groups

Compared with the non-recurrence group, the levels of SOD (41.26 kU/L ± 7.01 kU/L *vs* 46.82 kU/L ± 6.12 kU/L) and GSH (29.40 kU/L ± 7.92 kU/L *vs* 39.44 kU/L ± 8.90 kU/L) were lower in the recurrence group, and the levels of MDA (5.78 nmol/L ± 0.92 nmol/L *vs* 4.18 nmol/L ± 0.82 μmol/L) and UA (376.27 μmol/L ± 82.90 μmol/L *vs* 281.36 μmol/L ± 84.86 μmol/L) were higher ($P < 0.05$) (Table 2).

Analysis of recurrence risk factors

The clinicopathological features (including TNM stage, tumor differentiation, lymph node metastasis), serum oxidative stress level, and UA level as the independent variables and recurrence (0 = no recurrence, 1 = recurrence) as the dependent variable were incorporated into the logistic regression model. It was shown that UA (Exp (B) = 5.899, P = 0.019], SOD [Exp (B) = 0.844, P = 0.043], MDA [Exp (B) = 11.465, P = 11.465], and GSH [Exp (B) = 0.889, P = 0.029] were risk factors for postoperative recurrence ($P < 0.05$) (Table 3).

Analysis of the relationship between the risk factors

SOD was negatively correlated with the TNM stage and lymph node metastasis (r = -0.203, -0.219; P = 0.033, 0.021). MDA was positively correlated with the TNM stage and lymph node metastasis (r = 0.275, 0.216; P = 0.004, 0.024). GSH was negatively correlated with lymph node metastasis (r = -269; P = 0.004). UA showed no correlation with SOD (r = -0.185, P = 0.053). UA was positively correlated with MDA (r = 0.395, $P < 0.001$) (Figure 1A), and negatively correlated with GSH (r = -0.204, P = 0.032) (Figure 1B).

AUC evaluated predictive power

AUC of SOD, MDA, GSH, and UA in predicting postoperative recurrence was 0.276 [95% confidence interval (95%CI): 0.179-0.373], 0.910 (95%CI: 0.858-0.963), 0.199 (95%CI: 0.110-0.288), and 0.784 (95%CI: 0.697-0.871), respectively, all $P <$ 0.001 (Table 4, Figure 2).

DISCUSSION

Chronic HBV infection is closely related to HCC, and deterioration of chronic HBV infection can lead to liver cancer[9]. Early effective diagnosis is of great significance for improving prognosis and reducing recurrence. Clinically, an ultrasound examination is used for early diagnosis. However, abdominal B-ultrasound requires a high level of operation and is highly subjective[10]. Therefore, the identification of effective diagnostic indicators to improve the diagnosis of HBV-related liver cancer is urgently needed.

This study found that compared with patients without recurrence, the levels of SOD and GSH in patients with recurrence were lower, and the levels of MDA and UA were higher. SOD, GSH, MDA, and UA were closely related to postoperative recurrence, which was similar to the results of related studies[11]. It is suggested that the antioxidant capacity of patients with postoperative recurrence is low, and the oxidative stress response of tissues and organs is strong. Oxidative stress occurs throughout the process of liver fibrosis. Oxidative stress is considered to be the most critical factor in the transition from simple fatty liver to nonalcoholic steatohepatitis[12]. SOD and GSH are important

Table 1 Comparison of clinicopathological features between the recurrence group and non-recurrence group, *n* (%)

Groups	Recurrence group (*n* = 69)	Non-recurrence group (*n* = 41)	*t* value	*P* value
Age (mean ± SD, yr)	54.63 ± 15.58	55.10 ± 15.29		
Gender			3.497	0.061
Men	40 (57.97)	31 (75.61)		
Female	29 (42.03)	10 (24.39)		
HbsAg			0.313	0.576
Negative	22 (31.88)	11 (26.83)		
Positive	47 (68.12)	30 (73.17)		
TNM staging			10.959	0.001
Stage I-II	28 (40.58)	30 (73.17)		
Stage III-IV	41 (59.42)	11 (26.83)		
Tumor diameter			0.979	0.323
< 5 cm	27 (39.13)	20 (48.78)		
≥ 5 cm	42 (60.87)	21 (51.22)		
Degree of tumor differentiation			6.353	0.012
Low differentiation	30 (43.48)	28 (68.29)		
High differentiation	39 (56.52)	13 (31.71)		
Lymph node metastasis			5.208	0.022
Yes	30 (43.48)	9 (21.95)		
No	39 (56.52)	32 (78.05)		
Number of tumors			0.298	0.585
Multiple	44 (63.77)	24 (58.54)		
Single	25 (36.23)	17 (41.46)		
Alpha-fetoprotein (μg/L)			3.137	0.077
< 200	37 (53.62)	29 (70.73)		
≥ 200	32 (46.38)	12 (29.27)		

Table 2 Comparison of preoperative serum oxidative stress level and serum uric acid between the two groups (mean ± SD)

Groups	Oxidative stress			Serum UA (μmol/L)
	SOD (kU/L)	MDA (nmol/L)	GSH (kU/L)	
Recurrence group (*n* = 69)	41.26 ± 7.01	5.78 ± 0.92	29.40 ± 7.92	376.27 ± 82.90
Non-recurrence group (*n* = 41)	46.82 ± 6.12	4.18 ± 0.82	39.44 ± 8.90	281.36 ± 84.86
t value	4.212	9.176	6.137	5.755
P value	< 0.001	< 0.001	< 0.001	< 0.001

SOD: Superoxide dismutase; MDA: Malondialdehyde; GSH: Glutathione; UA: Uric acid.

antioxidants and oxygen-free radical scavengers. MDA, GSH, and SOD are indicators that are usually used to assess the body's ability to produce and save oxygen-free radicals[13]. SOD is a natural superoxide radical. Other enzymes in the body will immediately decompose hydrogen peroxide into harmless water[14]. Therefore, SOD can specifically remove harmful free radicals in the body, in order to remove the damage caused by free radical oxidation of some components in the body. It can be seen that the lower the SOD level, the weaker the body's antioxidant capacity, and the more difficult it is to protect liver cells from oxidative stress injury. The synthesis of GSH can enable cells to escape the damage caused by oxidative stress, so that the cells are in a state of redox balance, thereby preventing cell death induced by lipid peroxidation[15]. The decrease in GSH level in patients with recurrence suggests lipid peroxidation damage, which eventually

Table 3 Multivariate logistic regression analysis of the prognosis of patients with hepatitis B-related liver cancer

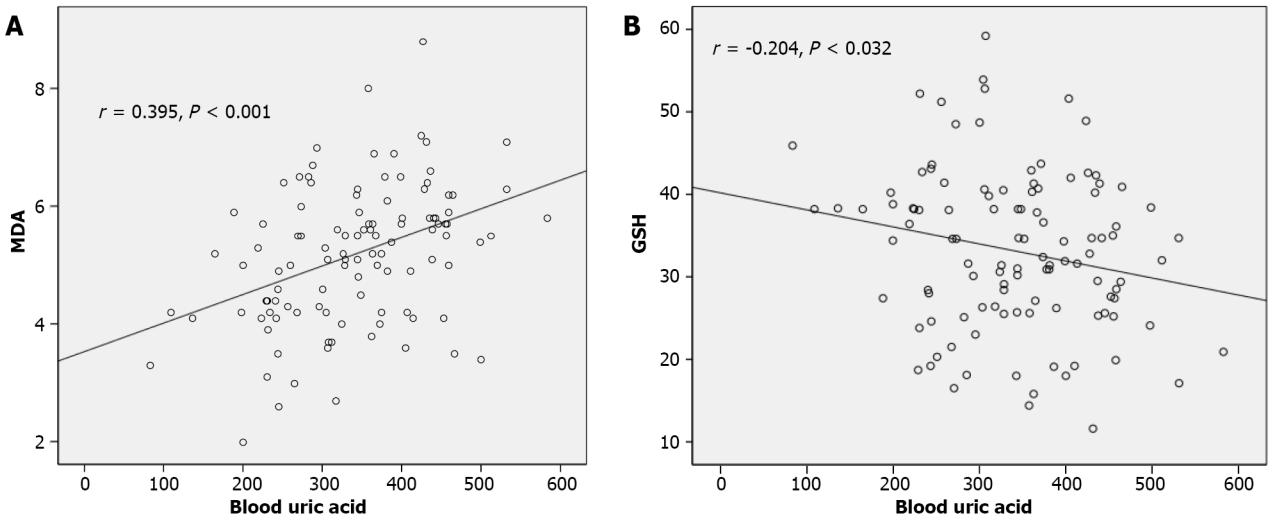
Independent variable	*B*	*S. E*	*Wals*	*P* value	*Exp (B)*	95%CI	
						Lower limit	Upper limit
TNM staging	1.026	0.879	1.361	0.243	2.789	0.498	15.628
Degree of tumor differentiation	1.775	0.914	3.774	0.052	5.899	0.984	35.355
Lymph node metastasis	-1.183	1.005	1.387	0.239	0.306	0.043	2.194
SOD	-0.17	0.084	4.098	0.043	0.844	0.716	0.995
MDA	2.439	0.714	11.676	0.001	11.465	2.83	46.454
GSH	-0.117	0.054	4.74	0.029	0.889	0.8	0.988
Serum UA	0.013	0.005	5.541	0.019	1.013	1.002	1.024

95%CI: 95% confidence interval; SOD: Superoxide dismutase; MDA: Malondialdehyde; GSH: Glutathione; UA: Uric acid.

Table 4 Area under the receiver operating characteristic curve of preoperative serum oxidative stress and serum uric acid levels in predicting prognosis of patients with hepatitis B-related liver cancer

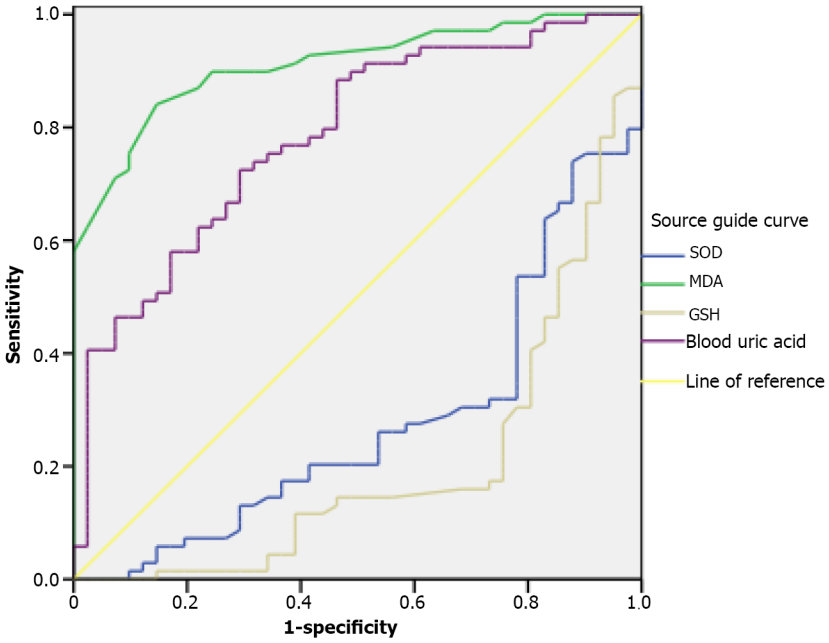
Variable	AUC	Standard error	*P* value	95%CI	
				Lower limit	Upper limit
SOD	0.276	0.050	< 0.001	0.179	0.373
MDA	0.910	0.027	< 0.001	0.858	0.963
GSH	0.199	0.045	< 0.001	0.110	0.288
Serum UA	0.784	0.044	< 0.001	0.697	0.871

95%CI: 95% confidence interval; SOD: Superoxide dismutase; MDA: Malondialdehyde; GSH: Glutathione; UA: Uric acid; AUC: Area under the receiver operating characteristic curve.



DOI: 10.4240/wjgs.v15.i9.1995

Figure 1 Relationship between serum uric acid and malondialdehyde levels and glutathione levels. A: Malondialdehyde levels; B: Glutathione levels; MDA: Malondialdehyde; GSH: Glutathione.



DOI: 10.4240/wjgs.v15.i9.1995

Figure 2 Area under the receiver operating characteristic curve of preoperative serum oxidative stress and serum uric acid levels in predicting prognosis of patients with hepatitis B-related liver cancer. SOD: Superoxide dismutase; MDA: Malondialdehyde; GSH: Glutathione.

leads to hepatocyte necrosis[16,17]. MDA is formed by lipid peroxidation of the membrane, which causes serious damage to the membrane[18]. The more MDA, the more intense the membrane lipid peroxidation. SOD is negatively correlated with MDA, usually after oxidative stress stimulation, SOD decreases and MDA increases[19]. The increase in serum MDA in relapsed patients can indicate that the oxidative stress state of cells is at a higher level, and the decrease in antioxidant capacity of cells indicates a higher possibility of liver injury. UA is mainly a product formed by hydrolysis and oxidation of purine nucleotides. Human purines are mainly derived from liver synthesis or nucleotide degradation (endogenous), the part of purine involved in the formation of UA accounted for 80% of all UA[20]. Several studies have proposed a correlation between UA and primary liver cancer. UA may be used as an auxiliary serological diagnostic indicator and a nutritional assessment indicator for patients with liver cancer[21]. Current conclusions on the relationship between UA and the degree of liver function damage are inconsistent. Our study showed that higher UA is more likely to cause recurrence, similar to the results of related studies[22]. SOD, MDA, GSH, and UA have clinical significance in predicting recurrence in patients. The AUC of MDA and UA was 0.910 and 0.784, respectively. This also shows that preoperative serum oxidative stress levels as well as UA are closely related to the prognosis of hepatitis B-related liver cancer.

There were limitations to this study. We only analyzed the clinicopathological features, oxidative stress level, and blood UA level of patients with and without recurrence of HBP-related liver cancer after surgery and did not analyze other factors, such as the expression levels of WNT1 and WNT2 in cancerous tissues and adjacent tissues, and serum enzymes before surgery. These confounding factors may affect the study results, and further research is required in the future. In addition, this is a retrospective study and selective bias, information bias, and confounding bias may exist. Therefore, prospective randomized controlled trials are needed to verify the findings of this study.

CONCLUSION

The preoperative serum levels of SOD, GSH, MDA, and UA in patients with postoperative recurrence of hepatitis B-related liver cancer were lower, and the preoperative serum levels of SOD, GSH, MDA, and UA were higher. The preoperative serum levels of SOD, GSH, MDA, and UA had a higher predictive effect on postoperative recurrence. However, the small sample size in this study may have led to bias in the results. Future research should be undertaken to explore the optimal prediction thresholds of SOD, MDA, GSH, and UA to further improve the prediction efficiency of postoperative recurrence.

ARTICLE HIGHLIGHTS

Research background

Liver cancer is one of the most common malignant tumors in China and is associated with high morbidity and mortality

rates, which seriously threaten the health and life of Chinese residents. The prognosis following conventional hepatectomy is not ideal, with a recurrence rate of up to 70%.

Research motivation

The purpose of this study was to analyze the correlation between preoperative serum oxidative stress level and serum uric acid (UA), and prognosis in patients with hepatitis B-related liver cancer. This relationship was determined to identify simple and effective evaluation indicators for the assessment of disease condition and prognosis, and to provide data support for clinical improvement of treatment.

Research objectives

To explore the correlation between serum oxidative stress level and serum UA, and prognosis before hepatitis B-related liver cancer recurrence. It was found that serum oxidative stress level and serum UA before hepatitis B-related liver cancer were closely related to prognosis, which is helpful for clinicians to more effectively evaluate prognosis, recurrence and to guide treatment decision-making.

Research methods

The analysis methods used in this study involved a logistic regression model, Pearson analysis, Spearman analysis, and a receiver operating characteristic (ROC) curve, and the analysis target was the correlation between serum oxidative stress level, serum UA, and recurrence of hepatitis B-related liver cancer. The analysis of different research data layer by layer was rigorous and scientific.

Research results

This study found that superoxide dismutase (SOD), glutathione (GSH), malondialdehyde (MDA), and UA were all risk factors for postoperative recurrence in patients with hepatitis B-related liver cancer. Serum UA was positively correlated with MDA and negatively correlated with GSH. MDA and UA can predict the prognosis of patients with hepatitis B-related liver cancer. However, we could not determine the specific mechanism of the effect of these four indicators on postoperative recurrence in patients with hepatitis B-related liver cancer.

Research conclusions

This study found that SOD, GSH, MDA, and UA were all risk factors for postoperative recurrence in patients with hepatitis B-related liver cancer. Furthermore, ROC curve analysis showed that only MDA and UA predicted an AUC above 0.5, which was different to previous studies.

Research perspectives

Future research should include a larger sample and prospectively focus on the specific mechanism of oxidative stress level and UA level on the prognosis of hepatitis B-related liver cancer.

FOOTNOTES

Author contributions: Hou JX contributed to manuscript drafting and revision; Wang YB contributed to study design and data analysis; Hou JX and Wang YB contributed equally to this work and are co-first authors; Zhang ZM provided guiding support; Wu J, Ding GS, and Wu Y collected the data; Wei LH and Wang F sorted the data; all authors have read and approved the final manuscript.

Supported by the Gansu Health Industry Research Plan Project, No. GSWSKY-2019-16; and Lanzhou Science and Technology Development Plan Project, No. 2019-ZD-101.

Institutional review board statement: The study was reviewed and approved by the Gansu Provincial Hospital (Approval No. 2023-288).

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

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

Data sharing statement: Data for this study can be obtained from the corresponding author.

Country/Territory of origin: China

ORCID number: Jin-Xia Hou 0009-0007-0685-0478; Yu-Bin Wang 0009-0003-7393-2853; Jing Wu 0000-0001-6196-0695; Guo-sheng Ding 0009-0003-9159-2936; Yang Wu 0000-0002-2786-5894; Lian-Hua Wei 0000-0001-7194-0292; Fang Wang 0000-0002-4381-9265; Zhe-Mei Zhang 0009-

0008-0094-9212.

S-Editor: Chen YL
L-Editor: A
P-Editor: Chen YL

REFERENCES

1 **Sohn W**, Lee HW, Lee S, Lim JH, Lee MW, Park CH, Yoon SK. Obesity and the risk of primary liver cancer: A systematic review and meta-analysis. *Clin Mol Hepatol* 2021; **27**: 157-174 [PMID: 33238333 DOI: 10.3350/cmh.2020.0176]
2 **Liu ZP**, Wang MD, Chen ZY, Yang T. Primary prevention of hepatitis B-related liver cancer. *J Hepatobiliary Surg* 2021; **29**: 341-344 [DOI: 10.3969/j.issn.1006-4761.2021.05.007]
3 **Bian J**, Zhang PH, Li JJ. The Relationship Between EGF Gene Polymorphism and the Sensitivity of HBV-related Primary Liver Cancer to Cisplatin. *Pract J Cancer* 2022; 37: 404-407 [DOI: 10.3969/j.issn.1001-5930.2022.03.014]
4 **Yang Q**, Wei WH, Chen LL, Zhong QY, Wang YY. Value of microRNA in differential diagnosis of chronic HBV infection and HBV-related liver cancer. *Chin J Nosocomiol* 2022; **32**: 21-25 [DOI: 10.11816/cn.ni.2022-210438]
5 **Hou YF**, Guo HY, Li F. Relationship between preoperative serum high-sensitivity C-reactive protein and prognosis of hepatitis B-related hepatocellular carcinoma. *Chin J Curr Adv Gen Surg* 2021; **24**: 548-552 [DOI: 10.3969/j.issn.1009-9905.2021.07.010]
6 **Chen Y**, Yuan LP, Wang BY, Hao FF, Yang YS, Xiao PY. Periplaneta Americana extract plays an anti-fibrosis role in inhibiting oxidative stress *via* Nrf2/HO-1 pathway. *Chin J Hosp Pharm* 2022; **42**: 367-372 [DOI: 10.13286/j.1001-5213.2022.04.05]
7 **Luo D**, Wu JX, Qin GY, Liao XW. Correlation analysis of serum uric acid with early-onset epilepsy and oxidative stress levels in patients with acute cerebral in-farction. *Trauma Crit Care Med* 2021; **9**: 206-210 [DOI: 10.16048/j.issn.2095-5561.2021.03.10]
8 **Pinato DJ**, Cortellini A, Sukumaran A, Cole T, Pai M, Habib N, Spalding D, Sodergren MH, Martinez M, Dhillon T, Tait P, Thomas R, Ward C, Kocher H, Yip V, Slater S, Sharma R. PRIME-HCC: phase Ib study of neoadjuvant ipilimumab and nivolumab prior to liver resection for hepatocellular carcinoma. *BMC Cancer* 2021; **21**: 301 [PMID: 33757459 DOI: 10.1186/s12885-021-08033-x]
9 **Chen C**, Yao L, Qiu BD, Wang XY. Serum GP73 and hepcidin levels are corelated with the prognosis of hepatitis B-related liver cancer patients. *Chin Hepatol* 2021; **26**: 1007-1010 [DOI: 10.3969/j.issn.1008-1704.2021.09.017]
10 **Zeng SL**, Zhu W, Fang CH, He SS, Zhang P, Wen S, Zhang K. Three-dimensional visualization evaluation and VR study of giant liver cancer with blood vessels as the axis. *Chin J Gen Surg* 2019; **34**: 323-327 [DOI: 10.3760/cma.j.issn.1007-631X.2019.04.009]
11 **Yu M**, Zhang C, Tang H, Xiao C. Correlation between Serum Oxidative Stress Level and Serum Uric Acid and Prognosis in Patients with Hepatitis B-Related Liver Cancer before Operation. *J Healthc Eng* 2022; **2022**: 1964866 [PMID: 35449838 DOI: 10.1155/2022/1964866]
12 **Xi XL**, Ye ML. Effects of gypenoside capsule on glycolipid metabolism, oxidative stress and liver fibrosis in patients with nonalcoholic fatty liver disease. *Anhui Yiyao Zazhi* 2022; **26**: 824-828 [DOI: 10.3969/j.issn.1009-6469.2022.04.042]
13 **Zhou SF**, Zhan W, Bian CF. Effect of dexmedetomidine on oxidative stress, liver function and expression of Toll-like receptor 2 and Toll-like receptor 4 in peripheral blood monouclear cells in patients with primary liver cancer undergoing hepalobectomy. *Xinxiang Med Univ* 2020; **37**: 869-872 [DOI: 10.7683/xxyxyxb.2020.09.015]
14 **Mao LY**, Lu SZ, Wang WQ, Zhang CB, Zhang LN. Correlation between CXCL3 and cellular oxidative stress in the liver cancer cell SMMC-7721. *Linchuang Zhongliuxue Jichu Zazhi* 2022; **35**: 93-99 [DOI: 10.3969/j.issn.1673-5412.2022.02.001]
15 **Zhao YF**, Tao Y. Emerging insights into the functional role of the SLC7A11 gene in malignant neoplasms. *Chin J Clin Oncol* 2019; **46**: 795-799 [DOI: 10.3969/j.issn.1000-8179.2019.15.809]
16 **Huang MQ**, Hu LX, Chu XF. Effect of simultaneous chemotherapy of systemic chemotherapy with glutathione on hepatic function in patients with metastatic liver cancer and its safety analysis. *Anhui Yiyao Zazhi* 2019; **23**: 2279-2282 [DOI: 10.3969/j.issn.1009-6469.2019.11.042]
17 **Qiu XY**, Jia LQ, Song L, Wang Q. Study on Effect and Mechanism of Huayu Qutan Fomula on Mice with High-Fat and Liver Cancer Based on Ferroptosis Related Protein. *Zhongguo Jianzhu Chuantong Yixue* 2021; **39**: 137-141 [DOI: 10.13193/j.issn.1673-7717.2021.09.035]
18 **Jin FD**, Zhang T, Zhang Z, Yin XZ, Quan JS. Protective effect of rutin on oxidative stress injury of HepG2 cells and its mechanism. *J Jilin Univ (Med Ed)* 2020; **46**: 1117-1123 [DOI: 10.13481/j.1671-587x.20200602]
19 **Liu HY**. The therapeutic effect of fluorouracil combined with radiotherapy on patients with primary liver cancer and its effect on serum LPO and MDA levels. *Gonggong Weisheng Yixue Zazhi* 2020; **31**: 105-108 [DOI: 10.3969/j.issn.1006-2483.2020.01.024]
20 **Cui HT**, Zhao HM, Wu YP, Dong J, Zhang X. Correlation analysis of serum UA, Alb and sFas levels with primary liver cancer. *Chin J Clin Ration Drug Use* 2015; **22**: 136-137 [DOI: 10.15887/j.cnki.13-1389/r.2015.22.087]
21 **Liu Y**, Ou X, Yan YR, Lu XC, Li M, Zhou MJ. Serum uric acid and albumin levels and their correlation analysis in 144 patients with liver cancer. *J Pract Med* 2014; **16**: 2652-2654 [DOI: 10.3969/j.issn.1006-5725.2014.16.042]
22 **Wang D**, Zhu JY, Li GM, Leng XS. Results of long-time follow up of patients who survived more than 5 years after liver transplantation: A single center experience. *J Peking Univ Health Sci* 2011; **43**: 612-615 [DOI: 10.3969/j.issn.1671-167X.2011.04.030]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 2003-2011

DOI: 10.4240/wjgs.v15.i9.2003

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Multifactor analysis of the technique in total laparoscopic gastric cancer

Jia-Kun Shi, Bo Wang, Xin-Sheng Zhang, Pin Lv, Yun-Long Chen, Shuang-Yi Ren

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Ikeda H, Japan; Triggi M, United Kingdom

Received: June 30, 2023
Peer-review started: June 30, 2023
First decision: July 18, 2023
Revised: July 24, 2023
Accepted: August 8, 2023
Article in press: August 8, 2023
Published online: September 27, 2023

Jia-Kun Shi, Pin Lv, Yun-Long Chen, Department of Gastrointestinal Surgery, Dalian Friendship Hospital, Dalian 116000, Liaoning Province, China

Bo Wang, Xin-Sheng Zhang, Shuang-Yi Ren, Department of Gastrointestinal Surgery, The Second Affiliated Hospital of Dalian Medical University, Dalian 116011, Liaoning Province, China

Corresponding author: Shuang-Yi Ren, MD, Attending Doctor, Department of Gastrointestinal Surgery, The Second Affiliated Hospital of Dalian Medical University, No. 467 Zhongshan Road, Shahekou District, Dalian 116011, Liaoning Province, China.
pao54313345736@126.com

Abstract

BACKGROUND

Esophageal gastric anastomosis is a common surgical technique used to treat patients with gastric cancer who undergo total gastrectomy. However, using simple anastomosis techniques alone may not meet the needs of patients in some cases and can lead to complications such as anastomotic stenosis and ulceration. In order to overcome these issues and improve patient prognosis, muscle flap reconstruction technique has emerged. Muscle flap reconstruction is a method of improving gastric-esophageal anastomosis by transplanting muscle tissue. By covering the anastomotic site with muscle tissue, it not only enhances the stability of the anastomosis site but also increases blood supply, promoting healing and recovery of the anastomosis. Therefore, the use of muscle flap reconstruction technique in esophageal gastric anastomosis during total gastrectomy for gastric cancer is increasingly widely applied.

AIM

To determine the effectiveness of esophagogastric anastomosis using the muscle flap reconstruction technology in total abdominal gastrectomy for gastric cancer and perform follow-up experiments to understand the factors affecting patients' prognosis.

METHODS

The study subjects were 60 patients with gastric cancer who were admitted to our hospital between October 2018 and January 2022. All patients underwent esophagogastric anastomosis using the double muscle flap reconstruction technology in total abdominal gastrectomy. Perioperative indicators were determined, and

patients were followed up for 1 year. Furthermore, patient outcomes were observed within 1 year, followed by patient classification based on different outcomes. Moreover, clinicopathological parameters were observed and relevant factors affecting patient prognosis were analyzed.

RESULTS

The operation time was 318 ± 43 min, the formation time of esophageal double muscle flap anastomosis was 110 ± 13 min, the number of lymph node dissections was 26 ± 6, the incision length was 3 ± 0.6 cm, intraoperative bleeding volume was 48 ± 15 mL, first anal exhaust time was 5.3 ± 1.8 d, first meal time was 6.0 ± 1.6 d, length of hospital stay was 11.8 ± 2.5, and treatment cost was 5.8 ± 0.7 thousand yuan. The patient experienced three postoperative complications: 2 cases of pulmonary infection and 1 case of respiratory discomfort. During 1-year follow-up, 50 patients survived and 10 died. Univariate analysis revealed that histological types, tumor size, tumor-node-metastasis staging, vascular invasion, and postoperative adjuvant radiotherapy and chemotherapy were the main factors affecting the prognosis of surviving patients. Furthermore, Cox regression analysis revealed that postoperative adjuvant radiotherapy and chemotherapy were the main factors affecting patient prognosis. The survival time of the survival group was significantly higher than that of the death group ($P < 0.05$).

CONCLUSION

Esophagogastric anastomotic using muscle flap reconstruction exhibits good effects on patients who undergo total abdominal gastrectomy for cancer. Postoperative adjuvant radiotherapy and chemotherapy are the main factors affecting patient prognosis.

Key Words: Esophagogastric anastomotic muscle flap reconstruction technique; Total abdominal radical gastrectomy for gastric cancer; Gastric cancer; Perioperative indicators; Prognosis; Pathological parameters

Core Tip: This study evaluated the effectiveness of esophagogastric anastomosis using muscle flap reconstruction technology in total abdominal gastrectomy for gastric cancer. The study found that this technique had positive effects on patient outcomes, and postoperative adjuvant radiotherapy and chemotherapy were important factors affecting prognosis. Univariate analysis revealed that histological types, tumor size, tumor-node-metastasis staging, vascular invasion, and postoperative adjuvant radiotherapy and chemotherapy were major factors affecting the prognosis of surviving patients. Cox regression analysis showed that postoperative adjuvant radiotherapy and chemotherapy were the main factors affecting overall patient prognosis. The findings of this study may contribute to improving treatment options and decision-making for patients with gastric cancer undergoing total abdominal gastrectomy, ultimately leading to better patient outcomes.

Citation: Shi JK, Wang B, Zhang XS, Lv P, Chen YL, Ren SY. Multifactor analysis of the technique in total laparoscopic gastric cancer. *World J Gastrointest Surg* 2023; 15(9): 2003-2011
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/2003.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.2003

INTRODUCTION

Gastric cancer is one of the most common tumors of the digestive system worldwide. Although gastric cancer may not have significant manifestations in the early stage, as the disease progresses, systemic symptoms such as emaciation, anemia, and gastric perforation are observed[1]. Surgery is the main treatment strategy for gastric cancer. With recent advances in total laparoscopy, total laparoscopic radical resection has gradually become an important treatment strategy for gastric cancer. Conventional laparoscopic surgery may require at least 5-6 incisions, whereas total laparoscopic surgery requires only 3-4 small incisions, decreasing surgical trauma and postoperative pain[2]. Furthermore, because total laparoscopic surgery is less invasive than conventional laparoscopic surgery, patients can generally return to normal living and working conditions more quickly[3]. Moreover, total laparoscopic surgery does not leave obvious surgical scars; therefore, it is advantageous for patients who pay attention to appearance[4]. Esophagogastrostomy is a method used to repair gastrointestinal anastomosis, called the "double muscle valve". This technique requires folding the fundus of the stomach, followed by sealing it with two layers of tissue, forming a structure similar to a valve. The application of esophagogastrostomy to total laparoscopic radical resection for gastric cancer can effectively decrease the incidence of complications such as anastomotic incontinence and bile reflux and improve the surgical cure rate and postoperative quality of life, which is a recent topic of interest for surgeons. At present, systematic multivariate analyses of the application effects of esophagogastrostomy in total laparoscopic surgery for gastric cancer and their effects on prognosis remain scarce[5]. In the present study, we conducted surgery and postoperative follow-up of patients with gastric cancer and collected relevant clinical data for esophagogastric anastomosis during postoperative resection for gastric cancer to

provide a reference for the clinical improvement of surgical effects, treatment levels, and postoperative rehabilitation efficiency.

MATERIALS AND METHODS

General information

To obtain a definite diagnosis, the study subjects were 60 patients with gastric cancer who were admitted to our hospital from October 2018 to January 2022. The inclusion criteria were as follows: (1) Patients with gastric cancer; (2) Patients whose preoperative pathology was adenocarcinoma; (3) Preoperative computed tomography, ultrasound, and magnetic resonance imaging confirmed tumor presence without distant organ metastasis; (4) Patients who underwent total laparoscopic esophageal plasty; (5) Patients with no history of abdominal surgery; and (6) Patients with complete clinical data. The exclusion criteria were as follows: (1) Tumor involving the dentate line and lower esophageal segment; (2) Patients who did not undergo surgery; (3) Patients who received preoperative radiotherapy, chemotherapy, or targeted therapy; (4) Patients with severe disease and dysfunction; (5) Patients with other or tumor history; (6) Patients with missing follow-up data; and (7) Patients with mental and psychological illnesses.

Surgical procedure

For all patients with intravenous inhalation compound anesthesia, supine position, according to the laparoscopic radical gastric cancer conventional 5-hole placement Trocar, laparoscopic conventional exploration, along the lower edge of the liver ligament, lower separation to the right cardia, cut the right diaphragm, suspension liver, complete lymph node dissection, laparoscopic linear cutter from the esophagus, stomach, specimen in specimen bag, close pneumoperitoneum, all around the umbilical mouth (3.5 cm) specimen, confirm the tumor far and near. The pneumoperitoneum was rebuilt to maintain a pressure of 10-12 mmHg and the "H" shape was labeled at the tip of the remnant stomach, with a width of approximately 2.5 cm and a spacing of 3.5 cm up and down. The plasma muscle layer and middle muscle layer were prepared and incised to prepare the cytoplasmic muscle flap of the anterior gastric wall. Next, the mucosal layer was incised under the H-shaped transverse flap to prepare for subsequent esophageal anastomosis. The posterior wall of the esophagus was pulled 4 cm from the broken end of the esophagus and the plasma muscle layer was continuously stitched on the gastric wall using barbed threads. The broken end and remnant stomach were fixed, the closed section of the esophagus was incised, and the broken end and remnant stomach were anatomized. The whole layer of the posterior wall of the broken end and the mucosal layer and submucosa of the remnant stomach was closed. A barbed thread was used to continuously suture the full layer of the anterior wall of the broken end and the H shape of the remnant stomach. The anterior gastric wall was sutured using a Y-shaped intermittent suture to realize wrapping around the anastomosis. During surgery, a gastroscope was used to check the esophagus and residual gastric anastomosis, including whether the ana-stomosis was intact and whether there was bleeding. After hemostasis of the surgical wound surface, the abdominal cavity was washed with distilled water, and a single drainage tube was placed after the anastomosis of the esophagus and stomach.

Observed indicators

Perioperative index: The perioperative index was observed, and the operating room nurse recorded the operation time, shaping time of esophagogastric double muscle flap anastomosis, number of lymph node dissections, incision length, and intraoperative bleeding volume (calculated using the sterile gauze weighing method). On the other hand, the inpatient nurse recorded postoperative first anal exhaust time, first feeding time, hospitalization time, treatment cost, and the probability of complications during postoperative hospitalization. Information on sex, age, Borrmann classification, histological type, tumor size, tumor-node-metastasis (TNM) stage, vascular invasion, postoperative adjuvant chemoradiotherapy, and lymph node metastasis was collected by inquiring or consulting medical records. Among them, the Borrmann classification can be divided into types I-IV, which refer to mushroom umbrella-type nodules (tumor nodules, polyp shape, ulcer, and ulcer surface can be shallow), local ulcer-type nodules (ulcer degree, edge, and tumor limitation), infiltration ulcer-type nodules (ulcer chassis, unclear edge, and deep infiltration), and diffuse infiltration-type nodules (infiltration of cancer tissue in the stomach wall), respectively. The follow-up records of the patients within 1 year postoperatively were analyzed and patients were grouped based on whether they survived or died. The clinicopathological characteristics of the two patient groups were observed. Statistically significant indicators were included in the Cox regression model, and the relevant factors affecting patient prognosis were analyzed.

Statistical methods

SPSS27.0 was used for data processing, with (n, %), and cross χ^2 test. Measurement data showing normal distribution are expressed as (mean ± SD), using the independent sample t-test. Relevant factors that affected prognosis were analyzed by Cox regression analysis. Values at $P < 0.05$ were considered statistically significant.

RESULTS

Perioperative indicators of the patients

The following perioperative indicators were observed: Operation time (318 ± 43 min); time of esophageal anastomosis double muscle valve forming (110 ± 13 min); number of lymph node dissection (26 ± 6); incision length (3.4 ± 0.6 cm); intraoperative bleeding volume (48 ± 15 mL); anal first vent time (5.3 ± 1.8 d); first feeding time (6.0 ± 1.6 d); hospitalization time (11.8 ± 2.5); and treatment cost (5.8 ± 0.7 ten thousand yuan). The specific bar chart ratio is shown in Figure 1. The patients suffered from three postoperative complications, two pulmonary infection-related and one respiratory discomfort-related complication. The number of complications in Figure 2.

Univariate analysis of patients with different prognoses

The univariate analysis showed histological type, tumor size, TNM stage, vascular invasion, and postoperative adjuvant chemoradiotherapy as the main factors affecting the prognosis ($P < 0.05$). Details are presented in Table 1.

Impact factors affecting patient prognosis

The data were assessed before performing Cox regression analysis. Patient survival was a dependent variable, whereas other statistical differences were independent variables. Details are shown in Table 2. The Cox regression analysis showed that postoperative adjuvant chemoradiotherapy was the main factor affecting the prognosis of patients ($P < 0.05$). Details are shown in Table 3. The patient survival function plot is shown in Figure 3. The survival time of the subsisting group (10.78 ± 1.52 mo) was significantly higher than that of the death group (7.40 ± 1.51 mo), and the difference was statistically significant ($t = 6.444$, $P < 0.001$) (Figure 3).

DISCUSSION

Gastric cancer is a malignant tumor occurring in gastric epithelial tissues. The cause of its occurrence has not been thoroughly studied. However, most scholars believe that factors such as curing, smoking, high salt consumption, high-fat consumption, drinking, and eating stale food increase the risk of gastric cancer (history of benign gastric diseases)[6]. Furthermore, chronic atrophic gastritis, gastric polyps, and *Helicobacter pylori* infection may also increase the probability of gastric cancer occurrence. According to statistics, gastric cancer is one of the most common cancers worldwide; however, its incidence in developed countries has decreased significantly. Conversely, its incidence in Asian countries, such as China, South Korea, and Japan, is still high, which can be attributed to the long-term use of high salt and pickled food[7]. Surgery is a common way to treat gastric cancer. With the development of laparoscopic technology and improvement in medical sciences, the total laparoscopic radical resection of gastric cancer has gradually become the mainstream operation of gastric cancer[8]. Esophagogastric anastomoplasty is a technique in which the esophagus and gastric resection are connected by surgery to restore the gastrointestinal digestive function of patients. Combining it with the total laparoscopic radical resection of gastric cancer can further restore the gastrointestinal function of patients, and such a combination has been applied in treating diseases including esophageal and cardiac cancers[9,10].

The perioperative indicators showed in this study, such as operation time (318 ± 43 min), esophageal anastomosis time (110 ± 13 min), lymph node dissection (26 ± 6), incision length (3.4 ± 0.6 cm), intraoperative bleeding (48 ± 15 mL), anal first discharge time (5.3 ± 1.8 d), first feeding time (6.0 ± 1.6 d), hospitalization time (11.8 ± 2.5), treatment cost (5.8 ± 0.7 thousand yuan), and a poor prognosis ratio of about 16.67%, were consistent with the results of Tian *et al*[11]. The results of the present study indicate that the double muscle valve plasty of esophagogastric stomosis can indeed be combined with the total laparoscopic radical surgery of gastric cancer to achieve a good curative effect in the near future. Laparoscopic surgery combined with gastric anastomosis double muscle valve plasty can retain the function of the upper stomach and lower esophagus and reduce the effect of surgery on the digestive function of the patient. Furthermore, the double muscle valve structure can avoid gastric content reflux into the esophagus and improve surgical safety. Additionally, autologous tissue repair can avoid the risk of foreign body infection. Simultaneously, as the entire operation was performed using full laparoscopic technology, the operation site was visible, which aided in the accuracy of the operation so as to better protect the nerve and vascular tissues, avoid surgical injury, and improve the efficiency of postoperative rehabilitation to some extent. To summarize, considering patient efficacy, total laparoscopic gastric cancer radical resection with esophagogastric stomosis exhibits remarkable advantages such as high surgical accuracy, high resection rate, low postoperative pain, quick recovery, and digestive function retention.

Statistical data show that the one-year survival rate of patients with gastric cancer treated with radical surgery is about 70%-90%[12]. In the present study, after the one-year follow-up of the 60 patients, their one-year survival rate was 83.33%, consistent with the epidemiological statistics. The univariate analysis showed differences in histological type, tumor size, TNM stage, vascular invasion, and postoperative adjuvant chemoradiation between the surviving and dying patients. This is similar to the conclusion of the Tougeron *et al*[13]. The histological types of gastric cancer usually include adenocarcinoma, papillary adeno-carcinoma, and mucinous adenocarcinoma, and some differences occur in the prognosis of these different histological types. A study has shown that patients with mucinous adenocarcinoma usually exhibit a higher survival rate compared with patients with the other types[13]. Tumor size is another important factor affecting the prognosis of patients with gastric cancer. Generally, the smaller the tumor, the better the prognosis. Clinically, the tumor size is usually graded according to the diameter, and patients with tumors of 5 cm or less usually exhibit a high survival rate[14]. TNM stage is an important indicator to examine the prognosis of patients with gastric cancer, which can be divided into four stages: Stage I (localized gastric cancer), stage II (locally spread gastric cancer),

Table 1 Univariate analysis of the patients with different prognoses

Factor	Classify	Survival (n = 50)	Death (n = 10)	χ^2	P value
Sex	Male	34 (68.00)	6 (60.00)	0.240	0.624
	Female	16 (32.00)	4 (40.00)		
Age	> 60 yr	21 (42.00)	7 (70.00)	2.625	0.105
	Admidia 60 yr	29 (58.00)	3 (30.00)		
Bommann classification	I-II mold	35 (70.00)	4 (40.00)	3.297	0.069
	III-IV mold	15 (30.00)	6 (60.00)		
Histological type	Poorly differentiated	30 (60.00)	1 (10.00)	10.141	0.006
	Moderately differentiated	11 (22.00)	3 (30.00)		
	Well-differentiated	9 (18.00)	6 (60.00)		
Tumor size	≤ 5 cm	38 (76.00)	2 (20.00)	11.760	< 0.001
	> 5 cm	12 (24.00)	8 (80.00)		
TNM by stages	I-II designated time	35 (70.00)	1 (10.00)	12.500	< 0.001
	III-IV designated time	15 (30.00)	9 (90.00)		
Vascular invasion	Have	13 (26.00)	6 (60.00)	4.452	0.035
	Not have	37 (74.00)	4 (40.00)		
Postoperative adjuvant chemoradiation therapy	Not have	16 (32.00)	8 (80.00)	8.000	0.005
	Have	34 (68)	2 (20)		
Lymphatic metastasis	Have	10 (20)	3 (30)	0.491	0.483
	Not have	40 (80)	7 (70)		

TNM: Tumor-node-metastasis.

Table 2 Assignment of the regression analysis

Factor	Factor pattern	The assignment situation
Patient	Classified variable	1: Survival, 2: Death
Histological type	Classified variable	1: Poorly differentiated, 2: Moderately differentiated, 3: Highly differentiated
Tumor size	Classified variable	1: ≤ 5 cm, 2: > 5 cm
TNM by stages	Classified variable	1: I period, 2: About period
Vascular invasion	Classified variable	1: Yes, 2: None
Postoperative adjuvant chemoradiation therapy	Classified variable	1: None, 2: To have

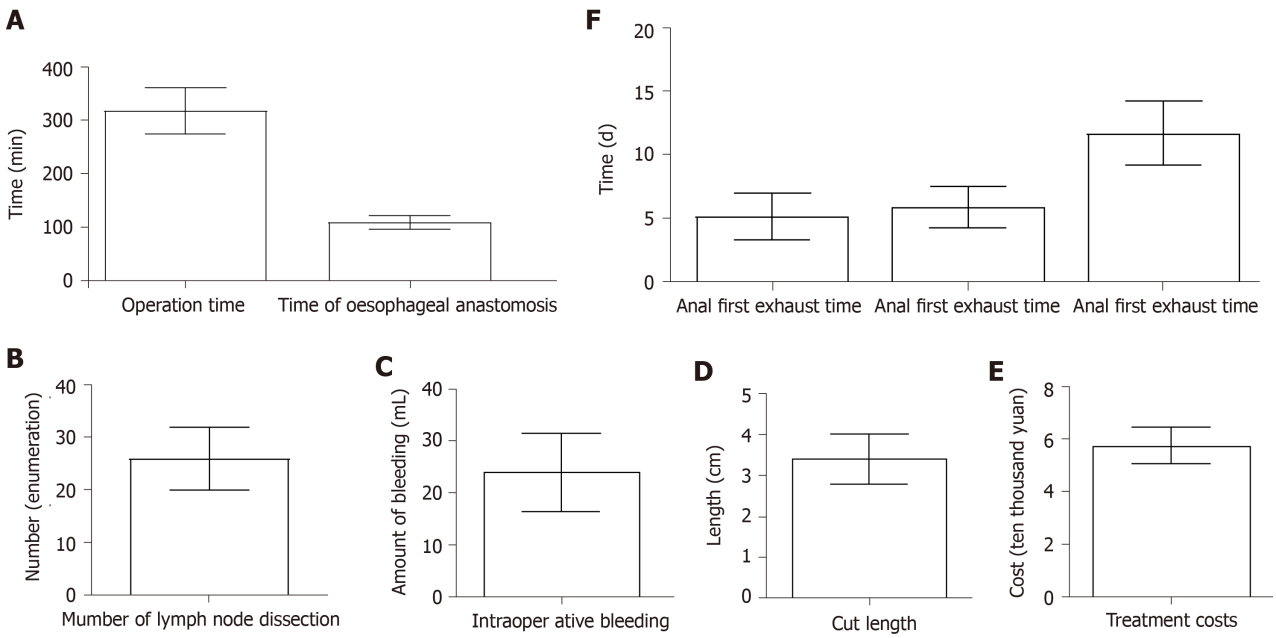
TNM: Tumor-node-metastasis.

stage III (lymph node metastasis gastric cancer), and stage IV (distant organ metastasis gastric cancer). Most studies have shown that the higher the grade of the stage, the lower the survival proportion[15]. Vascular invasion is another important indicator associated with the survival rate of patients with gastric cancer, and its survival proportion is usually lower for patients whose tumor has invaded lymphatic or blood vessels[16]. This suggests a possible connection between the histological type, tumor size, TNM stage, vascular invasion, postoperative adjuvant chemoradiotherapy, and prognosis of patients with gastric cancer undergoing esophagogastric anastomosis valvuloplasty combined with total laparoscopic gastrectomy. The Cox regression analysis showed that postoperative adjuvant chemoradiotherapy was the main factor affecting the prognosis of patients, and patients who did not receive postoperative adjuvant chemoradiotherapy had a higher risk of a poor prognosis. The reason may be that postoperative adjuvant chemoradiotherapy removes the residual cancer cells after surgery and reduces the risk of tumor recurrence and metastasis by eliminating the small metastatic focus, thus improving the survival rate of patients[17-19].

Table 3 Factors influencing the patient outcomes

Factor	B	SE	Wald	Free degree	Conspicuousness	Exp (B)	A 95.0%CI of exp (B)	
							Lower limit	Superior limit
Histological type	0.179	0.192	0.862	1	0.353	1.196	0.82	1.743
Tumor size	0.119	0.346	0.118	1	0.732	1.126	0.571	2.221
TNM by stages	0.618	0.335	3.404	1	0.065	1.855	0.962	3.574
Vascular invasion	0.133	0.348	0.146	1	0.702	1.142	0.578	2.26
Postoperative adjuvant chemoradiation therapy	0.702	0.355	3.913	1	0.048	2.018	1.006	4.046

CI: Confidence interval; TNM: Tumor-node-metastasis.

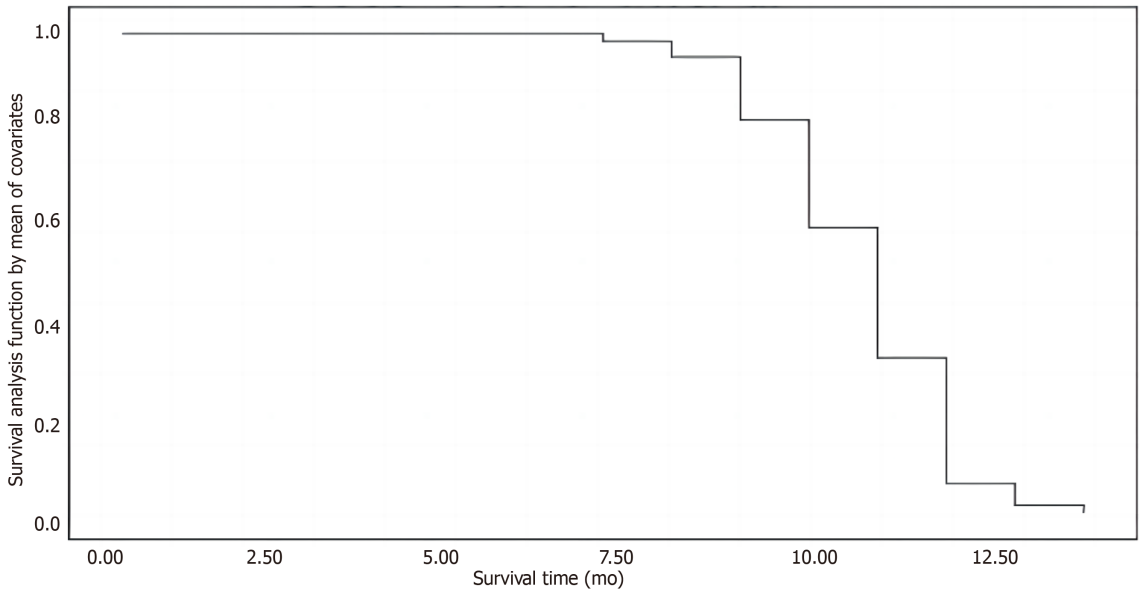


DOI: 10.4240/wjgs.v15.i9.2003

Figure 1 The specific bar chart ratio. A: Bar chart depicting the patient's operation time and the time of esophageal anastomosis; B-E: Histogram depicting the numbers of lymph node dissection (B), intraoperative blood loss (C), the incision length (D) and the treatment cost (E); F: Bar chartdepicting time of first anal exhaust, time of first food intake and length of hospitalization.

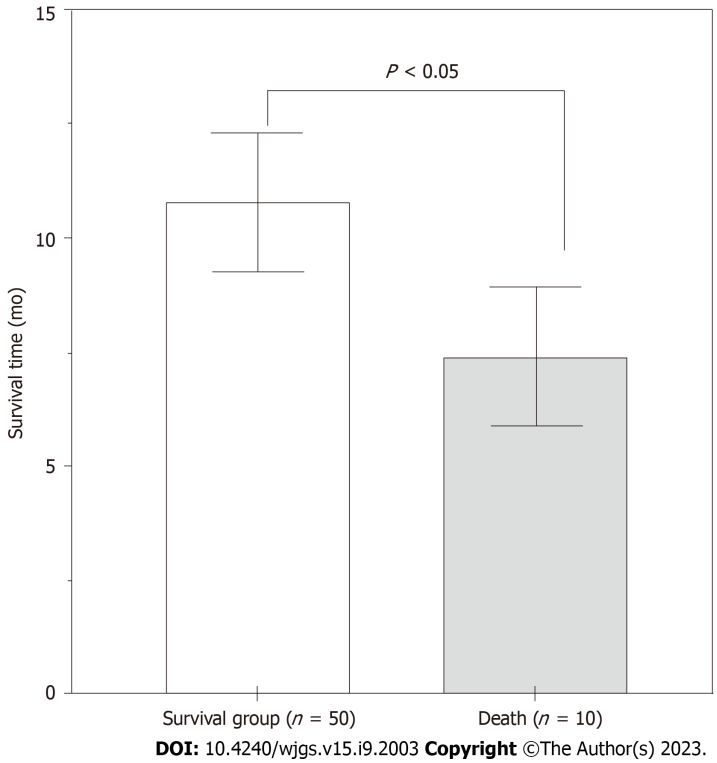
CONCLUSION

In conclusion, esophagogastric-stapled muscle valvuloplasty showed good results in total abdominal gastric cancer. Postoperative adjuvant chemoradiotherapy was the main factor affecting the prognosis of patients. However, the study has the following limitations: The small number of samples, the single source, and the lack of analysis of the long-term efficacy of patients. Thus, large-sample, multi-center, and long-term studies are needed in the future to confirm the present results.



DOI: 10.4240/wjgs.v15.i9.2003 **Copyright** ©The Author(s) 2023.

Figure 2 The patient survival function plots.



DOI: 10.4240/wjgs.v15.i9.2003 **Copyright** ©The Author(s) 2023.

Figure 3 Bar graph depicting the survival time of patients who survived and died.

ARTICLE HIGHLIGHTS

Research background

Esophageal gastric anastomosis is a common surgical technique used in the treatment of gastric cancer patients undergoing total gastrectomy. However, complications such as anastomotic stenosis and ulceration can arise when simple anastomosis techniques are used alone, which may not adequately meet patient needs. To address these issues and improve patient prognosis, the muscle flap reconstruction technique has emerged. Muscle flap reconstruction involves transplanting muscle tissue to enhance gastric-esophageal anastomosis. By covering the anastomotic site with muscle tissue, it not only improves stability but also enhances blood supply, promoting healing and recovery. Therefore, the application of muscle flap reconstruction in esophageal gastric anastomosis during total gastrectomy for gastric

cancer is increasingly widespread.

Research motivation

Gastric cancer is a significant health concern, and total gastrectomy is a common surgical treatment for this condition. However, traditional esophagogastric anastomosis techniques have limitations, leading to complications and suboptimal patient outcomes. The emergence of muscle flap reconstruction technique provides a potential solution to overcome these challenges. By transplanting muscle tissue, the technique improves the stability and blood supply of the anastomosis site, promoting healing and recovery.

Research objectives

The objective of this study was to evaluate the effect of esophagogastrostomy with muscle flap reconstruction technique on the prognosis of patients undergoing total gastrectomy for gastric cancer.

Research methods

This study included 60 patients with gastric cancer who underwent total abdominal gastrectomy with esophagogastric anastomosis using double muscle flap reconstruction technique. Perioperative indicators, such as operation time, formation time of esophageal double muscle flap anastomosis, number of lymph node dissections, incision length, intraoperative bleeding volume, were recorded. Patients were followed up for one year to observe outcomes and classify patients based on different outcomes. Clinicopathological parameters were analyzed to identify factors affecting patient prognosis.

Research results

The study involved 60 patients with gastric cancer who underwent total abdominal gastrectomy with esophagogastric anastomosis using double muscle flap reconstruction technique. The operation time averaged (318 ± 43 min), formation time of esophageal double muscle flap anastomosis was (110 ± 13 min), and other perioperative indicators were measured. Three postoperative complications were recorded: 2 cases of pulmonary infection and 1 case of respiratory discomfort. During the one-year follow-up, 50 patients survived while 10 died. Univariate analysis identified histological types, tumor size, tumor-node-metastasis staging, vascular invasion, and postoperative adjuvant radiotherapy and chemotherapy as the main factors affecting prognosis in surviving patients. Cox regression analysis confirmed the significance of postoperative adjuvant therapy on patient prognosis. The survival time of the survival group was significantly higher than that of the death group ($P < 0.05$).

Research conclusions

The study concludes that esophagogastric anastomosis with muscle flap reconstruction is effective for patients undergoing total abdominal gastrectomy for gastric cancer. The technique improves the stability of the anastomosis site and enhances blood supply, promoting healing and recovery. Esophagogastric anastomosis with muscle flap reconstruction technique shows positive outcomes in patients undergoing total abdominal gastrectomy for gastric cancer, and postoperative adjuvant therapy plays a vital role in improving patient prognosis.

Research perspectives

Future research can focus on optimizing the muscle flap reconstruction technique to further enhance surgical outcomes and minimize complications. Additionally, investigating the long-term effects of postoperative adjuvant radiotherapy and chemotherapy on patient prognosis would provide valuable insights. Furthermore, evaluating the cost-effectiveness of this technique and comparing it with other surgical methods will help guide decision-making in clinical practice.

ACKNOWLEDGEMENTS

I would like to express my sincere thanks to all those who participated in the manuscript.

FOOTNOTES

Author contributions: Shi JK and Wang B proposed the concepts for this study; Zhang XS and Lv P collected the data; Shi JK, Chen LY, and Ren SY contributed to formal analysis; Ren SY and Shi JK contributed to the investigation; Shi JK, Chen LY, and Ren SY contributed to the methodology; Wang B supervised the research; Shi JK validated this study; Shi JK and Ren SY contributed to the visualization of research; Shi JK, Wang B, Zhang XS, Lv P, Chen LY, and Ren SY reviewed and edited the manuscript.

Institutional review board statement: The study was reviewed and approved by the institutional review board of Dalian Friendship Hospital.

Informed consent statement: This study has obtained informed consent from patients.

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

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Jia-Kun Shi 0009-0001-5943-5055; Xin-Sheng Zhang 0000-0002-1915-3205; Shuang-Yi Ren 0009-0000-7056-2963.

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

REFERENCES

1 **Lordick F**, Carneiro F, Cascinu S, Fleitas T, Haustermans K, Piessen G, Vogel A, Smyth EC; ESMO Guidelines Committee. 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 **Li Z**, Shan F, Ying X, Zhang Y, E JY, Wang Y, Ren H, Su X, Ji J. Assessment of Laparoscopic Distal Gastrectomy After Neoadjuvant Chemotherapy for Locally Advanced Gastric Cancer: A Randomized Clinical Trial. *JAMA Surg* 2019; **154**: 1093-1101 [PMID: 31553463 DOI: 10.1001/jamasurg.2019.3473]

3 **Liu X**, Wang X, Mao T, Yin X, Wei Z, Fu J, Wu J, Li X. Characteristic analysis of early gastric cancer after Helicobacter pylori eradication: a multicenter retrospective propensity score-matched study. *Ann Med* 2023; **55**: 2231852 [PMID: 37450336 DOI: 10.1080/07853890.2023.2231852]

4 **Zhang H**, Liu X, Zheng Z, Yin J, Zhang J. Safety, efficacy, and selection strategy of laparoscopic local gastrectomy for gastrointestinal stromal tumors in the esophagogastric junction. *Front Surg* 2022; **9**: 1015126 [PMID: 36238859 DOI: 10.3389/fsurg.2022.1015126]

5 **Lu J**, Wu Z, Liu G, Wang B, Shi L. The clinical effectiveness of establishing a proximal jejunum pouch after laparoscopic total gastrectomy: A propensity score-based analysis. *Asian J Surg* 2022; **45**: 425-430 [PMID: 34315672 DOI: 10.1016/j.asjsur.2021.07.002]

6 **Ecker J**, Benedetti E, Kindt ASD, Höring M, Perl M, Machmüller AC, Sichler A, Plagge J, Wang Y, Zeissig S, Shevchenko A, Burkhardt R, Krumsiek J, Liebisch G, Janssen KP. The Colorectal Cancer Lipidome: Identification of a Robust Tumor-Specific Lipid Species Signature. *Gastroenterology* 2021; **161**: 910-923.e19 [PMID: 34000281 DOI: 10.1053/j.gastro.2021.05.009]

7 **Yan S**, Li B, Bai ZZ, Wu JQ, Xie DW, Ma YC, Ma XX, Zhao JH, Guo XJ. Clinical epidemiology of gastric cancer in Hehuang valley of China: a 10-year epidemiological study of gastric cancer. *World J Gastroenterol* 2014; **20**: 10486-10494 [PMID: 25132766 DOI: 10.3748/wjg.v20.i30.10486]

8 **Ueda Y**, Shiroshita H, Etoh T, Inomata M, Shiraishi N. Laparoscopic proximal gastrectomy for early gastric cancer. *Surg Today* 2017; **47**: 538-547 [PMID: 27549773 DOI: 10.1007/s00595-016-1401-x]

9 **Liu J**, Wang G, Zhao J, Liu X, Zhang K, Gong G, Pan H, Jiang Z. LncRNA H19 Promoted the Epithelial to Mesenchymal Transition and Metastasis in Gastric Cancer *via* Activating Wnt/β-Catenin Signaling. *Dig Dis* 2022; **40**: 436-447 [PMID: 34348271 DOI: 10.1159/000518627]

10 **Yanni F**, Singh P, Tewari N, Parsons SL, Catton JA, Duffy J, Welch NT, Vohra RS. Comparison of Outcomes with Semi-mechanical and Circular Stapled Intrathoracic Esophagogastric Anastomosis following Esophagectomy. *World J Surg* 2019; **43**: 2483-2489 [PMID: 31222637 DOI: 10.1007/s00268-019-05057-0]

11 **Tian P**, Liu Y, Bian S, Li M, Zhang M, Liu J, Jin L, Zhang P, Zhang Z. Laparoscopic Proximal Gastrectomy Versus Laparoscopic Total Gastrectomy for Proximal Gastric Cancer: A Systematic Review and Meta-Analysis. *Front Oncol* 2020; **10**: 607922 [PMID: 33585228 DOI: 10.3389/fonc.2020.607922]

12 **Sun KK**, Wu YY. Current status of laparoscopic proximal gastrectomy in proximal gastric cancer: Technical details and oncologic outcomes. *Asian J Surg* 2021; **44**: 54-58 [PMID: 32981822 DOI: 10.1016/j.asjsur.2020.09.006]

13 **Tougeron D**, Hamidou H, Scotté M, Di Fiore F, Antonietti M, Paillot B, Michel P. Esophageal cancer in the elderly: an analysis of the factors associated with treatment decisions and outcomes. *BMC Cancer* 2010; **10**: 510 [PMID: 20868479 DOI: 10.1186/1471-2407-10-510]

14 **Kunisaki C**, Makino H, Takagawa R, Oshima T, Nagano Y, Ono HA, Akiyama H, Shimada H. Efficacy of laparoscopy-assisted distal gastrectomy for gastric cancer in the elderly. *Surg Endosc* 2009; **23**: 377-383 [PMID: 18443861 DOI: 10.1007/s00464-008-9949-1]

15 **Zurleni T**, Gjoni E, Ballabio A, Casieri R, Ceriani P, Marzoli L, Zurleni F. Sixth and seventh tumor-node-metastasis staging system compared in gastric cancer patients. *World J Gastrointest Surg* 2013; **5**: 287-293 [PMID: 24520426 DOI: 10.4240/wjgs.v5.i11.287]

16 **Yao C**, Wu S, Kong J, Sun Y, Bai Y, Zhu R, Li Z, Sun W, Zheng L. Angiogenesis in hepatocellular carcinoma: mechanisms and anti-angiogenic therapies. *Cancer Biol Med* 2023; **20**: 25-43 [PMID: 36647777 DOI: 10.20892/j.issn.2095-3941.2022.0449]

17 **Liu Z**, Liu XW, Fang XD, Ji FJ. [Application of Overlap anastomosis to Billroth I digestive tract reconstruction after laparoscopic distal gastrectomy in gastric cancer]. *Zhonghua Wei Chang Wai Ke Za Zhi* 2019; **22**: 441-445 [PMID: 31104429 DOI: 10.3760/cma.j.issn.1671-0274.2019.05.009]

18 **Ahn HS**, Chang MS, Han DS. Comparing the surgical outcomes of dual-port laparoscopic distal gastrectomy and three-port laparoscopic distal gastrectomy for gastric cancer. *Ann Surg Treat Res* 2021; **100**: 18-24 [PMID: 33457393 DOI: 10.4174/astr.2021.100.1.18]

19 **Wei J**, Yang X, Gao R, Wang W, Li X, Ji G. Initial experience with triple port laparoscopic distal gastrectomy. *Front Oncol* 2022; **12**: 1042314 [PMID: 36776381 DOI: 10.3389/fonc.2022.1042314]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 2012-2020

DOI: 10.4240/wjgs.v15.i9.2012

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Value of enhanced computed tomography in differentiating small mesenchymal tumours of the gastrointestinal from smooth muscle tumours

Wen-Jun Nie, Zhao Jing, Mo Hua

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Alorro MG, Australia; Sherf-Dagan S, Israel

Received: June 30, 2023
Peer-review started: June 30, 2023
First decision: July 18, 2023
Revised: July 24, 2023
Accepted: August 4, 2023
Article in press: August 4, 2023
Published online: September 27, 2023

Wen-Jun Nie, Mo Hua, Department of Radiology, Changzhou Geriatric Hospital Affiliated to Soochow University, Changzhou No. 7 People's Hospital Radiology Department, Changzhou 213011, Jiangsu Province, China

Zhao Jing, Medical Area, Eastern Theater General Hospital, Qinhuai District Medical Area, Nanjing 210000, Jiangsu Province, China

Corresponding author: Mo Hua, MD, Attending Doctor, Department of Radiology, Changzhou Geriatric Hospital Affiliated to Soochow University, Changzhou No. 7 People's Hospital Radiology Department, No. 288 Yanling East Road, Changzhou 213011, Jiangsu Province, China. mohuafsk913044@sina.com

Abstract

BACKGROUND

Computed tomography (CT) technology has been gradually used in the differentiation of small mesenchymal tumors of the stomach and intestines from smooth muscle tumours.

AIM

To explore the value of enhanced CT in the differentiation of small mesenchymal tumors of the stomach and intestines from smooth muscle tumours.

METHODS

Clinical data of patients with gastric mesenchymal or gastric smooth muscle tumours who were treated in our hospital from May 2018 to April 2023 were retrospectively analysed. Patients were divided into the gastric mesenchymal tumor group and the gastric smooth muscle tumor group respectively (n = 50 cases per group). Clinical data of 50 healthy volunteers who received physical examinations in our hospital during the same period were selected and included in the control group. Serum levels of carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), carbohydrate antigen 19-9 (CA19-9), CA-125 and cytokeratin 19 fragment antigen 21-1 were compared among the three groups. The value of CEA and CA19-9 in the identification of gastric mesenchymal tumours was analysed using the receiver operating characteristic (ROC) curve. The Kappa statistic was used to analyse the consistency of the combined CEA and CA19-9 test in identifying gastric mesenchymal tumours.

RESULTS
CEA levels varied among the three groups in the following order: The gastric mesenchymal tumour group > the control group > the gastric smooth muscle tumour group. CA19-9 levels varied among the three groups in the following order: The gastric mesenchymal group > the gastric smooth muscle group > the control group, the difference was statistically significant ($P < 0.05$). ROC analysis showed that the area under the curve of CEA and CA19-9 was 0. 879 and 0. 782, respectively.

CONCLUSION
Enhanced CT has shown value in differentiating small mesenchymal tumors of the stomach and intestines from smooth muscle tumors.

Key Words: Smooth muscle tumour; Stomach; Intestines; Differentiation

Core Tip: Endoscopic ultrasound can accurately localise the lesion characteristics, and there are significant differences in the echogenic characteristics of intragastric mesenchymal tumours and smooth muscle tumours. In view of the fact that early metastases can occur in gastrointestinal mesenchymal tumours of less than 2 cm in diameter, endoscopic resection is recommended for the definitive diagnosis and simultaneous treatment or closer follow-up of intrinsic mesenchymal tumours with a clear echogenic border and less than 2 cm in diameter.

Citation: Nie WJ, Jing Z, Hua M. Value of enhanced computed tomography in differentiating small mesenchymal tumours of the gastrointestinal from smooth muscle tumours. *World J Gastrointest Surg* 2023; 15(9): 2012-2020
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/2012.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.2012

INTRODUCTION

Gastric cancer is one of the most common malignancies and is among the top three leading causes of cancer-related deaths worldwide[1-11]. According to the Japanese Classification Criteria for Gastric Cancer, early gastric cancer is defined as a lesion in which tumour infiltration is limited to the mucosa or submucosa without consideration of lymph node metastasis (LNM)[12]. In recent years, with the development of endoscopic techniques, endoscopic submucosal dissection (ESD) has been widely used for the treatment of early gastric cancer without LNM, and the indications for ESD in early gastric cancer published by the Japan Gastric Cancer Association classify gastric cancer into differentiated and undifferentiated types[13]. Gastrointestinal mesenchymal tumours (GIMTs), as a mesenchymal-derived tumour with specific histological features, are mainly located in the gastrointestinal tract and abdominal cavity and have a certain chance of malignant transformation and are therefore often diagnosed and treated differently from gastric smooth muscle tumours in clinical practice[14-20].

Although previous clinical reports have shown that GIMTs are rare[21], recent epidemiological studies have shown that 10%-30% of patients with GIMTs have no obvious clinical symptoms, but 15%-50% of patients may have metastases to the liver and abdominal cavity once detected, missing the best time for treatment. Currently, the clinical diagnosis of GIMTs mainly relies on imaging and pathology; however, imaging methods such as ultrasound endoscopy and computed tomography (CT) are influenced by the operator's experience and image quality, and cannot accurately determine the nature of the lesion. Besides, the pathological examination requires endoscopy or surgery to obtain the pathological tissue, which is invasive and painful for patients, and pathological examination is not real-time[22-27]. As a convenient and common clinical test, CT has been widely used in the diagnosis, efficacy and prognosis of clinical tumors, and can be used for the identification of GIMTs[28]. Herein, we retrospectively analysed the clinical data of patients (volunteers) who received treatment or health check-ups in our hospital in recent years and investigated the value of CT in the differential diagnosis of patients with gastric mesenchymal tumours and gastric smooth muscle tumours.

MATERIALS AND METHODS

General information

The clinical data of patients with gastric mesenchymal or gastric smooth muscle tumours who were treated in our hospital from May 2018 to April 2023 were retrospectively analyzed. Patients were divided into the gastric mesenchymal tumor group and the gastric smooth muscle tumor group respectively ($n = 50$ cases per group). Clinical data of 50 healthy volunteers who underwent physical examination in the same hospital during the same period were selected and included in the control group. The gastric mesenchymal tumor group included 24 males and 26 females, aged 38 to 72 years (mean

age: 56.73 ± 7.46 years) and with a body mass index (BMI) of 18-24 kg/m^2 (mean BMI: 21.76 ± 2.21 kg/m^2). The gastric smooth muscle tumor group included 22 males and 28 females, aged 36 to 71 years (mean age: 57.11 ± 7.18 years) and with a BMI of 18-24 kg/m^2 (mean BMI: 21.89 ± 2.14 kg/m^2). The control group included 21 males and 29 females, aged 38-70 years (mean age: 55.82 ± 7.39 years) and with a BMI of 18-24 kg/m^2 (mean BMI: 21.76 ± 2.21 kg/m^2). The differences between the three groups were not statistically significant (P > 0. 05) and were comparable. Confidentiality of all patient information was maintained in this study.

Inclusion criteria

Inclusion criteria including: (1) Patients with gastric mesenchymal tumour or gastric smooth muscle tumour, all confirmed by postoperative pathological histology, healthy volunteers with no significant abnormalities by gastric ultrasound; (2) 42-72 years old; and (3) Complete clinical data of patients (or volunteers).

Exclusion criteria

Exclusion criteria including: (1) Organic heart, liver, or kidney dysfunction; (2) Patients with combined cancer of other tissues or a history of radiotherapy; (3) Unable to participate in this study due to psychiatric illness or other reasons; (4) Combined coagulation disorders or autoimmune diseases; and (5) A history of gastrectomy.

Methodology

Approximately 5 mL of fasting venous blood was collected from all patients (or volunteers) during the preoperative examination, centrifuged and stored at -80 °C, and the serum levels of carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), carbohydrate antigen 19-9 (CA19-9), CA-125 and cytokeratin 19 fragment antigen 21-1 (CYFRA21-1) were measured by electrochemiluminescence. The immunoassay was performed using relevant kits on a Beckman Coulter AU5800 fully automated biochemical analyzer (Beckman, United States).

Observation indicators

Serum levels of CEA, AFP, CA19-9, CA-125 and CYFRA21-1 levels were compared among the three groups. The value of CEA and CA19-9 in identifying gastric mesenchymal tumours was analysed using the receiver operating characteristic (ROC) curve. The ROC curves of CEA and CA19-9 in identifying gastric mesenchymal tumours were plotted separately based on the pathological results of the patients. The area of the lower curve for each measure was calculated, and the area of the lower curve > 0.5 indicated that the measure had diagnostic efficacy, and the closer it was to 1, the higher its diagnostic efficacy.

Statistical methods

All data were processed using SPSS 22. 0 statistical software and were expressed as mean ± standard deviation (mean ± SD) or percentages (%). The χ^2 test was used to analyze categorical variables. One-way ANOVA was used to compare multiple groups. The ROC curve was used to analyze the value of CEA and CA19-9 in the diagnosis of gastric mesenchymal tumours. The Kappa test was used for consistency.

RESULTS

Gastric mesenchymal and smooth muscle tumours on plain gastroscopy and endoscopic ultrasound

Both intragastric mesenchymal tumours and smooth muscle tumours were found in the fundus and body of the stomach, with no statistically significant difference in the distribution of lesions (P = 0.32). The diameter of mesenchymal tumours was larger than that of smooth muscle tumours, and the difference was statistically significant (P < 0.05). Both mesenchymal and smooth muscle tumours were smooth, erosive, or ulcerated in surface morphology, with no statistically significant difference (P = 0.61). The intrinsic muscular layer and the mucosal muscular layer were the most common sites of origin for both mesenchymal tumours and smooth muscle tumours. The difference was not statistically significant (P = 1.0). At endoscopic ultrasound (EUS), mesenchymal tumours appeared as hypoechoic lesions and smooth muscle tumours appeared as hypoechoic and isoechoic lesions. In terms of echogenicity, the echogenic non-uniformity of mesenchymal tumours was more pronounced than that of smooth muscle tumours (P < 0.05) see Table 1.

Comparison of the levels of each tumour marker among the three groups

CEA levels varied among the three groups in the following order: The gastric mesenchymal tumour group > the control group > the gastric smooth muscle tumour group. CA19-9 levels varied among the three groups in the following order: The gastric mesenchymal group > the gastric smooth muscle group > the control group, the differences were statistically significant (P < 0. 05) see Table 2.

ROC curve analysis of CEA and CA19-9 levels for the identification of gastric mesenchymal tumours

The area under the curve (AUC) for the identification of gastric mesenchymal tumours by CEA and CA19-9 was 0. 879 and 0. 782, respectively (Table 3). The ROC curves for the identification of gastric mesenchymal tumours by CEA and CA19-9 are shown in Figure 1.

Table 1 Gastric mesenchymal and smooth muscle tumours on plain gastroscopy and endoscopic ultrasound

Clinical parameters	Intragastric mesenchymal tumour	Smooth muscle tumour
Male	24 (48.0)	22 (44.0)
Female	26 (52.0)	28 (56.0)
Age, yr	50.5 ± 14.0[a]	57.9 ± 9.5
Location, %		
Cardia	0	1 (2.0)
Gastric base	26 (52.0)	12 (24.0)
Gastric body	18 (36.0)	11 (22.0)
Gastric sinus	9 (18.0)	2 (4.0)
Diameter, mm	16.2 ± 9.9[a]	9.7 ± 5.0
Level of origin, %		
Mucosal muscle layer	2 (3.8)	1 (2.0)
Inherent muscle layer	48 (96.0)	25 (50.0)
Indicated ulcers, %		
Yes	6 (12.0)	2 (4.0)
None	47 (94.0)	24 (48.0)
Echo characteristics, %		
Low echo	50 (100)	47 (94.0)
Waiting for an echo	0	1 (2.0)
High echo		0
Echo uniformity, %		
Uniformity	25 (49.1)[a]	50 (100)
Non-homogeneous	27 (50.0)[a]	0

[a]$P < 0.05$ compared with the gastric mesenchymal tumour group.

Table 2 Comparison of tumour marker levels among the three groups (mean ± SD)

Group	*n*	CEA (ng/mL)	CA19-9 (ng/mL)	CA-125 (kU/L)	AFP (ng/mL)	CYFRA21-1 (U/mL)
Gastric mesenchymal tumour group	50	1.53 ± 0.24	9.32 ± 2.18	44.34 ± 10.67	5.46 ± 1.18	8.17 ± 1.57
Gastric smooth muscle tumour group	50	0.67 ± 0.15[a]	8.37 ± 1.81[a]	41.56 ± 8.74	5.03 ± 0.86	7.44 ± 1.69
Control group	50	1.04 ± 0.18[a,b]	6.45 ± 1.39[a,b]	39.67 ± 7.98	5.29 ± 0.74	7.67 ± 1.88
F value		198.507	25.753	2.608	2.100	1.888
P value		0.000	0.000	0.078	0.127	0.156

[a]$P < 0.05$ compared with the gastric mesenchymal tumour group.
[b]$P < 0.05$ compared with the gastric smooth muscle group.
CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; CA-125: Carbohydrate antigen 125; AFP: Alpha-fetoprotein; CYFRA21-1: Cytokeratin 19 fragment antigen 21-1.

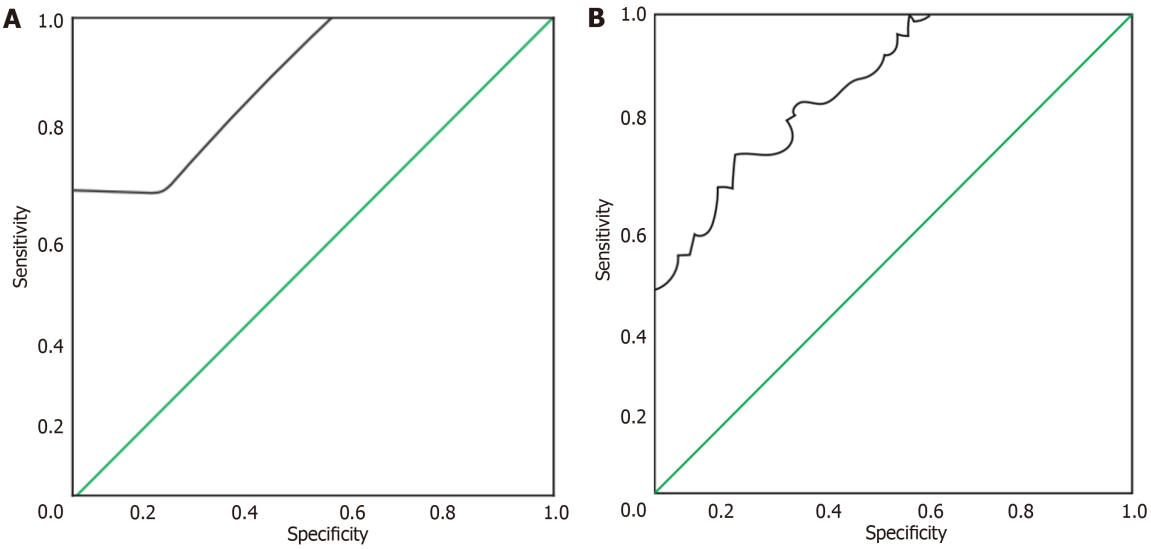
DISCUSSION

The treatment methods for GIMTs have been rapidly changing with the development of medical treatment technology in recent years, and there are various methods commonly used for differential diagnosis in clinical practice[29-35]. However, the sensitivity of single tumour markers is low, and there is a certain degree of underdiagnosis; thus, combined detection of tumour markers is necessary for the diagnosis of GIMTs[36]. The present study analysed the expression of

Table 3 Receiver operating characteristic curve analysis of carcinoembryonic antigen and carbohydrate antigen 19-9 levels for the diagnosis of gastric mesenchymal tumour

Indicators	Area under the curve	Standard error	*P* value	95%CI	Optimal cut-off value	Sensitivity	Specificity
CEA	0.879	0.036	0.000	0.808-0.950	1.145	0.850	0.675
CA19-9	0.782	0.050	0.000	0.684-0.880	8.880	0.600	0.800

CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9.



DOI: 10.4240/wjgs.v15.i9.2012

Figure 1 Receiver operating characteristic curve for the diagnosis of gastric mesenchymal tumour. A: Carcinoembryonic antigen; B: Carbohydrate antigen 19-9.

CEA, AFP, CA19-9, CA-125 and CYFRA21-1 in patients with gastric mesenchymal and smooth muscle tumours to provide a reference for clinical diagnosis. The results showed that CEA levels varied among the three groups in the following order: The gastric mesenchymal tumour group > control group > gastric smooth muscle tumour group, and CA19-9 levels varied in the following order: The gastric mesenchymal tumour group > gastric smooth muscle group > control group, suggesting that CEA and CA19-9 were differentially expressed in patients (or volunteers) with different gastric lesions. Tumour markers are chemical substances that reflect the presence of tumours and are synthesised and released by tumour cells during tumourigenesis and proliferation or are important for the host's responsiveness to cancer [37]. Their formation or change in expression in the blood can indicate the nature of the tumour and thus help the clinician to understand their role in tumour histogenesis, cell differentiation and cell function. Common tumour markers can be classified into embryonic antigens, glycoproteins, kinins, enzymes and oncogene products according to their composition, with CEA being a protein and CA19-9 and CA-125 being glycoantigens[38].

Mesenchymal and smooth muscle tumours are the predominant mesenchymal-derived tumours of the gastrointestinal tract and the most common cause of submucosal lesions. Mesenchymal tumours originate from the interstitial cells of Cajal or mesenchymal stem cells in the gastrointestinal tract. It is currently thought that mutations in the C-kit or platelet-derived growth factor receptor A gene activation are important causes of mesenchymal tumours. Mesenchymal tumours are characterised by dynamic non-directional differentiation and potential malignancy, and even mesenchymal tumours with very low malignant potential may metastasise[39].

Pathological examination and immunohistochemistry are the gold standard for differentiating mesenchymal tumours from smooth muscle tumours. EUS is a non-invasive method that can assist in the diagnosis of the nature of the lesion and the choice of treatment by observing the level of origin, size and echogenicity of the lesion. The identification of the differences by comparing EUS features of intragastric mesenchymal tumours with those of smooth muscle tumours may spare patients with smooth muscle tumours from undergoing resection, while smaller diameter mesenchymal tumours may be diagnosed early, and intervention may be possible.

The data from this study show that mesenchymal tumours are more common than smooth leiomyosarcomas in the augmentation of the stomach, which is consistent with the finding in national studies[40-43]. Both appear as round or oval submucosal masses on plain endoscopy, with some visible surface erosions or ulcers, making differential diagnosis difficult. On EUS, mesenchymal tumours are usually of intramucosal origin, with a few originating in the mucosal layer, and appear as round or oval masses, which may be homogeneously hypoechoic, heterogeneously echogenic or hype-

rechoic with hyperechogenicity. A careful analysis of the endoscopic features of the two tumours revealed no statistically significant differences in the distribution of lesions within the stomach or in the level of origin. In terms of tumour size, the diameter of the mesenchymal tumour was larger than that of the smooth muscle tumour, and the difference was statistically significant. Surface ulceration is an important criterion for differentiating benign and malignant GIMTs, and is often used as a criterion for differentiating mesenchymal tumours from smooth muscle tumours[44]. However, our study found no statistically significant difference between mesenchymal and smooth muscle tumours. The difference in internal echogenicity was statistically significant, particularly in the presence of hyperechoic hyperechogenicity, which was only observed in mesenchymal tumours and not in smooth muscle tumours. The greater the difference in the density between the two sides of the interface and the faster the speed of sound, the higher the acoustic impedance and the echogram signal.

Therefore, the number of cells, their tight arrangement, the presence of liquefied necrosis, calcification and the amount of fibrous cell content are the factors that make up the ultrasound interface and the pathological basis of the ultrasound image in submucosal tumours. As previously discussed, mesenchymal tumours are richer in cells, more variable in their morphology and arrangement and more likely to undergo secondary changes than smooth muscle tumours, leading to differences in their echogenic characteristics.

CONCLUSION

In summary, EUS can accurately localise lesion characteristics, and there are significant differences in the echogenic characteristics of intragastric mesenchymal and smooth muscle tumours. Since early metastases can occur in GIMTs of less than 2 cm in diameter, endoscopic resection is recommended for the definitive diagnosis and simultaneous treatment or closer follow-up of intrinsic mesenchymal tumours with a clear echogenic border and less than 2 cm in diameter. The diagnosis of smooth muscle tumour is more likely for lesions with homogeneous echogenicity, well-defined borders and an intrinsic muscle layer of less than 2 cm in diameter, and patients can be advised to follow up. Overall, EUS can provide a strong basis for differentiating mesenchymal and smooth muscle tumours of less than 2 cm in diameter in the stomach and for clinical decision-making.

ARTICLE HIGHLIGHTS

Research background

With the development of computed tomography technology, the differentiation of small mesenchymal tumors of the stomach and intestines from for smooth muscle tumors has been gradually used in this method.

Research motivation

To retrospectively analyze the clinical data of patients with gastric mesenchymal tumor and gastric smooth muscle tumor treated in our hospital from May 2018 to April 2023, and include them into the gastric mesenchymal tumor group and the gastric smooth muscle tumor group respectively, both groups consisted of 50 cases, and the clinical data of 50 healthy volunteers who received physical examination in our hospital during the same period were selected and included into the control group; to compare the serum carcinoembryonic antigen (CEA), alpha-fetoprotein, carbohydrate antigen 19-9 (CA19-9).

Research objectives

The Kappa test was used to analyse the consistency of the combined CEA and CA19-9 test in identifying gastric mesenchymal tumours.

Research methods

Clinical data of patients with gastric mesenchymal or gastric smooth muscle tumours who were treated in our hospital from May 2018 to April 2023 were retrospectively analysed. The value of CEA and CA19-9 in the identification of gastric mesenchymal tumours was analysed using the receiver operating characteristic curve.

Research results

When comparing the CEA levels of the three groups, the gastric mesenchymal tumour group > the control group > the gastric smooth muscle tumour group; when comparing the CA19-9 levels of the three groups, the gastric mesenchymal group > the gastric smooth muscle group > the control group, the difference was statistically significant ($P < 0.05$). The area under the curve of CEA and CA19-9 was 0. 879 and 0. 782, respectively, by receiver operating characteristic analysis.

Research conclusions

We proposed the theory of nodular and vesicle types domestically through observation, and made breakthroughs in overcoming the issue of inaccurate diagnosis based on a few independent early-stage case reports.

Research perspectives

According to the different partings under endoscopy, the clinical symptoms, therapeutic efficacy, and prognosis of patients with primary enteric lymphangiectasis were observed.

FOOTNOTES

Author contributions: Nie WJ and Hua M contributed equally to this work; Hua M designed the study; Zhao J contributed to the analysis of the manuscript; Nie WJ and Hua M were involved in the data and writing of this article; and all authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the (Changzhou Geriatric Hospital Affiliated to Soochow University, Changzhou No. 7 People's Hospital Radiology Department) Institutional Review Board.

Informed consent statement: All study participants and their legal guardians provide informed written consent before the study recruitment.

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

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Wen-Jun Nie 0009-0005-7627-2621; Mo Hua 0009-0006-4489-3391.

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

REFERENCES

1 **Miettinen M**, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch Pathol Lab Med* 2006; **130**: 1466-1478 [PMID: 17090188 DOI: 10.5858/2006-130-1466-GSTROM]
2 **Xing JJ**, Huang WP, Wang F, Chai YR, Gao JB. Computed tomography features and clinicopathological characteristics of gastric glomus tumor. *BMC Gastroenterol* 2022; **22**: 174 [PMID: 35397495 DOI: 10.1186/s12876-022-02241-w]
3 **Papanikolaou IS**, Triantafyllou K, Kourikou A, Rösch T. Endoscopic ultrasonography for gastric submucosal lesions. *World J Gastrointest Endosc* 2011; **3**: 86-94 [PMID: 21772939 DOI: 10.4253/wjge.v3.i5.86]
4 **Jo VY**, Doyle LA. Refinements in Sarcoma Classification in the Current 2013 World Health Organization Classification of Tumours of Soft Tissue and Bone. *Surg Oncol Clin N Am* 2016; **25**: 621-643 [PMID: 27591490 DOI: 10.1016/j.soc.2016.05.001]
5 **Tanaka J**, Oshima T, Hori K, Tomita T, Kim Y, Watari J, Oh K, Hirota S, Matsumoto T, Miwa H. Small gastrointestinal stromal tumor of the stomach showing rapid growth and early metastasis to the liver. *Dig Endosc* 2010; **22**: 354-356 [PMID: 21175497 DOI: 10.1111/j.1443-1661.2010.01032.x]
6 **Virani N**, Pang J, Lew M. Cytologic and Immunohistochemical Evaluation of Low-Grade Spindle Cell Lesions of the Gastrointestinal Tract. *Arch Pathol Lab Med* 2016; **140**: 1038-1044 [PMID: 27684974 DOI: 10.5858/arpa.2016-0235-RA]
7 **Kudo M**. Immuno-Oncology Therapy for Hepatocellular Carcinoma: Current Status and Ongoing Trials. *Liver Cancer* 2019; **8**: 221-238 [PMID: 31602367 DOI: 10.1159/000501501]
8 **Vij M**, Agrawal V, Kumar A, Pandey R. Gastrointestinal stromal tumors: a clinicopathological and immunohistochemical study of 121 cases. *Indian J Gastroenterol* 2010; **29**: 231-236 [PMID: 21221881 DOI: 10.1007/s12664-010-0079-z]
9 **Miura H**, Tanaka K, Umeda Y, Ikenoyama Y, Yukimoto H, Hamada Y, Yamada R, Tsuboi J, Nakamura M, Katsurahara M, Horiki N, Nakagawa H. Usefulness of magnifying endoscopy with acetic acid and narrow-band imaging for the diagnosis of duodenal neoplasms: proposal of a diagnostic algorithm. *Surg Endosc* 2022; **36**: 8086-8095 [PMID: 35449476 DOI: 10.1007/s00464-022-09239-1]
10 **Hirano K**, Nagata A, Akahane K, Yonekura H, Tomioka I, Kobayashi T, Kawa S, Shimakura K, Oguchi H, Furuta S. [Clinical significance of the fecal chymotrypsin test in chronic pancreatitis--comparative study of its value with the pancreozymin-secretin test, PFD test, and endoscopic retrograde pancreatography]. *Nihon Shokakibyo Gakkai Zasshi* 1985; **82**: 2964-2972 [PMID: 3831448]
11 **Sakamoto H**, Kitano M, Kudo M. Diagnosis of subepithelial tumors in the upper gastrointestinal tract by endoscopic ultrasonography. *World J Radiol* 2010; **2**: 289-297 [PMID: 21160683 DOI: 10.4329/wjr.v2.i8.289]
12 **Akahoshi K**, Oya M, Koga T, Shiratsuchi Y. Current clinical management of gastrointestinal stromal tumor. *World J Gastroenterol* 2018; **24**: 2806-2817 [PMID: 30018476 DOI: 10.3748/wjg.v24.i26.2806]
13 **Akahoshi K**, Sumida Y, Matsui N, Oya M, Akinaga R, Kubokawa M, Motomura Y, Honda K, Watanabe M, Nagaie T. Preoperative diagnosis of gastrointestinal stromal tumor by endoscopic ultrasound-guided fine needle aspiration. *World J Gastroenterol* 2007; **13**: 2077-2082 [PMID:

17465451 DOI: 10.3748/wjg.v13.i14.2077]
14 **Levy MJ**, Jondal ML, Clain J, Wiersema MJ. Preliminary experience with an EUS-guided trucut biopsy needle compared with EUS-guided FNA. *Gastrointest Endosc* 2003; **57**: 101-106 [PMID: 12518144 DOI: 10.1067/mge.2003.49]
15 **Xiu H**, Zhao CY, Liu FG, Sun XG, Sun H, Liu XS. Comparing about three types of endoscopic therapy methods for upper gastrointestinal submucosal tumors originating from the muscularis propria layer. *Scand J Gastroenterol* 2019; **54**: 1481-1486 [PMID: 31814460 DOI: 10.1080/00365521.2019.1692064]
16 **Gheorghe G**, Bacalbasa N, Ceobanu G, Ilie M, Enache V, Constantinescu G, Bungau S, Diaconu CC. Gastrointestinal Stromal Tumors-A Mini Review. *J Pers Med* 2021; **11** [PMID: 34442339 DOI: 10.3390/jpm11080694]
17 **Fernandes MR**, Ghezzi CLA, Grezzana-Filho TJ, Feier FH, Leipnitz I, Chedid AD, Cerski CTS, Chedid MF, Kruel CRP. Giant hepatic extra-gastrointestinal stromal tumor treated with cytoreductive surgery and adjuvant systemic therapy: A case report and review of literature. *World J Gastrointest Surg* 2021; **13**: 315-322 [PMID: 33796218 DOI: 10.4240/wjgs.v13.i3.315]
18 **Kim HJ**, Park JY, Kim BJ, Kim JG, Kim HS, Park JM. Gastric Gastrointestinal Stromal Tumor with Repeated Recurrence at the Anastomosis Site in a Very Elderly Patient. *Korean J Gastroenterol* 2020; **76**: 206-210 [PMID: 33100316 DOI: 10.4166/kjg.2020.76.4.206]
19 **Martínez-Camblor P**, Pardo-Fernández JC. Smooth time-dependent receiver operating characteristic curve estimators. *Stat Methods Med Res* 2018; **27**: 651-674 [PMID: 29187044 DOI: 10.1177/0962280217740786]
20 **Chiu PWY**, Yip HC, Teoh AYB, Wong VWY, Chan SM, Wong SKH, Ng EKW. Per oral endoscopic tumor (POET) resection for treatment of upper gastrointestinal subepithelial tumors. *Surg Endosc* 2019; **33**: 1326-1333 [PMID: 30604266 DOI: 10.1007/s00464-018-06627-4]
21 **Mekras A**, Krenn V, Perrakis A, Croner RS, Kalles V, Atamer C, Grützmann R, Vassos N. Gastrointestinal schwannomas: a rare but important differential diagnosis of mesenchymal tumors of gastrointestinal tract. *BMC Surg* 2018; **18**: 47 [PMID: 30045739 DOI: 10.1186/s12893-018-0379-2]
22 **Roberto GA**, Rodrigues CMB, Peixoto RD, Younes RN. Gastric neuroendocrine tumor: A practical literature review. *World J Gastrointest Oncol* 2020; **12**: 850-856 [PMID: 32879663 DOI: 10.4251/wjgo.v12.i8.850]
23 **Balakrishnan M**, George R, Sharma A, Graham DY. Changing Trends in Stomach Cancer Throughout the World. *Curr Gastroenterol Rep* 2017; **19**: 36 [PMID: 28730504 DOI: 10.1007/s11894-017-0575-8]
24 **Japanese Gastric Cancer Association**. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101-112 [PMID: 21573743 DOI: 10.1007/s10120-011-0041-5]
25 **Rausei S**, Dionigi G, Boni L. Evaluation of the Seventh American Joint Committee on Cancer/International Union Against Cancer Classification of gastric adenocarcinoma in comparison with the sixth classification. *Cancer* 2011; **117**: 2823-4; author reply 2824 [PMID: 21264825 DOI: 10.1002/cncr.25801]
26 **Seo HS**, Lee GE, Kang MG, Han KH, Jung ES, Song KY. Mixed Histology Is a Risk Factor for Lymph Node Metastasis in Early Gastric Cancer. *J Surg Res* 2019; **236**: 271-277 [PMID: 30694766 DOI: 10.1016/j.jss.2018.11.055]
27 **Takizawa K**, Ono H, Kakushima N, Tanaka M, Hasuike N, Matsubayashi H, Yamagichi Y, Bando E, Terashima M, Kusafuka K, Nakajima T. Risk of lymph node metastases from intramucosal gastric cancer in relation to histological types: how to manage the mixed histological type for endoscopic submucosal dissection. *Gastric Cancer* 2013; **16**: 531-536 [PMID: 23192620 DOI: 10.1007/s10120-012-0220-z]
28 **Russel SM**, Geraghty JR, Renaldy H, Thompson TM, Hirshfield LE. Training for Professional Uncertainty: Socialization of Medical Students Through the Residency Application Process. *Acad Med* 2021; **96**: S144-S150 [PMID: 34348371 DOI: 10.1097/ACM.0000000000004303]
29 **Santiago JM**, Sasako M, Osorio J. [TNM-7th edition 2009 (UICC/AJCC) and Japanese Classification 2010 in Gastric Cancer. Towards simplicity and standardisation in the management of gastric cancer]. *Cir Esp* 2011; **89**: 275-281 [PMID: 21256476 DOI: 10.1016/j.ciresp.2010.10.011]
30 **Japanese Gastric Cancer Association**. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer* 2021; **24**: 1-21 [PMID: 32060757 DOI: 10.1007/s10120-020-01042-y]
31 **Ikeguchi M**, Murakami D, Kanaji S, Ohro S, Maeta Y, Yamaguchi K, Tatebe S, Kondo A, Tsujitani S, Kaibara N. Lymph node metastasis of gastric cancer: comparison of Union International Contra Cancer and Japanese systems. *ANZ J Surg* 2004; **74**: 852-854 [PMID: 15456431 DOI: 10.1111/j.1445-1433.2004.03188.x]
32 **Gotoda T**, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, Kato Y. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000; **3**: 219-225 [PMID: 11984739 DOI: 10.1007/pl00011720]
33 **Park HK**, Lee KY, Yoo MW, Hwang TS, Han HS. Mixed Carcinoma as an Independent Prognostic Factor in Submucosal Invasive Gastric Carcinoma. *J Korean Med Sci* 2016; **31**: 866-872 [PMID: 27247494 DOI: 10.3346/jkms.2016.31.6.866]
34 **Yang S**, Gu X, Tao R, Huo J, Hu Z, Sun F, Ni J, Wang X. Relationship between histological mixed-type early gastric cancer and lymph node metastasis: A systematic review and meta-analysis. *PLoS One* 2022; **17**: e0266952 [PMID: 35427370 DOI: 10.1371/journal.pone.0266952]
35 **Yang P**, Zheng XD, Wang JM, Geng WB, Wang X. Undifferentiated-predominant mixed-type early gastric cancer is more aggressive than pure undifferentiated type: a systematic review and meta-analysis. *BMJ Open* 2022; **12**: e054473 [PMID: 35393309 DOI: 10.1136/bmjopen-2021-054473]
36 **Song KY**, Hyung WJ, Kim HH, Han SU, Cho GS, Ryu SW, Lee HJ, Kim MC; Korean Laparoscopic Gastrointestinal Surgery Study (KLASS) Group. Is gastrectomy mandatory for all residual or recurrent gastric cancer following endoscopic resection? A large-scale Korean multi-center study. *J Surg Oncol* 2008; **98**: 6-10 [PMID: 18521830 DOI: 10.1002/jso.21074]
37 **Ryu KW**, Choi IJ, Doh YW, Kook MC, Kim CG, Park HJ, Lee JH, Lee JS, Lee JY, Kim YW, Bae JM. Surgical indication for non-curative endoscopic resection in early gastric cancer. *Ann Surg Oncol* 2007; **14**: 3428-3434 [PMID: 17899290 DOI: 10.1245/s10434-007-9536-z]
38 **Hatta W**, Gotoda T, Oyama T, Kawata N, Takahashi A, Yoshifuku Y, Hoteya S, Nakagawa M, Hirano M, Esaki M, Matsuda M, Ohnita K, Yamanouchi K, Yoshida M, Dohi O, Takada J, Tanaka K, Yamada S, Tsuji T, Ito H, Hayashi Y, Nakaya N, Nakamura T, Shimosegawa T. A Scoring System to Stratify Curability after Endoscopic Submucosal Dissection for Early Gastric Cancer: "eCura system". *Am J Gastroenterol* 2017; **112**: 874-881 [PMID: 28397873 DOI: 10.1038/ajg.2017.95]
39 **Takizawa K**, Ono H, Muto M. Current indications of endoscopic submucosal dissection for early gastric cancer in Japan. *Jpn J Clin Oncol* 2019; **49**: 797-802 [PMID: 31322655 DOI: 10.1093/jjco/hyz100]
40 **Mikami K**, Hirano Y, Futami K, Maekawa T. Expansion of lymph node metastasis in mixed-type submucosal invasive gastric cancer. *Asian J Surg* 2018; **41**: 462-466 [PMID: 28732676 DOI: 10.1016/j.asjsur.2017.04.004]
41 **Sun F**, Zhang S, Wang X, Yao M, Zhang C, Liu Z, Ai S, Guan W, Wang M. Mixed Histologic Type is a Risk Factor for Lymph Node Metastasis in Submucosal Invasive Early Gastric Cancer. *J Surg Res* 2023; **282**: 160-167 [PMID: 36306586 DOI: 10.1016/j.jss.2022.09.013]

42 **Komatsu S**, Ichikawa D, Miyamae M, Shimizu H, Konishi H, Shiozaki A, Fujiwara H, Okamoto K, Kishimoto M, Otsuji E. Histological mixed-type as an independent prognostic factor in stage I gastric carcinoma. *World J Gastroenterol* 2015; **21**: 549-555 [PMID: 25593472 DOI: 10.3748/wjg.v21.i2.549]

43 **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]

44 **Chen JN**, Wang QW, Zhang QW, Tang ZR, Li XB. Poorly differentiated is more significant than signet ring cell component for lymph node metastasis in mixed-type early gastric cancer: a retrospective study from a large-volume hospital. *Surg Endosc* 2021; **35**: 1558-1565 [PMID: 32277355 DOI: 10.1007/s00464-020-07532-5]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 2021-2031

DOI: 10.4240/wjgs.v15.i9.2021

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Risk factors for myocardial injury during living donor liver transplantation in pediatric patients with biliary atresia

Yu-Li Wu, Tian-Ying Li, Xin-Yuan Gong, Lu Che, Ming-Wei Sheng, Wen-Li Yu, Yi-Qi Weng

Specialty type: Anesthesiology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Tchilikidi KY, Russia; Tsoulfas G, Greece

Received: June 23, 2023
Peer-review started: June 23, 2023
First decision: July 4, 2023
Revised: July 10, 2023
Accepted: July 27, 2023
Article in press: July 27, 2023
Published online: September 27, 2023

Yu-Li Wu, The First Central Clinical School, Tianjin Medical University, Tianjin 300192, China

Tian-Ying Li, School of Medicine, Nankai University, Tianjin 300071, China

Xin-Yuan Gong, Department of Science and Education, Tianjin First Central Hospital, Tianjin 300192, China

Lu Che, Ming-Wei Sheng, Wen-Li Yu, Yi-Qi Weng, Department of Anesthesiology, Tianjin First Central Hospital, Tianjin 300192, China

Corresponding author: Yi-Qi Weng, Doctor, PhD, Chief Physician, Professor, Department of Anesthesiology, Tianjin First Central Hospital, No. 24 Fukang Road, Nankai District, Tianjin 300192, China. wyq2023@nankai.edu.cn

Abstract

BACKGROUND

Cold ischemia-reperfusion of the liver is an inevitable occurrence in liver transplantation that may also cause damage to the heart. Perioperative myocardial injury during liver transplantation can increase the incidence of post-operative mortality, but there is little research on the incidence of myocardial injury in children who undergo living donor liver transplantation (LDLT). Therefore, this study mainly explores the independent risk factors for myocardial injury in children who undergo LDLT.

AIM

To analyze the data of children who underwent LDLT to determine the risk factors for intraoperative myocardial injury.

METHODS

We retrospectively analyzed the inpatient records of pediatric patients who underwent LDLT in Tianjin First Central Hospital from January 1, 2020, to January 31, 2022. Recipient-related data and donor-related data were collected. The patients were divided into a myocardial injury group and a nonmyocardial injury group according to the value of the serum cardiac troponin I at the end of surgery for analysis. Univariate analysis and multivariate logistic regression were used to evaluate the risk factors for myocardial injury during LDLT in pediatric patients.

RESULTS
A total of 302 patients met the inclusion criteria. The myocardial injury group had 142 individuals (47%), and the nonmyocardial injury group included 160 patients (53%). Age, height, and weight were significantly lower in the myocardial injury group ($P < 0.001$). The pediatric end-stage liver disease (PELD) score, total bilirubin, and international standardized ratio were significantly higher in the myocardial injury group ($P < 0.001$). The mean arterial pressure, lactate, hemoglobin before reperfusion, duration of the anhepatic phase, cold ischemic time, incidence of postreperfusion syndrome (PRS), and fresh frozen plasma transfusion were significantly different between the two groups ($P < 0.05$). The postoperative intensive care unit stay and peak total bilirubin values in the first 5 d after LDLT were significantly higher in the myocardial injury group ($P < 0.05$). The pediatric patients with biliary atresia in the nonmyocardial injury group who underwent LDLT had a considerably higher one-year survival rate than those in the myocardial injury group ($P = 0.015$). Multivariate logistic regression revealed the following independent risk factors for myocardial injury: a high PELD score [odds ratio (OR) = 1.065, 95% confidence interval (CI): 1.013-1.121; $P = 0.014$], a long duration of the anhepatic phase (OR = 1.021, 95%CI: 1.003-1.040; $P = 0.025$), and the occurrence of intraoperative PRS (OR = 1.966, 95%CI: 1.111-3.480; $P = 0.020$).

CONCLUSION
A high PELD score, a long anhepatic phase duration, and the occurrence of intraoperative PRS were independent risk factors for myocardial injury during LDLT in pediatric patients with biliary atresia.

Key Words: Heart injuries; Child; Liver transplantation; Reperfusion injury; Prognosis

Core Tip: This is a retrospective study to investigate data for children who underwent living donor liver transplantation to determine risk factors for intraoperative myocardial injury. Myocardial injury during liver transplantation is associated with postoperative adverse outcomes in pediatric patients; it can increase the incidence of postoperative mortality. Our findings demonstrated that a high pediatric end-stage liver disease score, a long anhepatic phase duration, and the occurrence of intraoperative postreperfusion syndrome are independent risk factors for myocardial injury.

Citation: Wu YL, Li TY, Gong XY, Che L, Sheng MW, Yu WL, Weng YQ. Risk factors for myocardial injury during living donor liver transplantation in pediatric patients with biliary atresia. *World J Gastrointest Surg* 2023; 15(9): 2021-2031
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/2021.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.2021

INTRODUCTION

Cold ischemia-reperfusion of the liver is an inevitable pathophysiological occurrence in liver transplantation. This process not only causes liver damage but also causes damage to distant organs such as the heart, brain, and kidneys[1]. Huang *et al*[2] reported that the incidence of perioperative myocardial injuries in adult patients who underwent liver transplantation was 40.4%, while the 30-d mortality rate of patients who developed a myocardial injury was 11.4%, which was significantly higher than that of patients without a myocardial injury. In the research of Sheng *et al*[3], the serum cardiac troponin I (cTnI) level was detected in 123 children who underwent living donor liver transplantation (LDLT), and the results showed that the rate of myocardial injury (cTnI ≥ 0.07 ng/mL) at 30 min in the neohepatic stage was as high as 52%, and cardiovascular adverse events such as ventricular extrasystole and myocardial ischemia could occur during the operation[3]. After noncardiac surgery, myocardial injury is an independent predictor for 30-d mortality[4]. Studies have shown that a myocardial injury is an important cause of postoperative death, and it can lead to an increase in the incidence of postoperative mortality during liver transplantation[5,6]. For a long time, research on myocardial injury has mainly focused on adults, but there is relatively little information on the incidence of myocardial injury in children who have undergone LDLT. Therefore, in this study, our main objective was to further identify the independent risk factors for myocardial injury in pediatric LDLT to provide clinical direction for the prevention of a myocardial injury during LDLT in children.

MATERIALS AND METHODS

Patients

The Institutional Review Committee of Tianjin First Central Hospital (approval No. 2022DZX02) authorized this retrospective observational study. This study included 302 biliary atresia (BA) pediatric patients (< 18 years old) who

underwent LDLT in Tianjin First Central Hospital from January 1, 2020, to January 31, 2022.

Anesthesia protocol

The children arrived without having any anesthetic premedications and were monitored using ECG, pulse oximetry, and noninvasive monitoring. Anesthesia was induced with midazolam (0.15 mg/kg), propofol (2-3 mg/kg), fentanyl (2-5 μg/kg), and rocuronium (0.6-1.0 mg/kg). After intubation, mechanical air flow was performed with a fraction of inspired oxygen (FiO_2) of 50%-60%, a tidal extent of 8-10 mL/kg, a respiratory rate of 20-28/min, an inspiration-to-expiration ratio of (1.0:1.5)-2.0, and an end-tidal CO_2 partial pressure of 30-35 mmHg. Anesthesia was maintained with sevoflurane (1.5%-2.5%), intravenous infusion of propofol (9-15 mg/kg/h), intermittent intravenous fentanyl (1-3 μg/kg), and intravenous infusion of atracurium besylate (1-2 μg/kg/min). Right internal jugular vein puncture was performed under ultrasound guidance to monitor central venous pressure (CVP). A radial artery puncture was performed to monitor invasive arterial pressure. Based on hemodynamic parameters and CVP, albumin and acetate Ringer's solution were used for fluid therapy. Red blood cells (RBCs) were given to maintain a hemoglobin level of 80-100 g/L. The patients' coagulation functions were assessed using a Sonoclot analyzer (Sienco, Inc., Arvada, CO, United States). When there was an obvious coagulation disorder, fresh frozen plasma (FFP) was infused. The patients were monitored, and fluctuations in systolic blood pressure and heart rate during surgery were maintained within 20% of the baseline values. We administered anesthetics, cardioactive drugs, and fluids when hemodynamic changes occurred.

Surgical technique

For the donor, a left lobectomy was performed, and piggyback liver transplantation was performed for the recipient. Histidine-tryptophan-ketoglutarate (HTK) solution was used as a perfusion solution to perfuse the transplanted liver. The specific components of the HTK solution include NaCl, KCl, $MgCl_2 \cdot 6H_2O$, histidine·HCl·H_2O, histidine, tryptophan, mannitol, $CaCl_2 \cdot 2H_2O$, and 2-ketoglutarate-hydrogen-potassium. After occlusion of the inferior vena cava (IVC), the left hepatic vein of the transplanted liver was anastomosed with the recipient hepatic vein, and the IVC was opened after the anastomosis was completed. The donor and recipient portal veins were anastomosed. The opening of the portal vein indicates the start of reperfusion of the liver graft. Venovenous bypass was not performed during the operation. The left hepatic artery of the donor was anastomosed with the hepatic artery of the recipient. The bile duct was connected to the recipient's jejunum (Roux-en-Y cholangiojejunostomy) after arterial reperfusion. The vascular morphology and blood flow velocity were examined by ultrasound after hepatic artery opening and abdominal closure, respectively.

Myocardial injury

The third-generation enhanced AccuTnI assay (Beckman Coulter, Brea, CA, United States) was used to analyze the serum cTnI levels in this study. Myocardial injury was described as cTnI ≥ 0.07 ng/mL, which used to be the lowest value measurable with a 10% coefficient of variation above the 99th percentile upper reference limit (URL) per the manufacturer's instructions[3,4]. Patients were divided into 2 classes based on the serum cTnI level at the end of surgery. The myocardial injury group (cTnI ≥ 0.07 ng/mL) included 142 children, and the nonmyocardial injury group (cTnI < 0.07 ng/mL) included 160 children.

Data collection

The preoperative recipient variables included age, sex, height, weight, left ventricular ejection fraction (LVEF), QT_C interval, pediatric end-stage liver disease (PELD) score, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), international standardized ratio (INR), creatinine (Cr) and hemoglobin. The graft weight, cold ischemia time, hemodynamic parameters, blood gas parameters, central body temperature before reperfusion, anhepatic phase duration, incidence of postreperfusion syndrome (PRS), operation time, anesthesia duration, blood loss, urine volume, blood transfusion volume, and FFP transfusion volume were recorded during the operation. The postoperative observation indexes included the duration of mechanical ventilation, days in the intensive care unit (ICU), days of hospitalization, peak values of ALT, AST, and TB in the first 5 d after the operation, incidence of acute kidney injury (AKI), and 1-year survival rate. AKI was assessed using the kidney disease improving global outcomes (KDIGO) criteria[7].

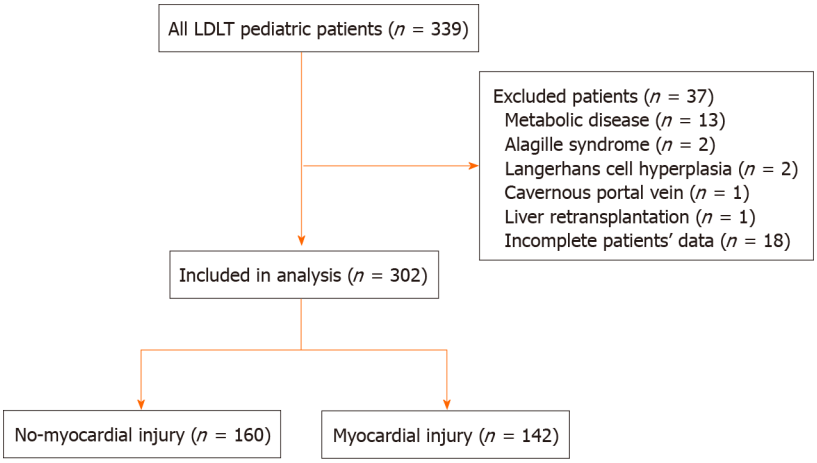
Statistical analysis

All continuous variable data were tested for normality by the Shapiro-Wilk test and Q-Q plots. Measures that conformed to the normal distribution are shown using the mean ± SD, and independent samples *t* tests were applied. The nonnormally distributed continuous variables were expressed using the median (interquartile range), and Mann-Whitney *U* tests were used. Categorical variables are shown by the number of cases and percentages, using the Pearson chi-square test. Potentially relevant variables with *P* values < 0.10 in the univariate analysis were further examined by stepwise binary logistic regression to find the independent risk factors connected to myocardial injury. The data are reported in the form of odds ratios (ORs) and corresponding 95% confidence intervals (CIs). The survival status of the patients was determined using the Kaplan-Meier method. The log-rank test was used to compare the survival status of the two groups. SPSS software version 20.0 (SPSS, Inc., Chicago, IL, United States) was used for statistical analysis. All variables with *P* values < 0.05 were considered statistically significant.

Table 1 Preoperative recipient-related data

Variable	Non-myocardial injury (*n* = 160)	Myocardial injury (*n* = 142)	*P* value
Age (mo)	9.5 (6.0-16.8)	7.0 (6.0-11.0)	< 0.001
Male gender (%)	78 (48.8)	72 (50.7)	0.735
Height (cm)	70 (65-82)	65 (62-70)	< 0.001
Weight (kg)	8.0 (6.5-11.0)	7.0 (6.0-8.0)	< 0.001
LVEF (%)	64 (62-67)	65 (62-67)	0.167
QTc(ms)	404 (387-427)	405 (384-424)	0.596
PELD score	14 (4-21)	22 (15-28)	< 0.001
ALT (U/L)	106 (61-168)	103 (70-172)	0.494
AST (U/L)	177 (103-319)	196 (129-295)	0.186
TB (μmol/L)	166 (40-278)	262 (157-349)	< 0.001
INR	1.29 (1.09-1.63)	1.52 (1.23-2.04)	< 0.001
Cr (μmol/L)	14.0 (12.0-16.0)	13.5 (10.0-16.0)	0.528
Hemoglobin (g/L)	93 ± 17	93 ± 16	0.671

LVEF: Left ventricular ejection fraction; PELD: Pediatric end-stage liver disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TB: Total bilirubin; INR: International normalized ratio; Cr: Creatinine.



DOI: 10.4240/wjgs.v15.i9.2021

Figure 1 Flow chart of patients' screening. LDLT: Living donor liver transplantation.

RESULTS

During the study period, 339 pediatric patients underwent LDLT. Metabolic disease occurred in 13 patients, Alagille syndrome in 2 patients, Langerhans cell hyperplasia in 2 patients, the cavernous portal vein in 1 patient, and liver retransplantation in 1 patient, and 18 patients had incomplete data and were excluded. Three hundred two patients with biliary atresia were included in this retrospective study; among them, 142 patients had myocardial injuries, and the incidence rate was 47% (Figure 1).

The demographic data of the recipients are shown in Table 1. The data in Table 1 show that the age [7.0 (6.0-11.0) *vs* 9.5 (6.0-16.8) mo; $P < 0.001$], height [65 (62-70) *vs* 70 (65-82) cm; $P < 0.001$], and weight [7.0 (6.0-8.0) *vs* 8.0 (6.5-11.0) kg; $P < 0.001$] of pediatric patients with myocardial injuries were significantly lower than those in the nonmyocardial injury group. The PELD score [22 (15-28) *vs* 14 (4-21); $P < 0.001$], TB level [262 (157-349) *vs* 166 (40-278) μmol/L; $P < 0.001$], and INR [1.52 (1.23-2.04) *vs* 1.29 (1.09-1.63); $P < 0.001$] in the myocardial injury group were significantly higher than those in the nonmyocardial injury group. The comparison of the preoperative data between the two groups showed that there was no significant difference in male sex, LVEF, QTc, preoperative liver function indexes (ALT, AST), Cr, and hemoglobin (Table 1).

The data in Table 2 show that the MAP before reperfusion [56 (51-62) *vs* 60 (54-67) mmHg; $P = 0.001$], lactate [2.7 (2.2-3.8) *vs* 2.5 (1.8-3.2) mmol/L; $P = 0.002$], hemoglobin before reperfusion [81 (72-91) *vs* 84 (75-93) g/L; $P = 0.038$], duration of

Table 2 Intraoperative recipient-related data and donor-related data

Variable	Non-myocardial injury (*n* = 160)	Myocardial injury (*n* = 142)	*P* value
Vital signs immediately before reperfusion			
HR (bpm/min)	118 ± 13	117±13	0.515
MAP (mmHg)	60 (54-67)	56 (51-62)	0.001
CVP (mmHg)	5 (4-7)	5 (3-7)	0.454
Temperature (°C)	36.5 (35.9-37.0)	36.5 (35.8-37.0)	0.652
Laboratory findings before reperfusion			
pH	7.39 ± 0.07	7.39 ± 0.07	0.952
PCO_2 (mmHg)	34 (30-39)	33 (30-38)	0.148
PO_2 (mmHg)	257 (176-309)	242 (170-312)	0.472
Lactate (mmol/L)	2.5 (1.8-3.2)	2.7 (2.2-3.8)	0.002
Base excess (mmol/L)	-4.2 (-6.5--1.7)	-4.8 (-6.8--3.1)	0.102
Ca (mmol/L)	1.08 (1.01-1.17)	1.09 (1.00-1.15)	0.648
K (mmol/L)	3.8±0.6	3.8±0.5	0.448
Hemoglobin (g/L)	84 (75-93)	81 (72-91)	0.038
Duration of anhepatic phase (min)	56 (47-67)	62 (50-76)	0.019
Donor-related data			
Cold ischemic time (min)	80 (64-106)	90 (71-111)	0.023
Graft weight (g)	244 (217-277)	243 (208-278)	0.654
PRS (%)	54 (33.8)	76 (53.5)	0.001
The data at the end of the surgery			
Duration of surgery (min)	542 (495-600)	540 (484-593)	0.814
Duration of anesthesia (min)	616 (555-651)	610 (559-650)	0.984
Blood loss (mL)	300 (200-400)	350 (200-400)	0.378
Urine output (mL)	400 (300-600)	400 (248-600)	0.909
RBCs transfusion (units)	2.0 (1.5-3.0)	2.0 (2.0-3.0)	0.078
FFP transfusion (mL)	0 (0-100)	0 (0-200)	0.009

HR: Heart rate; MAP: Mean arterial pressure; CVP: Central venous pressure; PRS: Postreperfusion syndrome; RBCs: Red blood cells; FFP: Fresh frozen plasma.

the anhepatic phase [62 (50-76) *vs* 56 (47-67) min; $P = 0.019$], cold ischemic time [90 (71-111) *vs* 80 (64-106) min; $P = 0.023$], incidence of PRS (53.5% *vs* 33.8%; $P = 0.001$), and FFP transfusion volume [0 (0-200) *vs* 0 (0-100) mL; $P = 0.009$] were significantly different between the two groups. There was no statistically significant difference in other intraoperative indexes (Table 2).

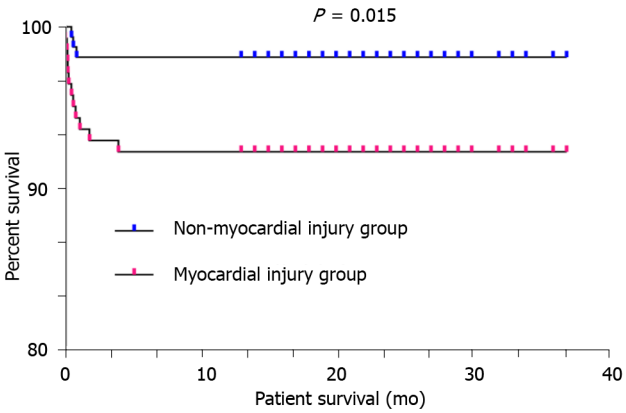
The postoperative data revealed no statistically significant differences between the two groups in terms of the duration of mechanical ventilation, number of hospitalization days, incidence of AKI, and peak ALT and AST values in the first five days following LDLT. However, the number of postoperative ICU stay days [3 (2.0-3.5) *vs* 2 (2.0-3.0) d, $P = 0.041$] and peak values of total bilirubin in the first 5 d after LDLT [88 (65-126) *vs* 80 (52-114) μmol/L, $P = 0.034$] in the myocardial injury group were significantly higher than those in the nonmyocardial injury group (Table 3). The pediatric patients with biliary atresia in the nonmyocardial injury group who underwent LDLT had a considerably higher one-year survival rate than those in the myocardial injury group (98.1% *vs* 92.3%, $P = 0.015$) (Figure 2).

The results of the univariate analysis showed that low height, low weight, a high PELD score, a high total bilirubin level, a high INR, a low MAP before reperfusion, high lactate and low hemoglobin levels before reperfusion, a long anhepatic phase duration, a long cold ischemic time, the occurrence of PRS, and massive FFP transfusion were identified as risk factors for myocardial injury in pediatric patients with biliary atresia (Table 4). The multivariate logistic regression analysis showed that a high PELD score (OR = 1.065, 95%CI: 1.013-1.121; $P = 0.014$), a long anhepatic phase duration (OR = 1.021, 95%CI: 1.003-1.040; $P = 0.025$), and the occurrence of PRS (OR = 1.966, 95%CI: 1.111-3.480; $P = 0.020$) were independent risk factors for myocardial injury (Table 4).

Table 3 Postoperative recipient-related data

Variable	Non-myocardial injury (*n* = 160)	Myocardial injury (*n* =142)	*P* value
Ventilation time (min)	220 (129-351)	196 (146-321)	0.785
ICU stay (d)	2 (2.0-3.0)	3 (2.0-3.5)	0.041
hospital stay (d)	20 (16-29)	21 (17-26)	0.732
AKI (%)	35 (21.9)	35 (24.6)	0.569
Liver function test during the first five days after LDLT			
Peak ALT (U/L)	551 (386-972)	619 (416-1151)	0.108
Peak AST (U/L)	666 (472-1186)	748 (495-1386)	0.103
Peak TB (μmol/L)	80 (52-114)	88 (65-126)	0.034
One-year survival rate (%)	157 (98.1)	131 (92.3)	0.015

ICU: Intensive care unit; AKI: Acute kidney injury; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TB: Total bilirubin.



DOI: 10.4240/wjgs.v15.i9.2021

Figure 2 Comparison of the one-year survival rate after living donor liver transplantation between the two groups.

DISCUSSION

Under normal circumstances, cTnI cannot pass through an intact cell membrane into the blood circulation, but after myocardial cell damage, cTnI will be released into the blood. CTnI is a commonly used marker that, when elevated, is indicative of myocardial injury[8]. There is reliable evidence showing that the measurement of troponin levels is not only the gold standard for the diagnosis of cardiac injury[9] but also an effective screening and risk stratification tool[10,11]. van Waes *et al*[4] conducted an observational cohort study and defined myocardial injury as a troponin I level > 0.06 ng/mL, which was the lowest value measurable with a 10% coefficient of variation above the 99th percentile (0.04 ng/mL) of the assay used. However, there are very few studies in which researchers provide reference cutoff values for elevated cTnI levels in pediatric patients. Bailey *et al*[12] found that TnI was exceptionally high at birth, abruptly decreased shortly after birth, and reached adult concentrations 3 mo after birth, and the manufacturer assay's 99th percentile URL was reasonable for children older than 3 mo. Sheng's study also showed that a cTnI level ≥ 0.07 ng/mL could be used as a specific marker of myocardial injury in pediatric living donor liver recipients[3]. Therefore, in our study, we defined myocardial injury as a cTnI level ≥ 0.07 ng/mL.

The PELD scoring system is used to evaluate the severity and prognosis of end-stage liver disease in children. Oh *et al*[13] found that a PELD score > 25 was an independent risk factor for graft function loss after LDLT in children. Sheng *et al*[14] conducted a retrospective analysis of LDLT in 112 children with biliary atresia and found that there was a positive correlation between the preoperative PELD score and the increase in intraoperative cTnI; that was, the higher the PELD, the higher the serum cTnI level at 30 min in the neohepatic stage. It has been suggested that the main cause of a myocardial injury associated with liver transplantation is the inflammatory response[15]. As the largest group of macrophages in the body, Kupffer cells can release many inflammatory factors during ischemic cold preservation and reperfusion injury, which becomes the most noteworthy factor that contributes to the occurrence of a myocardial injury[16,17]. The higher the preoperative PELD score of children with biliary atresia, the more sensitive the liver is to ischemia-reperfusion, the more likely Kupffer cells are activated and release inflammatory factors, and the more likely a cardiomyocyte injury will occur during the perioperative period.

Table 4 Univariate and multivariate analyses of risk factors for myocardial injury during pediatric living donor liver transplantation

Factor	Univariate analysis OR (95%CI)	*P* value	Multivariate analysis OR (95%CI)	*P* value
Preoperative recipient-related data				
Age	0.989 (0.974-1.003)	0.125		
Male gender	1.081 (0.688-1.699)	0.735		
Height	0.969 (0.951-0.988)	0.002	1.011 (0.964-1.060)	0.659
Weight	0.889 (0.827-0.955)	0.001	0.953 (0.800-1.136)	0.593
LVEF	1.044 (0.980-1.112)	0.178		
QTc	0.999 (0.990-1.008)	0.774		
PELD	1.074 (1.049-1.100)	< 0.001	1.065 (1.013-1.121)	0.014
ALT	1.001 (0.999-1.002)	0.540		
AST	1.001 (1.000-1.002)	0.218		
Total Bilirubin	1.004 (1.002-1.006)	< 0.001	1.001 (0.999-1.003)	0.353
INR	2.167 (1.435-3.272)	< 0.001	0.957 (0.554-1.653)	0.875
Creatinine	0.99 (0.951-1.031)	0.632		
Hemoglobin	1.031 (0.897-1.184)	0.670		
Vital signs immediately before reperfusion				
HR	0.994 (0.977-1.012)	0.513		
MAP	0.971 (0.949-0.993)	0.010	0.997 (0.971-1.023)	0.819
CVP	0.974 (0.896-1.057)	0.524		
Temperature	1.088 (0.819-1.444)	0.560		
Laboratory findings before reperfusion				
pH	0.902 (0.032-25.155)	0.952		
PCO_2	0.971 (0.935-1.009)	0.129		
PO_2	0.999 (0.996-1.002)	0.478		
Lactate	1.267 (1.092-1.469)	0.002	1.158 (0.990-1.355)	0.067
Base excess	0.946 (0.881-1.015)	0.122		
Ca	0.374 (0.066-2.117)	0.266		
K	0.857 (0.575-1.277)	0.447		
Hemoglobin	0.836 (0.713-0.981)	0.029	0.956 (0.828-1.105)	0.544
Duration of anhepatic phase	1.019 (1.004-1.035)	0.016	1.021 (1.003-1.040)	0.025
Donor-related data				
Cold ischemic time	1.006 (1.001-1.012)	0.016	1.003 (0.997-1.010)	0.334
Graft weight	0.999 (0.996-1.003)	0.755		
PRS	2.260 (1.420-3.598)	0.001	1.966 (1.111-3.480)	0.020
The data at the end of the surgery				
Duration of surgery	1 (0.998-1.002)	0.854		
Duration of anesthesia	1.001 (0.999-1.003)	0.481		
Blood loss	1.001 (1.000-1.002)	0.128		
RBCs transfusion	1.151 (0.970-1.366)	0.107		
FFP transfusion	1.002 (1.000-1.004)	0.017	1.001 (0.999-1.003)	0.441

LVEF: Left ventricular ejection fraction; PELD: Pediatric end-stage liver disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; INR: International normalized ratio; MAP: Mean arterial pressure; CVP: Central venous pressure; PRS: Postreperfusion syndrome; RBCs: Red blood cells; FFP: Fresh frozen plasma.

PRS is characterized by a decrease of more than 30% in the mean arterial pressure (MAP) that occurs in the first 5 min after liver graft reperfusion and lasts at least 1 min[18]. PRS is one of the most common perioperative complications of liver transplantation and has a reported incidence between 34.7% and 50%[19-22], which can lead to slower heart rate, lower blood pressure, arrhythmia, increased mortality, and a serious effect on the patients' quality of life after the operation[18,23]. At present, the mechanism of PRS has not been fully clarified. Prolonged cold ischemia time of the graft can lead to mitochondrial dysfunction, cell metabolic disorder, the release of reactive oxygen species and inflammatory factors, and aggravate hepatic ischemia-reperfusion injury[24]. Sahmeddini *et al*[25] showed that recipient age > 60 years, high end-stage liver disease model score and preoperative serum sodium < 130 mmol/L were independent risk factors for PRS in orthotopic liver transplantation. The literature showed that in LDLT, male sex, reduced left ventricular end-diastolic diameter and increased graft volume were risk factors for PRS, while increased serum calcium concentration and decreased pulmonary artery pressure before reperfusion were protective factors for PRS[26].

The anhepatic phase was defined as the time from the physical removal of the liver from the recipient to the recirculation of the graft[27]. The inferior vena cava needs to be blocked before anastomosing the left hepatic vein of the graft with the recipient hepatic vein. If the inferior vena cava is blocked for a long time, it will lead to a decrease in cardiac blood volume, a decrease in stroke volume, and a compensatory increase in heart rate. The above factors can lead to a decrease in the myocardial oxygen supply, an increase in oxygen consumption, an imbalance of cardiac oxygen supply and demand, and finally lead to myocardial injury. During the anhepatic period, the blood vessels of the donor's liver had not yet been anastomosed because of the resection of the diseased liver. At this time, the body is unable to metabolize acid substances, thereby making it extremely prone to metabolic acidosis and causing decreased blood pressure and unstable circulation. Because the coagulation factor of the human body depends on liver synthesis, a long anhepatic period can lead to a decrease in the coagulation factor level. A recent scientific study found that coagulation factor XI was a liver protein that could prevent diastolic dysfunction, maintain the ejection fraction, and protect the heart from injury [28]. Thus, it can be seen that the decrease in the coagulation factor levels not only affects the blood coagulation function but can also diminish heart function.

This study's sample size is very large, and thus far, there has been no retrospective study with a large sample size that has been conducted to evaluate the risk factors for intraoperative myocardial injury in children who are subjected to LDLT, which may be the advantage of this study. However, the limitation of this study is that the follow-up period was short, and the effect of myocardial injury on the long-term prognosis and quality of life of children who underwent liver transplantation has not been observed. In addition, different centers have different anesthetic management strategies, and the results of a single-center study may be biased, thus requiring multicenter large sample data for analysis in the future.

CONCLUSION

In summary, our study suggests that a high PELD score, a long anhepatic phase duration, and the occurrence of intraoperative PRS are independent risk factors for the development of a myocardial injury. For anesthesiologists, the findings may help predict the likelihood of a myocardial injury in pediatric patients who undergo LDLT. Effective anesthetic management strategies that have been designed to prevent the occurrence of a myocardial injury during LDLT will help to improve the prognosis and postoperative survival rate of the patients.

ARTICLE HIGHLIGHTS

Research background

Myocardial injury during liver transplantation is associated with postoperative adverse outcomes in pediatric patients; it can increase the incidence of postoperative mortality.

Research motivation

For a long time, research on myocardial injury has mainly focused on adults, but there is relatively little information on myocardial injury in children who have undergone living donor liver transplantation (LDLT).

Research objectives

To analyze the data of children who underwent LDLT to determine the risk factors for intraoperative myocardial injury.

Research methods

We retrospectively analyzed the inpatient records of pediatric patients who underwent LDLT in Tianjin First Central Hospital from January 1, 2020, to January 31, 2022. Recipient-related data and donor-related data were collected. The

patients were divided into a myocardial injury group and a nonmyocardial injury group according to the value of the serum cardiac troponin I at the end of surgery for analysis. Univariate analysis and multivariate logistic regression were used to evaluate the risk factors for myocardial injury during LDLT in pediatric patients.

Research results

A total of 302 patients met the inclusion criteria. The myocardial injury group had 142 individuals (47%), and the nonmyocardial injury group included 160 patients (53%). The pediatric patients with biliary atresia in the nonmyocardial injury group who underwent LDLT had a considerably higher one-year survival rate than those in the myocardial injury group (98.1% *vs* 92.3%, P = 0.015). Multivariate logistic regression revealed the following independent risk factors for myocardial injury: a high pediatric end-stage liver disease (PELD) score [odds ratio (OR) = 1.065, 95% confidence interval (CI): 1.013-1.121; P = 0.014], a long duration of the anhepatic phase (OR = 1.021, 95%CI: 1.003-1.040; P = 0.025), and the occurrence of intraoperative postreperfusion syndrome (PRS) (OR = 1.966, 95%CI: 1.111-3.480; P = 0.020).

Research conclusions

A high PELD score, a long anhepatic phase duration, and the occurrence of intraoperative PRS were independent risk factors for myocardial injury during LDLT in pediatric patients with biliary atresia.

Research perspectives

This study's sample size is very large, and thus far, there has been no retrospective study with a large sample size that has been conducted to evaluate the risk factors for intraoperative myocardial injury in children who are subjected to LDLT, which may be the advantage of this study. But different centers have different anesthetic management strategies, and the results of a single-center study may be biased, thus requiring multicenter large sample data for analysis in the future.

ACKNOWLEDGEMENTS

The authors would like to thank Professor Weng YQ for his contribution to this writing support and selfless help. In particular, the authors would like to thank the editors and reviewers for the recognition of our research.

FOOTNOTES

Author contributions: Wu YL and Weng YQ helped to write the manuscript; Li TY and Che L coordinated and supervised data collection; Gong XY performed the statistical analysis; Wu YL and Li TY created the tables and figures. Sheng MW revised the manuscript in detail; Weng YQ and Yu WL critically reviewed the manuscript for important intellectual content; Both Weng YQ and Yu WL were responsible for the study and contributed equally to this manuscript; all authors have read and agreed to the publication of the manuscript.

Supported by Science and Technology Foundation of Tianjin Health Bureau, No. ZC20052; Tianjin Key Medical Discipline (Specialty) Construction Project, No. TJYXZDXK-045A; Tianjin Anesthesia Research Development Program of Bethune Charitable Foundation, No. TJMZ2022-005; Natural Science Foundation of Tianjin, No. 21JCQNJC01730; and Young Talent Program of Tianjin First Central Hospital.

Institutional review board statement: The study was reviewed and approved by the ethics committee of the Tianjin First Central Hospital, No. 2022DZX02.

Informed consent statement: Informed consent was waived by the local ethics committee, given the study's retrospective nature.

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

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Yu-Li Wu 0000-0002-5724-9443; Tian-Ying Li 0009-0006-2988-2192; Xin-Yuan Gong 0000-0002-8587-0077; Lu Che 0000-0002-8582-3561; Ming-Wei Sheng 0000-0001-6847-6345; Wen-Li Yu 0000-0002-6374-1944; Yi-Qi Weng 0009-0004-8059-7923.

S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP

REFERENCES

1 **Daugaard TR**, Pommergaard HC, Rostved AA, Rasmussen A. Postoperative complications as a predictor for survival after liver transplantation - proposition of a prognostic score. *HPB (Oxford)* 2018; **20**: 815-822 [PMID: 29705344 DOI: 10.1016/j.hpb.2018.03.001]

2 **Huang S**, Apinyachon W, Agopian VG, Wray CL, Busuttil RW, Steadman RH, Xia VW. Myocardial injury in patients with hemodynamic derangements during and/or after liver transplantation. *Clin Transplant* 2016; **30**: 1552-1557 [PMID: 27653509 DOI: 10.1111/ctr.12855]

3 **Sheng M**, Lin Y, Weng Y, Xu R, Sun Y, Yu W, Du H. Predictive Value of Intraoperative Troponin I Elevation in Pediatric Living Donor Liver Transplant Recipients With Biliary Atresia. *Transplantation* 2017; **101**: 2385-2390 [PMID: 28319568 DOI: 10.1097/TP.0000000000001732]

4 **van Waes JA**, Nathoe HM, de Graaff JC, Kemperman H, de Borst GJ, Peelen LM, van Klei WA; Cardiac Health After Surgery (CHASE) Investigators. Myocardial injury after noncardiac surgery and its association with short-term mortality. *Circulation* 2013; **127**: 2264-2271 [PMID: 23667270 DOI: 10.1161/CIRCULATIONAHA.113.002128]

5 **Sun K**, Wang Y, Yan M, Xia VW. Pretransplant left ventricular hypertrophy in association with postoperative myocardial injury in liver transplantation. *Clin Transplant* 2020; **34**: e13847 [PMID: 32097498 DOI: 10.1111/ctr.13847]

6 **Vilchez-Monge AL**, Garutti I, Jimeno C, Zaballos M, Jimenez C, Olmedilla L, Piñeiro P, Duque P, Salcedo M, Asencio JM, Lopez-Baena JA, Maruszewski P, Bañares R, Perez-Peña JM. Intraoperative Troponin Elevation in Liver Transplantation Is Independently Associated With Mortality: A Prospective Observational Study. *Liver Transpl* 2020; **26**: 681-692 [PMID: 31944566 DOI: 10.1002/lt.25716]

7 **Inker LA**, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, Kurella Tamura M, Feldman HI. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis* 2014; **63**: 713-735 [PMID: 24647050 DOI: 10.1053/j.ajkd.2014.01.416]

8 **Chaulin A**. Cardiac Troponins: Contemporary Biological Data and New Methods of Determination. *Vasc Health Risk Manag* 2021; **17**: 299-316 [PMID: 34113117 DOI: 10.2147/VHRM.S300002]

9 **Thygesen K**, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019; **40**: 237-269 [PMID: 30165617 DOI: 10.1093/eurheartj/ehy462]

10 **de Lemos JA**, deFilippi CR. Prevalence and significance of detectable troponins as measured by highly sensitive assays in the general population. *Coron Artery Dis* 2013; **24**: 705-709 [PMID: 24201087 DOI: 10.1097/MCA.0000000000000048]

11 **Brown JL**, Hirsh DA, Mahle WT. Use of troponin as a screen for chest pain in the pediatric emergency department. *Pediatr Cardiol* 2012; **33**: 337-342 [PMID: 22089143 DOI: 10.1007/s00246-011-0149-8]

12 **Bailey D**, Colantonio D, Kyriakopoulou L, Cohen AH, Chan MK, Armbruster D, Adeli K. Marked biological variance in endocrine and biochemical markers in childhood: establishment of pediatric reference intervals using healthy community children from the CALIPER cohort. *Clin Chem* 2013; **59**: 1393-1405 [PMID: 23637247 DOI: 10.1373/clinchem.2013.204222]

13 **Oh SH**, Kim KM, Kim DY, Lee YJ, Rhee KW, Jang JY, Chang SH, Lee SY, Kim JS, Choi BH, Park SJ, Yoon CH, Ko GY, Sung KB, Hwang GS, Choi KT, Yu E, Song GW, Ha TY, Moon DB, Ahn CS, Kim KH, Hwang S, Park KM, Lee SG. Long-term outcomes of pediatric living donor liver transplantation at a single institution. *Pediatr Transplant* 2010; **14**: 870-878 [PMID: 20609169 DOI: 10.1111/j.1399-3046.2010.01357.x]

14 **Sheng MW**, Du HY, Weng YQ, Xu RB, Sun Y, Yu WL. Prognostic value of serum cardiac troponin I in acute lung injury after living-donor liver transplantation for children with biliary atresia. *Zhonghua Qigaung Yizhi Zazhi* 2016; **37**: 581-585 [DOI: 10.3760/cma.j.issn.0254-1785.2016.10.002]

15 **Chen JB**, Chen GY, Wei SD, Sun JJ, Liu GB, Xie ZT, Tang GF. Inflammatory factor in donor liver and its effect on recipient myocardial injury after liver transplantation. *Eur Rev Med Pharmacol Sci* 2017; **21**: 4362-4368 [PMID: 29077159]

16 **Tsuchihashi S**, Ke B, Kaldas F, Flynn E, Busuttil RW, Briscoe DM, Kupiec-Weglinski JW. Vascular endothelial growth factor antagonist modulates leukocyte trafficking and protects mouse livers against ischemia/reperfusion injury. *Am J Pathol* 2006; **168**: 695-705 [PMID: 16436682 DOI: 10.2353/ajpath.2006.050759]

17 **Buras JA**, Reenstra WR. Endothelial-neutrophil interactions during ischemia and reperfusion injury: basic mechanisms of hyperbaric oxygen. *Neurol Res* 2007; **29**: 127-131 [PMID: 17439696 DOI: 10.1179/016164107X174147]

18 **Jeong SM**. Postreperfusion syndrome during liver transplantation. *Korean J Anesthesiol* 2015; **68**: 527-539 [PMID: 26634075 DOI: 10.4097/kjae.2015.68.6.527]

19 **Chung IS**, Kim HY, Shin YH, Ko JS, Gwak MS, Sim WS, Kim GS, Lee SK. Incidence and predictors of post-reperfusion syndrome in living donor liver transplantation. *Clin Transplant* 2012; **26**: 539-543 [PMID: 22168355 DOI: 10.1111/j.1399-0012.2011.01568.x]

20 **Zhang L**, Tian M, Xue F, Zhu Z. Diagnosis, Incidence, Predictors and Management of Postreperfusion Syndrome in Pediatric Deceased Donor Liver Transplantation: A Single-Center Study. *Ann Transplant* 2018; **23**: 334-344 [PMID: 29773782 DOI: 10.12659/AOT.909050]

21 **Hilmi I**, Horton CN, Planinsic RM, Sakai T, Nicolau-Raducu R, Damian D, Gligor S, Marcos A. The impact of postreperfusion syndrome on short-term patient and liver allograft outcome in patients undergoing orthotopic liver transplantation. *Liver Transpl* 2008; **14**: 504-508 [PMID: 18383079 DOI: 10.1002/lt.21381]

22 **Li T**, Wu Y, Gong X, Che L, Sheng M, Jia L, Li H, Yu W, Weng Y. Risk factors for postreperfusion syndrome during living donor liver transplantation in paediatric patients with biliary atresia: a retrospective analysis. *BMJ Paediatr Open* 2023; **7** [PMID: 37407250 DOI: 10.1136/bmjpo-2023-001934]

23 **Khosravi MB**, Sattari H, Ghaffaripour S, Lahssaee M, Salahi H, Sahmeddini MA, Bahador A, Nikeghbalian S, Parsa S, Shokrizadeh S, Malek-Hosseini SA. Post-reperfusion Syndrome and Outcome Variables after Orthotopic Liver Transplantation. *Int J Organ Transplant Med* 2010; **1**: 115-120 [PMID: 25013576]

24 **Ye L**, He S, Mao X, Zhang Y, Cai Y, Li S. Effect of Hepatic Macrophage Polarization and Apoptosis on Liver Ischemia and Reperfusion Injury During Liver Transplantation. *Front Immunol* 2020; **11**: 1193 [PMID: 32676077 DOI: 10.3389/fimmu.2020.01193]

25 **Sahmeddini MA**, Tehran SG, Khosravi MB, Eghbal MH, Asmarian N, Khalili F, Vatankhah P, Izadi S. Risk factors of the post-reperfusion syndrome during orthotopic liver transplantation: a clinical observational study. *BMC Anesthesiol* 2022; **22**: 89 [PMID: 35366808 DOI: 10.1186/s12871-022-01635-3]

26 **Umehara K**, Karashima Y, Yoshizumi T, Yamaura K. Factors Associated With Postreperfusion Syndrome in Living Donor Liver Transplantation: A Retrospective Study. *Anesth Analg* 2022; **135**: 354-361 [PMID: 35343925 DOI: 10.1213/ANE.0000000000006002]

27 **Ijtsma AJ**, van der Hilst CS, de Boer MT, de Jong KP, Peeters PM, Porte RJ, Slooff MJ. The clinical relevance of the anhepatic phase during liver transplantation. *Liver Transpl* 2009; **15**: 1050-1055 [PMID: 19718649 DOI: 10.1002/lt.21791]

28 **Cao Y**, Wang Y, Zhou Z, Pan C, Jiang L, Meng Y, Charugundla S, Li T, Allayee H, Seldin MM, Lusis AJ. Liver-heart cross-talk mediated by coagulation factor XI protects against heart failure. *Science* 2022; **377**: 1399-1406 [PMID: 36137043 DOI: 10.1126/science.abn0910]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 2032-2041

DOI: 10.4240/wjgs.v15.i9.2032

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Observational Study

Comparative detection of syndecan-2 methylation in preoperative and postoperative stool DNA in patients with colorectal cancer

Ji Hyeong Song, Tae Jeong Oh, Sungwhan An, Kyung Ha Lee, Ji Yeon Kim, Jin Soo Kim

Specialty type: Surgery

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

Peer-review model: Single blind

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

P-Reviewer: Kisiel JB, United States; Lucke-Wold B, United States

Received: June 8, 2023
Peer-review started: June 8, 2023
First decision: July 7, 2023
Revised: July 13, 2023
Accepted: August 4, 2023
Article in press: August 4, 2023
Published online: September 27, 2023

Ji Hyeong Song, Jin Soo Kim, Department of Surgery, Chungnam National University Sejong Hospital, Sejong 30099, South Korea

Tae Jeong Oh, Sungwhan An, Genomictree, Inc., Daejeon 34027, South Korea

Kyung Ha Lee, Ji Yeon Kim, Jin Soo Kim, Department of Surgery, College of Medicine, Chungnam National University, Daejeon 35015, South Korea

Corresponding author: Jin Soo Kim, MD, PhD, Assistant Professor, Surgery, Chungnam National University Sejong Hospital, 20, Bodeum 7-ro, Sejong-si, Republic of Korea, Sejong 30099, South Korea. jskim7562@gmail.com

Abstract

BACKGROUND

Early detection of colorectal cancer (CRC) is essential to reduce cancer-related morbidity and mortality. Stool DNA (sDNA) testing is an emerging method for early CRC detection. Syndecan-2 (*SDC2*) methylation is a potential biomarker for the sDNA testing. Aberrant DNA methylation is an early epigenetic event during tumorigenesis and can occur in the normal colonic mucosa during aging, which can compromise the sDNA test results.

AIM

To determine whether methylated *SDC2* in sDNA normalizes after surgical resection of CRC.

METHODS

In this prospective study, we enrolled 151 patients with CRC who underwent curative surgical resection between September 2016 and May 2020. Preoperative stool samples were collected from 123 patients and postoperative samples were collected from 122 patients. A total of 104 samples were collected from both preoperative and postoperative patients. Aberrant promoter methylation of *SDC2* in sDNA was assessed using linear target enrichment quantitative methylation-specific real-time polymerase chain reaction. Clinicopathological parameters were analyzed using the results of *SDC2* methylation.

RESULTS

Detection rates of *SDC2* methylation in the preoperative and postoperative stool samples were 88.6% and 19.7%, respectively. Large tumor size (3 cm, P = 0.019)

and advanced T stage (T3–T4, $P = 0.033$) were positively associated with the detection rate of *SDC2* methylation before surgery. Female sex was associated with false positives after surgery ($P = 0.030$). Cycle threshold (C_T) values were significantly decreased postoperatively compared with preoperative values ($P < 0.001$). The postoperative negative conversion rate for preoperatively methylated *SDC2* was 79.3% (73/92).

CONCLUSION

Our results suggested that the *SDC2* methylation test for sDNA has acceptable sensitivity and specificity. However, small size and early T stage tumors are associated with a low detection rate of *SDC2* methylation. As the cycle threshold values significantly decreased after surgery, *SDC2* methylation test for sDNA might have a diagnostic value for CRC.

Key Words: Biomarkers; DNA methylation; Syndecan-2; Colorectal cancer

Core Tip: This prospective study evaluated the detection of syndecan-2 (*SDC2*) methylation in preoperative and postoperative stool DNA samples of colorectal cancer (CRC) patients. The study demonstrated that the *SDC2* methylation test showed high sensitivity (88.6%) for detecting CRC before surgery, indicating its potential as a non-invasive diagnostic tool. Postoperatively, the detection rate decreased to 19.7%, suggesting the normalization of *SDC2* methylation after surgical resection. The study highlights the diagnostic value of *SDC2* methylation in preoperative and postoperative stool samples, supporting its role as a non-invasive screening tool for CRC.

Citation: Song JH, Oh TJ, An S, Lee KH, Kim JY, Kim JS. Comparative detection of syndecan-2 methylation in preoperative and postoperative stool DNA in patients with colorectal cancer. *World J Gastrointest Surg* 2023; 15(9): 2032-2041
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/2032.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.2032

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and second leading cause of cancer-related deaths worldwide[1]. According to the 2019 Korean statistics, the prevalence of CRC was the third highest, following thyroid and lung cancer. From 2015 to 2019, the 5-year survival rate of CRC patients in Korea was 74.3%[2]. Patients with metastatic CRC have a 5-year survival rate of < 10%, whereas those with early detection of CRC have a 5-year survival rate of > 90%[3]. Therefore, the early detection of CRC is essential to reduce cancer-related morbidity and mortality.

Most patients with early-stage CRC are mostly asymptomatic. There are several screening tools for detecting asymptomatic CRC. The fecal occult blood test and fecal immunochemical test are non-invasive, inexpensive, and convenient methods. However, these tests have low sensitivity and specificity[4]. Computed tomography colonography can be used as an alternative examination for colonoscopy, which non-invasively examines the entire colon beyond the obstructive. However, there are concerns about radiation hazards and the disadvantage of detecting small polyps < 5mm in size. Colonoscopy is the most accurate method with the advantage of being able to perform procedures such as biopsy and polypectomy. In the NordICC trial, a prospective, multinational, and randomized controlled trial investigating the effectiveness of colonoscopy on CRC incidence and mortality, colonoscopy as a screening tool showed good compliance, a high rate of adenoma yield, and adequate performance[5]. However, colonoscopy is an invasive procedure that requires mechanical bowel preparation and carries the risk of complications, such as perforation or electrolyte imbalance. Therefore, there is a need to develop a non-invasive and highly accurate CRC screening tool, especially for those reluctant to undergo colonoscopy.

CRC carcinogenesis is associated with the accumulation of genetic and epigenetic alterations[6]. Aberrant DNA methylation is one of the most common molecular alterations involved in CRC[7]. Because exfoliated cells from tumors are present in stool samples from CRC patients, detection of aberrant methylation is emerging as a non-invasive diagnostic tool for CRC[8]. Several stool DNA (sDNA)-based methylation markers are available for the early detection of CRC[9,10]. Among these, syndecan-2 (*SDC2*) has been reported as a potential biomarker for sDNA testing[11-13]. Aberrant DNA methylation is an early epigenetic event during tumorigenesis that can occur in the normal colonic mucosa during aging[14], which may compromise the sDNA test results. If preoperatively methylated *SDC2* (me*SDC2*) normalizes after the surgical resection of CRC, it may have diagnostic value and may be used for postoperative surveillance[15]. Therefore, we conducted a prospective observational study to compare *SDC2* methylation in the sDNA of patients with CRC before and after surgery.

MATERIALS AND METHODS

Patients

In this prospective study, we enrolled 151 patients diagnosed with CRC who underwent surgical resection with curative intent between September 2016 and May 2020 at the Department of Surgery, Chungnam National University Hospital (South Korea). This observational study was approved by the Institutional Review Board of our institute (No. 2016-05-018). The exclusion criteria were as follows: (1) Patients under 18 or over 80 years of age; (2) Difficulty in obtaining informed consent due to mental health issues; (3) Tumor complications such as bleeding, perforation, or obstruction; and (4) Palliative operation. Among the 151 enrolled patients, four dropped out. Two patients were transferred to other hospitals, and two were unresectable. Clinical data were collected for 147 patients. Stool samples were collected from 123 patients preoperatively and 122 patients postoperatively, excluding those due to poor sample quality and inadequate sample amount. A total of 104 samples were collected from both preoperative and postoperative patients. Figure 1 shows the flowchart of the enrolled patients.

Stool collection, DNA isolation, and bisulfite treatment

For each subject, at least 2 g of voided stool sample was collected in 20 mL of preservative buffer (Genomictree, Inc., Daejeon, South Korea) using a disposable spatula from four to five different locations. The samples were collected from the patients before and after definitive surgery. Inadequate stool specimens were not included in the methylation analysis (*e.g.*, diarrhea or loose stools).

sDNA was isolated using the GT Nucleic Acid PREP Kit II (Genomictree, Inc., Daejeon, South Korea) according to the manufacturer's instructions. The Qubit dsDNA BR Assay Kit (Thermo Fisher Scientific, MA, United States) was used to determine the DNA concentration. Briefly, all stool samples were weighed and homogenized in a preservative buffer using a multiple vortex mixer (MIULAB, Hangzhou, China). After homogenization, 1–2 g of each stool sample was used for DNA isolation.

Each two μg of stool-derived genomic DNA was chemically modified with sodium bisulfite using the EZ DNA Methylation-Gold Kit (ZYMO Research, CA, United States) according to the manufacturer's instructions. Bisulfite-converted DNA was purified using a Zymo-Spin IC column (ZYMO Research) and eluted with 10 μL of distilled water. Bisulfite-converted DNA was either used immediately for methylation analysis or stored at -20 °C until use.

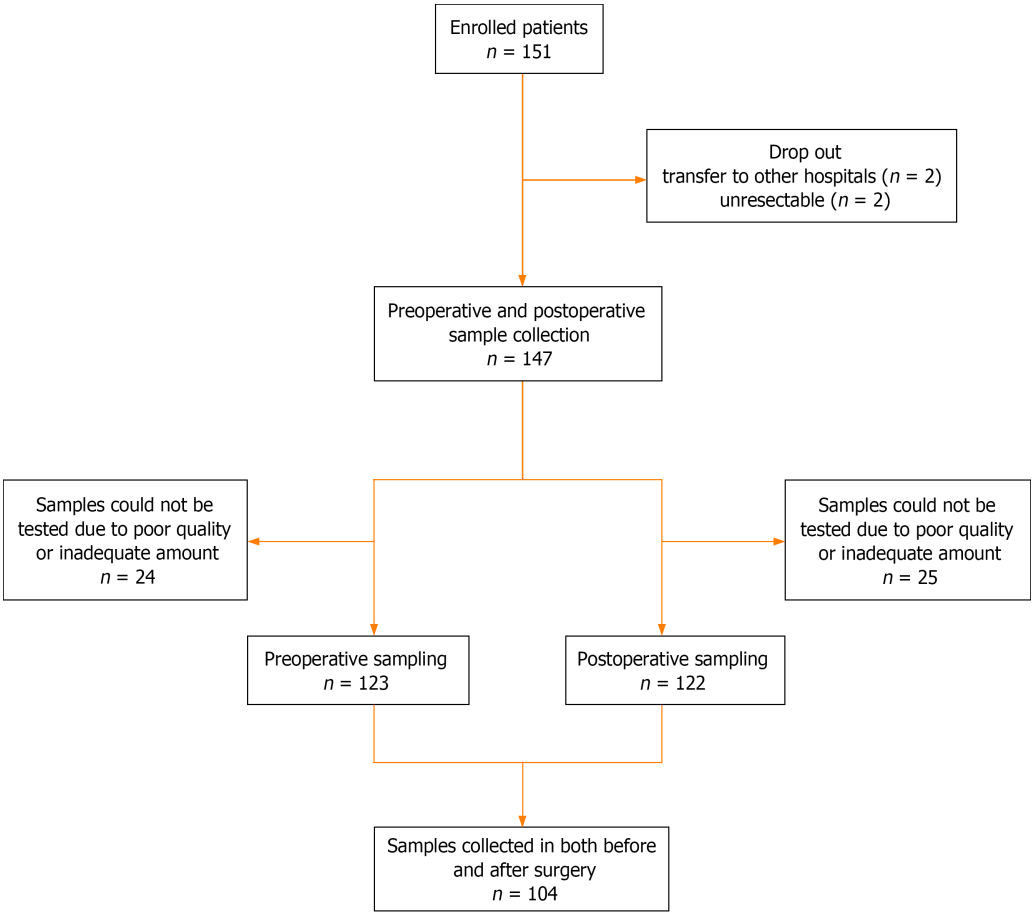
Analysis of SDC2 methylation in sDNA using meSDC2 linear target enrichment-quantitative methylation-specific real-time polymerase chain reaction test and data

The me*SDC2* linear target enrichment (LTE)-quantitative methylation-specific real-time polymerase chain reaction (qMSP) assay was performed in duplicate reactions for each sample as described by Han *et al*[13]. A highly sensitive two-step me*SDC2* LTE-qMSP assay was used to measure *SDC2* methylation in sDNA. First, LTE was used to enrich me*SDC2* target DNA and control *COL2A1* DNA from the bisulfite-modified DNA. The region of the *COL2A1* gene lacking CpG dinucleotides was used as a control to estimate the amount of amplifiable template and the adequacy of bisulfite conversion. The LTE reaction mixture (20 μL) containing 2.0 μg of bisulfite-converted sDNA, 50 nmol/L each of *SDC2* methylation-specific antisense (5′-AAAGATTCGGCGACCACCGAACGACTCAAACTCGAAAACTCG-3′) and *COL2A1* gene-specific antisense primers (5′-AAAGATTCGGCGACCACCGACTAICCCAAAAAAACCCAATCCTA-3′) attached to a 5′ universal sequence (5′-AAAGATTCGGCGACCACCGA-3′), and 4 μL of 5× AptaTaq polymerase chain reaction (PCR) master mix (Roche Diagnostics, Basel, Switzerland) was prepared. The thermal cycling conditions were as follows: 95 °C for 5 min, followed by 35 cycles of 95 °C for 15 s and 60 °C for 60 s. Next, the reaction mixture volume was scaled up to 40 μL, containing 8 μL of 5× AptaTaq PCR master mix, 250 nmol/L *SDC2* methylation-specific sense primer (5′-GTAGAAATTAATAAGTGAGAGGGC-3′), 125 nmol/L *SDC2* probe (5′-FAM-TTCGGGGCGTAGTTGCGGGCGG-3′), 125 nmol/L *COL2A1* sense primer (5′GTAATGTTAGGAGTATTTTGTGGITA-3′), 62.5 nmol/L *COL2A1* probe (5′-Cy5-AGAAGAAGGGAGGGGTGTTAGGAGAGG-3′), and 250 nmol/L universal sequence primer. Thermal cycling conditions were as follows: 95 °C for 5 min followed by 40 cycles of 95 °C for 15 s and 60 °C for 60 s. Heating and cooling rates were 20 °C/s and 15 °C/s, respectively. For each run, bisulfite-converted methylated (HCT116) and unmethylated genomic DNA (whole-genome amplified human lymphocyte DNA) were used as methylation controls. Non-template and non-template bisulfite-converted controls were also included in the study.

PCR for *SDC2* and *COL2A1* was performed in a single tube. me*SDC2* LTE-qMSP was performed using Rotor-Gene Q real-time PCR instrument (Qiagen, Hilden, Germany). The cycle threshold (C_T) value was calculated using the Rotor-Gene Q software. Lower C_T values indicated higher levels of *SDC2* methylation. For PCR analysis, *SDC2* methylation was detected if the C_T was less than 40 cycles. It was not detected if C_T was not measurable. Samples were categorized as positive if at least one of the two reactions showed detectable *SDC2*, and they were considered negative if *SDC2* methylation was not measurable in both reactions. The test results were acceptable only when the C_T value of *COL2A1* was < 31. If *COL2A1* was not detected, or the C_T value was > 31, the test was repeated. Neither the personnel involved in laboratory work nor data analysis of the *SDC2* methylation results was informed of colonoscopic findings or pathology outcomes as reference standards. Oh TJ and An S are employees and shareholders of Genomictree, Inc.

Statistical analysis

Statistical analysis of the data was performed using IBM SPSS Statistics 26 (SPSS Inc., Chicago, IL, United States). Chi-square and/or Fisher's exact tests were used for categorical variables. Detection rates were evaluated dichotomously as '0' for methylation-negative and '1' for methylation-positive.



DOI: 10.4240/wjgs.v15.i9.2032

Figure 1 Flowchart of preoperative and postoperative sample collection in patients with colorectal cancer.

The C_T values before and after surgery according to tumor node metastasis (TNM) stage were compared using analysis of variance (ANOVA). A paired *t*-test was performed to compare C_T values before and after surgery for each patient. A P value < 0.05 was considered statistically significant.

In addition, we retrieved literatures by Reference Citation Analysis to supplement the latest cutting-edge research results.

RESULTS

Patient characteristics are described in Table 1. In total, 97 male (66%) and 50 female (34%) patients were included in the preoperative or postoperative sampling. The mean age was 62.3. Total colonoscopy was performed before surgery in 133 patients (90.5%), and remnant advanced adenoma (RAA) was present in 18 patients (12.2%). Among the 18 patients with RAA, five remained *SDC2* methylation-positive after surgery. The recurrence rate was 6.8% in all patients.

Detection rates of the SDC2 methylation test

Figure 2 shows the detection rates of *SDC2* methylation according to TNM stage. The positivity rate of the *SDC2* methylation test before surgery was 88.6% (109/123), and the false negative rate was 11.4% (14/123). The positivity rates for stages 0, I, II, III, and IV were 75% (3/4), 83.9% (26/31), 91.1% (41/45), 89.2% (33/37), and 100% (6/6), respectively (Figure 2A). The detection rate of *SDC2* methylation after surgery was 19.7% (24/122). The detection rates for stages 0, I, II, III, and IV were 25% (1/4), 31.2% (10/32), 17.5% (7/40), 14.0 (6/43), and 0% (0/3), respectively (Figure 2B). The demographic analysis of patients according to the preoperative and postoperative *SDC2* methylation results is presented in Table 2. Large tumor size (3 cm, P = 0.019) and advanced T stage (T3–T4, P = 0.033) were associated with positivity of *SDC2* methylation before surgery. Additionally, female patients showed more false positives after surgery (P = 0.030).

C_T values of SDC2 methylation

The distribution of C_T values in preoperative and postoperative *SDC2* methylation according to TNM stage is shown in Figure 3. There were no significant differences in the C_T values of *SDC2* methylation preoperatively (P = 0.901) or postoperatively (P = 0.332) according to TNM stage.

Table 1 Characteristics of patients

	Patients with preoperative or postoperative stool sampling, *n* = 147 (%)	Patients with preoperative and postoperative stool sampling, *n* = 104 (%)
Sex		
Male	97 (66.0)	66 (63.5)
Female	50 (34.0)	38 (36.5)
Age, yr		
Mean (range)	62.3 (35-80)	62.8 (35-80)
Tumor location		
Right colon	45 (30.6)	29 (27.9)
Left colon	62 (42.2)	51 (49.0)
Rectum	40 (27.2)	24 (23.1)
Histology		
WD	6 (4.1)	4 (3.8)
MD	132 (89.8)	94 (90.4)
PD	9 (3.4)	5 (4.8)
Mucinous	4 (2.7)	1 (1.0)
Tumor size, cm		
Mean (range)	3.7 (0.0-15.0)	3.5 (0.0-9.0)
T stage		
Tis	5 (3.4)	4 (3.8)
T1	22 (15.0)	15 (14.4)
T2	27 (18.4)	19 (18.3)
T3	74 (50.3)	52 (50.0)
T4	19 (12.9)	14 (13.5)
N stage		
N0	93 (63.3)	66 (63.5)
N+	54 (36.7)	38 (36.5)
TCF before surgery		
Not done	14 (9.5)	9 (8.7)
Done	133 (90.5)	95 (91.3)
RAA		
Not present	129 (87.8)	90 (86.5)
Present	18 (12.2)	14 (13.5)
Recurrence		
No	137 (93.2)	98 (94.2)
Yes	10 (6.8)	6 (5.8)

WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated; TCF: Total colonoscopy; RAA: Remnant advanced adenoma.

Figure 4 shows the C_T values of me*SDC2* for each patient before and after surgery. Among the 104 patients from whom stool samples were obtained before and after surgery, 92 patients showed positive results for preoperative *SDC2* methylation. The postoperative negative conversion rate for preoperatively me*SDC2* was 79.3% (73/92). The C_T values of *SDC2* methylation significantly decreased postoperatively compared to the preoperative values ($P < 0.001$).

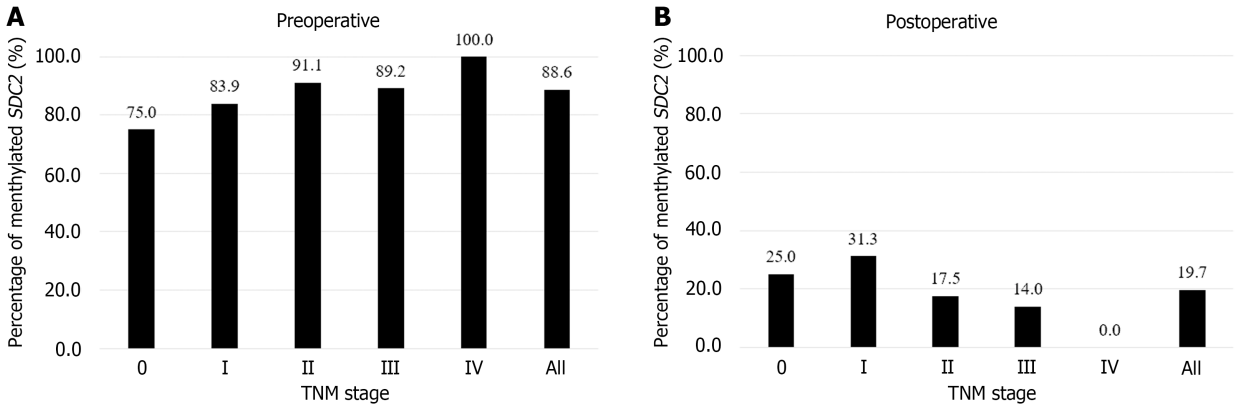
Table 2 Demographic analysis of patients according to preoperative and postoperative syndecan-2 methylation test

Characteristics	Preoperative (*n* = 123)			Postoperative (*n* = 122)		
	Negative, *n* = 14 (%)	Positive, *n* = 109 (%)	*P* value	Negative, *n* = 98 (%)	Positive, *n* = 24 (%)	*P* value
Sex			0.375			0.030
Male	11 (78.6)	69 (63.3)		68 (69.4)	11 (45.8)	
Female	3 (21.4)	40 (36.7)		30 (30.6)	13 (54.2)	
Age, yr			0.512			0.845
< 65	9 (64.3)	60 (55.0)		55 (56.1)	14 (58.3)	
≥ 65	5 (35.7)	49 (45.0)		43 (43.9)	10 (41.7)	
Location			0.664			0.079
Right colon	5 (35.7)	30 (27.5)		34 (34.7)	3 (12.5)	
Left colon	7 (50.0)	51 (46.8)		42 (42.9)	12 (50.0)	
Rectum	2 (14.3)	28 (25.7)		22 (22.4)	9 (37.5)	
Histology			0.226			1.000
WD/MD	12 (85.7)	103 (94.5)		92 (93.9)	23 (95.8)	
PD/Mucinous	2 (14.3)	6 (5.5)		6 (6.1)	1 (4.2)	
Tumor size, cm			0.019			0.145
< 3	10 (71.4)	42 (38.5)		41 (41.8)	14 (58.3)	
≥ 3	4 (28.6)	67 (61.5)		57 (58.2)	10 (41.7)	
T stage			0.033			0.137
Tis-T2	9 (64.3)	34 (31.2)		33 (33.7)	12 (50.0)	
T3-T4	5 (35.7)	75 (68.8)		65 (66.3)	12 (50.0)	
N stage			0.769			0.152
N0	10 (71.4)	70 (64.2)		58 (59.2)	18 (75.0)	
N+	4 (28.6)	39 (35.8)		40 (40.8)	6 (25.0)	
TNM stage			0.769			0.152
0-II	10 (71.4)	70 (64.2)		58 (59.2)	18 (75.0)	
III-IV	4 (28.6)	39 (35.8)		40 (40.8)	6 (25.0)	
TCF before surgery			0.627			0.685
Not done	2 (14.3)	10 (9.2)		9 (9.2)	1 (4.2)	
Done	12 (85.7)	99 (90.8)		89 (90.8)	23 (95.8)	
RAA			0.692			0.172
Not present	13 (92.9)	94 (86.2)		88 (89.8)	19 (79.2)	
Present	1 (7.1)	15 (13.8)		10 (10.2)	5 (20.8)	

SDC2: Syndecan-2; WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated; TCF: Total colonoscopy; RAA: Remnant advanced adenoma.

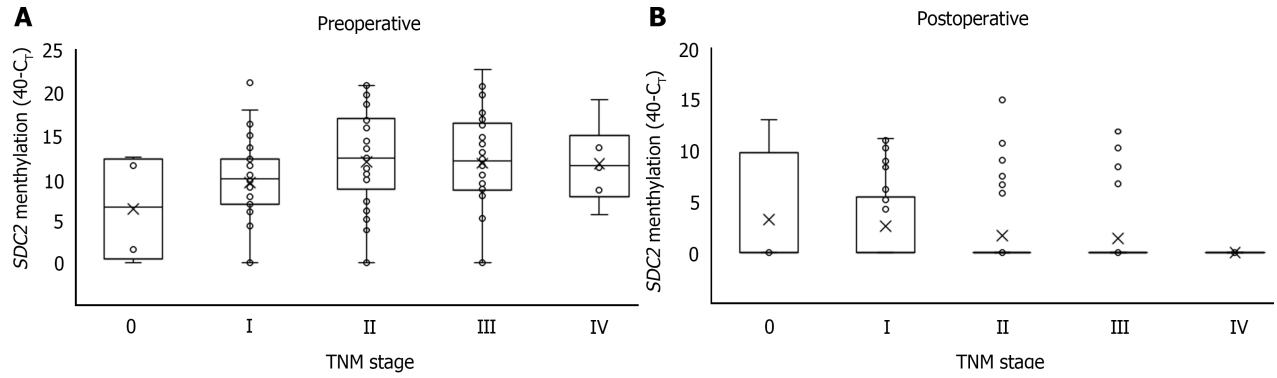
DISCUSSION

Various screening tools are used for the early detection of CRC to reduce cancer-related morbidity and mortality. Among the screening tools, colonoscopy is the most accurate method and is considered the gold standard with high sensitivity and specificity. However, colonoscopy is an invasive procedure that requires mechanical bowel preparation and carries the risk of complications, such as perforation or electrolyte imbalance. Hence, it is not yet useful as a mass-screening test [16]. Recently, non-invasive and highly accurate tests using sDNA methylation have been reported[6,7,9,10]. Among the several known sDNA biomarkers, *SDC2* was found to be the most accurate single gene[17]. Therefore, *SDC2* methylation in sDNA has been proposed as a non-invasive mass-screening tool for the early detection of CRC.



DOI: 10.4240/wjgs.v15.i9.2032 **Copyright** ©The Author(s) 2023.

Figure 2 Percentages of syndecan-2 methylation test results according to tumor node metastasis stage. Using the 1/2 algorithm, the percentage of samples with detectable methylated syndecan-2 is presented by bars. A: Preoperative stool samples were collected from 123 patients. Overall sensitivity was 88.6%; B: Postoperative stool samples were collected from 122 patients. Overall specificity was 80.3%. *SDC2*: Syndecan-2; TNM: Tumor node metastasis.



DOI: 10.4240/wjgs.v15.i9.2032 **Copyright** ©The Author(s) 2023.

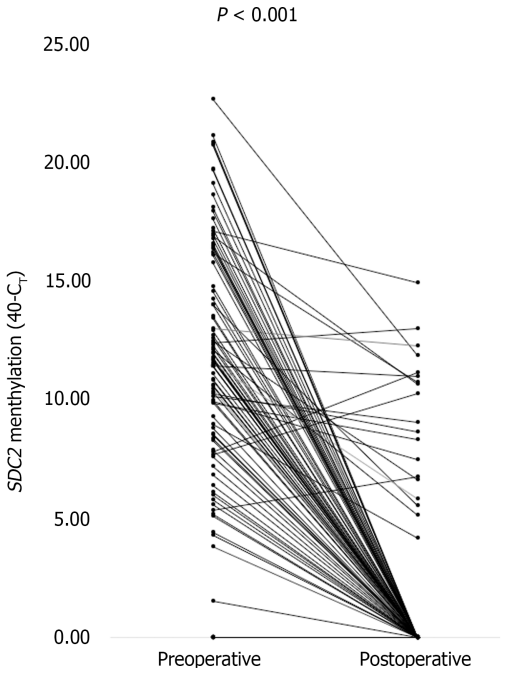
Figure 3 Distribution of syndecan-2 methylation according to tumor node metastasis stage. The cycle threshold (C_T) values for each sample were calculated as 40-C_T. A higher 40-C_T indicates a higher methylation level of syndecan-2 (*SDC2*). If *SDC2* methylation was not detected, it was expressed as 0. A: Preoperative (n = 123); B: Postoperative (n = 122). *SDC2*: Syndecan-2; C_T: Cycle threshold; TNM: Tumor node metastasis.

Recently, Wang *et al*[18] reported a meta-analysis that evaluated the diagnostic performance of the *SDC2* methylation test for detecting CRC. Twelve studies were included in the meta-analysis, and all articles were retrospective studies. Among them, seven studies measured me*SDC2* in sDNA, and five studies measured it in blood. The overall sensitivity was 80% and the specificity was 95%; and the sensitivity and specificity of sDNA test were 83% and 94%, respectively. In the present study, the detection rates of *SDC2* methylation in preoperative and postoperative were 88.6% and 19.7%, respectively. These values represent a sensitivity of 88.6% (109/123, 95%CI: 82%–96%) and specificity of 80.3% (98/122, 95%CI: 72%–87%), and the results were comparable to those of several previous studies.

Zhao *et al*[19] reported the detection rate of me*SDC2* in stool samples from 94 patients with CRC and 124 normal healthy individuals. There were no significant differences in the detection rates of me*SDC2* based on the age, sex, or stage. As the tumor size increased, the positive detection rate of me*SDC2* also increased ($P < 0.05$). Similarly, we found that a large preoperative tumor size and advanced T stage were associated with high detection rates of *SDC2* methylation. Females showed more false positive results after surgery. This result was thought to be due to the small sample size. The combination of *SDC2* with other biomarkers may improve CRC detection rates[9,19].

Several studies have reported that *SDC2* methylation is not related to the clinical stage[11,13,18]. The present study also showed similar results. There was no association between the detection rate of *SDC2* methylation and clinical stage. Although there was no statistically significant difference, the detection rate of *SDC2* methylation according to stage showed a gradual increase. Moreover, Oh *et al*[12] found that the sensitivity of *SDC2* methylation test tended to gradually increase with an increase in the stage. Further studies are needed to validate whether clinical stage affects the detection rate of me*SDC2*.

Few studies have compared sDNA test results before and after surgery. Kisiel *et al*[15] evaluated sDNA markers (*NDRG4* and *BMP3*) in 22 patients with CRC before and after surgery. They demonstrated that methylated sDNA markers present in patients normalized following surgical resection. Nishioka *et al*[20] compared the preoperative and postoperative sDNA levels of 54 patients with CRC who underwent surgical resection. Aberrant methylation of sDNA markers (*CDH4* and *GATA5*) was detected in 23 (42.3%) preoperative stool samples from patients with CRC. Methylated alleles of these genes were not found in the postoperative sDNA. To the best of our knowledge, no studies have



DOI: 10.4240/wjgs.v15.i9.2032

Figure 4 Paired cycle threshold values of syndecan-2 methylation before and after surgery for each patient (*n* = 104). The cycle threshold (C_T) values were calculated as 40-C_T. A higher 40-C_T indicated a higher methylation level of syndecan-2 (*SDC2*). If *SDC2* methylation was not detected, it was expressed as 0. *P* value was calculated using a paired *t*-test. *SDC2*: Syndecan-2; C_T: Cycle threshold.

compared me*SDC2* levels before and after surgery. We compared the preoperative and postoperative C_T values of me *SDC2* in 92 patients who tested positive for *SDC2* methylation before surgery. The C_T values of *SDC2* methylation in sDNA were significantly decreased postoperatively compared to the preoperative values. These results indicate that *SDC2* methylation test has diagnostic value and may be used for surveillance.

In our study, twenty-four (19.7%) patients with CRC remained positive for me*SDC2* in the sDNA after surgical resection. Among these patients, there was no recurrence after surgery during the median follow-up period of 46 (1–67) months. Since molecular-level methylation precedes phenotypic tumorigenesis, these patients require follow-up with concern for possible recurrence. However, six patients who experienced recurrence after surgery showed negative results for *SDC2* methylation. The correlation between postoperative *SDC2* methylation and recurrence was not statistically significant ($P = 0.597$). Therefore, based on these results, the present study seemed unlikely to show the usefulness of me *SDC2* in the sDNA as surveillance after CRC surgery. In addition, the liver and peritoneum are the most common sites for CRC metastasis[21], with rare occurrences in other parts of the body[22]. These recurrent cases of metastasis are difficult to detect with a sDNA test, making it difficult to use stool tests as a surveillance tool.

Similar to stool DNA testing, dysbiosis in the microbiota can be used as a test for early detection of CRC by obtaining fecal samples[23]. Several microbial species, such as *F. nucleatum*, *B. fragilis*, and *F. Prausnitzii*, are known to act as a driving force in the occurrence of CRC. Hence, detecting these microbial species in stool samples can aid in the early identification of CRC[24]. Non-invasive fecal biomarkers, such as aberrant methylation of sDNA tests or dysbiosis in the microbiota, can be expected to make important contributions to the early diagnosis and therapeutic implications of CRC in the future.

The present study had several limitations. First, selection bias may have existed because this study was conducted at a single institution with a small sample size. Second, it is insufficient to determine its value as a surveillance tool because *SDC2* methylation was only compared before and after surgery, without long-term follow-up. Therefore, multicenter prospective studies with long-term follow-up are necessary to assess the feasibility of surveillance.

CONCLUSION

We demonstrated that the *SDC2* methylation test in sDNA has acceptable sensitivity and specificity. However, small-size and early T stage tumors are associated with a low detection rate of *SDC2* methylation. As the C_T values significantly decrease after surgery, *SDC2* methylation of the sDNA test exhibits diagnostic value for CRC.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) is a significant cause of morbidity and mortality worldwide, emphasizing the need for early detection. Stool DNA (sDNA) testing is a promising non-invasive method for CRC detection, and syndecan-2 (*SDC2*) methylation has been identified as a potential biomarker for this test.

Research motivation

The study aimed to investigate whether *SDC2* methylation in sDNA normalizes after surgical resection of CRC, which could have implications for the diagnostic value and postoperative surveillance of *SDC2* methylation.

Research objectives

The study aimed to compare the detection rates of *SDC2* methylation in preoperative and postoperative stool samples of CRC patients and assess the association between *SDC2* methylation and clinicopathological parameters. The study also sought to evaluate the change in *SDC2* methylation levels before and after surgery.

Research methods

A prospective study enrolled 151 CRC patients who underwent surgical resection. Stool samples were collected before and after surgery, and *SDC2* methylation in sDNA was assessed using a quantitative methylation-specific real-time polymerase chain reaction. The association between *SDC2* methylation and clinicopathological parameters was analyzed.

Research results

The detection rate of *SDC2* methylation was significantly higher in preoperative stool samples (88.6%) compared to postoperative samples (19.7%). Large tumor size and advanced T stage were associated with higher detection rates before surgery, while female sex was associated with false positives after surgery. The cycle threshold (C_T) values significantly decreased after surgery, indicating a normalization of *SDC2* methylation. The postoperative negative conversion rate for preoperatively methylated *SDC2* was 79.3%.

Research conclusions

The study findings suggest that the *SDC2* methylation test in sDNA has acceptable sensitivity and specificity for CRC detection. However, the detection rate is lower for small-size and early T stage tumors. The significant decrease in C_T values after surgery indicates the diagnostic value of *SDC2* methylation testing for CRC.

Research perspectives

Further research is needed to validate the findings and assess the long-term utility of *SDC2* methylation testing as a surveillance tool for postoperative CRC patients. Multicenter prospective studies with extended follow-up periods are warranted to evaluate the feasibility and effectiveness of *SDC2* methylation testing in clinical practice.

FOOTNOTES

Author contributions: Song JH collected and analyzed the clinical data, drafted the manuscript, and prepared the figures; Oh TJ and An S drafted the manuscript; Lee KH and Kim JY collected the stool samples; Kim JS participated in study design, collected the stool samples, collected and analyzed the clinical data, drafted the manuscript, and prepared the figures; All authors read and approved the final manuscript.

Supported by the Research Fund of Chungnam National University, No. 2018-0626-01.

Institutional review board statement: This observational study was approved by the Institutional Review Board of our institute (IRB No. 2016-05-018).

Informed consent statement: Written informed consent was obtained from all subjects.

Conflict-of-interest statement: The authors declare that they have no competing interests.

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

Country/Territory of origin: South Korea

ORCID number: Ji Hyeong Song 0000-0002-7501-7259; Tae Jeong Oh 0000-0001-6212-1949; Sungwhan An 0000-0001-8781-4186; Kyung Ha Lee 0000-0002-0035-9000; Ji Yeon Kim 0000-0001-7964-5060; Jin Soo Kim 0000-0002-3362-574X.

S-Editor: Zhang H
L-Editor: A

P-Editor: Cai YX

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

2 Korean statistics 2019. [cited 2023 Jun 8]. Korean Statistical Information Service [Internet]. Available from: https://kosis.kr/

3 **Dashwood RH**. Early detection and prevention of colorectal cancer (review). *Oncol Rep* 1999; **6**: 277-281

4 **Morikawa T**, Kato J, Yamaji Y, Wada R, Mitsushima T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. *Gastroenterology* 2005; **129**: 422-428

5 **Bretthauer M**, Kaminski MF, Løberg M, Zauber AG, Regula J, Kuipers EJ, Hernán MA, McFadden E, Sunde A, Kalager M, Dekker E, Lansdorp-Vogelaar I, Garborg K, Rupinski M, Spaander MC, Bugajski M, Høie O, Stefansson T, Hoff G, Adami HO; Nordic-European Initiative on Colorectal Cancer (NordICC) Study Group. Population-Based Colonoscopy Screening for Colorectal Cancer: A Randomized Clinical Trial. *JAMA Intern Med* 2016; **176**: 894-902

6 **Berger BM**, Ahlquist DA. Stool DNA screening for colorectal neoplasia: biological and technical basis for high detection rates. *Pathology* 2012; **44**: 80-88

7 **Kadiyska T**, Nossikoff A. Stool DNA methylation assays in colorectal cancer screening. *World J Gastroenterol* 2015; **21**: 10057-10061

8 **Vedeld HM**, Goel A, Lind GE. Epigenetic biomarkers in gastrointestinal cancers: The current state and clinical perspectives. *Semin Cancer Biol* 2018; **51**: 36-49

9 **Chen J**, Sun H, Tang W, Zhou L, Xie X, Qu Z, Chen M, Wang S, Yang T, Dai Y, Wang Y, Gao T, Zhou Q, Song Z, Liao M, Liu W. DNA methylation biomarkers in stool for early screening of colorectal cancer. *J Cancer* 2019; **10**: 5264-5271

10 **Imperiale TF**, Ransohoff DF, Itzkowitz SH, Levin TR, Lavin P, Lidgard GP, Ahlquist DA, Berger BM. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med* 2014; **370**: 1287-1297

11 **Niu F**, Wen J, Fu X, Li C, Zhao R, Wu S, Yu H, Liu X, Zhao X, Liu S, Wang X, Wang J, Zou H. Stool DNA Test of Methylated Syndecan-2 for the Early Detection of Colorectal Neoplasia. *Cancer Epidemiol Biomarkers Prev* 2017; **26**: 1411-1419

12 **Oh TJ**, Oh HI, Seo YY, Jeong D, Kim C, Kang HW, Han YD, Chung HC, Kim NK, An S. Feasibility of quantifying SDC2 methylation in stool DNA for early detection of colorectal cancer. *Clin Epigenetics* 2017; **9**: 126

13 **Han YD**, Oh TJ, Chung TH, Jang HW, Kim YN, An S, Kim NK. Early detection of colorectal cancer based on presence of methylated syndecan-2 (SDC2) in stool DNA. *Clin Epigenetics* 2019; **11**: 51

14 **Toyota M**, Ahuja N, Ohe-Toyota M, Herman JG, Baylin SB, Issa JP. CpG island methylator phenotype in colorectal cancer. *Proc Natl Acad Sci U S A* 1999; **96**: 8681-8686

15 **Kisiel JB**, Yab TC, Taylor WR, Mahoney DW, Ahlquist DA. Stool methylated DNA markers decrease following colorectal cancer resection--implications for surveillance. *Dig Dis Sci* 2014; **59**: 1764-1767

16 **Ransohoff DF**. How much does colonoscopy reduce colon cancer mortality? *Ann Intern Med* 2009; **150**: 50-52

17 **Gachabayov M**, Lebovics E, Rojas A, Felsenreich DM, Latifi R, Bergamaschi R. Performance evaluation of stool DNA methylation tests in colorectal cancer screening: a systematic review and meta-analysis. *Colorectal Dis* 2021; **23**: 1030-1042

18 **Wang L**, Liu Y, Zhang D, Xiong X, Hao T, Zhong L, Zhao Y. Diagnostic accuracy of DNA-based SDC2 methylation test in colorectal cancer screening: a meta-analysis. *BMC Gastroenterol* 2022; **22**: 314

19 **Zhao G**, Liu X, Liu Y, Li H, Ma Y, Li S, Zhu Y, Miao J, Xiong S, Fei S, Zheng M. Aberrant DNA Methylation of SEPT9 and SDC2 in Stool Specimens as an Integrated Biomarker for Colorectal Cancer Early Detection. *Front Genet* 2020; **11**: 643

20 **Nishioka Y**, Ueki T, Hokazono K, Nagayoshi K, Tanaka M. Comparative detection of aberrantly methylated DNA in preoperative and postoperative stool from patients with colorectal cancers. *Int J Biol Markers* 2015; **30**: e81-e87

21 **Pretzsch E**, Bösch F, Neumann J, Ganschow P, Bazhin A, Guba M, Werner J, Angele M. Mechanisms of Metastasis in Colorectal Cancer and Metastatic Organotropism: Hematogenous versus Peritoneal Spread. *J Oncol* 2019; **2019**: 7407190

22 **Lucke-Wold B**, Bonasso PC, Cassim R. Primary colon adenocarcinoma with metastatic disease to the rectum followed by the left axilla. *Am Med Stud Res J* 2017; **4**: 57-61

23 **Villéger R**, Lopès A, Veziant J, Gagnière J, Barnich N, Billard E, Boucher D, Bonnet M. Microbial markers in colorectal cancer detection and/or prognosis. *World J Gastroenterol* 2018; **24**: 2327-2347

24 **Abdulla MH**, Agarwal D, Singh JK, Traiki TB, Pandey MK, Ahmad R, Srivastava SK. Association of the microbiome with colorectal cancer development (Review). *Int J Oncol* 2021; **58**

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 2042-2051

DOI: 10.4240/wjgs.v15.i9.2042

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Prospective Study

Preoperative prediction of microvascular invasion in hepatocellular carcinoma using ultrasound features including elasticity

Dong Jiang, Yi Qian, Bi-Bo Tan, Xia-Ling Zhu, Hui Dong, Rong Qian

Specialty type: Radiology, nuclear medicine and medical imaging

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Garcia-Tsao G, United States; Tam PKH, China

Received: May 24, 2023
Peer-review started: May 24, 2023
First decision: June 12, 2023
Revised: June 23, 2023
Accepted: July 27, 2023
Article in press: July 27, 2023
Published online: September 27, 2023

Dong Jiang, Yi Qian, Bi-Bo Tan, Xia-Ling Zhu, Department of Ultrasound, Eastern Hepatobiliary Surgery Hospital, Naval Medical University, Shanghai 200438, China

Hui Dong, Department of Pathology, Eastern Hepatobiliary Surgery Hospital, Naval Medical University, Shanghai 200438, China

Rong Qian, Department of Ultrasound, No. 905 Hospital of PLA Navy, Shanghai 200052, China

Corresponding author: Rong Qian, Doctor, MD, Chief Physician, Department of Ultrasound, No. 905 Hospital of PLA Navy, No. 1328 Huashan Road, Shanghai 200052, China.
2651184151@qq.com

Abstract

BACKGROUND

Microvascular invasion (MVI) is an important predictor of poor prognosis in patients with hepatocellular carcinoma (HCC). Accurate preoperative prediction of MVI in HCC would provide useful information to guide the choice of therapeutic strategy. Shear wave elastography (SWE) plays an important role in hepatic imaging, but its value in the preoperative prediction of MVI in HCC has not yet been proven.

AIM

To explore the value of conventional ultrasound features and SWE in the preoperative prediction of MVI in HCC.

METHODS

Patients with a postoperative pathological diagnosis of HCC and a definite diagnosis of MVI were enrolled in this study. Conventional ultrasound features and SWE features such as maximal elasticity (Emax) of HCCs and Emax of the periphery of HCCs were acquired before surgery. These features were compared between MVI-positive HCCs and MVI-negative HCCs and between mild MVI HCCs and severe MVI HCCs.

RESULTS

This study included 86 MVI-negative HCCs and 102 MVI-positive HCCs, including 54 with mild MVI and 48 with severe MVI. Maximal tumor diameters, surrounding liver tissue, color Doppler flow, Emax of HCCs, and Emax of the periphery of HCCs were significantly different between MVI-positive HCCs and

MVI-negative HCCs. In addition, Emax of the periphery of HCCs was significantly different between mild MVI HCCs and severe MVI HCCs. Higher Emax of the periphery of HCCs and larger maximal diameters were independent risk factors for MVI, with odds ratios of 2.820 and 1.021, respectively.

CONCLUSION
HCC size and stiffness of the periphery of HCC are useful ultrasound criteria for predicting positive MVI. Preoperative ultrasound and SWE can provide useful information for the prediction of MVI in HCCs.

Key Words: Hepatocellular carcinoma; Microvascular invasion; Conventional ultrasound; Shear wave elastography

Core Tip: Shear wave elastography (SWE) plays an important role in differentiating benign and malignant liver tumors and different types of malignant liver tumors. However, its value in the preoperative prediction of microvascular invasion (MVI) in hepatocellular carcinoma (HCC) has not yet been proven. We used conventional ultrasound and SWE to evaluate the features of HCCs for preoperative prediction of MVI in HCCs. Our results showed that higher maximal elasticity of the periphery of HCCs and larger maximal diameters were independent risk factors for MVI. Preoperative conventional ultrasound and SWE can provide useful information for the prediction of MVI in HCCs.

Citation: Jiang D, Qian Y, Tan BB, Zhu XL, Dong H, Qian R. Preoperative prediction of microvascular invasion in hepatocellular carcinoma using ultrasound features including elasticity. *World J Gastrointest Surg* 2023; 15(9): 2042-2051
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/2042.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.2042

INTRODUCTION

Hepatocellular carcinoma (HCC), as the third leading cause of cancer-related deaths worldwide and the second leading cause in China, represents a major health concern throughout the world, especially in China[1]. Microvascular invasion (MVI), the invasion of cancer cells into vascular lumen (including microbranches of the portal vein, hepatic artery, and lymphatic vessels), is a very important predictor of poor prognosis, postoperative recurrence, metastasis, and poor survival rate in patients with HCC after surgical resection or liver transplantation[2-5]. Accurate preoperative prediction of MVI in HCC would offer valuable insights to guide therapeutic strategy.

Some studies have demonstrated that preoperative imaging including contrast-enhanced computed tomography and contrast-enhanced magnetic resonance imaging (MRI) may help in the diagnosis of MVI[6-10]. Related studies have focused on contrast-enhanced ultrasound (CEUS)[11-14]. The study by Qin *et al*[11] showed that a deep learning model based on CEUS could accurately predict MVI in HCC and help identify high-risk patients. The study by Li *et al*[12] showed that features such as non-single nodules in the postvascular phase of preoperative Sonazoid CEUS was an independent risk factor for MVI in HCC.

Ultrasound elastography, especially quantitative shear wave elastography (SWE), plays an important role in hepatic imaging[15-17]. Compared with CEUS, contrast-enhanced computed tomography, or contrast-enhanced MRI, SWE has the advantage of the absence of contrast agent allergy and is generally less expensive and less time-consuming than other methods, making it a more practical option for many medical facilities. Zhang *et al*[7] reported that the stiffness of HCCs based on MR-elastography was an independent risk factor for MVI and may be useful for the preoperative prediction of MVI. However, only a few studies have focused on the value of SWE in the prediction of MVI[18].

In the present study, we explored the value of conventional ultrasound features and SWE in the preoperative prediction of MVI in HCC.

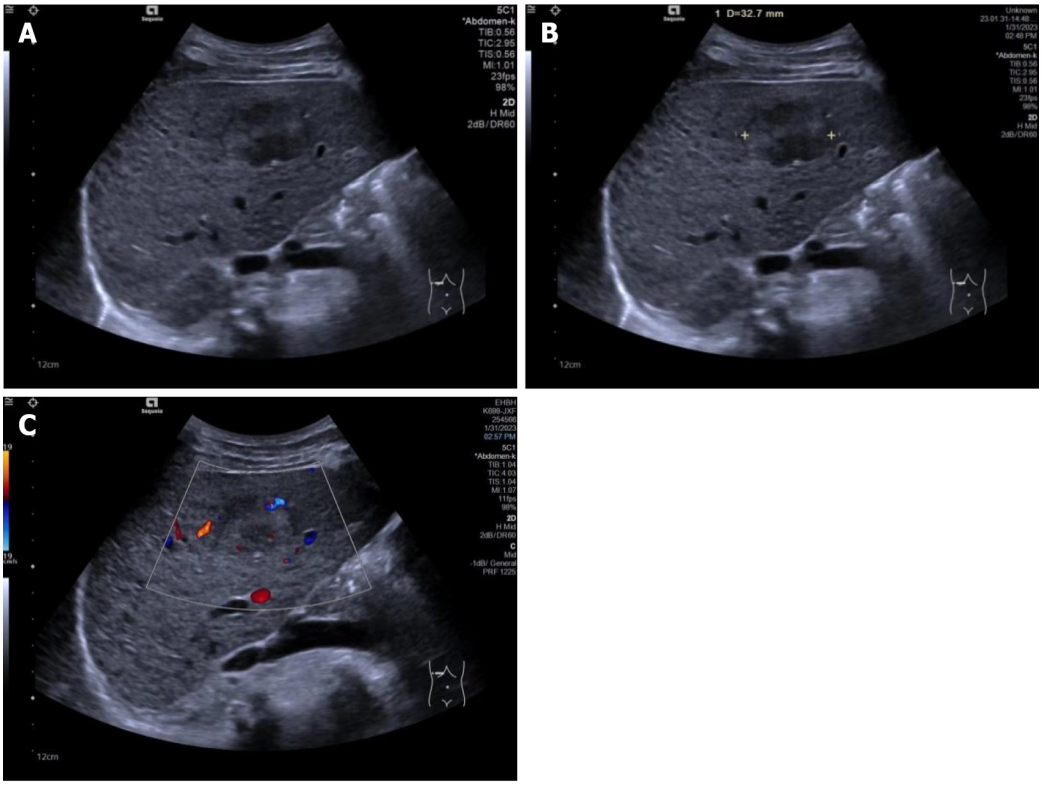
MATERIALS AND METHODS

Study design

This prospective study was approved by the Ethics Committee of Eastern Hepatobiliary Surgery Hospital (Approval No. EHBHKY2021-K-017). Each patient provided written informed consent before the ultrasound examinations.

Patients

Inpatients admitted to the Hepatobiliary Surgery Department at our hospital between November 2021 and July 2022 were included in this study if they met the following criteria: (1) Single liver tumor resected surgically and diagnosed as HCC pathologically; and (2) Ultrasound examinations including SWE successfully performed within 3 d before surgery. The exclusion criteria were: (1) A history of hepatectomy or abdominal malignant tumors; (2) A history of radiotherapy,



DOI: 10.4240/wjgs.v15.i9.2042

Figure 1 Conventional ultrasound images in patients with a hepatic tumor pathologically diagnosed as hepatocellular carcinoma. A: Conventional ultrasound showed the tumor to be hypoechoic with an unclear boundary and cirrhosis in the surrounding liver tissue; B: Conventional ultrasound measured the maximal diameter of the tumor to be 32.7 mm; C: Color Doppler flow imaging showed one vessel in the tumor, and microvascular invasion was recorded as mild.

chemotherapy, and other treatments before surgery; and (3) No definite pathological diagnosis of MVI.

Conventional ultrasound examination

All ultrasound examinations were performed within 3 d before surgery, using an Acuson Sequoia diagnostic ultrasound machine and a transabdominal 5C1 probe (Siemens Medical Solutions, Mountain View, CA, United States). The patients were instructed to fast for a minimum of 8 h prior to the examinations.

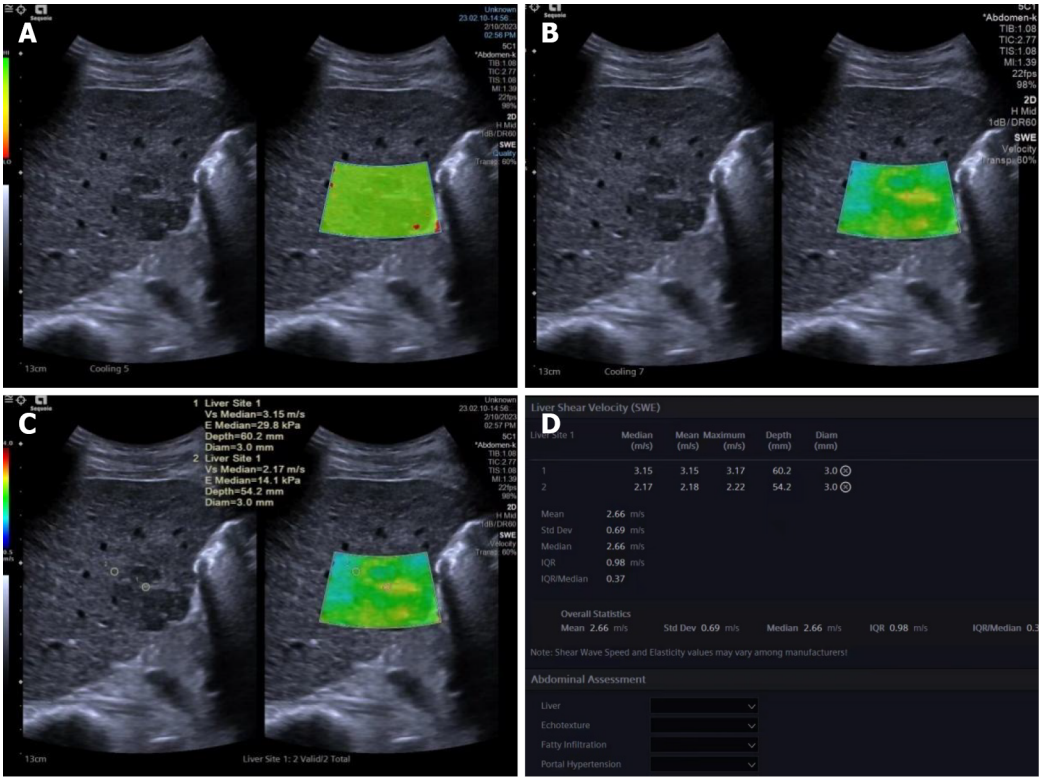
All conventional ultrasound examinations were performed by a single ultrasound physician with 15 years of experience in liver ultrasound. Maximal tumor diameter, echogenicity (hypo- if the tumor was mainly hypoechoic compared with surrounding liver tissue, or hyper- if the tumor was mainly hyperechoic compared with surrounding liver tissue), boundary (clear or unclear), surrounding hepatic tissue (liver cirrhosis, fatty liver, or normal liver), and tumor vascularity (none if no vessels were seen in the tumor using color Doppler flow imaging, rich if more than three vessels were seen, or mild if one to three vessels were seen) were observed and recorded (Figure 1).

SWE examination

The same ultrasound equipment and probe were used for the SWE examination. Another ultrasound physician with 5 years of experience in both liver ultrasound and ultrasound elastography performed all the SWE examinations. During the examination, the patients were instructed to lie flat and breathe gently. They were instructed to hold their breath for a few seconds if necessary. The targeted tumor was shown on the screen before activation of the SWE mode. The whole tumor (or partial if the tumor was too large) and some surrounding hepatic tissues were included in the region of interest (ROI). Quality mode was used to evaluate the SWE image quality; green in the ROI means image quality is excellent and the results are reliable. In the velocity mode, the speed bar was set as 0.5-4.0 m/s. One circular ROI (diameter of 3 mm) was placed at the stiffest part of the tumor; another ROI of the same size was placed at the periphery of the tumor. The maximum values within the two ROIs were recorded as Emax for both the tumor and the periphery of the tumor, respectively. These values were then used for further analysis (Figure 2).

Pathological MVI examination

One pathologist, who had 20 years of experience in HCC pathology and was blind to all clinical data, reviewed the specimens. The extent of MVI was graded as MVI-negative (no MVI detected), mild MVI (MVI ≤ 5, occurring in the proximal non-neoplastic adjacent hepatic tissues), and severe MVI (MVI > 5, in non-neoplastic adjacent hepatic tissues, Figure 3)[2].



DOI: 10.4240/wjgs.v15.i9.2042

Figure 2 Shear wave elastography images in a pathologically confirmed hepatocellular carcinoma. A: Quality mode showed hepatocellular carcinoma (HCC) as green, indicating that the 2D-shear wave elastography image was of good quality; B: Velocity mode showed that the HCC was stiffer than the surrounding liver tissue. The speed barb was set as 0.5-4.0 m/s; C: Two circular regions of interest (with a diameter of 3 mm) were placed at the stiffest part of the HCC and at the periphery of the HCC; D: Maximal values of the two regions of interest were recorded as maximal elasticity.

Statistical analysis

For statistical analysis, SPSS version 24.0 software (IBM Corporation, Armonk, NY, United States) was used. $P < 0.05$ was considered statistically significant. Measurement data with normal distribution were reported as mean ± standard deviation and compared using the independent sample *t*-test; otherwise, data were reported as median (25^{th}-75^{th} percentile) and compared using the Mann-Whitney test. The cutoff point of Emax was calculated by a receiver operating characteristic curve.

Enumerative data were described as numbers and percentage and compared using the Pearson c^2 test. Bivariate logistic regression analysis was performed to determine independent predictors of MVI from the ultrasound characteristics that showed statistical significance using univariate analysis.

RESULTS

Patients and MVI results

One hundred and eighty-eight patients with single HCCs (156 males and 32 females; aged 24-76 years, mean age 56.25 years ± 9.93 years) were enrolled in this study, including 86 who were MVI-negative and 102 who were MVI-positive (54 had mild MVI and 48 had severe MVI). Sex and age were not significantly different between the MVI-negative patients (70 males and 16 females; mean age 56.94 years ± 10.12 years) and the MVI-positive patients (86 males and 16 females; mean age 55.67 years ± 9.77 years).

Conventional ultrasound results

Comparisons of conventional ultrasound results between MVI-negative and MVI-positive HCCs are shown in Table 1. The maximal diameters of MVI-positive HCCs were significantly greater than those of MVI-negative HCCs. The cutoff point for maximal tumor diameters was 61.95 mm with an area under the curve (AUC) of 0.663. MVI-positive HCCs were more likely to have a background of liver cirrhosis and a rich blood flow and less likely to have a fatty liver background.

Comparisons of conventional ultrasound results between mild MVI and severe MVI HCCs are shown in Table 2. There were no statistically significant differences in either maximal tumor diameter or other ultrasound characteristics between the two groups.

Table 1 Comparisons of conventional ultrasound results between microvascular invasion-negative and microvascular invasion-positive hepatocellular carcinomas, *n* (%)

MVI	Tumor maximal diameter in mm	Echogenecity		Boundary		Surrounding liver tissue			Color Doppler flow		
		Hypo-	Hyper-	Clear	Unclear	Liver cirrhosis	Fatty liver	Normal	None	Mild	Rich
MVI negative, *n* = 86	35.45 (24.00-49.28)	55 (29.3)	31 (16.5)	55 (29.3)	31 (16.5)	38 (20.2)	17 (9.0)	31 (16.5)	34 (18.1)	12 (6.4)	40 (21.3)
MVI positive, *n* = 102	46.95 (32.75-71.03)	63 (33.5)	39 (20.7)	58 (30.9)	44 (23.4)	52 (27.7)	7 (3.7)	43 (22.9)	20 (10.6)	20 (10.6)	62 (33.0)
Z/χ^2	3.841	0.096		0.978		7.255			9.079		
P value	0.000	0.757		0.323		0.027			0.011		

MVI: Microvascular invasion.

Table 2 Comparisons of conventional ultrasound results between mild microvascular invasion and severe microvascular invasion hepatocellular carcinomas

MVI	Tumor maximal diameter in mm	Echogenecity		Boundary		Surrounding liver tissue			Color Doppler flow		
		Hypo-	Hyper-	Clear	Unclear	Liver cirrhosis	Fatty liver	Normal	None	Mild	Rich
Mild MVI, *n* = 54	50.15 (33.80-65.90)	36 (35.3)	18 (17.6)	33 (32.4)	21 (20.6)	25 (24.5)	4 (3.9)	25 (24.5)	8 (7.8)	9 (8.8)	37 (36.3)
Severe MVI, *n* = 48	43.20 (30.83-73.68)	27 (26.5)	21 (20.6)	25 (24.5)	23 (22.5)	27 (26.5)	3 (2.9)	18 (17.6)	12 (11.8)	11 (10.8)	25 (24.5)
Z/χ^2	0.496	1.168		0.844		1.063			2.980		
P value	0.622	0.280		0.358		0.641			0.254		

MVI: Microvascular invasion.

SWE results

The differences in SWE results between MVI-negative and MVI-positive HCCs are shown in Table 3. The Emax of MVI-positive HCCs was significantly higher than that of MVI-negative HCCs. The Emax of the periphery of MVI-positive HCCs was significantly higher than that of MVI-negative HCCs. The cutoff point for the Emax of HCCs was 2.340 with an AUC of 0.598; the cutoff point for the Emax of the periphery of HCCs was 1.305 with an AUC of 0.622 (Figure 4).

The differences in SWE results between mild MVI and severe MVI HCCs are shown in Table 4. There were no significant differences between the Emax of mild MVI and severe MVI HCCs. However, the Emax of the periphery of severe MVI HCCs was significantly higher than that of mild MVI HCCs.

Bivariate logistic regression results

The results of bivariate logistic regression of the features suggestive of positive MVI are shown in Table 5. Higher Emax of the periphery of HCCs and larger maximal diameters were independent risk factors for MVI, with odds ratios of 2.820 and 1.021, respectively.

DISCUSSION

In this study, we investigated the efficacy of conventional ultrasound features and SWE in the preoperative prediction of MVI in HCC. Our findings revealed that a higher Emax in the periphery of HCCs coupled with larger maximal diameters were independent risk factors for MVI.

There were no significant differences in the distributions of sex and age between patients with MVI-positive HCCs and those with MVI-negative HCCs. These results were similar to those in a previous study[19]. Our results also showed that the maximal diameters of MVI-positive HCCs were significantly larger than those of MVI-negative HCC, and a larger maximal diameter was an independent risk factor for MVI-positive HCCs with an odds ratio of 1.021. Tumor size is an established independent prognostic factor for HCC[20,21]. Our research has revealed that HCC size was also an independent prognostic factor for positive MVI. Consequently, it is of utmost importance to have precise preoperative measurements of HCC size for accurate prediction of MVI status and prognosis.

Table 3 Comparisons of shear wave elastography results between microvascular invasion-negative and microvascular invasion-positive hepatocellular carcinomas

MVI	Emax of the periphery of tumors in m/s	Emax of the tumors in m/s
MVI negative, *n* = 86	1.38 (1.18-1.65)	2.14 (1.71-2.49)
MVI positive, *n* = 102	1.50 (1.31-1.88)	2.29 (2.00-2.63)
Z	2.879	2.312
P value	0.004	0.021

Emax: Maximal elasticity; MVI: Microvascular invasion.

Table 4 Comparisons of shear wave elastography results between mild microvascular invasion and severe microvascular invasion hepatocellular carcinomas

MVI	Emax of the periphery of tumors in m/s	Emax of the tumors in m/s
Mild MVI, *n* = 54	1.42 (1.23-1.84)	2.24 (2.00-2.56)
Severe MVI, *n* = 48	1.67 (1.37-1.98)	2.37 (2.03-2.67)
Z	2.437	0.811
P value	0.014	0.420

Emax: Maximal elasticity; MVI: Microvascular invasion.

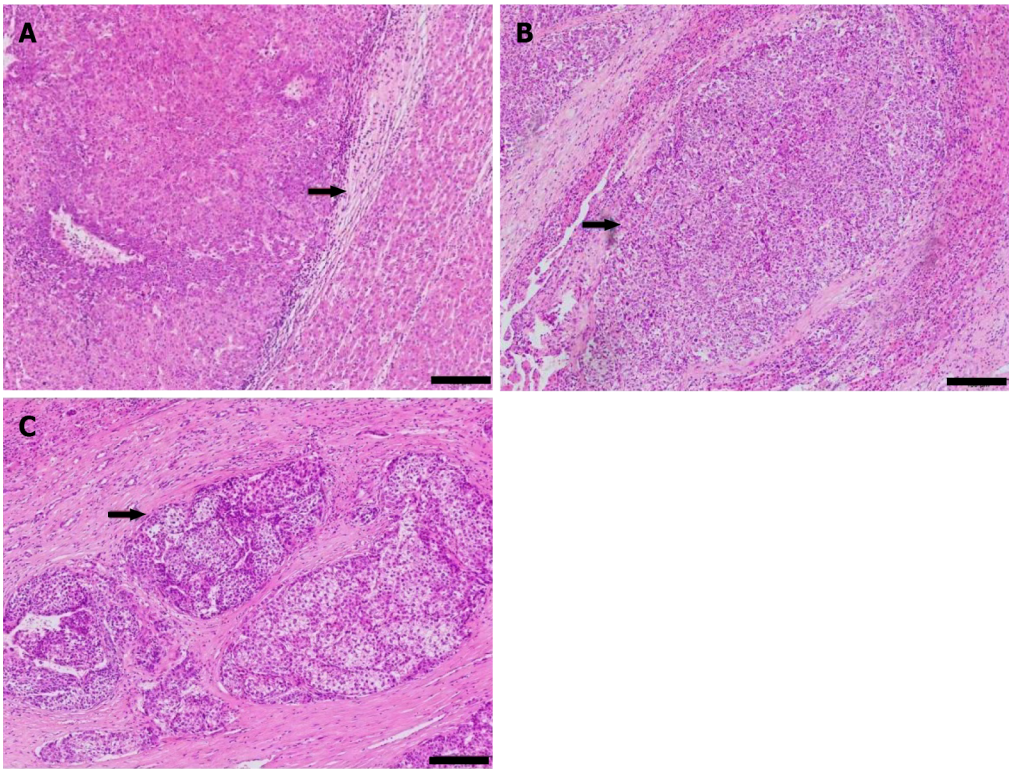
Table 5 Results of bivariate logistic regression of the features suggestive of positive microvascular invasion

Ultrasound features	β coefficient	Odd ratios	95% confidence interval	*P* value
Emax of the periphery of HCC	1.037 ± 0.467	2.820	1.128-7.049	0.027
Emax of HCC	0.114 ± 0.272	0.893	0.524-1.521	0.676
Maximal tumor diameter	0.021 ± 0.008	1.021	1.003-1.037	0.007
Surrounding liver tissue	0.329 ± 0.230	0.719	0.459-1.128	0.152
Color Doppler flow	0.324 ± 0.190	1.383	0.953-2.006	0.088

Emax: Maximal elasticity; HCC: Hepatocellular carcinoma.

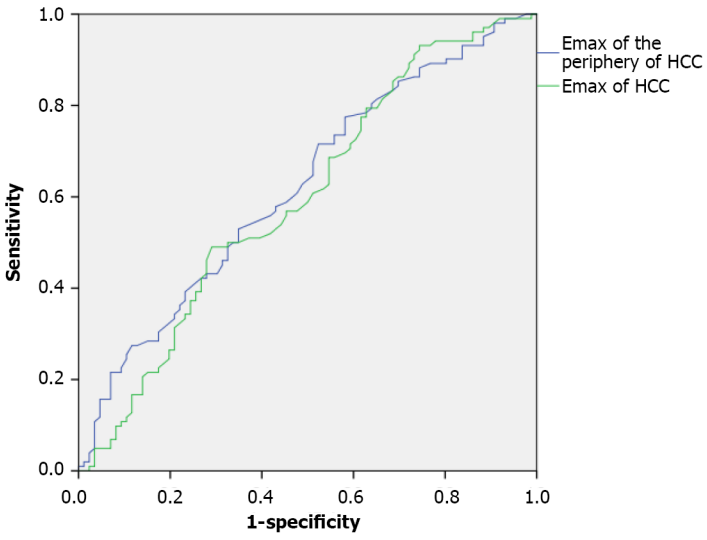
Conventional ultrasound is the first imaging choice for hepatology and plays an important role in both focal hepatic lesions and diffuse liver diseases. Our study showed that ultrasound features such as tumor boundary or tumor echogenicity were not significantly different between MVI-positive and MVI-negative HCCs, similar to the results of Zhou *et al*[22], which showed that ultrasound features including echogenicity, margin, shape, and halo sign were not significantly different between MVI-positive and MVI-negative HCCs. According to our findings, MVI-positive HCCs were more likely to have a rich blood flow. As MVI reflects the invasion of cancer cells into microvessels, it may cause a change in the blood supply in tumors. Some CEUS studies have also confirmed that MVI-positive HCCs have increased blood flow perfusion, compared with MVI-negative HCCs[13,14]. However, the study by Zhou *et al*[22] showed different results as the distribution of blood flow was not significantly different between MVI-positive and MVI-negative HCCs. The reason for this may be due to the different ultrasound machines used. The sensitivity of color Doppler can vary greatly between ultrasound machines. Also, the correct setting of machine parameters is very important[23]. The application of new Doppler techniques, such as superb microvascular imaging, would be useful[24]. Our study revealed that MVI-positive HCCs were more likely to have a background of liver cirrhosis and less likely to have a background of fatty liver, indicating that HCCs with a background of liver cirrhosis are likely MVI-positive. The surrounding liver background of HCCs should be taken into consideration for preoperative evaluation.

Our previous studies have shown that the value of SWE with Emax in the differential diagnosis between benign and malignant focal liver lesions or among different pathological types of malignant focal liver lesions[15]. In this study, we found that the Emax of HCCs and the Emax of the periphery of HCCs were significantly different between MVI-positive HCCs and MVI-negative HCCs. The Emax of the periphery of HCCs was an independent risk factor for MVI-positive HCC with an odds ratio of 2.820. Our results indicated that MVI-positive HCCs were stiffer than MVI-negative HCCs, and this was similar to the results of other studies based on MR-elastography[7,25]. One probable reason is that positive



DOI: 10.4240/wjgs.v15.i9.2042 **Copyright** ©The Author(s) 2023.

Figure 3 Pathological images showed microvascular invasion in hepatocellular carcinoma. Hematoxylin and eosin stain, magnification: × 100. A: No microvascular invasion (MVI) detected, recorded as MVI-negative; B: One MVI detected, recorded as mild MVI; C: More than 5 MVIs detected, recorded as severe MVI. Scale bar: 100 μm.



DOI: 10.4240/wjgs.v15.i9.2042 **Copyright** ©The Author(s) 2023.

Figure 4 Receiver operating characteristic curve for maximal elasticity of the periphery of the hepatocellular carcinoma and maximal elasticity of the hepatocellular carcinoma. Emax: Maximal elasticity; HCC: Hepatocellular carcinoma.

MVI may change the blood supply in the tumor and then modify its stiffness. As MVI usually invades the capsule of HCCs first, the periphery of the HCC is usually involved early[2]. This early change in blood flow and tissue stiffness could potentially have significant implications. Zhang *et al*[26] reported rim enhancement in the arterial phase and peritumoral hypointensity in the hepatobiliary phase in gadobenate-enhanced MRI as independent risk factors for MVI. In addition, our findings suggest that the stiffness of the periphery of HCCs may serve as an important independent predictor of MVI risk. Specifically, we observed that higher stiffness in this region of HCCs was significantly associated with an increased risk of developing MVI. Furthermore, differences in Emax values at the periphery of HCCs were found

to distinguish between HCCs with mild and severe MVI, highlighting the potential diagnostic value of this parameter in MVI detection.

There were some limitations to our study that should be acknowledged. First, laboratory data, including total bilirubin and alpha fetoprotein, were not taken into account. The inclusion of these laboratory indices in conjunction with the ultrasound indices would be valuable in developing a predictive model. This will be a focus of our future research.

CONCLUSION

In summary, HCC size and stiffness of the periphery of HCCs are useful ultrasound criteria for predicting positive MVI. Thus, preoperative ultrasound and SWE could provide useful information for the prediction of MVI in HCCs.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC), as the third leading cause of cancer-related deaths worldwide and the second leading cause in China, represents a major health concern throughout the world, especially in China. Microvascular invasion (MVI) is a very important predictor of poor prognosis in patients with HCC after surgical resection or liver transplantation. Accurate preoperative prediction of MVI in HCC would offer valuable insights to guide therapeutic strategy. Preoperative imaging including contrast-enhanced computed tomography, contrast-enhanced magnetic resonance imaging, and contrast-enhanced ultrasound may help in the diagnosis of MVI.

Research motivation

Shear wave elastography (SWE) has the advantage of the absence of contrast agent allergy and is generally less expensive and less time-consuming than other methods, making it a more practical option for many medical facilities. Our previous study showed promising results using SWE with maximal elasticity (Emax) as the parameter to differentiate malignant focal liver lesions from benign lesions and to differentiate among different pathological types of malignant focal liver lesions. However, only a few studies have focused on the value of SWE in the prediction of MVI.

Research objectives

We aimed to explore the value of conventional ultrasound features and SWE in the preoperative prediction of MVI in HCC.

Research methods

In this study, we enrolled patients with a postoperative pathological diagnosis of HCC and a definite diagnosis of MVI. Conventional ultrasound features and SWE features such as Emax of HCCs and Emax of the periphery of HCCs were acquired before surgery. These features were compared between MVI-positive HCCs and MVI-negative HCC and between mild MVI HCCs and severe MVI HCCs.

Research results

There were a total of 86 MVI-negative HCCs and 102 MVI-positive HCCs in this study, including 54 with mild MVI and 48 with severe MVI. Maximal tumor diameters, surrounding liver tissue, color Doppler flow, Emax of HCCs, and Emax of the periphery of HCCs were significantly different between MVI-positive HCCs and MVI-negative HCCs. In addition, Emax of the periphery of HCCs was significantly different between mild MVI HCCs and severe MVI HCCs. Higher Emax of the periphery of HCCs (> 2.340 m/s, area under the curve as 0.598) and larger maximal diameters (> 61.95 mm, area under the curve as 0.663) were independent risk factors for MVI, with odds ratios of 2.820 and 1.021, respectively.

Research conclusions

HCC size and stiffness of the periphery of HCCs are useful ultrasound criteria for predicting positive MVI. Thus, preoperative ultrasound and SWE could provide useful information for the prediction of MVI in HCCs.

Research perspectives

In this study, we demonstrated the value of conventional ultrasound features and SWE in the preoperative prediction of MVI in HCC. Prospective studies to explore the value of multimodal ultrasound imaging including conventional ultrasound, ultrasound elastography, superb microvascular imaging, and contrast-enhanced ultrasound in the preoperative prediction of MVI in HCC would be beneficial.

FOOTNOTES

Author contributions: Jiang D, Dong H, and Qian R designed the study; Qian Y, Tan BB, and Zhu XL performed the research and

collected ultrasound data; Dong H reviewed and analyzed pathological specimens; Jiang D and Qian R performed statistical analysis; Jiang D and Qian R wrote the manuscript; All authors read and approved the final manuscript.

Supported by the Key Program of Science and Technology Commission Foundation of Changning, No. CNKW2022Y61.

Institutional review board statement: This prospective study was approved by the Ethics Committee of Eastern Hepatobiliary Surgery Hospital (Approval No. EHBHKY2021-K-017).

Clinical trial registration statement: This study is registered at clinical hospital center "Eastern Hepatobiliary Surgery Hospital, Naval Medical University" trial registry. The registration identification number is ChiCTR2100049831.

Informed consent statement: Each patient provided written informed consent before the ultrasound examinations.

Conflict-of-interest statement: All authors confirm having no conflicts of interest.

Data sharing statement: No additional data are available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

Country/Territory of origin: China

ORCID number: Rong Qian 0009-0007-2567-8722.

S-Editor: Chen YL
L-Editor: Filipodia
P-Editor: Chen YL

REFERENCES

1 **International Agency for Research on Cancer**; World Health Organization. Liver Source: Globocan 2020. [cited 7 July 2023]. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf

2 **Zhou J**, Sun H, Wang Z, Cong W, Wang J, Zeng M, Zhou W, Bie P, Liu L, Wen T, Han G, Wang M, Liu R, Lu L, Ren Z, Chen M, Zeng Z, Liang P, Liang C, Yan F, Wang W, Ji Y, Yun J, Cai D, Chen Y, Cheng W, Cheng S, Dai C, Guo W, Hua B, Huang X, Jia W, Li Y, Liang J, Liu T, Lv G, Mao Y, Peng T, Ren W, Shi H, Shi G, Tao K, Wang X, Xiang B, Xing B, Xu J, Yang J, Yang Y, Ye S, Yin Z, Zhang B, Zhang L, Zhang S, Zhang T, Zhao Y, Zheng H, Zhu J, Zhu K, Shi Y, Xiao Y, Dai Z, Teng G, Cai J, Cai X, Li Q, Shen F, Qin S, Dong J, Fan J. Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma (2019 Edition). *Liver Cancer* 2020; **9**: 682-720 [PMID: 33442540 DOI: 10.1159/000509424]

3 **Chen ZH**, Zhang XP, Wang H, Chai ZT, Sun JX, Guo WX, Shi J, Cheng SQ. Effect of microvascular invasion on the postoperative long-term prognosis of solitary small HCC: a systematic review and meta-analysis. *HPB (Oxford)* 2019; **21**: 935-944 [PMID: 30871805 DOI: 10.1016/j.hpb.2019.02.003]

4 **Beaufrère A**, Caruso S, Calderaro J, Poté N, Bijot JC, Couchy G, Cauchy F, Vilgrain V, Zucman-Rossi J, Paradis V. Gene expression signature as a surrogate marker of microvascular invasion on routine hepatocellular carcinoma biopsies. *J Hepatol* 2022; **76**: 343-352 [PMID: 34624411 DOI: 10.1016/j.jhep.2021.09.034]

5 **Wu F**, Sun H, Zhou C, Huang P, Xiao Y, Yang C, Zeng M. Prognostic factors for long-term outcome in bifocal hepatocellular carcinoma after resection. *Eur Radiol* 2023; **33**: 3604-3616 [PMID: 36700957 DOI: 10.1007/s00330-023-09398-2]

6 **Liu HF**, Zhang YZ, Wang Q, Zhu ZH, Xing W. A nomogram model integrating LI-RADS features and radiomics based on contrast-enhanced magnetic resonance imaging for predicting microvascular invasion in hepatocellular carcinoma falling the Milan criteria. *Transl Oncol* 2023; **27**: 101597 [PMID: 36502701 DOI: 10.1016/j.tranon.2022.101597]

7 **Zhang L**, Li M, Zhu J, Zhang Y, Xiao Y, Dong M, Zhang L, Wang J. The value of quantitative MR elastography-based stiffness for assessing the microvascular invasion grade in hepatocellular carcinoma. *Eur Radiol* 2023; **33**: 4103-4114 [PMID: 36435877 DOI: 10.1007/s00330-022-09290-5]

8 **Shi H**, Duan Y, Shi J, Zhang W, Liu W, Shen B, Liu F, Mei X, Li X, Yuan Z. Role of preoperative prediction of microvascular invasion in hepatocellular carcinoma based on the texture of FDG PET image: A comparison of quantitative metabolic parameters and MRI. *Front Physiol* 2022; **13**: 928969 [PMID: 36035488 DOI: 10.3389/fphys.2022.928969]

9 **Park S**, Kim JH, Kim J, Joseph W, Lee D, Park SJ. Development of a deep learning-based auto-segmentation algorithm for hepatocellular carcinoma (HCC) and application to predict microvascular invasion of HCC using CT texture analysis: preliminary results. *Acta Radiol* 2023; **64**: 907-917 [PMID: 35570797 DOI: 10.1177/02WJGS-15-20421221100318]

10 **Liu P**, Tan XZ, Zhang T, Gu QB, Mao XH, Li YC, He YQ. Prediction of microvascular invasion in solitary hepatocellular carcinoma ≤ 5 cm based on computed tomography radiomics. *World J Gastroenterol* 2021; **27**: 2015-2024 [PMID: 34007136 DOI: 10.3748/wjg.v27.i17.2015]

11 **Qin X**, Zhu J, Tu Z, Ma Q, Tang J, Zhang C. Contrast-Enhanced Ultrasound with Deep Learning with Attention Mechanisms for Predicting Microvascular Invasion in Single Hepatocellular Carcinoma. *Acad Radiol* 2022 [PMID: 36567144 DOI: 10.1016/j.acra.2022.12.005]

12 **Li X**, Han X, Li L, Su C, Sun J, Zhan C, Feng D, Cheng W. Dynamic Contrast-Enhanced Ultrasonography with Sonazoid for Diagnosis of Microvascular Invasion in Hepatocellular Carcinoma. *Ultrasound Med Biol* 2022; **48**: 575-581 [PMID: 34933756 DOI: 10.1016/j.ultrasmedbio.2021.11.005]

13 **Dong Y**, Qiu Y, Yang D, Yu L, Zuo D, Zhang Q, Tian X, Wang WP, Jung EM. Potential application of dynamic contrast enhanced ultrasound in predicting microvascular invasion of hepatocellular carcinoma. *Clin Hemorheol Microcirc* 2021; **77**: 461-469 [PMID: 33459703 DOI: 10.3233/CH-201085]

14 **Dong Y**, Zuo D, Qiu YJ, Cao JY, Wang HZ, Yu LY, Wang WP. Preoperative prediction of microvascular invasion (MVI) in hepatocellular carcinoma based on kupffer phase radiomics features of sonazoid contrast-enhanced ultrasound (SCEUS): A prospective study. *Clin Hemorheol Microcirc* 2022; **81**: 97-107 [PMID: 35001883 DOI: 10.3233/CH-211363]

15 **Guo J**, Jiang D, Qian Y, Yu J, Gu YJ, Zhou YQ, Zhang HP. Differential diagnosis of different types of solid focal liver lesions using two-dimensional shear wave elastography. *World J Gastroenterol* 2022; **28**: 4716-4725 [PMID: 36157921 DOI: 10.3748/wjg.v28.i32.4716]

16 **Naganuma H**, Ishida H. Factors other than fibrosis that increase measured shear wave velocity. *World J Gastroenterol* 2022; **28**: 6512-6521 [PMID: 36569278 DOI: 10.3748/wjg.v28.i46.6512]

17 **Fang C**, Rafailidis V, Konstantatou E, Yusuf GT, Barrow I, Pagkalidou E, Romanos O, Agarwal K, Quaglia A, Sidhu PS. Comparison Between Different Manufacturers' 2-D and Point Shear Wave Elastography Techniques in Staging Liver Fibrosis in Chronic Liver Disease Using Liver Biopsy as the Reference Standard: A Prospective Study. *Ultrasound Med Biol* 2022; **48**: 2229-2236 [PMID: 36008215 DOI: 10.1016/j.ultrasmedbio.2022.06.009]

18 **Xu C**, Jiang D, Tan B, Shen C, Guo J. Preoperative diagnosis and prediction of microvascular invasion in hepatocellularcarcinoma by ultrasound elastography. *BMC Med Imaging* 2022; **22**: 88 [PMID: 35562688 DOI: 10.1186/s12880-022-00819-0]

19 **Wang WT**, Yang L, Yang ZX, Hu XX, Ding Y, Yan X, Fu CX, Grimm R, Zeng MS, Rao SX. Assessment of Microvascular Invasion of Hepatocellular Carcinoma with Diffusion Kurtosis Imaging. *Radiology* 2018; **286**: 571-580 [PMID: 28937853 DOI: 10.1148/radiol.2017170515]

20 **Wang X**, Fu Y, Zhu C, Hu X, Zou H, Sun C. New insights into a microvascular invasion prediction model in hepatocellular carcinoma: A retrospective study from the SEER database and China. *Front Surg* 2023; **9**: 1046713 [PMID: 36684226 DOI: 10.3389/fsurg.2022.1046713]

21 **Hu J**, Gong N, Li D, Deng Y, Chen J, Luo D, Zhou W, Xu K. Identifying hepatocellular carcinoma patients with survival benefits from surgery combined with chemotherapy: based on machine learning model. *World J Surg Oncol* 2022; **20**: 377 [PMID: 36451200 DOI: 10.1186/s12957-022-02837-2]

22 **Zhou H**, Sun J, Jiang T, Wu J, Li Q, Zhang C, Zhang Y, Cao J, Sun Y, Jiang Y, Liu Y, Zhou X, Huang P. A Nomogram Based on Combining Clinical Features and Contrast Enhanced Ultrasound LI-RADS Improves Prediction of Microvascular Invasion in Hepatocellular Carcinoma. *Front Oncol* 2021; **11**: 699290 [PMID: 34307168 DOI: 10.3389/fonc.2021.699290]

23 **Bhide A**, Acharya G, Baschat A, Bilardo CM, Brezinka C, Cafici D, Ebbing C, Hernandez-Andrade E, Kalache K, Kingdom J, Kiserud T, Kumar S, Lee W, Lees C, Leung KY, Malinger G, Mari G, Prefumo F, Sepulveda W, Trudinger B. ISUOG Practice Guidelines (updated): use of Doppler velocimetry in obstetrics. *Ultrasound Obstet Gynecol* 2021; **58**: 331-339 [PMID: 34278615 DOI: 10.1002/uog.23698]

24 **Jeon SK**, Lee JY, Kang HJ, Han JK. Additional value of superb microvascular imaging of ultrasound examinations to evaluate focal liver lesions. *Eur J Radiol* 2022; **152**: 110332 [PMID: 35552066 DOI: 10.1016/j.ejrad.2022.110332]

25 **Gao S**, Zhang Y, Sun W, Jin K, Dai Y, Wang F, Qian X, Han J, Sheng R, Zeng M. Assessment of an MR Elastography-Based Nomogram as a Potential Imaging Biomarker for Predicting Microvascular Invasion of Hepatocellular Carcinoma. *J Magn Reson Imaging* 2022; **58**: 392-402 [PMID: 36479914 DOI: 10.1002/jmri.28553]

26 **Zhang L**, Yu X, Wei W, Pan X, Lu L, Xia J, Zheng W, Jia N, Huo L. Prediction of HCC microvascular invasion with gadobenate-enhanced MRI: correlation with pathology. *Eur Radiol* 2020; **30**: 5327-5336 [PMID: 32367417 DOI: 10.1007/s00330-020-06895-6]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 2052-2062

DOI: 10.4240/wjgs.v15.i9.2052

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Prospective Study

Quantitative evaluation of colorectal tumour vasculature using contrast-enhanced ultrasound: Correlation with angiogenesis and prognostic significance

Ming-Hui Li, Wei-Wei Li, Ling He, Jian-Fang Li, Sun-Yan Zhang

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

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

P-Reviewer: Garcia K, Spain; Johnson CH, United States

Received: June 14, 2023
Peer-review started: June 14, 2023
First decision: July 3, 2023
Revised: July 11, 2023
Accepted: July 26, 2023
Article in press: July 26, 2023
Published online: September 27, 2023

Ming-Hui Li, Wei-Wei Li, Ling He, Department of Ultrasound, Tumor Hospital Affiliated to Xinjiang Medical University, Urumqi 830011, Xinjiang Uygur Autonomous Regions, China

Jian-Fang Li, Department of Medical Imaging, Baoding Maternal and Child Health Hospital, Baoding 071023, Hebei Province, China

Sun-Yan Zhang, Department of Ultrasonography, Nantong Haimen District People's Hospital, Nantong 226100, Jiangsu Province, China

Corresponding author: Sun-Yan Zhang, MD, Attending Doctor, Department of Ultrasonography, Nantong Haimen District People's Hospital, No. 1201 Beijing Road, Haimen District, Nantong 226100, Jiangsu Province, China. klts1223@sohu.com

Abstract

BACKGROUND

Ultrasound is a vital tool for the diagnosis and management of colorectal cancer (CRC). Contrast-enhanced ultrasound (CEUS) is a non-invasive, safe, and cost-effective method for evaluating tumour blood vessels, that play a crucial role in tumour growth and progression.

AIM

To explore CEUS's role in the quantitative evaluation of CRC blood vessels and their correlation with angiogenesis markers and prognosis.

METHODS

This study prospectively enrolled 100 patients with CRC confirmed by histopathology. All patients received preoperative CEUS examinations. Quantitative parameters, such as peak intensity (PI), time to peak (TTP), and area under the curve (AUC), were derived from time-intensity curve (TIC) analysis. Tumour tissue samples were obtained during surgery and examined immunohistochemically to assess the expression of angiogenesis markers, including vascular endothelial growth factor (VEGF) and microvessel density (MVD). The correlation between CEUS parameters, angiogenesis markers, and clinicopathological features was evaluated using appropriate statistical tests.

RESULTS

Quantitative CEUS parameters (PI, TTP, and AUC) showed significant correlations with VEGF expression ($P < 0.001$) and MVD ($P < 0.001$), indicating a strong link between tumour blood vessels and angiogenesis. Increased PI, reduced TTP, and expanded AUC values were significantly related to higher tumour stage ($P < 0.001$), lymph node metastasis ($P < 0.001$), and distant metastasis ($P < 0.001$). Furthermore, these parameters were recognized as independent predictors of overall survival and disease-free survival in multivariate analysis ($P < 0.001$).

CONCLUSION

CEUS has a high potential in guiding treatment planning and predicting patient outcomes. However, more comprehensive, multicentre studies are required to validate the clinical utility of CEUS in CRC management.

Key Words: Contrast-enhanced ultrasound; Colorectal cancer; Tumour angiogenesis; Prognosis; Microvessel density; Vascular endothelial growth factor; Tumour

Core Tip: This study investigates the role of contrast-enhanced ultrasound (CEUS) in evaluating colorectal cancer (CRC) blood vessels and their correlation with angiogenesis markers and prognosis. The study enrolled 100 patients with CRC, and quantitative CEUS parameters showed significant correlations with angiogenesis markers and clinicopathological features. The study concludes that CEUS has high potential in guiding treatment planning and predicting patient outcomes but requires further validation through multicentre studies.

Citation: Li MH, Li WW, He L, Li JF, Zhang SY. Quantitative evaluation of colorectal tumour vasculature using contrast-enhanced ultrasound: Correlation with angiogenesis and prognostic significance. *World J Gastrointest Surg* 2023; 15(9): 2052-2062
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/2052.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.2052

INTRODUCTION

Colorectal cancer (CRC) is the third most prevalent cancer and the second leading cause of cancer-related fatalities globally, with approximately 1.8 million new cases and nearly 900000 deaths in 2021[1]. The high mortality rate is attributed to late diagnosis, insufficient staging, and ineffective treatment approaches. Therefore, early detection and precise staging are crucial for optimizing treatment plans and improving patient outcomes[2]. In recent decades, advancements in medical imaging techniques have significantly improved diagnostic precision in CRC[3]. Among these imaging methods, contrast-enhanced ultrasound (CEUS) has gained increased interest for its potential in evaluating tumour blood flow and vascularization.

Tumour vasculature plays a critical role in its growth, progression, and metastasis. Rapidly expanding tumours require a substantial blood supply to ensure sufficient delivery of nutrients and oxygen, while simultaneously eliminating waste products[4]. This demand for blood supply is met through angiogenesis, a process of formation of new blood vessels from pre-existing ones. Angiogenesis is regulated by a fine equilibrium between pro-angiogenic and anti-angiogenic factors, with vascular endothelial growth factor (VEGF) being the strongest promoter of angiogenesis[5]. Tumour blood vessel density, also known as microvessel density (MVD), serves as a surrogate marker for angiogenesis and has been associated with tumour aggressiveness and unfavourable prognosis in various cancers, including CRC[6].

CEUS is a relatively novel imaging technique that employs intravenously administered microbubble contrast agents to improve ultrasound images[7]. The echogenicity of microbubbles enhances visualization of blood flow within the vasculature. By utilizing the non-linear behaviour of microbubbles, CEUS can produce real-time, high-resolution images of tissue perfusion and vascular structure with a high signal-to-noise ratio[8,9]. Compared with other imaging techniques, such as ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), *etc.*, CEUS has several advantages for CRC imaging. First, CEUS can provide high-resolution images of tumour vasculature without being affected by bone or gas interference[10]. Second, CEUS can offer real-time dynamic information on tissue perfusion and blood flow velocity with a high temporal resolution[11]. Third, CEUS can provide quantitative parameters for tumour vascularization analysis using time-intensity curve (TIC) analysis[12]. Fourth, CEUS is a non-invasive, safe, and cost-effective method that does not expose patients to ionizing radiation or nephrotoxic contrast agents[13].

Several studies have examined the potential of CEUS in assessing tumour vasculature in CRC[14-17]. Most of these studies have only focused on qualitative or semi-quantitative analyses, such as visual grading of enhancement patterns or evaluating TIC parameters without thoroughly investigating their correlation with angiogenesis markers and prognostic factors. Additionally, a majority of these studies have been limited by small sample sizes and a lack of standardized CEUS examination and analysis techniques.

Considering these limitations, the present study aimed to explore the role of CEUS in quantitatively evaluating colorectal tumour vasculature and its correlation with angiogenesis markers (VEGF and MVD) and prognostic factors. We hypothesized that quantitative CEUS parameters would significantly correlate with angiogenesis markers, and

elevated CEUS-derived parameter values would be associated with aggressive tumour features and poor prognosis. To investigate these hypotheses, we conducted a prospective study with a relatively large cohort of patients with histologically confirmed CRC who underwent preoperative CEUS examinations using standardized techniques. Moreover, we used a comprehensive approach to data analysis, including assessment of TIC-derived parameters and their correlation with angiogenesis markers, clinicopathological characteristics, and survival outcomes.

This study aimed to provide valuable insights into the potential of CEUS as a non-invasive tool for evaluating tumour vasculature in CRC and establish its clinical utility in guiding treatment decisions and predicting patient outcomes. The study's findings may contribute to the growing evidence supporting the use of CEUS in CRC management and pave the way for future large-scale, multicentre trials to validate and expand upon these findings.

MATERIALS AND METHODS

Study population

This study prospectively enrolled 100 patients with histologically confirmed CRC from January 2020 to December 2022. Inclusion criteria were as follows: (1) Age ≥ 18 years; (2) Pathologically confirmed primary colorectal adenocarcinoma; (3) No history of chemotherapy or radiotherapy; and (4) Ability to provide informed consent. Exclusion criteria were as follows: (1) Contraindications to ultrasound contrast agents, such as severe allergic reactions; (2) Pregnancy or lactation; and (3) Severe comorbidities affecting survival outcomes, such as end-stage renal disease, chronic heart failure, or uncontrolled diabetes. This study was approved by the Xinjiang Medical University Affiliated Cancer Hospital institutional review board and adhered to the standards of the Declaration of Helsinki.

CEUS examination

All patients underwent CEUS examinations within two weeks before surgery using a high-end ultrasound system (LOGIQ E9, GE Healthcare, Milwaukee, WI, United States) with a 1-6 MHz convex array transducer (C1-6, GE Healthcare) and dedicated contrast-specific imaging software (Contrast Harmonic Imaging, GE Healthcare). Patients were placed in a supine position, and a baseline grayscale and colour Doppler ultrasound examinations were conducted to assess tumour's location, size, and morphology.

A 2.4 mL dose of SonoVue (Bracco, Milan, Italy), a microbubble contrast agent containing sulphur hexafluoride gas encapsulated in a phospholipid shell, was administered intravenously as a single bolus injection, followed by a 10 mL saline flush. CEUS examination began immediately after injection and continued for 5 min. Mechanical index was set at a low level (≤ 0.1) to minimize microbubble destruction. Imaging parameters, including gain, time gain compensation, and focal zone, were adjusted to optimize image quality and maintain consistent contrast-enhanced image appearance. Experienced sonographers, blinded to patients' clinical information, performed all CEUS examinations.

CEUS image analysis

CEUS images were stored in DICOM format and analysed offline using VueBox software (Bracco, Milan, Italy). Regions of interests (ROIs) were manually drawn to encompass the entire enhancing tumour area on CEUS images. The software generated TICs for the selected ROIs, displaying the change in intensity over time. Three quantitative CEUS parameters were derived from the TIC analysis: Peak intensity (PI), time to peak (TTP), and area under the curve (AUC). PI represented the maximum intensity reached within the ROI during the observation period, TTP indicated the time required reaching the PI, and AUC corresponded to the total amount of contrast agent within the ROI during the examination.

Immunohistochemical analysis

During surgery, cancerous tissue samples were collected, preserved in 40 g/L neutral buffered formaldehyde, and embedded in paraffin before being sliced into 4 μm-thick sections. These sections were deparaffinised, rehydrated, and subjected to antigen retrieval using a citrate buffer (pH = 6.0) and microwave heat treatment. Subsequently, they were treated with 3% hydrogen peroxide for 10 min to neutralize endogenous peroxidase activity and incubated overnight at 4 °C with primary antibodies targeting VEGF (1:200, rabbit polyclonal, Abcam, Cambridge, United Kingdom) and CD34 (1:100, mouse monoclonal, Dako, Glostrup, Denmark). After rinsing with phosphate-buffered saline, the sections were treated with secondary antibodies conjugated to horseradish peroxidase for 1 h at room temperature and counterstained with haematoxylin. Immunoreactivity was detected using a 3,3'-diaminobenzidine substrate. The percentage of VEGF-positive tumor cells and CD34-positive microvessels were counted using ImageJ software (National Institutes of Health, Bethesda, MD, United States). Five random fields of view per section were selected and captured at 400 × magnification. The number of positive cells or microvessels and the total number of cells or microvessels were counted manually. The percentage was calculated as the ratio of positive cells or microvessels to total cells or microvessels multiplied by 100.

VEGF expression was evaluated with a semi-quantitative measurement method, which accounted for both the percentage of tumour cells expressing VEGF and the intensity of staining. The percentage of VEGF-positive tumour cells were scored as follows: 0 (0%), 1 (1%-25%), 2 (26%-50%), 3 (51%-75%), and 4 (76%-100%). The intensity of staining was rated using the following categories: 0 (absent), 1 (faint), 2 (moderate), and 3 (vivid). The percentage and intensity scores were multiplied to calculate the final VEGF expression score, ranging from 0-12. High VEGF expression was defined as a score of 6 or higher.

MVD was assessed by enumerating CD34-positive microvessels in the highly vascularized areas of the tumour, termed as 'hotspots'. These hotspots were located using a low-magnification (100 ×) lens, followed by counting of the

microvessels under high magnification (400 ×). Each endothelial cell or cluster, clearly distinguishable from adjacent microvessels, tumour cells, and connective tissues, qualified as a countable microvessel, regardless of lumen presence. MVD was expressed as the mean quantity of microvessels within each high-power field.

Statistical analyses

The patients' clinicopathological characteristics, CEUS parameters, and immunohistochemical findings are summarized using descriptive statistics. The relationships between CEUS parameters, angiogenesis markers, and clinicopathological factors were examined using either the Spearman's rank correlation coefficient or Pearson's correlation coefficient, depending on the situation. The Mann-Whitney *U* test or Kruskal-Wallis test was employed, as necessary, to evaluate differences in CEUS parameters concerning VEGF expression and MVD.

The Kaplan-Meier method was used to analyse survival, and the log-rank test was used to evaluate the differences in overall survival (OS) and disease-free survival (DFS) based on CEUS parameters, VEGF expression, and MVD. To identify independent prognostic factors for OS and DFS, a multivariate analysis was conducted using the Cox proportional hazards model. All statistical analyses were performed using the SPSS software (version 26.0, IBM Corp., NY, United States), and a two-sided P value < 0.05 was considered to be statistically significant. The statistical method of this study was reviewed by Li Y from the Baoding Maternal and Child Health Hospital.

RESULTS

Patient characteristics at baseline

The study enrolled 100 patients, including 57 men and 43 women, with a median age of 63 years (range: 38-84 years). Patients' clinicopathological traits are shown in Table 1. A majority of the tumours were located in the rectum (n = 52), while others were found in the sigmoid colon (n = 26), ascending colon (n = 12), and descending colon (n = 10). Based on the TNM staging system, 21 patients had stage I tumours, 29 had stage II tumours, 35 had stage III tumours, and 15 had stage IV tumours. Lymph node metastasis was observed in 50 patients, whereas 15 patients displayed distant metastasis.

CEUS parameters were positively correlated with angiogenesis markers

The average values of PI, TTP and AUC were 23.6 ± 7.8 dB, 16.5 ± 5.6 s and 1032.6 ± 361.3 dB × s, respectively. High VEGF expression was detected in 56 patients, and the median MVD was 52.5 (range: 12-125). Table 2 shows the correlations between CEUS parameters and angiogenesis markers. Significant positive correlations were observed between PI and both VEGF expression (r = 0.73, P < 0.001) and MVD (r = 0.75, P < 0.001). TTP demonstrated significant negative correlations with both VEGF expression (r = -0.68, P < 0.001) and MVD (r = -0.72, P < 0.001). Additionally, AUC demonstrated significant positive correlations with both VEGF expression (r = 0.71, P < 0.001) and MVD (r = 0.74, P < 0.001).

CEUS parameters were significantly correlated with aggressive clinicopathological characteristics

Table 3 shows the correlations between CEUS parameters, angiogenesis indicators, and clinicopathological characteristics. As expected, high VEGF expression and MVD were related to advanced tumour stage (P < 0.001), lymph node metastasis (P < 0.001), and distant metastasis (P < 0.001). Additionally, high PI, short TTP, and large AUC values were associated with advanced tumour stage (P < 0.001), lymph node metastasis (P < 0.001), and distant metastasis (P < 0.001). No significant correlations were found between CEUS parameters or angiogenesis markers and age, sex, or tumour location.

CEUS parameters acted as independent prognostic factors for poor OS and DFS

The average follow-up period was 26 mo (range: 3-36 mo). During this period, 28 patients experienced tumour recurrence and 22 patients died. The OS and DFS rates at 3 years were 78% and 72%, respectively. Figures 1 and 2 show the Kaplan-Meier survival curves for OS and DFS based on CEUS parameters, VEGF expression, and MVD, respectively. Poor OS (P < 0.001) and DFS (P < 0.001) were significantly associated with high PI, short TTP, and large AUC values. Additionally, poor OS (P < 0.001) and DFS (P < 0.001) were significantly associated with high VEGF expression and MVD. The multivariate analysis revealed that OS was independently influenced by prognostic factors, including PI [hazard ratio (HR) = 2.55, 95% confidence interval (CI): 1.36-4.78, P = 0.003], TTP (HR = 2.34, 95%CI: 1.24-4.41, P = 0.008), AUC (HR = 2.62, 95%CI: 1.38-4.96, P = 0.003), VEGF expression (HR = 2.47, 95%CI: 1.31-4.65, P = 0.005), and MVD (HR = 2.81, 95%CI: 1.49-5.30, P = 0.001). Similarly, DFS was also independently affected by prognostic factors, including PI (HR = 2.38, 95%CI: 1.28-4.42, P = 0.006), TTP (HR = 2.26, 95%CI: 1.20-4.26, P = 0.011), AUC (HR = 2.54, 95%CI: 1.34-4.81, P = 0.004), VEGF expression (HR = 2.31, 95%CI: 1.24-4.32, P = 0.008), and MVD (HR = 2.67, 95%CI: 1.42-5.03, P = 0.002). Table 4 summarizes the results of the multivariate analysis.

DISCUSSION

Our study demonstrated significant correlations between quantitative CEUS parameters (PI, TTP, and AUC) and angiogenesis markers (VEGF expression and MVD) in CRC. High PI, short TTP, and large AUC values were significantly associated with aggressive tumour features and unfavourable prognosis, independent of other clinicopathological factors. These results suggest that CEUS may be a useful non-invasive imaging modality for assessing tumour vasculature in CRC and could potentially help in guiding treatment planning and predicting patient outcomes.

Table 1 Patient characteristics

Characteristic	Number of patients	Percentage
Total patients	100	100%
Men	57	57%
Women	43	43%
Tumour location		
Rectum	52	52%
Sigmoid colon	26	26%
Ascending colon	12	12%
Descending colon	10	10%
Tumour stage		
Stage I	21	21%
Stage II	29	29%
Stage III	35	35%
Stage IV	15	15%
Metastasis		
Lymph node metastasis	50	50%
Distant metastasis	15	15%

Table 2 Correlations between contrast-enhanced ultrasound parameters and angiogenesis markers

Parameters	Pearson correlation coefficient (*r*)	*P* value
PI and VEGF	0.73	< 0.001
PI and MVD	0.75	< 0.001
TTP and VEGF	-0.68	< 0.001
TTP and MVD	-0.72	< 0.001
AUC and VEGF	0.71	< 0.001
AUC and MVD	0.74	< 0.001

PI: Peak intensity; VEGF: Vascular endothelial growth factor; TTP: Time to peak; MVD: Microvessel density; AUC: Area under the curve.

Table 3 Associations between contrast-enhanced ultrasound parameters, angiogenesis markers, and clinicopathological characteristics

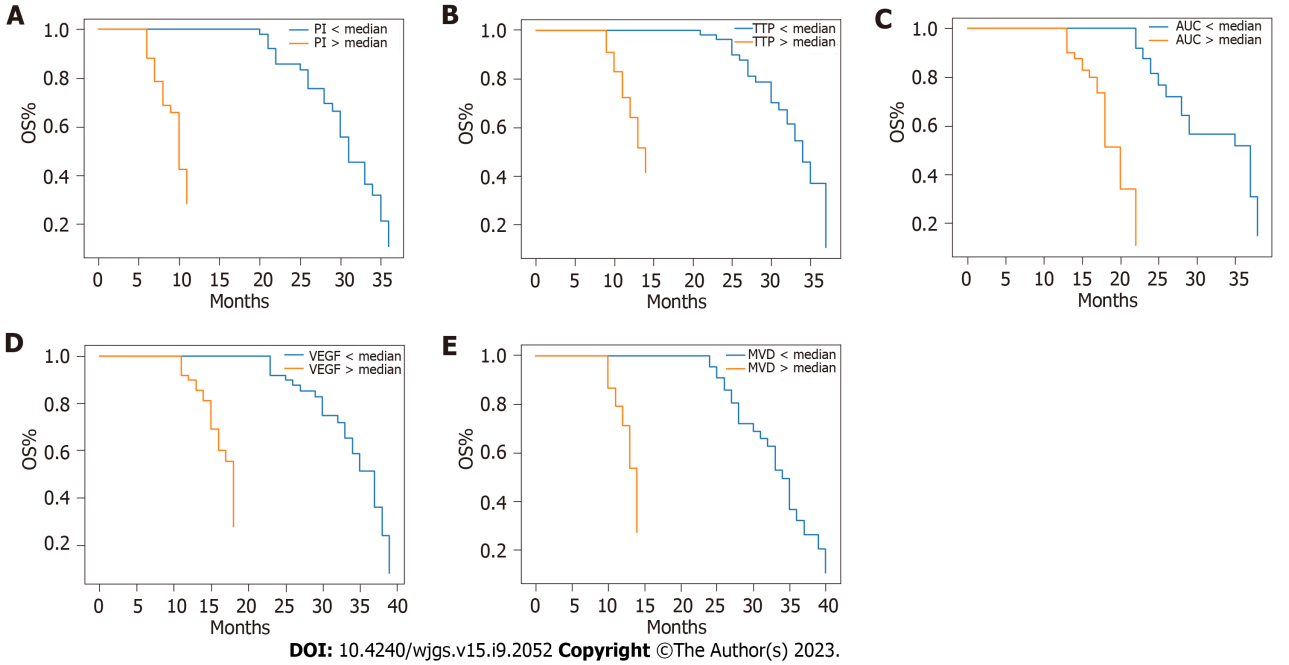
	Tumour stage	Lymph node metastasis	Distant metastasis	Age (yr)	Sex
PI	$P < 0.001$	$P < 0.001$	$P < 0.001$	NS	NS
TTP	$P < 0.001$	$P < 0.001$	$P < 0.001$	NS	NS
AUC	$P < 0.001$	$P < 0.001$	$P < 0.001$	NS	NS
VEGF expression	$P < 0.001$	$P < 0.001$	$P < 0.001$	NS	NS
MVD	$P < 0.001$	$P < 0.001$	$P < 0.001$	NS	NS

NS: No significant; PI: Peak intensity; TTP: Time to peak; AUC: Area under the curve; VEGF: Vascular endothelial growth factor; MVD: Microvessel density.

Table 4 Multivariate analysis of prognostic factors for overall survival and disease-free survival

Prognostic factor	Hazard ratio (OS)	95%CI (OS)	*P* value (OS)	Hazard ratio (DFS)	95%CI (DFS)	*P* value (DFS)
VEGF expression	2.47	1.31-4.65	0.005	2.31	1.24-4.32	0.008
MVD	2.81	1.49-5.30	0.001	2.67	1.42-5.03	0.002
PI	2.55	1.36-4.78	0.003	2.38	1.28-4.42	0.006
TTP	2.34	1.24-4.41	0.008	2.26	1.20-4.26	0.011
AUC	2.62	1.38-4.96	0.003	2.54	1.34-4. 81	0.004

OS: Overall survival; DFS: Disease-free survival; CI: Confidence interval; VEGF: Vascular endothelial growth factor; MVD: Microvessel density; PI: Peak intensity; TTP: Time to peak; AUC: Area under the curve.



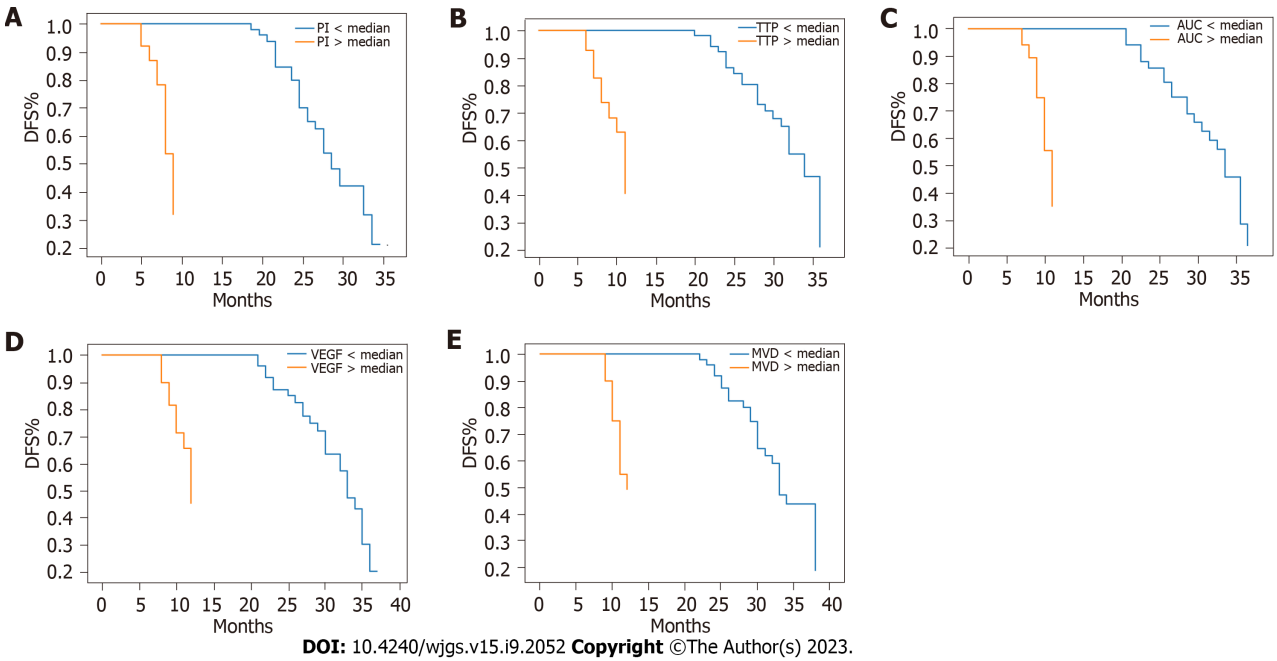
DOI: 10.4240/wjgs.v15.i9.2052

Figure 1 Kaplan-Meier survival curves for overall survival according to contrast-enhanced ultrasound parameters, vascular endothelial growth factor expression, and microvessel density. A: Kaplan-Meier curve for peak intensity; B: Kaplan-Meier curve for time to peak; C: Kaplan-Meier curve for area under the curve; D: Kaplan-Meier curve for vascular endothelial growth factor; E: Kaplan-Meier curve for microvessel density. OS: Overall survival; VEGF: Vascular endothelial growth factor; PI: Peak intensity; TTP: Time to peak; MVD: Microvessel density; AUC: Area under the curve.

The significant correlations between CEUS parameters and angiogenesis markers observed in our study align with the findings of previous literature[18-20]. The positive correlations between PI and VEGF expression and MVD can be explained by the generally greater density of blood vessels in tumours with high VEGF expression and MVD, which leads to increased blood flow and higher PI values on CEUS. Similarly, the negative correlations between TTP and VEGF expression and MVD can be attributed to the faster blood flow in tumours with high VEGF expression and MVD, resulting in a shorter time required to reach PI on CEUS.

The associations between CEUS parameters and clinicopathological characteristics observed in our study are also consistent with the findings of previous research. High PI, short TTP, and large AUC values have been found to correlate with advanced stage, lymph node metastasis, and distant metastasis in various cancers, including CRC[18,21,22]. These associations can be explained by the fact that aggressive tumours typically exhibit higher angiogenesis, leading to increased blood flow and more pronounced contrast enhancement on CEUS. Our survival analysis revealed that high PI, short TTP, and large AUC values were significantly associated with poor OS and DFS, independent of other clinicopathological factors. These results suggest that CEUS parameters could serve as potential prognostic biomarkers in CRC. Furthermore, the significant associations between high VEGF expression, MVD, and poor survival outcomes observed in our study are consistent with those in previous studies, further emphasizing the importance of tumour vasculature in CRC progression and prognosis[23,24].

CEUS provides multiple benefits compared with other imaging techniques, such as CT and MRI, in evaluating tumour vasculature. It is a real-time, non-invasive, and radiation-free imaging modality that provides high spatial and temporal resolution, allowing for a detailed assessment of tumour blood flow and microvasculature[25,26]. Moreover, microbubble contrast agents used in CEUS are purely intravascular, which enables a more accurate evaluation of blood vessel density



DOI: 10.4240/wjgs.v15.i9.2052

Figure 2 Kaplan-Meier survival curves for disease-free survival according to contrast-enhanced ultrasound parameters, vascular endothelial growth factor expression, and microvessel density. A: Kaplan-Meier curve for peak intensity; B: Kaplan-Meier curve for time to peak; C: Kaplan-Meier curve for area under the curve; D: Kaplan-Meier curve for vascular endothelial growth factor; E: Kaplan-Meier curve for microvessel density. DFS: Disease-free survival; VEGF: Vascular endothelial growth factor; MVD: Microvessel density; TTP: Time to peak; AUC: Area under the curve; PI: Peak intensity.

and perfusion characteristics compared to the contrast agents used in CT and MRI, which have a tendency to extravasate into the interstitial space[27]. Furthermore, CEUS is generally less expensive than CT and MRI, making it a more cost-effective option for patients and healthcare systems[28].

In addition to assessing tumour vasculature, CEUS has also been investigated for other clinical applications in CRC, including detecting and characterizing primary tumours, lymph node staging, and assessing treatment response[29,30]. It has shown to improve the accuracy of primary tumour detection in CRC compared to that of conventional ultrasound, particularly in early-stage tumours, where the sensitivity and specificity of CEUS are reported to be high[31]. Furthermore, CEUS has been investigated for differentiating benign and malignant colorectal lesions based on enhancement patterns and kinetics, with some studies reporting promising results in terms of diagnostic accuracy[32].

CEUS has demonstrated potential utility in identifying metastatic lymph nodes in CRC patients[33]. Several studies have reported that evaluation of lymph node vascularization using CEUS can help differentiate metastatic from non-metastatic lymph nodes, with higher accuracy than conventional ultrasound or CT[34-36]. However, further research is warranted to establish standardized criteria for assessing lymph node involvement using CEUS and to compare its performance with that of other imaging modalities, such as MRI or positron emission tomography.

Monitoring treatment response is another potential clinical application for CEUS in CRC. In recent years, neoadjuvant chemoradiotherapy has become a standard treatment approach for locally advanced rectal cancer, with the goal of downstaging the tumour and improving the likelihood of complete surgical resection[37]. Monitoring the response to neoadjuvant therapy is crucial for determining the optimal timing of surgery and predicting patient outcomes. CEUS has been investigated as a non-invasive method for monitoring changes in tumour vasculature during neoadjuvant treatment, with some studies suggesting that early changes in CEUS parameters can predict treatment response and long-term outcomes[38]. Further research is warranted to establish the role of CEUS in the assessment of treatment response in CRC and to determine the optimal timing and criteria for CEUS evaluation.

Although our study yielded encouraging results, it had certain limitations. First, a relatively small sample size could have affected the statistical power of our analysis. Future research with larger sample size is essential to validate and broaden the implications of our findings. Second, the retrospective design of our study may have led to selection bias; therefore, prospective studies are required to confirm the prognostic significance of CEUS parameters in CRC. Third, our study primarily focused on the correlations between CEUS parameters and angiogenesis markers; however, the underlying biological mechanisms remain to be elucidated. Therefore, further investigations, such as lab-based and animal studies, are required to explore the molecular pathways linking CEUS parameters to angiogenesis and tumour progression in CRC.

CONCLUSION

Our study demonstrated that quantitative CEUS parameters were significantly associated with angiogenesis markers and prognostic factors in CRC. These findings suggest that CEUS could be a valuable non-invasive tool for assessing tumour

vasculature in CRC and may have potential clinical utility in guiding treatment decisions and predicting patient outcomes. Future studies should focus on validating and expanding upon our findings in large cohorts and exploring the underlying biological mechanisms linking CEUS parameters to angiogenesis and tumour progression in CRC. Moreover, the potential applications of CEUS in other aspects of CRC management, such as primary tumour detection, lymph node staging, and treatment response assessment, should be further investigated to fully understand the clinical potential of this imaging modality.

ARTICLE HIGHLIGHTS

Research background

The background of this research study highlights the importance of ultrasound in the diagnosis and management of colorectal cancer (CRC). Contrast-enhanced ultrasound (CEUS) is a non-invasive, safe, and cost-effective method that allows for the evaluation of tumor blood vessels. Tumor angiogenesis, which involves the formation of new blood vessels, plays a critical role in tumor growth and progression.

Research motivation

The aim of this study was to investigate the role of CEUS in quantitatively assessing CRC blood vessels and their correlation with angiogenesis markers and prognosis.

Research objectives

Explore the role of CEUS in quantitative assessment of blood vessels in CRC and its correlation with angiogenic markers and prognosis. This study aims to prospectively recruit 100 CRC patients confirmed by histopathology and conduct preoperative CEUS examination.

Research methods

This study enrolled 100 patients with confirmed CRC through histopathology. Preoperative CEUS examinations were performed on all patients. From the CEUS images, quantitative parameters including peak intensity (PI), time to peak (TTP), and area under the curve (AUC) were derived using time-intensity curve analysis. During surgery, tumor tissue samples were obtained and examined immunohistochemically for the expression of angiogenesis markers, such as vascular endothelial growth factor (VEGF) and microvessel density (MVD). The researchers used appropriate statistical tests to evaluate the correlations between CEUS parameters, angiogenesis markers, and clinicopathological features.

Research results

The study findings revealed significant associations between the quantitative CEUS parameters (PI, TTP, and AUC) and VEGF expression, MVD, tumor stage, lymph node metastasis, distant metastasis, overall survival, and disease-free survival. The study concluded that CEUS holds potential for guiding treatment planning and predicting patient outcomes in CRC management but emphasized the need for more comprehensive multicenter studies to validate its clinical utility.

Research conclusions

Demonstrated that CEUS has a significant role in the quantitative evaluation of CRC blood vessels. The quantitative CEUS parameters (PI, TTP, and AUC) showed strong correlations with angiogenesis markers, specifically VEGF expression and MVD. These findings indicate the importance of tumor blood vessels in angiogenesis and tumor progression.

Research perspectives

The study demonstrates the potential of CEUS in guiding treatment decisions and predicting patient outcomes in CRC, further comprehensive studies involving multiple centers are necessary to validate its clinical utility.

ACKNOWLEDGEMENTS

Thank you to all those who have contributed to this manuscript.

FOOTNOTES

Author contributions: Li MH and Li JF designed and coordinated this study; Li WW and He L conducted experiments to obtain and analyze data; Zhang SY, Li MH, Li WW, and Zhang SY explained the data; Li JF, He L, Li WW, Li MH, and Zhang SY wrote the manuscript; and all authors have approved the final version of this article.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board at Tumor Hospital Affiliated to Xinjiang Medical University.

Clinical trial registration statement: The research registration number is 8823.

Informed consent statement: All participants provided written informed consent.

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

Data sharing statement: No additional data are available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

Country/Territory of origin: China

ORCID number: Ming-Hui Li 0009-0001-3514-5643; Sun-Yan Zhang 0009-0003-6411-1973.

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

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 **Benson AB**, Venook AP, Al-Hawary MM, Cederquist L, Chen YJ, Ciombor KK, Cohen S, Cooper HS, Deming D, Engstrom PF, Grem JL, Grothey A, Hochster HS, Hoffe S, Hunt S, Kamel A, Kirilcuk N, Krishnamurthi S, Messersmith WA, Meyerhardt J, Mulcahy MF, Murphy JD, Nurkin S, Saltz L, Sharma S, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Wuthrick E, Gregory KM, Gurski L, Freedman-Cass DA. Rectal Cancer, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2018; **16**: 874-901 [PMID: 30006429 DOI: 10.6004/jnccn.2018.0061]

3 **Goiffon RJ**, O'Shea A, Harisinghani MG. Advances in radiological staging of colorectal cancer. *Clin Radiol* 2021; **76**: 879-888 [PMID: 34243943 DOI: 10.1016/j.crad.2021.06.005]

4 **Carmeliet P**, Jain RK. Angiogenesis in cancer and other diseases. *Nature* 2000; **407**: 249-257 [PMID: 11001068 DOI: 10.1038/35025220]

5 **Ferrara N**, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nat Med* 2003; **9**: 669-676 [PMID: 12778165 DOI: 10.1038/nm0603-669]

6 **Weidner N**. Current pathologic methods for measuring intratumoral microvessel density within breast carcinoma and other solid tumors. *Breast Cancer Res Treat* 1995; **36**: 169-180 [PMID: 8534865 DOI: 10.1007/BF00666038]

7 **Blomley MJ**, Cooke JC, Unger EC, Monaghan MJ, Cosgrove DO. Microbubble contrast agents: a new era in ultrasound. *BMJ* 2001; **322**: 1222-1225 [PMID: 11358777 DOI: 10.1136/bmj.322.7296.1222]

8 **Dietrich CF**, Averkiou M, Nielsen MB, Barr RG, Burns PN, Calliada F, Cantisani V, Choi B, Chammas MC, Clevert DA, Claudon M, Correas JM, Cui XW, Cosgrove D, D'Onofrio M, Dong Y, Eisenbrey J, Fontanilla T, Gilja OH, Ignee A, Jenssen C, Kono Y, Kudo M, Lassau N, Lyshchik A, Franca Meloni M, Moriyasu F, Nolsøe C, Piscaglia F, Radzina M, Saftoiu A, Sidhu PS, Sporea I, Schreiber-Dietrich D, Sirlin CB, Stanczak M, Weskott HP, Wilson SR, Willmann JK, Kim TK, Jang HJ, Vezeridis A, Westerway S. How to perform Contrast-Enhanced Ultrasound (CEUS). *Ultrasound Int Open* 2018; **4**: E2-E15 [PMID: 29423461 DOI: 10.1055/s-0043-123931]

9 **Dietrich CF**, Ignee A, Frey H. Contrast-enhanced endoscopic ultrasound with low mechanical index: a new technique. *Z Gastroenterol* 2005; **43**: 1219-1223 [PMID: 16267707 DOI: 10.1055/s-2005-858662]

10 **Claudon M**, Dietrich CF, Choi BI, Cosgrove DO, Kudo M, Nolsøe CP, Piscaglia F, Wilson SR, Barr RG, Chammas MC, Chaubal NG, Chen MH, Clevert DA, Correas JM, Ding H, Forsberg F, Fowlkes JB, Gibson RN, Goldberg BB, Lassau N, Leen EL, Mattrey RF, Moriyasu F, Solbiati L, Weskott HP, Xu HX. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS) in the liver--update 2012: a WFUMB-EFSUMB initiative in cooperation with representatives of AFSUMB, AIUM, ASUM, FLAUS and ICUS. *Ultraschall Med* 2013; **34**: 11-29 [PMID: 23129518 DOI: 10.1055/s-0032-1325499]

11 **Quaia E**. The real capabilities of contrast-enhanced ultrasound in the characterization of solid focal liver lesions. *Eur Radiol* 2011; **21**: 457-462 [PMID: 21107578 DOI: 10.1007/s00330-010-2007-0]

12 **Wei K**, Le E, Bin JP, Coggins M, Thorpe J, Kaul S. Quantification of renal blood flow with contrast-enhanced ultrasound. *J Am Coll Cardiol* 2001; **37**: 1135-1140 [PMID: 11263620 DOI: 10.1016/s0735-1097(00)01210-9]

13 **Senior R**, Becher H, Monaghan M, Agati L, Zamorano J, Vanoverschelde JL, Nihoyannopoulos P. Contrast echocardiography: evidence-based recommendations by European Association of Echocardiography. *Eur J Echocardiogr* 2009; **10**: 194-212 [PMID: 19270054 DOI: 10.1093/ejechocard/jep005]

14 **Wang S**, Yang W, Zhang H, Xu Q, Yan K. The Role of Contrast-Enhanced Ultrasound in Selection Indication and Improveing Diagnosis for Transthoracic Biopsy in Peripheral Pulmonary and Mediastinal Lesions. *Biomed Res Int* 2015; **2015**: 231782 [PMID: 26090391 DOI: 10.1155/2015/231782]

15 **Cartana ET**, Gheonea DI, Cherciu IF, Streaţa I, Uscatu CD, Nicoli ER, Ioana M, Pirici D, Georgescu CV, Alexandru DO, Şurlin V, Gruionu

G, Săftoiu A. Assessing tumor angiogenesis in colorectal cancer by quantitative contrast-enhanced endoscopic ultrasound and molecular and immunohistochemical analysis. *Endosc Ultrasound* 2018; **7**: 175-183 [PMID: 28685747 DOI: 10.4103/eus.eus_7_17]

16 **Lassau N**, Chebil M, Chami L, Bidault S, Girard E, Roche A. Dynamic contrast-enhanced ultrasonography (DCE-US): a new tool for the early evaluation of antiangiogenic treatment. *Target Oncol* 2010; **5**: 53-58 [PMID: 20379790 DOI: 10.1007/s11523-010-0136-7]

17 **Lassau N**, Bonastre J, Kind M, Vilgrain V, Lacroix J, Cuinet M, Taieb S, Aziza R, Sarran A, Labbe-Devilliers C, Gallix B, Lucidarme O, Ptak Y, Rocher L, Caquot LM, Chagnon S, Marion D, Luciani A, Feutray S, Uzan-Augui J, Coiffier B, Benastou B, Koscielny S. Validation of dynamic contrast-enhanced ultrasound in predicting outcomes of antiangiogenic therapy for solid tumors: the French multicenter support for innovative and expensive techniques study. *Invest Radiol* 2014; **49**: 794-800 [PMID: 24991866 DOI: 10.1097/RLI.0000000000000085]

18 **Lassau N**, Koscielny S, Chami L, Chebil M, Benatsou B, Roche A, Ducreux M, Malka D, Boige V. Advanced hepatocellular carcinoma: early evaluation of response to bevacizumab therapy at dynamic contrast-enhanced US with quantification--preliminary results. *Radiology* 2011; **258**: 291-300 [PMID: 20980447 DOI: 10.1148/radiol.10091870]

19 **Wang Y**, Li L, Wang YX, Cui NY, Zou SM, Zhou CW, Jiang YX. Time-intensity curve parameters in rectal cancer measured using endorectal ultrasonography with sterile coupling gels filling the rectum: correlations with tumor angiogenesis and clinicopathological features. *Biomed Res Int* 2014; **2014**: 587806 [PMID: 24900973 DOI: 10.1155/2014/587806]

20 **Lassau N**, Lamuraglia M, Chami L, Leclère J, Bonvalot S, Terrier P, Roche A, Le Cesne A. Gastrointestinal stromal tumors treated with imatinib: monitoring response with contrast-enhanced sonography. *AJR Am J Roentgenol* 2006; **187**: 1267-1273 [PMID: 17056915 DOI: 10.2214/AJR.05.1192]

21 **Albrecht T**, Blomley M, Bolondi L, Claudon M, Correas JM, Cosgrove D, Greiner L, Jäger K, Jong ND, Leen E, Lencioni R, Lindsell D, Martegani A, Solbiati L, Thorelius L, Tranquart F, Weskott HP, Whittingham T; EFSUMB Study Group. Guidelines for the use of contrast agents in ultrasound. January 2004. *Ultraschall Med* 2004; **25**: 249-256 [PMID: 15300497 DOI: 10.1055/s-2004-813245]

22 **Lamuraglia M**, Escudier B, Chami L, Schwartz B, Leclère J, Roche A, Lassau N. To predict progression-free survival and overall survival in metastatic renal cancer treated with sorafenib: pilot study using dynamic contrast-enhanced Doppler ultrasound. *Eur J Cancer* 2006; **42**: 2472-2479 [PMID: 16965911 DOI: 10.1016/j.ejca.2006.04.023]

23 **Des Guetz G**, Uzzan B, Nicolas P, Cucherat M, Morere JF, Benamouzig R, Breau JL, Perret GY. Microvessel density and VEGF expression are prognostic factors in colorectal cancer. Meta-analysis of the literature. *Br J Cancer* 2006; **94**: 1823-1832 [PMID: 16773076 DOI: 10.1038/sj.bjc.6603176]

24 **Gao J**, Knutsen A, Arbman G, Carstensen J, Frånlund B, Sun XF. Clinical and biological significance of angiogenesis and lymphangiogenesis in colorectal cancer. *Dig Liver Dis* 2009; **41**: 116-122 [PMID: 19038587 DOI: 10.1016/j.dld.2008.07.315]

25 **Piscaglia F**, Nolsøe C, Dietrich CF, Cosgrove DO, Gilja OH, Bachmann Nielsen M, Albrecht T, Barozzi L, Bertolotto M, Catalano O, Claudon M, Clevert DA, Correas JM, D'Onofrio M, Drudi FM, Eyding J, Giovannini M, Hocke M, Ignee A, Jung EM, Klauser AS, Lassau N, Leen E, Mathis G, Saftoiu A, Seidel G, Sidhu PS, ter Haar G, Timmerman D, Weskott HP. The EFSUMB Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS): update 2011 on non-hepatic applications. *Ultraschall Med* 2012; **33**: 33-59 [PMID: 21874631 DOI: 10.1055/s-0031-1281676]

26 **Correas JM**, Bridal L, Lesavre A, Méjean A, Claudon M, Hélénon O. Ultrasound contrast agents: properties, principles of action, tolerance, and artifacts. *Eur Radiol* 2001; **11**: 1316-1328 [PMID: 11519538 DOI: 10.1007/s003300100940]

27 **Wilson SR**, Burns PN. Microbubble-enhanced US in body imaging: what role? *Radiology* 2010; **257**: 24-39 [PMID: 20851938 DOI: 10.1148/radiol.10091210]

28 **Strobel D**, Seitz K, Blank W, Schuler A, Dietrich C, von Herbay A, Friedrich-Rust M, Kunze G, Becker D, Will U, Kratzer W, Albert FW, Pachmann C, Dirks K, Strunk H, Greis C, Bernatik T. Contrast-enhanced ultrasound for the characterization of focal liver lesions--diagnostic accuracy in clinical practice (DEGUM multicenter trial). *Ultraschall Med* 2008; **29**: 499-505 [PMID: 19241506 DOI: 10.1055/s-2008-1027806]

29 **Piscaglia F**, Bolondi L; Italian Society for Ultrasound in Medicine and Biology (SIUMB) Study Group on Ultrasound Contrast Agents. The safety of Sonovue in abdominal applications: retrospective analysis of 23188 investigations. *Ultrasound Med Biol* 2006; **32**: 1369-1375 [PMID: 16965977 DOI: 10.1016/j.ultrasmedbio.2006.05.031]

30 **Puli SR**, Reddy JB, Bechtold ML, Choudhary A, Antillon MR, Brugge WR. Accuracy of endoscopic ultrasound to diagnose nodal invasion by rectal cancers: a meta-analysis and systematic review. *Ann Surg Oncol* 2009; **16**: 1255-1265 [PMID: 19219506 DOI: 10.1245/s10434-009-0337-4]

31 **Greis C**. Technology overview: SonoVue (Bracco, Milan). *Eur Radiol* 2004; **14** Suppl 8: P11-P15 [PMID: 15700328]

32 **Rappeport ED**, Loft A, Berthelsen AK, von der Recke P, Larsen PN, Mogensen AM, Wettergren A, Rasmussen A, Hillingsoe J, Kirkegaard P, Thomsen C. Contrast-enhanced FDG-PET/CT vs. SPIO-enhanced MRI vs. FDG-PET vs. CT in patients with liver metastases from colorectal cancer: a prospective study with intraoperative confirmation. *Acta Radiol* 2007; **48**: 369-378 [PMID: 17453514 DOI: 10.1080/02WJGS-15-20420701294560]

33 **Quaia E**, Calliada F, Bertolotto M, Rossi S, Garioni L, Rosa L, Pozzi-Mucelli R. Characterization of focal liver lesions with contrast-specific US modes and a sulfur hexafluoride-filled microbubble contrast agent: diagnostic performance and confidence. *Radiology* 2004; **232**: 420-430 [PMID: 15286314 DOI: 10.1148/radiol.2322031401]

34 **Sidhu PS**, Cantisani V, Dietrich CF, Gilja OH, Saftoiu A, Bartels E, Bertolotto M, Calliada F, Clevert DA, Cosgrove D, Deganello A, D'Onofrio M, Drudi FM, Freeman S, Harvey C, Jenssen C, Jung EM, Klauser AS, Lassau N, Meloni MF, Leen E, Nicolau C, Nolsoe C, Piscaglia F, Prada F, Prosch H, Radzina M, Savelli L, Weskott HP, Wijkstra H. The EFSUMB Guidelines and Recommendations for the Clinical Practice of Contrast-Enhanced Ultrasound (CEUS) in Non-Hepatic Applications: Update 2017 (Long Version). *Ultraschall Med* 2018; **39**: e2-e44 [PMID: 29510439 DOI: 10.1055/a-0586-1107]

35 **Rubaltelli L**, Khadivi Y, Tregnaghi A, Stramare R, Ferro F, Borsato S, Fiocco U, Adami F, Rossi CR. Evaluation of lymph node perfusion using continuous mode harmonic ultrasonography with a second-generation contrast agent. *J Ultrasound Med* 2004; **23**: 829-836 [PMID: 15244307 DOI: 10.7863/jum.2004.23.6.829]

36 **Liu LN**, Xu HX, Lu MD, Xie XY, Wang WP, Hu B, Yan K, Ding H, Tang SS, Qian LX, Luo BM, Wen YL. Contrast-enhanced ultrasound in the diagnosis of gallbladder diseases: a multi-center experience. *PLoS One* 2012; **7**: e48371 [PMID: 23118996 DOI: 10.1371/journal.pone.0048371]

37 **Sauer R**, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, Becker H, Raab HR, Villanueva MT, Witzigmann H, Wittekind C, Beissbarth T, Rödel C. Preoperative *versus* postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol* 2012; **30**: 1926-1933 [PMID: 22529255 DOI:

10.1200/JCO.2011.40.1836]

38 **Giesel FL**, Choyke PL, Mehndiratta A, Zechmann CM, von Tengg-Kobligk H, Kayser K, Bischoff H, Hintze C, Delorme S, Weber MA, Essig M, Kauczor HU, Knopp MV. Pharmacokinetic analysis of malignant pleural mesothelioma-initial results of tumor microcirculation and its correlation to microvessel density (CD-34). *Acad Radiol* 2008; **15**: 563-570 [PMID: 18423312 DOI: 10.1016/j.acra.2007.12.014]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 2063-2073

DOI: 10.4240/wjgs.v15.i9.2063

ISSN 1948-9366 (online)

CASE REPORT

Laparoscopy-assisted gastrectomy for advanced gastric cancer patients with situs inversus totalis: Two case reports and review of literature

Hong-Bo Liu, Xiao-Peng Cai, Zhao Lu, Bin Xiong, Chun-Wei Peng

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Kumar M, India; Park BK, South Korea; Shah OJ, India; Uhlmann D, Germany

Received: March 20, 2023
Peer-review started: March 20, 2023
First decision: June 17, 2023
Revised: July 1, 2023
Accepted: July 25, 2023
Article in press: July 25, 2023
Published online: September 27, 2023

Hong-Bo Liu, Xiao-Peng Cai, Zhao Lu, Bin Xiong, Chun-Wei Peng, Department of Gastrointestinal Surgery, Hubei Key Laboratory of Tumor Biological Behaviors & Hubei Cancer Clinical Study Center, Wuhan Peritoneal Cancer Clinical Medical Center, Zhongnan Hospital of Wuhan University, Wuhan 430070, Hubei Province, China

Hong-Bo Liu, School of Nursing, Wuhan University, Wuhan 430070, Hubei Province, China

Corresponding author: Chun-Wei Peng, MD, PhD, Doctor, Department of Gastrointestinal Surgery, Hubei Key Laboratory of Tumor Biological Behaviors & Hubei Cancer Clinical Study Center, Wuhan Peritoneal Cancer Clinical Medical Center, Zhongnan Hospital of Wuhan University, No. 169 Donghu Road, Wuchang District, Wuhan 430070, Hubei Province, China. whupengcw@whu.edu.cn

Abstract

BACKGROUND

Situs inversus totalis (SIT) is a rare condition in which the positions of abdominal and thoracic organs present a "mirror image" of the normal ones in the median sagittal plane. Although minimally invasive surgery has evolved to achieve laparoscopic gastrectomy for gastric cancer (GC) patients with SIT, it is difficult to perform lymphadenectomy (LND) in such a transposed anatomical condition. Herein, we report the cases of two patients with SIT who successfully underwent laparoscopy-assisted gastrectomy (LAG) with D2 LND.

CASE SUMMARY

Case 1: A 65-year-old man was admitted for intermittent abdominal pain and distension, occasional belching, and acid reflux for 4 mo. He was diagnosed with GC (cT3N1-2M0) with SIT. Before surgery, he had undergone four cycles of neoadjuvant chemotherapy and immunotherapy. Then, the patient was evaluated as having a partial response, and laparoscopy-assisted distal gastrectomy with D2 LND and Billroth II reconstruction were performed. The operation was performed successfully within 240 min with an estimated blood loss of 50 mL and no severe complications. The patient was discharged on postoperative day (POD) 9. Case 2: A 55-year-old man was admitted for upper abdominal distension with pain and discomfort after eating for 3 mo. He was diagnosed with GC (cT3N1M0) with SIT. He had a history of hypertension for more than 10 years; however, his blood pressure was well-controlled *via* regular medication. We performed laparoscopy-

assisted total gastrectomy with D2 LND and Roux-en-Y reconstruction. The operation was performed successfully within 168 min with an estimated blood loss of 50 mL and no severe complications. The patient was discharged on POD 10.

CONCLUSION
LAG with D2 LND could be considered an accessible, safe, and curative procedure for advanced GC patients with SIT.

Key Words: Situs inversus totalis; Laparoscopy-assisted gastrectomy; Advanced gastric cancer; Surgery modality; Lymphadenectomy; Case report

Core Tip: Laparoscopic surgery in situs inversus totalis (SIT) patients with gastric cancer (GC) is exceedingly rare and challenging. We report the cases of two advanced GC patients with SIT who successfully underwent laparoscopy-assisted gastrectomy with D2 lymphadenectomy. In this report, we share our experience and review the literature in the previous 11 years to summarize the general consensus on laparoscopic radical gastrectomy in patients with SIT.

Citation: Liu HB, Cai XP, Lu Z, Xiong B, Peng CW. Laparoscopy-assisted gastrectomy for advanced gastric cancer patients with situs inversus totalis: Two case reports and review of literature. *World J Gastrointest Surg* 2023; 15(9): 2063-2073
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/2063.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.2063

INTRODUCTION

Situs inversus totalis (SIT), a rare autosomal recessive disorder characterized by a complete congenital mirror-image malposition of the thoracic and abdominal organs, has an incidence of about 1/10000-1/20000[1]. Due to the inverted anatomical disposition of organs in patients with SIT, surgeons are required to adopt unfamiliar operating habits, which also increases the difficulty of identifying anatomical structures. Despite the rarity of encountering this anomaly, focusing on SIT may compensate for the lack of experience in surgery.

Laparoscopic radical gastrectomy has been performed in specialized centers in recent years for its minimal invasiveness and association with uneventful recovery. However, this operation is still challenging due to the change in traditional operating habits and increased difficulty in identifying anatomical structures under the local visual field, which are also difficulties encountered in patients with SIT. Moreover, no tactility can be of significant influence during surgery, making it more complicated to implement laparoscopic radical gastrectomy in patients with SIT. In light of such patients, it is still worth summarizing experience and exploring the most feasible ways of optimizing surgery.

In this report, we present the cases of two patients having advanced gastric cancer (GC) with SIT, both of whom underwent laparoscopy-assisted gastrectomy and standard D2 lymphadenectomy (LND). We also review the literature to discuss the current surgical strategies for GC patients with SIT.

CASE PRESENTATION

Chief complaints

Case 1: A 65-year-old Chinese man presented with intermittent abdominal pain and distension, occasional belching, and acid reflux with no obvious cause.

Case 2: A 55-year-old Chinese man presented with upper abdominal distension with pain and discomfort after eating.

History of present illness

Case 1: In April 2022, the patient presented at a local hospital with intermittent abdominal pain and distension, occasional belching, and acid reflux of no obvious etiology for 4 mo, all of which were unrelated to eating. He denied nausea, vomiting, hematemesis, black stool, diarrhea, and constipation. Upper gastrointestinal endoscopy identified poor motility of the gastric antrum, with a large ulcer covered with black scabs and blood clots. Furthermore, tissue biopsy with histopathology revealed the presence of poorly or moderately differentiated adenocarcinoma. The patient did not receive any anti-tumor treatment before hospitalization. Since the onset of the disease, his spirit, appetite, sleep, physical strength, and weight did not change significantly. The patient was admitted to our hospital for further treatment.

Case 2: In December 2019, the patient visited a local hospital for postprandial upper abdominal distension with pain and

discomfort for 3 mo. He denied nausea, vomiting, hematemesis, black stool, diarrhea, and constipation. Also, the self-administered gastric protective medicine was ineffective. Upper gastrointestinal endoscopy identified a gastric cardia ulcer, which tissue biopsy identified as poorly differentiated adenocarcinoma and partly signet-ring cell carcinoma. The patient did not receive any anti-tumor treatment before hospitalization. Since the onset of the disease, his spirit, appetite, sleep, and physical strength did not change significantly, except for his weight which decreased slightly. Then, the patient was admitted to our hospital for further treatment.

History of past illness

Case 1: The patient denied any history of a chronic illness. He had no history of abdominal surgery.

Case 2: The patient acknowledged a history of hypertension for ten more years that was properly controlled with regular medication. He had no history of abdominal surgery.

Personal and family history

Case 1: The patient denied any family history of malignant tumors.

Case 2: The patient denied any family history of malignant tumors.

Physical examination

Case 1: Physical examination revealed an apical heartbeat on the right side.

Case 2: Physical examination revealed mild lower abdominal tenderness and an apical heartbeat on the right side.

Laboratory examinations

Case 1: No obvious abnormal tumor markers were observed.

Case 2: Carbohydrate antigen CA199 level was 365.2 (normal range: 0–37.0) U/mL.

Imaging examinations

Case 1: The detailed imaging results are presented in Figure 1. Abdominal contrast-enhanced computed tomography (CT) revealed mirror transposition of all organs (Figure 1A) and thickening of the antral wall (Figure 1B). Besides, positron emission tomography-CT performed in a local hospital revealed increased metabolism in the gastric antrum and surrounding lymph nodes. No abnormal course of vascularity was found in this process.

Case 2: Abdominal contrast-enhanced CT revealed mirror transposition of all organs (Figure 1G), localized thickening of the cardia and smaller curvature of the stomach, and increased numbers of peri-gastric small lymph nodes (Figure 1H). No abnormal course of vascularity was found in this process.

FURTHER DIAGNOSTIC WORK-UP

Case 1

A preoperative pathological examination was performed. The analysis of the biopsy segment resected from the gastric antrum ulcer revealed poorly to moderately differentiated adenocarcinoma (cT3N1-2M0). Immunohistochemical analyses revealed that the tumor cells tested positive for MSH2 and MSH6 and negative for HER-2, MLH1, and PMS2, which signifies a loss of MMR expression.

Case 2

No preoperative pathological examination was performed.

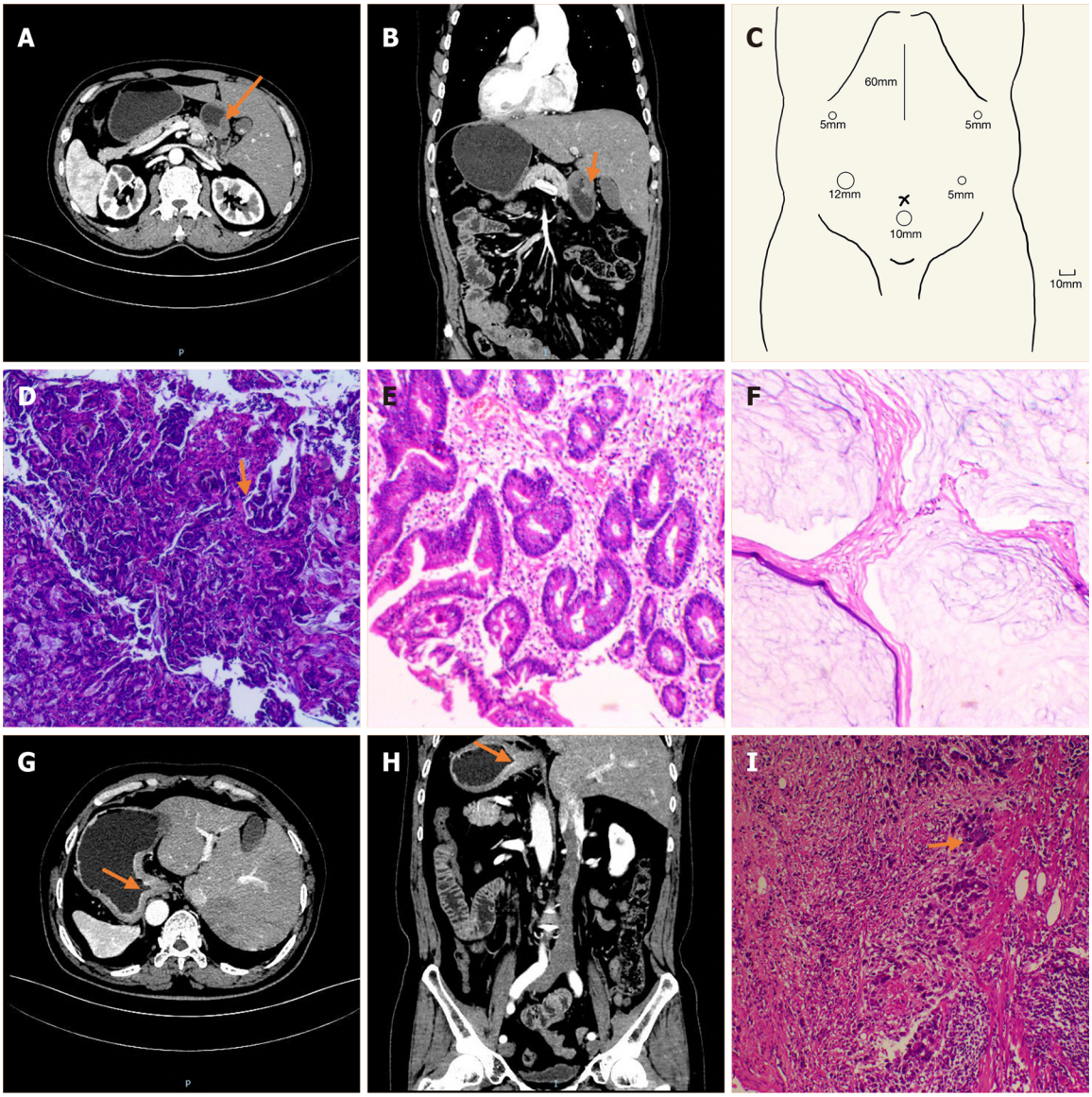
FINAL DIAGNOSIS

Case 1

The patient was diagnosed with adenocarcinoma of the gastric antrum (cT3N1-2M0) with SIT.

Case 2

The patient was diagnosed with gastric cardia malignancy (cT3N1M0) with SIT.



DOI: 10.4240/wjgs.v15.i9.2063

Figure 1 Imaging and pathological features of the two patients. A–F: Case 1; A: Computed tomography (CT) image showing the inverse positioning of intra-abdominal organs; B: CT image showing antral wall thickening; C: Sites of trocar placement. A 12-mm trocar was placed in the right hypochondriac region, and the other three 5-mm trocars were placed (one each) in the right subcostal region, the right lateral abdominal region, and the left lateral abdominal region; D: Preoperative (after neoadjuvant chemotherapy) pathologic biopsies showing that tumor nests still existed; E: Postoperative pathologic biopsies showing that there were no nidi; F: Postoperative pathologic biopsies showing no nidi; G–I: Case 2; G: CT image showing the inverse positioning of all intra-abdominal organs; H: CT image revealing the thickening of the cardia and smaller curvature of gastric tissue and enlarged peri-gastric small lymph nodes; I: Postoperative pathologic biopsies showing that nidi still existed.

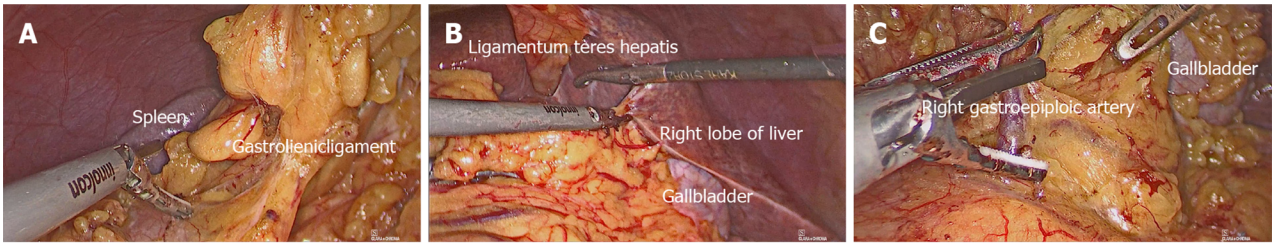
TREATMENT

Case 1

Before surgery, four cycles of neoadjuvant chemotherapy with the S-1 and oxaliplatin (SOX) regimen (oxaliplatin 230 mg on day 1, tegafur 60 mg twice daily on days 1–14, and sintilimab 200 mg once every 3 wk) and immunotherapy was given. The preoperative (after neoadjuvant chemotherapy) pathologic biopsies are presented in Figure 1D.

Laparoscopy-assisted distal gastrectomy with standard D2 LND and Billroth II reconstruction were performed. During surgery, the surgeon stood on the right side of the patient (opposite to the usual side for patients undergoing laparoscopic gastrectomy). A 10-mm trocar was created 10 mm below the umbilicus, and carbon dioxide was injected into the peritoneal cavity at 10 mmHg. The other four trocars were placed in the bilateral subcostal and lateral abdominal area, arranged in a "U" shape (Figure 1C). No implantation metastasis or vascular variants were found (Figure 2).

The procedure lasted for 240 min, and the estimated blood loss was 50 mL. A total of 34 lymph nodes were retrieved. The lesion was located in the antrum, and there were enlarged lymph nodes; also, there was no visible invasion of the serous layer. The final pathological stage was ypT0N0M0. None of the 34 retrieved lymph nodes (Figure 1E and F) showed metastasis.



DOI: 10.4240/wjgs.v15.i9.2063

Figure 2 Images of surgery. A: The surgical field showing that the spleen in the right side of the patient; B: The surgical field showing that the gallbladder and right lobe of the liver in the left side of the patient; C: The key procedure during surgery: Dissecting station 6 lymph nodes.

Case 2

The patient accepted laparoscopy-assisted total gastrectomy with standard D2 LND and Roux-en-Y reconstruction. The position of the surgeon and placement of trocars were the same as those in Case 1. No implantation metastasis or vascular variants were found.

The procedure lasted for 168 min, and the estimated blood loss was 50 mL. A total of 34 lymph nodes were retrieved. The lesion was located at the bottom of the gastric body and cardia, and it measured 2.5 cm × 2.3 cm × 0.3 cm. It was identified as poorly differentiated adenocarcinoma invading nerves, vasculature, and fibroadipose tissue in the serous membrane of the stomach wall. The final pathological stage was pT3N3aM0. Eleven of the 34 retrieved lymph nodes showed metastasis (Figure 1I).

OUTCOME AND FOLLOW-UP

Case 1

We implemented enhanced recovery after surgery on the patient, and his postoperative course was uneventful. The patient was able to resume drinking water on postoperative day (POD) 3 and eating liquid food on POD 5. Thereafter, he was discharged on POD 9. Eight months after the operation, he is doing well without recurrence.

Case 2

Without any complication, the patient was discharged on POD 10. Notably, the patient was administered six cycles of postoperative adjuvant chemotherapy with the SOX regimen. The patient had metastasis of supraclavicular lymph nodes in the twelfth postoperative month; however, there has been no sign of local recurrence.

DISCUSSION

Literature review

SIT may be caused by a genetic mutation; however, its specific mechanism remains unknown. A study conducted by Reish *et al*[2] suggested that the homozygous *NME7* mutation results in the deletion of amino acids essential for its interaction with the γ-TuRC, which is associated with the impaired left-right asymmetry that manifests as SIT. Although the majority of patients with SIT lead normal lives, a subset of individuals (15%–25%) exhibit accompanying respiratory anomalies (Kartagener syndrome), cardiovascular anomalies (Fallot tetralogy), and digestive anomalies[3]. In addition to these malformations, patients with SIT may also be at an increased risk of cancer due to malfunction of the KIF3 complex [4]. Reports indicate that SIT can be associated with multiple cancers[5], including lung cancer, esophageal cancer, gallbladder cancer, and colon cancer[6-9]. In recent years, laparoscopic radical surgery, including laparoscopic cholecystectomy, laparoscopic colectomy, laparoscopic fundoplication, and laparoscopic gastric band surgery, has increasingly been adopted for cancer patients with SIT[10].

In 1936, Allen[11] described the first case of gastrectomy in a GC patient with SIT. In 2003, the first case of laparoscopic gastrectomy performed on a GC patient with SIT was reported[12], followed by the first case of laparoscopic gastrectomy combined with D2 LND in 2015[10].

In terms of our surgery and summary, we searched PubMed for previously reported cases of GC with SIT in which the patients underwent gastrectomy within the last 11 years (from January 1, 2012 to February 31, 2023). The terms used for topic searches of PubMed were "situs inversus totalis" AND "gastric cancer" or "situs inversus totalis" AND "gastrectomy". Two cases[13,14] in which gastrectomy was introduced as previous surgery and a case[15] in which a non-cancer patient underwent prophylactic gastrectomy were excluded. Consequently, a total of 33 cases were identified, including the two cases that we had previously introduced (from 30 articles). The detailed profiles of the patients in the reported cases are presented in Table 1. Among the patients in the included cases, 22 were men and 11 were women; the patients were aged 40–84 years. According to the articles identified, modified surgical procedures to cope with anatomical malposition are what surgeons concentrate on the most, including the surgery modality, extent of LND, and

Table 1 Reported cases of gastric cancer patients with situs inversus totalis in the previous 11 years

Ref.	Age, gender	Abnormal course of vascularity	Surgery modality	Reconstruction	Extent of LND	Surgeon position (trocars placement for robotic surgery)	Operation time (min)	Blood loss (mL)	Discharged on POD	Remarks
Pan *et al*[25], 2012	52, M	NA	OPG	Billroth I	D2	NA	NA	NA	15	Complication: Mechanical obstruction
Kim *et al*[18], 2012	47, M	NA	LADG (robotic-assisted)	Billroth II	D1+ β	Usual side	300	NA	8	
Fujikawa *et al*[26], 2013	60, F	ALHA from CA	LADG	Billroth I	D1+	Opposite	234	5	8	
Min *et al*[27], 2013	52, M	CHA from SMA, 2 branches from LGA	LADG	Billroth I	D1+	Usual side	220	100	8	Abdominal surgery history: Right inguinal hernia repair
Min *et al*[27], 2013	68, M	None	TLDG	Billroth I	D1+	Usual side	117	50	5	Comorbidities: Chronic kidney disease and hypothyroidism
Sumi *et al*[17], 2014	42, M	LHA from SMA	LADG	Billroth I	D1+ No. 7, 8a, 9	Opposite	313	90	10	
Zhu *et al*[28], 2015	66, F	None	ODG	Billroth I	D2	Usual side	NA	NA	NA	
Isobe *et al*[29], 2015	79, F	LHA from AO	OTG splenectomy cholecystectomy	Roux-en-Y	D2	NA	288	150	19	
Ye *et al*[10], 2015	60, F	None	LADG	Billroth II	D2	Opposite	230	50	8	
Morimoto *et al*[30], 2015	58, M	None	LATG	Roux-en-Y	D1+ No. 7, 8a, 9	Opposite (except for No. 5, 7, 8a, 9)	359	90	7	
Suh[31], 2017	50, M	None	ODG	NA	D2	NA	180	NA	10	
Kigasawa *et al*[32], 2017	40, M	None	LADG	Billroth I	D1+	Opposite	284	40	NA	
Alhossaini and Hyung[33], 2017	52, F	None	TLDG (robotic-assisted)	gastroduodenostomy	D1+ No. 7, 8, 9	Opposite	195	30	5	
Cao *et al*[34], 2017	60, M	RHA from SMA bridged by GDA, LGA from ALHA	TLTG (robotic-assisted)	Roux-en-Y	D2	NA	NA	NA	8	
Gündeş *et al*[35], 2018	72, F	None	ODG	Billroth II enteroenterostomy	D1	Usual side	150	100	8	

Namikaw *et al* [36], 2018	66, F	None	OTG	Roux-en-Y	D2	Usual side	375	380	14	
Dai *et al*[21], 2018	53, M	NA	TLDG (total robotic)	Billroth II	D2	Usual side	180	50	5	
Shibata *et al*[37], 2018	79, M	RGEA above RGEV	TLTG	Roux-en-Y	D2 (without splenectomy)	Usual side	232	110	10	
Xue *et al*[16], 2019	61, M	NA	ODG	Billroth II	D2	Usual side	NA	NA	14	Abdominal surgery history: Rectal cancer resection
Ojima *et al*[38], 2019	80, F	None	LADG (total robotic)	Billroth I	D2	Usual side	260	20	14	
Namikawa *et al* [39], 2021	74, M	CHA from SMA	TLDG	Roux-en-Y	D2	Opposite	335	20	12	Comorbidity: Emphysema
Abbey *et al*[19], 2021	69, M	None	LADG (robotic-assisted) intestinal adhesiolysis	Roux-en-Y	D2	Usual side	205	20	15	
Takeno *et al*[40], 2021	71, F	None	LAPG (robotic-assisted)	Esophagogastrostomy	D1+	Usual side	448	45	10	
Yoshimoto *et al* [20], 2021	84, M	NA	LATG (robotic-assisted)	Roux-en-Y	D2	Opposite	NA	30	13	
Fujita *et al*[24], 2022	67, M	CHA from SMA	LADG	Roux-en-Y	D2	Usual side	446	3	14	
Sagawa *et al* [41], 2022	64, M	LGA from LHA	TLDG (total robotic)	Billroth I	D1+	Usual side	286	44	7	
Katano *et al*[42], 2022	62, M	Lack of CHA, PHA from SMA, ALHA from LGA, 2 branches from LGV, 3 branches from LGA	TLPG (robotic-assisted) lower esophagectomy	Esophagogastrostomy	D2 (including lower mediastinal LND)	Opposite	296	NA	11	
Lamture *et al* [43], 2022	48, F	NA	ODG	Billroth II anastomosis of a part of the transverse colon	NA	Opposite	NA	NA	NA	
Doden *et al*[44], 2023	74, M	None	LADG	Billroth I	D1+	Opposite	220	100	10	
Huang *et al*[45], 2023	58, M	None	LADG (3D)	Billroth II	D2	Opposite	220	10	8	
Lee *et al*[46], 2023	79, F	NA	TLTG (single-port)	Roux-en-Y	D1+	Opposite	269	NA	14	
Present case 1	55, M	None	LATG	Roux-en-Y	D2	Opposite	168	50	10	Comorbidity:

										Hypertension
Present case 2	65, M	None	LADG	Billroth II	D2	Opposite	240	50	9	

POD: Postoperative day; LND: Lymphadenectomy; M: Male; F: Female; NA: Not available; ALHA: Accessory left hepatic artery; CA: Celiac artery; CHA: Common hepatic artery; SMA: Superior mesenteric artery; LGA: Left gastric artery; LHA: Left hepatic artery; AO: Aorta; RHA: Right hepatic artery; GDA: Gastroduodenal artery; RGEA: Right gastroepiploic artery; RGEV: Right gastroepiploic vein; PHA: Proper hepatic artery; LGV: Left gastric vein; ODG: Open distal gastrectomy; OPG: Open proximal gastrectomy; OTG: Open total gastrectomy; LADG: Laparoscopy-assisted distal gastrectomy; LATG: Laparoscopy-assisted total gastrectomy; LAPG: Laparoscopy-assisted proximal gastrectomy; TLDG: Total laparoscopy distal gastrectomy; TLPG: Total laparoscopy proximal gastrectomy; TLTG: Total laparoscopy gastrectomy.

position of the surgeon.

Surgery modality

Surgical modality selection is a significant concern when treating GC in patients with SIT. Minimally invasive surgery is usually preferred due to its less invasive nature and shorter associated recovery time. However, in 8 of the 33 cases collected from PubMed, the patients underwent open gastrectomy. Surgeons performing open surgery claimed that they took the patient's high body fat and anatomical difficulties of total visceral inversion into consideration comprehensively. Furthermore, laparotomy could provide not only a broader field of vision but also a pathway to insert an applicator for intraoperative radiotherapy[16]. In contrast, laparoscopic surgery is helpful for visualizing vessels and nerves due to the magnified operating field[17]. The application of radical laparoscopic surgery in patients with SIT may have several benefits (such as reduced trauma, milder postoperative pain, and shorter recovery times) compared to traditional open surgical procedures. From our perspectives, identifying anatomical structures may prove problematic; however, an experienced surgeon may overcome this challenge to a certain extent. So, we opted for laparoscopic surgery in our two cases. Nonetheless, laparoscopic gastrectomy requires much expertise, and each patient should be evaluated on an individual basis. The choice of surgical modality should depend on the doctor's technique and the patient's physical condition.

Robotic surgery has been a promising approach for GC patients with SIT. The first case of a GC patient with SIT treated by robotic-assisted distal gastrectomy was reported in 2012[18], and ten cases have been reported so far. Robotic surgery can reduce the errors caused by the cooperation of multiple operators in laparoscopic surgery[19]. Yoshimoto *et al*[20] concluded that compared to conventional laparoscopic surgery, robotic surgery has two main advantages: (1) It circumvents the need to consider the standing position; and (2) The operator can handle the devices with the nondominant hand with almost the same accuracy as the dominant hand. Although robotic surgery can sew faster and remove deep lymph nodes more easily, it lacks tactility and takes longer[21]. Long-term and short-term comparative studies have shown that robotic gastrectomy is as acceptable as laparoscopic gastrectomy in surgical and oncologic outcomes for normal GC patients[22,23]. Further evidence is needed to fully evaluate the efficacy of robotic surgery in GC patients with SIT.

Extent of LND

Regional LND is an essential requirement for radical gastrectomy, with D2 surgery being widely recognized as the standard surgical procedure for advanced GC. D2 LND is performed under an extrasac that originates from the anterior transverse mesenteric lobe to the pancreatic capsule. We performed complete resection of the anterior transverse mesangial lobe, greater omentum, pancreatic capsule, and hepatogastric ligaments, ligation of the blood vessels involved at the root, and thorough removal of the corresponding second station lymph nodes according to the tumor site.

Therefore, it is crucial to differentiate the relevant important blood vessels (including hepatoduodenal ligaments, abdominal trunk, common hepatic artery (CHA), splenic artery initiation, superior mesenteric vein, *etc.*). However, in the case of SIT, the occurrence of vascular anomalies is not common. Out of the 33 cases that are reviewed in the literature, 10 involving vascular anomalies have been described. The most common anomaly observed was that the CHA exited from the superior mesenteric artery, with three cases reported. The solution proposed by Fujita *et al*[24] re-confirmed the anatomical landmarks of LND in the suprapancreatic area as the upper borders of the pancreas, portal vein, and left gastric artery from the celiac axis. Therefore, during the preoperative evaluation period, sufficient imaging examination is necessary to detect the normal anatomy and variations in the branching pattern of the celiac trunk, which could significantly reduce the duration of surgery and the intraoperative blood loss. With the advent of imaging technology, the three-dimensional reconstruction image of CT angiography (3DCTA) has been widely used to confirm surgical anatomy. Several studies have reported that 3DCTA adequately demonstrates vascular anomalies. In our cases, a contrast-enhanced CT scan was performed, and no abnormal course of vascularity was found in this process.

Position of the surgeon

The appropriate surgical positioning for surgeons during GC surgery in patients with SIT has been a topic of ongoing debate. To this day, there is still no definitive conclusion on the optimal standing position of the surgeon during this type of surgery. The surgical positioning of the surgeon may be related to the surgical modality. In open surgeries, the surgeon's position was reported in five out of eight cases, with four of them being performed on the patient's left side (the usual side). These surgical procedures were carried out according to the principle of precise manipulation of local lymph nodes and smooth transition of the cleaned area. The optimal positioning for the surgeon during laparoscopic gastrectomy in patients with SIT is still controversial. It is natural to think that it is better for the surgeon to stand in the reverse position due to the left-right reversal of the positions of organs. Out of 15 counted laparoscopic gastrectomy cases, 11 were performed on the patient's right side (opposite to the usual side). However, a few surgeons hold a different view, as they believe that standing on the opposite side from where they normally stand would require them to dissect with their nondominant hand, leading to inevitable difficulties. Nevertheless, we still chose to stand on the opposite side. Thanks to our sophisticated skills and well-coordinated team, the procedure was smooth and without complications.

Robotic surgery provides a new solution to this obstacle. In robotic gastrectomy, the robotic arm performs most of the operation, enabling the surgeon to perform the operation without changing their position or experiencing any confusion resulting from the patient's reversed anatomy. This technology may overcome the difficulties encountered in laparoscopic gastrectomy for patients with SIT, and it could be considered a safe and effective surgical approach.

Furthermore, we summarize the clinical features, estimated blood loss, surgery time, and prognoses of 31 reported cases of GC with SIT. The majority of cases occurred in middle-aged and elderly men, and these cases were reported in Japan, China, and Korea (15, 10, and 6 cases, respectively). However, there is a paucity of studies on the correlation and regional differences between GC and SIT. The main treatment methods were surgical resection, reconstruction, and chemotherapy, which effectively improved patients' survival. Combining the experiences of others and ours, our suggestion is that, first of all, a sufficient preoperative imaging evaluation is recommended as it can help predict abnormal anatomical positions and vascular directions. Contrast-enhanced abdominal CT can help the surgeon initially predict the abnormal anatomical positions and vascular directions, and this helps to clarify the problem and avoid accidental injury during surgery. Second, the operation should be performed patiently and carefully. Careful confirmation of the patient's anatomy and vascular location can mitigate intraoperative complications. After postoperative discussions, we all agreed on the fact that the main difficulties facing surgery are the patient's vascular anatomy and precision of manipulation. Finally, it is obvious that an experienced surgical team is a necessity. A sophisticated surgeon and a well-coordinated team can alleviate the awkwardness caused by abnormal anatomical positions, enabling the operation to be completed smoothly.

CONCLUSION

In conclusion, laparoscopic gastrectomy with D2 LND should be considered an accessible, safe, and curative procedure for advanced GC with SIT.

FOOTNOTES

Author contributions: Liu HB and Peng CW contributed to manuscript writing and editing, and data collection; Cai XP and Lu Z contributed to data analysis; Xiong B and Peng CW contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

Supported by National Natural Science Foundation of China, No. 81401515; Zhongnan Hospital of Wuhan University Science Technology and Innovation Seed Fund, No. znpy2018030; "351Talent Project (Luojia Young Scholars)" of Wuhan University.

Informed consent statement: Informed written consent was obtained from both patients for the publication of this case report.

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

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

Country/Territory of origin: China

ORCID number: Hong-Bo Liu 0000-0002-4356-7555; Zhao Lu 0000-0002-1489-205x; Chun-Wei Peng 0000-0001-6349-1618.

S-Editor: Lin C
L-Editor: Wang TQ
P-Editor: Wu RR

REFERENCES

1 **Eitler K**, Bibok A, Telkes G. Situs Inversus Totalis: A Clinical Review. *Int J Gen Med* 2022; **15**: 2437-2449 [PMID: 35264880 DOI: 10.2147/ijgm.S295444]
2 **Reish O**, Aspit L, Zouella A, Roth Y, Polak-Charcon S, Baboushkin T, Benyamini L, Scheetz TE, Mussaffi H, Sheffield VC, Parvari R. A Homozygous Nme7 Mutation Is Associated with Situs Inversus Totalis. *Hum Mutat* 2016; **37**: 727-731 [PMID: 27060491 DOI: 10.1002/humu.22998]
3 **Aziret M**, Karaman K, Ercan M, Bostancı EB, Akoğlu M. Laparoscopic sleeve gastrectomy on a morbidly obese patient with situs inversus totalis: A case study and systematic review of the literature. *Obes Res Clin Pract* 2017; **11**: 144-151 [PMID: 28034698 DOI: 10.1016/j.orcp.2016.12.003]
4 **Haruki T**, Maeta Y, Nakamura S, Sawata T, Shimizu T, Kishi K, Miyasaka S, Maeta H, Morimoto K, Taniguchi I. Advanced cancer with situs inversus totalis associated with KIF3 complex deficiency: report of two cases. *Surg Today* 2010; **40**: 162-166 [PMID: 20107958 DOI: 10.1007/s00595-009-4005-x]
5 **Liu XS**, Wu RM, Wan HB, Chen YJ, Tan F, Zeng DB, Yang Y, Pei ZJ. Situs Inversus Totalis on (18)F-FDG PET/CT: A Case Report and a Literature Review. *Front Med (Lausanne)* 2022; **9**: 840795 [PMID: 35355611 DOI: 10.3389/fmed.2022.840795]
6 **Chen LJ**, Qiu X, Sun H, Xu PF, Yin FM, Xu LJ. Two types of lung cancer with situs inversus totalis: a case report and review of the literature. *J Int Med Res* 2020; **48**: 300060520944107 [PMID: 33106071 DOI: 10.1177/0300060520944107]
7 **Feng Q**, Yao J, Lu S. Gastrointestinal: Situs inversus totalis with esophageal cancer. *J Gastroenterol Hepatol* 2020; **35**: 709 [PMID: 31770819 DOI: 10.1111/jgh.14904]
8 **Rungsakulkij N**, Tangtawee P. Fluorescence cholangiography during laparoscopic cholecystectomy in a patient with situs inversus totalis: a case report and literature review. *BMC Surg* 2017; **17**: 43 [PMID: 28427402 DOI: 10.1186/s12893-017-0242-x]
9 **Xu Q**, Liu W, Lin C, Dang Y. Transverse colon cancer with obstruction in a patient with situs inversus totalis: A case report and review of literature. *Asian J Surg* 2020; **43**: 1186-1188 [PMID: 32994114 DOI: 10.1016/j.asjsur.2020.09.003]
10 **Ye MF**, Tao F, Xu GG, Sun AJ. Laparoscopy-assisted distal gastrectomy for advanced gastric cancer with situs inversus totalis: A case report. *World J Gastroenterol* 2015; **21**: 10246-10250 [PMID: 26401091 DOI: 10.3748/wjg.v21.i35.10246]
11 **Allen FRWK**. A Case of Malignant Tumour of the Stomach in a Male with Transposition of the Viscera. *Ind Med Gaz* 1936; **71**: 32 [PMID: 29012980]
12 **Yamaguchi S**, Orita H, Yamaoka T, Mii S, Sakata H, Hashizume M. Laparoscope-assisted distal gastrectomy for early gastric cancer in a 76-year-old man with situs inversus totalis. *Surg Endosc* 2003; **17**: 352-353 [PMID: 12404047 DOI: 10.1007/s00464-002-4504-y]
13 **Sumi Y**, Tomono A, Suzuki S, Kuroda D, Kakeji Y. Laparoscopic hemicolectomy in a patient with situs inversus totalis after open distal gastrectomy. *World J Gastrointest Surg* 2013; **5**: 22-26 [PMID: 23515492 DOI: 10.4240/wjgs.v5.i2.22]
14 **Zhou P**, Lan Y, Qin X, Huang X, Zeng F. Bilateral chylothorax and pericardial effusion following subtotal gastrectomy in a patient with situs inversus totalis. *ANZ J Surg* 2019; **89**: E480-E481 [PMID: 30192067 DOI: 10.1111/ans.14783]
15 **Sivakumar J**, Crosthwaite G. Prophylactic laparoscopic total gastrectomy in a patient with situs inversus totalis. *J Surg Case Rep* 2021; **2021**: rjaa475 [PMID: 34025963 DOI: 10.1093/jscr/rjaa475]
16 **Xue W**, Li Y, Zhao Z, Li W, Wang S, Zhang M, Liu T, Wang M. Solitary adrenal metastasis from advanced gastric cancer invading duodenal bulb with situs inversus totalis: A case report. *Medicine (Baltimore)* 2019; **98**: e15244 [PMID: 30985730 DOI: 10.1097/md.0000000000015244]
17 **Sumi Y**, Maehara R, Matsuda Y, Yamashita K, Nakamura T, Suzuki S, Kuroda D, Kakeji Y. Laparoscopy-assisted distal gastrectomy in a patient with situs inversus totalis. *JSLS* 2014; **18**: 314-318 [PMID: 24960499 DOI: 10.4293/108680813x13693422521953]
18 **Kim HB**, Lee JH, Park DJ, Lee HJ, Kim HH, Yang HK. Robot-assisted distal gastrectomy for gastric cancer in a situs inversus totalis patient. *J Korean Surg Soc* 2012; **82**: 321-324 [PMID: 22563541 DOI: 10.4174/jkss.2012.82.5.321]
19 **Abbey E**, Yang F, Qi L, Wu JJ, Tong L, Zhen Z. Situs inversus totalis patients with gastric cancer: Robotic surgery the standard of treatment?-A case report. *Int J Surg Case Rep* 2021; **81**: 105818 [PMID: 33887833 DOI: 10.1016/j.ijscr.2021.105818]
20 **Yoshimoto T**, Yoshikawa K, Tokunaga T, Nishi M, Takasu C, Kashihara H, Nakasu C, Shimada M. Robotic-assisted total gastrectomy in a patient with gastric cancer associated with situs inversus totalis: With video. *Asian J Endosc Surg* 2021; **14**: 297-300 [PMID: 32875706 DOI: 10.1111/ases.12860]
21 **Dai HB**, Wang ZC, Feng XB, Wang G, Li WY, Hang CH, Jiang ZW. Case report about a successful full robotic radical gastric cancer surgery with intracorporeal robot-sewn anastomosis in a patient with situs inversus totalis and a two-and-a-half-year follow-up study. *World J Surg Oncol* 2018; **16**: 41 [PMID: 29499701 DOI: 10.1186/s12957-018-1311-z]

22 **Shen W**, Xi H, Wei B, Cui J, Bian S, Zhang K, Wang N, Huang X, Chen L. Robotic *vs* laparoscopic gastrectomy for gastric cancer: comparison of short-term surgical outcomes. *Surg Endosc* 2016; **30**: 574-580 [PMID: 26208497 DOI: 10.1007/s00464-015-4241-7]

23 **Obama K**, Kim YM, Kang DR, Son T, Kim HI, Noh SH, Hyung WJ. Long-term oncologic outcomes of robotic gastrectomy for gastric cancer compared with laparoscopic gastrectomy. *Gastric Cancer* 2018; **21**: 285-295 [PMID: 28639136 DOI: 10.1007/s10120-017-0740-7]

24 **Fujita S**, Etoh T, Kono Y, Fujishima H, Suzuki K, Ninomiya S, Ueda Y, Shiroshita H, Shiraishi N, Inomata M. Laparoscopic distal gastrectomy for advanced gastric cancer with situs inversus totalis: a case report. *Surg Case Rep* 2022; **8**: 182 [PMID: 36163524 DOI: 10.1186/s40792-022-01532-4]

25 **Pan K**, Zhong D, Miao X, Liu G, Jiang Q, Liu Y. Situs inversus totalis with carcinoma of gastric cardia: a case report. *World J Surg Oncol* 2012; **10**: 263 [PMID: 23227934 DOI: 10.1186/1477-7819-10-263]

26 **Fujikawa H**, Yoshikawa T, Aoyama T, Hayashi T, Cho H, Ogata T, Shirai J, Oshima T, Yukawa N, Rino Y, Masuda M, Tsuburaya A. Laparoscopy-assisted distal gastrectomy for an early gastric cancer patient with situs inversus totalis. *Int Surg* 2013; **98**: 266-270 [PMID: 23971782 DOI: 10.9738/intsurg-d-13-00054.1]

27 **Min SH**, Lee CM, Jung HJ, Lee KG, Suh YS, Shin CI, Kim HH, Yang HK. Laparoscopic distal gastrectomy in a patient with situs inversus totalis: a case report. *J Gastric Cancer* 2013; **13**: 266-272 [PMID: 24511424 DOI: 10.5230/jgc.2013.13.4.266]

28 **Zhu H**, Yang K, Hu JK. Gastrectomy for gastric carcinoma with situs inversus totalis: case report and literature review. *Hippokratia* 2015; **19**: 360-362 [PMID: 27703309]

29 **Isobe T**, Ogata S, Kaku H, Hashimoto K, Kizaki J, Matono S, Ishikawa H, Murakami N, Kinugasa T, Aoyagi K, Akagi Y. A Patient with Advanced Gastric Cancer and Situs Inversus Totalis: Report of a Case. *Kurume Med J* 2015; **61**: 73-76 [PMID: 26460309 DOI: 10.2739/kurumemedj.MS64006]

30 **Morimoto M**, Hayakawa T, Kitagami H, Tanaka M, Matsuo Y, Takeyama H. Laparoscopic-assisted total gastrectomy for early gastric cancer with situs inversus totalis: report of a first case. *BMC Surg* 2015; **15**: 75 [PMID: 26087838 DOI: 10.1186/s12893-015-0059-4]

31 **Suh BJ**. A Case of Gastric Cancer with Situs Inversus Totalis. *Case Rep Oncol* 2017; **10**: 130-135 [PMID: 28203176 DOI: 10.1159/000456539]

32 **Kigasawa Y**, Takeuchi H, Kawakubo H, Fukuda K, Nakamura R, Takahashi T, Wada N, Kitagawa Y. Laparoscopy-assisted distal gastrectomy in a case of gastric cancer with situs inversus totalis: a case report. *Asian J Endosc Surg* 2017; **10**: 47-50 [PMID: 27739194 DOI: 10.1111/ases.12326]

33 **Alhossaini R**, Hyung WJ. Robotic Assisted Distal Gastrectomy for Gastric Cancer in a Patient with Situs Inversus Totalis: with Video. *J Gastrointest Surg* 2017; **21**: 2144-2145 [PMID: 28900793 DOI: 10.1007/s11605-017-3576-x]

34 **Cao Y**, Li J, Shen L, Wang J, Xia Z, Tao K, Wang G, Cai K. Gastric cancer in a situs inversus totalis patient with multiple intestinal and vessel variations related to gastrectomy surgery: A case report and literature review. *Medicine (Baltimore)* 2017; **96**: e8209 [PMID: 28953685 DOI: 10.1097/md.0000000000008209]

35 **Gündeş E**, Çetin DA, Aday U, Çiyiltepe H, Bozdağ E, Senger AS, Gülmez S, Değer KC, Uzun O, Polat E. Gastric cancer with situs inversus totalis: does it really create difficulties for surgeons? *Prz Gastroenterol* 2018; **13**: 47-51 [PMID: 29657611 DOI: 10.5114/pg.2018.74563]

36 **Namikawa T**, Tsuda S, Fujisawa K, Iwabu J, Uemura S, Tsujii S, Maeda H, Kitagawa H, Kobayashi M, Hanazaki K. Superficial Spreading-type Gastric Cancer with Situs Inversus Totalis. *In Vivo* 2018; **32**: 685-689 [PMID: 29695579 DOI: 10.21873/invivo.11294]

37 **Shibata K**, Kawamura H, Ichikawa N, Shibuya K, Yoshida T, Ohno Y, Homma S, Taketomi A. Laparoscopic total gastrectomy for advanced gastric cancer in a patient with situs inversus totalis. *Asian J Endosc Surg* 2018; **11**: 39-42 [PMID: 28677888 DOI: 10.1111/ases.12404]

38 **Ojima T**, Nakamura M, Nakamori M, Yamaue H. Robotic distal gastrectomy with D2 Lymphadenectomy for gastric cancer in a patient with situs inversus totalis. *Surg Oncol* 2019; **30**: 98-99 [PMID: 31500795 DOI: 10.1016/j.suronc.2019.06.007]

39 **Namikawa T**, Maeda M, Yokota K, Tanioka N, Iwabu J, Munekage M, Uemura S, Maeda H, Kitagawa H, Nagata Y, Kobayashi M, Hanazaki K. Laparoscopic Distal Gastrectomy for Synchronous Gastric Cancer and Gastrointestinal Stromal Tumor With Situs Inversus Totalis. *In Vivo* 2021; **35**: 913-918 [PMID: 33622883 DOI: 10.21873/invivo.12331]

40 **Takeno A**, Masuzawa T, Katsuyama S, Murakami K, Kawai K, Katsura Y, Ohmura Y, Kagawa Y, Takeda Y, Hata T, Murata K. Robotic-assisted proximal gastrectomy using the double-flap technique for early gastric cancer with situs inversus totalis: a case report. *Surg Case Rep* 2021; **7**: 172 [PMID: 34337695 DOI: 10.1186/s40792-021-01262-z]

41 **Sagawa H**, Ito S, Hayakawa S, Ueno S, Okubo T, Tanaka T, Ogawa R, Takahashi H, Matsuo Y, Mitsui A, Kimura M, Takiguchi S. Robotic distal gastrectomy for gastric cancer in a patient with situs inversus totalis and a vascular anomaly. *Int Cancer Conf J* 2022; **11**: 253-260 [PMID: 36186219 DOI: 10.1007/s13691-022-00554-x]

42 **Katano K**, Inaki N, Yamaguchi T, Saito H, Shimada M, Terai S, Okamoto K, Moriyama H, Kinoshita J, Nakamura K, Ninomiya I. Robot-assisted transhiatal lower esophagectomy and proximal gastrectomy for Siewert type II advanced esophagogastric junction cancer with situs inversus totalis: a case report. *Surg Case Rep* 2022; **8**: 40 [PMID: 35286497 DOI: 10.1186/s40792-022-01393-x]

43 **Lamture Y**, Gharde P, Gajbhiye V, Nagtode T, Mastud K, Kulkarni V, Patel D. Adenocarcinoma of the Stomach With Situs Inversus Totalis: A Rare Case. *Cureus* 2022; **14**: e31538 [PMID: 36540458 DOI: 10.7759/cureus.31538]

44 **Doden K**, Watanabe T, Yoshimura T, Shibata S, Yamagishi Y, Kimura K, Iwaki Y, Kawaguchi M, Kato H, Inaki N. Indocyanine green fluorescence imaging-guided laparoscopy-assisted distal gastrectomy for early gastric cancer in a patient with situs inversus totalis: A case report with video. *Asian J Endosc Surg* 2023; **16**: 95-100 [PMID: 35799403 DOI: 10.1111/ases.13105]

45 **Huang S**, Lin W, Qiu X. Three-dimensional laparoscopic treatment of situs inversus totalis combined with gastric cancer: Case report with review of literature. *J Minim Access Surg* 2023; **19**: 147-151 [PMID: 36722540 DOI: 10.4103/jmas.jmas_311_21]

46 **Lee IY**, Lee D, Lee CM. Case Report: Single-port laparoscopic total gastrectomy for gastric cancer in patient with situs inversus totalis. *Front Oncol* 2023; **13**: 1094053 [PMID: 36741026 DOI: 10.3389/fonc.2023.1094053]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 2074-2082

DOI: 10.4240/wjgs.v15.i9.2074

ISSN 1948-9366 (online)

CASE REPORT

Acute flare of systemic lupus erythematosus with extensive gastrointestinal involvement: A case report and review of literature

Hua Huang, Ping Li, Dan Zhang, Ming-Xuan Zhang, Kai Yu

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Makovicky P, Slovakia; Yale SH, United States

Received: April 24, 2023
Peer-review started: April 24, 2023
First decision: June 12, 2023
Revised: July 9, 2023
Accepted: July 28, 2023
Article in press: July 28, 2023
Published online: September 27, 2023

Hua Huang, Ping Li, Ming-Xuan Zhang, Department of Rheumatology and Immunology, General Hospital of Northern Theater Command, Shenyang 110000, Liaoning Province, China

Dan Zhang, Department of Nutrition, General Hospital of Northern Theater Command, Shenyang 110000, Liaoning Province, China

Kai Yu, Department of Gastroenterology, General Hospital of Northern Theater Command, Shenyang 110000, Liaoning Province, China

Corresponding author: Ping Li, PhD, Doctor, Department of Rheumatology and Immunology, General Hospital of Northern Theater Command, No. 83 Wenhua Road, Shenhe District, Shenyang 110000, Liaoning Province, China. graceli008@sohu.com

Abstract

BACKGROUND

Lupus mesenteric vasculitis (LMV) is a serious condition that may occur as an acute manifestation of gastrointestinal (GI) involvement and is not easily diagnosed by physicians. Delayed diagnosis and treatment of LMV may lead to rapid disease progression and can be life threatening.

CASE SUMMARY

A previously healthy 27-year-old woman presented with abdominal pain following a history of fatigue and consumption of cold water. Laboratory investigations, physical examinations, and enhanced abdominal computed tomography (CT) suggested systemic lupus erythematosus complicated by LMV. She received treatments, such as GI decompression, somatostatin, glucocorticoids, and immunosuppressants, and was evaluated using color ultrasonography. Twenty days later, the patient reported no stomach discomfort and was able to consume semi-liquid food. Laboratory investigations showed that inflammatory factors decreased to normal levels and complement levels increased slightly. One year after discharged, she recovered with methylprednisolone being tapered to 4 mg per day, mycophenolate mofetil to 0.75 g bid, and hydroxychloroquine to 0.2 g bid; however, only C3 complement level was slightly below the normal level.

CONCLUSION

Early diagnosis of LMV is essential for successful treatment; this depends on a combination of clinical manifestations, laboratory investigations, and imaging findings. Enhanced CT is preferred, but ultrasonography can be used for prompt screening and follow-up.

Key Words: Systemic lupus erythematosus; Gastrointestinal involvement; Lupus enteritis; Lupus mesenteric vasculitis; Ultrasonography; Computer tomography; Case report

Core Tip: When a systemic lupus erythematosus patient presenting with gastrointestinal symptoms, lupus mesenteric vasculitis (LMV) must be considered despite being rare. Enhanced abdominal computed tomography revealing thicked jejunal wall (target sign) and engorgement of the mesenteric vessels (comb sign) were suggestive of mesenteric vasculitis and provide evidence for accurately treatment. Abdominal ultrasonography can be a reliable tool used for preliminary screening, therapeutic evaluation and follow-up for LMV.

Citation: Huang H, Li P, Zhang D, Zhang MX, Yu K. Acute flare of systemic lupus erythematosus with extensive gastrointestinal involvement: A case report and review of literature. *World J Gastrointest Surg* 2023; 15(9): 2074-2082
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/2074.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.2074

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune disease of unknown etiology. Under the influence of genetic predisposition and environmental risk factors, alterations in the immune response include hyperactivation of T and B lymphocytes, loss of self-tolerance and formation of circulating pathogenic immune complexes and subsequent deposition in several organs, thereby causing damage. The incidence of SLE is approximately 30–70 cases per 100000 individuals in China[1]. Females of reproductive age are mostly affected.

Gastrointestinal (GI) symptoms are present in > 50% of SLE patients throughout the course of the disease[2]. Among the wide spectrum of SLE-associated GI complications, including abdominal serositis/peritonitis, protein-losing enteropathy, intestinal pseudo-obstruction, hepatic involvement, and pancreatitis, lupus mesenteric vasculitis (LMV) is rare, but one of the most serious complications of SLE with high mortality[3]. Early diagnosis of LMV is crucial for prompt treatment.

LMV or lupus enteritis (LE), was originally proposed by Hoffman and Katz[4] in 1980. The early clinical presentation of LE comprises abdominal pain, nausea, vomiting, or severe GI bleeding, which is unremarkable and non-specific and is easily mistaken for infectious gastroenteritis and medication-related adverse effects. The rarity of LE in SLE, which makes it unincluded in any SLE classification criteria or weighted in the SLE Disease Activity Index (SLEDAI), makes early clinical suspicion difficult to elicit. In the British Isles Lupus Assessment Group disease activity index, LE is defined as either vasculitis or inflammation of the small or large bowel with supportive imaging and/or biopsy findings[5]. Since histological evidence is difficult to obtain, it is important to find a rapid, reliable, and safe diagnostic tool. This case review aimed to identify possible strategies for early diagnosis of LE among women of reproductive age.

CASE PRESENTATION

Chief complaints

A 27-year-old woman was referred to our department on account of abdominal pain that had persisted for six days.

History of present illness

The patient was initially transferred to our department after an enhanced abdominal computed tomography (CT) examination and GI decompression.

History of past illness

The patient had no photosensitivity, alopecia, oral ulcers, arthritis, or Raynaud's phenomenon, and was previously healthy.

Personal and family history

The patient had no family history of SLE.

Physical examination

Upon examination, the abdomen was distended with no tenderness or rebound pain. No palpable masses or active bowel sounds were detected.

Laboratory examinations

Antinuclear antibody titer was 1:320, and anti-U1 ribonucleoprotein and anti-Sjogren's syndrome A antibodies were positive, whereas anti-double-stranded DNA (anti-dsDNA) antibody and anti-Smith antibody were negative. The levels of C3 and C4 compliments decreased to 0.245 g/L (0.7–1.4 g/L) and 0.024 g/L (0.1–0.4 g/L), respectively. Immunoglobulin G (IgG) level was 10.45 g/L (7–16 g/L), and direct antiglobulin "Coombs" test results were positive. Routine blood tests showed a white blood cell count of 1.40 × 10^{10}/L (3.5× 10^{9}–9.5 × 10^{9}/L), platelet count of 2.01 × 10^{11}/L (1.25 × 10^{11}–3.50 × 10^{11}/L), and hemoglobin level of 114 g/L (115–150 g/L). Urine microscopy revealed a pathological tube-type 1 per low power field. Liver enzyme levels and renal function were normal. Moreover, serum albumin level was 33.2 g/L (40–55 g/L); erythrocyte sedimentation rate (ESR) was 3 mm/h (0-22 mm/h); C-reactive protein (CRP) level was 1.28 mg/L (< 10 mg/L); procalcitonin level was 0.293 ng/mL (0–0.046 ng/mL); blood potassium level was 2.9 mmol/L (3.5–5.3 mmol/L); cardiac enzyme levels were normal; and 24 h total urine protein level was 0.51 g/d (0.01–0.15 g/d).

Imaging examinations

Lung CT showed bilateral pleural effusion (Figure 1). Enhanced abdominal CT showed the typical "target and comb signs" performance (Figure 2). Further investigation revealed LMV and incomplete intestinal obstruction. Some segmental bowel walls of the transverse colon were thickened by approximately 5 mm, and the main color flow of the superior mesenteric artery was well filled without embolism (Figures 3 and 4).

FINAL DIAGNOSIS

According to the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for SLE, autoimmune hemolysis (4 points) + pleural or pericardial effusion (5 points) + low C3 and C4 (4 points) + proteinuria (4 points) = 17 points, which was > 10 points, and the patient met the diagnostic criteria; therefore, LMV and lupus nephritis were diagnosed. The SLEDAI-2K score was eight.

TREATMENT

After fasting, GI decompression, intravenous nutrition, methylprednisolone 80 mg per day intravenously, and immunoglobulin 20 g per day intravenously for five days, the symptoms were relieved, and the patient was able to tolerate semi-liquid food. Furthermore, the methylprednisolone dose was gradually decreased to 40 mg per day intravenously. Fourteen days later, the methylprednisolone dose was adjusted to 36 mg per day orally, and this dosage was maintained for approximately one month, even after the patient was discharged. Moreover, she was treated with cyclophosphamide 0.2 g qod intravenously twice with a cumulative dose of 0.4 g, which was switched to mycophenolate mofetil (MMF) 0.75 g bid orally. Owing to the GI inflammation, intravenous antibiotics were administered for 15 d. Somatostatin reduced the intestinal inflammation, exudation, and gastric acid secretion. Nadroparin calcium was administered to prevent micro- or small mesenteric thrombosis.

OUTCOME AND FOLLOW-UP

Twenty days after the treatment, the patient was able to eat semi-liquid food without stomach discomfort. Bowel sounds returned to normal. Laboratory investigations showed complement levels had increased. The IgG level was 15.6 g/L (7–16 g/L), and renal function, hepatic enzyme levels, and electrolyte levels were normal. Routine urine and stool test results were normal. Ten days after the treatment, ultrasonography was used to assess the patient's condition, which demonstrated that the local intestinal wall was approximately 0.35 cm at its thickest part (Figure 5), and that there was no effusion in the pleural, abdominal, or pelvic cavities. Most of the intestinal wall thickness decreased to a normal size. Finally, the intestinal lumen did not expand, and the multiserous cavity effusion disappeared. The abdominal signs and symptoms reduced, and the patient tolerated full feeding and was discharged.

The patient was follow-up at two-weekly intervals for the first three months and monthly thereafter. One year later, the patient was treated with methylprednisolone, which was tapered to 4 mg per day, MMF 0.75 g bid, and hydroxychloroquine 0.2 g bid. The C4 complement level was normalized, but the C3 complement level was 0.663 g/L (0.7–1.4 g/L), still slightly below the normal level. Table 1 shows the timeline from symptom onset to the last follow-up visit.

DISCUSSION

LE, also known LMV[6], is rare and one of the most devastating complications of SLE. The incidence of LMV is estimated to range between 0.2%–9.7% among patients already diagnosed with SLE and between 13.0%–62.5% in patients with isolated LE as the initial presentation of SLE[7].

Table 1 Timeline from symptom onset to the last follow-up visit

	Time of admission (March 29, 2022)	Time of discharge (April 4, 2022)	Last follow-up (June 16, 2023)
WBC (3.5×10^9-9.5×10^9/L)	6.4	4.3	6.2
Hemoglobin (115–150 g/L)	98	100	133
Platelet (1.25×10^{11}–3.50×10^{11}/L)	212	226	224
CRP (0–6 mg/L)	0.4	1.28	0.2
ESR (0–20 mm/h)	3	11	6
IgG (7–16 g/L)	10.45	15.6	11.56
IgA (0.7–4 g/L)	0.81	1.02	0.78
IgM (0.4–2.3 g/L)	0.46	0.603	0.72
C3 (0.9–1.8 g/L)	0.245	0.449	0.663
C4 (0.1–0.4 g/L)	0.027	0.082	0.143
Serum albumin (40–55 g/L)	22.8	38.3	43.5
Alanine aminotransferase (7–40 U/L)	9.22	14	13.31
Aspartate aminotransferase (13–35 U/L)	20.86	9	22.37
Serum creatinine (41-73 μmol/L)	73.2	42	52.2
Serum urea nitrogen (3.1–8 mmol/L)	8.24	3.84	3.74
Lung CT	Bilateral pleural effusion	Normal	Normal
Ultrasonography	Bowel walls were thickened by approximately 5 mm	Bowel walls were thickened by approximately 3.5 mm	Normal

WBC: White blood cell; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IgG: Immunoglobulin G; IgA: Immunoglobulin A; IgM: Immunoglobulin M; CT: Computed tomography.

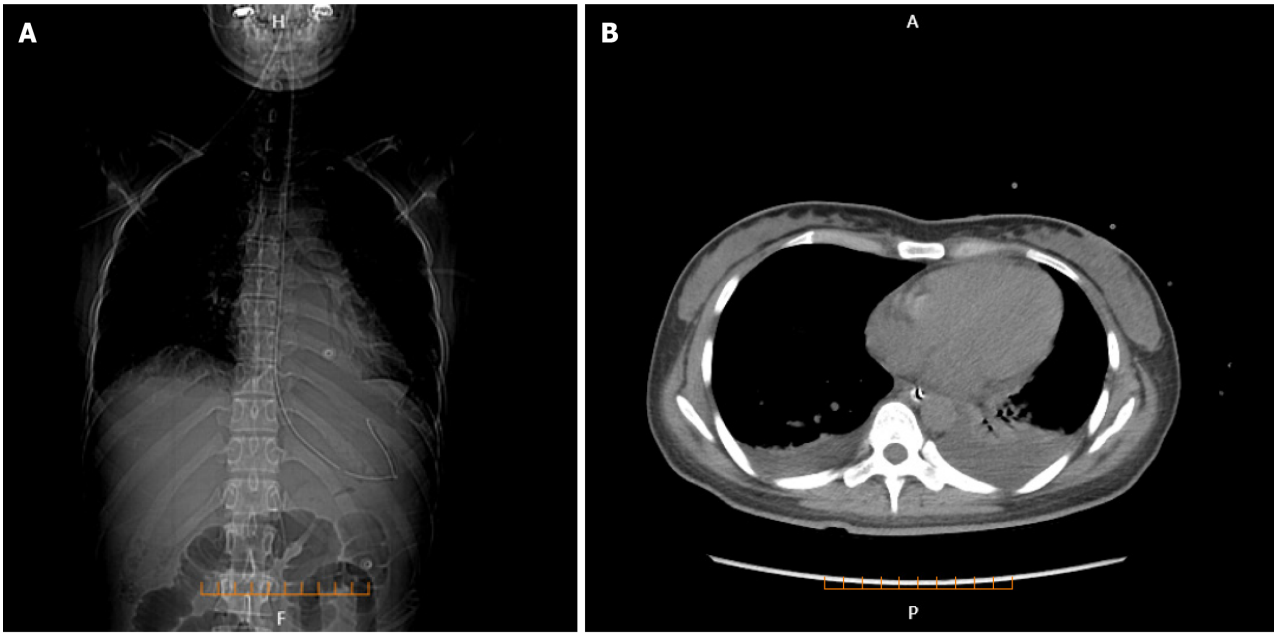
The pathophysiology of LMV is leukocytoclastic vasculitis secondary to the deposition of immune complexes in vascular walls, and antiphospholipid antibody-associated vasculopathy leading to thrombosis[8]. Ischemia causes the greatest damage to the mucosal mesenteric vessels, followed by the vasculature of the muscularis propria, submucosa, and plasma membrane[6]. Certain triggering factors (bacterial or viral infections, chemicals, *etc.*) can activate endothelial cells and expose them to cryptic antigens, resulting in the production of anti-endothelial cell antibodies, activation of complement, and deposition of immune complexes on inflamed blood vessel walls, which can lead to vascular damage and thrombosis[6]. The literature reported that vasculitis was histologically confirmed by biopsy samples of the affected intestinal segments[9]. The submucosa, filled with a mild diffuse inflammatory infiltrate of mononuclear cells, becomes edematous, and hemorrhage can be observed mostly in the muscular and subserosal layers; fibrinoid necrosis, leukocytoclasis on the vascular wall, and fibrin thrombus formation can be observed in the subserosal vessels.

The initial presenting signs and symptoms of LE are heterogeneous and commonplace and are usually mistaken for GI infections, peptic ulcers, lithiasis cholecystitis, or side effects of medications. However, the most common symptom in more than 90% of patients is abdominal pain of varying intensity caused by intestinal ischemia secondary to vasculitis [10]. Signs and symptoms of impaired GI motility and peritonitis are also common in patients with SLE. Diarrhea was frequent, with a frequency of 43.5%–64.7% in different studies[11]. Vomiting was found among 39.5%–72.2% of Asian patients[12]. Ascites was also frequently reported in the literature (27.9%–94.1%). This was also observed in our patient. GI bleeding is a rare but serious presentation that may be due to intestinal ischemia and intestinal necrosis. If not recognized in time, it may lead to perforation with a mortality rate of up to 50%[13]. The ileum and jejunum were the most frequently involved intestinal sites (> 80%) reported in the literature[14].

Timely and accurate diagnosis of LMV is a great challenge due to the lack of knowledge about LMV. Therefore, it is necessary to explore the factors associated with LMV.

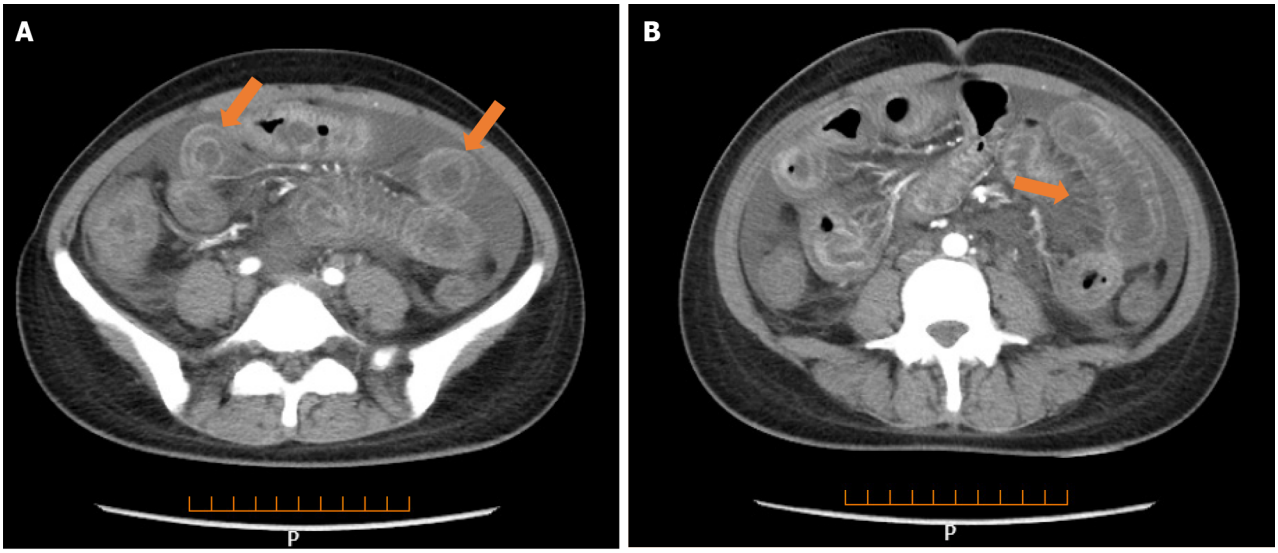
Several studies have found that patients accompanied by oral ulcers or lupus urinary tract involvement have a greater risk of encountering LMV[15-17]. Therefore, clinicians should suspect LMV when clinical laboratory results suggest lupus involvement of oral ulcers and the urinary system.

Previous studies have shown that there is no significant difference in SLEDAI scores in patients with SLE presenting with abdominal pain, regardless of the presence or absence of LE[14]. In patients with LMV, there was no difference in SLEDAI scores for serious adverse events, such as intestinal hemorrhage, infarction, perforation, or death due to serious complications, suggesting that SLE activity does not correlate with the severity of LMV[9]. Although SLEDAI was higher



DOI: 10.4240/wjgs.v15.i9.2074 **Copyright** ©The Author(s) 2023.

Figure 1 Lung computed tomography. A: Bilateral pleural effusion and the position of gastrointestinal decompression tube (coronal plane); B: Bilateral pleural effusion (axial plane).



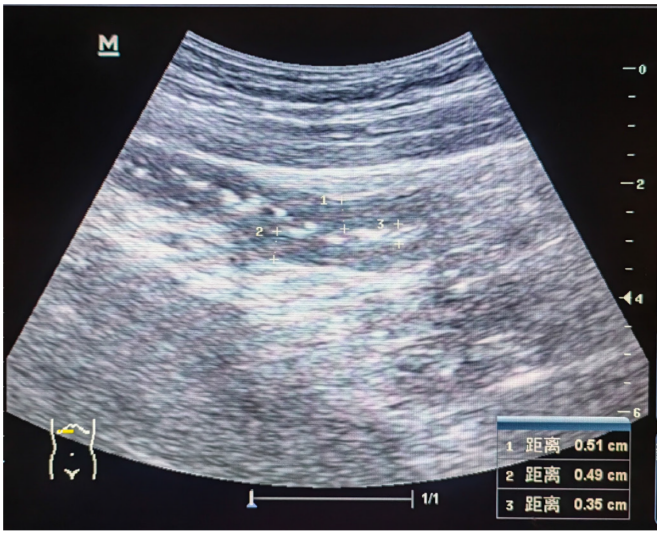
DOI: 10.4240/wjgs.v15.i9.2074 **Copyright** ©The Author(s) 2023.

Figure 2 Full enhanced abdominal computed tomography. A: Thickened bowel loops (target sign); B: Engorgement and increased visibility of the mesenteric vessels (comb sign).

at baseline in LE patients than in non-LE patients, it did not predict the development of LE[18].

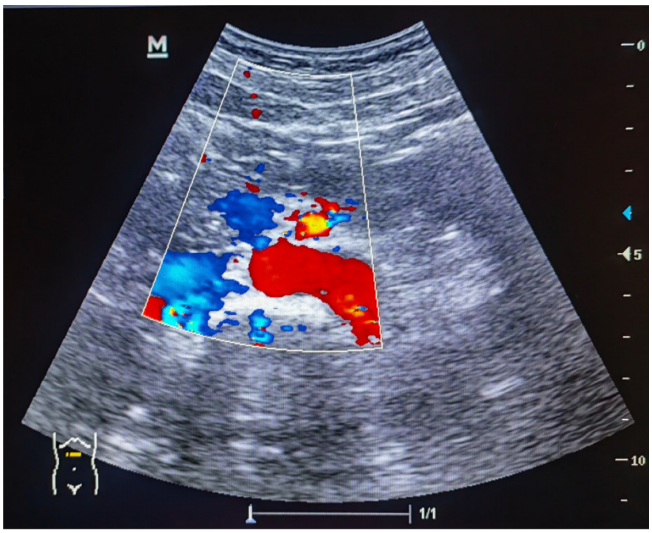
Laboratory tests are of value in the diagnosis of LE. However, CRP is usually normal and complement levels are decreased[7]. In seropositive cases, antibodies were more reliable, with increased titers of antinuclear, anti-dsDNA, and anti-Smith antibodies, which were approximately 92%, 80%, and 20%, respectively[19]. These autoimmune and inflammatory markers, while informative in diagnosis, are not essential. LE can occur without clinically active lupus[7]. Other researchers did not find laboratory parameters, including complement, ESR, CRP, lupus-related antibodies, and antiphospholipid antibodies to be correlated with the risk of LE[8,14].

Multiple methods, including ultrasonography, CT, magnetic resonance imaging, and GI endoscopy, have been used to evaluate LMV. However, CT is fast and non-invasive and can be used to perform image reconstruction and post-processing, to observe the LMV in multiple directions, and to observe lesions of the mesentery and blood vessels. Enhanced abdominal CT is more sensitive in detecting intestinal abnormalities, as it can reveal thickened and swollen bowel walls that contain enhanced mucosal, edematous submucosal, and enhanced serosal layers. Normal bowel wall thickness visualized by CT was < 3 mm; 3–5 mm thick bowel walls were considered mildly thickened, 6–7 mm



DOI: 10.4240/wjgs.v15.i9.2074 **Copyright** ©The Author(s) 2023.

Figure 3 Ultrasonography of the transverse colon showing thickened segmental bowel walls of approximately 5 mm.



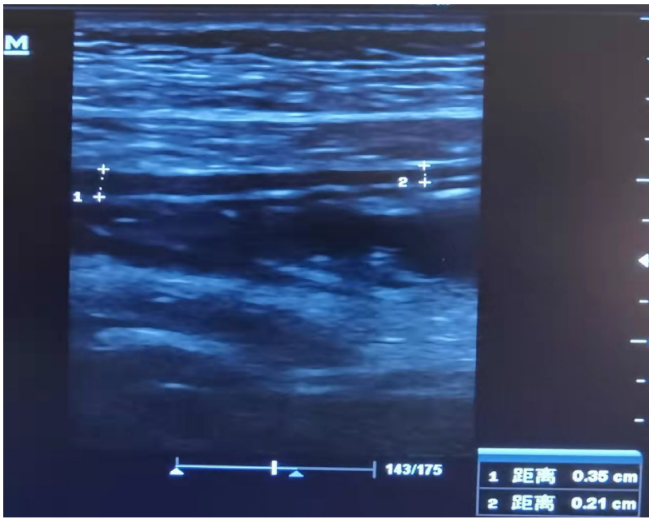
DOI: 10.4240/wjgs.v15.i9.2074 **Copyright** ©The Author(s) 2023.

Figure 4 Ultrasonography of the superior mesenteric artery showing the main color flow of the superior mesenteric artery was well-filled without embolism.

moderately thickened, and > 8 mm markedly thickened[20]. This categorization is important in judging the occurrence of LE[9,21]. There are three typical abdominal CT findings in patients with LE, and these can appear alone or concurrently: Bowel wall thickening (> 3.0 mm), which leads to separation of the mucosa and muscle layers and "target sign" appearance; mesenteric vasodilation with "comb sign" appearance; and increased attenuation of mesenteric fat[15,19,22-25]. The co-occurrence of "target sign" and "comb sign" is particularly specific to LE, and can be used to establish a diagnosis. Unfortunately, these imaging manifestations are not uncommon in inflammatory bowel disease, intestinal ischemia, and mesenteric vein thrombosis.

Magnetic resonance enterography can also be used to diagnose LE. The main advantages of magnetic resonance enterography are that it allows for a holistic assessment of the bowel, both intestinal and extra-intestinal, as well as a high degree of safety as the examination can be repeated in a short period of time[26]. However, the slightly longer scan time, the radiologist's manipulation, and the patient's tolerance of the contrast agent may limit magnetic resonance enterography.

Ultrasonography is likely to be the most readily available imaging method, and a valuable alternative to CT when the latter is not available or is contraindicated. Being a safe and more accessible technique, ultrasonography was the first imaging examination when our patient presented to the emergency room. The study[27] have described patients with LE who had characteristic intestinal wall edema and ascites based on ultrasonography. Ultrasonography revealed thickening of the intestinal wall, in which the submucosal edema of the Kerckring fold resembled an accordion[28], dilation of intestinal segments, increased reflectivity of mesenteric fat, and mild ascites. CT confirmed these features, suggesting that



DOI: 10.4240/wjgs.v15.i9.2074

Figure 5 Ultrasonography showing the local intestinal wall with approximately 0.35 cm at its thickest part.

both methods have similar sensitivities for LE diagnosis. Regarding specificity, ultrasonography has similar limitations with CT. If the patient is a young woman of childbearing age, ultrasonography is likely to be the best screening examination for suspected LMV diagnosis and follow-up[14]. Therefore, ultrasonography is a reliable and accessible tool.

Although the gold standard for diagnosing LE is pathology, the positive rate is low. Therefore, endoscopy is not used as a routine diagnostic tool. Only a few cases present intestinal edema, congestion and ischemia with or without ulceration or necrosis[7].

Due to the lack of prospective randomized controlled clinical trials, there are currently no available guidelines or recommendations for LE treatment.

The prognosis is good when the diagnosis is made early, and high-dose steroids are started in a timely manner; however, patients may occasionally experience recurrence. Glucocorticoids are the primary medications used to treat LE. Cyclophosphamide is one of the most commonly used immunosuppressants used for SLE treatment in China, and its combination with corticosteroids results in a good response[29]. Cyclophosphamide, whether intravenous pulse or not, has been useful in preventing relapses of lupus flares[2]. However, considering its lower reproductive toxicity, we switched to MMF treatment, which is preferred in young men and women due to the high risk of testicular and ovarian failure following cyclophosphamide[30]. Although rituximab, an anti-CD20 antibody, showed promising potential in observational studies, the LUNAR randomized controlled trials did not show that rituximab combined with MMF had additional benefits during remission compared with MMF alone[31].

LMV causes inflammation in the intestinal wall, which enhances its permeability. Dysregulation of the intestinal microbiota can lead to intestinal infection. Antibiotics were administered to control the risk of infection. Octreotide treatment may be effective, owing to its immunomodulatory effects, regulation of intestinal microvasculature blood flow, and amelioration of lymphatic dilatation[32]. Considering the aforementioned effects of somatostatin, we administered it to the patient and good outcomes were achieved.

CONCLUSION

Despite being rare, LMV must always be considered in any SLE patient presenting with GI symptoms. The diagnosis of LMV requires a combination of history and clinical and immunological indicators. Moreover, enhanced CT examination can reveal the extent and scope of GI lesions involved in SLE and provide evidence for timely clinical diagnosis and treatment. For pregnant women, or physicians in primary hospitals, ultrasonography can be an alternative method for preliminary screening and follow-up.

ACKNOWLEDGEMENTS

We are grateful to the patient for permitting us to publish this study.

FOOTNOTES

Author contributions: Huang H and Li P contributed to manuscript drafting; Zhang MX was the physician responsible for the patient's

diagnosis and treatment in the Rheumatology and Immunology Department; Zhang D was the patient's nutritionist and provided nutritional guidance; Yu K was the patient's admitting physician in the Gastroenterology Department; All authors were responsible for the revision of the manuscript and final approval for submission.

Informed consent statement: Consent was obtained from the patient, both verbally and in written form and has been attached to this submission.

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

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

Country/Territory of origin: China

ORCID number: Hua Huang 0009-0006-8989-7193; Ping Li 0000-0001-9008-0937; Dan Zhang 0009-0004-4056-7340; Ming-Xuan Zhang 0009-0008-0821-9775; Kai Yu 0009-0001-8623-8639.

S-Editor: Lin C
L-Editor: A
P-Editor: Guo X

REFERENCES

1 **Zeng QY**, Chen R, Darmawan J, Xiao ZY, Chen SB, Wigley R, Le Chen S, Zhang NZ. Rheumatic diseases in China. *Arthritis Res Ther* 2008; **10**: R17 [PMID: 18237382 DOI: 10.1186/ar2368]
2 **Chng HH**, Tan BE, Teh CL, Lian TY. Major gastrointestinal manifestations in lupus patients in Asia: lupus enteritis, intestinal pseudo-obstruction, and protein-losing gastroenteropathy. *Lupus* 2010; **19**: 1404-1413 [PMID: 20947549 DOI: 10.1177/0961203310374337]
3 **Fawzy M**, Edrees A, Okasha H, El Ashmaui A, Ragab G. Gastrointestinal manifestations in systemic lupus erythematosus. *Lupus* 2016; **25**: 1456-1462 [PMID: 27055518 DOI: 10.1177/0961203316642308]
4 **Hoffman BI**, Katz WA. The gastrointestinal manifestations of systemic lupus erythematosus: a review of the literature. *Semin Arthritis Rheum* 1980; **9**: 237-247 [PMID: 6996096 DOI: 10.1016/0049-0172(80)90016-5]
5 **Isenberg DA**, Rahman A, Allen E, Farewell V, Akil M, Bruce IN, D'Cruz D, Griffiths B, Khamashta M, Maddison P, McHugh N, Snaith M, Teh LS, Yee CS, Zoma A, Gordon C. BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. *Rheumatology (Oxford)* 2005; **44**: 902-906 [PMID: 15814577 DOI: 10.1093/rheumatology/keh624]
6 **Ju JH**, Min JK, Jung CK, Oh SN, Kwok SK, Kang KY, Park KS, Ko HJ, Yoon CH, Park SH, Cho CS, Kim HY. Lupus mesenteric vasculitis can cause acute abdominal pain in patients with SLE. *Nat Rev Rheumatol* 2009; **5**: 273-281 [PMID: 19412194 DOI: 10.1038/nrrheum.2009.53]
7 **Janssens P**, Arnaud L, Galicier L, Mathian A, Hie M, Sene D, Haroche J, Veyssier-Belot C, Huynh-Charlier I, Grenier PA, Piette JC, Amoura Z. Lupus enteritis: from clinical findings to therapeutic management. *Orphanet J Rare Dis* 2013; **8**: 67 [PMID: 23642042 DOI: 10.1186/1750-1172-8-67]
8 **Kwok SK**, Seo SH, Ju JH, Park KS, Yoon CH, Kim WU, Min JK, Park SH, Cho CS, Kim HY. Lupus enteritis: clinical characteristics, risk factor for relapse and association with anti-endothelial cell antibody. *Lupus* 2007; **16**: 803-809 [PMID: 17895303 DOI: 10.1177/0961203307082383]
9 **Yuan S**, Ye Y, Chen D, Qiu Q, Zhan Z, Lian F, Li H, Liang L, Xu H, Yang X. Lupus mesenteric vasculitis: clinical features and associated factors for the recurrence and prognosis of disease. *Semin Arthritis Rheum* 2014; **43**: 759-766 [PMID: 24332116 DOI: 10.1016/j.semarthrit.2013.11.005]
10 **Zhang W**, Huang G, Lin J, Lin Q, Zheng K, Hu S, Zheng S, Du G, Matucci-Cerinic M, Furst DE, Wang Y. Predictive model of risk and severity of enteritis in systemic lupus erythematosus. *Lupus* 2022; **31**: 1226-1236 [PMID: 35750508 DOI: 10.1177/09612033221110743]
11 **Koo BS**, Hong S, Kim YJ, Kim YG, Lee CK, Yoo B. Lupus enteritis: clinical characteristics and predictive factors for recurrence. *Lupus* 2015; **24**: 628-632 [PMID: 25391541 DOI: 10.1177/0961203314558858]
12 **Chen L**, He Q, Luo M, Gou Y, Jiang D, Zheng X, Yan G, He F. Clinical features of lupus enteritis: a single-center retrospective study. *Orphanet J Rare Dis* 2021; **16**: 396 [PMID: 34565417 DOI: 10.1186/s13023-021-02044-4]
13 **Trapani S**, Rubino C, Simonini G, Indolfi G. Gastrointestinal and hepatic involvement in paediatric systemic lupus erythematosus. *Clin Exp Rheumatol* 2021; **39**: 899-906 [PMID: 33666164 DOI: 10.55563/clinexprheumatol/oebrcq]
14 **Lee CK**, Ahn MS, Lee EY, Shin JH, Cho YS, Ha HK, Yoo B, Moon HB. Acute abdominal pain in systemic lupus erythematosus: focus on lupus enteritis (gastrointestinal vasculitis). *Ann Rheum Dis* 2002; **61**: 547-550 [PMID: 12006332 DOI: 10.1136/ard.61.6.547]
15 **Chu YC**, Hsu BB, Tseng KC. Lupus mesenteric vasculitis with GI and genitourinary tract involvement. *Clin Gastroenterol Hepatol* 2014; **12**: e69-70; quiz e71 [PMID: 24393805 DOI: 10.1016/j.cgh.2013.12.024]
16 **Shimizu A**, Tamura A, Tago O, Abe M, Nagai Y, Ishikawa O. Lupus cystitis: a case report and review of the literature. *Lupus* 2009; **18**: 655-658 [PMID: 19433468 DOI: 10.1177/0961203308099634]
17 **Tan TC**, Wansaicheong GK, Thong BY. Acute onset of systemic lupus erythematosus with extensive gastrointestinal and genitourinary involvement. *Lupus* 2012; **21**: 1240-1243 [PMID: 22833436 DOI: 10.1177/0961203312455111]

18 **Duarte-García A**, Hocaoglu M, Osei-Onomah SA, Dabit JY, Giblon RE, Helmick CG, Crowson CS. Population-based incidence and time to classification of systemic lupus erythematosus by three different classification criteria: a Lupus Midwest Network (LUMEN) study. *Rheumatology (Oxford)* 2022; **61**: 2424-2431 [PMID: 34718442 DOI: 10.1093/rheumatology/keab807]

19 **Smith LW**, Petri M. Lupus enteritis: an uncommon manifestation of systemic lupus erythematosus. *J Clin Rheumatol* 2013; **19**: 84-86 [PMID: 23364660 DOI: 10.1097/RHU.0b013e318284794e]

20 **Si-Hoe CK**, Thng CH, Chee SG, Teo EK, Chng HH. Abdominal computed tomography in systemic lupus erythematosus. *Clin Radiol* 1997; **52**: 284-289 [PMID: 9112946 DOI: 10.1016/s0009-9260(97)80055-4]

21 **Kim YG**, Ha HK, Nah SS, Lee CK, Moon HB, Yoo B. Acute abdominal pain in systemic lupus erythematosus: factors contributing to recurrence of lupus enteritis. *Ann Rheum Dis* 2006; **65**: 1537-1538 [PMID: 17038460 DOI: 10.1136/ard.2006.053264]

22 **Goh YP**, Naidoo P, Ngian GS. Imaging of systemic lupus erythematosus. Part II: gastrointestinal, renal, and musculoskeletal manifestations. *Clin Radiol* 2013; **68**: 192-202 [PMID: 22901453 DOI: 10.1016/j.crad.2012.06.109]

23 **Lin HP**, Wang YM, Huo AP. Severe, recurrent lupus enteritis as the initial and only presentation of systemic lupus erythematosus in a middle-aged woman. *J Microbiol Immunol Infect* 2011; **44**: 152-155 [PMID: 21439520 DOI: 10.1016/j.jmii.2009.12.001]

24 **Sran S**, Sran M, Patel N, Anand P. Lupus enteritis as an initial presentation of systemic lupus erythematosus. *Case Rep Gastrointest Med* 2014; **2014**: 962735 [PMID: 25295199 DOI: 10.1155/2014/962735]

25 **Alves SC**, Fasano S, Isenberg DA. Autoimmune gastrointestinal complications in patients with systemic lupus erythematosus: case series and literature review. *Lupus* 2016; **25**: 1509-1519 [PMID: 27329649 DOI: 10.1177/0961203316655210]

26 **Cicero G**, Blandino A, D'Angelo T, Bottari A, Cavallaro M, Ascenti G, Mazziotti S. Magnetic resonance enterography appraisal of lupus enteritis: A case report. *Radiol Case Rep* 2018; **13**: 915-919 [PMID: 30069281 DOI: 10.1016/j.radcr.2018.06.008]

27 **Demiselle J**, Sayegh J, Cousin M, Olivier A, Augusto JF. An Unusual Cause of Abdominal Pain: Lupus Enteritis. *Am J Med* 2016; **129**: e11-e12 [PMID: 26841297 DOI: 10.1016/j.amjmed.2016.01.011]

28 **Shirato M**, Hisa N, Fujikura Y, Ohkuma K, Kutsuki S, Hiramatsu K. [Imaging diagnosis of lupus enteritis--especially about sonographic findings]. *Nihon Igaku Hoshasen Gakkai Zasshi* 1992; **52**: 1394-1399 [PMID: 1448334]

29 **Chen Z**, Li MT, Xu D, Yang H, Li J, Zhao JL, Zhang HH, Han SM, Xu T, Zeng XF. Protein-losing enteropathy in systemic lupus erythematosus: 12 years experience from a Chinese academic center. *PLoS One* 2014; **9**: e114684 [PMID: 25490025 DOI: 10.1371/journal.pone.0114684]

30 **Soares PM**, Borba EF, Bonfa E, Hallak J, Corrêa AL, Silva CA. Gonad evaluation in male systemic lupus erythematosus. *Arthritis Rheum* 2007; **56**: 2352-2361 [PMID: 17599762 DOI: 10.1002/art.22660]

31 **Rovin BH**, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, Maciuca R, Zhang D, Garg JP, Brunetta P, Appel G; LUNAR Investigator Group. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum* 2012; **64**: 1215-1226 [PMID: 22231479 DOI: 10.1002/art.34359]

32 **Kubo M**, Uchida K, Nakashima T, Oda S, Nakamura T, Hashimoto S, Watada T, Nakamura H, Araki J, Matsuzaki M, Yano M. [Protein-losing enteropathy with systemic lupus erythematosus effectively treated with octreotide and medium chain triglyceride diet: A case report]. *Nihon Rinsho Meneki Gakkai Kaishi* 2015; **38**: 421-425 [PMID: 26725864 DOI: 10.2177/jsci.38.421]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 2083-2088

DOI: 10.4240/wjgs.v15.i9.2083

ISSN 1948-9366 (online)

CASE REPORT

Surgical management of gallstone ileus after one anastomosis gastric bypass: A case report

Elie El Feghali, Rhea Akel, Bilal Chamaa, Daniel Kazan, Ghassan Chakhtoura

Specialty type: Surgery

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Dilek ON, Turkey; Wang ZF, China

Received: May 25, 2023
Peer-review started: May 25, 2023
First decision: June 19, 2023
Revised: June 27, 2023
Accepted: July 25, 2023
Article in press: July 25, 2023
Published online: September 27, 2023

Elie El Feghali, Bilal Chamaa, Daniel Kazan, Ghassan Chakhtoura, Department of General Surgery, Saint Joseph University, Beirut 1107, Lebanon

Rhea Akel, Department of Radiology, Saint Joseph University, Beirut 1107, Lebanon

Corresponding author: Elie El Feghali, MD, Postdoc, Department of General Surgery, Saint Joseph University, Rue Damas, Ashrafieh, Beirut 1107, Lebanon. egf995@gmail.com

Abstract

BACKGROUND

Gallstone ileus following one anastomosis gastric bypass (OAGB) is an exceptionally rare complication. The presented case report aims to highlight the unique occurrence of this condition and its surgical management. Understanding the clinical presentation, diagnostic challenges and successful surgical intervention in such cases is crucial for healthcare professionals involved in bariatric surgery.

CASE SUMMARY

We present a case report of gallstone ileus following OAGB and discuss its diagnosis and surgical management. A 66-year-old female with a history of OAGB presented to the emergency room with symptoms of small bowel obstruction. Computed tomography scan revealed a gallstone impacted in the distal ileum, causing obstruction. The patient underwent a laparoscopically assisted enterolithotomy, during which the gallstone was extracted and the enterotomy was closed. The patient had an uneventful recovery and was dis-charged on postoperative day four.

CONCLUSION

Gallstone ileus should be considered as a possible complication after OAGB, and prompt surgical intervention is usually required for its management. This case report contributes to the limited existing literature, providing insights into the management of this uncommon complication.

Key Words: Gallstone ileus; One anastomosis gastric bypass; Bariatric surgery; Intestinal occlusion; Bilio-digestive fistula; Enterolithotomy; Case report

Core Tip: Gallstone ileus is a rare but serious complication that can occur after bariatric surgery, including one anastomosis gastric bypass (OAGB). Prompt diagnosis and appropriate surgical management are crucial for successful outcomes. In this case report, we present a rare instance of gallstone ileus after OAGB, highlighting the importance of considering this condition in patients presenting with small bowel obstruction symptoms post-bariatric surgery. A laparoscopically assisted enterolithotomy was performed, leading to the successful extraction of the gallstone and subsequent resolution of symptoms. Surgeons should be aware of the increased risk of cholelithiasis after bariatric surgery and consider preventive measures or early intervention to minimize the occurrence of gallstone-related complications.

Citation: El Feghali E, Akel R, Chamaa B, Kazan D, Chakhtoura G. Surgical management of gallstone ileus after one anastomosis gastric bypass: A case report. *World J Gastrointest Surg* 2023; 15(9): 2083-2088
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/2083.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.2083

INTRODUCTION

One anastomosis gastric bypass (OAGB) or mini bypass was first performed by Dr. Robert Rutledge in 1997[1]. It is both a restrictive and malabsorptive bariatric surgical procedure for the treatment of morbid obesity. It was developed as a faster and simpler alternative to the Roux en Y gastric bypass and is the fourth most performed bariatric technique in Europe and in Asia[2]. It is an effective surgical technique in terms of both weight loss and the resolution of comorbidities [3]. Nevertheless, like any other surgical procedure, OAGB can be associated with potential complications such as anastomotic leaks in 0.5 to 5.0 percent of cases, bleeding 0.2 to 2.0 per cent, nutritional deficiencies 5 to 50 per cent[4]. In addition, intestinal obstruction or occlusion is a possible complication after the OAGB with an incidence of 1 to 10 per cent[5] causing symptoms such as abdominal pain, nausea and vomiting and constipation. The most common etiologies of intestinal occlusion post-OAGB include internal hernias, adhesions, strictures and bowel kinking and/or twisting. In our case report, we are going to be present a rare cause of intestinal occlusion post-OAGB, the gallstone ileus (GI).

CASE PRESENTATION

Chief complaints

A 66-year-old female presented to the ER for abdominal pain and vomitting.

History of present illness

She had a 4-d history of food intolerance with post-prandial vomiting and diffuse colic type abdominal pain, her bowel movements were maintained. She denied having previously experienced similar symptoms or symptoms suggesting of cholecystitis during her post-operative interval.

History of past illness

She is known to have bipolar disease treated with Perphrenazine 8 mg and known to be a 5 pack/year smoker. She was operated of OAGB 6 years ago for morbid obesity [body mass index (BMI): 66.7 kg/m^2]. Previous comorbidities that included hypertension and diabetes mellitus were rectified after her weight loss of 90 Kg (BMI: 26.66 kg/m^2). Previous surgical interventions include 2 C-section deliveries.

Personal and family history

She has no significant family history.

Physical examination

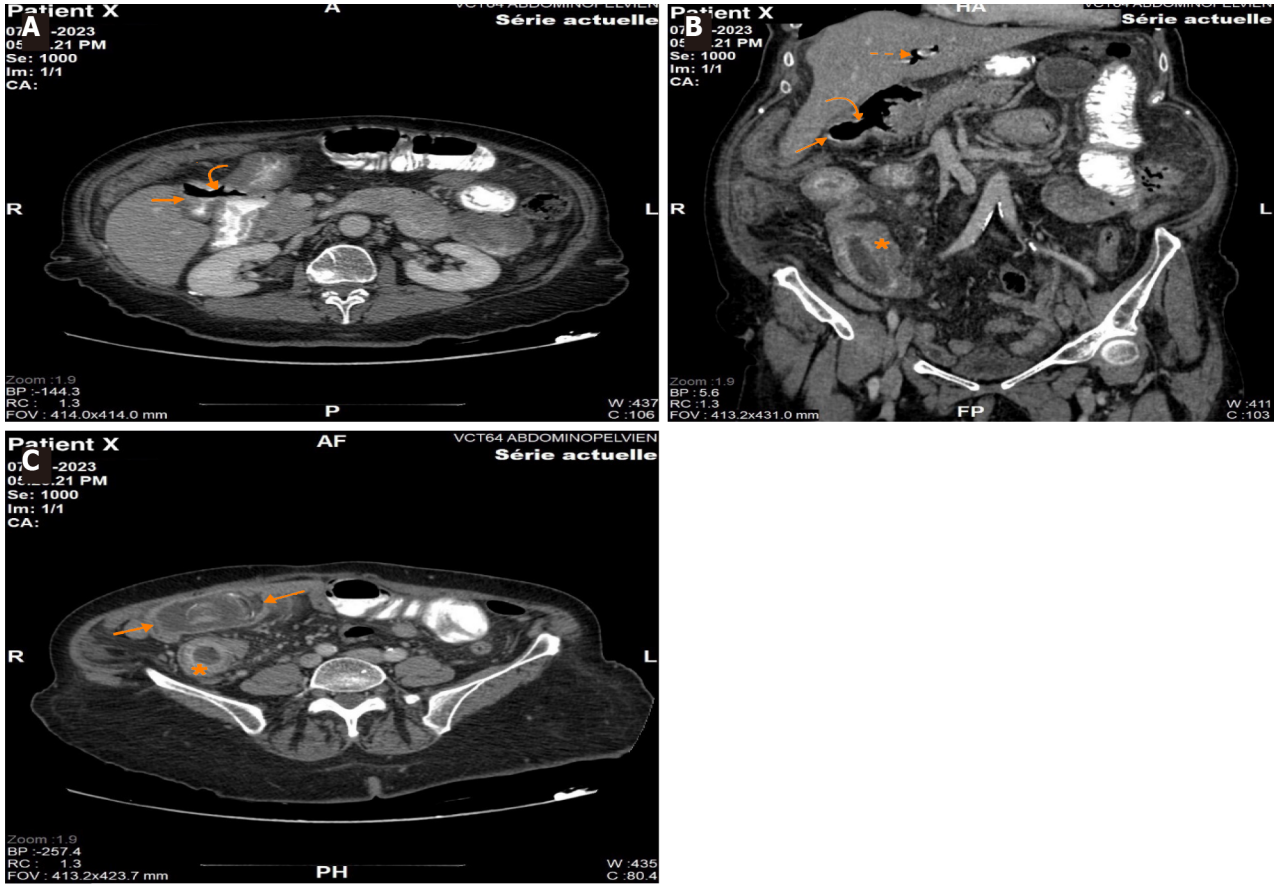
On physical examination, her abdomen was soft with mild tenderness in the lower right quadrant. She had a supra-umbilical hernia from her previous intervention.

Laboratory examinations

Her labs showed a mild hyper-leukocytosis white blood cell 12000 and C-reactive protein level was 80.8, her liver enzymes were in the normal range.

Imaging examinations

An abdomino-pelvic computed tomography scan with injection and ingestion of contrast was ordered (Figure 1). It showed a fistulous tract between the gallbladder and the duodenal bulb, extending over 15 mm. The fistula was confirmed with the leakage of the ingested contrast in the lumen of the gallbladder, which was not distended and contained an air-fluid level. It was associated with pneumobilia and small bowel dilation of 42 mm in diameter, with an



DOI: 10.4240/wjgs.v15.i9.2083 **Copyright** ©The Author(s) 2023.

Figure 1 Computed tomography scan. A: Axial section of contrast-enhanced computed tomography (CT) shows a gallbladder containing a hydro-aeric level with passage of ingested contrast medium (straight arrow) associated to a visible communication of 15 mm between the gallbladder and the duodenal bulb (curved arrow); B: Coronal reconstructed image (using multiplanar reconstruction) of contrast-enhanced CT shows the defect between the gallbladder and the duodenal bulb (curved arrow), the gallbladder filled with air (straight arrow) as well as pneumobilia within the intrahepatic biliary ducts (dotted straight arrow). Note that the distal ileum is mildly dilated, markedly thickened with increased mucosal enhancement (asterisks); C: Axial section of contrast-enhanced CT shows a gallstone measuring almost 45 mm (two arrows) impacted in the distal ileum, with marked thickening and increased mucosal enhancement within the upstream ileum (asterisks).

intestinal segment in the right lower quadrant showing parietal thickening and submucosal edema upstream of a transition zone located at the level of the right iliac fossa, downstream of a probable oval intraluminal calculus of 45 mm. The previous findings evoking a GI with a probable gallstone located at the level of the efferent alimentary loop. It is associated with a trabeculation of the fat at the level of the two flanks, especially on the right, with perihepatic and pelvic ascites of low abundance. Sequelae of gastric surgery with gastro-jejunal anastomosis (Roux en Omega) was identified.

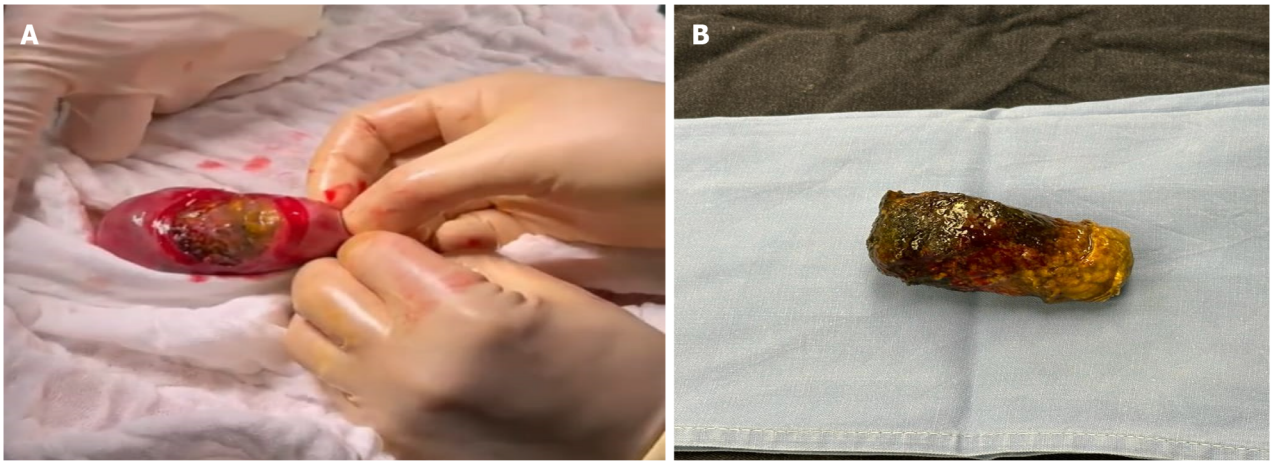
FINAL DIAGNOSIS

She was thus admitted for adequate treatment of her GI.

TREATMENT

After establishing the diagnosis of GI and acquiring the written consent of the patient, she was transferred to the operating room for a diagnostic laparoscopy and subsequent enterolithotomy. A nasogastric tube was inserted and she was adequately hydrated.

Open coelioscopy was performed and a 10 mm port was introduced. Pneumoperitoneum was created with a PCO2 of 12 mmHg. Two para-umbilical 5 mm ports were introduced under vision. There were multiple adhesions over the previous gastro-jejunal anastomosis and over the gallblader. The entero-biliary fistulae were not visualized, even after adhesyolysis. The afferent biliopancreatic loop was normal in diameter whereas the efferent alimentary loop was distended. The small bowel was run downwards until the obstructed ileal loop was identified. A 5 cm para-umbilical midline incision was made and the bowel segment was exteriorized. A horizontal enterotomy was performed to allow the extraction of an ovoid shaped yellow-brown stone measuring 5 cm × 3 cm × 1 cm approximately (Figure 2). The enterotomy was closed transversely with a double layer of absorbable sutures, and the small bowel was returned to the



DOI: 10.4240/wjgs.v15.i9.2083

Figure 2 Gallstone. A: Intraoperative photo of gallstone after enterolithotomy; B: Gallstone.

abdomen. The incision was approximated with non-absorbable monofilament sutures.

OUTCOME AND FOLLOW-UP

The patient's recovery was uneventful with return of bowel function on postoperative day two and diet advanced as tolerated. The patient was discharged home in improved condition on postoperative day four.

DISCUSSION

Rapid weight loss after bariatric surgery is associated with an increase in cholelithiasis, especially when the weight loss is greater than 25 per cent of the preoperative weight[6] with 38 per cent of patients developing gallstones within 6 mo, of which, 41 per cent will ultimately develop symptomatic cholelithiasis[7].

Gallstone ileus or Bouveret's Syndrome is a rare but serious complication of cholelithiasis as it occurs in 0.3 per cent of patients[8,9]. It results when a supracentimetric gallstone, which was formed during a medically treated or neglected cholecystitis, migrates from the gallbladder to the bowel through a biliary enteric fistula, the most common being a cholecystoduodenal fistula, and causes an obstruction, in more than 70% of cases at the level of the terminal ileum[10].

GI is considered to be implicated in 1 to 4 per cent of mechanical bowel obstruction, and accounts for a quarter of non-strangulated small bowel obstruction in patients above the age of 65 years, with a mortality rate between 15 to 18 per cent [9] with a female to male ratio of 3.5-6.1[11].

The diagnosis of GI is both clinical and radiological. GI has nonspecific symptoms such as nausea and/or vomiting associated with abdominal pain, bloating and constipation. The abdominal computed-tomography scan is the gold standard to establish the diagnosis. Rigler's triad of pneumobilia with small bowel obstruction caused by an ectopic gallstone within the bowel is observed in 40 to 50 per cent of cases[12].

Conservative measures such as nil per os status, nasogastric tube decompression with adequate intravenous hydration may be sufficient in select clinically stable patients with partial bowel obstruction and stones < 2 cm in size[8]. However, GI often requires urgent surgical management, laparoscopically in 10% of cases[13], which allows delineation of the anatomy with decreased bowel manipulation and subsequent safe stone extraction and reduced risk of intestinal content spillage.

The choice of surgical intervention is a subject of controversy[14]. A one or two stage procedure may be proposed: either enterolithotomy alone or enterolithotomy with cholecystectomy and eventual repair of the biliary fistula[15]. Nevertheless, the one stage approach is discouraged in view of the significant mortality (16.9%) compared with the two staged procedure (11.7%)[9]. In addition, laparoscopically assisted enterolithotomy has been credited with a favorable impact as it can be recommended for both diagnosis and treatment[16]. Prevention of symptomatic cholelithiasis after gastric bypass could be achieved by either prophylactic cholecystectomy or administration of ursodiol. In the one hand, prophylactic cholecystectomy during gastric bypass is a debatable subject. Its supporters argue that it is safe and would prevent both the morbidity associated with symptomatic cholelithiasis and a subsequent operation. Those who oppose to it cite that the safety of secondary cholecystectomy with an increase in operative time and length of stay do not justify the prophylactic cholecystectomy[17]. In the other hand, administration of a daily dose of 600 mg of ursodiol after gastric bypass was associated with a significant reduction in the incidence of cholelithiasis compared with placebo at 6 mo (2% *vs* 32%)[18].

To our knowledge, this is the first documented report of GI in a patient after OAGB. The GI diagnosis was established after correlation of the clinical and radiological findings of the patient. The fact that the patient presented to the emergency department with small bowel obstruction symptoms and the CT-scan confirmed the GI diagnosis with the presence of Rigler's triad previously discussed. The decision was to perform a two-staged procedure. Laparoscopically assisted enterolithotomy was preformed because it is in our opinion the safest and fastest therapeutic modality. At our institution, our current practice is to perform the OAGB without prophylactic cholecystectomy given that, if needed, a laparoscopic cholecystectomy is feasible in the case of a symptomatic cholelithiasis.

CONCLUSION

In conclusion, the incidence of cholelithiasis significantly increases after bariatric surgery and may lead to serious complications such as gallstone ileus, which require further operations.

FOOTNOTES

Author contributions: El Feghali E wrote the manuscript; Akel R provided the radiology images and their respective annotations; Chamaa B and Kazan D performed the research; Chakhtoura G designed the research study; and all authors have read and approve the final manuscript.

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

Conflict-of-interest statement: There are no conflict-of-interest to disclose.

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

Country/Territory of origin: Lebanon

ORCID number: Elie El Feghali 0009-0004-0075-1792.

S-Editor: Chen YL
L-Editor: A
P-Editor: Chen YL

REFERENCES

1 **Rutledge R**. The mini-gastric bypass: experience with the first 1,274 cases. *Obes Surg* 2001; **11**: 276-280 [PMID: 11433900 DOI: 10.1381/096089201321336584]
2 **Angrisani L**, Santonicola A, Iovino P, Formisano G, Buchwald H, Scopinaro N. Bariatric Surgery Worldwide 2013. *Obes Surg* 2015; **25**: 1822-1832 [PMID: 25835983 DOI: 10.1007/s11695-015-1657-z]
3 **Abou Ghazaleh R**, Bruzzi M, Bertrand K, M'harzi L, Zinzindohoue F, Douard R, Berger A, Czernichow S, Carette C, Chevallier JM. Is Mini-Gastric Bypass a Rational Approach for Type-2 Diabetes? *Curr Atheroscler Rep* 2017; **19**: 51 [PMID: 29063974 DOI: 10.1007/s11883-017-0689-3]
4 **Musella M**, Susa A, Manno E, De Luca M, Greco F, Raffaelli M, Cristiano S, Milone M, Bianco P, Vilardi A, Damiano I, Segato G, Pedretti L, Giustacchini P, Fico D, Veroux G, Piazza L. Complications Following the Mini/One Anastomosis Gastric Bypass (MGB/OAGB): a Multi-institutional Survey on 2678 Patients with a Mid-term (5 Years) Follow-up. *Obes Surg* 2017; **27**: 2956-2967 [PMID: 28569357 DOI: 10.1007/s11695-017-2726-2]
5 **Scavone G**, Caltabiano DC, Gulino F, Raciti MV, Giarrizzo A, Biondi A, Piazza L, Scavone A. Laparoscopic mini/one anastomosis gastric bypass: anatomic features, imaging, efficacy and postoperative complications. *Updates Surg* 2020; **72**: 493-502 [PMID: 32189194 DOI: 10.1007/s13304-020-00743-4]
6 **Li VK**, Pulido N, Fajnwaks P, Szomstein S, Rosenthal R, Martinez-Duartez P. Predictors of gallstone formation after bariatric surgery: a multivariate analysis of risk factors comparing gastric bypass, gastric banding, and sleeve gastrectomy. *Surg Endosc* 2009; **23**: 1640-1644 [PMID: 19057954 DOI: 10.1007/s00464-008-0204-6]
7 **Karadeniz M**, Görgün M, Kara C. The evaluation of gallstone formation in patients undergoing Roux-en-Y gastric bypass due to morbid obesity. *Ulus Cerrahi Derg* 2014; **30**: 76-79 [PMID: 25931899 DOI: 10.5152/UCD.2014.2538]
8 **Duzgun AP**, Ozmen MM, Ozer MV, Coskun F. Internal biliary fistula due to cholelithiasis: a single-centre experience. *World J Gastroenterol* 2007; **13**: 4606-4609 [PMID: 17729415 DOI: 10.3748/wjg.v13.i34.4606]

9 **BUETOW GW**, CRAMPTON RS. Gallstone ileus. A report of 23 cases. *Arch Surg* 1963; **86**: 504-511 [PMID: 14016662 DOI: 10.1001/archsurg.1963.01310090154029]

10 **Trump D**. Commentary on: "Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES study." Escudier B, Porta C, Bono P, Powles T, Eisen T, Sternberg CN, Gschwend JE, De Giorgi U, Parikh O, Hawkins R, Sevin E, Négrier S, Khan S, Diaz J, Redhu S, Mehmud F, Cella D. Bernard Escudier, Institut Gustave Roussy, Villejuif; Emmanuel Sevin, Centre François Baclesse, Caen; Sylvie Négrier, Leon Berard Cancer Center, Lyon, France; Camillo Porta, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico S. Matteo, Pavia; Cora N Sternberg, San Camillo Forlanini Hospital, Rome; Ugo De Giorgi, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola, Italy; Petri Bono, Helsinki University Central Hospital, Helsinki, Finland; Thomas Powles, Barts Experimental Cancer Medicine Centre, Barts Cancer Institute, Queen Mary University of London, London; Tim Eisen, Cambridge University Health Partners, Cambridge; Omi Parikh, Royal Preston Hospital, Lancashire; Robert Hawkins, Christie Cancer Research UK, Manchester; Sadya Khan, Jose Diaz, and Faisal Mehmud, GlaxoSmithKline, Uxbridge, United Kingdom; Jürgen E Gschwend, Klinikum Rechts der Isar der Technischen Universität München, Munich, Germany; Suman Redhu, GlaxoSmithKline, Collegeville, PA; David Cella, Northwestern University Feinberg School of Medicine, Chicago, IL.: J Clin Oncol. 2014 May 10;32(14):1412-1418; doi: 10.1200/JCO.2013.50.8267. [Epub 2014 Mar 31]. *Urol Oncol* 2016; **34**: 251 [PMID: 25937427 DOI: 10.1016/j.urolonc.2015.03.015]

11 **Micheletto G**, Danelli P, Morandi A, Panizzo V, Montorsi M. Gallstone ileus after biliointestinal bypass: report of two cases. *J Gastrointest Surg* 2013; **17**: 2162-2165 [PMID: 23897084 DOI: 10.1007/s11605-013-2290-6]

12 **Yu CY**, Lin CC, Shyu RY, Hsieh CB, Wu HS, Tyan YS, Hwang JI, Liou CH, Chang WC, Chen CY. Value of CT in the diagnosis and management of gallstone ileus. *World J Gastroenterol* 2005; **11**: 2142-2147 [PMID: 15810081 DOI: 10.3748/wjg.v11.i14.2142]

13 **Nuño-Guzmán CM**, Marín-Contreras ME, Figueroa-Sánchez M, Corona JL. Gallstone ileus, clinical presentation, diagnostic and treatment approach. *World J Gastrointest Surg* 2016; **8**: 65-76 [PMID: 26843914 DOI: 10.4240/wjgs.v8.i1.65]

14 **Lê P**, Chambon H, Madeuf E. [Gallstone ileus]. *J Chir (Paris)* 2003; **140**: 169-170 [PMID: 12910216]

15 **Doko M**, Zovak M, Kopljar M, Glavan E, Ljubicic N, Hochstädter H. Comparison of surgical treatments of gallstone ileus: preliminary report. *World J Surg* 2003; **27**: 400-404 [PMID: 12658481 DOI: 10.1007/s00268-002-6569-0]

16 **Moberg AC**, Montgomery A. Laparoscopically assisted or open enterolithotomy for gallstone ileus. *Br J Surg* 2007; **94**: 53-57 [PMID: 17058318 DOI: 10.1002/bjs.5537]

17 **Hamad GG**, Ikramuddin S, Gourash WF, Schauer PR. Elective cholecystectomy during laparoscopic Roux-en-Y gastric bypass: is it worth the wait? *Obes Surg* 2003; **13**: 76-81 [PMID: 12630618 DOI: 10.1381/096089203321136638]

18 **Sugerman HJ**, Brewer WH, Shiffman ML, Brolin RE, Fobi MA, Linner JH, MacDonald KG, MacGregor AM, Martin LF, Oram-Smith JC. A multicenter, placebo-controlled, randomized, double-blind, prospective trial of prophylactic ursodiol for the prevention of gallstone formation following gastric-bypass-induced rapid weight loss. *Am J Surg* 1995; **169**: 91-6; discussion 96 [PMID: 7818005 DOI: 10.1016/s0002-9610(99)80115-9]

World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 September 27; 15(9): 2089-2097

DOI: 10.4240/wjgs.v15.i9.2089

ISSN 1948-9366 (online)

CASE REPORT

Dual transformation therapy for giant hepatocellular carcinoma: Two case reports and review of literature

Qiang Gao, Guang-Zhi Zhu, Chuang-Ye Han, Xin-Ping Ye, Hua-Sheng Huang, Shu-Tian Mo, Tao Peng

Specialty type: Surgery

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Akbulut S, Turkey; Martín Del Olmo JC, Spain

Received: May 30, 2023
Peer-review started: May 30, 2023
First decision: July 4, 2023
Revised: July 12, 2023
Accepted: August 1, 2023
Article in press: August 1, 2023
Published online: September 27, 2023

Qiang Gao, Guang-Zhi Zhu, Chuang-Ye Han, Xin-Ping Ye, Hua-Sheng Huang, Shu-Tian Mo, Tao Peng, Department of Hepatobiliary Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning 530000, Guangxi Zhuang Autonomous Region, China

Corresponding author: Tao Peng, PhD, Chief Doctor, Department of Hepatobiliary Surgery, The First Affiliated Hospital of Guangxi Medical University, No. 6 Shuangyong Road, Nanning 530000, Guangxi Zhuang Autonomous Region, China. pengtaogmu@163.com

Abstract

BACKGROUND

In the translational therapy of giant hepatocellular carcinoma (HCC), hepatic arterial infusion chemotherapy (HAIC) combined with anti-PD-1 immunotherapy and tyrosine kinase inhibitors (TKI) after laparoscopic portal vein ligation (PVL) is extremely rare. This is a dual conversion therapy that combines surgery and oncology. Here, we report two cases of successful surgical completion after dual conversion therapy.

CASE SUMMARY

We report that a 54-year-old man and a 69-year-old woman were diagnosed with primary HCC combined with hepatitis B cirrhosis (case 2 also combined with fatty liver) on physical examination. Due to the insufficient residual liver volume assessed before surgery, laparoscopic right PVL was performed, followed by HAIC combined with anti-PD-1 immunotherapy and TKI. Finally, surgical resection was successfully completed, and pathology confirmed that the tumor was mostly necrotic (90%) in one case, and no live tumor tissue was found in the other case.

CONCLUSION

In the process of surgical transformation, our treatment plan takes into account the control and transformation of oncology at the same time, which is expected to provide more opportunities for radical hepatectomy and improve the prognosis of patients with large liver cancer.

Key Words: Giant hepatocellular carcinoma; Laparoscopic right portal vein ligation; hepatic arterial infusion chemotherapy; Anti-PD-1 immunotherapy; Tyrosine kinase inhibitor; Case report

Core Tip: There have been many clinical studies on translational therapy for giant hepatocellular carcinoma, but simply seeking surgical transformation always carries the risk of tumor progression. There's a combination of control and transformation in oncology either immunotherapy, targeted therapy, or a combination of both. In addition, we added hepatic arterial infusion chemotherapy to seek better prognosis. In addition to the success of surgical transformation in the 2 patients reported by us, the postoperative pathology also suggested good oncology control and transformation. This treatment regimen is promising to provide more opportunities for radical hepatectomy and better prognosis for patients with large liver cancer.

Citation: Gao Q, Zhu GZ, Han CY, Ye XP, Huang HS, Mo ST, Peng T. Dual transformation therapy for giant hepatocellular carcinoma: Two case reports and review of literature. *World J Gastrointest Surg* 2023; 15(9): 2089-2097
URL: https://www.wjgnet.com/1948-9366/full/v15/i9/2089.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i9.2089

INTRODUCTION

The incidence and mortality rate of hepatocellular carcinoma (HCC) are comparable, making it one of the most common malignant tumors worldwide. According to global cancer statistics data in 2020, there were 600000 new cases of HCC worldwide, with over half of the cases occurring in China[1,2]. Surgical resection remains the first choice for HCC treatment, but the recurrence rate after surgery can be as high as 70%[3]. Some HCC patients may not be suitable for extensive liver resection due to insufficient future liver remnant (FLR) volume[4]. According to the results of the BRIDGE study, 64% of liver cancer patients in China are diagnosed at CNLC-Stage II and III [Barcelona Clinic Liver Cancer (BCLC) Stage B and C], with a median survival period of approximately 2 years[5,6]. Most patients in the advanced stages are not suitable for surgical resection and should receive mainly local and systemic treatments. In recent years, non-surgical treatments for liver cancer have made significant progress. Drug therapy, especially the combination of anti-angiogenic drugs and immune therapy, can achieve an objective response rate of about 30% and a median survival period of around 20 mo in the treatment of advanced or unresectable liver cancer[7-9].

The reasons for unresectability of liver cancer can be divided into two levels. One level is unresectability from a surgical perspective, including patients who cannot tolerate surgical trauma due to their overall condition, cannot tolerate liver dysfunction, or have insufficient FLR volume, which is considered unresectable from a surgical perspective. The other level is technically resectable, but the postoperative efficacy is not better than non-surgical treatment, which is considered unresectable from an oncological or biological perspective. The goal of conversion therapy is to eliminate these two reasons and achieve conversion from unresectable to resectable liver cancer[10]. The main methods of surgical conversion therapy for insufficient FLR volume include associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), portal vein ligation (PVL), and portal vein embolization (PVE), but there is still a risk of tumor progression while the residual liver volume is growing. In our previous clinical study of 30 cases of conversion resection with insufficient FLR volume in HCC using PVL combined with apatinib (anti-VEGFR2) and camrelizumab (anti-PD1), the median preoperative estimated FLR/standard liver volume (SLV) was 32.9% (19.1%-39.9%). According to mRECIST, 4 cases (13.3%) achieved complete response (CR) and 8 cases (26.7%) achieved partial response (PR). Twenty-three cases (76.7%) met the criteria for second-stage surgery, and 20 of them (66.7%) completed second-stage liver tumor resection. Double conversion therapy had better clinical outcomes than simple surgical conversion. However, the control of tumors after PVL in our systemic therapy (objective response rate of 40%, disease control rate of 76.7%) was comparable to that of targeted immunotherapy. Considering the promising results of local combined systemic therapy in tumor control, we added hepatic arterial infusion chemotherapy (HAIC) on the basis of PVL combined with targeted immunotherapy.

Here, we report two cases of successful treatment of large liver cancer patients at our center. After PVL, the patients underwent HAIC combined with targeted immunotherapy, and finally successfully completed right hepatectomy.

CASE PRESENTATION

Chief complaints

Case 1: A 54-year-old Chinese male was admitted to the Department of Hepatobiliary Surgery due to upper abdominal discomfort for 2 wk.

Case 2: A 69-year-old Chinese woman was admitted to the hepatobiliary surgery clinic for 20 d due to physical examination.

History of present illness

Case 1: The patient reported right upper abdominal discomfort without obvious inducement more than half a month ago, presenting intermittent dull pain, each lasting 1-2 min.

Case 2: The patient reported a solid space occupying lesion in the liver during abdominal computed tomography (CT) examination 20 d ago.

History of past illness

Case 1: Hepatitis B cirrhosis for more than 30 years without systematic treatment.

Case 2: Hepatitis B cirrhosis for more than 30 years without systematic treatment; He had a history of fatty liver 3 years ago and was treated regularly with drugs.

Personal and family history

The patient denied any family history of malignant tumours.

Physical examination

There were no positive signs in either.

Laboratory examinations

Case 1: Laboratory tests indicated that AFP was 876.62 ng/mL and PIVKA-II was 12943.43 mAU/mL. Liver function, blood routine, prothrombin time, and international normalized ratio were all within normal ranges. AFP and PIVKA-II were 6.16 ng/mL and 114.89 mAU/mL before right hemihepatectomy.

Case 2: Laboratory tests showed no abnormalities.

Imaging examinations

Case 1: The outer edge of the liver was not smooth, and the proportion of each lobe was disordered. Irregular masses with slightly low density were seen in S5, 6, and 8 segments of the liver, with the size of about 6.7 cm × 6.5 cm × 7.5 cm, complete capsule and small difficult vessels were seen, and the density was not uniform. After enhancement, three stages of scanning were performed: The lesion enhancement was obvious in the arterial stage, but decreased in the portal and equilibrium stages, and the density was lower than that of liver parenchyma. Diagnosis: S5, 6, 8 segments of liver occupying, massive liver cancer was considered. Cirrhosis of the liver (Figure 1A and B). The preoperative SLV was estimated to be 1370.52 mL, and the FLR was estimated to be 418.39 mL using a three-dimensional CT reconstruction system. FLR/SLV was 30.5% (Figure 1C).

Case 2: A round mixed low-density mass with a size of 8.0 cm × 7.5 cm × 6.2 cm was seen in the right lobe of liver (S7/8 segment), with a clear margin. The third stage of enhancement scan showed that the edge of the disease showed continuous enhancement, mainly marginal enhancement, with a density slightly lower than that of open parenchyma, and patchy non-enhancement lesions were still seen in the equilibrium stage. The remaining hepatic parenchyma density was normal and no abnormal enhancement was observed. Diagnosis: right lobe of liver mass, primary liver cancer (mixed type?) was considered (Figure 2A and B). The preoperative SLV was estimated to be 913.5 mL, and the FLR was estimated to be 310.59 mL using a three-dimensional CT reconstruction system. FLR/SLV was 34% (Figure 2C).

FINAL DIAGNOSIS

Case 1

Combined with the patient's medical history, the final diagnosis was HCC (CNLC Ib stage, BCLC A grade, Child-Pugh A grade); hepatitis B cirrhosis.

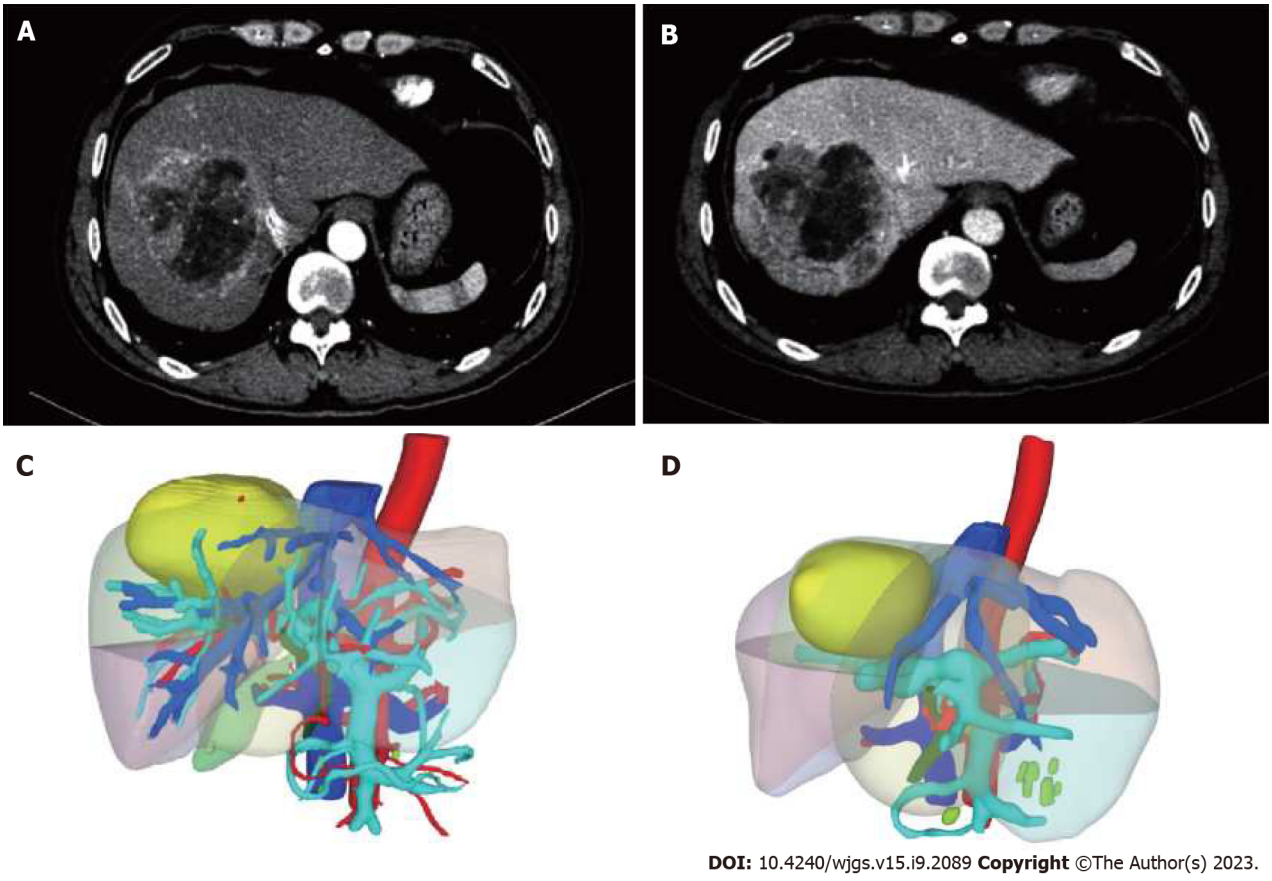
Case 2

Combined with the patient's medical history, the final diagnosis was HCC (CNLC Ib stage, BCLC A grade, Child-Pugh A grade); hepatitis B cirrhosis; fatty liver.

TREATMENT

PVL

Both patients in this series underwent complete laparoscopic right PVL surgery. The surgical steps were as follows: The patient was placed in a supine position, and pneumoperitoneum was established with trocar placement. Intraoperative ultrasound was used to confirm the location and boundaries of the tumor. The right portal vein branch near the first porta hepatis was dissected within the Glisson's sheath, and then titanium clips or No. 7 sutures were used for ligation. An electrocautery hook was used to mark the ischemic line on the liver surface (Figure 3). Case 1 and case 2 completed PVL on July 12 and 29, 2022, respectively.



DOI: 10.4240/wjgs.v15.i9.2089 **Copyright** ©The Author(s) 2023.

Figure 1 Image data of case 1. A: Arterial phase; B: Portal stage; C and D: 3D imaging before and after treatment.

HAIC combined with targeted immunotherapy

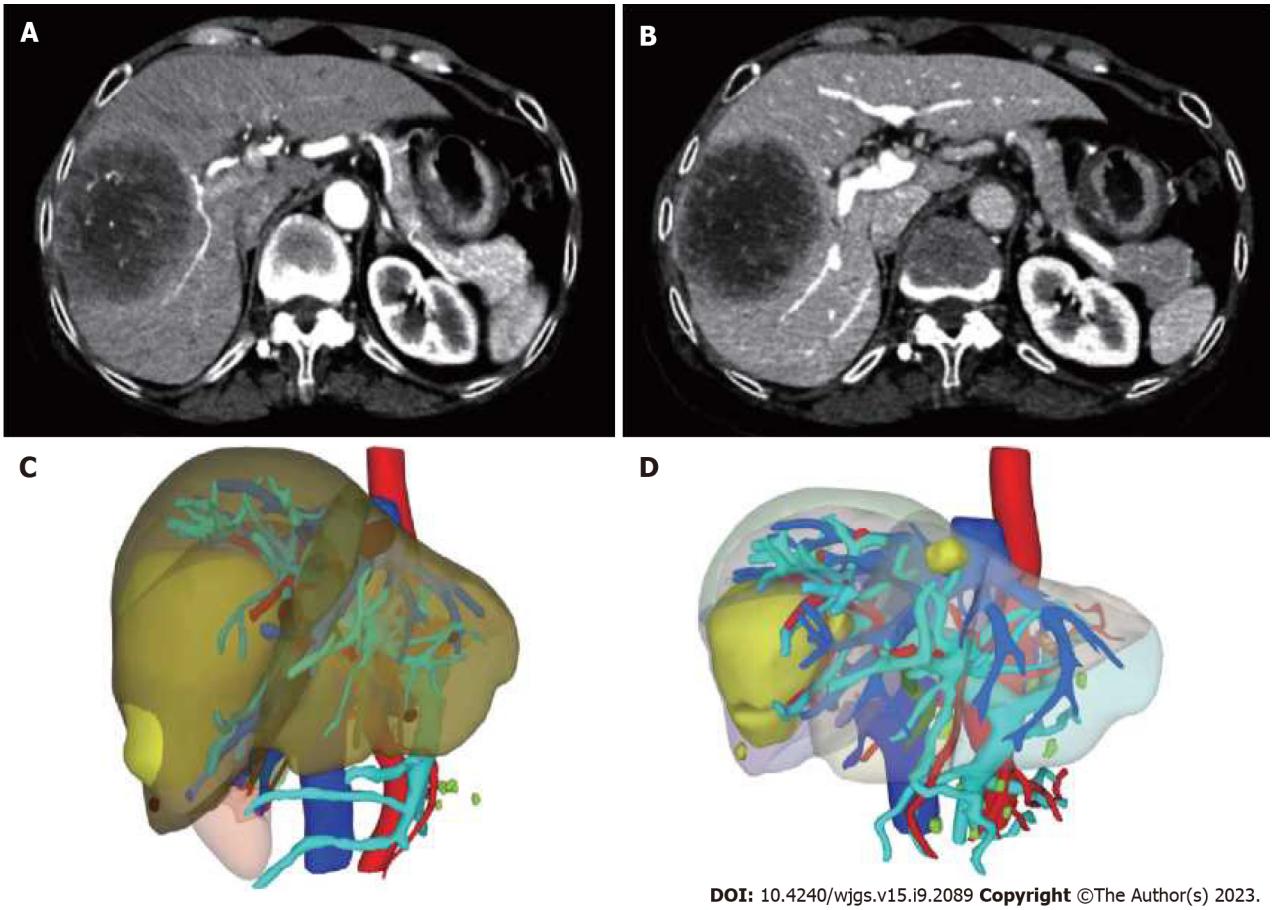
Case 1: The patient underwent a total of 4 cycles of HAIC combined with targeted immunotherapy, using the FOLFOX regimen for 46 h. The microcatheter is pushed into the hepatic artery and the drug is transfused through the hepatic artery. Oxaliplatin, 130 mg/m^2 before 2 h on day 1, calcium folinate, 400 mg/m^2 from 2-3 h on day 1, fluorouracil 400 mg/m^2 at 3 h on day 1, 2400 mg/m^2 over 24 h. On the following dates: July 15, 2022; August 8, 2022; September 6, 2022; and October 13, 2022. Bevacizumab was administered intravenously at a dose of 200 mg on July 18, 2022; August 11, 2022; September 9, 2022; and October 16, 2022. In addition, the patient received oral lenvatinib starting from July 18, 2022, until prior to surgery. After discontinuation of the medication for four weeks, the FLR to SLV ratio was reevaluated and found to be 60.5% (Figure 1D). Right hemihepatectomy was performed on November 25, 2022.

Case 2: On August 12 and September 16, 2022, the patient received HAIC treatment using the same protocol as before. On September 19, Carfilzomib was administered intravenously at a dose of 200mg. After a four-week drug holiday, the FLR/SLV was re-evaluated and found to be 47% (as shown in Figure 2D). On October 26, right hepatectomy was performed to remove the right half of the liver.

Right hemihepatectomy

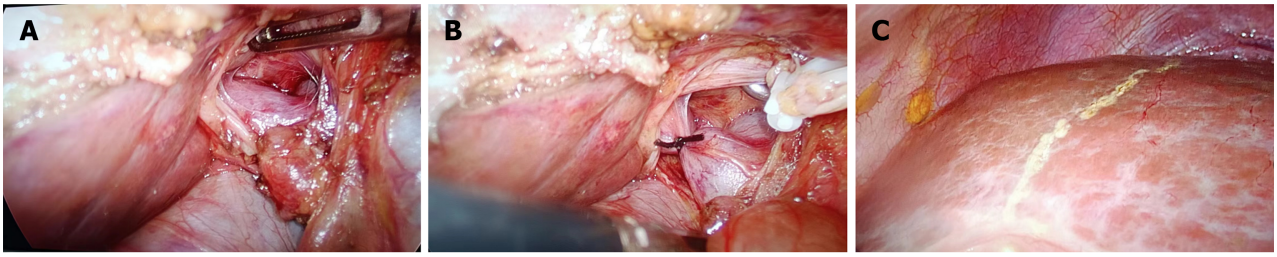
Case 1: During the initial surgical exploration, left liver hypertrophy was easily observed (Figure 4). After separation of adhesions, right hepatic pedicle was dissected intrafascially. Then, the liver parenchyma was continuously separated along the previously marked ischemic line using an ultrasonic knife. The right hepatic vein was transected with a stapling closure device until complete removal of the diseased liver. There were no major complications during the postoperative recovery period. Histopathological examination of the tumor confirmed that the majority of the tumor was necrotic (90% necrosis), with some residual viable tumor tissue at the periphery. The tumor was classified as HCC grade II, with a nodular pattern, with approximately 40% of tumor cells showing clear cell changes and approximately 40% of tumor cells showing macrovesicular fatty changes. Fibrous tissue proliferation with foam cell and multinucleated giant cell reactions were observed, along with deposition of hemosiderin and infiltration of lymphocytes. No satellite nodules or neural bundle invasion were observed, and the microvascular invasion was graded as MO. There was no tumor involvement in the liver capsule or surgical margins. The surrounding liver tissue showed chronic hepatitis changes, with a CS grade of C3S3 (Figure 5A).

Case 2: The postoperative pathological examination revealed extensive necrosis with no residual viable tumor tissue. Fibrous tissue proliferation with abundant lymphocyte and plasma cell infiltration, hemosiderin deposition, and foam cell reaction were observed around the necrotic tissue, consistent with changes after interventional treatment. Microvascular



DOI: 10.4240/wjgs.v15.i9.2089 **Copyright** ©The Author(s) 2023.

Figure 2 Image data of case 2. A: Arterial phase; B: Portal stage; C and D: 3D imaging before and after treatment.



DOI: 10.4240/wjgs.v15.i9.2089 **Copyright** ©The Author(s) 2023.

Figure 3 Complete laparoscopic right portal vein ligation surgery. A: Dissection of the right branch of the portal vein within the Glisson's sheath at the first porta hepatis; B: Occlusion with titanium clip or ligation with No. 7 silk suture; C: Marking of the ischemic line on the surface of the liver with an electrocautery hook.

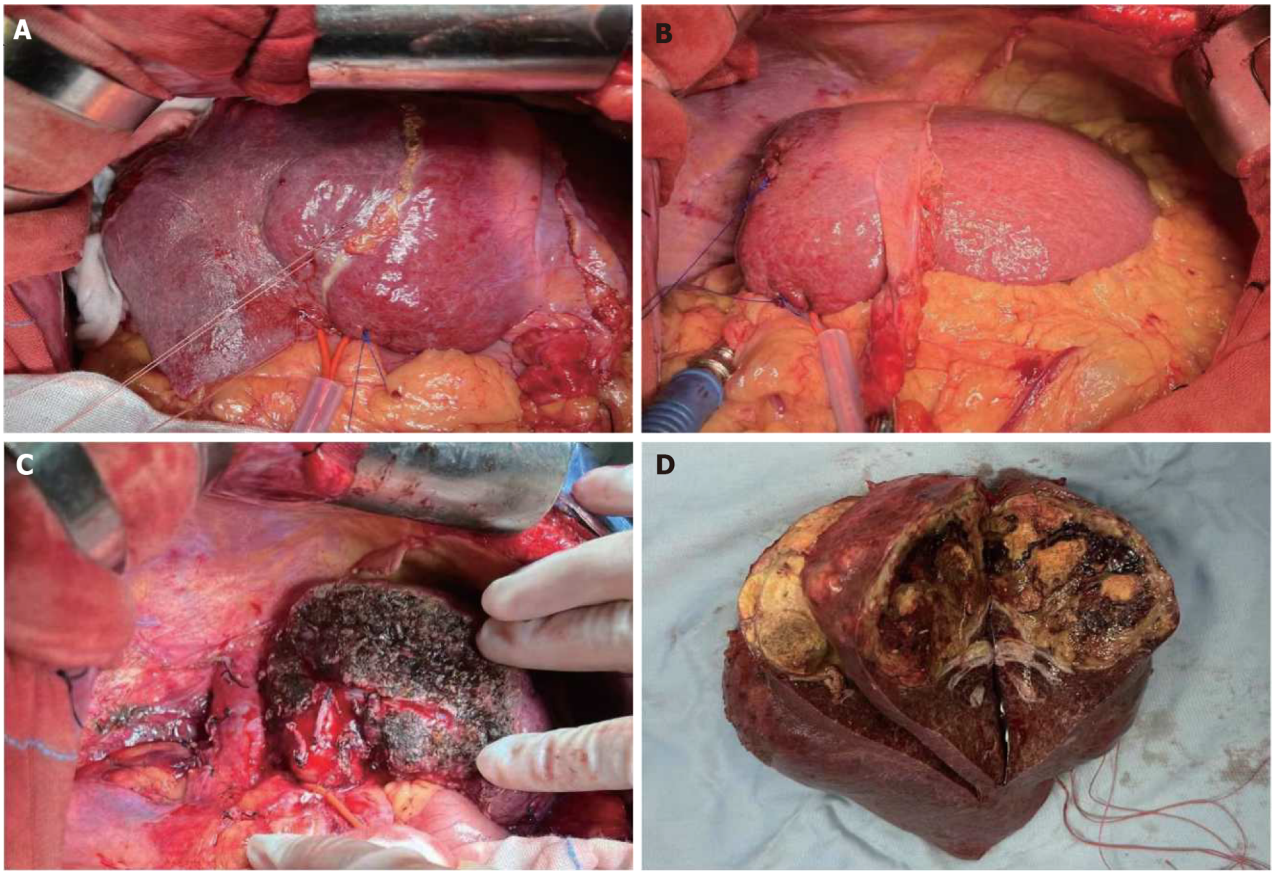
invasion and nerve bundle invasion could not be assessed due to the absence of viable tumor components. There was no tumor involvement in the liver capsule or surgical margins. The surrounding liver tissue showed chronic hepatitis with a grade of G2S2 (Figure 5B).

OUTCOME AND FOLLOW-UP

Cases 1 and 2: As of July 2023, the patient is still alive and has no recurrence.

DISCUSSION

Currently, international centers have similar criteria for determining the required liver reserve function for safe liver



DOI: 10.4240/wjgs.v15.i9.2089

Figure 4 Right hemihepatectomy. A: Intraoperative exploration revealed hypertrophied left lobe of the liver and a marked ischemic line; B: Postoperative left lobe of the liver; C: Surgical section; D: Tumor specimen.

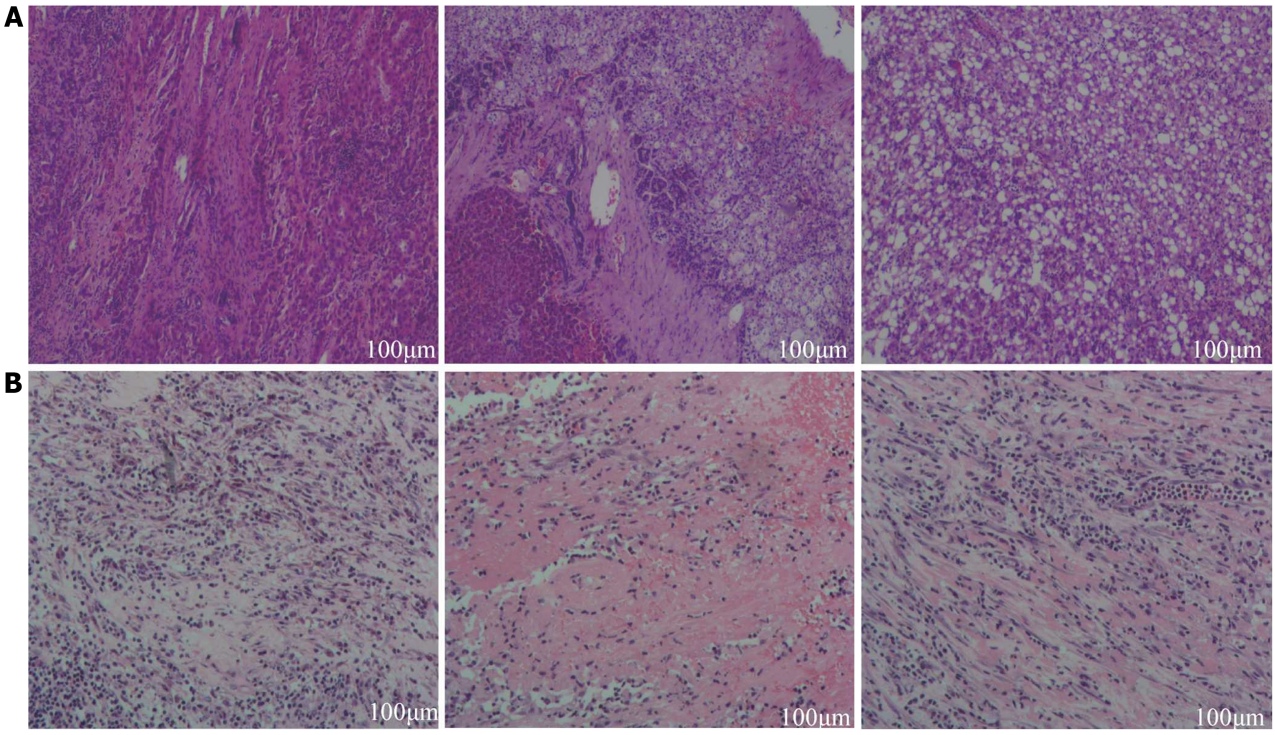
resection, which includes normal liver function (Child-Pugh Class A) with a retention rate of indocyanine green at 15 min (ICG-R15) of 20% to 30%; patients with chronic liver disease or liver parenchymal damage (including cirrhosis, severe fatty liver, and liver damage related to chemical drug treatment) require a FLR to SLV ratio of > 40%; for patients with impaired liver function, a higher FLR is required (*e.g.*, ICG-R15 of 10% to 20%, and patients with chronic liver disease and cirrhosis require FLR/SLV > 50%)[10,11]. Insufficient FLR is an important criterion for unresectable liver cancer, and the goal of conversion therapy is to achieve a sufficient FLR.

In 1990, Makuuchi *et al*[12] reported the first series of PVE in 14 patients with hilar cholangiocarcinoma, demonstrating the safety and feasibility of this technique in reducing postoperative liver failure. PVE has been used in clinical practice for a long time, with a conversion success rate of 60% to 80% and a complication rate of 10% to 20%. The time required for residual liver hypertrophy after PVE is relatively long (usually 4 to 6 wk, during which time tumor progression may occur). In addition, more than 20% of patients may lose the opportunity for surgery due to tumor progression or insufficient volume of residual liver hypertrophy[13-15]. This has prompted exploration of alternative techniques. There is no significant difference in the induction of FLR hypertrophy between PVE and PVL (relative increase in FLR volume: PVE 43.2%, PVL 38.5%). The induction of FLR hypertrophy with PVL also takes 4 to 8 wk. However, the resection rate with PVL is higher than with PVE, resulting in significantly fewer patients who have to cancel surgery due to insufficient FLR hypertrophy. There is no statistically significant difference in the incidence of postoperative complications and mortality between the two techniques[16,17].

In 2012, ALPPS was first described as a surgical technique for increasing FLR in patients with liver tumors[18]. It is a more radical method of portal vein occlusion and elimination of collateral vessels from FLR to the diseased segment, resulting in faster and more extensive FLR enhancement. ALPPS can induce FLR hypertrophy of up to 47% to 192% within 1-2 wk, which is much higher than PVE. Due to the short interval between the two-stage surgeries, it can minimize the risk of tumor progression, with a tumor resection rate of 95% to 100%[19]. The main limitation of this technique is its high morbidity and mortality rates. Compared to PVE, the 90-d mortality rate remains at 8%-9%[20], and both mortality and morbidity rates are increased[21]. These findings were initially attributed to increased invasiveness of the surgery and subsequent bile leakage, with bile leakage occurring in 20% of the cases reported by Schnitzbauer *et al*[18].

When the tumor volume is too large, involves critical ducts, or cannot achieve an R0 resection, tumor reduction through anti-tumor treatment can be achieved before surgery to further improve long-term outcomes. Treatment options include local therapy, systemic therapy, and combination therapy[11].

In clinical practice, there is no consensus on which systemic treatment regimen to choose for potentially resectable liver cancer patients. Based on current clinical research data on first-line systemic treatment for liver cancer, lenvatinib has a



DOI: 10.4240/wjgs.v15.i9.2089

Figure 5 Histopathological image. A: Case 1; B: Case 2.

higher objective response rate (ORR) than sorafenib[22]. Combination targeted therapy and immunotherapy (targeted immunotherapy combination)[7,8,23,24], represented by lenvatinib combined with pembrolizumab, nivolumab combined with ramucirumab, and bevacizumab, and atezolizumab combined with cetuximab, has an ORR > 20% for treating unresectable liver cancer, with stronger potential for conversion. Zhu *et al*[25] reported a conversion resection rate of 23.8% in 101 cases of initially unresectable liver cancer patients treated with PD-1 inhibitors combined with tyrosine kinase inhibitors (TKIs)[25]. Zhu *et al*[26] reported a conversion resection rate of 15.9% in 63 cases of initially unresectable liver cancer patients treated with PD-1 inhibitors combined with TKIs. At the 2022 Annual Meeting of the American Association for the Study of Liver Diseases, we reported the effectiveness and safety of hepatic portal vein ligation (PVL) combined with apatinib (anti-VEGFR2) + camrelizumab (anti-PD1) (also known as double A combination) in treating insufficient FLR volume HCC. According to mRECIST, among them, 4 cases (13.3%) achieved CR, 8 cases (26.7%) achieved PR, 11 cases (36.7%) had stable disease (SD), and 7 cases (23.3%) had progressive disease (PD), with an ORR of 40% and a disease control rate (DCR) of 76.7%. This is a dual conversion regimen that considers both surgical and oncological aspects. The results of this study suggest that PVL combined with apatinib and camrelizumab may become a potential treatment option for insufficient FLR volume HCC.

In Asia, particularly in Japan and South Korea, HAIC has been used to improve the prognosis of advanced HCC and has been incorporated into treatment guidelines[27]. In a randomized phase III study (9810) announced at ESMO 2020, the surgical conversion rate of unresectable HCC with HAIC (oxaliplatin, fluorouracil, and folinic acid) was 23.8% in the HAIC group compared to 11.5% in the transarterial chemoembolization group ($P < 0.004$). Furthermore, the study also found that the ORR of advanced HCC treated with HAIC plus targeted therapy and immune therapy according to mRECIST criteria was 67.6%[28]. The results of clinical studies by Luo *et al*[29] and Zhang *et al*[30] at their respective centers, using HAIC in combination with targeted immunotherapy for advanced liver cancer, were encouraging, with objective tumor response rates of 57.2% and 96%, respectively, and good safety profiles. These studies demonstrate that combined systemic and local treatment can lead to better tumor response, providing new options for future HAIC-based conversion therapies.

In the two cases reported in our study, the main feature was the increase in FLR volume after PVL combined with systemic and local treatment. FLR increased by 30% and 13% in case 1 and case 2, respectively, with time intervals of 17 wk and 12 wk, respectively. Postoperative pathology confirmed that the majority of the tumor in case 1 had necrotized (90% necrosis), and the tumor in case 2 had completely necrotized, with both cases showing good recovery during follow-up. Dual conversion in terms of surgical and oncological outcomes was achieved, indicating that PVL combined with HAIC and targeted immunotherapy is a safe and effective dual conversion treatment approach.

CONCLUSION

Our treatment approach aims to achieve surgical conversion while also addressing tumor control and conversion,

offering potential opportunities for curative liver resection in patients with advanced HCC and improving their prognosis. However, research in this area is limited at present. Further studies are needed to confirm the safety, feasibility, and efficacy of our approach.

FOOTNOTES

Author contributions: Gao Q, Zhu GZ, and Han CY contributed to data curation and writing of the original draft; Ye XP and Huang HS contributed to data curation; Mo ST, and Peng T contributed to manuscript review and editing; all authors have read and approved the final manuscript.

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

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

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

Country/Territory of origin: China

ORCID number: Guang-Zhi Zhu 0000-0001-5958-7289; Xin-Ping Ye 0000-0002-9200-1312; Hua-Sheng Huang 0000-0003-1112-5071; Tao Peng 0000-0001-6133-7078.

S-Editor: Yan JP
L-Editor: A
P-Editor: Cai YX

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 M**, Li H, Sun D, Chen W. Cancer burden of major cancers in China: A need for sustainable actions. *Cancer Commun (Lond)* 2020; **40**: 205-210 [PMID: 32359212 DOI: 10.1002/cac2.12025]

3 **General Office of National Health Commission**. Diagnosis and Treatment Guidelines for Primary liver Cancer (2022 edition). *Linchuang Gandanbing Zazhi* 2022; **38**: 288-303 [DOI: 10.3969/j.issn.1001-5256.2022.02.009]

4 **Chan A**, Zhang WY, Chok K, Dai J, Ji R, Kwan C, Man N, Poon R, Lo CM. ALPPS Versus Portal Vein Embolization for Hepatitis-related Hepatocellular Carcinoma: A Changing Paradigm in Modulation of Future Liver Remnant Before Major Hepatectomy. *Ann Surg* 2021; **273**: 957-965 [PMID: 31305284 DOI: 10.1097/SLA.0000000000003433]

5 **Park JW**, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, Kudo M, Johnson P, Wagner S, Orsini LS, Sherman M. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. *Liver Int* 2015; **35**: 2155-2166 [PMID: 25752327 DOI: 10.1111/liv.12818]

6 **Zhou J**, Sun H, Wang Z, Cong W, Wang J, Zeng M, Zhou W, Bie P, Liu L, Wen T, Han G, Wang M, Liu R, Lu L, Ren Z, Chen M, Zeng Z, Liang P, Liang C, Yan F, Wang W, Ji Y, Yun J, Cai D, Chen Y, Cheng W, Cheng S, Dai C, Guo W, Hua B, Huang X, Jia W, Li Y, Liang J, Liu T, Lv G, Mao Y, Peng T, Ren W, Shi H, Shi G, Tao K, Wang X, Xiang B, Xing B, Xu J, Yang J, Yang Y, Ye S, Yin Z, Zhang B, Zhang L, Zhang S, Zhang T, Zhao Y, Zheng H, Zhu J, Zhu K, Shi Y, Xiao Y, Dai Z, Teng G, Cai J, Cai X, Li Q, Shen F, Qin S, Dong J, Fan J. Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma (2019 Edition). *Liver Cancer* 2020; **9**: 682-720 [PMID: 33442540 DOI: 10.1159/000509424]

7 **Finn RS**, Ikeda M, Zhu AX, Sung MW, Baron AD, Kudo M, Okusaka T, Kobayashi M, Kumada H, Kaneko S, Pracht M, Mamontov K, Meyer T, Kubota T, Dutcus CE, Saito K, Siegel AB, Dubrovsky L, Mody K, Llovet JM. Phase Ib Study of Lenvatinib Plus Pembrolizumab in Patients With Unresectable Hepatocellular Carcinoma. *J Clin Oncol* 2020; **38**: 2960-2970 [PMID: 32716739 DOI: 10.1200/JCO.20.00808]

8 **Xu J**, Shen J, Gu S, Zhang Y, Wu L, Wu J, Shao G, Xu L, Yin T, Liu J, Ren Z, Xiong J, Mao X, Zhang L, Yang J, Li L, Chen X, Wang Z, Gu K, Pan Z, Ma K, Zhou X, Yu Z, Li E, Yin G, Zhang X, Wang S, Wang Q. Camrelizumab in Combination with Apatinib in Patients with Advanced Hepatocellular Carcinoma (RESCUE): A Nonrandomized, Open-label, Phase II Trial. *Clin Cancer Res* 2021; **27**: 1003-1011 [PMID: 33087333 DOI: 10.1158/1078-0432.CCR-20-2571]

9 **Yau T**, Kang YK, Kim TY, El-Khoueiry AB, Santoro A, Sangro B, Melero I, Kudo M, Hou MM, Matilla A, Tovoli F, Knox JJ, Ruth He A, El-Rayes BF, Acosta-Rivera M, Lim HY, Neely J, Shen Y, Wisniewski T, Anderson J, Hsu C. Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib: The CheckMate 040 Randomized Clinical Trial. *JAMA Oncol* 2020; **6**: e204564 [PMID: 33001135 DOI: 10.1001/jamaoncol.2020.4564]

10 **Sun HC**, Xie Q, Jia WD, Zhao M, Liu XF, Bi XY, Li G, Bai XL, Ji Y, Xu L, Wang Z, Zhu XD. Chinese Expert Consensus on transformation

Therapy for liver Cancer (2021 edition). *Zhongguo Shiyong Waike Zazhi* 2021; **41**: 618-632 [DOI: 10.19538/j.cjps.issn1005-2208.2021.06.02]

11 **Zhao HT**, Bi XY, Zhao H, Sun YK, Zhou JG, Chen B, Zhang W. Chinese expert consensus on neoadjuvant and translational therapy for hepatocellular carcinoma. *Ganai Dianza Zazhi* 2022; **9**: 23-28 [DOI: 10.3969/j.issn.2095-7815.2022.01.002]

12 **Makuuchi M**, Thai BL, Takayasu K, Takayama T, Kosuge T, Gunvén P, Yamazaki S, Hasegawa H, Ozaki H. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. *Surgery* 1990; **107**: 521-527 [PMID: 2333592]

13 **Aloia TA**. Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy: Portal Vein Embolization Should Remain the Gold Standard. *JAMA Surg* 2015; **150**: 927-928 [PMID: 26308668 DOI: 10.1001/jamasurg.2015.1646]

14 **Piron L**, Deshayes E, Escal L, Souche R, Herrero A, Pierredon-Foulongne MA, Assenat E, le Lam N, Quenet F, Guiu B. [Portal vein embolization: Present and future]. *Bull Cancer* 2017; **104**: 407-416 [PMID: 2WJGS-15-189270 DOI: 10.1016/j.bulcan.2017.03.009]

15 **European Association for the Study of the Liver**; European Organisation for research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 908-943 [PMID: 22424438 DOI: 10.1016/j.jhep.2011.12.001]

16 **Jaeck D**, Oussoultzoglou E, Rosso E, Greget M, Weber JC, Bachellier P. A two-stage hepatectomy procedure combined with portal vein embolization to achieve curative resection for initially unresectable multiple and bilobar colorectal liver metastases. *Ann Surg* 2004; **240**: 1037-49; discussion 1049 [PMID: 15570209 DOI: 10.1097/01.sla.0000145965.86383.89]

17 **Isfordink CJ**, Samim M, Braat MNGJA, Almalki AM, Hagendoorn J, Borel Rinkes IHM, Molenaar IQ. Portal vein ligation versus portal vein embolization for induction of hypertrophy of the future liver remnant: A systematic review and meta-analysis. *Surg Oncol* 2017; **26**: 257-267 [PMID: 28807245 DOI: 10.1016/j.suronc.2017.05.001]

18 **Schnitzbauer AA**, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA, Fichtner-Feigl S, Lorf T, Goralcyk A, Hörbelt R, Kroemer A, Loss M, Rümmele P, Scherer MN, Padberg W, Königsrainer A, Lang H, Obed A, Schlitt HJ. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. *Ann Surg* 2012; **255**: 405-414 [PMID: 22330038 DOI: 10.1097/SLA.0b013e31824856f5]

19 **Popescu GA**, Alexandrescu ST, Grigorie RT, Stoica L, Apavaloaie CA, Hrehoreţ D. GOOD TO KNOW: The ALPPS Procedure - Embracing a New Technique. *Chirurgia (Bucur)* 2017; **112**: 332-341 [PMID: 28675369 DOI: 10.21614/chirurgia.112.3.332]

20 **Sandström P**, Røsok BI, Sparrelid E, Larsen PN, Larsson AL, Lindell G, Schultz NA, Bjørnbeth BA, Isaksson B, Rizell M, Björnsson B. ALPPS Improves Resectability Compared With Conventional Two-stage Hepatectomy in Patients With Advanced Colorectal Liver Metastasis: Results From a Scandinavian Multicenter Randomized Controlled Trial (LIGRO Trial). *Ann Surg* 2018; **267**: 833-840 [PMID: 28902669 DOI: 10.1097/SLA.0000000000002511]

21 **Eshmuminov D**, Raptis DA, Linecker M, Wirsching A, Lesurtel M, Clavien PA. Meta-analysis of associating liver partition with portal vein ligation and portal vein occlusion for two-stage hepatectomy. *Br J Surg* 2016; **103**: 1768-1782 [PMID: 27633328 DOI: 10.1002/bjs.10290]

22 **Kudo M**, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018; **391**: 1163-1173 [PMID: 29433850 DOI: 10.1016/S0140-6736(18)30207-1]

23 **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]

24 **Ren Z**, Fan J, Xu J, Bai Y, Xu A, Cang S, Du C, Liu B, Li Q, Lu Y, Chen Y, Shao G, Guo Y, Chen Z, Yang Y, Chen M, Wang Y, Zhou H. LBA2 Sintilimab plus bevacizumab biosimilar vs sorafenib as first-line treatment for advanced hepatocellular carcinoma (ORIENT-32)2. *Ann Oncol* 2020; **31** Suppl 6: S1287 [DOI: 10.1016/j.annonc.2020.10.134]

25 **Zhu XD**, Huang C, Shen YH, Xu B, Ge NL, Ji Y, Qu XD, Chen L, Chen Y, Li ML, Zhu JJ, Tang ZY, Zhou J, Fan J, Sun HC. Hepatectomy After Conversion Therapy Using Tyrosine Kinase Inhibitors Plus Anti-PD-1 Antibody Therapy for Patients with Unresectable Hepatocellular Carcinoma. *Ann Surg Oncol* 2023; **30**: 2782-2790 [PMID: 36178565 DOI: 10.1245/s10434-022-12530-z]

26 **Zhu XD**, Huang C, Shen YH, Ji Y, Ge NL, Qu XD, Chen L, Shi WK, Li ML, Zhu JJ, Tan CJ, Tang ZY, Zhou J, Fan J, Sun HC. Downstaging and Resection of Initially Unresectable Hepatocellular Carcinoma with Tyrosine Kinase Inhibitor and Anti-PD-1 Antibody Combinations. *Liver Cancer* 2021; **10**: 320-329 [PMID: 34414120 DOI: 10.1159/000514313]

27 **Kokudo N**, Takemura N, Hasegawa K, Takayama T, Kubo S, Shimada M, Nagano H, Hatano E, Izumi N, Kaneko S, Kudo M, Iijima H, Genda T, Tateishi R, Torimura T, Igaki H, Kobayashi S, Sakurai H, Murakami T, Watadani T, Matsuyama Y. Clinical practice guidelines for hepatocellular carcinoma: The Japan Society of Hepatology 2017 (4th JSH-HCC guidelines) 2019 update. *Hepatol Res* 2019; **49**: 1109-1113 [PMID: 31336394 DOI: 10.1111/hepr.13411]

28 **Shi M**, Li Q, He M, Guo R. 981O Hepatic arterial infusion chemotherapy (HAIC) with oxaliplatin, fluorouracil, and leucovorin (FOLFOX) vs transarterial chemoembolization (TACE) for unresectable hepatocellular carcinoma (HCC): A randomised phase III trial. *Ann Oncol* 2020; **31**: S688

29 **Luo L**, Xiao Y, Zhu G, Huang A, Song S, Wang T, Ge X, Xie J, Deng W, Hu Z, Wen W, Mei H, Wan R, Shan R. Hepatic arterial infusion chemotherapy combined with PD-1 inhibitors and tyrosine kinase inhibitors for unresectable hepatocellular carcinoma: A tertiary medical center experience. *Front Oncol* 2022; **12**: 1004652 [PMID: 36237309 DOI: 10.3389/fonc.2022.1004652]

30 **Zhang J**, Zhang X, Mu H, Yu G, Xing W, Wang L, Zhang T. Surgical Conversion for Initially Unresectable Locally Advanced Hepatocellular Carcinoma Using a Triple Combination of Angiogenesis Inhibitors, Anti-PD-1 Antibodies, and Hepatic Arterial Infusion Chemotherapy: A Retrospective Study. *Front Oncol* 2021; **11**: 729764 [PMID: 34868921 DOI: 10.3389/fonc.2021.729764]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com